RAMB

JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

AMB Associação Médica Brasileira

WMA

Volume **66** Number **5 May 2020**
ISSN **0104-4230**
ISSN **1806-9282** (On-line)

SECTIONS

ARTICLES

RAMB REVISTA DA ASSOCIAÇÃO MÉDICA BRASILEIRA
JOURNAL OF THE BRAZILIAN MEDICAL ASSOCIATION

Personalized functional gynecology: a new direction?

Dirceu Henrique Mendes Pereira
Silvana Chedid Grieco
Symara De Angelis Trivellato
Simone Nahas
Regina Teixeira Teixeira Gomes
Alexandre de Luca
José Maria Soares Júnior
Edmund Chada Baracat

e-mail: jsoares415@hotmail.com

http://dx.doi.org/10.1590/1806-9282.66.5.560

In recent decades, technological evolution has allowed for a monumental leap in the quality of disease diagnosis and treatment. The medical care in acute diseases is almost always successful thanks to the technological adequacy of hospitals and the therapeutic options currently available. However, when it comes to chronic non-communicable diseases (CNCD) we are still finding our way regarding the correction of molecular, metabolic, and immuno-inflammatory dysfunctions that constitute the background of the physiopathology of these nosological entities[1,2].

CNCDs are cutting our existence short, destroying our quality of life, burdening the government budget, and threatening the health of future generations. Unfortunately, conventional medicine has failed in responding to this challenge, and, as a result, the prevalence of chronic diseases continues to rise.

CNCDs are difficult to manage, costly to treat, require a multidisciplinary team, and, typically, are present throughout the second half of life. The forecast is that within the next few years, with the increase in longevity, 75% of the ´population will be affected, with a loss of autonomy and causing family and social dependence. The current therapeutic intervention is not enough to prevent or revert the evolution of morbidity. Recent reports suggest that over 85% of chronic diseases are caused by factors such as inappropriate diet, sedentary lifestyle, distorted behavior/lifestyle habits, and environmental toxins[1,3].

There is fear that the two types of therapeutic approaches are mutually exclusive. However, this fear is unfounded. The personalized functional intervention is based on the foundations of conventional medicine and adds other resources to the semiotics and treatment, with a focus on the individual behavior and environment, without ignoring the diagnosis of the disease, which can manifest in different ways depending on the individuality[4].

Six basic principles constitute the foundation upon which this modality of intervention was developed to correct functional disorders[4]:

1. Genomic and biochemical individuality of human beings.
2. Therapeutic intervention focused on the individual (anthropocentric).
3. Search for a dynamic balance between mind, body, and soul.
4. Familiarity with the interconnectivity of internal physiological factors.
5. Identification of health as 'positive vitality' and not merely as the absence of disease.
6. Promotion of organic reserves as a means of increasing the extent of health and not merely the extension of life.

Functional intervention is based on the integration of the information that comprises the biography of individuals, obtained through anamnesis, making it possible to identify antecedents, mediators, and "triggers" of physical, emotional, or environmental circumstances that trigger the body's interconnectivity system. These transgressive agents can cause metabolic and biochemical imbalances that, over time, trigger and perpetuate CNCD. Identifying the source of the imbalance, by obtaining the upstream flow of symptoms and signs, is extremely relevant in the therapeutic care because it enables to cut the roots of the problem, minimizing unfavorable outcomes to the patient or sequelae[5].

The Institute of Functional Medicine, in the United States of America*, believes that pathophysiological mechanisms originate from biomolecular changes and that they are related to the intricate relationship between gene expression, lifestyle, and ecosystem quality*[4]*. This paradigm shift is based on the concept that every human being has a genetic, biochemical, and metabolic identity*[4].

Fundamental physiological processes take place in the cell framework and the extracellular matrix integrated into an extensive network of intercommunication. A huge cascade of substances, organelles, receptors, hormones, growth factors, transcription factors, prostaglandins, cytokines, interleukins, and others, act at this stage executing a harmonious dance, in ideal conditions, or an anarchic and disastrous spectacle when in a state of adversity[5.6].

Aiming to broaden the quality of care for patients in the Climacteric Ambulatory of HC-FMUSP, we have recently started care and research activity that introduces this modality of intervention that operates primarily in the correction of lifestyle, environmental awareness, social adaptation of the patients. To accomplish this task, we have put together a multidisciplinary team of physicians, nutritionists, psychologists, physical educators, etc.

Gynecologists need to be prepared to explore more deeply the history of women's lives beyond what they learned in the basic curriculum. For a long time in their lives (from the fertile years to the menopausal transition) women are under the medical care of obstetrician-gynecologists[7]. The prevention of CNCD must occur in this stage of life through the correction of metabolic and biochemical imbalances. In the supplementary interview, it is necessary to observe adverse conditions in the everyday life of the individual (lifestyle and environment) that can act as a trigger for biochemical and metabolic instability. These include (a) the quality of the air, water, and soil; (b) exposure to microorganisms; c) physical activity and reduction of sedentary behavior; d) previous physical or emotional trauma; e) psychosocial factors, such as family, work, community, economic condition, and daily stress; (f) use of licit and/or illicit drugs; g) exposure to pollutants; h) contact with actinic radiation (solar).

Depending on the individuals' genetic susceptibility, exposure to these factors can generate oxidative stress and/or chronic inflammation, almost always preceded by biochemical and metabolic disorders that trigger and perpetuate the disease and are worsened with obesity[5].

At the turn of the millennium, there was a scientific achievement of the utmost importance for humanity: the completion of the Human Genomic Project, coordinated by the *National Institutes of Health and the US Department of Energy*[8] and with the participation of *Celera Genomics*[9]. It found that the human genome is composed of 50.000 genes, 3.2 billion base pairs, and 3 million SNPs (single nucleotide polymorphisms). That opened up the possibility of using specific genomic profiles that could assist in the prevention and treatment of diseases[10].

However, mutant genes are expressed only when activated by stressor agents, internal and/or external, upon protein transcription. It is clear that genetic modification is not pre-determined and that lifestyle and environmental conditions play a role in the outbreak and maintenance of the disease[5].

More recently, the concept of epigenetics emerged as the result of the molecular modification of nitrogenous bases without changing the gene sequence. Changes in methylation, acetylation, and non-coding DNA arising from the interaction with lifestyle and the environment cause functional disorders in individuals' phenotypes[11].

In 2009, the scientific community completed a further achievement that would contribute significantly to functional therapeutic interventions: The Human Microbiome Project. This is the genomic identification of the microbiota, by using 16 S DNA sequencing, that comprises a quadrillion microorganisms (10 times the number of cells) potentially able to interact with the intricate communication system of the organism[12.13].

These scientific achievements will require major adaptations in the teaching of biological sciences, demonstrating that pathophysiological disorders occur primarily in the intrinsic cellular function

and manifesting in different ways in the organs and systems that integrate our body[14]. Identifying the source of imbalance is perhaps more important than the very nosological diagnosis, which is manifested differently depending on the individuality of each human being.

The genomic era has enabled the identification of mutations and polymorphisms (SNPs) that affect the expression of CYPs involved in the metabolism of estrogens, presenting an opportunity to individualize the prescription of sexual hormones to prevent oncogenesis. Thus, it is possible to assess the significance of mutations in genes involved in the carcinogen metabolism, metabolic biosynthesis of estrogens, activation of steroid receptors, and response to DNA damage[15].

Environmental pollutants are a growing threat to our health. Heavy metals (lead, mercury, cadmium, aluminum, etc) as well as the persistent organic pollutants (POPs), molecules that have a similar configuration to estrogen, and motivate a state of relative hyperestrogenism[16]. We are experiencing an unprecedented degradation of the ecosystem, which generates detriments capable of inducing hormonal disruption, oxidative stress, and DNA damage[17].

Oxidative stress is the result of an accumulation of reactive oxygen species (ROSs) which surpass the body's antioxidative potential (AntiOx). several studies have shown that reactive oxygen species can harm the cell microenvironment, particularly the organelles and membranes, destabilizing the protein, lipid, and carbohydrate molecules, and nuclear and mitochondrial DNA[18].

The social changes associated with the degradation of the environment had consequences on the female reproductive life, inducing the emergence of dysfunctions that contributed to affect their health. In the field of gynecology, we will be able to advance in the treatment of various ailments, from the strictly dysfunctional (primary dysmenorrhoea, premenstrual syndrome, mastalgia, vaginosis, infertility with no apparent cause, and other illnesses) to expansive pelvic states (fibroma, endometriosis) and precursor lesions of genital neoplasms[19,20].

The goal is to correct the biological, psychological, endocrine, immune, and metabolic imbalances that originate the disease, thus anticipating unfavorable outcomes. In doing so, the disorders are corrected at the origin of the cascade of events that invariably contribute to the genesis and maintenance of gynecological affections and diseases[18-21].

The functional intervention model is inclusive by introducing the "focus on the individual" in a propedeutic assessment, thus increasing the scope of traditional medicine, which is focused predominantly on the disease. Identifying the dysfunctions that precede the disease provides the opportunity to act on its source, decreasing the possibility of recurrence of symptoms and signs. By identifying the origin of diseases characterized as "idiopathic", they can receive specific corrective treatment instead of 'off label' or empirical interventions, for which we do not have scientific evidence of efficacy and safety. Functional nutrition, tailored physical activity, stress management all in tune with the circadian rhythm, and with environmental awareness constitute the most important tools for achieving this goal[21-24]. CNCD patients can greatly benefit from the association of both interventions (conventional and functional) to restore their health and vitality. However, such integration between different areas of health and well-controlled long-term studies are still challenges we must face to offer personalized functional gynecology to the population.

REFERENCES

1. World Health Organization. Burden: mortality, morbidity and risk factors. In: Global status report on noncommunicable diseases 2010. Geneva: WHO; 2010. p.9-32.
2. Holman H. Chronic disease: the need for a new clinical education. JAMA. 2004;292(9):1057-9.
3. Terzic A, Waldman S. Chronic disease: the emerging pandemic. Clin Transl Sci. 2011;4(3):225-6.
4. Jones SJ. Textbook of functional medicine. Gig Harbor: Institute for Functional Medicine; 2005.
5. Hyman M, Baker SM, Jones DS. Functional medicine and biochemical individuality: paradigm shift in medicine. In: Jones DS, ed. Textbook of functional medicine. Gig Harbor: Institute for Functional Medicine; 2005. p.55-75.
6. Lodish H, Berk A, Kaiser CA, Krieger M, Bretscher A, Ploegh H, et al. Biologia celular e molecular. 7ª ed. Porto Alegre: Artmed; 2014.
7. Pompei LM, Machado RB, Wender MCO, Fernandes CE. Consenso brasileiro de terapia hormonal da menopausa. São Paulo: SOBRAC; 2018.
8. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al. International Human Genome Sequencing Consortium. Initial sequencing and analysis of human genome. Nature. 2001;409(6822):860-921.
9. Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, et al. The sequence of the human genome. Science. 2001;291(5507):1304-51.
10. Jameson JL. The human genome project. In: Jameson JL, ed. Principles of molecular medicine. Basel: Springer Nature Switzerland AG; 2018. p.59-63.

11. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet. 2003;33(Suppl):245-54.

12. Human Microbiome Project Consortium. A framework for human microbiome research. Nature. 2012;486(7402):215-21.

13. Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med. 2016;375(24):2369-79.

14. Berg JM, Tymoczko JL, Stryer L. Metabolism is composed of many coupled, interconnecting reactions. In: Biochemistry. 5th ed. New York: WH Freeman; 2002.

15. Dunning AM, Dowsett M, Healey CS, Tee L, Luben RN, Folkerd E. Polymorphisms associated with circulating sex hormones levels in postmenopausal women. J Natl Cancer Inst. 2004;96(12):936-45.

16. ACOG Committee Opinion Nº 575. Exposure to toxic environmental agents. Fertil Steril. 2013;100(4):931-4.

17. Godson WH 3rd, Lowe L, Carpenter DO, Gilbertson M, Manaf Ali A, Lopez de Cerain Salsamendi A, et al. Assessing the carcinogenic potential of low-dose exposures to chemical mixtures in the environment: the challenge ahead. Carcinogenesis. 2015;36(Suppl 1):S254-96.

18. Lemos A. Controle dos vários tipos de estresse para a manutenção da saúde. 2ª ed. Rio de Janeiro: Artur Lemos; 2018.

19. Baracat EC, Soares Júnior JM. Condutas em ginecologia baseadas em evidências: protocolos assistenciais, clínica ginecológica, Hospital das Clínicas - FMUSP. São Paulo: Atheneu; 2016.

20. Hayes B. Perimenopause, menopause and women's health. In: Jones SJ, ed. Textbook of functional medicine. Gig Harbor: Institute for Functional Medicine; 2005. p.622-35.

21. Bland JS. Clinical nutrition: a functional approach. In: Jones DS, ed. Textbook of functional medicine. Gig Harbor: Institute for Functional Medicine; 2005.

22. McEwen BS. Neurobiological and systemic effects of chronic stress. Chronic Stress (Thousand Oaks). 2017;1.

23. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT; Lancet Physical Activity Series Working Group. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380(9838):219-29.

24. Voigt RM, Forsyth B, Keshavarzian A. Circadian disruption: potential implications in inflammatory and metabolic diseases associated with alcohol. Alcohol Res. 2013;35(1):87-96.

Does online pornography influence the sexuality of adolescents during COVID-19?

Ana Larissa Perissini[1]
Luís Cesar Fava Spessoto[2]
Fernando Nestor Facio Junior[2]

1. Doutoranda no Programa de Ciências da Saúde, Faculdade de Medicina (FAMERP), São José do Rio Preto, SP, Brasil.
2. Professor de Urologia, Departamento de Urologia. Faculdade de Medicina (FAMERP/FUNFARME), São José do Rio Preto, SP, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.564

KEYWORDS: *Adolescent. Pandemics. Erotica. Sexuality. COVID-19. Coronavirus infections.*

Recently, there was an outbreak of a new disease called Coronavirus 2019 (COVID-19) in Wuhan, China, which spread rapidly to other regions in China and around the world. This pandemic is impacting the entire population, including adolescents, in physical, intellectual, emotional, and sexual activities.[1]

We are aware that during the pandemic, when emotions are intense, and adolescents are more socially isolated than ever, online pornography can increase.

Online pornography is a relatively recent phenomenon and, therefore, studies on this subject are limited. It is known that the effects of the pornography in society imply deep problems concerning emotional aspects and relationships of this generation.[2] The sexual content currently available ranges from partial nudity to violent sexual activities or images of abuse.[3]

Online pornography differs from past pornography because online content is active and portable, allowing quick and easy access from a variety of electronic devices. Participation in it is private and anonymous, which allows adolescents to seek materials that would not be available in traditional media such as television. In addition, it is difficult for parents to monitor online media, such as smartphones.[4]

With the pandemic and schools closed for weeks or more, adolescents are no longer under the watchful eyes of their teachers, community, and family due to a forced change of priorities. In this scenario, exposure to the sexual content freely available on the internet and in videogames contributes to the early development of beliefs and sexual attitudes in adolescents.[4]

A study has shown that the consumption of pornography by adolescents exerts a negative influence on sexuality.[5] Although most adolescents during this cognitive and volitive stage may not suffer consequences, in some cases there may be a reduction in desire, an increase in masturbation practices and a reduced interest in sex, due to the distance between what is possible and what is fantasized.[5]

Access containment measures for such practices should be studied since we still require moderators of effect and assessments on the extent to which the use

DATE OF SUBMISSION: 27-Apr-2020
DATE OF ACCEPTANCE: 28-Apr-2020
CORRESPONDING AUTHOR: Fernando Nestor Fácio Júnior
Av. Brig. Faria Lima, 5416, São José do Rio Preto, SP, Brasil - 15090-000
Tel: +55 17 3232-0199 / Fax: +55 17 3229-1777
E-mail: fnfacio@yahoo.com.br

of the content available on these medium affects the beliefs and sexual behaviors of adolescents.[4]

The extent to which access to digital pornography changes attitudes and sexual practices is still unknown. It is possible that online pornography normalizes eccentric practices. The industry is harming contemporary culture, and online pornography is likely to be replacing the conventional ways of learning about sex and relationships since adolescents are presented with distorted and unhealthy versions of masculinity and sexual identity.[6]

Therefore, while we face these challenges, parents and caregivers can help reduce the use of pornography in several ways, such as encouraging live video chats among friends, relatives, and teachers, collaborating with adolescents during the pandemic.

Thus, researchers point out the need to educate adolescents about the safe and responsible use of the Internet and its contents on smartphones, showing them that pornography is a potential health problem in terms of dependence, paraphilia, and sexual disorders.[5]

Conflict of interest

No potential conflict of interest relevant to this article was reported.

PALAVRAS-CHAVE: *Adolescente. Pandemias. Literatura erótica. Sexualidade. COVID-19. Infecções por coronavirus.*

REFERENCES

1. Rosenthal CM, Thompson LA. Child abuse awareness month during the coronavirus disease 2019 pandemic. JAMA Pediatr. 2020;10.1001/jamapediatrics.2020.1459. doi:10.1001/jamapediatrics.2020.1459.
2. Harper C, Hodgins DC. Examining correlates of problematic internet pornography use among university students. J Behav Addict. 2016;5(2):179-91.
3. Livingstone S, Smith PK. Annual research review: Harms experienced by child users of online and mobile technologies: the nature, prevalence and management of sexual and aggressive risks in the digital age. J Child Psychol Psychiatry. 2014;55(6):635-54.
4. Collins RL, Strasburger VC, Brown JD, Donnerstein E, Lenhart A, Ward LM. Sexual media and childhood well-being and health. Pediatrics. 2017;140(Suppl. 2):S162-6.
5. Pizzol D, Bertoldo A, Foresta C. Adolescents and web porn: a new era of sexuality. Int J Adolesc Med Health. 2016;28(2):169-73.
6. Mercer D, Parkinson D. Video gaming and sexual violence: rethinking forensic nursing in a digital age. J Forensic Nurs. 2014;10(1):27-35.

Delirium as the first presentation of lung adenocarcinoma brain metastasis

Rita Almeida Leite[1]
José Coutinho Costa[2]
Tiago Santos[1]

1. Departamento de Psiquiatria e Saúde Mental, Centro Hospitalar Baixo Vouga, Aveiro, Portugal.
2. Hospital Geral, Centro Hospitalar da Universidade de Coimbra, Coimbra, Portugal.

http://dx.doi.org/10.1590/1806-9282.66.5.566

Dear Editor,

A substantial part of patients without significant medical history and who were not previously diagnosed with brain tumors present to the Emergency Department complaining about new symptoms. Tumors metastasizing to the brain account for 15% to 25% of all brain tumors[1]. Non-small cell lung cancer (NSCLC) is the most common primary tumor to spread to the brain[2] and, in rare cases, metastatic tumors may present primarily with acute psychiatric symptoms[3], which underlines the importance of adequate differential diagnosis when working in Psychiatry Emergency Departments.

We report the clinical case of a patient with no previous psychiatry and medical history, with a subacute onset of delirium, behavioral changes, and reported depressive symptoms, as the first presentation of lung adenocarcinoma brain metastasis.

The patient was a 48-year-old man, smoker, who attended the Emergency Department due to mental confusion, spatiotemporal disorientation, and reported depressive symptoms of subacute onset with anorexia, i.e., weight loss of 8 kg in the past few months, apparently due to his low mood. Simple laboratory tests were performed and came back normal. Chest X-ray revealed right hilar enlargement.

Our Psychiatry Emergency Unit was requested to attend the patient. He presented a quite incoherent speech and his cognitive performance was grossly affected. His wife reported behavioral changes, with no psychotic symptoms. He had no previous psychiatry and medical history.

An urgent head computerized tomography (CT) scan evidenced multiple space-occupying lesions conditioning mass effect on adjacent structures, compatible with brain metastasis, namely involving the cerebellar hemispheres, right striatocapsular, and temporal region, as well as the bilateral frontoparietal regions, with a notable lesion in the left frontobasal region, of 3.4 cm diameter. This lesion was accompanied by extensive edema and deviation of the median structures to the right by about 7 mm (Figure 1).

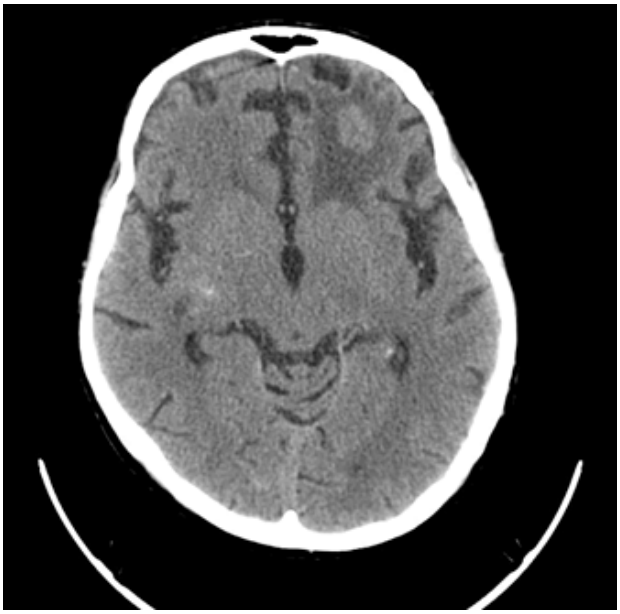
The patient was hospitalized at the Internal Medicine Ward for etiological study.

During his hospitalization, a chest/abdomen/pelvis CT scan identified multiorgan metastatic disease affecting both lungs, bones (costal, vertebral and iliac metastasis), stomach, and brain, multiple adenopathies (right pulmonary hilum and perigastric) and multinodular thyroid.

Upper digestive endoscopy with biopsy revealed endoscopic lesions compatible with secondary

DATE OF SUBMISSION: 20-Oct-2019
DATE OF ACCEPTANCE: 10-Nov-2019
CORRESPONDING AUTHOR: Rita Almeida Leite
Department of Psychiatry and Mental Health, Baixo Vouga Hospital Centre - Avenida Doutor Artur Ravara, Aveiro, Portugal - 3810-193
Tel: +351 919406845
E-mail: rita.almeidaleite3@gmail.com

FIGURE 1. HEAD COMPUTERIZED TOMOGRAPHY: LESION IN THE LEFT FRONTOBASAL REGION OF 3.4 CM OF DIAMETER, WITH EXTENSIVE EDEMA AND DEVIATION OF THE MEDIAN STRUCTURES TO THE RIGHT BY APPROXIMATELY 7 MM.



neoplastic involvement of primitive lung adenocarcinoma (CK7 and TTF1 positivity, with negativity for CK 20).

Bone scintigraphy revealed metastatic lesions as well, especially in the iliac.

Finally, genetic tests showed no mutations in the EGFR gene in exons 18, 19, 20, or 21.

From all the studies, it was concluded that the patient had a lung adenocarcinoma with diffuse bony, pulmonary, gastric, and brain metastasis, with no mutations in the EGFR gene. There was no indication for targeted anti-EGFR therapies.

During the hospitalization, the patient remained disoriented, with episodes of psychomotor agitation, despite the therapeutics instituted (maximum doses of haloperidol 10 mg id, olanzapine 10 mg id, chlorpromazine 50 mg id), which motivated physical restraint and difficulted the use of complementary means of diagnosis. After corticotherapy and holocranial radiotherapy (20 Gy in 5 fractions), progressive improvement of the state of consciousness was observed, despite some periods of disorientation that made him dependent when performing basic daily living activities.

At the end of the hospitalization, there was a clinical worsening with sepsis probably due to respiratory infection and MRSA isolation. Despite the measures instituted, the patient died.

A study by Keschner et al.[4] reported that 78% of 530 patients with brain tumors had psychiatric symptoms. However, 18% of the 530 presented only with these symptoms as the first clinical manifestation[5]. According to Mainio et al.[5], depression was found in 44% of all brain tumor patients, primary and metastic, and was associated with functional impairment, cognitive dysfunction, reduced quality of life, and reduced survival. Diagnosis of psychiatric symptoms secondary to brain tumors starts from having a clinical suspicion[3] since an adequate differential diagnosis is key to the early treatment of potentially fatal conditions.

REFERENCES

1. Price TR, Goetz KL, Lovell MR. Neuropsychiatric aspects of brain tumors. In: Yudofsky SC, Hales RE, Snyder SH, eds. The American Psychiatric Publishing textbook of neuropsychiatry and behavioral neurosciences. 5th ed. Arlington: American Psychiatric Publishing; 2007. p.735-64.
2. Ostrom QT, Wright CH, Barnholtz-Sloan JS. Brain metastases: epidemiology. Handb Clin Neurol. 2018;149:27-42.
3. Madhusoodanan S, Ting MB, Farah T, Ugur U. Psychiatric aspects of brain tumors: a review. World J Psychiatry. 2015;5(3):273-85.
4. Keschner M, Bender MB, Strauss I. Mental symptoms associated with brain tumor: a study of 530 verified cases. JAMA. 1938;110(10):714-8.
5. Manio A, Hakko H, Niemelä A, Koivukangas J, Räsänen P. Depression in relation to anxiety, obsessionality and phobia among neurosurgical patients with a primary brain tumor: a 1-year follow-up study. Clin Neurol Neurosurg. 2011;113(8):649-53.

Is ultrasound-guided thoracic paravertebral nerve block better than intercostal nerve block for video-assisted thoracic surgery under spontaneous-ventilating anesthesia?

Daoyun Lei[1]
Yeqin Sha[2]
Lianping He[2]

1. Jiangsu University, Jiangsu, Zhenjiang 212013, China.
2. Department of Immunology, Nanjing medical university, Nanjing, Jiangsu 211166, China.

Daoyun Lei and Yeqin Sha contributed to this work.

http://dx.doi.org/10.1590/1806-9282.66.5.568

Dear Editor,

We read with great interest the study by Zheng et al.[1]. It revealed that patients under ultrasound-guided thoracic paravertebral nerve block had a lower incidence of severe mediastinal flutter (grade three) during video-assisted thoracic surgery for pulmonary lobectomy compared with those under ultrasound-guided intercostal nerve block. The authors concluded that thoracic paravertebral nerve block was better than intercostal nerve block during video-assisted thoracic surgery for pulmonary lobectomy. This is of great significance in the selection of techniques for blocking chest nerves during thoracic surgery. However, in my opinion, more factors should be taken into consideration for drawing this conclusion.

Firstly, only some patients are suitable for spontaneous-ventilating anesthesia. Therefore, the authors should confirm the types of thoracoscopic surgery. Additionally, no relevant data indicated the specific types of thoracoscopic surgery. The postoperative analgesic effect in different anesthesia approaches was not evaluated. The Visual Analogue Scale (VAS)[2] or other methods should be used to assess the postoperative analgesic effect.

There are several postoperative complications for video-assisted thoracic surgery, such as intensive care stay, total hospital stay, and mortality rate[3]. However, only the incidence of mediastinal flutter was explored in this study. Therefore, more clinical data should be collected to exclude the side effect of ultrasound-guided thoracic paravertebral nerve block and intercostal nerve block so that a conclusion can be reached.

REFERENCES

1. Zheng Y, Wang H, Ma X, Cheng Z, Cao W, Sgao D. Comparison effect of ultrasound-guided thoracic paravertebral nerve block and intercostal nerve block for video-assisted thoracic surgery under spontaneous-ventilating anesthesia. Rev Assoc Med Bras. 2020;68(4);452-457.
2. Li X, Vigil JM, Stith SS, Brockelman F, Keeling K, Hall B. The effectiveness of self-directed medical cannabis treatment for pain. Complement Ther Med. 2019;46:123-30.
3. Popovici BI, Matei D, Iacoban L, Simion I, Man M, Al Hajjar N, et al. The impact of thoracic paravertebral block over post-operatory evolution in open lobectomy. Ann Ital Chir. 2019;90:551-9.

DATE OF SUBMISSION: 14-Oct-2019
DATE OF ACCEPTANCE: 08-Nov-2019
CORRESPONDING AUTHOR: Lianping He
Longmian road, Department of Immunology, Nanjing Medical University, Nanjing, Jiangsu, China - 211166
Tel./Fax: +86 553-2871221
E-mail: lianpinghe@126.com

GOLD B COPD patients: are they all the same?

José Coutinho Costa[1]
João Neiva Machado[1]
Lídia Marília Valente Marques Sousa Gomes[1]
Cidália Maria Regino Rodrigues[1]

1. Pneumology Unit, University Hospital Center of Coimbra, Hospital Geral, Coimbra, Portugal.

http://dx.doi.org/10.1590/1806-9282.66.5.569

Dear Editor,

COPD is a disease characterized by progressive and persistent airflow limitation. The objectives of COPD assessment are to determine the level of airflow limitation, its impact on the health status of the patient, and the risk of future events (such as exacerbations, hospital admissions, or death). In order to achieve these objectives, the assessment should consider the severity of the airflow limitation, the magnitude of the patient's symptoms, the history of exacerbations, and the presence of comorbidities[1].

The natural history of GOLD B COPD patients is not well described or understood[2]. GOLD B patients are defined by low rates of exacerbation (<2 exacerbations per year without hospitalization) and high symptom burden. These patients may have more exacerbations in the future and, consequently, change their GOLD category. In the ECLIPSE study[2], only 36% of patients in group B remained stable after 1 year, 7% and 35% deteriorated into higher-risk categories, i.e., C and D, respectively, and 22% improved to group A.

GOLD B COPD patients, although very symptomatic, are considered low risk. Studies have also shown that these patients have a high morbidity and mortality rate, which may influence future follow-up and therapy options. Moreover, there appears to be some heterogeneity in group B, in which a subgroup of patients progresses over time to higher risk categories.

The objective of our study is to evaluate the functional and clinical characteristics of COPD patients belonging to group B and explain the driving factors for their tendency to shift to group D over time.

Our study is a prospective analysis of a convenience sample of COPD patients attending a pulmonology appointment at the Pneumology Unit, University Hospital Center of Coimbra. Demographic, functional, and clinical data of all the patients from 2017 were analyzed, and a second evaluation took place 12 months later. Patients with other chronic respiratory diseases, such as Asthma/COPD Overlap, interstitial disease, cystic fibrosis, or lung cancer, were excluded.

The statistical analysis was completed using the IBM SPSS® statistical program, version 20. The categorical variables were described with percentages and the quantitative variables with mean and standard deviation. All associations were established using the Chi-Square Test or Fisher Exact Test for categorical variables and the T-Test for independents samples or the Mann Whitney Test for continuous variables. All the tests were considered significant when the p-value did not exceed 0.05.

We included 53 patients, 85% male, aged 55 to 94 years. In 2017, our sample consisted of 25% (13) GOLD A patients, 54% (29) GOLD B, 8% (4) GOLD C, and 13% (7) GOLD D. In the comparative analysis between

DATE OF SUBMISSION: 20-Oct-2019
DATE OF ACCEPTANCE: 10-Nov-2019
CORRESPONDING AUTHOR: José Coutinho Costa
Quinta dos Vales, São Martinho do Bispo, Coimbra, Portugal - 3041-801
E-mail: josecoutinhocosta99@gmail.com

group A and B, we found that the FEV1 % predicted was similar between the two groups [50,8% (1385ml) vs 45,3% (1250ml), p=0.138], and a significant proportion of patients in group B had emphysema (79.3% vs 38.5%, p=0.015), chronic bronchitis (68.9% vs 30.7%, p=0.041), and cardiovascular comorbidities (89.6% vs 53.8%, p=0.016). The cardiovascular comorbidities considered were heart failure, atrial fibrillation, ischemic heart disease, diabetes mellitus, and high blood pressure.

After 12 months of follow-up, of the 29 GOLD B patients, the majority (18) was stable and remained in group B; 10 patients progressed to GOLD D; and 1 patient was reclassified to GOLD A. Considering the baseline characteristics in 2017, patients who progressed to GOLD D had a FEV1 % predicted significantly lower than patients who remained in group B [mean 48.6% (1320ml) vs 36.9% (790ml), p=0.014]. There were no statistically significant differences regarding age, gender, body mass index, smoking status, chronic bronchitis, emphysema, cardiovascular comorbidities, degree of dyspnea, and FVC (Table 1). There were no changes in inhaled treatment during the follow-up period.

TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS FROM 2017 WHO REMAINED GOLD B AND PATIENTS PROGRESSED TO GOLD D AT 12 MONTHS OF FOLLOW-UP

Variables	GOLD		p-value
	B (n=18)	D (n=10)	
Age – years (Mean ± SD)	74.7±8.9	72.5±8.1	p=0.591
BMI - (Kg/m2) (Mean ± SD)	28.5±4.1	27.2±4.9	p=0.573
Pack years (Mean ± SD)	50.4±22.8	43.8±17.7	p=0.629
Chronic bronchitis (%)	50% (9)	80% (8)	p=0.099
Emphysema (%)	88.9% (16)	100% (10)	p=0.5
Cardiovascular comorbidity (%)	72.2% (13)	90% (9)	p=0.118
Dyspnoea - mMRC (median)	2	2	p=0.121
FVC% (Mean ± SD)	66.9%±9.9	66.8%±12.3	p=0.980
FEV1% (Mean ± SD)	48.6%±14.3	36.9%±11.3	p=0.014

Several studies have investigated predictive factors for exacerbation and mortality in COPD. Although FEV1 by itself is not sufficiently accurate as a predictor of exacerbation, we know that there is a significant relationship between airflow limitation and the risk of exacerbation and death[1]. The risk factors for a greater decline in FEV1 are current smoking, emphysema, and exacerbations[3]. Recently, Lange et al.[4] reported that the rate of decline in FEV1 in patients with COPD with low FEV1 in early adulthood (indicating suboptimal lung growth) is lower in comparison with COPD patients with normal FEV1 in early adulthood (27ml versus 52ml/year, respectively). These findings suggest that the variation in lung function decline in COPD is influenced by multiple factors. We also know that COPD is associated with multiple comorbidities that may have a significant impact on prognosis[1]. Comorbidities are not associated with the degree of obstruction and have a cumulative effect on mortality[2].

Overall, in our study, GOLD B patients had more cardiovascular comorbidities, emphysema, and chronic bronchitis than GOLD A patients, which may contribute to their high symptom burden. In addition, GOLD B patients who progressed to GOLD D had significantly lower FEV1, indicating that deterioration in airflow limitation is associated with an increased prevalence of exacerbations and disease progression. We think that these data should be taken preciously as the re-classification of patients based on an event (i.e. exacerbation) might be dangerous. However, this study has limitations that must be mentioned. The fact that our sample consisted of a convenience sample of only 53 patients may have conditioned our results.

REFERENCES

1. Global Initiative for Chronic Obstructive Lung Disease – GOLD. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2018 Report. [cited 2019 Sept 05]. Available from: https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf
2. Agusti A, Edwards LD, Celli B, Macnee W, Calverley PM, Müllerova H, et al; ECLIPSE Investigators. Characteristics, stability and outcomes of the 2011 GOLD COPD groups in the ECLIPSE cohort. Eur Respir J. 2013;42(3):636-46.
3. Vestbo J, Edwards LD, Scanlon PD, Yates JC, Agusti A, Bakke P, et al; ECLIPSE Investigators. Changes in forced expiratory volume in 1 second over time in COPD. N Engl J Med. 2011;365(13):1184-92.
4. Lange P, Marott JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M, et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. Am J Respir Crit Care Med. 2012;186(10):975-81.

Hemostasis profile in COVID-19 infection

Fernando Barroso Duarte[1]
Rosângela Pinheiro Gonçalves Machado[2]
Romélia Pinheiro Gonçalves Lemes[3]
Isabella Araújo Duarte[4]
Beatrice Araújo Duarte[4]
Clarissa Maria Gonçalves Machado[4]
João Vitor Araújo Duarte[4]
Samuel Gonçalves Machado da Rocha[4]
Anna Thawanny Gadelha Moura[5*]
Rosangela de Albuquerque Ribeiro Rodrigues Holanda[6]

1. Departamento de Cirurgia - Universidade federal do Ceará, Fortaleza, CE, Brasil.
2. Centro de Ciências da Saúde, Departamento de Medicina - Universidade de Fortaleza (UNIFOR), Fortaleza, CE, Brasil.
3. Departamento de Análises Clínicas e Toxicológicas (DACT) - Universidade federal do ceará, Fortaleza, CE, Brasil.
4. Faculdadse de Medicina -Faculdade Christus, Fortaleza, CE, Brasil.
5. Laboratório de Pesquisa em Hemoglobinopatias e Doenças Genéticas e Hematológicas - Universidade Federal do Ceará, Fortaleza, CE, Brasil.
6. Hospital Universitário Walter Cantídio - Universidade Federal do Ceará, Fortaleza, CE, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.571

KEYWORDS: *COVID-19. Coronavirus infections. Hemostasis.*

Dear Editor,

According to some current studies, the infection by COVID-19 (SARS- CoV-2) appears to be associated with the involvement of hemostasis in the Chinese population, developing to Acute Respiratory Distress Syndrome (ARDS). The context reported here focuses on cases with ARDS, which has been implicated with the presence of an endothelial lesion, production of pro-coagulating factors, and generation of fibrin degradation product (D-dimer), compatible with disseminated intravascular coagulation (DIC).[1] The increase in the concentration of D-dimer 3-4 times above the normal levels was associated with the outcome of death and there are reports of thromboembolic phenomena, and factors of worse prognosis, such as advanced age, low immunity, neutrophilia, and organ and coagulation dysfunction.[2] Patients who develop a more severe response to the disease may evolve to dyspnea and hypoxemia within one week from the onset of the disease and may progress rapidly to ARDS or target organ failure. Among other possibilities, coagulation, in the cases that have been reported in the literature, consists of prolonged prothrombin time (PT) and partial activated thromboplastin time (APTT) in 2.1% and 9.7%, respectively, of the patients who had ARDS. Epidemiological data report that changes in coagulation, in COVID-19 infections, associated with ARDS and the systemic inflammatory process, may react releasing a large amount of pro-inflammatory

DATE OF SUBMISSION: 27-Apr-2020
DATE OF ACCEPTANCE: 28-Apr-2020
CORRESPONDING AUTHOR: Anna Thawanny Gadelha Moura
Departamento de Análises Clínicas e Toxicológicas (DACT) - Universidade Federal do Ceará
Rua Capitão Francisco Pedro, 1210, Rodolfo Teófilo, Ceará, Brasil - 60430-370
E-mail: thawanny.anna@gmail.com

cytokines - tumor necrosis factor, interleukin (IL) -1, IL -6 and IL-8 - although the pathogenesis of human COVID19 has not yet been fully clarified. Studies reinforce the hypothesis that the great increase in the production of cytokines is associated with a deficient immune system and are the two main triggers of events that culminate in the serious evolution of the infection.[1,2] In this context, it is important to develop preventive measures, as well as laboratory tests and early prognostic markers of patients who will present the severe form, so that a therapeutic approach is performed in the initial phase in patients affected by COVID-19. This way, it will be possible to avoid the evolution to death in this group of patients, since the course of the disease can be quick, progressing to ARDS within one week from the onset of the disease, in addition to target organ failure.[2] Comparing the laboratory tests of patients with and without ARDS, it was noticed that the group with ARDS had significant changes in index values, i.e., liver injury, renal dysfunction, related to inflammation and coagulation function. Also, the lymphocyte count and CD8 T cells were significantly decreased. In addition to this worrying matter, patients who developed ARDS did not respond well to treatments with antiretrovirals.[2] Given these facts, it is of utmost importance to evaluate the benefit laboratory tests and prognostic markers, on hospital admission, could bring to favor those patients who will evolve to the severe form, aiming at early preventive and therapeutic measures, to avoid evolution to unfavorable outcomes. Among the important tests so far, we can mention blood count, PT, APTT, and D-dimer, which have all been mentioned and whose correlations were observed in the literature as prognostic markers, as follows: severe lymphopenia, neutrophilia, and thrombocytopenia at the complete blood count; extended PT and increased D-dimer are associated with cases of severe evolution.[3-5] However, the guidance to patients who were already using oral anticoagulant medications, before contracting COVID-19, is to continue with the treatment; however, greater laboratory and clinical monitoring of these patients is necessary, as recommended by Chinese studies that note that altered PT, even at mild levels, is also a factor of poor prognosis and reinforce that, in this scenario, the patient/control relationship should be used instead of the INR.

Acknowledgments

We thank all health professionals at the Walter Cantídio University Hospital.

Conflict of interest

The authors have no competing interests.

PALAVRAS-CHAVE: *COVID-19. Infecções por coronavirus. Hemostasia.*

REFERENCES

1. Fan BE, Chong VCL, Chan SSW, Lim GH, Lim KGE, Tan GB, et al. Hematologic parameters in patients with COVID-19 infection. Am J Hematol. 2020;10.1002/ajh.25774. doi:10.1002/ajh.25774.
2. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;e200994. doi:10.1001/jamainternmed.2020.0994.
3. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
4. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844-7.
5. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, et al. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-6.

Epidemiological clinical profile of COVID-19 cases in a municipality of Northeast Brasil

Adeilton Gançalves da Silva Junior [1]
Klynger Farias da Costa[1]
Paula Teles Vasconcelos [1]
Tatiane Malta dos Santos [1]
Rodrigo Feliciano do Carmo[2,3]
Carlos Dornels Freire de Souza[4,5]

1. Diretoria de Vigilância em Saúde, Secretaria Municipal de Saúde, Juazeiro, BA
2. Pós-Graduação em Ciências da Saúde e Biológicas, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina, PE, Brasil.
3. Pós-Graduação em Biociências, Universidade Federal do Vale do São Francisco (UNIVASF), Petrolina, PE, Brasil.
4. Complexo de Ciências Médicas e Enfermagem, Departamento de Medicina, Universidade Federal de Alagoas (UFAL), Arapiraca, AL, Brasil.
5. Programa de Pós-graduação Em Saúde da Família (PROFSAÚDE/ FIOCRUZ/UFAL), Maceió, AL, Brasil

http://dx.doi.org/10.1590/1806-9282.66.5.573

KEYWORDS: *COVID-19. Coronavirus infections. Epidemiology. Pandemics.*

Dear Editor,

The first cases of COVID-19 were registered in Wuhan, a city of 11 million people in the People's Republic of China. Caused by the new coronavirus, SARS-CoV-2, the disease quickly spread across the world[1]. On March 11, 2020, the World Health Organization (WHO) declared a global pandemic[2].

As of April 20, 2020, there were more than 2.49 million confirmed cases and 171,652 deaths from the disease in the world[3]. The first confirmed case in Brasil occurred on February 26, 2020[4]. Since then, the disease has spread throughout the Brazilian territory, reaching cities in the interior. As of April 20, 40,581 cases and 2,575 deaths had already been registered in Brasil[4].

Considering the spread of the disease in Brasil, this study describes the clinical and epidemiological profile of the first confirmed cases of COVID-19 in the municipality of Juazeiro, Bahia.

A descriptive study was carried out, based on data provided by the Health Department of the city of Juazeiro. The municipality is located in the Northern region of the state of Bahia, and it borders the city of Petrolina, which is located in the state of Pernambuco. Juazeiro has an estimated population of 210,000 inhabitants, and it is one of the most important centers of irrigated fruit in Brasil[5]. Clinical and epidemiological variables have been described.

The first suspected case in the municipality was notified on March 17, 2020. Between that date and April 20, there were 9 confirmed cases of the disease in the municipality. The first two confirmed cases were notified on March 17 and 18, 2020. Both were elderly individuals, members of the same family, with history of international travel. Community transmission was confirmed on March 31, with the notification of a nurse who had no travel history. The age of confirmed cases ranged from 22 to 77 years; four health professionals (two with higher education and

DATE OF SUBMISSION: 28-Apr-2020
DATE OF ACCEPTANCE: 28-Apr-2020
CORRESPONDING AUTHOR: Carlos Dornels Freire de Souza
Núcleo de Estudos em Medicina Social e Preventiva (NEMSP), Departamento de Medicina, Universidade Federal de Alagoas
Avenida Manoel Severino Barbosa, Bom Sucesso, Arapiraca/AL, Brasil CEP: 57309-005. – Tel: (82) 3482-1800
E-mail: carlos.freire@arapiraca.ufal.br

two technicians) were confirmed with COVID-19. Cardiovascular disease, diabetes, and chronic respiratory disease were the comorbidities observed in three individuals. A 63-year-old man required hospitalization and died from COVID-19 (Table 1).

The observed profile is in line with the world literature[6]. However, the following three reflections are necessary to understand the dynamics of the pandemic and its consequences: i. the importance of travelers in the chain of disease dissemination; ii. community transmission; and iii. the involvement of health professionals.

The importance of travelers in the chain of dissemination of the disease.

There is no doubt that national and international travel has contributed to the spread of SARS-CoV-2 around the world. To limit cross-border spread, both regionally and globally, many countries have swiftly adopted sweeping measures, including full lockdowns of shops and companies, shutting down airports, imposing travel restrictions, and completely sealing their borders in order to contain transmission[7].

Restrictions on people coming from risk areas can be important at the beginning of an epidemic, as they allow control measures to be implemented in advance; however, they have little effect once community transmission has been established. According to the WHO, banning incoming flights from areas with high numbers of cases of COVID-19 does not prevent infected individuals from arriving from areas with intermediate numbers where controls are less stringent[8]. Furthermore, the movement of people between cities by land can also favor the spread of the disease regardless of air traffic.

The WHO thus recommends that travelers returning from affected areas self-monitor for symptoms for

TABLE 1.CHARACTERIZATION OF THE FIRST CONFIRMED CASES OF COVID-19 IN JUAZEIRO, BAHIA, NORTHEAST, BRASIL, 2020.

Case	Notification Date	Sex	Age years	Occupation	Signs and symptoms	Comorbidities	Travel History	Suspicious case contact	Hospitalized / IMV	Outcome
1	03/17/2020	F	77	Retired	Cough, myalgia/ arthralgia	None	Yes (São Paulo, Africa, Dubai, Abu Dhabi)	No	No	Cure
2	03/18/2020	M	74	Retired	Fever, cough, runny nose, irritability, adynamia	Cardiovascular disease	Yes (São Paulo, Africa, Dubai, Abu Dhabi)	No	No	Cure
3	03/31/2020	F	59	Nurse	Fever, cough, myalgia	None	No	No	No	Symptomatic[1]
4	04/08/2020	M	63	Retired	Fever, cough, dyspnea, O2 saturation < 95%.	Cardiovascular disease and diabetes	No	No	Yes	Death
5	04/08/2020	F	32	Nurse	Cough, sore throat, runny nose, headache, nausea/vomiting, myalgia/arthralgia, adynamia/ weakness, enlarged lymph nodes	None	No	Yes	No	Symptomatic[1]
6	04/11/2020	F	33	Secretary	Cough, headache, diarrhea, myalgia/ arthralgia	None	No	Yes	No	Symptomatic[1]
7	04/13/2020	F	25	Nurse technician	Runny nose, chills, hoarseness	None	No	Yes	No	Symptomatic[1]
8	04/14/2020	M	22	Nurse technician	Cough, runny nose, sneezing	None	No	Yes	No	Symptomatic[1]
9	04/15/2020	M	69	Retired	Fever, cough, dyspnea	Chronic respiratory disease	No	No	No	Symptomatic[1]

Legend: F: female; IMV: invasive mechanical ventilation; M: male. [1]Individual still without a clinical cure

14 days. If symptoms, such as fever, cough, or difficulty of breath occur, travelers are advised to contact local healthcare providers, preferably by phone, and inform them of their symptoms and travel history[8].

Community transmission

The Brazilian Ministry of Health recognized that community transmission was occurring across the country on March 20 as a strategic measure to ensure collective efforts to reduce transmission on the part of all Brazilians[9]. Since then, social distancing, store closing, and suspension of academic activities have been implemented by state governments as preventive measures.

Social distancing is one of the main methods to interrupt the disease transmission cycle, mainly due to the presence of asymptomatic carriers who may be able to transmit the virus. Accordingly, a recent study revealed that the viral load detected in asymptomatic patients was similar to that in symptomatic patients, which suggests the transmission potential of asymptomatic or minimally symptomatic patients[10]. Therefore, surveillance actions and expansion of testing are important to avoid the emergence of new cases.

The involvement of health professionals

The outbreak of COVID-19 could be particularly risky for healthcare workers due to their ongoing professional exposure to the virus. The National Health Commission of the People's Republic of China has reported that, as of February 24, 2020, a total of 3,387 out of 77,262 patients with COVID-19 (4.4%) in China were healthcare workers or individuals who worked in medical facilities[11]. As of April 05, 2020, 12,252 health workers in Italy tested positive for COVID-19, accounting for 10% of Italy's COVID-19 cases; furthermore, 80 medical doctors and 25 nurses have died[12]. There are no official data from Brasil, but it is estimated that by the beginning of April, around 7,000 health professionals had been removed from work since the beginning of the pandemic due to suspicious symptoms.

Inadequate personal protection of healthcare workers at the beginning of the epidemic was a central issue since the form of contagion was not yet fully understood, and awareness of personal protection was not strong enough[13]. Today, with more information and protocols established to prevent COVID-19 infection, other issues contribute to the transmission of infection among health professionals, including the following: protective equipment (PPE) shortage, the intensity of work, and lack of rest[13]. Healthcare workers play a crucial role in combating COVID-19. Adequate provision of PPE, food, rest, and psychological support are essential measures to ensure the safety and quality of life of these professionals[14].

In the present study, we describe the first cases of COVID-19 in the municipality of Juazeiro, Bahia, located in an important fruit center in the São Francisco Valley region. The cases are mainly composed of individuals with a history of travel in risk areas, health professionals, and contact with infected individuals. Tackling the pandemic is a complex process, which requires a wide range of measures to be developed simultaneously and in an articulated manner. No measure carried out in isolation will be able to contain the expansion of the pandemic.

Authors' contribuitions

Adeilton Gonçalves da Silva Junior: Participated in the concept and planning of the study, data collection and analysis, discussion of the results, drafting of the manuscript, as well as the revision and approval of the final version of the work.

Klynger Farias da Costa: Participated in the concept and planning of the study, data collection and analysis, discussion of the results, drafting of the manuscript, as well as the revision and approval of the final version of the work.

Paula Teles Vasconcelos: Participated in the concept and planning of the study, data collection and analysis, discussion of the results, drafting of the manuscript, as well as the revision and approval of the final version of the work.

Tatiane Malta dos Santos: Participated in the concept and planning of the study, data collection and analysis, discussion of the results, drafting of the manuscript, as well as the revision and approval of the final version of the work.

Rodrigo Feliciano do Carmo: Participated in the concept and planning of the study, data collection and analysis, discussion of the results, drafting of the manuscript, as well as the revision and approval of the final version of the work.

Carlos Dornels Freire de Souza: Participated in the concept and planning of the study, data collection and analysis, discussion of the results, drafting of the manuscript, as well as the revision and approval of the final version of the work.

PALAVRAS-CHAVES: *COVID-19. Infecções por coronavirus. Epidemiologia. Pandemias.*

REFERENCES

1. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33.
2. World Health Organization. Coronavirus disease 2019 (COVID-19): situation report – 51. Geneva: World Health Organization; 2020. [cited 2020 Apr 20]. Available from: https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200311-sitrep-51-covid-19.pdf?sfvrsn=1ba62e57_10
3. Johns Hopkins University. COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU). [cited 2020 Apr 20]. Avaliable from: https://coronavirus.jhu.edu/map.html
4. Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde. Doença pelo Coronavírus 2019. Boletim Epidemiológico do Centro de Operações em Emergência em Saúde Pública. Brasília: Ministério da Saúde; 2020.
5. Instituto Brasileiro de Geografia e Estatística (IBGE). IBGE cidade. 2020. [cited 2020 Apr 20]. Available from: https://cidades.ibge.gov.br/brasil/ba/juazeiro/panorama
6. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
7. Gostin LO, Wiley LF. Governmental public health powers during the COVID-19 pandemic: stay-at-home orders, business closures, and travel restrictions. JAMA. 2020;10.1001/jama.2020.5460. doi:10.1001/jama.2020.5460.
8. World Health Organization. Updated WHO recommendations for international traffic in relation to COVID-19 outbreak. Geneva: World Health Organization; 2020. [cited 2020 Apr 20]. Available from: https://www.who.int/news-room/articles-detail/updated-who-recommendations-for-international-traffic-in-relation-to-covid-19-outbreak
9. Croda J, Oliveira WK, Frutuoso RL, Mandetta LH, Baia-da-Silva DC, Brito-Souza JD, et al. COVID-19 in Brasil: advantages of a socialized unified health system and preparation to contain cases. Rev Soc Bras Med Trop. 2020;53:e20200167. Doi: 10.1590/0037-8682-0167-2020.
10. Zou L, Ruan F, Huang M, Liang L, Huang H, Hong Z, et al. SARS-CoV-2 viral load in upper respiratory specimens of infected patients. N Engl J Med. 2020;382(12):1177-9.
11. Zhan M, Qin Y, Xue X, Zhu S. Death from COVID-19 of 23 health care workers in China. N Engl J Med. 2020; NEJMc2005696. doi:10.1056/NEJMc2005696.
12. Chirico F, Nucera G, Magnavita N. COVID-19: protecting healthcare workers is a priority. Infect Control Hosp Epidemiol. 2020;1-4. doi: 10.1017/ice.2020.148.
13. Wang J, Zhou M, Liu F. Reasons for healthcare workers becoming infected with novel coronavirus disease 2019 (COVID-19) in China. J Hosp Infec. 2020. doi: 10.1016/j.jhin.2020.03.002.
14. The Lancet. COVID-19: protecting health-care workers. Lancet (London, England). 2020;395(10228):922. doi: 10.1016/S0140-6736(20)30644-9.

Brazilian Justice response to protect the prison population from Covid-19

Carlos Dornels Freire de Souza[1,2]

1.Complexo de Ciências Médicas e Enfermagem, Departamento de Medicina, Universidade Federal de Alagoas (UFAL), Arapiraca, Alagoas, Brasil.
2.Programa de Pós-graduação Em Saúde da Família (PROFSAÚDE/ FIOCRUZ/UFAL), Arapiraca, Alagoas, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.577

KEYWORDS: *COVID-19. Coronavirus infections. Public health. Justice administration system. Prisoners.*

Dear Editor,

Since the confirmation of the first case of Covid-19 in Brazilian territory, on February 26, 2020, all government agencies have sought to develop strategies to contain the progress of the pandemic in the country[1]. As of April 16, 2020, there are already 30,425 confirmed cases and 1,924 deaths caused by the disease in the country, with daily growth[2].

An additional concern related to Covid-19's entry into Brasil's criminal justice system. The Brazilian prison population is the third largest in the world and undergoing intense growth, behind only the US and China, first and second places, respectively. There are more than 760,000 individuals deprived of their liberty, confined in prison units without the minimum infrastructure capable of guaranteeing resocialization, expressing a clear violation of human rights[3]. Overcrowding [*over 150%*], associated with the profile of the prison population [*characterized by the high prevalence of risk factors for Covid-19, such as cardiovascular, respiratory, metabolic and immunosuppressive diseases, drug use and unhealthy lifestyle habits, as well as of elderly individuals, pregnant women and other vulnerable groups*] and the context of violation of the most basic rights generate a high risk scenario for the spread of the coronavirus[3,4]. On April 17, 2020, the first death of an individual deprived of liberty, a 73-year-old elderly man who was serving time at the Cândido Mendes Penal Institute, in the state of Rio de Janeiro, was registered. The criminal institution is aimed at the elderly population and has a capacity for 246 prisoners, but it houses 305[5].

MEASURES ADOPTED BY THE BRAZILIAN JUSTICE

In order to reduce the risk of Covid-19 entering the prison system in Brasil and considering the responsibility of the Brazilian Justice with regard to the

DATE OF SUBMISSION: 29-Apr-2020
DATE OF ACCEPTANCE: 29-Apr-2020
CORRESPONDING AUTHOR: Carlos Dornels Freire de Souza
Núcleo de Estudos em Medicina Social e Preventiva (NEMSP), Departamento de Medicina, Universidade Federal de Alagoas
Avenida Manoel Severino Barbosa, Bom Sucesso, Arapiraca/AL, Brasil CEP: 57309-005. – Tel: (82) 3482-1800
E-mail: carlos.freire@arapiraca.ufal.br

protection of life and the guarantee of the dignity of this population, the National Council of Justice (CNJ) issued recommendation 62, of March 17, 2020, with the purpose of guiding the adoption of preventive measures for the spread of infection by the new coronavirus within the scope of the criminal and socio-educational justice systems[6].

The measures adopted by the criminal justice system may have an impact on reducing the epidemiological risk of spreading the virus in the community deprived of liberty, with benefits extended to the entire Brazilian population. Such recommendations are in line with global guidelines and based on solid scientific evidence. For educational purposes, we have grouped these recommendations into five interdependent categories: a) Recommendations focusing on risk groups; b) Reduction of population gatherings; c) Maintain social distancing and/or social isolation; d) Management measures; e) Acting on suspected cases.

a) Recommendations focusing on risk groups:

Considering the risk groups for Covid-19[7,8], CNJ recommended the re-evaluation of provisional prisons giving priority to *pregnant women, nursing mothers, mothers or persons responsible for children up to twelve years old or for people with disabilities, as well as elderly, indigenous, people with disabilities or are part of the risk group* (Article 4). For this same population group, early exit from closed and semi-open regimes was allowed.

b) Reduction of population gatherings

With the purpose of reducing population gatherings, an essential condition for the reduction of community contagion[9], it was recommended to reevaluate provisional prisons and to grant early exit from closed and semi-open regimes, giving priority to people arrested in criminal institutions who:

- *are over-occupied;*
- *do not have a healthcare team assigned to the institution;*
- *are under an interdiction order, with precautionary measures determined by an organ of the international jurisdictional system or;*
- *have facilities that favor the spread of the new coronavirus.*

In addition, it recommended the maximum exceptionality of new preventive detention orders and the preparation and implementation of a contingency plan within the scope of visitation rules, providing for a change in the regime of visits and delivery of items to persons deprived of their liberty, mandatory cleaning of visitation spaces and provision of masks and individual protection items to visitors, prohibiting the entry of visitors with fever or respiratory symptoms associated with Covid and priority adoption of fractionation of visitation at different days and times.

c) Maintain social distancing and/or social isolation

In line with the international guidelines on the importance of social distancing and/or isolation[9,10] in the containment of the Covid-19 pandemic, the main recommendations are:

1- Suspension of the duty of periodic presence to the court of persons in provisional liberty or conditional suspension of the case, for a period of 90 (ninety) days;

2- Granting of house arrest in relation to all persons imprisoned while serving sentences under an open and semi-open regime, subject to conditions to be defined by the judge responsible for enforcement;

3- Temporary suspension of the duty of regular presentation in court of persons under sentence in the open regime, house arrest, penalties restricting rights, suspension of enforcement of the sentence and conditional release, for a period of ninety days;

4- Possibility of house arrest for people arrested for alimony debt;

5- Rescheduling of hearings in cases where the defendant is released and held by videoconference in the event that the person is deprived of liberty.

6- Possible extension of the return period or postponement of the temporary exit benefit. In the event of postponement, rescheduling of the temporary exit must be guaranteed after the end of the sanitary restriction period.

d) Management Measure

In the component of the criminal system management, the following recommendations stand out:

1- Preparation and implementation of a contingency plan by the local Executive Branch, including health education actions, screening of suspected cases at the time of admission to the prison unit, preventive hygiene measures, supply of medicines and supplies, guarantee of uninterrupted water supply, measures to avoid the collective transport of persons deprived of their liberty, equipment for professionals and planning in case of professionals showing symptoms;

2- Allocation of financial penalties decreed during the public health emergency period for the purchase of cleaning, protection and healthcare equipment.

e) Acting on suspected cases

Faced with a suspected case of Covid-19, it is recommended:

1- The isolation of a person with symptoms compatible with Covid-19 and immediate referral for the implementation of a health treatment protocol, as recommended by the Ministry of Health;

2- The immediate referral for treatment at a reference healthcare facility for people who have severe breathing difficulties associated with Covid-19. In such cases, it is possible to replace the prison in a closed environment by a non-custodial measure, particularly in the absence of adequate isolation space or healthcare staff.

FINAL NOTES

Even considering the CNJ's efforts to face the pandemic and to protect the population deprived of liberty in Brasil, an effort by the public authorities to guarantee sufficient resources to implement these recommendations is necessary. The criminal system, for decades, has suffered a chronic crisis [*not only financial but also in its moral and legal foundations*], the solution of which goes far beyond public policy or the injection of financial resources[11].

Finally, there are reasons to believe that, despite all the recommendations, the entry of the new coronavirus in the Brazilian criminal justice system will further deepen the double crisis (health and criminal procedure) the country is facing. If based on the evidence on the characteristics of the virus (infectivity, pathogenicity, virulence and lethality) and the very historical context of the penitentiary system, there is a predictable and announced tragedy, the consequences of which will reach the entire Brazilian people.

Acknowledgments

The authors report no relationships that could be construed as a conflict of interest.

Financial support

This study did not receive financial aid.

PALAVRAS-CHAVES: *COVID-19. Infecções por coronavirus. Saúde pública. Sistema de Justiça. Prisioneiros.*

REFERENCES

1. Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde. Situação epidemiológica da COVID-19: doença pelo coronavírus 2019. Boletim Epidemiológico 09 do Centro de Operações em Emergência em Saúde Pública. 2020. [cited 2020 Apr 14]. Available from: https://portalarquivos.saude.gov.br/images/pdf/2020/April/12/2020-04-11-BE9-Boletim-do-COE.pdf
2. Brasil. Ministério da Saúde. COVID 19: painel coronavírus. [cited 2020 Apr 14]. Available from: https://covid.saude.gov.br/
3. Brasil. Ministério da Justiça. Conselho Nacional do Ministério Público. A visão do Ministério Público sobre o sistema prisional brasileiro. Vol. 3. Brasília: Conselho Nacional do Ministério Público; 2018. [cited 2020 Apr 14]. Available from: https://www.cnmp.mp.br/portal/images/Publicacoes/documentos/2019/BOOK_SISTEMA_PRISIONAL.pdf
4. Brasil. Ministério da Justiça. Conselho Nacional do Ministério Público. A visão do Ministério Público brasileiro sobre o sistema prisional brasileiro. Brasília: Conselho Nacional do Ministério Público; 2016. [cited 2020 Apr 14]. Available from: https://www.cnmp.mp.br/portal/images/Publicacoes/documentos/2016/Livro_sistema_prisional_web_7_12_2016.pdf
5. Barbon J. Brasil registra primeira morte de presidiário por coronavírus. 2020. [cited 2020 Apr 17]. Available from: https://www1.folha.uol.com.br/cotidiano/2020/04/brasil-registra-primeira-morte-de-presidiario-por-coronavirus.shtml
6. Brasil. Ministério da Justiça. Conselho Nacional de Justiça. Recomendação nº 62, de 17 de março de 2020. Recomenda aos Tribunais e magistrados a adoção de medidas preventivas à propagação da infecção pelo novo coronavírus – Covid-19 no âmbito dos Sistemas de Justiça Penal e Socioeducativo. [cited 2020 Apr 14]. Available from: https://www.cnj.jus.br/wp-content/uploads/2020/03/62-Recomenda%C3%A7%C3%A3o.pdf
7. Kwok KO, Li KK, Chan HHH, Yi YY, Tang A, Wei WI, et al. Community responses during early phase of COVID-19 Epidemic, Hong Kong. Emerg Infect Dis. 2020;26(7): 10.3201/eid2607.200500. doi:10.3201/eid2607.200500.
8. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al.; China Medical Treatment Expert Group for Covid-19. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;382(18):1708-20.
9. Remuzzi A, Remuzzi G. COVID-19 and Italy: what next? Lancet. 2020;395(10231):1225-8.
10. Ghinai I, Woods S, Ritger KA, McPherson TD, Black SR, Sparrow L, et al. Community transmission of SARS-CoV-2 at two family gatherings - Chicago, Illinois, February-March 2020. MMWR Morb Mortal Wkly Rep. 2020;69(15):446-50.
11. Brasil. Ministério da Justiça. Conselho Nacional do Ministério Público. Meta 2: a impunidade como alvo. Diagnóstico da investigação de homicídios no Brasil. Brasília: Conselho Nacional do Ministério Público; 2012. [cited 2020 Apr 14]. Available from: https://www.cnmp.mp.br/portal/images/stories/Enasp/relatorio_enasp_FINAL.pdf

Immunohistochemistry contribution in the diagnosis of splenic marginal zone lymphoma

Juliene Lima Mesquita[1]
Yensy Mariana Zelaya Rosales[1]
Yhasmine Delles Oliveira Garcia[1]
Francisco Dario Rocha Filho[2]
Beatriz Stela Gomes de Sousa Pitombeira Araujo[2]
João Paulo de Vasconcelos Leitão[2]
Jesus Irajacy Costa[2]
Beatrice Araújo Duarte[3]
João Vitor Araújo Duarte[3]
Romélia Pinheiro Gonçalves Lemes[4]
Fernando Barroso Duarte[5]

1. Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade Federal do Ceará. Fortaleza, Ceará, Brasil.
2. Médico no Serviço de Hematologia, Hospital Universitário Walter Cantídio, Fortaleza, Ceará. Brasil.
3. Estudante de Medicina no Centro Universitário Christus. Fortaleza. Ceará. Brasil.
4. Professor, Departamento de Análises Clínicas, Faculdade de Farmácia, Universidade Federal do Ceará. Fortaleza, Ceará, Brasil.
5. Professor do Departamento de Cirurgia e Diretor do Serviço de Transplante de Medula Óssea da Universidade Federal do Ceará. Fortaleza, Ceará, Brasil

http://dx.doi.org/10.1590/1806-9282.66.5.580

Dear Editor,

Splenic marginal zone B-cell lymphoma is a rare type of non-Hodgkin B-cell lymphoma, without preference for sex, which affects individuals mainly over 50 years. In many cases, the disease is asymptomatic, with absent splenomegaly and lymphadenomegaly. The changes in the peripheral blood, when present, are lymphocytosis, anemia, and thrombocytopenia; cytopenias are mostly due to hypersplenism. The presence of B symptoms and increased LDH is rare[1,2]. The immunophenotype pattern is characterized by pan-B cell expression with positive CD19, CD20, CD22, CD79a, IgM, and IgD. CD5 is found only in 15%, and CD23 in 30% of cases. It presents as the most common cytogenetic alteration the heterogeneous expressions of chromosome 7, the (9:14) (p13: q32), which overlaps the IgH and PAX-5[3] genes. The marrow infiltration patterns are highly variable and consist of nodular, paratrabecular, and interstitial[4,5]. The finding of the intrasinusoidal pattern is more easily observed by CD20 or CD34 immunohistochemistry. Spleen histology shows micronodular infiltration of white pulp with biphasic pattern and a variable degree of red pulp involvement. Differential diagnosis should be made with other chronic B7 cell lymphoproliferative diseases[5].

The clinical course is mostly indolent with a median global survival of 10 years. There is no standard therapy; so, splenectomy is the most used

DATE OF SUBMISSION: 26-Sep-2019
DATE OF ACCEPTANCE: 10-Oct-2019
CORRESPONDING AUTHOR: Juliene Mesquita
Pós-Graduação em Ciências Farmacêuticas - Universidade Federal do Ceará
Rua Capitão Francisco Pedro, 1210 – Rodolfo Teófilo – Fortaleza, Ceará – Brasil – 60430-370 – Tel: 55 85-3366.8058
E-mail: julmesq@gmail.com

therapeutic approach since it helps in diagnosis as well as in the improvement of symptoms related to cytopenias. Other therapies using chlorambucil or cyclophosphamide, alone or in combination with other agents (CVP, CHOP), have limited results. Immunotherapy with an anti-CD20 antibody is a molecular target for the treatment of non-Hodgkin B cell lymphoma with CD20 positive protein[6,7]. Results of anti-CD20 monotherapy demonstrated a 17-month duration of response and global survival of 80% up to 6 years and progression-free survival of 60% up to 4 years.

We report the case of a patient with splenic marginal zone lymphoma with positive markers for B-lymphocytes, who presented asymptomatic and with splenomegaly, and review some aspects related to this disease.

A 50-year-old male, businessman, from Fortaleza (CE), presented, in 2019, at a hematology service unit asymptomatic with splenomegaly and blood count results within normal limits. A bone marrow biopsy presented normal results for hematoxylin-eosin (HE), but immunohistochemistry was positive for CD20 in sinusoid, diagnosed with marginal zone lymphoma (Figure 1). A significant white and red pulp labeling for CD20 was observed, while the markers CD5, CD3, cyclin D1, BCL-6, and CD10 were not significant. CD23 marks dendritic and Ki67 follicular cells in 30% of the cells; normal cytogenetics. Splenectomy was performed with the anatomopathological study of the spleen (Figures 2), and the diagnosis was confirmed as marginal splenic zone lymphoma. The first recovery cycle was started and has shown stability and no toxicity until now.

Splenic marginal zone lymphoma infiltrated into the bone marrow, usually used with multiple patterns and usually forming lymphoid nodules with germinal centers; the cellular pattern is similar to the initial site. The sinusoidal pattern is strongly associated with marginal zone lymphoma; however, the most recent reports have shown that this pattern is very nonspecific, rarely happens as the only infiltration pattern and that immunohistochemistry is necessary to identify the infiltrations.

We presented a case that reinforces the importance of anatomopathological examination of the bone marrow, whenever possible, complementary to other laboratory tests (peripheral blood, cytogenetics, immunophenotyping, and molecular), as well as the study of immunohistochemistry and interpretation in

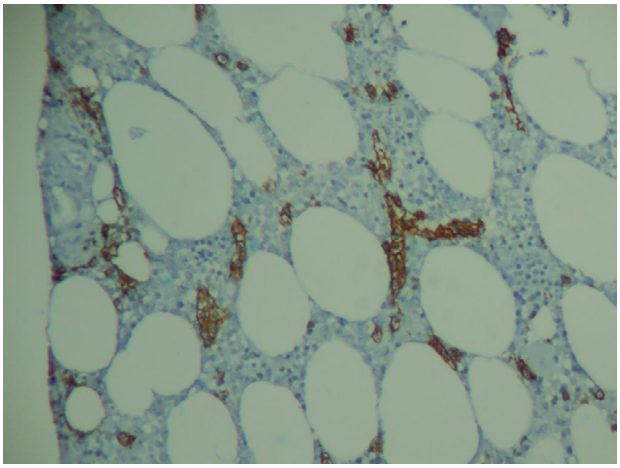
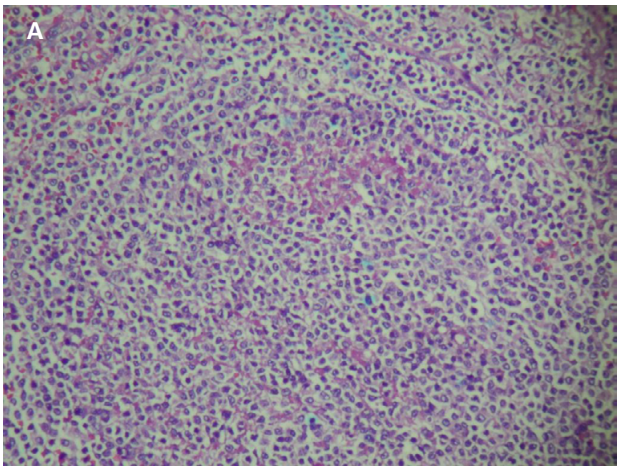


FIGURE 1. INTRASINUSOIDAL MEDIAL INFILTRATION BY SPLENIC MARGINAL ZONE NHL-B (CD20 +) (200X IMMUNOHISTOCHEMICAL STUDY)



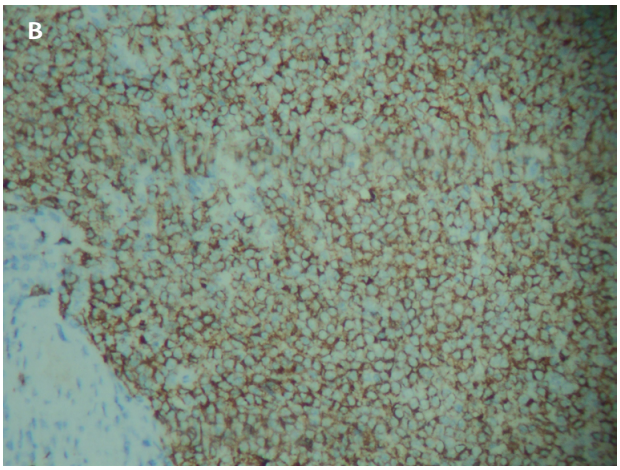


FIGURE 2. A: MARGINAL ZONE SPLENIC NON-HODGKIN'S LYMPHOMA, NODULAR ASPECT (HE 200X). B: SPLENIC LNH-B, FROM THE MARGINAL ZONE WITH STRONG EXPRESSION OF CD20 (200X IMMUNOHISTOCHEMICAL STUDY)

the clinical context. Anatomopathological examination of the spleen was also important to define the diagnosis of splenic marginal zone lymphoma.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES

1. Zinzani PL. The many faces of marginal zone lymphoma. Hematology Am Soc Hematol Educ Program. 2012;2012:426-32.
2. Arcaini L, Rossi D, Paulli M. Splenic marginal zone lymphoma: from genetics to management. Blood. 2016;127(17):2072-81.
3. Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, et al.; International Agency for Research on Cancer, World Health Organization. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer; 2008.
4. Santos TSD, Tavares RS, Farias DLC. Splenic marginal zone lymphoma: a literature review of diagnostic and therapeutic challenges. Rev Bras Hematol Hemoter. 2017;39(2):146-54.
5. Kent SA, Variakojis D, Peterson LC. Comparative study of marginal zone lymphoma involving bone marrow. Am J Clin Pathol. 2002;117(5):698-708.
6. Behdad A, Bailey NG. Diagnosis of splenic B-cell lymphomas in the bone marrow: a review of histopathologic, immunophenotypic, and genetic findings. Arch Pathol Lab Med. 2014;138(10):1295-301.
7. Debiasi M, Hehnemann M, Garicochea B. Rituximab monotherapy for splenic marginal zone lymphoma with villous lymphocytes: report on long-term disease control for two patients with recurrence after splenectomy. Sao Paulo Med J. 2010;128(6):375-7.

Multiple lidocaine infusions for relief of neuropathic pain: systematic review and meta-analysis

Participants:
Antonio Silvinato[1]
Idevaldo Floriano[1]
Wanderley Marques Bernardo[2]

Created on: 22 May, 2020

1. Programa Diretrizes da Associacao Medica Brasileira, Sao Paulo, SP, Brasil
2. Coordenador do Programa Diretrizes da Associacao Medica Brasileira, Sao Paulo, SP, Brasil

E-mail: wmbernardo@usp.br

INTRODUCTION

Chronic pain can be broadly classified into three categories of causation: due to a tissue disorder or injury (nociceptive); due to a somatosensory disorder or injury (neuropathic pain), or a combination of nociceptive and neuropathic pain (mixed pain). Neuropathic pain due to an injury or disease affecting the somatosensory system [1] continues to be a challenging clinical problem because the pain is often severe and incapacitating [2]. Population studies indicate that its prevalence ranges from 7 to 10%, based on validated screening tools [3].

The effectiveness of certain antidepressants, anticonvulsants, opioid analgesics, and various agents has been established in systematic reviews [4] and several evidence-based guidelines for the management of neuropathic pain [5]. However, these studies consistently show that less than 50% of the patients achieve adequate control of pain in the short term, and a recent prospective study, of observational results, showed that only about a quarter reached clinically significant improvement in pain and function in the long term, after up to 12 months of follow-up [6].

Lidocaine has the ability to block sodium channels. Therefore, it can be expected to act only in the subset of neuropathic symptoms mediated by the abnormal activation of the sodium channels [7].

Intravenous infusions of lidocaine in the dose of 5 mg kg-1 provide significant relief of pain in comparison with a placebo, for up to six hours after the infusion, with a peak of 1 to 2 hours after the infusion [8].

Given the short-term effect of systemic lidocaine and the intravenous route, it would not be practical for the management of pain in the long term. Given this, it is justified to evaluate, in the long term, the role of the intravenous infusions of lidocaine in the treatment of chronic neuropathic pain.

OBJECTIVE

The goal of this assessment is to identify the efficacy and safety of multiple infusions of lidocaine in the relief of pain in patients with neuropathic pain, in comparison with a placebo.

METHODS

The clinical question is: What is the impact of therapy with multiple infusions of lidocaine on outcomes of pain relief for up to four weeks and adverse events in the treatment of patients with neuropathic pain, compared with a placebo?

The eligibility criteria for the studies are:

1. An adult patient with neuropathic pain due to any cause;
2. Treatment with multiple applications of intravenous lidocaine compared with placebo therapy;
3. Outcomes - pain relief for up to four weeks and adverse events;
4. Excluded outcomes - evaluation of relief of pain in the period immediately after the infusion, i.e., soon after the infusion and up to 1-3 days after the infusion;
5. Randomized clinical trial;
6. No time or language restrictions;
7. Full text available for access.

The search for evidence was carried out the virtual databases Medline/Pubmed using the following search strategy - (Intravenous OR infusions OR infusion OR parenteral OR systemic) AND (lidocaine OR lignocaine) AND (Pain OR fibromyalgia OR Neuralgia OR Peripheral Nervous System Diseases OR Neuromuscular Diseases OR Nervous System Diseases OR Neuropathic Pain OR Neuralgia, Postherpetic OR Diabetic Neuropathies OR Peripheral Nerve Injuries) AND Random*; and on CENTRAL / Cochrane with the search strategy - (Intravenous OR infusions OR infusion OR parenteral OR systemic) AND (lidocaine OR lignocaine) AND (neuropathic pain). The search in these databases was performed up to the month of March 2020, and a systematic review was performed according to the PRISMA recommendations. [9]

We extracted the following data from the studies: name of the author and year of publication, study population, intervention and comparison methods, pain scores as mean (SD), the absolute number of adverse events, and time of follow-up.

Randomized clinical trials will have their risk of biases analyzed according to the following criteria: randomization, blinded allocation, double-blinding, losses, prognostic characteristics, presence of relevant outcome, time for the outcome, the method for outcome measurement, sample size calculation, early interruption, presence of other biases.

The results were expressed by the difference of the mean (SD) of the pain scores, or the risk of adverse events between therapy with multiple lidocaine infusions and a placebo treatment. No distinction was made on the severity of each adverse event. The confidence level adopted was 95%.

The results of the studies included will be meta-analyzed by RevMan 5.3[10], and the difference in overall risk or mean will be the final measurements used to support the synthesis of evidence that will answer the clinical question of this review.

The quality of evidence will be graded as high, moderate, low, or very low using the GRADE instrument[11] and taking into account the risk of bias, the presence of inconsistency, vagueness or indirect evidence in the meta-analysis of the outcomes (pain relief and adverse events), and the presence of publication bias.

RESULTS

The search for evidence retrieved 1,031 papers, of which 30 studies on intravenous lidocaine therapy were selected based on their title and abstract, for the treatment of patients with various etiologies of neuropathic pain, in comparison with a placebo. The 30 studies were accessed for analysis of the full text. Of the 30 studies, three (parallel RCTs) were selected, for meeting all the eligibility criteria, to support this assessment[12-14]; the grounds for exclusion and the list of studies excluded are available in the references, *Figure 1*, and *Table 5* in the *ANNEXES*.

The population included is of 110 patients with neuropathic pain who underwent therapy with infused lidocaine over a period of one hour, once a week, for 4 weeks (N=55), compared to a placebo (n =55), and followed-up to measure the outcomes of pain relief and adverse events after 4 weeks (Table 1).

Regarding the risks of bias of the 3 studies included [12-14], 2 of them presented uncertainty in the blinded allocation and two uncertainty in double-blinding. Two did not carry out analysis by intention to treat (Table 2).

All studies assessed the outcome of pain relief for up to four weeks after multiple infusions and adverse events (Table 3). The overall risk of bias among the studies is moderate.

TABLE 1. CHARACTERISTICS OF THE STUDIES INCLUDED

STUDY	Study design	Population	Intervention	Comparison	Evolution time
Vlainich et al. 2010[12]	RCT	30 patients; 44.7 ± 10.5 years in the saline group, and 40.9 ± 11.6 years in the lidocaine group; patients with fibromyalgia Exclusion criteria: changes in thyroid, rheumatic, renal, and hepatic function, trauma, rheumatic, neuromuscular, or psychiatric diseases, infectious arthritis, other pain syndromes.	N = 15; Lidocaine 240 mg diluted in 125 ml of saline, infused over a period of 1 hour, once a week, for 4 weeks. All patients received amitriptyline.	N = 15; 0.9% saline All patients received amitriptyline	4 weeks
Albertoni et al. 2016[13]	RCT	42 patients; 47 ± 9.8 years in the saline group, and 42.4 ± 9.4 years in the lidocaine group; patients with fibromyalgia. Patients were excluded if: abnormal laboratory tests; trauma; known psychiatric, rheumatic, neuromuscular or liver diseases; arrhythmia; heart failure, recent myocardial infarction, glaucoma, hypothyroidism or hyperthyroidism; infectious arthritis; another painful syndrome.	N = 19 Lidocaine 240 mg diluted in 125 ml of saline infused over a period of 1 hour, once a week, for 4 weeks. All patients received amitriptyline	N = 19 0.9% saline All patients received amitriptyline	4 and 8 weeks
Kim et al. 2018[14]	RCT	43 patients; 62.71 ± 13.06 years in the saline group, and 62.86 ± 12.5 years in the lidocaine group; patients with postherpetic neuralgia (PHN), and complex regional pain syndrome (CRPS) type II; NRS pain greater than or equal to 4 for at least 3 months, without satisfactory pain relief, with the conservative treatment Patients were excluded if: fibromyalgia, diabetic polyneuropathy, medullary injury; concomitant severe systemic diseases such as myasthenia gravis, decreased pulmonary function, liver problems, severe renal insufficiency, shock or hypokalemia or hyperkalemia, cardiac arrhythmia; psychiatric disorders (schizophrenia, somatization or acute anxiety).	N = 21 Lidocaine 3 mg/kg infused over a period of 1 hour, once a week, for 4 weeks. No changes in analgesics were allowed, including non-steroidal anti-inflammatory drugs, opioids, anticonvulsants, and antidepressants, with the exception of acetaminophen as a rescue analgesic drug.	N = 21 0.9% saline	4 weeks

RCT = Randomized Clinical Trial; NRS = 11-point numerical rating scale; N = number of patients.

TABLE 2. NEUROPATHIC PAIN THERAPY WITH MULTIPLE LIDOCAINE INFUSIONS. DESCRIPTION OF THE RISK BIASES OF THE STUDIES INCLUDED

Study	Random	Allocation Blinded	Double Blind	Losses	Characteristics (prognostic)	Outcomes	Sample calculation	ITT	Early termination
Vlainich 2010[12]									
Albertoni 2016[13]									
Kim 2018[14]									

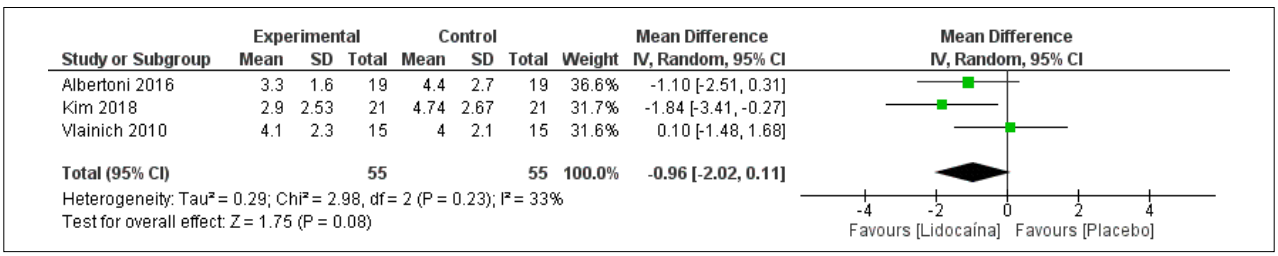
Description of the biases of the studies included (orange = presence; blue = absence; Yellow = unclear risk of bias) ITT = analysis by intention to treat

The three studies allowed the assessment of the outcome of neuropathic pain relief for up to 4 weeks, comparing infused lidocaine once a week, for 4 weeks, with a placebo (saline solution 0.9%); there was no difference in pain reduction between the two groups (MD -0.96; 95% CI -2.02 to 0.11; p = 0.08, I^2 = 33%), Figure 2.

TABLE 3. STUDY RESULTS FOR THE OUTCOME OF DEATH.

Study	Pain scale used	Lidocaine Mean (SD)	Placebo Mean (SD)
Vlainich 2010[12]	VAS 10	4.1 (2.3)	4 (2.1)
Albertoni 2016[13]	VAS10	3.2 (1.6)	4.4 (2.7)
Kim 2018[14]	VAS 10	2.9 (2.53)	4.74 (2.67)

FIGURE 2. COMPARISON FOREST PLOT: 1 LIDOCAINE VERSUS PLACEBO, OUTCOME: 1.1 PAIN RELIEF AFTER 4 INFUSIONS (ONCE A WEEK) OF LIDOCAINE.



ADVERSE EVENTS

The three parallel RCTs included in this review do not allow to assess the safety of IV lidocaine due to a lack of data; therefore, the result of a systematic review with meta-analysis[15], which included crossover studies that evaluated the relief of neuropathic pain (various etiologies) soon after the infusion and up to 1-3 days after the infusion will be used to answer the clinical question. Dizziness, drowsiness, perioral paresthesia, nausea, headache, dysarthria, dry mouth, metallic taste were some of the most common side effects observed in the studies included in this meta-analysis. Three hundred and seventeen patients received lidocaine, while 318 received a placebo. One hundred and thirty-two patients (41.6%) in the lidocaine group experienced adverse events, in comparison with 53 patients (16.7%) in the placebo group (increase in the absolute risk of 25%, 95% CI 18.1 to 31.7%; NNH = 4, 95% CI 3 to 6).

QUALITY OF EVIDENCE: OUTCOME OF PAIN RELIEF IN 4 WEEKS

Summary of Results: Lidocaine in multiple infusions compared to a Placebo for neuropathic pain

Patient or population: neuropathic pain
Background: Therapeutic efficacy and safety
Intervention: Lidocaine in multiple infusions
Comparison: Placebo

Outcome Nº of participants (studies)	Relative Effect (95% CI)	Potential absolute effects (95% CI)			Certainty	Comments
				Difference		
Pain relief after 4 lidocaine infusions (once a week) Follow-up: 4 weeks average No. of participants: 110 (3 RCTs)	-	The average pain relief after 4 infusions (once a week) of lidocaine was 0	-	MD 0.96 lower (2.02 lower for 0.11 higher)	⊕⊕⊕○ MODERATE	None
Adverse events with the use of intravenous lidocaine Nº of participants: 635 (15 RCTs)	RR 2.50 (1.89 to 3.30)	16.7%	41.6% (31.5 to 55)	25.0% more (18.1 more to 31.7 more)	⊕⊕○○ LOW [b]	None

* The risk in the intervention group (and its confidence interval of 95%) is based on the risk assumed in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; MD: Mean difference; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially differentLow certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

SYNTHESIS OF EVIDENCE

In patients with neuropathic pain, infused lidocaine once a week, for 4 weeks, compared with a placebo (saline solution 0.9%) showed no difference in pain reduction in up to 4 weeks. Moderate quality of evidence.

Intravenous lidocaine increases the risk of adverse events (any) in 25% (95% CI 18 to 31%) in comparison with a placebo (saline solution 0.9%), and it is necessary to treat 4 patients for one to present an adverse event (95% CI 3 to 6). Low quality of evidence.

Dizziness, drowsiness, perioral paresthesia, nausea, headache, dysarthria, dry mouth, metallic taste are some of the most common side effects.

DISCUSSION

A large number of trials tested IV lidocaine for neuropathic pain; however, most included few patients (<30) and reported the use of a diverse range of dosages and times of infusion. These studies also assessed pain scored after several periods of time, and most evaluated the efficacy of IV lidocaine in the period immediately post-infusion and in a single dose, while only 4 assessed lidocaine transfused over a period of 4 weeks, to study its persistent effect in the long term.

Our assessment suggests that the effect of lidocaine in humans is transitory and does not last for a long period of time, which can be explained by the pharmacokinetics of the drug. It starts acting between 30 and 60 min and its effects can last from 2 to 6 hours after the end of the infusion, after which the analgesic effect disappears quickly [8].

Based on the retrieved results, we have shown that patients receiving IV lidocaine are more prone to adverse events in comparison with placebo; however, no serious adverse event was reported.

It was not possible to perform a subgroup analysis based on the specific etiology of neuropathic pain, considering the limited number of studies available.

ANNEXES

The selection of retrieved from the virtual databases of scientific information is detailed in the flowchart below:

FIGURE 1. FLOWCHART

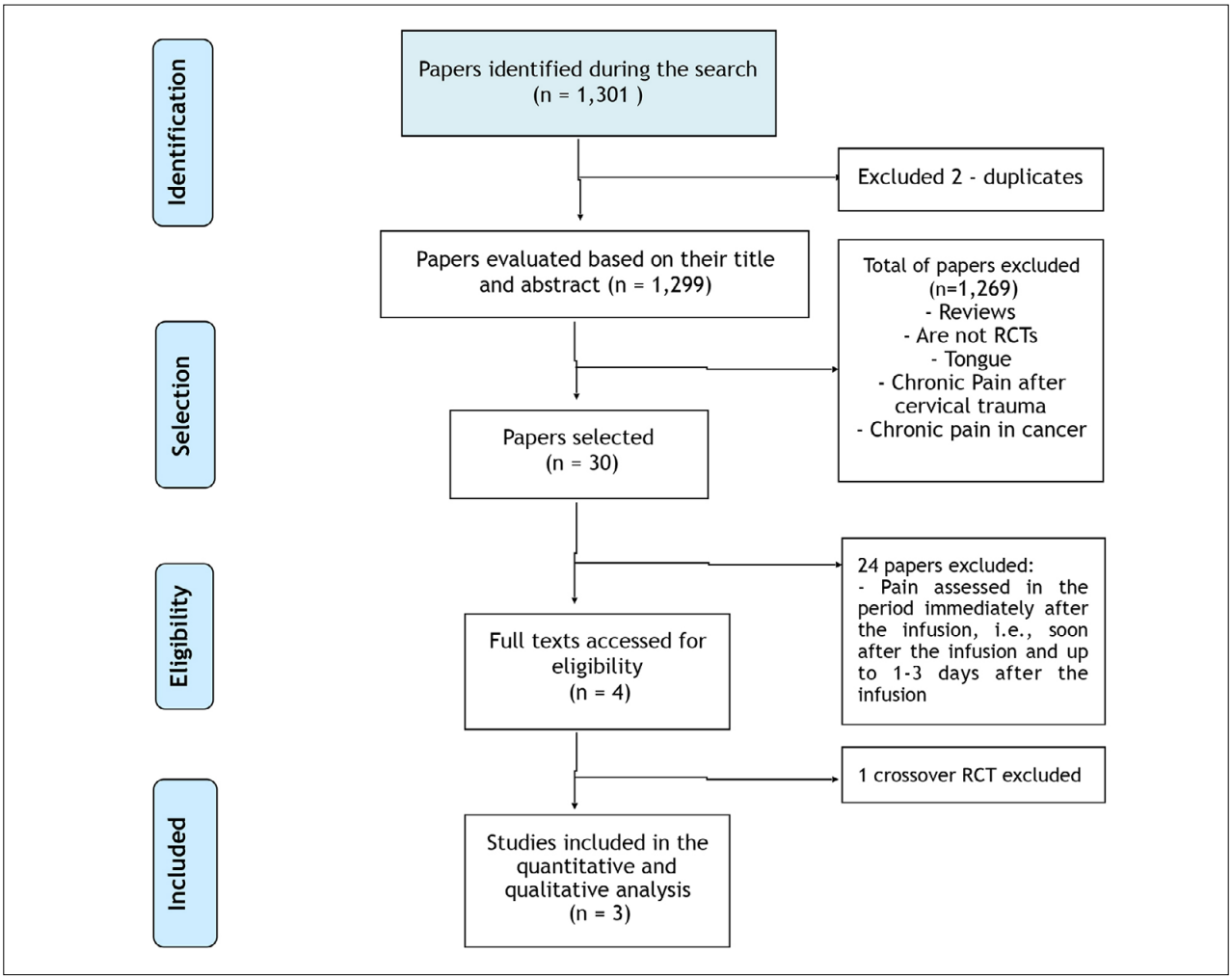


TABLE 4. PAPERS EXCLUDED AND REASON FOR EXCLUSION AFTER READING THE FULL TEXT

Study	Reason for exclusion
Moulin DE, et al. 2019	Crossover RCT without data from the first phase

REFERENCES

1. Treede RD, Jensen TS, Campbell JN, et al. Neuropathic pain: redefinition and a grading system for clinical and research purposes. Neurology 2008; 70: 1630-5.
2. Gilron R, Watson CPN, Cahill CM, Moulin DE. Neuropathic pain: a practical guide for the clinician. CMAJ 2006; 175: 265-75.
3. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. J Pain 2006; 7: 281-9.
4. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2012; 85: S3-14.
5. Attal N, Cruccu G, Baron R, et al. European Federation of Neurological Societies. EFNS Guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. Eur J Neurol 2010; 17: 1113-23.
6. Moulin DE, Clark AJ, Gordon MD, et al. Long term outcome of the management of chronic neuropathic pain – a prospective observational study. J Pain 2015; 16: 852-61.
7. Attal N, Rouaud J, Brasseur M, Chauvin M, Bouhassira D. Systemic lidocaine in pain due to peripheral nerve injury and predictors of response. Neurology. 2004;62:218–225.
8. Challapalli V, Tremont-Lukats IW, McNicol ED, Lau J, Carr DB. Systemic administration of local anesthetic agents to relieve neuropathic pain. Cochrane Database Syst Rev 2005; 19: CD003345.

9. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Disponível em: www.prisma-statement.org.

10. Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

11. GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2015 (developed by Evidence Prime, Inc.). Available from gradepro.org.

12. Vlainich R, Issy AM, Sakata RK. Effect of intravenous lidocaine associated with amitriptyline on pain relief and plasma serotonin, norepinephrine, and dopamine concentrations in fibromyalgia. Clin J Pain 2011;27:285-8. PMID: 21178598

13. Albertoni Giraldes AL, Salomão R, Leal PD, Brunialti MK, Sakata RK. Effect of intravenous lidocaine combined with amitriptyline on pain intensity, clinical manifestations and the concentrations of IL-1, IL-6 and IL-8 in patients with fibromyalgia: A randomized double-blind study. Int J Rheum Dis. 2016;19:946-953. PMID: 27309886

14. Kim YC, Castañeda AM, Lee CS, Jin HS, Park KS, Moon JY. Efficacy and Safety of Lidocaine Infusion Treatment for Neuropathic Pain: A Randomized, Double-Blind, and Placebo-Controlled Study. Reg Anesth Pain Med 2018;43:415-424. PMID: 29381569

15. Zhu B, Zhou X, Zhou Q, Wang H, Wang S, Luo K. Intra-Venous Lidocaine to Relieve Neuropathic Pain: A Systematic Review and Meta-Analysis. Front Neurol 2019 18;10:954. PMID: 31620064

Hysterosalpingography: balloon catheter or metal cannula?

Antonio Silvinato[1]
Wanderley Marques Bernardo[2]

Contact: wmbernardo@usp.br

1. Programa Diretrizes – Associação Médica Brasileira, São Paulo, SP, Brasil
2. Coordenador do Programa Diretrizes da Associação Médica Brasileira, São Paulo, SP, Brasil

http://dx.doi.org/10.1590/1806-9282.66.5.589

Question: Is the use of a hysterosalpingography (HSG) intrauterine balloon catheter safe and effective in comparison with a metal cannula?

Answer: In patients submitted to HSG, the use of a balloon catheter, in comparison with a metal cannula, reduces pain during the procedure and up to one hour after it and can also reduce nausea. The quality of the evidence that supports this result is high.

REFERENCE

1. Silvinato A, Bernardo WB – Hysterosalpingography: Balloon Catheter or Metal Cannula? - REV ASSOC MED BRAS 2020; 66(3):252-255

Thrombopoietin is associated with a prognosis of gastric adenocarcinoma

Chang-Lin Zhou[1]
Hai-Long Su[2]
Hong-Wei Dai[3]

1. Medical Oncology of Jining No.1 People's Hospital, Health Road 6th of Jining City, Jining, Shandong, 272100, P.R., China
2. Department of General Surgery, Yantai Yuhuangding Hospital Affiliated to Qingdao University, No.20 Yuhuangding East Road, Yantai, Shandong, 264000, P.R. China
3. Department of Blood Transfusion, Suizhou Central Hospital, Hubei University of Medicine, No. 60 Longmen street, Suizhou, Hubei, 441300, P.R., China

http://dx.doi.org/10.1590/1806-9282.66.5.590

SUMMARY

OBJECTIVE: *Thrombopoietin (THPO) is well-known as a megakaryocyte growth and development factor (MGDF) involved in megakaryocyte proliferation and maturation. To explore the biological effects of THPO in gastric adenocarcinoma, we conducted this study. Methods: By accessing the TCGA database, the expression level of THPO was determined in tumor tissues. The association between THPO expression and clinical features, or prognostic significance was described by Cox regression analysis and Kaplan-Meier. The SiRNA method was used to decline the THPO expression; then cell viability, invasion, and migration were detected to verify the effects of the knockdown of THPO. qPCR and western blotting were implemented to examine the expression level of THPO. Results: The expression of THPO was increased in tumor tissue and cells, its high-regulation was associated with a poor prognosis in patients with gastric adenocarcinoma. Cell viability, invasion, and migration were suppressed in AGS with the down-regulation of THPO. Furthermore, on the basis of si-THPO transfection, E-cadherin was promoted while N-cadherin and Vimentin were attenuated.*

CONCLUSION: *Our results revealed that THPO may be a potent marker of gastric adenocarcinoma, providing a novel potential screening method for gastric adenocarcinoma.*

KEYWORDS: *Adenocarcinoma. Stomach neoplasms. Thrombopoietin. Prognosis. Cell movement. Epithelial-mesenchymal transition.*

INTRODUCTION

Gastric cancer is a type of universal malignancy, which ranks fifth regarding cancer incidence rate and third in mortality worldwide[1]. Different regions cause different occurrences. It is well known that China is also a region with a frequent occurrence of gastric cancer[2,3].

Thrombopoietin (THPO) is a key protein, also regarded as megakaryocyte growth and development factor (MGDF), which is encoded by *the THPO* gene in human[s4,5]. Increasing evidence has demonstrated that THPO levels could affect diverse diseases that consist of hematological diseases, acute coronary syndromes, cardiovascular damage, and sepsis[6-8]. In hepatoblastoma cells, THPO can promote cell migration and adjust various signaling pathways[9]. Nevertheless, there is seldom an understanding of the potential effect of THPO in gastric adenocarcinoma.

Hence, in this exploration, we analyzed the THPO expression level in gastric adenocarcinoma tissue and gastric cancer cells.

DATE OF SUBMISSION: 26-Sep-2019
DATE OF ACCEPTANCE: 10-Oct-2019
CORRESPONDING AUTHOR: Hong-Wei Dai
Department of Blood Transfusion, Suizhou Central Hospital, Hubei University of Medicine, 60 Longmen street, Suizhou, Hubei, 441300, P.R., China Tel.: 86-722-3252089
E-mail:daihw8@163.com

METHODS

Cell lines and clinical samples

The study was supported by the TCGA database, which provided us with THPO expressional profiles, including 32 human normal tissues and 375 tumor tissues. Based on the data derived from the TCGA dataset, the overall survival curve of 366 patients with gastric adenocarcinoma was drawn, and analysis of clinical features and Cox regression were elaborated. Four gastric cancer cell lines (BGC-823, MKN-45, and AGS) and one human normal gastric epithelial cell line GES-1 were purchased from the Cell Biology Department of the Chinese Academy of Sciences (Shanghai, China).

Cell culture and transfection

All the cells were maintained in RPMI-1640 medium containing 10% fetal bovine serum (FBS), 100 U/mL penicillin, and 0.1g/mL streptomycin. The cell culture environment should be held at 37º and 5% CO2. For the following experiments, the siRNA strategy was used to deal with cells and conducted by Lipofectamine2000 in line with the manufacturer's instructions. At 24 h post-transfection, the expression level of THPO could be observed. The sequences of siRNAs were as follows: si-THPO#1: 5'-CGGACATTTCCTCAGGAACATCTC-3'; si-THPO#2: 5'-AGCTAGCTCTTTGGTCTATTTC-3'; si-con: 5'-CTTCTCCTAACTGCAAGGCTA-3'.usedd

RNA extraction and quantitative reverse transcription-polymerase chain reaction (qRT-PCR)

To examine the relative expression of THPO, we carried out the qRT-PCR method. Briefly, total RNA was collected from cells using TRIzol solution (Invitrogen, Carlsbad, CA, USA). Then, the first-strand cDNA was synthesized by SuperScript III RNase H Reverse Transcriptase (Thermo Fisher Scientific, Inc., Waltham, MA, USA).

Lastly, cDNA was subjected to RT-PCR on ABI 7500 fast Real-Time PCR system (Applied Biosystems; Thermo Fisher Scientific, Inc. Waltham, MA, USA) with SYBR Green PCR Master Mix (Thermo Fisher Scientific, Inc., Waltham, MA, USA). GAPDH was considered as a standard control. The qRT-PCR was run at 95º for 5min, then 95º for 30s and 40 cycles, 60º for 45s, and 72º for 30min. The following primers were presented: THPO: 5'-GATACTCGAAGGACAGGCCG-3', 5'-CAGAGTAGGGTGGGGCAAAG-3'; GAPDH: 5'-GCTCTCTGCTCCTCCTGTTC-3', 5'-CGACCAAATCCGTTGACTCC-3'. They were synthesized by GenePharma Co., Ltd (Shanghai, China) and the expression level was calculated through $2^{-\Delta\Delta CT}$ method.

Protein isolation and western blot analysis

After 48 h transfection, cells were lysed with RIPA lysis buffer (protease inhibitor; Thermo Fisher Scientific, MA, USA) to extract protein on ice. The concentration was identified by the BCA method followed by centrifugation, and 5 × SDS loading buffer was used to denature protein at 95º for 5 min. Each sample containing 20μg protein was resolved by SDS-PAGE (Sigma-Aldrich, MO, USA), transferred to a PVDF membrane, and blocked with 5% non-fat milk for 1 h. Subsequently, the membrane was incubated in primary antibodies (at a 1:1, 000 dilution, Abcam, Cambridge, UK) overnight and secondary antibody (at a 1:2, 000 dilution, Abcam, Cambridge, UK) for 1 h. Finally, the membrane was washed using TBST and developed via adding ECL. These antibodies were purchased from Abcam, including THPO (ab196026), E-cadherin (ab40772), N-cadherin (ab18203), Vimentin (ab92547), and GAPDH (ab181602).

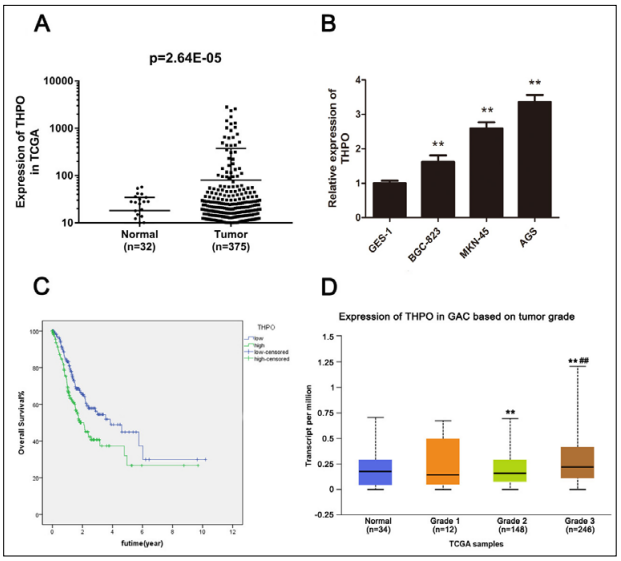


FIGURE 1. THPO WAS UP-REGULATED IN GASTRIC ADENOCARCINOMA TISSUE AND CELL; MEANWHILE, THE HIGH EXPRESSION OF THPO COULD CAUSE POOR SURVIVAL.

(A) The specimens of THPO expression from the TCGA dataset, P = 2.64E-05. (B) Different expression level of THPO in five cell lines, *P < 0.05 and **P < 0.01 versus GES-1. (C) The overall survival curve of gastric adenocarcinoma patients was plotted by Kaplan-Meier, P = 0.004. (D) Relative expression of THPO in gastric adenocarcinoma based on tumor grade, **P < 0.01 versus Normal and ##P < 0.01 versus Grade 1.

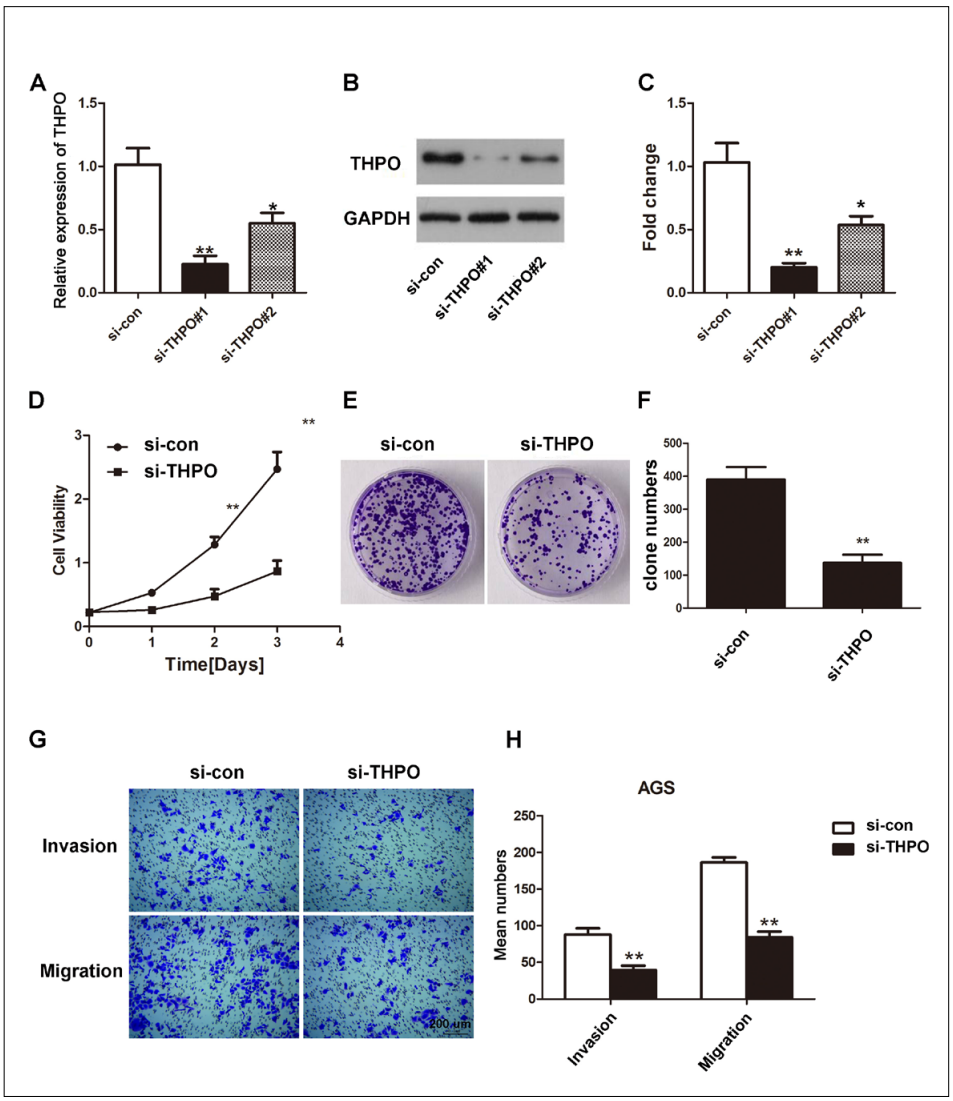


FIGURE 2. THE KNOCKDOWN EFFICIENCY WAS ASSESSED, AND THE REDUCTION OF THPO REPRESSED CELL MALIGNANT BIOLOGICAL PROPERTIES IN AGS.

(A) Detection of transfection efficiency by qRT-PCR, *P < 0.05 and **P < 0.01 versus the si-con group. (B) THPO expression was examined by western blot and (C) quantified, *P < 0.05 and **P < 0.01 versus the si-con group. (D) The reduction of THPO inhibited cell proliferation by MTT assay, **P < 0.01 versus the si-con group. (E) Clone ability was indicated using colony formation assay and (F) the clone numbers were counted, **P < 0.01 versus the si-con group. (G) The representative pictures of invasion and migration, bar = 200 μm, and (H) the number of migratory and invasive cells were calculated, **P < 0.01 versus the si-con group.

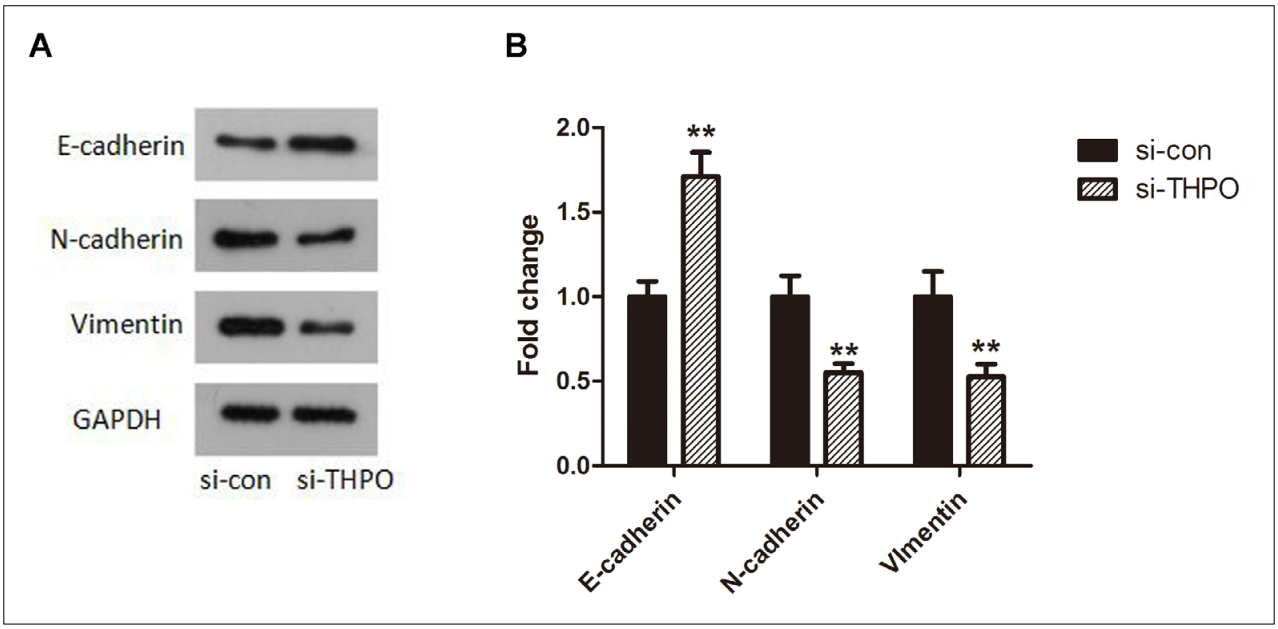


FIGURE 3. THE IMPACT OF THPO SILENCE ON THE EMT PROCESS WAS ASSESSED.

(A) The protein expression level of EMT markers. (B) The comparison of fold change between the si-con group and si-THPO group, **P < 0.01 versus the si-con group.

Colony formation assay

Briefly, cells were digested and blown into single cells to make cell suspension, inoculated in a 60 mm dish at a density of 500 cells at 37° with 5% CO2. After maintained for two weeks, cells were fixed with 4% paraformaldehyde and stained with 0.1% crystal violet for 30 min. Then the staining solution was gently removed and pictures were captured randomly.

Cell proliferation, migration and invasion assay

To assess the proliferative ability, cells were cultured in a 96-well plate, until reaching 3×10^3 cells/hole. Adding 100 μL MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) reagent, we detected the absorbance at 1 d, 2 d, 3 d with 590 nm.

Statistical analysis

GraphPad Prism 5.0 (GraphPad Software, San Diego, CA, USA) and SPSS22.0 (IBM Corp., Armonk, NY, USA) was applied to conduct statistical analysis. The overall survival was analyzed based on the Kaplan-Meier method with a log-rank test. Data were determined as mean ± standard deviation (SD) and p-value < 0.05 was considered significant.

RESULTS

THPO was highly regulated in gastric adenocarcinoma tissues and cells

Data of qRT-PCR obtained from the TCGA database was applied to evaluate the differential mRNA expression level of THPO in human normal tissue and gastric adenocarcinoma tissue. Compared with normal tissue, THPO was dramatically up-regulated in gastric adenocarcinoma tissue (Figure. 1 A, $P < 0.001$). To verify this result, THPO expression in gastric cancer cell lines (BGC-823, MKN-45, and AGS) and one normal human gastric epithelial cell line GES-1 was examined by the qRT-PCR method. As shown in Figure. 1 B, we observed that all gastric cancer cell lines had higher expression of THPO when the THPO expression in GES-1 was considered as standard control ($P < 0.05$). Analyzed together, these results indicated that THPO might be a cancer-promoting gene in gastric adenocarcinoma, which is implicated in tumorigenesis.

The over-expression of THPO was associated with poor prognosis of gastric adenocarcinoma patients

To further confirm the role of THPO, the prognostic value of THPO in patients with gastric adenocarcinoma was investigated. By analyzing the data from the TCGA database using the Kaplan-Meier method, gastric adenocarcinoma patients with a high expression of THPO presented a lower survival rate than those with a low expression of THPO (Figure. 1 C, $P = 0.004$). The low and high expressions of THPO were remarkably linked with grade (data not shown, $P = 0.001$). Figure 1 D shows that the THPO expression level varied in the different grades of tumor samples ($P < 0.05$).

Knockdown of THPO impaired aggressive behaviors of gastric adenocarcinoma cells

To completely confirm the function of THPO, we performed MTT, transwell, and colony formation assays in gastric adenocarcinoma cells after transfection with si-THPO. We compared with the si-con group, si-THPO#1 and si-THPO#2 sharply interfered with the THPO expression in both the mRNA and protein levels (Figure 2 A-C, $P < 0.05$). Next, MTT assay was implemented to measure the influence of the knockdown of THPO, and the results demonstrated that the down-regulation of THPO inhibited cell proliferation in AGS cells (Figure 2 D, $P < 0.01$). Moreover, the transfection of si-THPO also blocked cell viability through colony formation assay (Figure 2 E and 2 F, $P < 0.01$). As seen in Figure 2 G and 2 H, the migratory and invasive abilities were all impaired when compared with the si-con group ($P < 0.01$).

The reduction of THPO induced the inactivation of the EMT process in AGS cells

The image of protein bands revealed that E-cadherin expression was enhanced (Figure 3 A). By contrast, N-cadherin and Vimentin expression were minified (Figure. 3 A). In addition, the fold change of protein intensity also confirmed the effect of the down-regulation of THPO on EMT markers (Figure 3 B, $P < 0.01$).

DISCUSSION

We predicted that THPO may be a potential independent risk factor in cancer progression. Moreover, a large number of studies have verified the significance of THPO in sets of cancers: THPO was able to facilitate cell growth and survival in acute myeloid leukemia[10,11]; the self-renewal of colorectal cancer cells was promoted by THPO and then diffused into the liver[12]; the platelet produced under THPO regulation could contribute to cell proliferation,

migration, and invasion in cancers, both intracellularly and extracellularly[13].

We found that THPO was highly expressed in gastric adenocarcinoma tissue compared with normal tissue. Meanwhile, we depicted the overall survival curve in patients with gastric adenocarcinoma and found that high expression of THPO shortened lifespan. Functional experiments *in vitro* showed the knockdown of THPO inhibited the biological behaviors in AGS cells in comparison to the si-con control. The EMT process is a vital initial step in cancer and many studies have inferred that EMT induction is the essential molecular mechanism by which tumor cells achieved malignant phenotypes and metastasis[14,15].

Here, we detected the role of THPO expression in gastric adenocarcinoma and indeed had positive results. Consistent with these findings, other relevant cytokines of platelet have been revealed to be associated with the biological viability of tumor cells, such as MMP-2, GPIIb/IIIa, and P-selectin[16-18]. But in line with research by Lang et al.[19], no evident significance was proven in clonal growth when four types of human tumor cells (prostate, breast, cervix, colon) were exposed to thrombopoietin. Therefore, subsequent tests should pay attention to the reason for this difference.

CONCLUSION

We concluded that THPO can promote the progression of gastric adenocarcinoma and may be a potential candidate for tumor diagnosis as well as targeted treatment.

Declaration of conflicting interest

The author(s) declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Funding

None.

Author Contributions

Chang-Lin Zhou and Hai-Long Su contributed equally to the work. Conceptualization, Chang-Lin Zhou; formal analysis, Chang-Lin Zhou; writing—original draft preparation, Hai-Long Su; writing—review and editing, Hong-Wei Dai; supervision, Hai-Long Su; funding acquisition, Hong-Wei Dai.

RESUMO

OBJETIVO: *Trombopoetina (THPO) é um conhecido fator de desenvolvimento e crescimento megacariócito (MGDF) envolvido na proliferação e maturação de megacariócitos. Realizamos este estudo para explorar os efeitos biológicos do THPO no adenocarcinoma gástrico. Metodologia: O nível de expressão do THPO em tecidos tumorais foi determinado acessando a banco de dados TCGA. A associação entre a expressão de THPO e características clínicas ou relevância no prognóstico foi descrita através da análise de Kaplan-Meier e regressão de Cox. O método SiRNA foi utilizado para reduzir a expressão da THPO e, em seguida, a viabilidade, invasão, e migração celular foram detectadas para verificar os efeitos da redução do THPO. qPCR e western blotting foram utilizados para examinar o nível de expressão do THPO. Resultados: A expressão do THPO estava aumentada em tecido e células tumorais, esse aumento estava associado com um prognóstico negativo para pacientes com adenocarcinoma gástrico. A invasão e migração celular foram suprimidos em AGS com a redução do THPO. Além disso, com base na transfecção de si-THPO, a E-caderina foi promovida, enquanto a N-caderina e Vimentina foram atenuadas. Conclusão: Nossos resultados demonstram que o THPO pode ser um potente marcador de adenocarcinoma gástrico, com potencial para ser um novo tipo de triagem para adenocarcinoma gástrico.*

PALAVRAS-CHAVE: *Adenocarcinoma. Neoplasias gástricas. Trombopoetina. Prognóstico. Movimento celular. Epithelial-mesenchymal transition.*

REFERENCES

1. Wippel HH, Santos MDM, Clasen MA, Kurt LU, Nogueira FCS, Carvalho CE, et al. Comparing intestinal versus diffuse gastric cancer using a PEFF-oriented proteomic pipeline. J Proteomics. 2018;171:63-72.
2. Sun W, Yan L. Gastric cancer: current and evolving treatment landscape. Chin J Cancer. 2016;35(1):83.
3. Zheng R, Zeng H, Zhang S, Chen W. Estimates of cancer incidence and mortality in China, 2013. Chin J Cancer. 2017;36(1):66.
4. Gurney AL, de Sauvage FJ. Dissection of c-Mpl and thrombopoietin function: studies of knockout mice and receptor signal transduction. Stem Cells. 1996;14(Suppl 1):116-23.
5. Kaushansky K, Drachman JG. The molecular and cellular biology of thrombopoietin: the primary regulator of platelet production. Oncogene. 2002;21(21):3359-67.
6. Cerutti AP, Custodi P, Duranti M, Noris P, Balduini CL. Thrombopoietin

levels in patients with primary and reactive thrombocytosis. Br J Haematol. 1997;99(2):281-4.

7. Senaran H, Ileri M, Altinbaş A, Koşar A, Yetkin E, Oztürk M, et al. Thrombopoietin and mean platelet volume in coronary artery disease. Clin Cardiol. 2001;24(5):405-8.
8. Zakynthinos SG, Papanikolaou S, Theodoridis T, Zakynthinos EG, Christopoulou-Kokkinou V, Katsaris G, et al. Sepsis severity is the major determinant of circulating thrombopoietin levels in septic patients. Crit Care Med. 2004;32(4):1004-10.
9. Romanelli RG, Petrai I, Robino G, Efsen E, Novo E, Bonacchi A, et al. Thrombopoietin stimulates migration and activates multiple signaling pathways in hepatoblastoma cells. Am J Physiol Gastrointest Liver Physiol. 2006;290(1):G120-8.
10. Wolber EM, Dame C, Fahnenstich H, Hofmann D, Bartmann P, Jelkmann W, et al., Expression of the thrombopoietin gene in human fetal and neonatal tissues. Blood. 1999;94(1):97-105.
11. Pulikkan JA, Madera D, Xue L, Bradley P, Landrette SF, Kuo YH, et al. Thrombopoietin/MPL participates in initiating and maintaining RUNX1-ETO acute myeloid leukemia via PI3K/AKT signaling. Blood. 2012;120(4):868-79.
12. Wu Z, Wei D, Gao W, Xu Y, Hu Z, Ma Z, et al. TPO-induced metabolic reprogramming drives liver metastasis of colorectal cancer CD110+ tumor-initiating cells. Cell Stem Cell. 2015;17(1):47-59.
13. Bambace NM, Holmes CE. The platelet contribution to cancer progression. J Thromb Haemost. 2011;9(2):237-49.
14. Acloque H, Adams MS, Fishwick K, Bronner-Fraser M, Nieto MA. Epithelial-mesenchymal transitions: the importance of changing cell state in development and disease. J Clin Invest. 2009;119(6):1438-49.
15. Hwang HS, Go H, Park JM, Yoon SY, Lee JL, Jeong SU, et al. Epithelial-mesenchymal transition as a mechanism of resistance to tyrosine kinase inhibitors in clear cell renal cell carcinoma. Lab Invest. 2019;99(5):659-70.
16. Dashevsky O, Varon D, Brill A. Platelet-derived microparticles promote invasiveness of prostate cancer cells via upregulation of MMP-2 production. Int J Cancer. 2009;124(8):1773-7.
17. Trikha M, Zhou Z, Timar J, Raso E, Kennel M, Emmell E, et al. Multiple roles for platelet GPIIb/IIIa and alphavbeta3 integrins in tumor growth, angiogenesis, and metastasis. Cancer Res. 2002;62(10):2824-33.
18. Ludwig RJ, Boehme B, Podda M, Henschler R, Jager E, Tandi C, et al. Endothelial P-selectin as a target of heparin action in experimental melanoma lung metastasis. Cancer Res. 2004;64(8):2743-50.
19. Lang SH, West CM, Jones L, Brooks B, Kasper C, deWynter E, et al. In vitro effects of recombinant human megakaryocyte growth and development factor on primary human tumour colony growth. Oncology. 1997;54(2):141-5.

ORIGINAL ARTICLE

Ibuprofen increases the serum Omentin levels in rats after abdominal surgery

Mustafa Sit[1]
Gulali Aktas[2]
Bahri Ozer[3]
Oguz Catal[4]

1. Associate Professor, Abant Izzet Baysal University Hospital, Department of General Surgery, Bolu, Turkey
2. Associate Professor, Abant Izzet Baysal University Hospital, Department of Internal Medicine, Bolu, Turkey
3. Assistant Professor, Abant Izzet Baysal University Hospital, Department of General Surgery, Bolu, Turkey
4. Assistant Professor, Abant Izzet Baysal University Hospital, Department of General Surgery, Bolu, Turkey

http://dx.doi.org/10.1590/1806-9282.66.5.596

SUMMARY

AIMS: *Omentin is an adipokine primarily produced by visceral adipose tissue and its reduced levels have been shown to be associate with worse metabolic outcomes. We aimed to study the effects of preoperative ibuprofen on postoperative omentin levels in rats after surgery.*

METHODS: *Forty-eight albino Wistar rats, 6 in each of 8 groups according to the surgical procedure (laparotomy, laparotomy plus ibuprofen (IBU), nephrectomy, nephrectomy plus IBU, hepatectomy, hepatectomy plus IBU, splenectomy and splenectomy plus IBU). The Omentin levels of the groups were postoperatively analyzed.*

RESULTS: *The mean omentin was significantly higher in the laparotomy plus IBU group compared to the laparotomy group (p<0.001). Mean Omentin was significantly higher in the hepatectomy plus IBU group compared to the hepatectomy group (p=0.01). Mean Omentin was significantly higher in the nephrectomy plus IBU group compared to the nephrectomy group (p=0.001).*

CONCLUSION: *We suggest that preoperative ibuprofen may enhance circulating levels of Omentin, which has beneficial effects in trauma and inflammation settings in subjects that undergo minor or major abdominal surgery.*

KEYWORDS: *Ibuprofen. Adipokines. Rats, Wistar. Surgical procedures, operative. Abdomen/surgery.*

INTRODUCTION

The main purpose of body functions after trauma is maintaining hemostasis by developing systemic and local responses against trauma. The neuroendocrine response to trauma, release of mediators, intracellular and intercellular metabolic changes vary according to the time and type of the trauma. Regardless of the size, surgery is trauma and promotes a chain reaction in the body that causes various metabolic endocrine responses.

The central nervous system plays an important role in the regulation of the inflammatory response. Traditionally, the autonomic nervous system regulates the heart rate, blood pressure, respiration rate, gastrointestinal motility, and body temperature. Specific sites of inflammation send afferent signals to the hypothalamus. As a result, anti-inflammatory messages quickly swing to reduce inflammatory mediators[1].

The central nervous system responds to

DATE OF SUBMISSION: 11-Oct-2019
DATE OF ACCEPTANCE: 12-Nov-2019
CORRESPONDING AUTHOR: Mustafa Sit
Abant Izzet Baysal University Hospital, Department of Internal Medicine, Golkoy, 14280, Bolu, Turkey
Phone: +903742534656, Fax: +903742534615
Email: drmustafasit@yahoo.com.tr

immunological signals via circulation and the neural pathways. Although the blood-brain barrier blocks many substances, it allows the passage of inflammatory factors, such as tumor necrosis factor (TNF). Symptoms including fever, anorexia, and depression occur by the humoral pathway of inflammatory signals. Cytokines, baroreceptors, chemoreceptors, and thermoreceptors carry afferent stimulus to the vagal nerve from the site of trauma. Vagal stimulation decreases heart rate, increases intestinal motility, dilates the arterioles, constricts the pupil, and regulates inflammation.

Cytokines, especially TNF and interleukin-1 (IL-1) are known to have effects on energy metabolism and appetite. It is demonstrated in many studies that these effects of cytokines were associated with adipokines[2].

Omentin is a 34 kDa new adipokine primarily produced by visceral adipose tissue. Decreased omentin levels have been shown to be associated with worse metabolic outcomes in diabetic patients[3].

Cytokines are known to increase after operations or injury. Ibuprofen (IBU) prevents the production of proinflammatory prostaglandins by inhibiting cyclooxygenase 1 and 2. It is thought that ibuprofen improves appetite by the same way[4].

Although it has been shown in the literature that several adipokines were associated with appetite affected by surgery and ibuprofen treatment, to our knowledge, there is no report about omentin in this regard. Observing omentin levels in rats after surgery may provide useful clinical information due to the potentially common pathogenesis. Therefore, we aimed to study the effects of preoperative ibuprofen on postoperative omentin levels in rats after surgery.

METHODS

Forty-eight Wistar albino rats (6 rats in each group) were included in the study. Study groups were as follows: laparotomy (L); laparotomy + IBU (LI); hepatectomy (H); hepatectomy + IBU (HI); nephrectomy (N); nephrectomy + IBU (NI); splenectomy (S); and splenectomy + IBU (SI). The rats in LI, HI, NI, and SI groups were weighed 18 hours before surgery, and 30mg/kg of ibuprofen was administered via gastric tube. Retro-orbital blood samples were obtained from the rats 18 hours after surgery. The same surgeons performed surgical interventions under general anesthesia with an intramuscular injection of 50mg/kg of Ketamine (Ketalar 50 mg/ml, Eczacıbaşı, İstanbul) and 5mg/kg of Xylazine (Rompun 20 mg/ml, Bayer, İstanbul). After disinfection, a 3cm median incision was done on all rats. After the incision, partial hepatectomy, splenectomy, or unilateral nephrectomy was performed and the skin sutured with 000 silk sutures after hemostasis. Postoperatively, 3ml of blood samples were obtained from the abdominal aorta under general anesthesia, after the experimental protocol finished.

The omentin levels were assessed from postoperative blood samples. Venous blood samples were centrifuged for ten minutes at 1000 rpm for separation of the serum. Omentin in these sera was studied by sandwich ELISA kits of Biovendor (Brno, Czech Republic) according to the manufacturer's instructions.

Data was analyzed with SPSS software (SPSS 15.0 for Windows, IBM Co., Chicago, Il, USA). Independent samples t-test was used in the comparison of omentin between the study groups. Data were expressed as mean ± standard deviation. A p-value <0.05 considered as statistically significant.

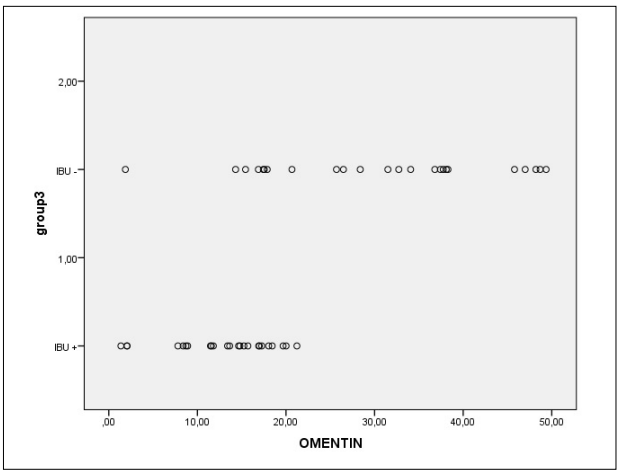


TABLE 1. OMENTIN LEVELS OF THE STUDY GROUPS

Groups	Omentin (ng/mL)	P
L (n=6)	8.8 ± 5.7	<0.001
LI (n=6)	34.9 ± 10	
H (n=6)	13.9 ± 3.5	0.01
HI (n=6)	31.8 ± 14.4	
N (n=6)	14.9 ± 4	0.001
NI (n=6)	34 ± 9.5	
S (n=6)	14.1 ± 7.9	0.37
SI (n=6)	20.7 ± 15.1	

RESULTS

There were 6 rats in each of the L, LI, H, HI, N, NI, S, and SI groups. The mean omentin levels of the L and LI groups were 8.8 ± 5.7 ng/mL and 34.9 ± 10 ng/mL, respectively (p<0.001). The mean omentin levels of the H and HI groups were 13.9 ± 3.5 ng/mL and 31.8 ± 14.4 ng/mL, respectively (p=0.01).

The mean omentin levels of the N and NI groups were 14.9 ± 4 ng/mL and 34 ± 9.5 ng/mL, respectively (p=0.001). The mean omentin levels of the S and SI groups were 14.1 ± 7.9 ng/mL and 20.7 ± 15.1 ng/mL, respectively (p=0.37). Table 1 shows the omentin levels of the study population. Figure 1 shows the omentin levels of the subjects received or not received ibuprofen.

DISCUSSION

The main discovery of the present study is that the preoperative administration of ibuprofen increases the serum levels of Omentin in rats that undergo minor and major surgery, which may be beneficial in the treatment of subjects after a surgical procedure.

Omentin is an adipokine that is produced in visceral adipose tissue[5]. Recent data support that it has a crucial role in the regulation of inflammation. Decreased levels of omentin in synovia have been reported in rheumatoid arthritis[6], and reduced omentin messenger RNA expression has been reported in the omentum of subjects with Chrohn's disease[7]. Authors reported reduced omentin levels in acute appendicitis[8] and mesenteric ischemia settings[9]. On the other hand, the effects of C-reactive protein and tumor necrosis factor-alpha on endothelial cells were reduced by omentin[10]. These reports suggest that omentin is an anti-inflammatory cytokine.

Authors have reported elevated omentin in neoplastic disease. Increased omentin has been reported in subjects with prostate cancer[11]. The elevation of adipokine in cancer could be a defense mechanism of the body since it induces apoptosis in tumor cells[12].

Omentin is also associated with conditions that are characterized by low burden inflammation. For instance, the omentin receptor gene in adipose tissue is down-regulated in obese subjects[4]. As a result, serum omentin decreases in obesity. Body mass index, serum leptin, and waist circumference, the markers of obesity, are inversely correlated with circulating omentin levels[13]. Current literature not only suggests that omentin is lower in obese subjects, but also that weight reduction promotes elevation in circulating omentin levels[14]. Serum omentin levels are also decreased in subjects with type 2 diabetes mellitus, another low inflammatory condition[15]. Omentin levels in patients with polycystic ovary syndrome are reported to be reduced[16]. Polycystic ovary syndrome is also associated with obesity, insulin resistance, and low-grade inflammation.

Reduced omentin has been reported in other clinical conditions too. Omentin was significantly decreased in pregnant women compared to non-pregnant age-matched controls[17]. Tekce et al.[18] reported that omentin levels decreased in patients with chronic kidney disease. Indeed, laparotomy, hepatectomy, and nephrectomy all cause a significant amount of inflammation, which could reduce the circulating omentin levels. Anti-inflammatory agents may not only reduce inflammation but also increase omentin and thus have beneficial effects after surgery. Ibuprofen is a non-steroidal anti-inflammatory drug. It inhibits the synthesis of prostaglandins from the Arachidonic acid pathway. Our data suggest that omentin may also mediate the anti-inflammatory properties of ibuprofen.

Limitations of the present study are the lack of measurement of other inflammatory markers, such as C-reactive protein. Another limitation could be the low number of test subjects in each study group. However, the results of the present study indicating the importance of ibuprofen administration on omentin levels are very important.

In conclusion, we suggest that preoperative ibuprofen may enhance circulating levels of omentin, which has beneficial effects in a trauma and inflammation setting, in subjects that undergo minor or major abdominal surgery. Prospective studies about the effects of omentin and preoperative ibuprofen on surgical complications, length of hospital stay, and related factors are needed.

COI statement and funding statement

The authors have no conflict of interest. This work has not received any funds or grants from any organizations.

Author's Contributions

MS, BO, and OC designed the study. MS and OC performed the literature search. MS and BO performed surgical procedures. BO, OC, GA performed the statistical analyses. GA and MS wrote the manuscript. BO and OC performed the critical review of the first draft

RESUMO

OBJETIVOS: *A omentina é uma adipocina produzida principalmente pelo tecido adiposo visceral e níveis reduzidos dela foram associados a piores desfechos metabólicos. Nosso objetivo foi estudar os efeitos do uso pré-operatório do ibuprofeno nos níveis pós-operatórios da omentina em ratos.*

METODOLOGIA: *Quarenta e oito ratos Wistar albinos foram divididos em 8 grupos (6 em cada), de acordo com o procedimento cirúrgico: laparotomia, laparotomia e ibuprofeno (IBU), nefrectomia, nefrectomia e IBU, hepatectomia, hepatectomia e IBU, esplenectomia, e esplenectomia e IBU. Os níveis de omentina dos grupos foram analisados após a cirurgia.*

RESULTADOS: *A omentina média foi significativamente maior no grupo de laparotomia e IBU do que no grupo de laparotomia (p<0,001). A omentina média foi significativamente maior no grupo de hepatectomia e IBU do que no grupo de hepatectomia (p = 0,01). A omentina média foi significativamente maior no grupo de nefrectomia e IBU do que no grupo de nefrectomia (p = 0,001).*

CONCLUSÃO: *Sugerimos que o uso pré-operatório de ibuprofeno pode aumentar os níveis circulantes de omentina, que têm efeitos benéficos em um contexto de trauma e inflamação em indivíduos submetidos cirurgia abdominal.*

PALAVRAS-CHAVE: *Ibuprofeno. Adipocinas. Ratos, Wistar. Procedimentos cirúrgicos, operatórios. Abdome/cirurgia.*

REFERENCES

1. Wang Z, Nakayama T. Inflammation, a link between obesity and cardiovascular disease. Mediators Inflamm. 2010;2010:535918.
2. Zivna H, Zivny P, Palicka V. Serum leptin concentrations after surgery in young rats. Nutrition. 2002;18(7-8):643-6.
3. Yoo HJ, Hwang SY, Hong HC, Choi HY, Yang SJ, Seo JA, et al. Association of circulating omentin-1 level with arterial stiffness and carotid plaque in type 2 diabetes. Cardiovasc Diabetol. 2011;10:103.
4. Tan BK, Adya R, Randeva HS. Omentin: a novel link between inflammation, diabesity, and cardiovascular disease. Trends Cardiovasc Med. 2010;20(5):143-8.
5. Yang RZ, Lee MJ, Hu H, Pray J, Wu HB, Hansen BC, et al. Identification of omentin as a novel depot-specific adipokine in human adipose tissue: possible role in modulating insulin action. Am J Physiol Endocrinol Metab. 2006;290(6):E1253-61.
6. Senolt L, Polanská M, Filková M, Cerezo LA, Pavelka K, Gay S, et al. Vaspin and omentin: new adipokines differentially regulated at the site of inflammation in rheumatoid arthritis. Ann Rheum Dis. 2010;69(7):1410-1.
7. Schäffler A, Neumeier M, Herfarth H, Fürst A, Schölmerich J, Büchler C. Genomic structure of human omentin, a new adipocytokine expressed in omental adipose tissue. Biochim Biophys Acta. 2005;1732(1-3):96-102.
8. Sit M, Catal O, Aktas G, Yilmaz EE, Tosun M, Savli H. Serum amyloid A and Omentin levels in acute appendicitis: a preliminary study for a novel diagnostic approach. Clin Ter. 2014;165(1):e35-8.
9. Sit M, Aktas G, Yilmaz EE, Tosun M, Terzi EH, Alcelik A. Serum omentin levels predicts mesenteric ischemia. Bratisl Lek Listy. 2015;116(3):173-6.
10. Tan BK, Adya R, Farhatullah S, Chen J, Lehnert H, Randeva HS. Metformin treatment may increase omentin-1 levels in women with polycystic ovary syndrome. Diabetes. 2010;59(12):3023-31.
11. Zhou L, He W, Wang W, Zhou D. Altered circulating levels of adipokine omentin-1 in patients with prostate cancer. OncoTargets Ther. 2019;12:3313-9.
12. Zhang YY, Zhou LM. Omentin-1, a new adipokine, promotes apoptosis through regulating Sirt1-dependent p53 deacetylation in hepatocellular carcinoma cells. Eur J Pharmacol. 2013;698(1-3):137-44.
13. Souza Batista CM, Yang RZ, Lee MJ, Glynn NM, Yu DZ, Pray J, Ndubuizu K, et al. Omentin plasma levels and gene expression are decreased in obesity. Diabetes. 2007;56(6):1655-61.
14. Moreno-Navarrete JM, Catalán V, Ortega F, Gómez-Ambrosi J, Ricart W, Frühbeck G, et al. Circulating omentin concentration increases after weight loss. Nutr Metab (Lond). 2010;7:27.
15. Pan HY, Guo L, Li Q. Changes of serum omentin-1 levels in normal subjects and in patients with impaired glucose regulation and with newly diagnosed and untreated type 2 diabetes. Diabetes Res Clin Pract. 2010;88(1):29-33.
16. Tan BK, Adya R, Farhatullah S, Lewandowski KC, O'Hare P, Lehnert H, et al. Omentin-1, a novel adipokine, is decreased in overweight insulin-resistant women with polycystic ovary syndrome: ex vivo and in vivo regulation of omentin-1 by insulin and glucose. Diabetes. 2008;57(4):801-8.
17. Aktas G, Alcelik A, Ozlu T, Tosun M, Tekce BK, Savli H, et al. Association between omentin levels and insulin resistance in pregnancy. Exp Clin Endocrinol Diabetes. 2014;122(3):163-6.
18. Tekce H, Tekce BK, Aktas G, Alcelik A, Sengul E. Serum omentin-1 levels in diabetic and nondiabetic patients with chronic kidney disease. Exp Clin Endocrinol Diabetes. 2014;122(8):451-6.

ORIGINAL ARTICLE

Physical activity impact on motor development and oxidative stress biomarkers in school children with intellectual disability

Ahmad H. Alghadir[1]
Sami A. Gabr[1]

1. Rehabilitation Research Chair, College of Applied Medical Sciences, King Saud University, Riyadh, KSA

http://dx.doi.org/10.1590/1806-9282.66.5.600

SUMMARY

OBJECTIVE: *Lower physical fitness and poor motor performance were shown to be linked with higher levels of oxidative stress in children and adolescents with intellectual disabilities. Therefore, a moderate aerobic exercise for 12-weeks was performed to evaluate the effects of physical activity scores on motor functions, oxidative stress, and intelligence quotients (IQ) in school children with intellectual disability.*

METHODS: *A total of 65 school children aged (12-18 Yrs) were randomly included in this study. Intellectual disability (ID),motor skills,-physical fitness(VO2max), total energy expenditure (TEE), MDA, 8-OHdG, TAC, NO, and total oxidative stress(OS)were assessed using pre-validated WISC-IQ score test, BOT-2 test, PA questionnaire, and immunoassay techniques respectively.*

RESULTS: *WISC-IQ and BOT-2 set scores of intellectual and motor skills performance showed a significant correlation with physical activity status and the regulation of oxidative stress-free radicals in school children with mild and moderate ID following 12 weeks of moderate exercise. The intellectual and motor skills performance of the participants correlated positively with the increase in TAC activity and physical fitness scores and negatively with MDA, 8-OHdG, NO, and Total-OS, respectively. Stepwise multiple regression analysis of the demographic, physical status and oxidative stress parameters explained around78.0 to 93.4 % of intellectual disability variation among schoolchildren.*

CONCLUSION: *Moderate aerobic training for12 weeks has a positive impact on improving intellectual ability of schoolchildren with ID via modulating redox status, improves physical fitness, and motor skills proficiency.*

KEYWORDS: *Physical fitness. Exercise. Intellectual disability. Oxidative stress. Motor activity. Psychomotor performance.*

INTRODUCTION

Active life styles and normal diets play a significant role in maintaining normal health for both children and adult populations via controlling obesity and nutritional related chronic disorders[1,2].

Previous research studies reported that low levels of physical fitness and high rates of obesity were reported in individuals with intellectual disabilities (ID)[3,4]. These consequences promote health disturbances and increase the rates of morbidity and mortality among that populations[3-5].

Most individuals with ID have functional and cognitive decline[6], along with lower physical performance, less participation in social activities, and a sedentary lifestyle[7].

The disturbance in oxidant –antioxidant status of biological cells may be related to several reasons

DATE OF SUBMISSION: 16-Nov-2019
DATE OF ACCEPTANCE: 25-Nov-2019
CORRESPONDING AUTHOR: Sami A. Gabr
Rehabilitation Research Chair, College of Applied Medical Sciences, King Saud University – P.O. Box 10219 - Riyadh 11433, KSA
Tel:+966562060018 – Fax: +96614698541
Email: dr.samigabr@gmail.com

such as age-related diseases, metabolic disorders, sedentary lifestyle like poor physical activity, or mental stress as well as ID[7-11]. Abnormal signaling levels of NO were significantly reported in a variety of neurodegenerative pathologies including intellectual disabilities[12-14].

Also, 8-hydroxy-20-deoxyguanosine (8-OHdG) as oxidative biomarker was reported in the urine of individuals with severe motor and intellectual disabilities (SMID)[15]. Similarly, a significant increase in the levels of malondialdehyde (MDA) as oxidative free radicals was reported in children with cerebral palsy, ID, and autism[13-17].

Motor development and brain functions in healthy children and adolescents were shown to be correlated with active physical performance in healthy and ID children or adolescents with lower or poor motor functions.[2,18,19]. This was significantly associated with a sedentary lifestyle or low physical activity[20].

It was reported that participation of individuals with ID to programmed physical exercise interventions with varying intensities may have a positive impact results upon motor functions, ID scores, and quality of their life's[2,15-17]. However, the physiological and biochemical effects of physical exercise on the status of intellectual abilities among young individuals still have to be fully elucidated. Therefore, this study aims to evaluate the effects of 12-weeks of aerobic moderate exercise on motor functions and oxidative stress in school children with intellectual disability. In addition, we would like to see if there is any correlation between ID scores, motor function performance, and related oxidative stress biomarkers.

METHODS

Participants

A total of 85 school children aged (12-18 years) selected from different elementary and secondary public schools in Mansoura, Egypt between 2012 and 2013 randomly participated in this study. The sample size of 85 was selected from the list of students from different elementary and secondary public schools in a large geographical area of Mansoura to give estimate power of 95 % and a significance level of 0.05 with expected frequency of 6.3 %. None of the selected participants have any physical disabilities to prevent them from participating in exercise programs. Based on the intelligence quotients (IQ), the participants were classified into three groups; normal healthy group (no=25; IQ =90-114); mild ID group (no=23; IQ=50-70), and moderate ID group (no=37; IQ=35-49). Prior participation, written informed consent was obtained from all participants. The demographic and baseline data of participants were shown in Table 1.

Exercise Program

Participants were subjected to a supervised exercise program for 45–60 minutes three times per week for 12 weeks using treadmill[10-13]. This test provides the participants with maximum physical activities corresponding to 30%–45% of VO2 max uptake[13]. The maximum exercise of moderate- intensity (65%–75%) of each participant was calculated as training heart rate (THR) as previously reported[18,19]. Also, total energy expenditure (TEE) was evaluated by calculating basal metabolic rates (BMR) from body mass, height, age, sex, and type of physical activity of all participants using a pre-validated equation as previously reported[10,18,19].

Intelligence Assessment

A pre-validated Wechsler Intelligence Scale test was used to evaluate the intelligence quotients (IQ) of the participants before and after exercise interventions[15,16]. IQ measurements of the participants were in the range of normal (IQ =90-114) mild (IQ=50-70), and moderate (IQ=35-49) respectively.

Motor Assessment

Motor skills among the participants were efficiently evaluated before and after exercise interventions by the use of pre-validated Bruininks-Oseretsky Test of Motor Proficiency, 2nd Edition (BOT–2. A test is a short form of 8 subtests with14 test items which has good validity and reliability to assist motor skill deficits among students aged 4-21 years[16].

Assessment of Oxidative Stress

Estimation of total oxidative stress (OS)

The colorimetric test was evaluated to assess total oxidative stress (OS) from the fresh capillary blood of all participants by the use of CR 3000 instrument (free oxygen reactive measurement (FORM) system, Catellani Group, Callegari S.p.A, Parma, Italy). The principle of the test depends mainly on transition metals, such as iron catalyzes the breakdown of hydroperoxides into related active free radicals which measured at a wavelength (λ; 505 nm) as shown previously[2].

TABLE 1. CHANGES IN DEMOGRAPHIC VARIABLES, PHYSICAL ACTIVITY, WISC-IQ, AND BOT-2 SCORES OF THE STUDIED SUBJECTS FOLLOWING 12-WEEKS OF SUPERVISED AEROBIC TRAINING INTERVENTIONS (N= 85; MEANS ± SD).

Parameters	Normal (n=25; 29.4%) (IQ= 90-114)		Mild ID (n=23; 38.3%) (IQ=50-70)		Moderate ID (n=37; 61.7%) (IQ=35-49)	
	Pre	Post	Pre	Post	Pre	Post
Boys/Female	20/5	20/5	18/5	18/5	20/17	20/17
Age (years)	15.6 ± 1.8	15.6 ± 1.8	15.8 ± 2.8	15.8 ± 2.8	16.1 ± 3.0	16.1 ± 3.0
BMI (kg/m^2)	21.6 ± 3.5	21.2 ±2.5*	29.2 ± 2.6	22.6 ±1.8**	31.6 ± 1.5	27.6 ± 4.7**
Waist (cm)	78.5 ± 8.3	76.5 ±5.8*	103.9 ± 12.5	98.5±7.3**	108.5 ± 3.8	100± 8.3**
Hips (cm)	96.8 ± 3.4	92.6± 3.8*	82.3± 12.4	76.9 ± 3.2*	77.5 ± 16.4	74.9 ± 3.9*
WHR	0.81±0.09	0.78±0.12*	1.26±0.12	0.96±0.14*	1.4±0.15	1.1±0.16*
Systolic BP (mmHg)	126.5 ±3.6	120 ± 3.9*	115.6 ± 12.3	108 ± 4.6*	120.3 ± 5.7	112 ± 4.1*
Diastolic BP (mmHg)	72.8 ±12.4	71.8 ±12.8	87.5± 7.6*	82.9±16.4*	89.5± 11.2	87.9 ± 15.4*
FBS (mg/dl)	81.2± 2.7	78.6± 3.2*	90.1± 4.2	86.6±3.6**	98.1± 3.5	82.8± 1.5**
HbA1c (%)	2.5 ± 0.15	2.1± 0.18*	2.9 ± 1.2	2.6 ± 0.18*	3.1 ± 0.96	2.9 ± 0.15**
Physical activity (PA):						
VO_2 max (ml/kg*min)	38.7 ± 6.1	45.7±3.2**	21.6 ± 1.8	33.8 ± 2.9**	18.8 ± 3.8	28.2±5.3**
BMR (kcal/day)	2.95±3.65	3.9±2.8*	1.73 ± 2.54	2.1±4.8**	1.38 ±2.4	3.5±5.4**
TEE (kcal/day)	4.59 ± 6.4	7.85±4.5*	2.64 ± 4.5	4.65± 3.5**	2.15 ± 1.3	4.35± 5.8**
PA scores	3.9±2.1	5.8±2.5*	1.96 ± 1.3	2.6±1.8**	1.5 ±1.3	2.9±1.4**
WISC- IQ test scores	91.2 ± 2.1	102± 3.7*	51.3 ± 3.7	72.8 ± 4.5**	37.8 ± 5.1	58.2±6.5**
BOT-2 test scores:						
Fine motor precision	35.7 ± 3.5	41.4± 1.8*	21.4±8.0	28.8 ± 3.5**	15.4 ± 3.7	21.8 ± 3.6***
Fine motor integration	43.2± 3.1	58.4±2.98*	25.3±6.7	31.5 ±3.9**	12.3 ±3.7	18.1 ±2.6**
Manual dexterity	30.5 ± 2.7	36.5± 4.1*	10.5 ± 3.4	18.9 ± 2.9*	8.7 ± 2.4	15.4 ± 3.1*
Bilateral coordination	11.8± 1.85	25.9±352*	13.4 ± 1.8	22.7 ± 4.8**	9.5 ± 2.1	16.7 ± 4.6*
Balance	29.3 ± 2.6	35.1± 2.9*	18.9 ± 4.7	28.1 ± 3.9**	16.3 ± 4.3	24.1 ± 3.5*
Running speed & agility	26.1 ± 5.3	35.1± 3.1*	16.5 ±2.9	22.5 ±2.4**	11.6 ±3.5	17.5 ±3.5**
Upper limb coordination	23.7 ± 2.4	31.9± 4.2*	15.7±5.3	21.3 ± 1.5**	12.3±2.5	15.7 ± 2.5**
Strength	10.6 ±6.3	13.1±5.3*	9.7±4.7	11.4 ±5.6**	8.7±3.7	16.2 ±4.5**
Total Composite Score	48.8 ±3.4	56.6±5.8*	32.7±4.2	39.8 ±3.4**	23.6 ± 3.5	31.4 ± 2.6**

Values are expressed as mean ±SD; *p < 0.05, **p < 0.01, ***p < 0.001. Significance at p < 0.05. BMI: body mass index; WHR: waist to hip ratio; VO2 max: maximal oxygen uptake; FBS: fasting blood sugar; HbA1c: Glycated hemoglobin; BMR: basal metabolic rate (kcal/day); TEE: total energy expenditure (kcal/day); WISC- IQ: Wechsler Intelligence Scale test; BOT-2 test: Bruininks-Oseretsky Test of Motor Proficiency- Second Edition.

Estimation of nitric oxide levels (NO)

Nitric oxide (NO) concentrations were evaluated as nitrate and nitrite in all serum samples of the participants by the use of a Griess reagent as a chromophore agent. The developed color was estimated at a wavelength of (λ; 540 nm) using high-performance liquid chromatography assay and the NO concentration was determined as previously reported[2,18-20].

Estimation of Malondialdehyde (MDA) and 8-Hydroxyguanine (8-OHdG)

Malondialdehyde was estimated in the serum of the participants as a quantitative measure of lipid peroxidation using high-performance liquid chromatography as mentioned previously[2,18,19]. Serum 8-OHdG as an oxidative biomarker of DNA damage was evaluated using immunoassay ELISA kit (DNA Damage ELISA Kit, Product #: EKS-350, Stressgen Co., USA) as reported previously[19].

Estimation of total antioxidant capacity (TAC)

Serum samples of all participants obtained pre- and post-exercise sessions were subjected for the estimation of total antioxidant capacity (TAC) by the use of colorimetric assay kit (K274-100; BioVision, Milpitas, CA, USA). The antioxidant activity was measured as a function of Trolox concentration at a wavelength of (λ; 570 nm) as previously reported[18,19].

Statistical Analysis

The analyses of data were performed using SPSS version 17 and were expressed as mean ± SD. Both student's-test and Pearson's correlation coefficient were used to investigating the comparison and correlation of the studied oxidative variables with ID and motor skills of all participants' pre-and post-exercise sessions. The data was significant at P values <0.05.

RESULTS

A total of 85 school children aged 12–18 years were randomly recruited in this study. Based upon WISC-intelligence quotients (IQ) measurements, about 29.4 % of the participants (n=25) had normal IQ score of (90-114) with mean 91.2±2.1 WISC-IQ score, and 70.6% of the study population (n=60) diagnosed with intellectual disability; they were classified into mild IQ (score 50-70) and moderate (score 35-49) as shown in table (1). A significant increase ($p<0.01$) in body mass index (BMI) and waist to hip ratio (WHR) and decrease ($p<0.01$) in VO2 max, BMR, and TEE were reported in participants with mild and moderate ID compared to other normally group. Also, significant improvement in adiposity markers; waist, hip, BMI, WHR, and sugar parameters (FBS and HbA1c (%) were reported following interventions of supervised aerobic training (table 1).

The effects of supervised aerobic exercise on intellectual disability and total motor performance were reported in all participants. The data showed significant improvement in total WISC- IQ and BOT-2 test scores in schoolchildren with normal IQ ($p<0.05$), and those with mild ($p<0.01$),and moderate ($p<0.01$) intellectual disability (ID) respectively following 12 weeks of aerobic training compared to pre-test baseline data (Table 1) and figure (1A).

The influence of supervised aerobic training on BOT-2 scores was significantly ($p<0.01$) apparent in the improvement of specific areas of fine motor precision, running speed and agility, upper limb coordination, and strength while slightly moderate enhancement ($p<0.05$) was detected for the specific areas of bilateral coordination, and balance (Table 1) and figure (1B)..

In this study, energy expenditure rates (EER), BMR, and VO2 max were evaluated as fitness scores among the participants. There was significantly improvement in the level of PA fitness scores among subjects with normal, mild, and moderate ID following 12 weeks of aerobic training compared to pre-test baseline data (Table 1) and figure (1C). Similarly, oxidative stress makers TAC, OS, MDA, NO, and 8-OHdG were assessed in this study. There was a significant reduction in the levels of OS, MDA, NO, 8-OHdG, and increase in the levels of TAC in normal ($p=0.05$), mild ($p=0.01$), and moderate ($p=0.01$) ID subjects following interventions of supervised aerobic training Figure (1D, 1E, and 1F).

Also, the data showed that the improvements in motor performance among participants with mild and moderate ID correlated positively with TAC, TEE, physical fitness scores, and negatively with BMI and other stress biomarkers, OS, MDA, NO, and 8-OHdG respectively (Table2). stepwise multiple regression analysis revealed that, Body mass index (BMI), age, gender, total BOT-2 scores, total oxidative stress, MDA, NO, and 8-OHdG concentrations, TEE, and PA fitness explained around 78.0 to 93.4 % of intellectual disability variation among school children (Table 2).

DISCUSSION

Lower physical activity and sedentary lifestyles were reported among adolescents and children with intellectual disability (ID) than normal subjects[1,2,6,7].

Although, the participation of subjects with ID in exercise interventions with different intensities which positively helps in improving of motor performance parameters, daily activities and quality of life[18,21,22], still the effective role of oxidative stress on intellectual ability and its correlation with both exercise training and motor performance is not fully elucidated in school children which was our concern in this current study.

In the present study, intellectual ability among 65 school children aged 12-18 years was performed using WISC- IQ score. About 70.6% of the study population (n=60) diagnosed with intellectual disability;

TABLE2. BETA COEFFICIENTS AND CUMULATIVE R^{2*} VALUES DERIVED FROM STEPWISE MULTIPLE REGRESSION MODELS OF THE STUDIED DEMOGRAPHIC, PHYSICAL FITNESS, AND MOTOR PERFORMANCE SCORES (BOT-2 TEST) AMONG SCHOOL CHILDREN WITH ID (N=60)

Variables	Intellectual disability (WISC- IQ score), n=60	
	Mild (n=23), $R^2(\beta)$ *	Moderate (n=37), $R^2(\beta)$ **
Age	12.7 (0.35)	14.6 (0.45)
Gender	4.8 (0.16)	6.7 (0.28)
BMI (kg/m2)	-5.1 (0.18)	-8.4 (0.250)
Total BOT-2 scores	18.9(0.32)	17.9(0.45)
OS (mmol/l H2O2)	-4.9(0.12)	-6.2 (0.18)
MDA (nmol/dl)	-3.7(0.11)	-5.2(0.14)
NO (nmol/dL)	-5.9(0.14)	-7.4 (0.17)
8-OHG (ng/ml)	-2.9(0.16)	-4.1(0.21)
TAC (nmol/µl)	11.5 (-0.22)	12.9 (-0.15)
Physical fitness score (VO2 max)	3.7 (-0.38)	5.8 (-0.42)
TEE(kcal/day)	3.9(-0.17)	4.2(-0.27)
ΣR2 (%)	78%	93.4 %

Data presented as coefficient (R); *significance at p <0.01; **significance at p <0.001; BMI: body mass index; OS: total oxidative stress; MDA: Malondialdehyde; NO: nitric oxide; 8-OHdG: 8-Hydroxyguanine; TAC: total antioxidant capacity; VO2 max: maximal oxygen uptake; TEE: total energy expenditure (kcal/day).

they were classified into mild IQ (score 50-70) and moderate (score 35-49). A significant increase (BMI) and (WHR) and decrease in VO2 max, BMR, and TEE were reported in participants with mild and moderate ID compared to the normal groups. Consistent to our study, others reported higher rates of obesity and lower performance in physical fitness scores among individuals with intellectual disability[2-4,12-17]. In the same line, a significant correlation was reported between BMI, gender, age, physical fitness scores with levels of intellectual disability[20-22].

In the subjects with mild to moderate ID, oxidative stress-free radicals; T-OS, MDA, NO, 8-OHdG significantly increased and TAC activity significantly decreased. In support of our results, free radical oxidative stress was reported to play a pivotal role in most neurodegenerative brain disorders resulting from the side effects of drugs, lower physical activity, and poor diet[2,7-17]. Also, the severity of oxidative stress among participants with ID may be due to lack of physical activity, a mental disability which may be associated with free radicals oxidative cell damage and decrease in the antioxidants[13-16,20,21].

The decline in motor skills and brain functions were significantly reported in association with a lack of physical fitness in handling, precision of movements and motor activity[2,18-24].

The current study reported that there was a significant decrease in motor skills among schoolchildren with mild and moderate ID. The data showed an agreement with others[20-24], who reported a significant decline in both the intellect and the development of motor skills among children aged (7-12 years) with different mental retardation or disabilities. Also, the impairment in motor skills as measured by BOT-2 score test showed a significant correlation with higher

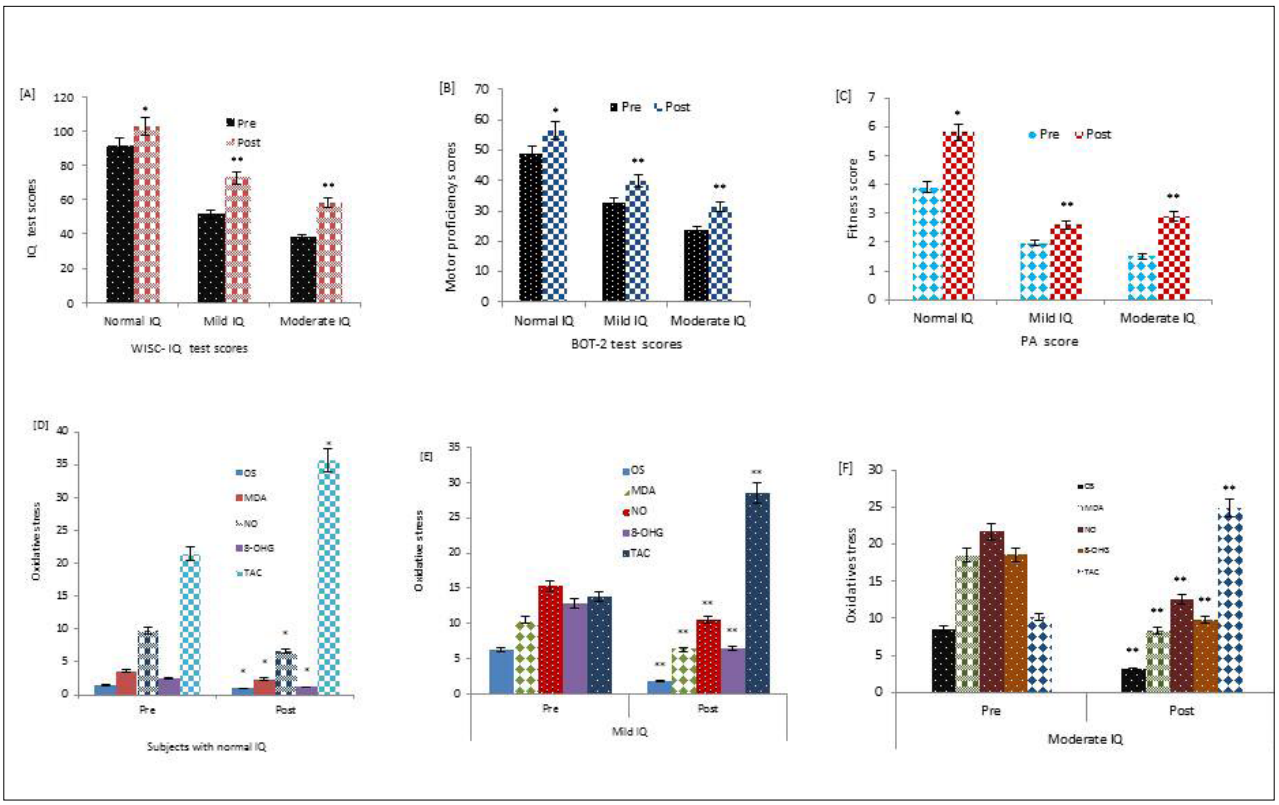


FIGURE 1: Changes in physical activity, of oxidative stress, WISC-IQ, and BOT-2 scores of the studied subjects following 12-weeks of supervised aerobic training interventions (n= 85; means ± SD). In this study, there was significant improvement in IQ scores [A]; motor proficiency scores [B]; and fitness scores [C] in normal (p=0.05), mild (p=0.01), and moderate (p=0.01) participants following 12-weeks of supervised aerobic training interventions. Similarly, there was significant reduction in the levels of OS, MDA, NO, 8-OHdG, and increase in the levels of TAC in normal (p=0.05), mild (p=0.01), and moderate (p=0.01) IQ subjects flowing interventions of supervised aerobic training.
Values are expressed as mean ±SD; *p < 0.05, **p < 0.01, ***p < 0.001. WISC- IQ: Wechsler Intelligence Scale test; BOT-2 test: Bruininks-Oseretsky Test of Motor Proficiency- Second Edition; OS: total oxidative stress; MDA: Malondialdehyde; NO: nitric oxide; 8-OHdG: 8-Hydroxyguanine; TAC: total antioxidant capacity; TEE: total energy expenditure (kcal/day); VO2 max: maximal oxygen uptake. Significance at p<0.05

values of adiposity markers; BMI, WHR, oxidative stress parameters, and lower physical fitness scores in schoolchildren with mild and moderate ID compared with a control group of standard IQ which consistently supported previously[12,17,22].

Previous research studies showed improvement in physical activity such as balance, strength, endurance and health self-perception along with a decrease in adiposity markers among participants with mild disability following participation in exercise programs[20-24].

However, rare data were found about supervised aerobic exercise programs and their influence on oxidative stress, motor skills, and IQ scores among schoolchildren with ID. So, the present study investigated the effects of 12-week aerobic training of moderate-intensity on ID, physical activity, motor skills, and oxidative stress in schoolchildren. The data obtained showed a significant improvement in intellectual abilities as measured by WISC- IQ score of all participants with mild and moderate ID following 12-week of moderate exercise interventions. Also, the influence of exercise was observed in the improvements of motor skills (BOT-2 scores), increase in TAC, physical fitness, and a reduction in all oxidative stress-free radicals; OS, MDA, NO, and 8-OHdG in all participants following exercise interventions for 12- weeks.

Previously, it was reported that targeted physical exercise programs significantly affects on physical fitness and enhance of IQ scores among children with ID[2,18-21]. Also, 10-week aerobic exercise interventions were shown to have positive beneficial effects on physical fitness score, exercise capacity, IQ scores, and an increment in maximum oxygen uptake (VO2 max)[21-23].

Finally, our study showed that motor skills (BOT-2) and IQ scores correlated positively with BMI, WHR, physical fitness, TAC, TEE variables, and negatively with oxidative markers OS, MDA, NO, and 8-OHdG. Also, motor skills such as motor precision, running speed, agility, upper limb coordination, strength, bilateral coordination, and balance were significantly improved in school children following 12-week of aerobic exercise. The data matched with recent research works which reported a significant link between motor skills and brain function developments with active physical performance[2,12-17], and that moderate aerobic exercise has a positive antioxidant effect on brain disorders via modulating the release of oxidative stress biomarkers[3-5,21-24]. Finally, stepwise multiple regression analysis of these parameters along with age and gender explained around 78.0 to 93.4 % of intellectual disability variation among school children.

The results of this study strengthen and signifying enclosure of physical exercise interventions, particularly those of a supervised training program to improve intellectual ability via improving physical fitness, motor skills proficiency and modulating redox status. In addition modulating redox status might be considered as diagnostic non-invasive predictors of intellectual abilities for clinical use in epidemiological contexts; however, further studies with larger sample size and studying gender influence are significantly required.

In conclusion, moderate aerobic training for 12 weeks has a positive impact on improving intellectual ability via improving physical fitness, motor skills proficiency, and modulating redox status of schoolchildren with intellectual disability.

Ethics approval and consent to participate

Based on the ethical guidelines of the 1975 Declaration of Helsinki, the study protocol was reviewed and approved by ethical committee of Rehabilitation Research Chair (RRC), King Saud University, Kingdom of Saudi Arabia, under file number ID: RRC-2014-014. Prior to data collection, written informed consent was obtained from the parents of all participating schoolchildren

Authors' Contributions

Research idea, design, and practical work were proposed by GSA. Review of literature was done by AHA. GSA executed data collection and analysis. Manuscript preparation and submission was done by GSA.

Acknowledgement/Funding

The authors are grateful to the Deanship of Scientific Research, King Saud University for funding through Vice Deanship of Scientific Research Chairs

Competing interests:

The authors declare that they have no competing interests.

RESUMO

OBJETIVO: *A baixa aptidão física e o baixo desempenho motor mostraram-se associados a níveis mais altos de estresse oxidativo em crianças e adolescentes com deficiência intelectual. Portanto, foi realizado um exercício aeróbico moderado por 12 semanas para avaliar os efeitos dos escores de atividade física nas funções motoras, estresse oxidativo e quocientes de inteligência (QI) em escolares com deficiência intelectual.*

MÉTODOS: *Um total de 65 crianças em idade escolar (12 a 18 anos) foi incluído aleatoriamente neste estudo. A incapacidade intelectual (DI), habilidades motoras, aptidão física (VO2máx), gasto energético total (ETE), MDA, 8-OHdG, TAC, NO e estresse oxidativo total (SG) foram avaliados pelo teste de pontuação Wisc-IQ pré-validado, teste BOT-2, questionário de PA e técnicas de imunoensaio, respectivamente.*

RESULTADOS: *Os escores do conjunto Wisc-IQ e BOT-2 do desempenho das habilidades intelectuais e motoras mostraram uma correlação significativa com o status da atividade física e a regulação dos radicais livres do estresse oxidativo em escolares com DI leve e moderada após 12 semanas de exercício moderado. O desempenho das habilidades intelectuais e motoras dos participantes correlacionou-se positivamente com o aumento dos escores de atividade TAC e aptidão física e negativamente com MDA, 8-OHdG, NO e Total-OS, respectivamente. Houve uma melhora significativa nas habilidades motoras, como áreas específicas de precisão motora fina, velocidade de corrida, agilidade, coordenação de membros superiores, força, coordenação bilateral e equilíbrio entre crianças em idade escolar após o programa de exercícios. A análise de regressão múltipla passo a passo dos parâmetros demográficos, do estado físico e do estresse oxidativo explicou em torno de 78,0 a 93,4% da variação da incapacidade intelectual entre os escolares.*

CONCLUSÃO: *O treinamento aeróbico moderado por 12 semanas tem um impacto positivo na melhoria da capacidade intelectual de escolares com DI por meio da modulação do status redox, melhora da aptidão física e proficiência em habilidades motoras.*

PALAVRAS-CHAVE: *Aptidão física. Exercício. Deficiência intelectual. Estresse oxidativo. Atividade motora. Desempenho psicomotor.*

REFERENCES

1. Kilgour AH, Starr JM, Whalley LJ. Associations between childhood intelligence (IQ), adult morbidity and mortality. Maturitas. 2010;65(2):98-105.
2. Carmeli E, Imam B, Bachar A, Merrick J. Inflammation and oxidative stress as biomarkers of premature aging in persons with intellectual disability. Res Dev Disabil. 2012;33(2):369-75.
3. Lima-Cabello E, Garcia-Guirado F, Calvo-Medina R, el Bekay R, Perez-Costillas L, Quintero-Navarro C, et al. An abnormal nitric oxide metabolism contributes to brain oxidative stress in the mouse model for the fragile X syndrome, a possible role in intellectual disability. Oxid Med Cell Longev. 2016;2016:8548910.
4. Michel T, Vanhoutte PM. Cellular signaling and NO production. Pflugers Arch. 2010;459(6):807-16.
5. Frackowiak J, Mazur-Kolecka B, Schanen NC, Brown WT, Wegiel J. The link between intraneuronal N-truncated amyloid - peptide and oxidatively modified lipids in idiopathic autism and dup (15q11.2-q13)/autism. Acta Neuropathol Commun. 2013;1:61.
6. Lam HMY. Assessment of preschoolers' gross motor proficiency: revisiting Bruininks-Oseretsky Test of Motor Proficiency. Early Child Development and Care. 2011;181(2):189-201.
7. Abdullah B, Jaafar WMW, Ayub AFM. The development of gross motor analysis system software: a preliminary concept. Procedia- Social and Behavioral Sciences. 2012;64:501-6.
8. Aaltonen S, Latvala A, Rose RJ, Pulkkinen L, Kujala UM, Kaprio J, et al. Motor development and physical activity: a longitudinal discordant twin-pair study. Med Sci Sports Exerc. 2015;47(10):2111-8.
9. Pitetti KH, Beets MW, Combs C. Physical activity levels of children with intellectual disabilities during school. Med Sci Sports Exerc. 2009;41(8):1580-6.
10. Westendorp M, Houwen S, Hartman E, Visscher C. Are gross motor skills and sports participation related in children with intellectual disabilities? Res Dev Disabil. 2011;32(3):1147-53.
11. Aouadi R, Nawi Alanazi HM, Tim G. Impact of physical exercise on reactive time and cognitive function in mentally deficient adolescents. J Clin Trials. 2015;5(1):206.
12. Lista I, Sorrentino G. Biological mechanisms of physical activity in preventing cognitive decline. Cell Mol Neurobiol. 2010;30(4):493-503.
13. Krick J, Murphy PE, Markham JF, Shapiro BK. A proposed formula for calculating energy needs of children with cerebral palsy. Dev Med Child Neurol. 1992;34(6):481-7.
14. Fleisch A. Basal metabolism standard and its determination with the "metabocalculator". Helv Med Acta. 1951;18(1):23-44.
15. Canivez G, Watkins M. Exploratory and higher-order factor analyses of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) adolescent subsample. School Psychology Quarterly. 2010;25(4):223-5.
16. Wechsler D. WAIS-IV: administration and scoring manual. Minneapolis: NCS Pearson Inc.; 2008.
17. Bruininks RH, Bruininks BD. Bruininks-Oseretsky test of motor proficiency. 2nd ed. Windsor: NFER-Nelson; 2005.
18. Carmeli E, Imam B, Bachar A, Merrick J. Inflammation and oxidative stress as biomarkers of premature aging in persons with intellectual disability. Res Dev Disabil. 2012;33(2):369-75.
19. Alghadir AH, Gabr SA, Al-Eisa ES. Effects of moderate aerobic exercise on cognitive abilities and redox state biomarkers in older adults. Oxid Med Cell Longev. 2016;2016:2545168.
20. Alghadir AH, Gabr SA, Anwer S, Al-Eisa E. Fatigue and oxidative stress response to physical activity in type 2 diabetic patients. Int J Diabetes Dev Ctries. 2016;36:59-64.
21. Top E. The effect of swimming exercise on motor development level in adolescents with intellectual disabilities. Am J Sports Science Med. 2015;3(5):85-9.
22. Lotan M, Isakov E, Kessel S, Merrick J. Physical fitness and functional ability of children with intellectual disability: effects of a short-term daily treadmill intervention. Scientific World J. 2004;4:449-57.
23. Wu CL, Lin JD, Hu J, Yen CF, Yen CT, Chou Y L, et al. The effectiveness of healthy physical fitness programs on people with intellectual disabilities living in a disability institution: six-month short-term effect. Res Dev Disabil. 2010;31(3):713-7.
24. Golubović Š, Maksimović J, Golubović B, Glumbić N. Effects of exercise on physical fitness in children with intellectual disability. Res Dev Disabil. 2012;33(2):608-14.
25. Khalili MA, Elkins MR. Aerobic exercise improves lung function in children with intellectual disability: a randomised trial. Aust Physiother. 2009;55(3):171-5.

ORIGINAL ARTICLE

Measles epidemiological profile in Brasil from 2013 to 2018

Natália Rodrigues Costa[1]
Rafaella Menegazzo Oneda[1]
Cecília Albertoni Rohenkohl[1]
Leonardo Saraiva[2]
Luciana Kase Tanno[3]
Cíntia Bassani[4,5]

1. Acadêmica de Medicina do Instituto Meridional (Imed), Passo Fundo, RS, Brasil
2. Cirurgião-dentista. Mestrando em Envelhecimento Humano da Universidade de Passo Fundo (UPF), Passo Fundo, RS, Brasil
3. Division of Allergy, Department of pulmonology, University Hospital, Montpellier, France and Sorbonne University, Imserm, Iplep, Epar team, Paris, France
4. Médica pediatra, alergista e imunologista, Mestra em Ciências da Saúde pelo Hospital Servidor Público Estadual de São Paulo (Iamspe), São Paulo, SP, Brasil
5. Docente do Instituto Meridional (Imed), Passo Fundo, RS, Brasil

http://dx.doi.org/10.1590/1806-9282.66.5.607

SUMMARY

BACKGROUND: *To determine the epidemiological profile of measles in Brasil from 2013 to 2018, and to evaluate the possible association between increased number of cases and vaccination coverage.*

METHODS: *This is an observational, descriptive, cross-sectional, retrospective study with quantitative approach, carried out through analysis of secondary data collected through the Notifiable Diseases Information System (SINAN), in the National Immunization Program (PNI).*

RESULTS: *The total number of reported cases was 10,886, with the year 2018 having the highest number (10,185). In the North macro-region (93.4%), male (55.53%), autochthonous cases from the city of residence (94.42%) and laboratory confirmation (99.09%) predominated. Regarding the age group, it was observed that in the period from 2013 to 2015 the highest prevalence occurred in <1 year, with 44.5%, 40.6% and 29.0%, respectively, while in 2018, the highest rate was in the 20-29 age group with 24.2%. Vaccination coverage was below 95%, except for SCR - D1 (first dose of triple viral) in the years 2013 to 2016. Regarding the outcome, there was a limited number of deaths secondary to measles (0.12%).*

CONCLUSIONS: *There was an exponential growth in the number of measles cases in Brasil in 2018, which represents a public health problem. In view of this, it is necessary to implement measures such as broad vaccination coverage and sanitary control at the borders, in order to reduce the incidence of this disease and, consequently, the number of deaths.*

KEYWORDS: *Measles. Morbillivirus. Incidence. Emigration and Immigration. Vaccination coverage.*

INTRODUCTION

Measles is an acute, transmissible and extremely infectious contagious, exanthematic disease. It is one of the major causes of morbimortality among children under five, especially in those countries where the per capita income is low, and the healthcare system is precarious. It is estimated that around 90% of non-immune people, when exposed to an infected individual, may contract the disease[1]. According to the World Health Organization (WHO), more than 20 million people are vulnerable to the disease every year, and, among those, 30% have the risk of developing complications[2,3].

DATE OF SUBMISSION: 04-Dec-2019
DATE OF ACCEPTANCE: 08-Dec-2019
CORRESPONDING AUTHOR: Leonardo Saraiva
BR 285 – Passo Fundo – Rio Grande do Sul -Brasil – 99052-900 - Tel:+55 54 33168384
E-mail: leo77saraiva@hotmail.com

Measles virus belongs to the *Morbillivirus* genus within the *Paramyxoviridae* Family[4], and it spreads directly between individuals – within four days amidst rash onset, up to four days after – via airborne respiratory droplets, aerosols and direct contact with nasal and throat secretions, and/or ocular mucosa. The incubation period ranges from 10 to 14 days, when the symptoms onset[5,6]. The initial symptoms (prodrome) are malaise, productive cough, ocular and nasal coryza, conjunctivitis, photophobia and growing fever – up to 40°C (104°F)[7].

Thus, the cervical and intra-abdominal lymph nodes can get slightly enlarged, which may lead the patient to report pain. At the end of the prodromal phase, that is, in the last 24 hours of it, Koplik spots can be seen in the premolars region: tiny white papules with a red halo – measles pathognomonic sign – which usually lasts for a short amount of time in the second phase of the disease[6]. The exanthematic phase is characterized by maculopapular rash, that intersect with areas of normal skin, and is distributed in cephalocaudal direction to the extremities, lasting five to six days[8]. After this period, the fever declines, the rash starts to fade and a thin peeling of the skin may occur – convalescence phase[9].

On the other hand, measles can cause severe manifestations, depending on the viral load and on the infected individual's immune system[3]. Diarrhea is the most common complication, and it may lead to reduced nutritional status and to dehydration[10]. However, pneumonia is responsible for 5% to 10% of children's deaths[11]. Blindness, otitis, encephalitis, acute disseminated encephalomyelitis and subacute sclerosing panencephalitis may also occur[12]. It should be noted that pregnant women, when contracting the *Morbillivirus* during pregnancy, carry increased risk for neonatal low birth weight, fetal malformation, spontaneous abortion, intrauterine fetal death, maternal death and premature birth[13].

Because of that, the Ministry of Health recommends that two blood samples must be collected between the first and the twenty-eighth day of the rash onset. Serological tests are performed in the acute phase of the disease to detect IgM antibodies in the blood and to provide viral identification. Serology is, therefore, extremely important to obtain a differential diagnosis, since diseases like rubella, exanthema subitum (roseola infantum) and scarlet fever present with similar systemic manifestations[14], while viral identification detects the genetic pattern of the circulating virus in the country, differentiating the wild from vaccine-derived virus, as well as the autochthonous from exogenous cases. In order to perform the viral genotyping, the samples must be obtained until the fifth day of the rash onset, preferably within the first three days[14].

There is no specific treatment to measles, only supportive measures to patients, especially to those who develop complications. The pivotal prevention and eradication measure is to vaccinate the susceptible population, and a high maintenance of vaccinal coverage is necessary – equal or greater than 95% - to reduce the possibility of the disease[15]. Hence, the Ministry of Health recommends the administration of a dose of the Triple Viral Vaccine (MMR – measles, mumps and rubella) at 12 months of age and a dose of Quadrivalent Vaccine (MMRV – measles, mumps, rubella and varicella) at 15 months. Nonetheless, the government recommends that during crisis periods, all children among 6 months to 11 months and 29 days should be immunized with an extra dose of MMR. Furthermore, healthcare professionals of all ages, and adults up to 29 years old are required to have two doses of the vaccine (it may be MMR or MMRV), but those older than 29 are required to have only one dose of MMR or MMRV. For those who have been exposed to the *Morbillivirus*, the vaccine should be given within the first 72 hours, so it can prevent the evolution of the disease and attenuate the clinical manifestations. Both the MMR and the MMRV vaccines are continuously available, for free, at the public healthcare network, in the entire country[8,15].

Since the year of 1968, measles has been included, for epidemiological surveillance purposes, in the Brazilian list of compulsory notifiable diseases. In the 1980s, among the infectious contagious diseases, measles was a leading cause of death in children between one and five years old. This situation led the government to implement, in 1992, the Plan for Measles Control and Elimination, which contributed with the end of autochthonous cases, last reported in the year 2000. All the confirmed cases in Brasil since then were imported or related to import – the last one was described in 2015. Therefrom, the country received, from the Pan-American Health Organization (PAHO), the Measles Eradication Certificate, in 2016[16,17].

Notwithstanding, in 2019 Brasil lost the certificate, as recent data confirm the resurgence of measles in 2018. According to the Ministry of Health, *Morbillivirus* resurgence is due to low levels of immunization, mainly as a result of the tough geographical reach, but also because of groups with misconceptions about the

risks of vaccination, religious and cultural beliefs, or immigration[16,18].

In view of the foregoing, the research of the epidemiological profile of measles in Brasil between 2013 and 2018 is extremely relevant, considering that once the deficits in public healthcare promotion policies have been identified, measures aiming the eradication of measles and the reduction of children morbimortality in the country can be implemented.

METHODS

This is an observational, descriptive, cross-sectional, retrospective study with quantitative approach. Data regarding the period between 2013 and 2018 were collected from Notifiable Diseases Information System (SINAN), National Immunization Program (PNI) and database (sent to the author's email) generated by SUS Department of Informatics (DATASUS) in association with the Department of Immunization and Communicable Diseases (DEIDT), the technical group for exanthematic diseases and the General Coordination of the National Immunization Program (CGPNI). Through them, we could observe the relation between Brazilian macro-regions and the following variables: number of confirmed cases, sex, age, coverage of the first (VC MMR - D1) and the second (VC MMR - D2) dose of Triple Viral vaccine, coverage of the Quadrivalent vaccine (VC – MMRV), number of doses of MMR – D1, MMR – D2 and MMRV, deaths, autochthonous cases in the city of residence, which state was a source of infection and the confirmation criteria of the disease.

This research includes all the confirmed cases of measles in Brazilian macro-regions among the period of 2013 to 2018, and registered by Notifiable Diseases Information System (SINAN). The unconfirmed cases were excluded.

Statistical analysis was performed using SPSS V20, Minitab 16 and Office Excel 2010 software. Because of that, the result of each comparison has a statistical variable called de p-value, which simplifies tests conclusions. This research has a significance level (the probability of rejecting the null hypothesis when it is true) of 0.05 (5%). Likewise, all of the confidence intervals in this research also met 95% of statistical confidence.

We performed the Two-Proportion Z Test, so that we could analyze the incidence of measles per 100,000 people in each macro-region, and the cases distribution of the disease in the country in each year based on sex, age, autochthonous cases of the city of residence and confirmation criteria. This test allows us to know whether the variables are valid or repeatable. We also performed the Analysis of Variance Test (ANOVA) – to compare the variance within each sample relative to the variance between the samples – so we could observe the statistical mean of vaccine coverage in each macro-region of the country among 2013 and 2018.

Finally, we performed the Pearson's correlation coefficient, a test that measures the statistical relationship or association between two continuous variables, so we could correlate the number of cases and incidence of measles to the vaccine coverage. If it is positive, when one variable increases, the other, the correlated one, will also increase. In case it is negative, the variables will be inversely proportional, which means that while one of them increases, the other will decrease, and vice-versa.

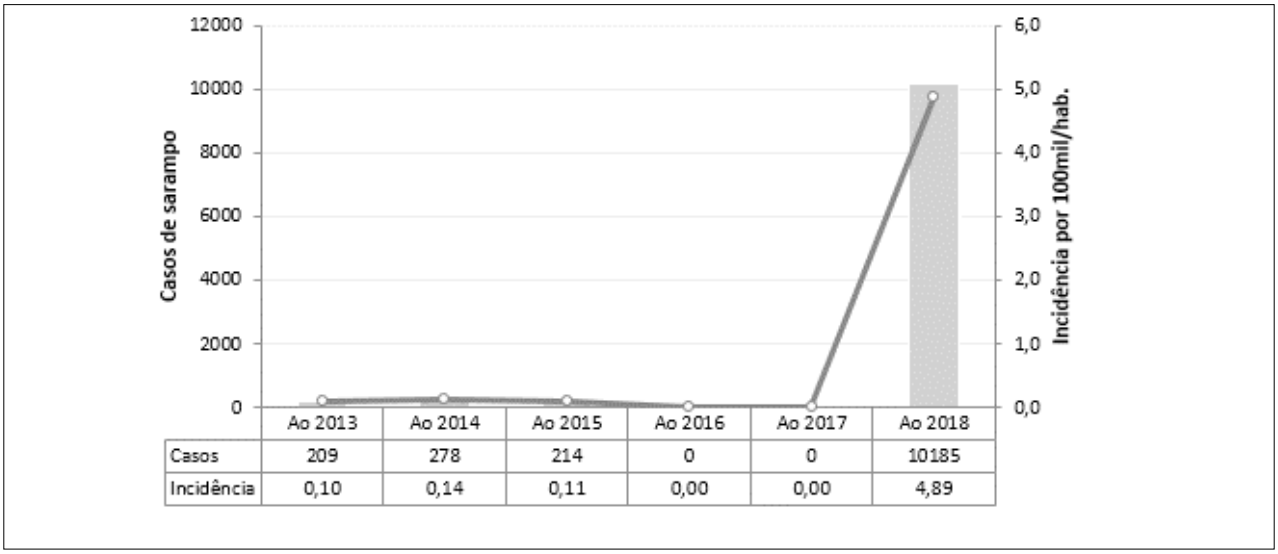
In this approach, since the data and the variables collected for this research are of public domain, and are available online at SINAN, this research is free of ethical risk, since there was no direct involvement of any individual.

RESULTS

In the years between 2013 and 2018, 10,886 cases of measles were confirmed in Brasil. Most of them were registered in 2018 (n= 10,185), followed by 2014 (n= 278), 2015 (n= 214) and 2013 (n= 209). There were no records of the disease during 2016 and 2017. When comparing the years of 2013 and 2018, we see that the incidence of measles has increased from 0.1 to 4.89 cases/100,000 people, as shown in figure 1.

Among the macro-regions, the prevalence was higher in the North (n= 10,168), followed by the Northeast (n= 678), Southeast (n= 28), South (n= 8) and, finally, the Midwest (n= 4) (figure 2). However, the Northeast region had higher notification rates during the years of 2013, 2014 and 2015 (n= 196, n= 266 e n= 211, respectively), indicators that, in 2018, were exceeded by the 10,164 occurrences of the North region.

Regarding the distinction by sex of the population, males represented 6,045 of the cases (55.53%), while females represented 4,841 (44.47%) of them. The individuals <1 year old, in 2013, 2014 and 2015, represented the largest group of prevalence, with rates of 44.5% (n= 93), 40.6% (n= 113) e 29.0% (n= 62) – respectively – while, in 2018, the most representative age group was between 20-29 years old, with 24.2% (n= 2,463).



	Ao 2013	Ao 2014	Ao 2015	Ao 2016	Ao 2017	Ao 2018
Casos	209	278	214	0	0	10185
Incidência	0,10	0,14	0,11	0,00	0,00	4,89

FIGURE 1. NUMBER OF CASES AND INCIDENCE OF MEASLES IN BRASIL BETWEEN 2013 AND 2018.

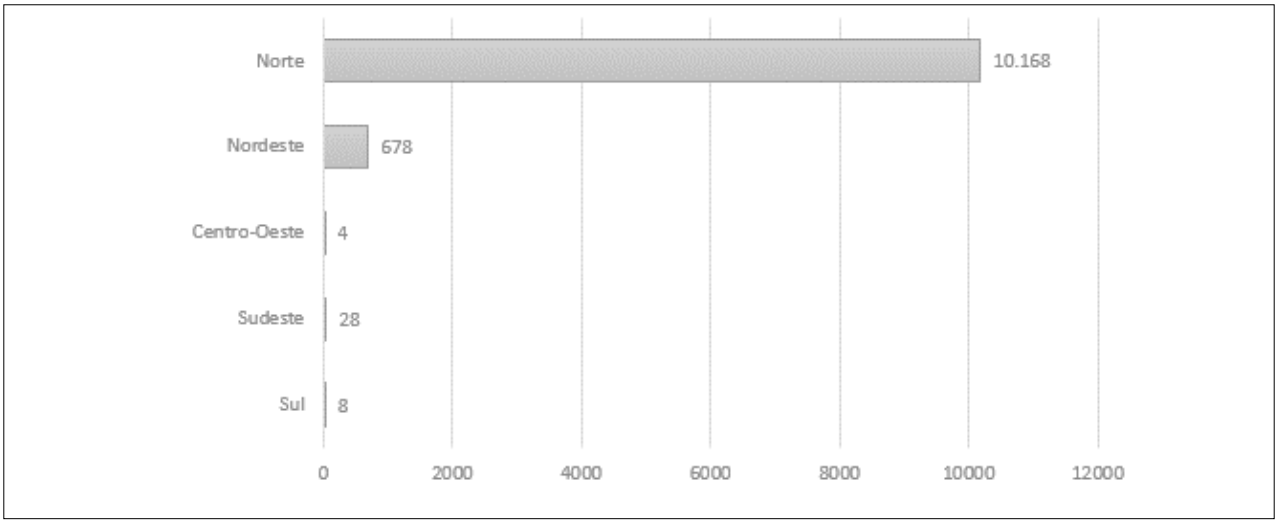
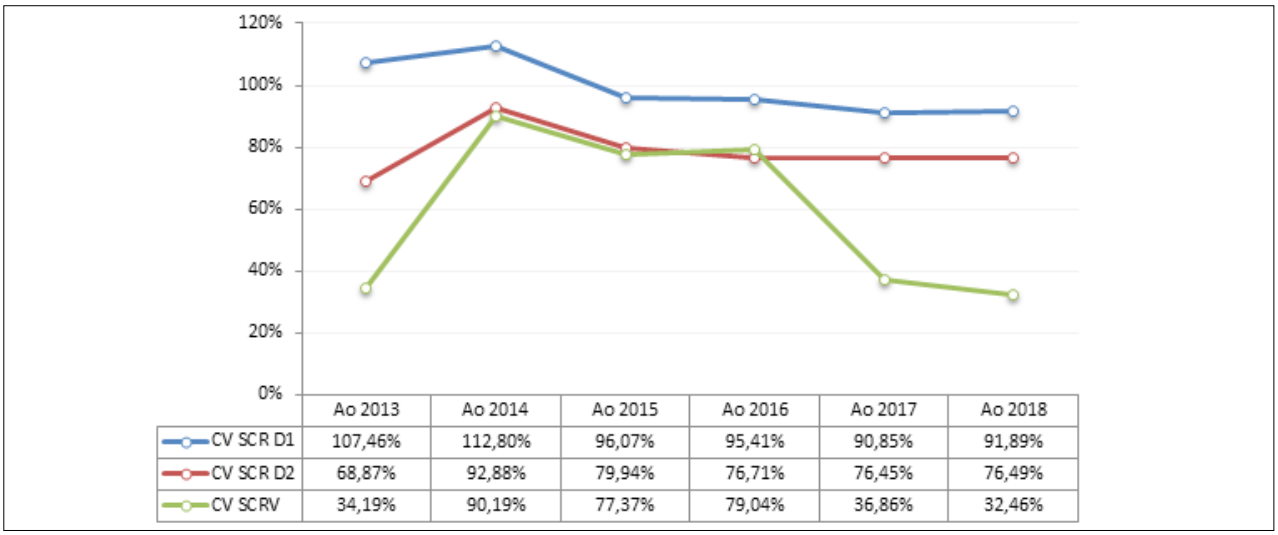


FIGURE 2. BRAZILIAN MACRO-REGIONS AND THE INCIDENCE OF MEASLES IN THE COUNTRY BETWEEN 2013 AND 2018.



	Ao 2013	Ao 2014	Ao 2015	Ao 2016	Ao 2017	Ao 2018
CV SCR D1	107,46%	112,80%	96,07%	95,41%	90,85%	91,89%
CV SCR D2	68,87%	92,88%	79,94%	76,71%	76,45%	76,49%
CV SCRV	34,19%	90,19%	77,37%	79,04%	36,86%	32,46%

FIGURE 3. COVERAGE OF TRIPLE VIRAL AND QUADRIVALENT VACCINES IN BRASIL BETWEEN 2013 AND 2018.

Concerning MMR – D1, MMR – D2 and MMRV vaccine coverage, each and every region showed better results in 2014, with rates of 112.8%, 92.88% and 90.19%, respectively. In contrast, one of the worst immunization rates happened in 2018 (Figure 3).

Alongside, the relation between vaccine coverage and measles incidence does not follow a simple pattern. In 2013, while the Northeast was the macro-region with the highest rate of cases (n= 196), it also was the macro-region with the second-best vaccine coverage for MMR – D1 (111.99%). In the South, region with the lowest rates of incidence (n= 1), the rates of immunization were considered the third best (107.25%). During 2014, the Northeast still had the highest rates of cases (n= 266) and the second-best vaccine coverage (116.38%). In comparison, Midwest had the lowest rates of incidence (n=2) and the best rates of vaccine coverage (122.52%). In 2015, the Northeast was the region with highest notification rates (n= 211) and it was ranked third regarding vaccine coverage (95.31%), while the North had the lowest rates of cases (n=1) and immunization (85.60%). In 2018, an atypical year, the North region had the highest incidence rates (n= 10,164), and the lowest vaccine coverage (84.41%), and the Northeast had the lowest rates of records (n= 5), and the second-best rate of immunization (93.46%).

This research also analyzed whether the population affected by measles was autochthonous or not.

TABLE 1. SOCIODEMOGRAPHIC CHARACTERISTICS IN PATIENTS DIAGNOSED WITH MEASLES BETWEEN 2013 A 2018. (N= 10.886)

Variables n	2013	2014	2015	2016	2017	2018
Confirmed cases of measles						
Brasil	209	278	214	0	0	10.185
North	0	3	1	0	0	10.164
Northeast	196	266	211	0	0	5
Midwest	2	2	0	0	0	0
Southeast	10	7	2	0	0	9
South	1	0	0	0	0	7
Sex						
Male	105	162	122	0	0	5.656
Female	104	116	92	0	0	4.529
Age group						
<1 year	93	113	62	0	0	1775
1–4 years	49	55	28	0	0	1179
5–9 years	6	11	13	0	0	489
10–14 years	16	15	10	0	0	506
15–19 years	5	22	21	0	0	2107
20–29 years	23	42	49	0	0	2463
30–39 years	5	12	17	0	0	1068
40–64 years	12	8	14	0	0	598
Vaccine Dose						
MMR – D1	3.131.123	3.276.483	2.787.903	2.839.666	2.703.996	2.622.897
MMR – D2	2.006.567	2.697.831	2.319.769	2.283.169	2.275.578	2.183.221
MMRV	996.287	2.619.821	2.245.170	2.352.531	1.097.158	926.437
Death as Evolution	1	0	0	0	0	12
Autochthonous of the city of residence						
Yes	74	116	135	0	0	9.954
No	62	51	31	0	0	230
Undetermined	73	111	48	0	0	1
Confirmation criteria						
Ignored/Blank	1	4	7	0	0	1
Laboratory	196	244	188	0	0	10.159
Clinical-epidemiological	9	6	6	0	0	25
Clinical	3	24	13	0	0	0

Note: the data in this table are partial, last updated in 16-Ict-2019, and subject to changes.

We discovered that, between 2013 and 2018, there was predominance of autochthonous (n= 10,279), followed by imported (n= 374) and undetermined cases (n= 233). Most of the cases were diagnosed by laboratorial parameters (n= 10,787), followed by clinical-epidemiological (n= 46) and clinical criteria (n= 40) and Ignored/Blank (n= 13). The fact that the rates of laboratory parameters had always been above 87% during the analyzed period must be highlighted.

As for the outcome of measles in Brasil, most patients remained alive (99.88%). Only 13 infected people (n= 10,886) died during the researched period, especially in 2013 (n= 1) and in 2018 (n= 12). Finally, Table 1 is the summary of information concerning MeV-infected citizens.

DISCUSSION

According to the World Health Organization (WHO), several countries have been facing diseases outbreaks in the last few years, and all continents are dealing with the sustained increase of measles cases[19]. In Europe, the number of cases increased by 300% in just one year, going from 5,273 cases in 2016, to 21,315 cases in 2017, registering 35 deaths. In the Americas, during 2017 – year of a major measles outbreak in Venezuela – 272 *Morbillivirus* infections were confirmed, and 104 of them occurred in the country. Due to ineffectiveness in containing the transmission of the disease in 12 months, according to criteria adopted by PAHO, Venezuela has lost the Measles Eradication Certificate in 2019[19].

Undoubtedly, the global resurgence of measles, after years of eradication, can be attributed to complacency with the disease, to the dissemination in Europe of misconceptions about vaccines, to a collapsed healthcare system in Venezuela, associated to intense emigration and to low rates of immunization in Africa[20,21].

This research showed that, in Brasil, between 2013 and 218, 10,886 cases of measles were confirmed, and the year of 2018 had the highest incidence of the disease. This rate was much higher than the country had registered in 2015 – the last year in which the disease was reported. The Ministry of Health attributes this fact to the anti-vaccine movement, to the decrease of vaccinal coverage in recent years, and to viral importation[16].

It is also worth mentioning that after the implementation of the Plan for Measles Control and Elimination in Brasil, in 1992, the disease presented endemic behavior and had epidemic peaks every two to three years. In 2013, the state that confirmed the most cases was Pernambuco (n = 108), and in 2014 and 2015, it was Ceará (n = 141 and n = 165, respectively). Due to surveillance and immunization actions, no more measles reporting had occurred until 2018, when imported cases triggered severe outbreaks in Roraima (n = 355), Amazonas (n = 9.778) and other states, but with lower prevalence[16,18].

Regarding viral characterization, the D8 genotype - the same one that is circulating in Venezuela - was identified in all states in 2018, except for a notification in Rio Grande do Sul (genotype B3 – circulating virus in Europe) and another in São Paulo (genotype D8 and infected person with a history of travel to Lebanon). Thus, it can be implied that the current outbreak in the country may be related to immigration and/or emigration. In addition, both Venezuela's and Northern Brasil's vaccination coverage are below 95%, percentage recommended by the WHO for group immunization to happen, facts that could facilitate measles virus infection[1,21].

Another point concerns the distribution of confirmed measles cases by sex, in which men were the most affected, with 55.53% of notifications. This result is similar to that found by Lemos[10], 58.6%, and also by Coelho and Rivemales[14], 64%. There is still no relevant factor to explain the large difference between the number of infected men and women, however, Lemos[10] believes that males tend to neglect their health, which leads to the immunization goal not being met by males.

Regarding the age group, we noticed that, between 2013 and 2015, the highest occurrence of measles happened in children <1 year. We believe that this may be related to the neglect of immunization, mainly due to the mistaken perception that measles had been eradicated, besides to the lack of confidence in the safety of the vaccines and its erroneous association with autism, a connection refuted by studies[22]. However, in 2018, the highest prevalence was between the 20-29 years age group, with 24.2% rates. We attribute this to the fact the this population have only received one dose of the triple viral vaccine, once the Ministry of Health introduced the second dose of MMR, which offers protection around 97%, only in 2004[23].

The research also showed a gradual reduction in MMR - D1 vaccination coverage from 2014 to 2017. In 2018, though, there was an increase of 1.04%. Nevertheless, it is possible to identify a reduction in the proportionality of MMR - D1 vaccination coverage, as there

was a decrease of 8.81% in the period from 2013 to 2018. WHO considers ideal immunization the one with values above 95%. From this number, it is considered that a group immunization is created, which also protects the unvaccinated. If the unvaccinated people exceed 8%, they become a risk factor for everyone else. Based on this research, we can see that between 2017 and 2018, the coverage of Triple Viral and Quadrivalent vaccines in Brasil was below the recommended by WHO[16].

Although insufficient coverage was noted, the present study did not find any statistical significance in correlating case-incidence and immunization rate. Nevertheless, we assumed that the 8.81% reduction in vaccine coverage may be related to the increase in the number of cases in the country.

The detection of autochthonous cases in the city of residence was observed in 94.4% of the confirmations, which differs from the pattern analyzed by Faversani et al.[24], in which Brasil has not reported this type of occurrence since 2000. Similar to other studies[4,10], in order to validate measles cases - from 2013 to 2018 - the laboratory diagnostic criteria (99.09%) was used. These criteria are essential, since it allows the detection of IgM/IgG antibodies and the identification of the genetic pattern of the circulating MeV in the country – differentiating the wild from the vaccine-derived virus, and the autochthonous from the imported ones.

Most of the infected citizens evolved to the cure (99.88%), while only 0.12% died due to complications of the disease. As to location, four deaths occurred in Roraima (two Brazilians and two Venezuelans, all <5 years old) and six in Amazonas (four in <1 year old and two in the 40-64 old age group) – three residents in Manaus, two in Autazes and one in Manacapuru. In Pará, two deaths occurred in the city of Belém, both indigenous Venezuelans <1 year old[18].

Zaidi et al.[3] found that the risk of developing measles complications is 30%, with the highest incidence in children under five years old and adults over twenty years old. The results of the present research are consistent with the ones about death age found by Zaidi et al.[3]. In addition, another study published in Science Journal[25], indicated that children and adults infected with MeV become immunosuppressed for a period, since measles causes immunological amnesia of 20% to 70% of the antibody repertoire of these people, leading loss of the immunity developed for other pathogens in the past. Thus, they are more susceptible to secondary infections and, consequently, to complications and death[25].

As a limitation of the study, we highlight the secondary source of data, which may present lack of case notifications, which often ends up making some information and statistical correlations unfeasible. Nevertheless, both SINAN and PNI are essential tools for maintaining epidemiological control.

CONCLUSION

The epidemiological analysis demonstrated that between the period from 2013 to 2018, 10,886 cases of measles were confirmed in the country, and the highest incidence of the disease, in 2018, erupted in the North region, with predominance of genotype D8 - similar to the genetic sequencing circulating in Venezuela. The age group <1 year old stood out from 2013 to 2015. However, in 2018, it was the 20-29 years old that was prominent. In addition, there was a male predominance among those infected by measles virus – autochthonous of the city of residence, laboratory diagnosis, evolution to the cure and insufficient vaccination coverage rates (<95%) of both Triple Viral and Quadrivalent vaccines, in most of the years analyzed.

Based on this context, is it stated that the only way to prevent and eradicate *Morbillivirus* is through vaccination. Thus, it is essential to highlight the relevance of active immunity, especially in children under 1 year old, and in people born until 2004. Moreover, the high flow of immigrants may have contributed to the reintroduction of MeV into Brazilian territory, therefore, sanitary control should be increased and vaccination intensified at borders in order to prevent further cases of the disease and, consequently, more deaths.

Acknowledgment

To the Institute Meridional (IMED) and the Hospital do Servidor Público of São Paulo (HSPE).

Author contributions

Natália Rodrigues Costa: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Software. Rafaella Menegazzo Oneda: Formal analysis, Resources, Writing-original draft. Cecília Albertoni Rohenkohl: Methodology, Resources, Writing-original draft. Leonardo Saraiva: Conceptualization, Methodology, Writing-review & editing. Luciana Kase Tanno: Supervision, Writing-review & editing. Cintia Bassani: Conceptualization, Supervision, Writing-original draft

RESUMO

OBJETIVO: *Determinar o perfil epidemiológico do sarampo no Brasil no período de 2013 a 2018, além da possível correlação entre incidência de casos e cobertura vacinal.*

MÉTODO: *Trata-se uma pesquisa observacional, com delineamento descritivo, transversal, retrospectivo e com abordagem quantitativa, feita por meio de análises de dados secundários coletados no Sistema Nacional de Agravos de Notificação (Sinan), no Programa Nacional de Imunizações (PNI).*

RESULTADOS: *O total de casos confirmados foi 10.886, sendo o ano de 2018 com o maior número (10.185). Predominou a macrorregião Norte (93,4%), sexo masculino (55,53%), casos autóctones do município de residência (94,42%) e confirmação laboratorial (99,09%). Com relação à faixa etária, observou-se que, no período de 2013 a 2015, a maior prevalência ocorreu em <1 ano, com 44,5%, 40,6% e 29,0%, respectivamente, enquanto que, em 2018, o maior índice foi na faixa de 20-29 anos, com 24,2%. A cobertura vacinal ficou abaixo de 95%, exceto a SCR – D1 (primeira dose da tríplice viral) nos anos de 2013 a 2016. Quanto ao desfecho, houve limitado número de óbitos secundários ao sarampo (0,12%).*

CONCLUSÃO: *Verifica-se um crescimento exponencial no número de casos de sarampo no Brasil em 2018, o que representa um problema de saúde pública. Diante disso, carece que medidas como ampla cobertura vacinal e controle sanitário, nas fronteiras, sejam implementadas, a fim de reduzir a incidência dessa enfermidade e, consequentemente, o número de óbitos.*

PALAVRAS-CHAVE: *Sarampo. Morbillivirus. Incidência. Emigração e imigração. Cobertura vacinal.*

REFERENCES

1. Brasil. Ministério da Saúde. Situação do sarampo no Brasil – 2018. [cited 2019 Nov 12]. Available from: https://portalarquivos2.saude.gov.br/images/pdf/2018/julho/19/Informe-Sarampo142.pdf
2. World Health Organization. Press release: WHO warns of increased risk of disease epidemics in Syria and in neighbouring countries as summer approaches, 3 June 2013. [cited 2019 Nov 12]. Available from: http://www.emro.who.int/press-releases/2013/disease-epidemics-syria.html
3. Zaidi SSZ, Hameed A, Ali N, Rana MS, Umair M, Alam MM, et al. Epidemiological and molecular investigation of a measles outbreak in Punjab, Pakistan, 2013-2015. J Med Virol. 2018;90(8):1297-303.
4. Palminha P, Vinagre E, Cordeiro R, Ribeiro C, Roque C. Diagnóstico laboratorial do sarampo em Portugal, 2011-2013. Instituto Nacional de Saúde. 2015;6(7):17-20. [cited 2019 Nov 12]. Available from: http://repositorio.insa.pt/bitstream/10400.18/3240/3/observacoesNEspecia6-2015_artigo6.pdf
5. European Centre for Disease Prevention and Control (ECDC). Rapid risk assessment: risk of measles transmission in the EU/EEA. [cited 2019 Nov 12]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Measles-rapid-risk-assessment-European-Union-countries_0.pdf
6. Zenner D, Nacul L. Predictive power of Koplik's spots for the diagnosis of measles. J Infect Dev Ctries. 2012;6(3):271-5.
7. Ballalai I, Michelin L, Kfouri R. Sarampo: diagnóstico, notificação e prevenção. [cited 2019 Nov 12]. Available from: https://www.sbp.com.br/fileadmin/user_upload/NOTA_TECNICA_CONJUNTA_SBIM-SBP-SBI-_sarampo-jul18__002_.pdf
8. Sociedade Brasileira de Pediatria. Atualização sobre sarampo. [cited 2019 Nov 12]. Available from: https://www.sbp.com.br/imprensa/detalhe/nid/atualizacao-sobre-sarampo/
9. Kuschnaroff T, Focaccia R. Sarampo. In: Veronesi R, Focaccia R, eds. Tratado de infectologia. 5ª ed. São Paulo: Atheneu; 2015. p.875-82.
10. Lemos DRQ. Epidemia de sarampo no Ceará no período pós-eliminação nas Américas: enfrentamento, resposta coordenada e avaliação de risco para reintrodução do vírus [Tese de Doutorado]. Fortaleza: Universidade Estadual do Ceará; 2016.
11. World Health Organization. Measles vaccines: WHO position paper. Weekly Epidemiological Record. 2009;35(35):349-60. [cited 2019 Nov 12]. Available from: https://www.who.int/wer/2009/wer8435.pdf?ua=1
12. Zeng SZ, Zhang B, Zhang Y, Xie LY, Xiong J, Yu T, et al. Identification of 12 cases of acute measles encephalitis without rash. Clin Infect Dis. 2016;63(12):1630-3.
13. Ogbuanu IU, Zeko S, Chu S, Muroua C, Gerber S, De Wee R, et al. Maternal, fetal, and neonatal outcomes associated with measles during pregnancy: Namibia, 2009-2010. Clin Infect Dis. 2014;58(8):1086-92.
14. Coelho LMG, Rivemales MCC. Doenças exantemáticas no Distrito Sanitário Barra/ Rio Vermelho (DSBRV) no período de 2003 a 2007. Rev Baiana Saúde Pública. 2009;33(4):509-21.
15. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde, Departamento de Vigilância das Doenças Transmissíveis. Plano de contingência para resposta às emergências de saúde pública: sarampo. [cited 2019 Nov 12]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/plano_contingencia_resposta_emergencias_sarampo.pdf
16. Ribeiro C, Menezes C, Lamas C. Sarampo: achados epidemiológicos recentes e implicações para a prática clínica. Almanaque Multidisciplinar de Pesquisa. 2015;1(2):4-16.
17. Brasil. Ministério da Saúde. Brasil recebe certificado de eliminação do sarampo. Brasília: Ministério da Saúde; 2016. [cited 2019 Oct 19]. Available from: http://saude.gov.br/noticias/agencia-saude/25846-brasil-recebe-certificado-de-eliminacao-do-sarampo
18. Brasil. Ministério da Saúde. Situação do sarampo no Brasil – 2019. Brasília: Ministério da Saúde; 2019. [cited 2019 Oct 19]. Available from: https://portalarquivos2.saude.gov.br/images/pdf/2019/janeiro/28/Informe-Sarampo-n36-24jan19aed.pdf
19. Secretaria de Saúde do Ceará. Boletim epidemiológico: doença exantemática. 2019. [cited 2019 Oct 19]. Available from: https://www.saude.ce.gov.br/wp-content/uploads/sites/9/2018/06/boletim_exantematica_20_03_2018.pdf
20. Robert A, Funk S, Kucharski AJ. The measles crisis in Europe: the need for a joined-up approach. Lancet. 2019;393(10185):2033.
21. Page KR, Doocy S, Reyna Ganteaume F, Castro JS, Spiegel P, Beyrer C. Venezuela's public health crisis : a regional emergency. Lancet. 2019;393(10177):1254-60.
22. Fadda GM, Cury VE. O enigma do autismo: contribuições sobre a etiologia do transtorno. Psicol Estudo. 2016;21(3):411-23.
23. Brasil. Secretaria de Vigilância em Saúde. Sarampo: atualização da Semana epidemiológica 34. Brasília: Secretaria de Vigilância em Saúde; 2019. [cited 2019 Oct 19]. Available from: https://portalarquivos2.saude.gov.br/images/pdf/2019/setembro/02/3.%20a%20-%202019_08_29%20-%20SARAMPO%20-%20CIT.pdf
24. Faversani MCSS, Kupek E, Westrupp MHB. Perfil epidemiológico do sarampo no estado de Santa Catarina, Brasil, de 1996 a 2000. Cad Saúde Pública. 2005;21(2):535-44.
25. Mina MJ, Kula T, Leng Y, Li M, Vries RD, Knip M, et al. Measles virus infection diminishes preexisting antibodies that offer protection from other pathogens. Science. 2019;366(6465):599-606.

ORIGINAL ARTICLE

Association of BDNF gene polymorphism with endophenotypes in posttraumatic stress disorder

Jun-Cheng Guo[1]
Xiang Li[2]
Min Guo[3]
Yun-Suo Gao[4]
Lin-Qiu Fu[5]
Xiang-Ling Jiang[6]
Lin-Mei Fu[7]
Tao Huang[7]

1. Central South University Xiangya School of Medical Affiliated Haikou Hospital, Haikou 570311, Hainan Province, China
2. The Third People's Hospital of Hubei Province, Wuhan 430060, P. R. China
3. Psychological Research Center of Hainan General Hospital, Haikou 570311, Hainan Province, China
4. Department of Equipment, Hainan General Hospital, Haikou 570311, Hainan Province, China
5. Department of Psychology, Hainan General Hospital, Haikou 570311, Hainan Province, China
6. Department of Clinical Laboratory, Hainan General Hospital, Haikou 570311, Hainan Province, China
7. Medical Center, Hainan General Hospital, Haikou 570311, Hainan Province, China

http://dx.doi.org/10.1590/1806-9282.66.5.615

SUMMARY

OBJECTIVE: *To explore the association of brain-derived neurotrophic factor gene (BDNF) polymorphism with the latent cognitive endophenotype of posttraumatic stress disorder (PTSD) after major natural disasters in Hainan Province, China.*

METHODS: *A total of 300 patients with PTSD and 150 healthy controls (HC) were surveyed by psychoanalysis scale to assess their cognitive functions. Polymerase chain reaction (PCR) and polyacrylamide gel electrophoresis (PAGE) were used to detect the BDNF gene polymorphism.*

RESULTS: *In terms of the cognitive function, the scores in the PTSD group were worse than those of the HC group ($P < 0.05$ or $P < 0.01$). There was a significant difference in the distribution of BDNF genotype and allele frequency between the two groups ($P < 0.05$). PTSD endophenotypes were significantly different among the BDNF genotypes in the PTSD group ($P \leq 0.01$).*

CONCLUSION: *There is a statistically significant difference in the polymorphism of BDNF gene between PTSD and HC groups, and the alleles are associated with the incidence of PTSD. Thus, it may be a risk factor for PTSD.*

KEYWORDS: *Stress disorders, post-traumatic. Endophenotypes. Polymorphism, genetic. Brain-derived neurotrophic factor.*

INTRODUCTION

Epidemiological surveys have shown that 50-90% of individuals have experienced at least one traumatic event in their lives, indicating that psychic trauma is one part of their life experiences.[1] When people experience or witness the life-threatening disastrous events, including natural disasters (such as earthquakes, floods, typhoons, tsunamis, etc.), man-made disasters (such as war, terrorist attacks, serious traffic accidents, fires, mine accidents, rape, robberies, etc.), major loss (such as a sudden death of a loved one, bankruptcy, loss of liberty or an important position) and other traumatic events, they would

DATE OF SUBMISSION: 28-Oct-2019
DATE OF ACCEPTANCE: 29-Dec-2019
CORRESPONDING AUTHOR: Min Guo,
Research Center, Hainan General Hospital, No. 19, Xiuhua Road, Xiuying District, Haikou 570311, Hainan, China.
E-mail: docminguo@163.com

endure tremendous suffering and feel terrified, fearful, helpless and other physical discomfort, leading to many serious consequences, and the most serious one is post-traumatic stress disorder.[2]

Few people know the neurocognitive function of post-traumatic stress disorder. There is also little literature on the executive function in patients with posttraumatic stress disorder (PTSD). We hypothesized that the incidence of PTSD is high and then attempted to determine the association of the executive function with PTSD on the basis of this hypothesis. In recent years, PTSD has become a new hot spot in the psychiatric department and psychological researches. However, there is still few understandings and researches on this field.[3] Cognitive function may be a characteristic indicator of PTSD. However, at present, there is relatively few genetic researches on cognitive function in patients with PTSD in China. Therefore, we attempted to study whether PTSD patients have a wide range of cognitive dysfunction, such as damages in memory, visual breadth, verbal function, attention, executive function and other aspects, in order to study the endophenotypes of cognitive impairment in PTSD patients.

METHODS

Subjects

Clinician administered PTSD scale (CAPS), compiled by Blake et al.[4]., the National Center for Posttraumatic Stress Disorder, which was used as a structured interview diagnosis of PTSD.

CAPS methods were used to screen the subjects. Those in line with the inclusion criteria were grouped into the PTSD group. With the help of a psychiatrist, investigators conducted one-on-one interviews using the executive function questionnaire. All investigators had received unified training. The consistency of the observation was higher than 95%. Unified guidance of the questionnaire was used to ensure integrity. Inclusion criteria for PTSD group included: 1. PTSD patients found in the epidemiological surveys of Hainan Province from October 2011 to July 2014; 2. aged 30-60 years; with a diagnosis of PTSD; 3. in good physical health, and the informed consent was provided; 4. post-traumatic stress disorder diagnosed using CAPS. Inclusion criteria for the HC group were as follows: 1. siblings, classmates, neighbors or friends of those selected into PTSD group; 2. aged 30-60 years, without any cancer or other consuming disease; 3. in good physical health, non-pregnant women, without genetic mental illness, and the informed consent was provided. Finally, there were 300 PTSD and 150 healthy controls meeting the corresponding criteria. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Hainan General Hospital. Written informed consent was obtained from all participants. Cognitive function scales included Hanoi tower (TOH), Wisconsin card sorting test (WCST), Trail making test (TMT) and Wechsler adult intelligence scale-revision by China (WAIS-RC).

Detection of brain-derived neurotrophic factor gene (BDNF) polymorphism

After the epidemiological survey and the scale assessment, all the subjects underwent 5-10 mL blood sample collection from the antecubital vein. The blood samples were anticoagulated with EDTA and stored at -20°C (-4°F) at the Central Laboratory of People's Hospital of Hainan Province until use. Genomic DNA was extracted from the blood samples using whole blood genomic DNA extraction kit (OMEGA, USA). The concentration and purity of genomic DNA were determined, and both of them met the requirement of polymerase chain reaction (PCR) amplification. The primer pair specific to *BDNF* gene was designed using Primer Premier 5.0 software. Primer pair for rs6265 locus: (forward) 5'-TTTCTCCCTACAGTTCCACCAG-3', (reverse) 5'-CTCCAAAGGCACTTGACTACTG-3', and the amplified product size was 343 bp. A total of 50 μL of the reaction system contained 1 μL of genomic DNA, 1 μL (10 μM) of each primer, 0.25 μL (5 U/μL) of pfu polymerase, 5 μL of 10× Buffer (200 mM Tris HCl, pH 8.8; 100 mM KCl; 20 mM MgSO4; 160 mM (NH4)2SO4; 1% Triton, 1 mg/mL BSA), 1 μL (10 mM) dNTPs and de-ionized water 40.75 μL. PCR amplification running conditions for rs6265 site included pre-denaturation at 98°C (208°F) for 3 minutes, 35 cycles of denaturation at 95°C (203°F) for 1 minute, annealing at 60°C (140°F) for 45 seconds, extension at 55°C (131°F) for 55 seconds, followed by extension at 72°C (162°F) for 8 minutes. PCR kit was purchased from Shanghai Jierui Biological Engineering Co., Ltd. The PCR products were sent to Sangon (Shanghai) Bioengineering Services Ltd. for sequencing.

Statistical analysis

Data were entered into epidata3.02 software by two persons individually, and then analyzed using SPSS v19.0 software. Data were presented as mean ±

standard deviation (SD). Mean of each parameter was calculated using Cohen's D value method. TOH, WCST, TMT and WAIS-RC scores between PTSD patients and healthy controls were compared using the independent sample t-test. ANOVA was used to compare the difference in each parameter among the genotypes of *BDNF rs6265* in PTSD group. The test level was set as 0.05. Multiple regression analysis encodes genotypes AA, AC, and CC as 0, 1, and 2, respectively; and has a Y code of 0, 1, indicating no disease and disease. One line per patient. The SNP genotype is AA, genotype CC, genotype AC, and so on. The data can be saved into an excel file. When analyzing, use "data analysis", single factor analysis, select CASE as the result variable, and SNP as the risk factor, and automatically give the required form.

RESULTS

Demographic characteristics

There were 300 patients in the PTSD group, aged 18-65 years, with an average age of 39.2 ± 6.3 years, including 182 males and 118 females, 257 married and 43 unmarried. Health control group included 150

TABLE 1. COMPARISON OF ETI SCORES BETWEEN THE TWO GROUPS.

Group	Number of cases	Intrusion	Avoidance	High alertness	Separation	Total scores of PTSD
PTSD	300	3.16±1.13	3.97±1.52	3.36±1.03	2.16±0.94	19.01±9.13
Control	150	4.73±1.19	5.01±1.88	4.15±1.21	2.97±1.13	25.23±8.43
t		13.649	6.309	7.227	8.042	6.986
P		<0.001	<0.001	<0.001	<0.001	<0.001

Note: Data are shown as mean ± SD.

TABLE 2. COMPARISONS OF COGNITIVE FUNCTION SCORES BETWEEN THE TWO GROUPS.

	Parameters	Patients with first-episode depression (n=300)	Healthy controls (n=150)	t	*p*
WAIS-RC	Knowledge	9.98±1.93	10.96±1.89	5.112	<0.001
	Comprehension	10.59±2.04	11.59±2.03	4.910	<0.001
	Arithmetics	10.32±2.12	10.75±2.70	1.846	0.066
	Similarity	10.30±2.18	11.09±2.01	3.718	<0.001
	Digit span	10.69±2.13	11.20±1.75	2.535	0.012
	Vocabulary	9.89±2.01	10.10±1.94	1.057	0.291
	Digit symbol	10.49±2.34	10.21±2.20	1.220	0.223
	Paint filling	8.79±2.14	9.01±2.03	1.046	0.296
	Block pattern	9.39±2.22	10.89±2.15	6.828	<0.001
	Picture alignment	9.75±2.36	10.06±2.03	1.374	0.170
	Object patching	9.84±2.26	11.06±2.13	5.501	<0.001
	Language intelligence	99.77±12.56	101.60±12.13	1.474	0.141
	Operational intelligence	97.39±12.09	100.70±11.03	2.817	0.005
	Total intelligence	98.58±12.23	101.15±11.66	2.823	0.005
M-WCST	Number of sorting	4.23±1.65	4.79±1.39	3.571	<0.001
	Number of mistakes	15.49±5.25	13.30±4.21	4.430	<0.001
	Number of correctness	31.76±6.32	34.10±5.25	3.910	<0.001
	Number of continuous mistakes	5.60±3.05	4.60±3.02	3.289	<0.001
	Number of random mistakes	8.09±3.29	7.09±3.64	2.932	0.004
TMT	A time-consuming (s)	52.40±11.14	45.75±11.57	5.893	<0.001
	B time-consuming (s)	80.75±12.12	69.73±12.15	9.085	<0.001
	Interference	28.39±3.62	24.00±2.59	13.250	<0.001
TOH	Time for planning	7.22±2.65	5.92±2.60	4.936	<0.001
	Time for execution	25.95±8.76	18.69±7.11	8.802	<0.001
	Total	33.17±10.15	24.61±10.43	8.327	<0.001

Note: Data are shown as mean ± SD.

TABLE 3. COMPARISONS OF COGNITIVE FUNCTION SCORES AMONG THE GENOTYPES OF BDNF RS6265 IN THE PTSD GROUP.

	Genotype			F	P*	P1*	P2#	P3&
	GG (N=93)	GA (N=139)	AA (N=68)					
Key symptom scores	11.22±3.21	11.10±2.62	10.40±2.36	1.978	0.140	-	-	-
WAIS-RC								
Knowledge	10.01±1.94	9.80±2.17	10.31±2.51	1.256	0.286	-	-	-
Comprehension	10.29±2.48	10.81±1.91	10.55±2.11	1.651	0.194	-	-	-
Arithmetics	10.61±2.70	10.39±1.92	9.78±2.21	2.792	0.063	-	-	-
Similarity	10.02±1.85	10.13±2.06	10.77±2.19	2.405	0.092	-	-	-
Digit span	10.69±1.68	10.91±2.09	10.24±2.12	2.616	0.074	-	-	-
Vocabulary	8.97±2.71	9.96±2.68	11.01±2.54	11.651	<0.001	0.007	<0.001	0.008
Digit symbol	9.40±1.85	10.86±2.37	11.22±2.32	16.967	<0.001	<0.001	<0.001	0.302
Paint filling	8.41±2.29	8.82±2.32	9.25±2.24	2.658	0.072	-	-	-
Block pattern	9.13±2.48	9.26±2.37	10.01±2.53	2.918	0.056	-	-	-
Picture alignment	9.46±2.37	9.67±2.46	10.31±2.34	2.595	0.076	-	-	-
Object patching	9.75±2.09	9.69±2.02	10.27±2.14	1.921	0.148	-	-	-
Language intelligence	102.20±13.65	96.39±12.01	103.36±12.70	9.352	<0.001	<0.001	0.548	<0.001
Operational intelligence	94.34±11.94	97.33±12.23	101.68±11.84	7.286	<0.001	0.067	<0.001	0.016
Total intelligence	97.48±12.69	98.86±12.01	102.52±12.25	3.448	0.033	0.403	0.013	0.042
M-WCST								
Number of sorting	3.84±1.64	4.26±1.37	4.70±1.52	6.578	0.002	0.036	<0.001	0.004
Number of mistakes	16.83±6.19	15.35±5.40	13.94±4.60	5.516	0.055	<0.001	<0.001	0.066
Number of correctness	32.12±6.03	32.04±5.75	30.70±6.21	1.406	0.247	-	-	-
Number of continuous mistakes	6.64±3.80	5.21±3.73	4.97±3.04	5.710	0.004	0.005	0.003	0.645
Number of random mistakes	9.45±4.20	7.55±3.72	7.33±3.30	8.773	<0.001	<0.001	<0.001	0.679
TMT								
A time-consuming (s)	52.64±9.79	51.22±10.07	53.52±11.12	1.289	0.277	-	-	-
B time-consuming (s)	83.32±13.80	80.71±12.02	77.05±11.34	4.977	0.007	0.128	0.003	0.037
Interference	28.75±5.71	28.45±3.42	27.78±3.25	1.056	0.349	-	-	-
TOH								
Time for planning	7.52±2.59	6.95±2.35	7.36±2.12	1.753	0.175	-	-	-
Time for execution	27.81±7.13	25.39±8.92	24.55±8.53	3.606	0.028	0.030	0.009	0.519
Total	35.33±8.73	32.34±9.71	31.91±9.54	3.625	0.027	0.017	0.019	0.764

Note: Data are shown as mean±SD. *Comparisons among genotypes GG, GA, and AA using one-way ANOVA; Comparisons between genotype GG and GA; #Comparisons between genotype GG and AA; &Comparisons between genotype GA and AA.

subjects, aged 26-64 years, with an average age of 41.75 ± 9.14 years, containing 79 males and 71 females, 132 married and 18 unmarried. There was no significant difference in age (t=-0.9532, P=-0.3398), gender (c^2=0.3721, P=0.5412), marital status (c^2=1.623, P=0.203) and education level (12.65 ± 5.72 years *vs.* l3.14 ± 4.77, t=0.4848, P=-0.6288) between the PTSD group and HC group. Total CAPS scores were 64.08 ± 9.67.

Comparison of ETI scores

Compared with the HC group, the scores of the symptoms such as intrusion, avoidance, high alertness and separation were significantly decreased and the total scores of PTSD were also reduced in the PTSD group (P<0.001, Table 1).

Comparison of cognitive functions

WAIS-RC scores showed that the scores of comprehension, similarity, block pattern, object patching, operational intelligence, total intelligence, and the parameters of M WCST, TMT and TOH tests in patients with first-episode depression were remarkably worse than those in the HC group (P<0.05 or P<0.01, Table 2).

Comparisons of cognitive function among the genotypes of BDNF rs6265

The cognitive function scores were compared among the genotypes of *BDNF rs6265* in PTSD patients using variance analysis (Table 3). The results showed that the scores of vocabulary, digit symbols,

language intelligence, paint filling, operating intelligence, total intelligence, B time-consuming (seconds), time for execution and total scores were prominently different among the three genotypes of *BDNF rs6265* in PTSD patients (P<0.05). Then pairwise comparisons were carried out using Bonferroni method (the test level was 0.02). The scores of vocabulary and digit sign in genotype AA were markedly better than those in genotype GG (P<0.05). The language intelligence scores in genotypes GG and AA were superior to that in genotype GA (P<0.05). The operating intelligence score in genotype GA was notably better than that in genotype GG (P<0.05). The overall intelligence in genotype GA was also superior to that in genotype GG (P<0.05). Except for the number of correctness, the other parameters of M-WCST were significantly different among the three genotypes (P<0.05). Furthermore, the time for execution of TOH in genotype GA was obviously better than that in genotype AA (P<0.05).

DISCUSSION

Endophenotype, proposed by Gottesman, is a description of an objective and measurable intermediate phenotype between genotypes and clinical phenotypes.[5] The endophenotype is thought to be "detectable by biochemical tests or microscopy". It is a potential quantitative trait carrying genetic load and being indirectly associated with the typical behavioral symptoms of a disease as defined by DSM-IV or ICD-10. Compared to the behavioral phenotypes, it has a closer relationship with the underlying genetic bases and can predict the likelihood of developing a particular disease. It is directly affected by gene effects and is thought to be determined by the genetic factors which are simpler than the disease phenotype.[6] It can be measured physiologically, neurobiologically and cognitively. In theory, as compared by the disease itself, it is less affected by the genetic and environmental risk factors. Therefore, the effects of heterogeneity can be reduced in studying the roles of individual genes so that the results of the association studies of candidate genes can be more reliable. Moreover, it can discern all the problematic family members (including the unaffected members) in the pedigrees so that the genealogical statistics are more effective. It can also find out the potential biological difference of the disease (heterogeneity of the disease). Endophenotype is the middle part of the gene-to-disease pathways, which not only compensates for the huge gap between the genetic and disease processes but also helps to elucidate or modify the problematic pathophysiological basis of the disease.

Clinical observations found that psychic trauma caused by traumatic events is not the only factor that contributes to the occurrence and development of PTSD. There must be more risk factors that can explain the vulnerability of individuals to PTSD after trauma. Many studies have found that these risk factors include inheritance, family history, specific personality and coping styles, past traumatic experiences, past history of mental and behavioral problems, characteristics of parental relationships, the intensity of the impact of the experiencing life events just before the trauma, and other factors after the trauma, such as social support, exposure to subsequent stressors, etc.[7] In addition, some studies have found that the intensity and number of discrete symptoms exhibited by an individual at the time of or just after a traumatic experience, the total number and overall severity of PTSD symptoms, are also the predictors of subsequent PTSD. According to domestic researches, the most important factor contributing to PTSD after the earthquake is the lack of post-disaster social supports rather than the exposure to stressors. For the earthquake-affected adolescents, the risk factors contributing to PTSD include the subjective perception of stressors, exposure level, sex (female), level of psychophylaxis and so on.[8] In recent years, more and more studies have found that some risk factors act at a relatively low exposure level, while some factors act at a relatively high exposure level. Other factors such as family financial status, internal cohesion of family members, family coping styles and so on may also be related to the occurrence of traumatic stress disorder after the incident. In addition, timely post-traumatic social support and the corresponding psychological intervention for patients will reduce the incidence of PTSD.[9] Until now, it remains unclear whether the risk factors for PTSD indicate a specific predisposition for PTSD or a general predisposition response of traumatic-induced mental disorders. However, the results of studies demonstrating the role of risk factors in the development of traumatic stress disorder suggest that the post-traumatic psychopathological response is neither a randomized process nor a result that can be completely determined by the nature of the traumatic event. Thus, as a result of an individual exposing to a traumatic event, the basic theoretical hypothesis that

PTSD may potentially occur in any individual exposed to a traumatic event remains to be demonstrated by further studies.

According to the central dogma of Molecular Biology, genetic information is transmitted from DNA to RNA and then translated into proteins that express the function.[10] If PTSD is associated with different genetic variations, each aberrant gene can cause a particular protein change and lead to a corresponding dysfunction. Even though the occurrence of PTSD may be related to multiple gene interactions and the interaction between genes and environmental factors, the corresponding dysfunctions caused by each pathogenic gene are generally identifiable. Without a given standard to determine the features of depression resulted from a single gene, the endophenotype of the disease can only be determined based on the findings and hypotheses in prior studies. It ranges from the clinical features, such as the melancholic temperament of the family members of PTSD patients, to the neurophysiological or neuropsychological measurements, brain areas with specific and important functions, and structural measurements of cerebral ventricles' sizes. PTSD genetic studies with important and representative endophenotypes especially emphasize the abnormalities of information processing, while more and more attention has been paid to the studies on the endophenotypes of cognitive dysfunction in PTSD. In the studies on the PTSD pathological endophenotypes,[11] cognitive function was evaluated using neuropsychological test scores. Our results showed that the key symptom scores of *BDNF rs6265* in PTSD patients with genotype AA were significantly higher than those in patients with genotype GA or GG. After further control with sex, age, course of disease and psychotic symptoms, there was a significant positive correlation between genotype AA and key symptom scores and a significant negative correlation between genotype GG and key symptom scores, suggesting that *BDNF* gene polymorphism is associated with depression endophenotype. Meanwhile, with regard to the endophenotype of cognitive function, the neuropsychological test scores except the amount of TMT interference showed significant differences among the three genotypes,[12] which were all superior in genotype GG to AA. In particular, M-WCST items and the time-consuming results of TMT-A and TMT-B were the best in the patients with genotypes GG, followed by those with GA, and then those with AA, which were all statistically significant, suggesting that the polymorphism of *BDNF* gene is related to the endophenotypes of cognitive function. The general cognitive function of the patients with genotype GG was superior to that in the patients with the other two genotypes, especially in the executive function, such as generalization, attention, working memory, cognitive transfer, visual discrimination, space perception, planning ability and so on, which were the worst in genotype AA. Our preliminary findings of the relationship between the *BDNF* polymorphisms and PTSD endophenotypes were consistent with foreign studies.[13] Baig et al.[14] conducted a controlled study on *BDNF Val66Met (rs6265)* gene polymorphisms in 203 schizophrenia patients and 133 healthy volunteers, and found that the working memory of the schizophrenia patients with *BDNF Met/Met* genotype were more severely damaged than those with *BDNF Val/Val.* Functional magnetic resonance imaging (fMRI) was also used to study the hippocampal function of healthy volunteers when they were undergoing revised Webster adult memory scale (WMS-R) and WAIS detection. The results showed that the response of the bilateral hippocampus tails in patients with genotype *Val/Met* was more abnormal than that in the patients with genotype *Val/Val* and displayed a decrease in neurointegration.[15] The researchers also found that such effects can affect the secretion and subcellular localization of BDNF by means of rat neuronal tissue culture. Therefore, it is speculated that the point mutation of Val to Met causes the structural change of BDNF molecule, resulting in the failure of normal BDNF transmission and secretion and then affecting memory formation and neuronal plasticity.[16] Other studies agree that Met-transfected hippocampal neurons produce an inefficient transport of BDNF to secretory vesicles, thereby reducing the activity-dependent BDNF secretion and decreasing the cognitive functions such as performance and memory.[17] There is a statistically significant difference in *BDNF Val66Met* polymorphism between PTSD patients and healthy volunteers. The *Met* allele is associated with the incidence of PTSD. It is a risk factor for PTSD. Its polymorphism is related to the endophenotype of PTSD. Patients with genotype *Met/Met* had more severe depression and more severe cognitive impairment than those with genotype *Val/Val*, especially in the executive functions, such as generalization, attention, working memory, cognitive transfer, visual discrimination, space perception and planning ability.

In recent years. researchers have identified a large number of complex diseases/traits-associated genetic variants by performing genome-wide association studies (Genome-wide association studies, GWAS), which may provide important clues on understanding the mechanisms of related diseases. However, GWAS has its own limitations in terms of false positive and false negative results, very few SNPs located in the functional areas and insensitive to detect rare and structural variations, which results in the application limitation of this method.The polymerase chain reaction (PCR) and polyacrylamide gel electrophoresis (PAGE) method were used to extract genomic DNA by whole-blood genomic DNA extraction kit. The concentration and purity were in accordance with PCR amplification requirements and became the identification of mental illness. The most effective strategy for causative genes is also used in the research and clinical diagnosis of complex disease susceptibility genes. Some foreign scholars studied the cognitive function of schizophrenia patients with *BDNF Val-66Met* and also found that the cognitive functions in patients with genotype *Val/Val* are superior to those with genotypes *Met/Met*.[18,19] However, the current studies on the relationship between the polymorphisms of *BDNF* gene and cognitive functions were mostly focused on animal experiments, and less were found on their correlation with PTSD.[20] Therefore, the conclusions of this study are yet to be further confirmed.[21]

In conclusion, this study investigated the cognitive function (inhibition, retrieval, working memory and planning) of PTSD, and found that the severe executive function of PTSD was consistent with the findings of PTSD patients caused by other causes. The results showed that the executive function of PTSD is impaired, which may mean abnormal changes of brain function and structure. PTSD is associated with neurocognitive impairment or linkage disequilibrium.

Acknowledgements

This work was funded by 2016 Hainan Priority Research and Development Plan (ZDYF2018227), National Natural Science Fund (81760255).

Conflicts of interest

The authors declare no conflict of interest.

Authors contributions

Jun-Cheng Guo and Xiang Li wrote the manuscript. Min Guo designed this paper and performed critical revision of the manuscript; Jun-Cheng Guo, Xiang Li and Yun-Suo Gao performed data collection; Lin-Qiu Fu, Xiang-Ling Jiang, Lin-Mei Fu and Tao Huang analyzed the date. All authors read and approved the final manuscript.

RESUMO

OBJETIVO: *Explorar a associação do polimorfismo do gene fator neurotrófico derivado do cérebro (BDNF) com o endofenótipo cognitivo latente de transtorno de estresse pós-traumático (TEPT) após grandes desastres naturais na província de Hainan, China.*

MÉTODOS: *Um total de 300 doentes com TEPT e 150 controles saudáveis (HC) foi investigado pela escala de psicanálise para avaliar as suas funções cognitivas. A reação em cadeia polimerase (PCR) e a eletroforese em gel de poliacrilamida (Page) foram usadas para detectar o polimorfismo do gene BDNF.*

RESULTADOS: *Em termos de função cognitiva, as pontuações no grupo TEPT foram piores do que as do grupo HC (P<0,05 ou P<0,01). Houve uma diferença significativa na distribuição do genótipo de BDNF e frequência do alelo entre os dois grupos (P<0,05). Os endofenótipos de TEPT foram significativamente diferentes entre os genótipos de BDNF do grupo TEPT (P≤0,01).*

CONCLUSÃO: *Existe uma diferença estatisticamente significativa no polimorfismo do gene BDNF entre o TEPT e os grupos HC, e os alelos estão associados à incidência do TEPT. Assim, pode ser um fator de risco para TEPT.*

PALAVRAS-CHAVE: *Transtornos de estresse pós-traumáticos. Endofenótipos. Polimorfismo genético. Fator neurotrófico derivado do cérebro.*

REFERENCES

1. Guo JC, Tian ZL, Wang XD, Guo M, Li MY, Gao YS, et al. Post-traumatic stress disorder after typhoon disaster and its correlation with platelet 5-HT concentrations. Asian Pac J Trop Med. 2016;9(9):913-5.
2. McCarron KK, Reinhard MJ, Bloeser KJ, Mahan CM, Kang HK. PTSD diagnoses among Iraq and Afghanistan veterans: comparison of administrative data to chart review. J Trauma Stress. 2014;27(5):626-9.
3. Chen T, Guo M, Gao Y, Chen F, Guo J, Liu T, et al. A comparative study on the levels of serum cytokines and cortisol among post-traumatic stress disorder patients of Li and Han ethnicities in Hainan. Chin Med J (Engl). 2014;127(15):2771-4.
4. Blake DD, Weathers FW, Nagy LM, Kaloupek DG, Gusman FD, Charney DS, et al. The development of a Clinician-Administered PTSD Scale. J Trauma Stress. 1995;8(1):75-90.
5. McGue M. Irving Gottesman and the concept of endophenotype. Am J Med Genet C Semin Med Genet. 2017;175(3):341-2.

6. Carlberg L, Scheibelreiter J, Hassler MR, Schloegelhofer M, Schmoeger M, Ludwig B, et al. Brain-derived neurotrophic factor (BDNF)-epigenetic regulation in unipolar and bipolar affective disorder. J Affect Disord. 2014;168:399-406.
7. Li L, Li MX, Pan LH, Wang GM, Guo M, Fu LQ, et al. Comparative analysis of platelet 5-HT concentrations in Han and Li patients with post-traumatic stress disorder. Genet Mol Res. 2016;15(3). doi: 10.4238/gmr.15038265.
8. Young G. PTSD in court II: risk factors, endophenotypes, and biological underpinnings in PTSD. Int J Law Psychiatry. 2017;51:1-21.
9. Belhadj-Tahar H, Vilamot B, Granberg M, Passamar M. Brain-derived neurotrophic factor (BDNF) as a predictive factor for post-traumatic stress disorder (PTSD). Eur Neuropsychopharmacol. 2014;24:S594-5.
10. Lee B, Shim I, Lee H, Hahm DH. Effect of oleuropein on cognitive deficits and changes in hippocampal brain-derived neurotrophic factor and cytokine expression in a rat model of post-traumatic stress disorder. J Nat Med. 2018;72(1):44-56.
11. Yahyavi ST, Zarghami M, Naghshvar F, Danesh A. Relationship of cortisol, norepinephrine, and epinephrine levels with war-induced posttraumatic stress disorder in fathers and their offspring. Braz J Psychiatry. 2015;37(2):93-8.
12. Wang T. Does BDNF Val66Met polymorphism confer risk for posttraumatic stress disorder? Neuropsychobiology. 2015;71(3):149-53.
13. Yang G, Vilamot B, Passamar M, Sadeg N, Belhadj-Tahar H. Pilot prospective study on BDNF (brain derived neurotrophic factor) as a predictive biomarker of the occurrence of PTSD (post traumatic stress disorder). J US-China Med Sci. 2015;12:12-9.
14. Baig BJ, Whalley HC, Hall J, McIntosh AM, Job DE, Cunningham-Owens DG, et al. Functional magnetic resonance imaging of BDNF val66met polymorphism in unmedicated subjects at high genetic risk of schizophrenia performing a verbal memory task. Psychiatry Res. 2010;183(3):195-201.
15. Besnard A, Sahay A. Adult hippocampal neurogenesis, fear generalization, and stress. Neuropsychopharmacology. 2016;41(1):24-44.
16. Domschke K. Clinical and molecular genetics of psychotic depression. Schizophr Bull. 2013;39(4):766-75.
17. Zaba M, Kirmeier T, Ionescu IA, Wollweber B, Buell DR, Gall-Kleebach DJ, et al. Identification and characterization of HPA-axis reactivity endophenotypes in a cohort of female PTSD patients. Psychoneuroendocrinology. 2015;55:102-15.
18. Kida S, Kato T. Microendophenotypes of psychiatric disorders: phenotypes of psychiatric disorders at the level of molecular dynamics, synapses, neurons, and neural circuits. Curr Mol Med. 2015;15(2):111-8.
19. Miller DR, Logue MW, Wolf EJ, Maniates H, Robinson ME, Hayes JP, et al. Posttraumatic stress disorder symptom severity is associated with reduced default mode network connectivity in individuals with elevated genetic risk for psychopathology. Depress Anxiety. 2017;34(7):632-40.
20. Su H, Tao J, Zhang J, Xie Y, Wang Y, Zhang Y, et al. The effects of BDNF Val66Met gene polymorphism on serum BDNF and cognitive function in methamphetamine-dependent patients and normal controls: a case-control study. J Clin Psychopharmacol. 2015;35(5):517-24.
21. Boccia M, Nemmi F, Guariglia C. Neuropsychology of environmental navigation in humans: review and meta-analysis of FMRI studies in healthy participants. Neuropsychol Rev. 2014;24(2):236-51.

ORIGINAL ARTICLE

Assessment of postoperative risk of complications on inguinal hernioplasty and its relation to risk factors

Maurício Chibata[1,2]
Oona Tomiê Daronch[3]

1. Cirurgião-geral do Hospital da Cruz Vermelha, Curitiba, PR, Brasil.
2. Professor da Faculdade de Medicina da Universidade Positivo, Curitiba, PR, Brasil.
3. Médica residente em cirurgia geral no Hospital de Clínicas UFPR, Curitiba, PR, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.623

SUMMARY

INTRODUCTION: *Abdominal wall hernias are a highly prevalent pathology, considering that 55 percent of the world population is affected by this disease at some point in their lives. As a large part of these patients present comorbidities, it is important to correlate the incidence of complications with the presence of previous pathologies.*

OBJECTIVES: *To evaluate whether the presence of comorbidities in patients submitted to inguinal hernioplasty increases the risk of acute and chronic complications in the postoperative period, as well as to explain which of these prior diseases present a greater association with the incidence of complications.*

METHODS: *This is a cross-sectional descriptive study carried out through the retrospective analysis of 313 medical records of patients submitted to open inguinal hernioplasty surgery between March and June 2017 at the General Surgery Service of the Cruz Vermelha Hospital - Paraná Branch, located in the City of Curitiba, state of Paraná, Brasil.*

RESULTS: *Of the 313 cases studied, the most prevalent comorbidities were: 107 patients with hypertension (34.19%), 52 smokers (16.61%), 30 cases with diabetes (9.58%), 14 with hypothyroidism (4,47%) and 10 with COPD (3.19%). Regarding the total of the sample evaluated, 130 patients (41.53%) did not present any comorbidity. When evaluating the complications, there were 49 cases (15.65%) of complications in the early postoperative period and 9 cases (2.88%) of chronic complications. The comorbidities that presented significant statistical influence ($p < 0.05$) on the incidence of acute complications were hypertension ($p = 0.02927$) and smoking ($p = 0.03196$). CONCLUSION: It is important to note the presence of acute postoperative complications of inguinal hernioplasty in patients who have hypertension or smoke, high prevalence diseases.*

KEYWORDS: *Hernia, inguinal. Herniorrhaphy. Postoperative complications.*

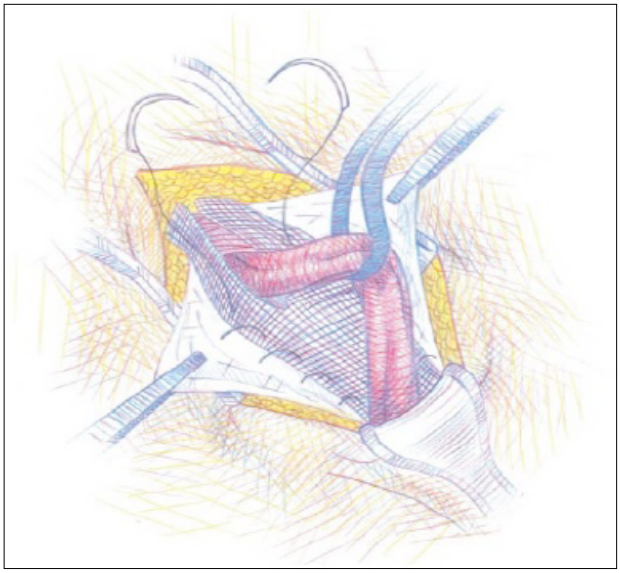
INTRODUCTION

Inguinal hernioplasty is the most commonly performed surgical procedure in abdominal wall surgery, with 80,000 surgeries performed annually in Great Britain, 100,000 in France and 700,000 in the US[1]. It is noteworthy that there is a higher prevalence of right unilateral hernia and in both adults and children, the indirect form is more common than the direct form. There is a predominance of males, and the delay in performing the surgery may progress to incarcerated hernia, increasing the rate of complications. Several surgical techniques have been described in the literature for the correction of inguinal hernia, among

DATE OF SUBMISSION: 29-Nov-2019
DATE OF ACCEPTANCE: 08-Dec-2019
CORRESPONDING AUTHOR: Oona Tomiê Daronch
Rua Coronel Dulcídio, 1255, Curitiba, PR, Brasil - 81280-330
Tel: +55 41 98897-3893 / +55 41 3232-6088
E-mail: oona.daronch@yahoo.com.br

which the Lichtenstein technique stands out in this work, as it is the most used and in which the mesh is used, preferably of polypropylene, which, being a multifilament, reduces the risk of exacerbated healing, as evidenced in Figure 1. Several risk factors influence the outcome of the long-term surgery, which can be modifiable or not modifiable. The first group includes obesity, smoking and poorly controlled hypertension. In this last set of comorbidities, liver cirrhosis, age, pro-inflammatory medical conditions, peripheral vascular disease and anxious depressive disorders stand out. The analysis of these preoperative risk factors can assist in the evaluation of the post-surgical result.

FIGURE 1. INGUINAL HERNIOPLASTY SURGERY USING THE LICHTENSTEIN TECHNIQUE, SHOWING THE PLACEMENT OF THE MESH AND OPENING FOR THE PASSAGE OF THE SPERMATIC CORD[2]



METHODS

This is a cross-sectional descriptive study carried out between March and June 2017, at the General Surgery Service of Hospital Cruz Vermelha – Paraná Branch, located in the city of Curitiba, state of Paraná, Brasil. Initially, patients who underwent inguinal hernioplasty using the original Lichtenstein technique under any anesthesia were selected, according a book of records of surgeries performed at this service, covering the period between January 2015 and April 2017.

By the number of the medical record obtained in the record book, an electronic medical record review was performed via Tasy and an electronic form was completed via Google Drive, in which patients were grouped by age, sex, laterality of the inguinal hernia, recurrences, comorbidities, early complications (one month) and late (more than one month).

The exclusion criteria were medical records that did not present minimum information for the correct completion of the form.

This work was submitted and approved by the Ethics Committee of the Hospital Cruz Vermelha – Paraná Branch under the registration number 8737264767. The names or any other data of the patients were not revealed, being the responsibility of these researchers the medical confidentiality according to the ethical and moral rules promulgated by the Code of Medical Ethics of the Federal Council of Medicine.

The results of quantitative variables were described by means, medians, minimum values, maximum values and standard deviations. Qualitative variables will be described by frequencies and percentages. The Chi-square test was used to assess possible associations. Values of $p < 0.05$ indicated statistical significance. The data were analyzed using the IBM SPSS Statistics v.20 computer program.

RESULTS

Sample profile

This study evaluated 313 cases of inguinal hernioplasty using the open technique performed during the three-year period at our service. In 13 cases (4.15%) there was no mesh placement due to the presence of infection, and in two of these cases (15.38%) the inguinal hernia was incarcerated. Regarding the profile of the sample, it consisted of 30 women (9.58%) and 283 men (90.42%). There were 111 cases (35.46%) of left hernioplasty, 154 cases (49.21%) of right hernioplasty and 48 cases (15.33%) of bilateral hernioplasty, according to Chart 1. The mean age of the patients was 56.26 years old (SD = 11.38). Regarding the average length of hospitalization, it was one day. There were 288 patients (92.01%) who were hospitalized for just one day; 11 (3.51%) were hospitalized for two days; five (1.60%) were hospitalized for three days; two for four days (0.64%); and one stayed ten days (0.32%) due to incarcerated hernia, as shown in Graph 2. In 33 patients (10.54%) the hernia was already recurrent. Of these, in 30 cases it was the second recurrence (9.58%); in two cases it was the third time (0.64%); and in one case (0.32%) it was the fourth time or more.

Main comorbidities

The incidence of comorbidities was calculated

jointly, that is, some patients had more than one comorbidity. Of the 313 patients, there were 30 cases with diabetes (9.58%), 107 with Systemic Hypertension (34.19%), 52 smokers (16.61%), 16 with mixed anxiety–depressive disorder – MADD (5.11%), three with cancer (0.96%), three with obesity (0.96%), ten with COPD (3.19%), 14 with hypothyroidism (4.47%), one with liver cirrhosis (0.32%), 17 (5.43%) with cardiac changes (previous MI, HF, arrhythmias), three with dyslipidemia (0.96%), immunosuppression in four cases (1.28%) – three of them with HIV. In relation to the total sample studied, 130 patients (41.53%) did not present any comorbidity.

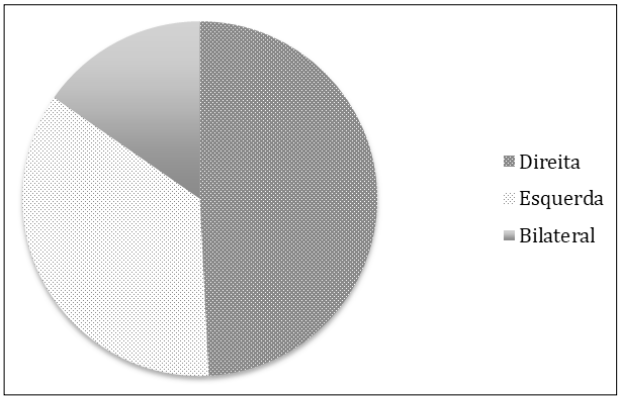
Early or late postoperative complications

Of the total of 313 patients who underwent open inguinal hernioplasty surgery, there were 49 (15.65%) complications in the early postoperative period. Of these, the main ones were post-spinal anesthesia headache in one case (2.04%), a cyst in the inguinal region (2.04%), a slight dehiscence of the surgical wound (2.04%), two cases of severe pain (4.08%), two situations of scrotal edema (4.08%), two cases of major edema (4.08%), one case of fever (2.04%), nine bruises (18.37%), two incarcerated hernias (4.08%), eight infections (16.32%), one case of orchialgia (2.04%), four orchitis (8.16%), one case of bleeding (2.04%) and 11 seromas (22.45%). Table 1 explains the acute complications. In the case of complications in the late postoperative period, there were nine cases (2.88%), of which the following stand out: chronic pain in two cases (22.22%), scrotal edema in one case (11.11%), two cases of inguinodynia (22.22%), one paresis at the surgery site (11.11%), bilateral recurrence (11.11%) and one unilateral recurrence (11.11%). Chart 3 quantifies chronic complications.

Profile of complications in the analyzed sample

Of the 30 women, two had complications in the immediate postoperative period (6.67%), one of which

GRAPH 1. LOCATION OF INGUINAL HERNIA IN PATIENTS WHO UNDERWENT INGUINAL HERNIOPLASTY



GRAPH 2. LENGTH OF HOSPITAL STAY OF PATIENTS UNDERGOING INGUINAL HERNIOPLASTY

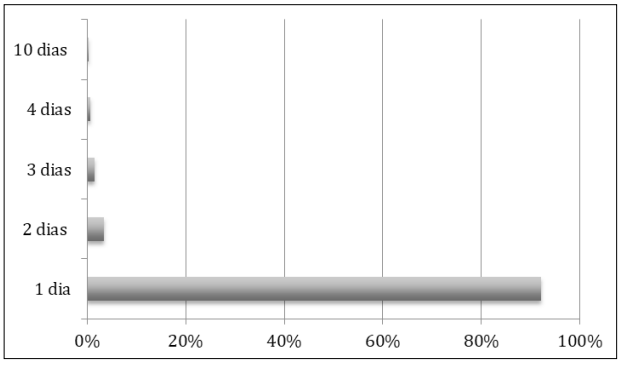
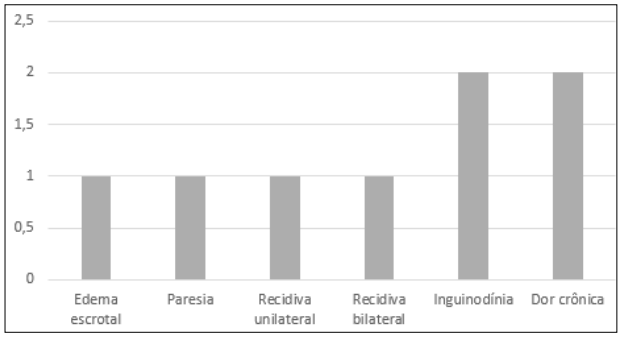


TABLE 1. ABSOLUTE AND RELATIVE FREQUENCIES OF ACUTE COMPLICATIONS

Acute complication	Absolute frequency	Relative frequency (%)
Post-spinal anesthesia headache	1	2.04
Inguinal cyst	1	2.04
Mild surgical wound dehiscence	1	2.04
Fever	1	2.04
Orchialgia	1	2.04
Bleeding	1	2.04
Severe pain	2	4.08
Scrotal edema	2	4.08
Major edema	2	4.08
Imprisoned hernia	2	4.08
Orchitis	4	8.16
Infection	8	16.32
Bruise	9	18.37
Seroma	11	22.45

GRAPH 3. ABSOLUTE FREQUENCY OF THE MAIN CHRONIC COMPLICATIONS



was infection and the other, hematoma. Of the 30 women, one (3.33%) presented complications in the late postoperative period, which was local pain. Of the 283 men, 47 (16.6%) had complications in the immediate postoperative period and eight (2.83%) had complications in the late postoperative period. There were more acute complications in men (p = 0.2357) and a higher incidence of chronic complications in women (p> 0.99999999). In neither case there was statistical significance (p <0.05) in relation to the higher incidence of early or late postoperative complications in men or women.

Of the total of 130 patients (41.53%) who did not present any comorbidity, 11 (8.46%) presented complications in the immediate postoperative period and three (2.31%) presented complications in the late postoperative period. Of the 183 patients who had some comorbidity (58.47%), 38 had complications in the immediate postoperative period (20.76%) and nine had complications in the late postoperative period (4.8%). Regarding the group without comorbidities and the group with comorbidities, when comparing the incidence of acute complications, the *p* was 0.004148; for late complications, *p* was 0.3778. The presence of comorbidities affected the immediate postoperative period, but not the late postoperative period.

Of the 202 patients under 65 years old (including those who were 65 years old), 30 (14.85%) had acute complications and six (2.97%) had chronic complications. Of the 110 patients over 65 years old, 19 had acute complications (17.27%) and three had chronic complications (2.73%). The *p* in both groups (first group including patients under 65 years old and second group including patients over 65 years old) for acute complications was 0.6836, and for chronic complications was >0.99999999.

Regarding the 278 patients without recurrent hernia, 45 had acute complications (16.19%) and five had chronic complications (1.80%). Of the 33 patients with recurrent hernia, four had acute complications (12.12%) and four had chronic complications (12.12%). The *p* for acute complications (comparing patients who had no recurrent hernia and patients who had recurrent hernia) was 0.7561, and for chronic complications was 0.01822.

A comparison was made between patients with recurrent inguinal hernia with comorbidities and patients with recurrent inguinal hernia without comorbidities. There were nine patients with recurrent hernia without comorbidities, and of these, two had acute complications (22.22%) and two had chronic complications (22.22%). In a total of 24 patients with recurrent hernia with comorbidities, two of them had acute complications (8.33%) and two had chronic complications (8.33%). The *p* for acute and chronic complications was the same (p = 0.5903).

The main comorbidities analyzed were diabetes in 30 cases (9.58%), hypertension in 107 (34.18%), smoking in 52 (16.61%), immunosuppression in four (1.28%), anxiety-depressive disorder in 16 (5.11%), obesity in three (0.96%), cardiac disorders in 17 (5.43%), COPD in ten (3.19%) and hypothyroidism in 14 (4.47%), according to Graph 4. It was noticed that these did not present a significant relationship with chronic complications, however, hypertension and smoking were relevant in the incidence of acute complications, as shown in Table 2 below.

DISCUSSION

According to current literature, hernias[1] "correspond to the partial or total protrusion of a viscera or organ contained in a bag with peritoneal lining outside the abdominal wall through a defect in the muscle-aponeurotic wall". Hernias can occur in different positions: umbilical (10%), epigastric (6%), incisional (10%), femoral (5%) or the most common one, inguinal (69%). The only definitive treatment available for hernias is surgical. Despite the large number of techniques available for treatment, the use of meshes has been recommended in the surgical correction of this pathology[3]. In our study, the mesh was placed in 300 cases (95.85%), except for those in which there was infection or when the hernia was infected, since in these cases there is less benefit in placing the mesh and a large increase in morbidity.

GRAPH 4. MAIN COMORBIDITIES FOUND IN RELATIVE FREQUENCY (%)

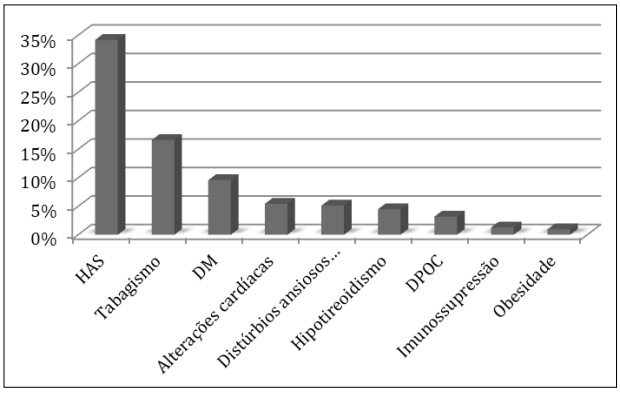


TABLE 2. MAIN COMORBIDITIES AND THEIR RELATIONSHIP WITH ACUTE AND CHRONIC COMPLICATIONS

Comorbidities	Acute complications	p	Chronic complications	p
Diabetes	7 (23.33%)	0.3369	3 (0.1%)	0.09006
Hypertension	24 (22.43%)	0.02927	4 (3.74%)	>0.9999999
Smoking	14 (26.92%)	0.03196	1 (1.92%)	>0.9999999
Immunosuppression	0	-	0	-
Anxiety-depression disorder	3 (18.75%) 0.5500	-	1 (6.25%)	0.7606
Obesity	1 (33.33%)	-	0	-
Cardiac alterations	3 (17.65%)	-	0	-
COPD	0	-	0	-
Hypothyroidism	2 (14.29%)	>0.9999999	1 (7.14%)	0.6824

There are techniques that use only primary aponeurotic sutures – which must be tension-free – and techniques that use synthetic prostheses, the meshes, which is the case in this study[4]. Inguinal hernias are more common indirect, unilateral, on the right side and in men, with the risk of presenting this change throughout life being 27% in men and 3% in women[5]. The epidemiological data from the studies already carried out coincide with this research, since in 263 cases (84.02%) the hernias were unilateral, in 152 patients (48.56%) they occurred on the right, and the study sample consisted of 283 men (90.42%), against 30 women (9.58%). Bilateral ones are rarer (they affect about 12% of patients), with direct and mixed ones being more frequent than indirect ones[6]. Regarding bilateral hernias, there was an incidence of 48 cases (15.33%).

Risk factors that are useful in predicting complications in an adult patient with an inguinal hernia include old age, short duration, femoral hernia and coexisting medical disease[7]. A study carried out in 2013, covering patients over 50 years old and who underwent inguinal hernioplasty, showed that the short-term morbidity of patients undergoing tension-free surgery was: postoperative urinary retention (1.75%), infection at the surgical site (superficial wound infection) (1.75%) and scrotal edema (3.5%)[7]. Making a comparison with our study, it is noticed that there was a higher incidence of immediate complications in patients older than 65 years of age, in comparison with the group of patients who are not elderly, but there was no statistically significant correlation (p = 0.6836). Regarding chronic complications, there was neither a higher incidence in the elderly population nor statistical significance (p> 0.99999999). It was also not possible to verify that elderly patients with comorbidities had a higher rate of acute complications (p = 0.2359) compared to a group of elderly people without comorbidities, or of chronic complications (p = 0.5365). On the other hand, the study shows that the population with comorbidities who underwent open inguinal hernioplasty has a higher risk of developing acute complications (p = 0.004148) compared to patients without comorbidities who underwent the same surgery, but there is no statistically significant increase in the incidence of chronic complications (p = 0.3778).

According to studies previously carried out, the main complications in the immediate postoperative period include pain (27.7%), seroma (1.5%), infection (1.5%) and ecchymosis (1.5%), but most patients (61.5%) have no complications during this period[8]. These data are not very similar to the present study, since from the sample studied, there were two cases of severe pain (4.08%), 11 cases of seroma (22.45%), eight cases of infection (16.32%) and nine cases of hematoma (18.37%). Among the other acute complications in our research, the following stand out: post-spinal anesthesia headache (2.04%), one inguinal cyst (2.04%), one mild surgical wound dehiscence (2.04%), two cases of scrotal edema (4.08%), two cases of major edema (4.08%), one case of fever (2.04%), two cases of incarcerated hernia (4.08%), one case of orchialgia (2.04%), four cases of orchitis (8.16%) and one case of bleeding (2.04%).

In the case of chronic complications in the late postoperative period, studies show a lower complication rate (5%), with a predominance of inguinodynia (3%) and local burning (2%)[8]. In the sample analyzed, there were 9 cases (2.88%) of chronic complications, of which chronic pain was more relevant in 2 cases (22.22%), scrotal edema in 1 case (11.11%), 2 cases of inguinodynia (22.22%), one paresis at the surgery site (11.11%), one bilateral recurrence (11.11%) and one unilateral recurrence (11.11%). It was also noticed that patients who presented recurrent hernia had higher rates of complications in the late postoperative period (p = 0.01822).

Literature data show that the presence of comorbidities is a factor that significantly influences the incidence of postoperative complications in inguinal hernioplasty[9-21]. Diabetes appears to increase the risk of postoperative complications within 30 days of inguinal hernia surgery, especially for complicated diabetes, but this disease does not appear to increase the long-term risk of reoperation for recurrence[9]. In contrast, this study did not show an increase in the incidence of acute (p = 0.3369) or chronic (p = 0.09006) complications in diabetic patients compared to non-diabetic individuals.

In addition to diabetes, other comorbidities quite present in the population, such as hypertension, smoking, immunosuppression, anxiety-depressive disorder, obesity, cardiac disorders, COPD and hypothyroidism were also analyzed. It was noticed that for chronic complications, none of them influenced significantly statistically (p> 0.05), but for acute complications, the presence of hypertension (p = 0.02927) and also smoking (p = 0, 03196) was decisive for the increase of these complications.

CONCLUSION

Inguinal hernia is one of the main surgical pathologies present in adult patients, and it is essential to know not only the surgical technique, but mainly the surgical clinic, in relation to the aspects involved in the preoperative and also its outcome. Among these issues, the study of the comorbidities of patients undergoing inguinal hernioplasty stands out, since the present study highlighted that the presence of systemic arterial hypertension and smoking have a statistically significant influence on the incidence of acute postoperative complications. Adequate control of these issues in the preoperative period and adequate guidance to the patient can help in the optimization of the surgical process of correcting inguinal hernia.

RESUMO

INTRODUÇÃO: *As hérnias da parede abdominal constituem uma patologia de alta prevalência; 55% da população mundial é acometida por essa enfermidade em algum momento de suas vidas. Como grande parte desses pacientes apresenta comorbidades, torna-se importante correlacionar a incidência de complicações com a presença de patologias prévias.*

OBJETIVOS: *Avaliar se a presença de comorbidades no paciente submetido a hernioplastia inguinal aumenta o risco de complicações agudas e crônicas no pós-operatório, bem como explicitar quais dessas doenças prévias apresentam maior associação com a incidência de complicações.*

METODOLOGIA: *Trata-se de um estudo transversal descritivo realizado por meio da análise retrospectiva de 313 prontuários dos pacientes submetidos à cirurgia de hernioplastia inguinal aberta, entre março e junho de 2017, no Serviço de Cirurgia Geral do Hospital Cruz Vermelha – Filial Paraná, localizado na cidade de Curitiba, estado do Paraná, Brasil.*

RESULTADOS: *Dos 313 casos estudados, as comorbidades mais prevalentes foram: 107 pacientes com HAS (34,19%), 52 com tabagismo (16,61%), 30 casos com diabetes (9,58%), 14 com hipotireoidismo (4,47%) e 10 com DPOC (3,19%). Em relação ao total da amostra avaliada, 130 pacientes (41,53%) não apresentaram nenhuma comorbidade. Ao avaliar as complicações, houve 49 casos (15,65%) de complicações no pós-operatório precoce e nove casos (2,88%) de complicações crônicas. As comorbidades que apresentaram influência significativamente estatística (p<0,05) na incidência de complicações agudas foram HAS (p=0,02927) e tabagismo (p=0,03196).*

CONCLUSÃO: *Percebe-se correlação importante entre a presença de complicações agudas no pós-operatório de hernioplastia inguinal nos pacientes que apresentam HAS ou tabagismo, doenças de alta prevalência.*

PALAVRAS-CHAVE: *Hérnia inguinal. Herniorrafia. Complicações pós-operatórias.*

REFERENCES

1. Grossi JV, Cavazzola LT, Breigeiron R. Inguinal hernia repair: can one identify the three main nerves of the region? Rev Col Bras Cir. 2015;42(3):149-53.
2. Goulart A, Martins S. Hérnia inguinal: anatomia, patofisiologia, diagnóstico e tratamento. Rev Port Cir. 2015;33:25-42.
3. Mizrahi H, Parker MC. Management of asymptomatic inguinal hernia: a systematic review of the evidence. Arch Surg. 2012;147(3):277-81.
4. Naveen N, Srinath R. A comparative study between modified Bassini's repair and Lichtenstein mesh repair (LMR) of inguinal hernias in rural population. J Clin Diagn Res. 2014;8(2):88-91.
5. Primatesta P, Goldacre MJ. Inguinal hernia repair: incidence of elective and emergency surgery, readmission and mortality. Int J Epidemiol. 1996;25(4):835-9.

6. Maciel GSB, Simões RL, Carmo FPT, Garcia JWR, Paulo DNS. Resultados da herniorrafia inguinal bilateral simultânea pela técnica de Lichtenstein. Rev Col Bras Cir. 2013;40(5):370-3.

7. Shyam DC, Rapsang AG. Inguinal hernias in patients of 50 years and above. Pattern and outcome. Rev Col Bras Cir. 2013;40(5):374-9.

8. Malik AM, Khan A, Talpur KA, Laghari AA. Factors influencing morbidity and mortality in elderly population undergoing inguinal hernia surgery. J Pak Med Assoc. 2010;60(1):45-7.

9. Mansouri M, Ekjam S, Hudairi A, Sannussi OI, Fakheri A. Emergency abdominal surgery in Libyan elderly patients. Sci Med J. 2005;17(3):57-65.

10. Gautam PV, Litake MM. A comparative study between STOPPA repair and Lichtenstein MESH repair in the treatment of bilateral inguinal hernia. Indian J Basic Appl Med Res. 2017;6(2):569-74.

11. Paajanen H. Do absorbable mesh sutures cause less chronic pain than nonabsorbable sutures after Lichtenstein inguinal herniorraphy? Hernia. 2002;6(1):26-8.

12. Minossi JG, Minossi VV, Silva AL. Manejo da dor inguinal crônica pós-hernioplastia (inguinodinia). Rev Col Bras Cir. 2011;38(1):59-65.

13. Vianna JLCM, Silva AL, Alves AS, Oliveira CA, Vieira Júnior A. Comparação entre as técnicas de Shouldice e Falci-Lichtenstein, no tratamento das hérnias inguinais em homens. Rev Col Bras Cir. 2004;31(2):117-23.

14. Hellspong G, Gunnarsson U, Dahlstrand U, Sandblom G. Diabetes as a risk factor in patients undergoing groin hernia surgery. Langenbecks Arch Surg. 2017;402(2):219-25.

15. Bugada D, Lavand'homme P, Ambrosoli AL, Cappelleri G, Saccani Jotti GM, Meschi T, et al. Effect of preoperative inflammatory status and comorbidities on pain resolution and persistent postsurgical pain after inguinal hernia repair. Mediators Inflamm. 2016;2016:5830347.

16. Rühling V, Gunnarsson U, Dahlstrand U, Sandblom G. Wound healing following open groin hernia surgery: the impact of comorbidity. World J Surg. 2015;39(10):2392-9.

17. Lagoo J, Wilkinson J, Thacker J, Deshmukh M, Khorgade S, Bang R. Impact of anemia on surgical outcomes: innovative interventions in resource-poor settings. World J Surg. 2012;36(9):2080-9.

18. Klinge U, Weyhe D. Hernia surgery: minimization of complications by selection of the "correct mesh". Chirurg. 2014;85(2):105-11.

19. Compagna R, Rossi R, Fappiano F, Bianco T, Accurso A, Danzi M, et al. Emergency groin hernia repair: implications in elderly. BMC Surg. 2013;13(Suppl. 2):S29.

20. Ozdemir T, Arıkan A. Postoperative apnea after inguinal hernia repair in formerly premature infants: impacts of gestational age, postconceptional age and comorbidities. Pediatr Surg Int. 2013;29(8):801-4.

21. Yunis J. Critical issues in groin hernia management. Surg Technol Int. 2009;18:119-24.

ORIGINAL ARTICLE

Prevalence of arterial hypertension and associated factors: a population-based study

Layanne Cristina de Carvalho Lavôr[1]
Rosana Rodrigues de Sousa[1]
Lays Arnaud Rosal Lopes Rodrigues[1]
Onias de Sousa Rodrigues Filho[2]
Adriana de Azevedo Paiva[1]
Karoline de Macêdo Gonçalves Frota[1]

1. Departamento de Nutrição, Centro de Ciências da Saúde, Universidade Federal do Piauí, Teresina, PI, Brasil.
2. Hospital Universitário da Universidade Federal do Piauí, Teresina, PI, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.630

SUMMARY

OBJECTIVE: *To estimate the prevalence of hypertension in adults and analyze its association with socioeconomic, demographic, and lifestyle risk factors.*

METHODS: *Home-based cross-sectional epidemiological study conducted with adults of both sexes living in the cities of Teresina and Picos (PI). The prevalence of hypertension was estimated by self-reported diagnosis. The associations between hypertension and the following variables were tested: age, gender, skin color, education, family income, marital status, alcohol and cigarette consumption, physical activity, and nutritional status.*

RESULTS: *A total of 1,057 adult individuals with a mean age of 38.6 ± 11.5 years participated in the study, of which 62.3% were female. The prevalence of hypertension in the population was 16.4%. In the crude analysis, a significant association was observed between the prevalence of hypertension and factors such as older age, lower education, single marital status, brown skin color, smoking, and overweight ($p < 0.05$). However, after adjustments, only the associations with older age, brown skin color, sedentary lifestyle and overweight remained significant.*

CONCLUSION: *Older age, brown skin color, sedentary lifestyle, and the presence of overweight or obesity were significantly associated with hypertension. Among the modifiable risk factors, a sedentary lifestyle and overweight stand out as important for the genesis of hypertension, subject to intervention measures.*

KEYWORDS: *Hypertension. Adult health. Health surveys. Risk factors.*

INTRODUCTION

Elevations in arterial pressure have been recognized as a health problem due to their impact on the mortality of the world population. Systemic arterial hypertension (SAH) is an important risk factor for cardiovascular diseases, and is responsible for 62% of cerebral vascular accidents and 49% of coronary artery diseases and renal diseases, with a significant contribution to the global burden of disease and years of life lost due to disability. Such consequences entail increased costs of health systems and relevant socioeconomic impact[1,2].

SAH is a challenge for public health with

DATE OF SUBMISSION: 31-Oct-2019
DATE OF ACCEPTANCE: 29-Dec-2019
CORRESPONDING AUTHOR: Karoline Frota
Ininga Teresina – Teresina, Piauí – Brasil 64.049-550 Tel:86981933610
E-mail: karolfrota@ufpi.edu.br

approximately 600 million hypertensive individuals worldwide and a tendency of a significant increase in its prevalence, with estimates of a global growth of 60% of the cases by 2025. In Brasil, it affects 32.5% (36 million) of adult individuals. In Teresina, in the Piauí state, the prevalence of self-reported hypertension is 20.8%[3-5].

Factors such as age, sex, education, smoking, alcoholism, and marital status have been associated with changes in blood pressure. Other factors such as population aging and behavioral factors, such as changes in dietary patterns and physical inactivity, have been attributed to the progressive increase of overweight and obesity, which are directly related to an increase in the prevalence of SAH[6,7].

Population health surveys have been increasingly used and are essential for establishing the health profile, distribution of risk factors and their trends, in addition to providing information about self-referred morbidity and lifestyle. Repeated with a certain periodicity, the surveys allow to consolidate information collected as a reference population database to surveil several chronic diseases and their determining factors[8].

Even with the advances in health, there are still controversial issues on SAH, especially regarding etiological and pathophysiological aspects that suggest appropriate forms of prophylaxis and early identification of the population at risk for hypertension[9].

Due to the high prevalence of SAH in the Brazilian population and the magnitude of the impact of its consequences in health and, consequently, in the productive capacity of the economically active population, which leads also to a greater financial impact in families, society, and the government, it is important to know the determining factors of this pathology to provide data that subsidize actions and policies of prevention and control.

Therefore, the objective of this study was to estimate the prevalence of arterial hypertension in adults of two municipalities of Piauí and analyze its association with socioeconomic, demographic, and lifestyle risk factors.

METHODS

This is a cross-sectional epidemiological study, household-based, with data from the Population-Based Health Survey in the Municipalities of Teresina and Picos - PI (ISAD-PI). For this study, we used a sample of 1057 adult individuals aged between 20 and 59 years.

The sample size was calculated based on complex probability sampling, by conglomerates, in two stages: the census sector and household. To improve the efficiency of sampling, the census sectors of the urban area were, when necessary, fanned or grouped according to pre-established criteria to obtain the primary sampling units (PSUs), which were then ordered, with probability proportional to size, so that all socioeconomic groups were represented.

In the second stage, thirty (30) sectors were systematically selected with probability proportional to size within each PSU and, finally, a systematic sampling of 25 to 30 households was randomly selected in each sector, in the cities of Teresina and Picos (PI), with an expectation of 20% of loss and 5% of closed households. All those residing in the households selected were invited to participate in the research.

The demographic, socioeconomic, lifestyle, and health profile data were obtained through structured questionnaires, adapted from surveys used previously in other Brazilian epidemiological studies[8,10]. The questionnaires were administered by trained researchers, using the Epicollect 5® application (*Imperial College London*) on mobile devices (https://five.epicollect.net/project/isad).

We collected data on demographic (age, gender, self-reported skin color, marital status, education), socioeconomic (family income), lifestyle (physical activity, smoking, and alcoholism), and self-reported medical diagnosis of hypertension. After the survey, we conducted an anthropometric assessment. In the case of closed households (absence), the interviewer returned up to three times before considering sample loss.

The anthropometric measurement was performed twice in each individual. The data of height and weight were measured according to the recommendations of Cameron[11] and Jelliffe & Jelliffe[12]. The weight was measured in kilograms (kg) using the SECA® digital scale, with a maximum capacity of 150 kg and an accuracy of 0.1 Kg. Height was measured in meters using a portable stadiometer, with an accuracy of 0.1 cm.

The classification of nutritional status was performed from the calculation of Body Mass Index (BMI), by dividing the weight in kilograms by the height in square meters[13]. The subsequent classification into underweight/eutrophic, overweight, and obesity was done according to the classification proposed by the WHO (2000).

All statistical analyzes were performed using the

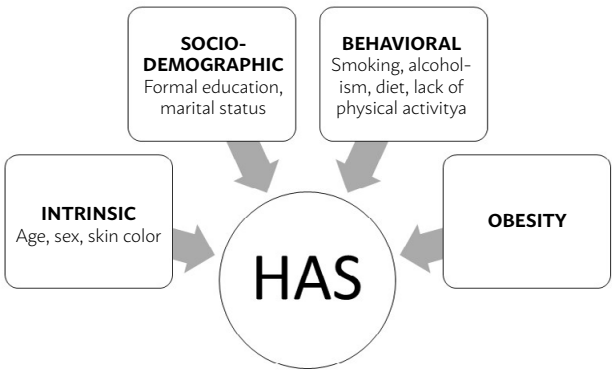


FIGURE 1. FACTORS ASSOCIATED WITH THE DEVELOPMENT OF SYSTEMIC ARTERIAL HYPERTENSION. LAVOR ET AL., 2019.

Stata version 13.0 software (*Stata Corporation, College Station*, TX, United States 13.0). The categorical variables were presented as absolute and relative frequencies. Pearson's chi-square test was applied to verify the association between the categorical variables. The association between hypertension and associated factors was by Poisson regression with robust variance, expressed as Prevalence Ratios (PR) and confidence intervals of 95% (95). The results were expressed in crude analysis and adjusted for potential confounding factors. |Variables with p<0.20 in the crude analysis were kept in the model. For all statistical tests, p-values <0.05 were established as statistically significant.

The research was approved by the Research Ethics Committee of the Federal University of Piauí (CEP/UFPI), decision No. 2.552 .426, pursuant to the legislation of ethics in research involving human beings, Resolution 466/12[14].

RESULTS

Of the 1,057 adults in the study, 658 (62.3%) were female. The average age of the population was 38.6 ± 11.5 years; 37.6 ± 11.6 for males and 39.3 ± 11.5 for females. As for the sociodemographic characteristics, most of the population were aged between 40 and 59 years, had studied up Upper Secondary Education, had a family income lower than two minimum wages per month, brown skin color, and were married or in a stable union (Table 1). With respect to lifestyle, most of the population did not smoke nor consumed alcohol in an abusive manner. However, 77.2% of the participants were sedentary, and 59.7% had excess weight.

The overall prevalence of SAH in the adult population was 16.4% (n=166), and it was significantly

TABLE 1. DESCRIPTIVE CHARACTERISTICS OF THE STUDY POPULATION.

Variables	n (%)	Prevalence of hypertension n (%)
Age		
20-29	276 (26.1)	11 (4.15)
30-39	284 (26.9)	28 (10.4)
40-59	497 (47.0)	127 (26.7)
Sex		
Male	399 (37.7)	59 (15.5)*
Female	658 (62.3)	107 (17.0)*
Formal education		
Illiterate	30 (2.8)	11 (6.5)
Elementary Education	303 (28.7)	69 (41.0)
Secondary Education	393 (37.2)	48 (28.6)
Higher Education	331 (31.3)	40 (23.8)
Family income		
≤ 2 minimum wages	599 (63.4)	107 (18.2)
> 2 minimum wages	346 (36.6)	48 (14.3)
Skin color		
White	185 (17.9)	38 (22.9)
Black	147 (14.3)	30 (18.1)
Brown	623 (60.5)	90 (54.2)
Others	75 (7.3)	8 (4.8)
Marital status		
Married	614 (59.6)	112 (18.5)
Single	330 (32.0)	37 (11.4)
Widowed/divorced	86(8.4)	17 (21.0)
Smoker		
Yes	226 (22.0)	109 (13.9)
No	800 (78.0)	57 (25.4)
Alcohol consumption		
Yes	158 (15.4)	25 (16.3)
No	869 (84.6)	140 (16.4)
Physical activity (n=960)		
Active	219 (22.8)	29 (13.9)
Sedentary	741 (77.2)	122 (17.2)
Nutritional status		
Eutrophy	424 (40.3)	35 (8.62)
Overweight	392 (37.2)	62 (16.5)
Obesity	237 (22.5)	69 (30.4)

associated with increased age, less schooling, single marital status, brown skin color, smoking, and excess weight. The population aged 40 to 59 years presented a prevalence ratio 6.44 times greater in relation to younger adults aged 20 to 29 years. Regarding the nutritional status, obese individuals presented a prevalence ratio for hypertension 3.52 times greater when compared to eutrophic individuals (Table 2).

However, after adjustments for the variables of age and skin color, only the SAH prevalence reasons of increased age, brown skin color, and excess

TABLE 2. PREVALENCE AND PREVALENCE RATIO OF ARTERIAL HYPERTENSION ACCORDING TO SOCIODEMOGRAPHIC, LIFESTYLE, AND NUTRITIONAL STATUS VARIABLES

	Prevalence ratio (PR)			
Variables	Crude (CI)	p	Adjusted (CI)*	p
Age				
20-29	1.0		1.0	
30-39	2.49 (1.2-4.9)	0.008	2.58 (1.3-5.2)	0.008
40-59	6.44 (3.5-11.7)	0.001	6.67 (3.6-12.3)	0.001
Gender				
Male	1.0		1.0	
Female	1.10 (0.79-1.50)	0.562	1.02 (0.74-1.40)	0.887
Formal education				
Illiterate	3.14 (1.60-6.13)	0.001	1.67 (0.85-3.30)	0.136
Elementary Education	1.89 (1.27-2.79)	0.001	1.21 (0.81-1.81)	0.350
Secondary Education	0.98 (0.63-1.49)	0.921	0.86 (0.56-1.31)	0.496
Higher Education	1.0		1.0	
Family income				
> 2 minimum wages	1.0		1.0	
≤ 2 minimum wages	1.27 (0.90-1.78)	0.166	1.24 (0.88-1.74)	0.210
Skin color				
White	1.0		1.0	
Black	0.98 (0.60-1.58)	0.934	1.03 (0.64-1.66)	0.895
Brown	0.69 (0.47-1.01)	0.063	0.66 (0.45-0.96)	0.033
Others	0.51 (0.24-1.09)	0.085	0.47 (0.22-1.02)	0.058
Marital status				
Married	1.0		1.0	
Single	0.61 (0.43-0.87)	0.011	1.06 (0.72-1.57)	0.734
Widowed/divorced	1.13 (0.71-1.78)	0.634	0.93 (0.56-1.56)	0.803
Smoking				
No	1.0		1.0	
Yes	1.82 (1.32-2.31)	0.001	1.37 (0.1-1.9)	0.057
Alcohol consumption				
No	1.0	0.979	1.0	0.843
Yes	0.99 (0.64-1.52)		1.04 (0.7-1.6)	
Physical activity				
Active	1.0		1.0	
Sedentary	1.23 (0.82-1.85)	0.301	1.53 (1.01-2.30)	0.040
Nutritional status				
Eutrophy	1.0		1.0	
Overweight	1.91 (1.26-2.90)	0.002	1.56 (1.03-2.37)	0.035
Obesity	3.52 (2.34-5.29)	0.001	2.64 (1.75-3.98)	0.001

*Adjusted for age and skin color.

weight remained significant. In addition, after these adjustments, sedentary individuals showed a ratio of prevalence 1.53 times higher for hypertension when compared to active individuals.

DISCUSSION

The prevalence of hypertension found in this study was 16.4% for adult individuals aged from 20 to 59 years, residents of the cities of Teresina and Picos (PI). This value was similar to that found in a study conducted on adults living in Campinas, whose prevalence of hypertension was 14.0[15]. On the other hand, the prevalence of the disease found in this study was lower than that found in a study performed with adults of the *sertão* region of Pernambuco, which was 27.4%[16]. This divergence between the studies may be due to differences in how the diagnosis of hypertension was obtained since, in the present study, it was self-reported form, whereas in the study mentioned it was measured.

The prevalence of hypertension was significantly associated with increased age, and this association remained significant even after adjustments for skin color. Similar results were observed in other Brazilian population studies[15,17-19]. The higher prevalence of hypertension in the population with advanced age may be explained by the natural hardening of arteries and aortas that occurs with the increase of age[20]. Over time, the walls of the great arteries, especially the aorta, thicken and lose elasticity, and this process results in an increased pulse wave velocity, a reliable measure of arterial stiffness. This increase of stiffness would reduce the dampening function of the arteries near the heart as well as increase the pulse wave velocity, causing higher systolic and pulse pressure[21].

As to the level of schooling, we found that the less formal education, the greater the prevalence ratio for arterial hypertension. This fact has been corroborated by other studies[15.17]. However, after adjustments for confounding variables, schooling was not significantly associated with hypertension.

As to skin color, we observed a significant association between individuals that self-reported as brown-skinned and the prevalence of hypertension, regardless of age, and we observed a lower ratio of prevalence of the disease in these individuals when compared to blacks and whites. This goes against the findings of a systematic review in which most of the studies investigated found that individuals of non-white skin color had a higher prevalence of SAH[22].

Regarding marital status, single individuals were significantly associated with the prevalence of hypertension, indicating protection against the outcome, since unmarried individuals showed less prevalence of hypertension when compared to those married, widowed, or divorced. This result corroborates that found by Zangirolani et al.[15], who observed a higher prevalence of the disease in individuals separated or widowed when compared to singles. However, in the present study, in the adjusted analysis, this association was not statistically significant.

In the crude analysis of the prevalence ratio, smoking was significantly associated with hypertension in our population, corroborating other studies performed with Brazilian adults [15,16,23]. Smoking causes higher blood pressure, increasing up to two times the risk of hypertension and causing a greater variability in blood pressure levels, which can lead to injuries in target organs[24]. However, in the present study, after adjustments for confounding variables, the association between smoking and hypertension was not significant.

Regarding physical activity, we observed that after the Poisson regression analysis adjusted for age and skin color, individuals with a sedentary lifestyle had a prevalence ratio significantly 1.53 times greater for hypertension when compared to active individuals. This corroborates the already well-established role of physical inactivity as an important risk factor for chronic non-communicable diseases, which are responsible for more than three million deaths yearly[15]. Several mechanisms explain the relationship between the regular practice of physical activity and the reduction of blood pressure levels, such as the improvement of oxidative stress, inflammation, endothelial function, body mass index, as well as the activity of the renin-angiotensin system, the parasympathetic system, renal function, and insulin sensitivity[25].

In the present study, the presence of excess weight and obesity presented as an important factor associated with the presence of hypertension in the adult population, increasing significantly the prevalence ratio for hypertension, the higher the condition of excess weight. In a systematic review, obesity appeared as the main anthropometric factor associated with the prevalence of SAH[24]. This was also observed in other Brazilian studies[15-19]. It is estimated that between 20 to 30% of the prevalence of this pathology can be explained by the association between excess weight and its increased risk[19].

This study has limitations, such as the self-reported diagnosis of hypertension, which can result in the underdiagnosis of the disease since many individuals may be hypertensive but not aware of it. In addition, the cross-sectional nature of the study does not allow to establish relations of causality between the exposure to the factors and the development of the disease. The strength of this study is the representativeness of the sample, which includes the capital and a city in the interior of Minas Gerais.

CONCLUSION

In this study, factors such as age, brown skin color, sedentary lifestyle, and overweight or obesity were significantly associated with the presence of hypertension. Among the modifiable risk factors, we highlight sedentary lifestyles and excess weight as important for the genesis of hypertension and modifiable based on intervention measures. In this sense,

it is important to emphasize the role of public policies to prevent and control excess weight in the population by encouraging the practice of regular physical activity and aiming not only to reduce the risk of hypertension as well as other chronic non-communicable diseases.

Contribution of the authors

Layanne Cristina de Carvalho Lavôr: the original draft (leadership). Data collection (egalitarian) Conceptualization (egalitarian), formal analysis (leadership), methodology (leadership), project management (egalitarian), supervision (egalitarian), visualization (leadership). Rosana Rodrigues de Sousa, Lays Arnaud Rosal Lopes Rodrigues and Onias de Sousa Rodrigues Filho: Data collection (egalitarian) Conceptualization (egalitarian), formal analysis (leadership), methodology (leadership), project management (egalitarian), supervision (egalitarian), visualization (leadership). Adriana de Azevedo Paiva and Karoline de Macêdo Gonçalves Frota: Conceptualization (egalitarian), formal analysis (leadership), methodology (leadership), project management (leadership), supervision (leadership), visualization (leadership).

RESUMO

OBJETIVO: *Estimar a prevalência de hipertensão arterial em adultos e analisar sua associação com fatores de risco socioeconômicos, demográficos e de estilo de vida.*

MÉTODOS: *Estudo epidemiológico transversal, de base domiciliar, realizado com adultos de ambos os sexos residentes nas cidades de Teresina e Picos (PI). A prevalência de hipertensão arterial foi estimada por meio de diagnóstico autorreferido. Foram testadas as associações entre a hipertensão arterial e as variáveis: idade, sexo, cor da pele, escolaridade, renda familiar, situação conjugal, consumo de álcool e cigarro, prática de atividade física e estado nutricional.*

RESULTADOS: *Participaram do estudo 1.057 indivíduos adultos com média de idade de 38,6 ± 11,5 anos, sendo 62,3% do sexo feminino. A prevalência de hipertensão arterial na população foi de 16,4%. Na análise bruta, observou-se associação significativa entre a prevalência de hipertensão e fatores como maior idade, menor escolaridade, estado civil solteiro, cor da pele parda, tabagismo e excesso de peso (p<0,05). Entretanto, após ajustes, apenas as associações com a maior idade, cor da pele parda, estilo de vida sedentário e excesso de peso mantiveram-se significativas.*

CONCLUSÃO: *A idade mais avançada, cor da pele parda, sedentarismo e a presença de sobrepeso ou obesidade apresentaram-se significativamente associados à hipertensão. Dentre os fatores de risco modificáveis, destaca-se o sedentarismo e o excesso de peso como importantes para a gênese de hipertensão e passíveis de medidas de intervenção.*

PALAVRAS-CHAVE: *Hipertensão. Saúde do adulto. Inquéritos epidemiológicos. Fatores de risco.*

REFERENCES

1. Lackland DT, Weber MA. Global burden of cardiovascular disease and stroke: hypertension at the core. Can J Cardiol. 2015;31(5):569-71.
2. Rimárová K, Dorko E, Diabelková J, Sulinová Z, Frank K, Baková J, et al. Anthropometric predictors of systolic and diastolic blood pressure considering intersexual differences in a group of selected schoolchildren. Cent Eur J *Public Health*. 2018;26(Suppl):S4-S11.
3. World Health Organization. Global status report on noncommunicable diseases 2014. Geneva: World Health Organization; 2014. 298p.
4. Malachias MVB, Souza WKSB, Plavnik FL, Rodrigues CIS, Brandão AA, Neves MFT, et al. 7a Diretriz brasileira de hipertensão arterial. Arq Bras Cardiol. 2016;107(3 Supl. 3):1-83.
5. Brasil. Ministério da Saúde, Agência Nacional de Saúde Suplementar. Vigitel Brasil 2015. Saúde suplementar: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico. Brasília: Ministério da Saúde; 2017. 170p.
6. Sebati RB, Monyeki KD, Monyeki MS, Motloutsi B, Toriola AL, Monyeki MJ. Ellisras longitudinal study 2017: the relationship between waist circumference, waist-to-hip ratio, skinfolds and blood pressure among young adults in Ellisras, South Africa (ELS 14). Cardiovasc J Afr. 2018;30(1):24-8.
7. Luz RH, Barbosa AR, d'Orsi E. Waist circumference, body mass index and waist-height ratio: Are two indices better than one for identifying hypertension risk in older adults? Prev Med. 2016;93:76-81.
8. Szwarcwald CL, Malta DC, Pereira CA, Vieira MLFP, Conde WL, Souza Junior PRB, et al. Pesquisa Nacional de Saúde no Brasil: concepção e metodologia de aplicação. Ciênc Saúde Coletiva. 2014;19(2):333-42.
9. Barreto Neto AC, Araújo EC, Silva KVP, Pontes LM. Prevalência de hipertensão e fatores associados em adolescentes escolares no sertão de Pernambuco. Adolesc Saúde. 2010;7(4):22-9.
10. Fisberg RM, Marchioni DML. Manual de avaliação do consumo alimentar em estudos populacionais: a experiência do inquérito de saúde em São Paulo (ISA). São Paulo: Faculdade de Saúde Pública da Universidade de São Paulo, 2012. 197p.
11. Cameron N. Anthropometric measurements. In: The measurement of human growth. London: Croom Helm; 1984. p.56-99.
12. Jelliffe DB, Jelliffe EFP. Anthropometry: major measurements. In: Jelliffe DB, Patrice Jelliffe, EF, eds. Community nutritional assessment. Oxford: Oxford University Press; 1989. p.68-105.
13. World Health Organization. Report of a WHO Consultation (WHO Technical Report Series 894). Geneva: World Health Organization; 2000.
14. Brasil. Ministério da Saúde. Resolução n. 466/12. Conselho Nacional de Pesquisa com Seres Humanos. Diário Oficial da União. Brasília: Ministério da Saúde; 2012.
15. Zangirolani LTO, Assumpção D, Medeiros MAT, Barros MBA. Hipertensão arterial autorreferida em adultos residentes em Campinas, São Paulo, Brasil:

prevalência, fatores associados e práticas de controle em estudo de base populacional. Ciênc Saúde Coletiva. 2018;23(4):1221-32.

16. Santiago ERC, Diniz AS, Oliveira JS, Leal VS, Andrade MIS, Lira PIC. Prevalência e fatores associados à hipertensão arterial sistêmica em adultos do sertão de Pernambuco, Brasil. Arq Bras Cardiol. 2019;113(4):687-95.

17. Silva EC, Martins MSAS, Guimarães LV, Segri NJ, Lopes MAL, Espinosa MM. Prevalência de hipertensão arterial sistêmica e fatores associados em homens e mulheres residentes em municípios da Amazônia Legal. Rev Bras Epidemiol. 2016;19(1):38-51.

18. Andrade SSCA, Malta DC, Iser BM, Sampaio PC, Moura L. Prevalência da hipertensão arterial autorreferida nas capitais brasileiras em 2011 e análise de sua tendência no período de 2006 a 2011. Rev Bras Epidemiol. 2014;(suppl PeNSE):215-26.

19. Muraro AP, Santos DF, Rodrigues PRM, Braga JU. Fatores associados à hipertensão arterial sistêmica autorreferida segundo VIGITEL nas 26 capitais brasileiras e no Distrito Federal em 2008. Ciênc Saúde Coletiva. 2013;18(5):1387-98.

20. Singh S, Shankar R, Singh GP. Prevalence and associated risk factors of hypertension: a cross-sectional study in urban Varanasi. Int J Hypertens. 2017;2017;5491838.

21. Sun Z. Aging, arterial stiffness and hypertension. Hypertension. 2015;65(2):252-6.

22. Galvão RRS, Soares DA. Prevalência de hipertensão arterial e fatores associados em adultos: uma revisão na literatura brasileira. Rev APS. 2016;19(1):139-49.

23. Malta DC, Bernal RTI, Andrade SSCA, Silva MMA, Velasquez-Melendez G. Prevalência e fatores associados com hipertensão arterial autorreferida em adultos brasileiros. Rev Saúde Pública. 2017;51(supl. 1):11s.

24. Marques AP, Szwarcwald CL, Pires DC, Rodrigues JM, Almeida WS, Romero D. Fatores associados à hipertensão arterial: uma revisão sistemática. Cien Saude Colet [periódico na internet] (2018/Out). [cited 2019 Oct 3]. Available from: http://www.cienciaesaudecoletiva.com.br/artigos/fatores-associados-a-hipertensao-arterial-uma-revisao-sistematica/16981?id=16981

25. Hegde SM, Solomon SD. Influence of physical activity on hypertension and cardiac structure and function. Curr Hypertens Rep. 2015;17(10):77.

ORIGINAL ARTICLE

Musculoskeletal computational analysis on muscle mechanical characteristics of drivers' lumbar vertebras and legs in different sitting postures

Fei Gao[1, 2]
Shi Zong[3]
Zhi-Wu Han[2]
Yang Xiao[1]
Zhen-Hai Gao[1]

1. State Key Laboratory of Automotive Simulation and Control, Jilin University, Changchun, 130025, China
2. Key Laboratory of Bionic Engineering (Ministry of Education), Jilin University, Changchun, 130022, Jilin, P. R. China
3. China-Japan Union Hospital of Jilin University, Changchun, 130033, China

http://dx.doi.org/10.1590/1806-9282.66.5.637

SUMMARY

Using computer-aided engineering (CAE) in the concept design stage of automobiles has become a hotspot in human factor engineering research. Based on human musculoskeletal biomechanical computational software, a seated human-body musculoskeletal model was built to describe the natural sitting posture of a driver. The interaction between the driver and car in various combinations of seat-pan/back-rest inclination angles was analyzed using an inverse-dynamics approach. In order to find out the "most comfortable" driving posture of the seat-pan/back-rest, the effect of seat-pan/back-rest inclination angles on the muscle activity degree, and the intradiscal L4-L5 compression force were investigated. The results showed that a much larger back-rest inclination angle, approximately 15°, and a slight backward seat-pan, about 7°, may relieve muscle fatigue and provide more comfort while driving. Subsequently, according to the findings above, a preliminary driving-comfort function was constructed.

KEYWORDS: *Automobile driving. Automobiles. Biomechanical Phenomena. Lumbar vertebrae. Leg. Models, biological. Models, theoretical. Musculoskeletal system*

INTRODUCTION

Today, prolonged sitting has been the most common work posture in the industrialized areas, especially for professions that need to use vehicles as a work tool, such as for taxi drivers. A highly comfortable car-seat not only increases the safety by relieving drivers' physical and mental fatigue but potentially enhances the psychological acceptance of consumers. Therefore, it is essential to investigate seat comfort in automotive seat development.

A reliable analysis method for measuring seat comfort must be established by combining objectively measurable comfort-quantifying parameters with subjective comfort. Traditional evaluation methods considered the content of survey items, the precise number of rating scales, a reasonable crowd positioning, and the motivation of the respondent[1-3]. However, it is difficult to accurately obtain information about the level of artificial muscle activity and joint strength by

DATE OF SUBMISSION: 22-Oct-2019
DATE OF ACCEPTANCE: 28-Dec-2019
CORRESPONDING AUTHOR: Zhen-Hai Gao
State Key Laboratory of Automotive Simulation and Control, Jilin University, No. 5988 Renmin Street, Changchun, 130025, China – Tel/Fax +86-431-85094338
E-mail: gaozh1973@163.com

measuring the pressure distribution using traditional development means[4,5].

In this study, we used a musculoskeletal human-body model from the analysis software named AnyBody to predict muscle-activity and spinal joint force and analyzed the interaction between a passenger and a vehicle in various combinations of seat-pan and back-rest inclination angles using an inverse dynamic approach. A preliminary driving-comfort function (DCF) was created by analyzing the simulation results.

METHODS

AnyBody Model

The Anybody Modeling System, initially developed at Aalborg University, was used as a musculoskeletal model and simulation program in the present work[6].

Car-seat models

A universal seat model is used in this study, which consists of five rigid bodies (head-rest, back-rest, seat-pan, leg-rest, and foot-rest) and several revolute joints to adjust the inclination angle of the back-rest and seat-pan.

Musculoskeletal human-body model

The musculoskeletal human-body model used is named "seated human model", downloaded from the public-domain AnyScript Model Repository. The model contains more than 500 individual rigid bones, joints, muscles, and tendons with characteristics of physiology.

Integration of the human body and seat models

In the present work, a finite element model of a seated human was established to analyze driving fatigue. It contained a simplified human-body musculoskeletal model and a generic car-seat model. Furthermore, the bones and soft-tissue muscles were used to develop the seat-human finite element model, and the shell components of the car-seat model comprised the foot-rest, seat-base, seat-pan back-face, back-rest back-face, and head-rest back-face, and three solid components in contact with the human body, including seat-pan, back-rest, and head-rest. According to the GB10000-88 for the average Chinese adult body size, we adjusted the original human model (167.8cm, 59kg) by adopting the 50th percentile of Chinese adult male body sizes, which could reflect the basic characteristics of a Chinese male.

RESULTS

Successful construction of a finite element model of a seated human

Fig.1a shows that the vertebral spine is divided into four sections. An apparent S-type for the entire upright spine is revealed, which is called the normal physiological curvature of the spine. As can be seen in Fig.1b, there are also many muscle groups in the leg that are involved in driving, including the gluteus maximus, semitendinosus, iliopsoas, sartorius, and anterior tibial. Ultimately, a seated human body model in a normal position was developed as shown in Fig.1c. According to the recommended sizes for the interior overall arrangement in passenger cars, the initial height of the seat could be set to 0.38m. The figures α, β represent the inclination angle of the back-rest and the seat-pan, respectively. The dimensions of other shell components were entered using the minimum size of design specifications, which are displayed in Fig.1c.

The effect of seat-pan/back-rest adjustment on the muscles of lumbar vertebra and legs

Next, we investigated the muscle activity degree and the distribution of the compression force in the major working muscle groups of the spine and leg using an inverse-dynamics approach in the present work.

In the musculoskeletal human-body model simulation test, the inclination angle of the back-rest and seat-pan was changed from 0° to 15° and adjusted 1.5° at a time. As the seat inclination angle changed, there were four major working muscles in the spine affected, namely the erector spinae, semispinalis, musculus obliquus externus abdominis, and musculus transversus abdominis, which are shown in Fig.2(a)-Fig.2(d). The effect of the inclination angle change for the back-rest and seat-pan on the erector spinae muscle activity degree is shown in Fig.2a. Careful observation can be found in Fig.2a, the muscle activity degree monotonically increases with the decrease of the inclination angle of the back-rest, and a reverse trend occurred for the adjustment of the seat-pan. Additionally, a larger rangeability is revealed by adjusting the inclination angle of the back-rest. Similar variation tendencies can be observed in Fig.2(b)-Fig.2(d), which describe the effect of the inclination angle change of the seat-pan

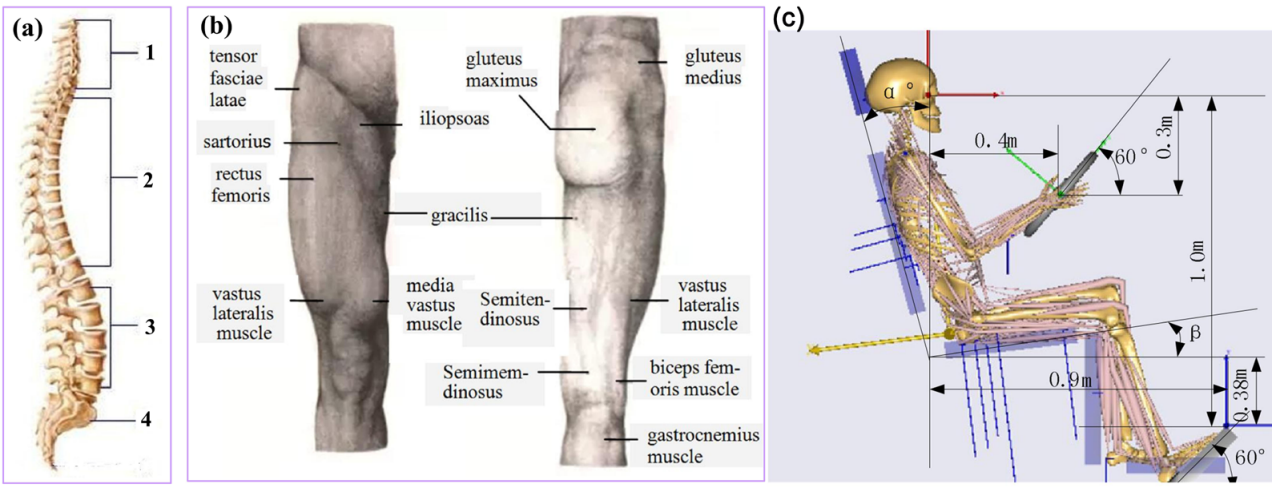


FIGURE 1. Fig.1 (a) Spinal anatomical structure in a natural upright position (1, cervical vertebra; 2, thoracic vertebra; 3, lumbar vertebra; 4, sacral vertebra) and (b) human muscle tissues of the legs. (c)The sitting posture for a typical driver's model.

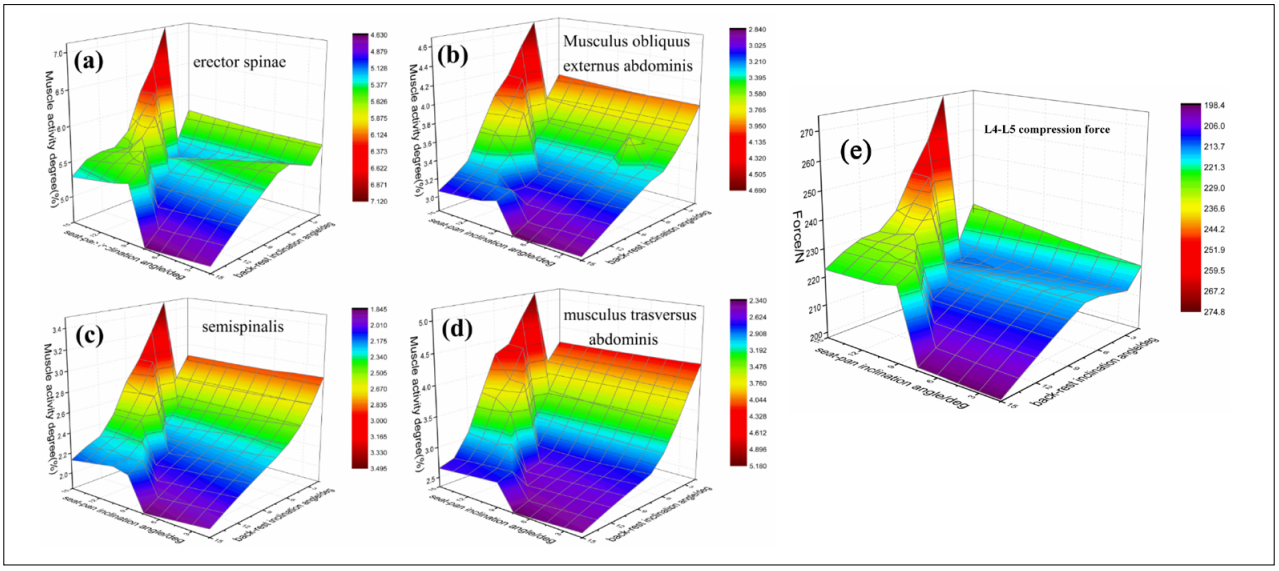


FIGURE 2. Fig.2 (a-d) The effect of inclination angle changes of the seat-pan and back-rest on the muscle activity degree of different tissues in the lumbar vertebra. (e) The effect of inclination angle changes of the seat-pan and back-rest on L4-L5 compression force.

and back-pan on the muscle activity degree of the musculus obliquus externus abdominis, semispinalis, and musculus transversus abdominis, respectively. Comparing the results in Fig.2(b)-Fig.2(d), it can be seen that the muscle activity degree of the erector spinae is the largest, about 7.12%, in the red area, when the inclination angle is in the original state.

The effect of changing the inclination angle of the seat-back and seat-pan on the magnitude of the compression force in the L4–L5 of lumbar vertebra, which are investigated because of the most frequent contact with the seat, is shown in Fig.2(e). Carefully observing the result of the simulation in Fig.2(e), it can be found that the compression force suffered by the musculus transversus abdominis gradually changes as the inclination angle of the seat-rest and seat-pan is adjusted. These results obtained and shown in Fig.2 demonstrate that the reasonable adjustment of the inclination angle for the seat-rest and seat-pan helped the human-body muscles to relax.

Fig 3 shows the effect of the seat inclination angle on the activity degree of muscles of the left and right legs, including the gluteus maximus, semitendinosus, iliopsoas, sartorius, and anterior tibial. Similar results can be seen in Fig.3.

Fig.3a shows that when the inclination angle of the seat-pan is about 6°, the muscle activity degree of the gluteus maximus in the left leg is almost reduced to zero, while the lowest muscle activity degree in the right leg found was about 10.5°. Similar results for

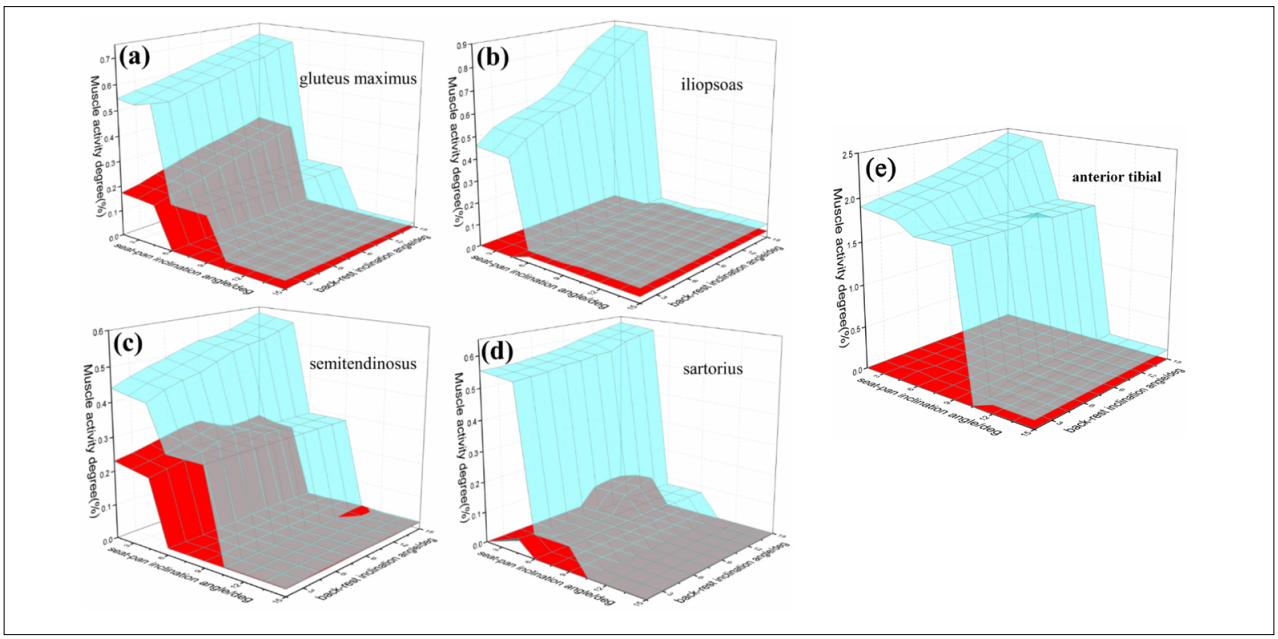


FIGURE 3. Fig.3 (a-d) The effect of variations in the seat-pan and back-rest inclination angle on muscle activity degree of the muscle tissues in legs (blue and red represent the muscle tissue in the right leg and left leg, respectively). (e) The effect of variations in the seat-pan and back-rest inclination angle on the anterior tibial muscle activity degree (blue and red represent the muscle tissue in the right leg and left leg, respectively).

the muscle tissues of the left leg can be observed in Fig.3(d)-(e), which is similar to the results shown in Fig.3a. Combined with the above analysis, from Fig.3 it can be concluded that the muscle activity degree monotonically decreases with the increase of the seat-pan and back-rest inclination angle.

Corresponding partial correlation coefficients

Furthermore, several pairs of muscles, like the musculus obliquus externus abdominis, semispinalis, gluteus maximus, and semitendinosus showed a high correlation coefficient (R>0.8) after analyzing the correlation data. For the sake of simplifying the analysis, the muscle activity of the erector spinae (MAES), musculus transversus abdominis (MAMTA), gluteus maximus (MAGM), and anterior tibial muscle (MAATM) should be considered in the investigation of the fatigue degree for drivers with a typical driving position. Furthermore, the compression force on the L4-L5 (CFL4-L5) is important in the investigation of the degree of fatigue of drivers. As a result, the driving-comfort function (DCF) can be written as the following general formula:

DCF=MAES+MAMTA+MAGM+MAATM+CFL4-L5 (1)

DISCUSSION

The demand for car-seat comfort is constantly increasing. It is worth mentioning that, from the perspective of human biomechanics, the human-body movement is a mechanical response that is accomplished by a complex mechanical interaction between muscles, ligaments, joints, and bones, which are controlled by numerous nervous systems[7,8]. The static or dynamic stabilities of the human body under gravitational and other loads and precise limb behaviors depend on the tensile forces formed by working muscles in the musculoskeletal systems[9]. According to previous literature, the thoracic vertebra section mainly bears the seat-back support, and the most stressed points are always on the T9, T10, and T12[10,11]. At the same time, the compression force in the lumbar vertebra from L1 to L5 changes with different distributions of body weight, and the largest value of stress force is distributed between L4 and L5[12,13]. The response of the human tendon tissues could be influenced by exterior activities, like stretching or extruding, which results in increased muscle activity and a long-term feeling of muscle soreness. When the muscle activity degree is greater than 1, it exceeds the limits of muscle fatigue activity and represents a state of exhaustion. In this state of fatigue, sustained muscle stretching results in damage to the muscle tissues.

The particularity of the driver's sitting posture when driving a car was taken into account during the process of developing the finite element model, i.e, the drivers' right feet in a seating position was maintained on the footrest and the hands were placed

on the steering wheel. For drivers who spend a lot of time driving, seating comfort control is affected by the distribution of the contact pressure on the contact interface of the seated human/car-seat.

By analyzing the relationship between the muscle activity degree and the inclination angle, we found that the activation intensity of the muscles in the lumbar vertebra is at its lowest when the inclination angle of the back-rest is 15°, and the inclination angle of the seat-pan only needs to be adjusted at 7.5°, that way the degree of muscle use can be at the minimum. However, for the muscles in legs, there is no significant influence on the muscle activity degree by adjusting the inclination angle of the back-rest, whereas a large rangeability is revealed by adjusting the inclination angle of the seat-pan.

The results in the present work demonstrated that the different muscle tissues are subject to varying degrees of compression force or activation, and the adjustment of the seat-pan/back-rest changes the pressure distribution on the muscle tissues, thus helping to relieve driving fatigue. Similar experimental methods and results have been reported in many literatures[14,15]. Moreover, it has been reported that lower maximum contact pressure and more uniform pressure distribution on the contact interface of the human-body/car-seat contribute to improved seating comfort[16].

The DCF was established as a new auxiliary reference method to provide a way for fabricating seats that more compliant with human comfort in the future. According to the DCF equation, the comfort of a car seat is related to the muscle activity of the working muscle groups and the compression force on the L4-L5. Hence, the driving comfort can be improved by carefully using the postural angles and seat adjustment levels.

CONCLUSIONS

This study clarified the effect of the seat-pan and back-rest inclination angle on the muscle activity degree and spinal joint force, which may improve design for car-driver comfort during driving.

Acknowledgments

This work was supported by the Nation Science Foundation of China (No.51775236), the National Key Research and Development Program of China (No. 2017YFB0102600).

Competing interests

The authors declare they have no competing interests.

Author Contributions

Conceptualization, Zhen-Hai Gao; formal analysis, Shi Zong; writing (original draft preparation), Fei Gao; writing (review and editing), Zhi-Wu Han; supervision, Yang Xiao; funding acquisition, Zhen-Hai Gao”

RESUMO

O uso de engenharia assistida por computador (CAE) na fase de projeto do conceito do automóvel tornou-se um ponto de acesso na pesquisa de fatores humanos. Com base no software computacional biomecânico musculoesquelético humano, foi construído um modelo musculoesquelético sentado para descrever a postura sentada natural de um condutor. A interação entre um motorista e um carro em várias combinações de ângulos de inclinação do assento-pan/encosto foi analisada usando uma abordagem dinâmica do verso. A fim de descobrir a postura de condução "mais confortável" do assento-pan/encosto, o efeito dos ângulos de inclinação do assento-pan/dorso sobre o grau de atividade muscular e a força de compressão intradiscal L4-L5 foi investigado. Os resultados mostraram que um ângulo de inclinação para trás muito maior, aproximadamente 15°, e um ligeiro assento-pan para trás, cerca de 7°, pode aliviar a fadiga muscular e levar a dirigir em uma posição confortável. Posteriormente, de acordo com as conclusões acima expostas, foi construída uma função preliminar de conforto ao dirigir.

PALAVRAS-CHAVE: *Condução de veículo. Automóveis. Fenômenos biomecânicos. Vértebras lombares. Perna (membro). Modelos biológicos. Modelos teóricos. Sistema musculoesquelético.*

REFERENCES

1. Guilford JP. Psychometric methods. 2nd. New York: McGraw-Hill; 1954.
2. Oppenheim AN. Questionnaire design and attitude measurement. New York: Basic Books; 1966.
3. Grigg AO. A review of techniques for scaling subjective judgements. Supplementary Report 379. Washington: Department of the Environment and Department of Transport; 1978.
4. Grujicic MB, Pandurangan B, Xie X, Gramopadhye AK, Wagner D, Ozen M. Musculoskeletal computational analysis of the influence of car-seat design/adjustments on long-distance driving fatigue. Int J Indust Ergon. 2010;40(3):345-55.
5. Majid NABA, Notomi M, Rasmussen J. Musculoskeletal computational analysis of the influence of car-seat design/adjustment on fatigue-induced

driving. In: Modeling, Simulation and Applied Optimization (ICMSAO), 2011 4th International Conference on (pp. 1-6). IEEE Press. https://doi.org/10.1109/ICMSAO.2011.5775600.

6. Damsgaard M, Rasmussen J, Christensen ST, Surma E, Zee M. Analysis of musculoskeletal systems in the anybody modeling system. Simul Model Pract Theory. 2006;14(8):1100-11.
7. El'ner AM. Postural adjustments to voluntary movements. Electrical activity of muscles and biomechanics of the human body in an upright position. Biofizika. 1993;38(1):187-91.
8. Lu TW, Chang CF. Biomechanics of human movement and its clinical applications. Kaohsiung J Med Sci. 2012;28(2 Suppl):S13-25.
9. Watkins J. Structure and function of the musculoskeletal system. 2nd ed. Champaign: Human Kinetics; 2010.
10. Iyer S, Christiansen BA, Roberts BJ, Valentine MJ, Manoharan RK, Bouxsein ML. A biomechanical model for estimating loads on thoracic and lumbar vertebrae. Clin Biomech (Bristol, Avon). 2010;25(9):853-8.
11. Borkowski SL, Sangiorgio SN, Bowen RE, Scaduto AA, He B, Bauer KL, et al. Strength of thoracic spine under simulated direct vertebral rotation: a biomechanical study. Spine Deform. 2016;4(2):85-93.
12. Corlett EM, Eklund JA. How does a backrest work? App Ergon. 1984;15(2):111-4.
13. Mehta CR, Tewari VK. Biomechanical model to predict loads on lumbar vertebra of a tractor operator. Int J Indust Ergon. 2015;47:104-16.
14. Ferrari R. Sitting biomechanics. Part II: optimal car driver's seat and optimal driver's spinal model. J Manipulative Physiol Ther. 2001;24(2):140-3.
15. Park SJ, Kim CB, Kim CJ, Lee JW. Comfortable driving postures for Koreans. Int J Indust Ergon. 2000;26(4):489-97.
16. Grujicic M, Pandurangan B, Arakere G, Bell WC, He T, Xie X. Seat-cushion and soft-tissue material modeling and a finite element investigation of the seating comfort for passenger-vehicle occupants. Materials & Design. 2009;30(10):4273-85.

ORIGINAL ARTICLE

Evaluation of 880 patients diagnosed with acute pancreatitis according to the Revised Atlanta Classification: A single-center experience

Omer Burcak Binicier[1]
Hatice Cilem Binicier[2]

1. Department of Gastroenterology, Tepecik Education, and Research Hospital. Izmir, Turkey.
2. Department of Gastroenterology, Dokuz Eylul University Faculty of Medicine, Izmir, Turkey.

http://dx.doi.org/10.1590/1806-9282.66.5.643

SUMMARY

OBJECTIVE: *The Revised Atlanta Classification (RAC) is increasingly used in the evaluation of patients diagnosed with acute pancreatitis (AP). In our study, we aimed to evaluate the etiology, disease severity, and mortality rates of patients diagnosed with AP in our center in the previous 6 years.*

METHODS: *Patients diagnosed with AP between 2013 and 2018 were evaluated. AP etiology, demographic data, disease severity, and mortality rates according to the RAC were evaluated.*

RESULTS: *A total of 880 patients were included in the study. Five hundred and eighteen (59%) patients were female and 362 (41%) were male. Regarding the etiology, 474 (53.9%) patients had biliary AP (BAP), 71 (8.1%) had hyperlipidemic AP (HAP), and 44 (5%) had alcoholic AP (AAP). According to the RAC, 561 (63.7%) patients were considered to be in the mild AP group (MAP), 268 (30.5%) in the moderately severe AP (MSAP), and 51 (5.8%) in the severe AP (SAP). The mortality rate was 4.8% in the MSAP group and 49% in the SAP group. Mortality was 2.3 times in patients over 65 years old and 3.7 times higher in patients with ischemic heart disease.*

CONCLUSIONS: *In our country, BAP is still the main etiology of acute pancreatitis. Over the years, we have seen a decrease in BAP and idiopathic AP cases, while there was an increase in HAP cases due to factors such as lifestyle changes and fatty nutrition. We found that mortality was associated with disease severity, advanced age (> 65 y), hypertension, and ischemic heart disease regardless of the etiology.*

KEYWORD: *Pancreatitis/etiology. Pancreatitis, acute necrotizing. Severity of illness index.*

INTRODUCTION

Acute pancreatitis (AP) is an important gastrointestinal clinical event with an increased incidence due to increased life expectancy, obesity, alcohol use, hyperlipidemia, drug use, and diagnostic methods. Despite the increasing incidence of the disease, early diagnosis methods and the understanding of its pathophysiology have been associated with decreases in the duration of hospitalization, cost, and mortality rates in recent decades[1].

There are several scoring systems for assessing AP prognosis and disease severity (Ranson Criteria, Modified Glasgow Score, Acute Physiology, and Chronic Health Evaluation (APACHE) II-IV, etc.). Studies conducted using all these scoring systems have shown that morbidity and mortality rates are closely related to disease severity and organ failure that persists for more than 48 hours, regardless of the underlying etiology[1]. Due to the complexity and difficulty of the use

DATE OF SUBMISSION: 25-Nov-2019
DATE OF ACCEPTANCE: 28-Dec-2019
CORRESPONDING AUTHOR: Omer Burcak Binicier
Tepecik Education and Research Hospital. 1140/1. Sk., No:1, Yenişehir, Konak, İzmir - 35180
Tel: +90 50654280695 / Fax: +90 2324330756
E-mail: binicieromer@yahoo.com

of these scoring systems, the use of scoring systems such as the bedside disease severity index (BISAP) or Atlanta Classification has increased in acute pancreatitis. By demonstrating the effects of AP-related organ failure and the presence of local/systemic complications on mortality and morbidity, the Atlanta classification, developed in 1992 and revised in 2012 uses the classifications of mild AP (MAP), moderate AP (MSAP), and severe AP (SAP)[2].

Although regional differences are observed in our country, biliary AP (BAP) cases constitute the main etiology of AP[3]. We planned to conduct a retrospective study on the demographic data, comorbid diseases, etiology, and clinical course of the Revised Atlanta Classification (RAC) in patients diagnosed with AP in our tertiary health center in the western part of Turkey.

METHODS

Patient groups and study design

The study included patients who were admitted to the emergency department with abdominal pain between January 2013 and December 2018, aged 18 years and older, who were hospitalized with the diagnosis of AP. AP severity was classified according to the RAC[2]. Age, gender, comorbidities, history of pancreatitis, etiology, disease severity according to the RAC, duration of hospitalization, and mortality rates were recorded.

AP etiologies were determined according to the history, laboratory findings, imaging methods (abdominal ultrasonography, computerized tomography (CT), magnetic resonance imaging, magnetic resonance cholangiopancreatography, endoscopic ultrasonography, and endoscopic retrograde cholangiopancreatography) and, if necessary, pathology results.

The study was approved by the local ethical committee of the XXX hospital (No: 2019/4-22).

Statistical analysis

Statistical analyses for the study were performed with the SPSS 22.0 (IBM Statistical Package for Social Sciences software version 22) package program. The numerical variables were described by medians and interquartile ranges (IQR). The Chi-square test was used to compare the categorical values between the groups. The Mann-Whitney U test was used to compare the continuous independent medians. The Wilcoxon signed-rank test was used to compare dependent medians. The mortality rate was evaluated by the Kaplan-Meier method, and predictive factors of mortality were evaluated by the Cox proportional hazard model. A p-value < 0.05 was accepted as statistically significant.

RESULTS

Demographic data and comorbid diseases

A total of 880 adult patients diagnosed with AP were included in the study. Five hundred and eighteen (59%) of the subjects were female and 362 (41%) were male. The mean age of females was 62.05 ± 17.99 and of males, it was 57.92 ± 16.50 (p > 0.5). Regarding comorbidities, upon examination, there was no additional comorbidity in 327 patients (37.2%), one in 296 (33.6%), two in 174 (19.8%), and three or more in 83 (9.4%) patients. The most common comorbidities were hypertension (HT) (41.9%), diabetes mellitus (DM) (26.8%), and ischemic heart disease (IHD) (12.4%).

Etiology

According to the etiology distribution, 474 (53.9%) patients were in the BAP group, 211 in the idiopathic AP (IAP) (24%), 71 (8.1%) in the hyperlipidemic AP (HAP), 44 in the (5%) in alcoholic AP (AAP), and 80 (9.1%) in the miscellaneous AP group. Although BAP was the most common etiology in both genders, it was found to be statistically more frequent in females (61% vs. 42%, p < 0.001). While BAP was the most frequent in all age groups of females, HAP and AAP were statistically more common in males (15% vs 5%, p < 0.001 and 10% vs 2%, p < 0.001). Figure 1 summarizes the changes in AP etiology rates of 2013 and 2018. Patient distributions by gender and age groups are summarized in Table 1.

FIGURE 1. CHANGES IN AP ETIOLOGY RATES BETWEEN 2013 AND 2018

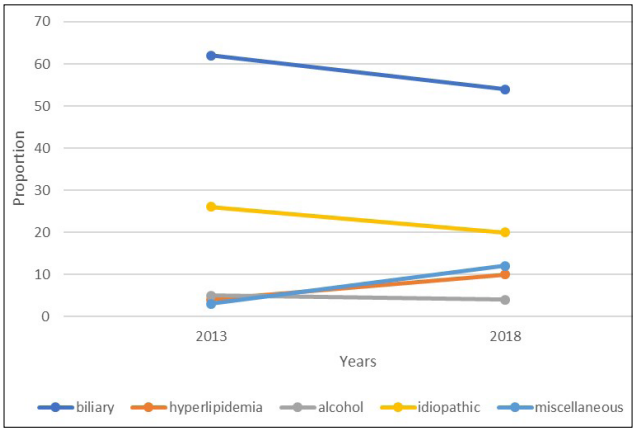


TABLE 1. DISTRIBUTION OF ACUTE PANCREATITIS PATIENTS ACCORDING TO GENDER AND AGE GROUPS

	Number of patients with acute pancreatitis (%)					
	biliary	hyperlipidemia	alcohol	idiopathic	miscellaneous	total
Male						
18-29	3 (18)	8 (47)	1 (5)	2 (12)	3 (18)	17
30-39	11 (25)	13 (30)	9 (20)	9 (20)	2 (5)	44
40-49	11 (23.5)	14 (30)	8 (17)	11 (23.5)	3 (6)	47
50-59	30 (37)	8 (10)	11 (17)	29 (35)	4 (5)	82
60-69	44 (56)	1 (1)	4 (5)	16 (21)	13 (17)	78
>70	57 (61)	2 (2)	3 (3)	21 (22)	11 (12)	94
all	156 (42)	56 (15)	36 (10)	88 (23)	36 (10)	362
Female						
18-29	23 (72)	0 (0)	1 (3)	6 (19)	2 (6)	32
30-39	23 (56)	8 (20)	1 (2)	9 (22)	0 (0)	41
40-49	22 (40)	6 (11)	0 (0)	20 (36)	7 (13)	55
50-59	51 (61)	8 (9)	3 (4)	15 (18)	7 (8)	84
60-69	75 (70)	2 (2)	1 (1)	25 (23)	4 (4)	107
>70	124 (62.5)	1 (0.5)	2 (1)	48 (24)	24 (12)	199
all	318 (61)	25 (5)	8(2)	123 (24)	44 (8)	518

A hundred and ten patients (12.5%) had recurrent AP events. In the subgroup analysis, recurrent AP was found in 39 patients (8.2%) of the BAP group, 22 (31%) of the HAP, 15 (34.1%) of the AAP, and 22 (10.4%) of the IAP.

Disease severity

According to the RAC, 561 (63.7%) patients were in the MAP group, 268 (30.5%) were in the MSAP group, and 51 (5.8%) in the SAP group. The median duration of hospitalization of all patients was 6 days (IQR=4) (5 days (IQR=3) in the MAP group, 9 (IQR=6) in the MSAP group, and 13 days (IQR=13) in the SAP group). According to the RAC groups, the median duration of hospitalization is summarized in Figure 2. Demographic data, etiology distributions of patients with AP according to the RAC severity are summarized in Table 2.

Mortality rates

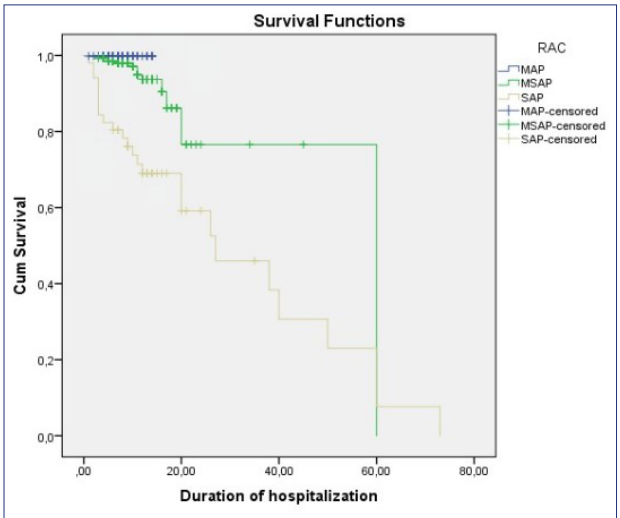
Mortality was seen in 39 (4.4%) of the 880 patients included in the study. Of these, 13 were in the MSAP group and 25 in the SAP group. The mortality rate was 4.8% in the MSAP group, and 49% in the SAP group ($p < 0.001$). There was no statistically significant difference between the etiology groups in terms of mortality rates ($p = 0.492$).

There were statistically significant differences between advanced age (> 65 y) ($p = 0.001$), HT ($p = 0.002$), IHD ($p = 0.001$) and mortality. According to the Cox regression analysis, mortality was 2.3 times higher (HR:2.3, 95% CI; 1.03-5.38, $p = 0.041$) in patients over 65 years old and 3.7 times higher (HR:3.7, 95% CI; 1.79-7.92, $p < 0.001$) in IHD patients.

DISCUSSION

Although the incidence and etiology of AP vary between countries and regions, BAP and AAP are often the two main etiologic factors (60-80%). In the literature, the incidence of AP varies between 4.6 and 100 per 100,000[4]. In Southern European countries, BAP comes first, while in Eastern European countries, AAP stands out. In Northern and Western Europe, BAP and AAP have similar rates[4]. In South

FIGURE 2. MEDIAN DURATION OF HOSPITALIZATION ACCORDING TO THE RAC GROUPS



RAC; Revised Atlanta Classification; MAP; mild AP, MSAP; moderate AP, SAP; severe AP

Korea, AAP ranks first, while BAP stands out in other Asian countries and the Arabian Peninsula[5-9]. In Latin American countries, BAP cases are reported to account for almost three-quarters of all cases[10]. In our country, in the review of AP cases between 1980 and 2016 by Calık et al.[3], it was reported that 70% of cases were BAP, 16% were idiopathic pancreatitis, 7% were AAP, and 4% were HAP. In our study, we observed that most patients were in the BAP group, while a decrease in the BAP rate and an increase in the HAP and miscellaneous group rates were observed. When we compared the etiology rates of AP patients in 2013 and 2018, a decrease in the BAP and IAP rates and an increase in the HAP and miscellaneous groups were observed. In accordance with the literature, we found that HAP and AAP are more common in middle-aged males, and BAP again came to the fore in females over the age of 50[4,11-13]. This trend can be attributed to improvements in diagnostic imaging and laboratory investigations, lifestyle changes, and increased hyperlipidemia due to fatty nutrition. Despite advances in diagnostic imaging and laboratory investigations, it is useful to say that IAP cases constitute almost ¼ of the cases, similar to the literature in our study[12,14].

TABLE 2. DEMOGRAPHIC DATA AND ETIOLOGY DISTRIBUTION OF PATIENTS WITH ACUTE PANCREATITIS ACCORDING TO THE RAC SEVERITY

Characteristic	MAP	MSAP	SAP
Gender (n, %)			
female	347 (61.9%)	139 (51.9%)	32 (62.7%)
Age (n, %)			
>65 y	206 (36.7%)	132 (49.2%)	43 (84.3%)
Comorbidities (n, %)			
Hypertension	199 (35.4%)	134 (50%)	36 (70.5%)
Diabetes mellitus	123 (21.9%)	92 (34.3%)	21 (41.1%)
Hyperlipidemia	25 (4.4%)	16 (5.9%)	3 (5.8%)
Ischemic heart disease	53 (9.4%)	47 (17.5%)	9 (17.6%)
Cerebrovascular disease	17 (3%)	11 (4.1%)	3 (5.8%)
Chronic renal failure	2 (0.3%)	19 (7%)	12 (23.5%)
COPD/Asthma	27 (4.8%)	15 (5.5%)	3 (5.8%)
Others	44 (7.8%)	17 (6.3%)	3 (5.8%)
Etiology (n, %)			
Biliary	302 (53.8%)	145 (54.1%)	27 (52.9%)
Hyperlipidemia	33 (5.8%)	34 (12.6%)	4 (7.8%)
Alcohol	25 (4.4%)	18 (6.7%)	1 (1.9%)
Idiopathic	152 (27%)	47 (17.5%)	12 (23.5%)
Miscellaneous	49 (8.7%)	24 (8.9%)	7 (13.7%)
Recurrent pancreatitis (n, %)	65 (11.5%)	37 (13.8%)	8 (15.6%)

Mild AP (MAP); moderately severe AP (MSAP); severe AP (SAP); chronic obstructive pulmonary disease (COPD)

In addition, recurrent pancreatitis developed in 12.5% of the patients included in our study, and it was more common in HAP and AAP cases. In the literature, the recurrent AP rate is reported to be 10-30%, and most of these are BAP and AAP cases[5,15]. In our study, we found that recurrent AP cases consisted of AAP (34%) and HAP (31%) cases, unlike the literature. We think that the lower rate of recurrent AP in patients with BAP (8%) may be due to early cholecystectomy without waiting for a second event. Considering that recurrent AP events may cause various complications and morbidities such as chronic pancreatitis, we can say that treatment such as early lipid apheresis in HAP cases, psychiatric support in AAP cases, and early cholecystectomy in BAP cases will be effective in reducing cost and mortality rates.

The Ranson scoring system is the first scoring system for AP that can be assessed 48 hours after the patient's admission. The low specificity of the Ranson scoring in predicting mortality may cause difficulties in differentiating patients in need of close follow-up and intensive care unit[16,17]. It has been shown in studies that the APACHE II-IV scoring system, which was introduced later, has a higher efficacy in predicting severe AP and mortality[16,18,19]. However, the computed severity index (CTSI) developed by Balthazar et al.[20], which is a scoring system based solely on imaging has also been reported as an effective scoring system for predicting SAP and mortality in some studies, and with moderate efficacy in other studies[18-20]. Studies have shown that both BISAP and RAC scoring systems are effective to predict disease severity and mortality[8,16,19,21]. In the literature, the incidence of SAP according to RAC is reported to be 10-20%, and mortality rates are reported to be 20-60%[2,4,12,22]. In our study, the SAP rate was lower than the literature (5.8%), while the mortality rate in this group was similar to the literature (49%). Also, the median duration of hospitalization and mortality rates correlated with RAC severity in accordance with the literature[12,23,24]. According to these data, it is possible to say that RAC is an effective classification method in determining patients who require close follow-up. Also, advanced age (> 65 y), HT, DM, chronic renal failure, and IHD were closely related to the severity of AP; advanced age (> 65 y), HT, and IHD were also especially closely related to mortality[1,25].

Our study has several limitations. The first is the retrospective nature of the study. The second is that it does not reflect country-wide data since it contains data from a single center. In addition, the study did not

include comparative data with other scoring systems.

In conclusion, BAP is still the main etiology in acute pancreatitis in our country. Although our study included regional data, it was observed that there was an increase in HAP cases due to factors such as lifestyle change and fatty nutrition while BAP and IAP cases have been decreasing over the years. We can say that the RAC is effective in determining the severity of the disease and cases that should be closely monitored.

Conflict of interest

No.

Authors' contributions

Concept: OBB. Design: OBB, HCB. Supervision: HCB. Materials: OBB. Data collection and/or processing: OBB. Analysis and/or interpretation: OBB. Literature search: OBB. Writing: OBB, HCB. Critical reviews: OBB, HCB.

RESUMO

OBJETIVO: *A Classificação de Atlanta revisada (RAC) é cada vez mais usada na avaliação de pacientes diagnosticados com pancreatite aguda (PA). Em nosso estudo, objetivamos avaliar a etiologia, a gravidade da doença e as taxas de mortalidade de pacientes diagnosticados com PA em nosso centro nos últimos seis anos.*

MÉTODOS: *Foram avaliados pacientes diagnosticados com PA entre 2013 e 2018. Avaliaram-se a etiologia da PA, os dados demográficos, a gravidade da doença e as taxas de mortalidade de acordo com a RAC.*

RESULTADOS: *Um total de 880 pacientes foi incluído no estudo. Quinhentos e dezoito (59%) pacientes eram do sexo feminino e 362 (41%) do sexo masculino. Na etiologia, 474 (53,9%) pacientes apresentaram PA biliar (PAB), 71 (8,1%) PA hiperlipidêmica (PAH) e 44 (5%) PA alcoólica (PAA). De acordo com a RAC, 561 (63,7%) pacientes estavam em PA leve (MAP), 268 (30,5%) estavam em PA moderadamente grave (MSAP) e 51 (5,8%) estavam em grupos de PA grave (SAP). A taxa de mortalidade foi de 4,8% no grupo MSAP e de 49% no grupo SAP. A mortalidade foi vista como 2,3 vezes em pacientes acima de 65 anos e 3,7 vezes em pacientes com cardiopatia isquêmica.*

CONCLUSÕES: *Em nosso país, o PAB ainda é a principal etiologia da pancreatite aguda. Ao longo dos anos, observamos uma diminuição nos casos de PAB e PA idiopática, enquanto houve um aumento nos casos de PAH devido a fatores como mudança de estilo de vida e nutrição gordurosa. Descobrimos que a mortalidade estava associada à gravidade da doença, idade avançada (>65 anos), hipertensão e cardiopatia isquêmica, independentemente da etiologia.*

PALAVRAS-CHAVE: *Pancreatite/etiologia. Pancreatite necrosante aguda. Índice de gravidade de doença.*

REFERENCES

1. Mandalia A, Wamsteker EJ, DiMagno MJ. Recent advances in understanding and managing acute pancreatitis. F1000Res. 2018;7.
2. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al; Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis-2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62(1):102-11.
3. Calik B. Acute pancreatitis cases in Turkey: a review of the literature from 1980 to 2016. In: Proceedings of 11th Global Gastroenterologists Meeting; Rome, Italy, 2017 June 12-13. J Gastrointest Dig Syst. 2017;7(3):54.
4. Roberts SE, Morrison-Rees S, John A, Williams JG, Brown TH, Samuel DG. The incidence and aetiology of acute pancreatitis across Europe. Pancreatology. 2017;17(2):155-65.
5. Mallick B, Shrama DJ, Siddappa P, Dhaka N, Malik S, Sinha SK, et al. Differences between the outcome of recurrent acute pancreatitis and acute pancreatitis. JGH Open. 2018;2(4):134-8.
6. Zhang W, Hu J, Yao B, Yang X, Song L, Yin T, et al. Evaluation of early prognostic factors of mortality in patients with acute pancreatitis: a retrospective study. Gastroenterol Res Pract. 2017;2017:8363561.
7. Padhan RK, Jain S, Agarwal S, Harikrishnan S, Vadiraja P, Behera S, et al. Primary and secondary organ failures cause mortality differentially in acute pancreatitis and should be distinguished. Pancreas. 2018;47(3):302-7.
8. Cho YS, Kim HK, Jang EC, Yeom JO, Kim SY, Yu JY, et al. Usefulness of the Bedside Index for severity in acute pancreatitis in the early prediction of severity and mortality in acute pancreatitis. Pancreas. 2013;42(3):483-7.
9. Wu D, Lu B, Xue HD, Yang H, Qian JM, Lee P, et al. Validation of Modified Determinant-Based Classification of severity for acute pancreatitis in a tertiary teaching hospital. Pancreatology. 2019;19(2):217-23.
10. Osvaldt AB, Viero P, Borges da Costa MS, Wendt LR, Bersch VP, Rohde L. Evaluation of Ranson, Glasgow, APACHE-II, and APACHE-O criteria to predict severity in acute biliary pancreatitis. Int Surg. 2001;86(3):158-61.
11. Chang MC, Su CH, Sun MS, Huang SC, Chiu CT, Chen MC, et al. Etiology of acute pancreatitis: a multi-center study in Taiwan. Hepatogastroenterology. 2003;50(53):1655-7.
12. Zhu Y, Pan X, Zeng H, He W, Xia L, Liu P, et al. A study on the etiology, severity, and mortality of 3260 patients with acute pancreatitis according to the revised Atlanta classification in Jiangxi, China over an 8-year period. Pancreas. 2017;46(4):504-9.
13. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas. 2006;33(4):323-30.
14. Kaya E, Dervisoglu A, Polat C. Evaluation of diagnostic findings and scoring systems in outcome prediction in acute pancreatitis. World J Gastroenterol. 2007;13(22):3090-4.
15. Lee PJ, Bhatt A, Holmes J, Podugu A, Lopez R, Walsh M, et al. Decreased severity in recurrent versus initial episodes of acute pancreatitis. Pancreas. 2015;44(6):896-900.
16. Mok SR, Mohan S, Elfant AB, Judge TA. The acute physiology and chronic health evaluation IV, a new scoring system for predicting mortality and complications of severe acute pancreatitis. Pancreas. 2015;44(8):1314-9.

17. Forsmark CE, Baillie J; AGA Institute Clinical Practice and Economics Committee; AGA Institute Governing Board. AGA Institute technical review on acute pancreatitis. Gastroenterology. 2007;132(5):2022-44.

18. Papachristou GI, Muddana V, Yadav D, O'Connell M, Sanders MK, Slivka A, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. Am J Gastroenterol. 2010;105(2):435-41.

19. He WH, Zhu Y, Zhu Y, Jin Q, Xu HR, Xion ZJ, et al. Comparison of multifactor scoring systems and single serum markers for the early prediction of the severity of acute pancreatitis. J Gastroenterol Hepatol. 2017;32(11):1895-901.

20. Balthazar EJ, Robinson DL, Megibow AJ, Ranson JH. Acute pancreatitis: value of CT in establishing prognosis. Radiology. 1990;174(2):331-6.

21. Chandra S, Murali A, Bansal R, Agarwal D, Holm A. The Bedside Index for Severity in Acute Pancreatitis: a systematic review of prospective studies to determine predictive performance. J Community Hosp Intern Med Perspect. 2017;7(4):208-13.

22. Cui J, Xiong J, Zhang Y, Peng T, Huang M, Lin Y, et al. Serum lactate dehydrogenase is predictive of persistent organ failure in acute pancreatitis. J Crit Care. 2017;41:161-5.

23. Choi JH, Kim MH, Cho DH, Oh D, Lee HW, Song TJ, et al. Revised Atlanta classification and determinant-based classification: which one better at stratifying outcomes of patients with acute pancreatitis? Pancreatology. 2017;17(2):194-200.

24. Wang X, Qin L, Cao J. Value of the revised Atlanta classification (RAC) and determinant-based classification (DBC) systems in the evaluation of acute pancreatitis. Curr Med Res Opin. 2018;34(7):1231-8.

25. Huh JH, Jeon H, Park SM, Choi E, Lee GS, Kim JW, et al. Diabetes mellitus is associated with mortality in acute pancreatitis. J Clin Gastroenterol. 2018;52(2):178-83.

ORIGINAL ARTICLE

High D-dimer levels are associated with prostate cancer

Senad Kalkan[1]
Selahattin Caliskan[2]

1. Bezmialem Vakif University, Faculty of Medicine, Department of Urology, Istanbul, Turkey.
2. Reyap Hospital, Department of Urology, Istanbul, Turkey.

http://dx.doi.org/10.1590/1806-9282.66.5.649

KEYWORDS: *Prostatic neoplasms. Thrombophilia. Biomarkers, tumor/blood. Fibrin fibrinogen degradation products.*

INTRODUCTION

Prostate cancer is one of the most common types of cancer among men in the world[1] and a significant health problem in developed and developing countries[2]. The association between cancer and hemostasis has been shown in several studies[3]. The main risk factors for coagulation activation and thrombosis are aging and malignancy[4]. The increased risk of thrombosis in cancer patients may be associated with high levels of coagulation markers (fibrinogen), and thrombogenesis markers (D-dimer) are likely evidence of this process[5].

Fibrinogen is an acute-phase protein that is mainly synthesized by hepatocytes and converted into insoluble fibrin by activated thrombin. It is also an important indicator of the coagulation system[6]. The plasma fibrinogen level increases in some circumstances, such as malignancy and systemic inflammation. D-dimer is a degradation product of fibrin which is produced by plasmin-induced fibrinolytic activity[7]. It is a biomarker that indicates the activation of hemostasis and fibrinolysis. Elevated plasma levels may be associated with some scenarios such as cancer, pregnancy, infectious diseases, trauma, surgery, and venous thromboembolism.

When fibrinogen levels are increased, they are deemed to be an unfavorable prognostic factor in some malignancies, such as those of the digestive system, gynecologic malignancies, urologic neoplasms, and soft tissue sarcomas[6]. A high level of D-dimer is a prognostic factor associated with increased mortality risk in patients with brain tumors, lymphomas, breast, lung, stomach, colorectal, pancreatic, and prostate cancers[7]. We investigated the levels of D-dimer and fibrinogen in patients with prostate cancer and benign prostate hyperplasia.

METHODS

Patients who had a pathological diagnosis of prostate disease by transrectal ultrasound-guided biopsy and transurethral surgery between January 2015 and January 2019 were enlisted. Plasma prostate specific antigen (PSA), free PSA (fPSA), percentage fPSA, D-dimer, and fibrinogen levels were measured before the

DATE OF SUBMISSION: 01-Sep-2019
DATE OF ACCEPTANCE: 12-Nov-2019
CORRESPONDING AUTHOR: Selahattin Çalışkan
Reyap Hospital - Yesilkent District 2011th Street No:25, Esenyurt/Istanbul, Turkey
Tel: +90 5547846552
E-mail: dr.selahattincaliskan@gmail.com

procedures (prostate biopsy and transurethral resection). The percentage of fPSA was calculated as fPSA/PSA * 100. Venous blood samples were collected into citrate tubes by sterile atraumatic venipunctures. Enzyme-linked immunosorbent assay (ELISA) (Diagnostic Stago, France) and the Clauss method (Sysmex, Japan) techniques were used to measure the plasma D-dimer and fibrinogen levels. Plasma fibrinogen and D-dimer levels were considered to be normal when between 175mg/dL and 350mg/dL and between 0ug/mL and 0.5ug/mL, respectively.Patients with a history of coagulopathy, hematuria, venous or pulmonary embolism, acute or chronic prostatitis, radiotherapy, malignancy, and using anticoagulant therapy were excluded from the study. The patients' data, including PSA, fPSA, percentage of fPSA, D-dimer, and fibrinogen levels, and patient age and pathology reports, were recorded. Patients who had a diagnosis of high-grade prostate intraepithelial neoplasia and atypical small acinar proliferation (9 patients) were excluded from the study. The remaining patients were then divided into two groups; the ones whose pathological report was benign prostate hyperplasia were placed in Group 1, and those who had prostate cancer in Group 2. The statistical analyses were performed using MedCalc Statistical Software demo version 16.2.0 (MedCalc Software bvba, Ostend, Belgium; https://www.medcalc.org; 2016). The data were verified for normal distribution using the Kolmogorov-Smirnov test and expressed as mean ± standard deviation (normal distribution), median values, and $p < 0.05$ was considered with statistical significance.

RESULTS

The current study included 218 patients. There were 161 patients in Group 1 and 57 patients in Group 2. The mean age of the patients was 66.37 ± 7.96 years and 69.33 ± 7.2 years in Group 1 and Group 2, respectively. The patients' characteristics are listed in Table 1.

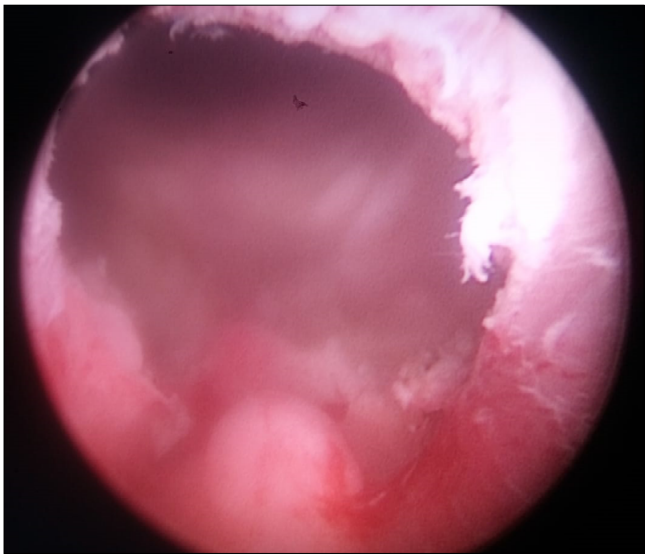
There was a statistically significant difference for age, PSA, fPSA, and D-dimer between the groups. In Group 2, D-dimer levels were higher (0.41 ug/mL and 0.38 ug/mL, $p<0.05$) than in Group 1. The patients were diagnosed using transrectal ultrasound-guided prostate biopsy and transurethral prostate surgery (Figure 1). Transrectal prostate biopsy and transurethral surgery were performed in 72 and 146 patients, respectively.

TABLE 1. PATIENTS' BIOCHEMICAL RESULTS

	Group 1	Group 2	p
Patients n(%)	161 (74)	57 (26)	
Age (years)	66.37+7.96	69.33+7.2	*<0.05
PSA (ng/ml)	5.93	12.74	*<0.05
fPSA (ng/ml)	1.2	1.94	*<0.05
Fibrinogen (mg/dl)	299	304	0.49
D-dimer (ug/ml)	0.38	0.41	*<0.05
Diagnosis			*<0.05
Transurethral resection n(%)	62 (38.5)	10 (17.5)	
Prostate Biopsy n(%)	99 (61.5)	47 (82.5)	

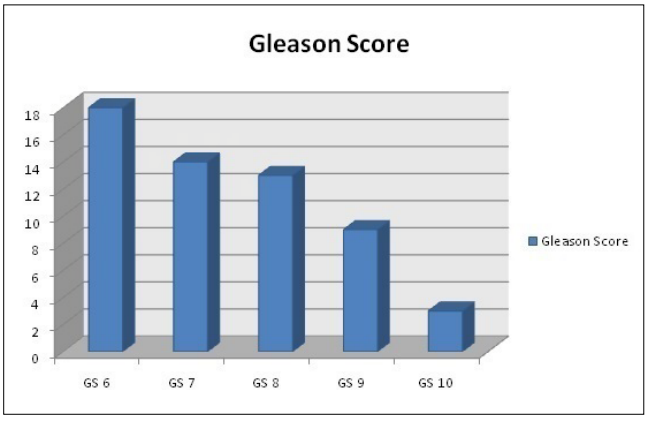
PSA: prostate specific antigen; fPSA: free PSA; *statistically significant

FIGURE 1. THE FINAL IMAGE OF THE PROSTATE AFTER SURGERY



In Group 2, 18 patients were reported as Gleason 6, 14 as Gleason 7, and 13 as Gleason 8. Gleason 9 and Gleason 10 were detected in nine and three patients, respectively (Figure-2).

FIGURE 2. THE GLEASON SCORE OF THE PATIENTS



DISCUSSION

Prostate cancer is the most common type of cancer in men[8]. The digital rectal examination and PSA testing are important screening methods to detect prostate cancer. These screening methods may lead to prostate biopsy, which is necessary to confirm the diagnosis of prostate cancer. A transrectal ultrasound-guided prostate biopsy is the gold standard method for the histopathological diagnosis of prostate cancer[9]. Mochtar et al.[10] described the transrectal ultrasound-guided sextant prostate biopsy, which is an inaccurate means of cancer detection with 10–30% of false-negative rates. The European Association of Urology guidelines suggests prostate biopsy by either the transrectal or transperineal approach for the initial diagnosis[11]. The authors reported that the prostate cancer detection rate was 13.3–35% in patients who underwent six and 12 prostate biopsies, respectively[8].

The pathogenesis of cancer-associated thrombosis depends on patient characteristics, tumor histology, stage, and treatment-related factors[12]. Abnormalities of the coagulation system have been investigated in cancer patients, and it has been reported that plasma levels of factors were altered[13,14]. In cancer patients, the systematic activation of coagulation occurs, which leads to augmented thrombin generation followed by fibrin formation[15]. It has been suggested that fibrin may contribute to tumor growth and facilitate tumor invasion and metastasis by promoting angiogenesis and the formation of a protective fibrin shield on tumor cells that makes them resistant to endogenous defense mechanisms. The interaction of fibrin, platelets, and tumor cells leads to the formation of aggregates that promote endothelial adhesion and metastatic potential[7]. Fibrin degradation products have strong angiogenic efficacy.

Fibrinogen is an important coagulation system factor and systemic inflammatory marker that enhances the progression and invasive potential of tumor cells through several mechanisms[6]. Firstly, fibrinogen is deposited around solid tumors and provides a stable framework to the extracellular matrix of the tumor. It also serves as a scaffold to support some growth factors to tumor cells, such as vascular endothelial growth factor and fibroblast growth factor, and promotes tumor proliferation and angiogenesis. Tumor cells have fibrinogen receptors, intercellular adhesion molecule-1, and $\alpha 5\beta 1$ integrin. These receptors play a role as a bridging factor between fibrinogen and tumor cells, thus enhancing the endothelial adhesion of tumor cell emboli in the vasculature of target organs, leading to metastasis. Additionally, fibrinogen promotes $\beta 3$-integrin-mediated adhesion of tumor cells to platelets, and the platelet-tumor cell aggregates thus formed can shield tumor cells from the immune system and lead to an increase of metastatic tumor cells[6]. The fibrinogen levels are increased because of tumor-associated cytokines or endogenous synthesis by tumor cells themselves in cancer patients[16]. The endogenous fibrinogen has a key role in promoting the growth of lung and prostate cancer cells through interaction with fibroblast growth factor[17]. D-dimer is one of the fibrin degradation products, and the level of D-dimer is a result of fibrinolysis activation[12]. Elevated plasma D-dimer levels are seen in patients with various types of cancer because procoagulant factors lead to constitutive activation of the coagulation cascade, which results in thrombin generation followed by fibrin formation[18]. Fibrin may also conversely form a protective shield on malignant tumor cells, protecting them from endogenous defense mechanisms and promoting angiogenesis, invasion, and metastasis of the tumor. Tumor cells themselves may convert fibrinogen to fibrin, and the fibrin is used for support, for the emergence of new vessels, invasion, and remodeling tumor stroma[19].

Elevated D-dimer levels have been reported in patients with breast, prostate, gynecologic, and lung cancers without clinical thrombosis[12]. D-dimer levels were the highest in patients with pancreatic cancer and lowest in patients with prostate cancer. The authors from the Vienna Cancer and Thrombosis Study reported that an increased D-dimer level was a prognostic parameter associated with increased mortality risk in patients with lymphomas, brain tumors, pancreatic, prostate, breast, lung, stomach, and colorectal cancers[7]. In addition, Ryu et al.[20] reported that D-dimer levels may support the diagnosis of cryptogenic stroke in critically ill cancer patients. Authors from Korea found that D-dimer levels were significantly higher in patients with prostate cancer than in patients without prostate cancer at prostate biopsy[19]. In another study, the investigators showed a significant increase of D-dimer level in patients with advanced prostate cancer compared with age-matched controls and patients with localized prostate cancer[4]. By contrast, Caine et al.[5] investigated the D-dimer levels after radical prostatectomy and found no significant difference 3 and 12 months after surgery. There are limited articles about prostate cancer and

fibrinogen and D-dimer levels in the literature. We found that the D-dimer level was higher in patients with prostate cancer than in other patients with benign prostate hyperplasia ($p < 0.05$) in 2017[21]. In the current study, the results were the same, and an elevated D-dimer level was detected in patients with prostate cancer ($p < 0.05$).

The authors found strong evidence that an elevated plasma fibrinogen level was an independent predictor of worse overall survival in patients with solid tumors[22]. Patients with an increased level of fibrinogen have significantly poorer disease-free survival and cancer-specific survival. Thurner et al.[16] found that there was a significant association between an elevated plasma fibrinogen level and poor cancer-specific and overall survival in patients with prostate cancer. Caine et al.[5] found a significant fall in fibrinogen level after radical prostatectomy 3 and 12 months after surgery. In a meta-analysis, the authors reported that high pretreatment plasma fibrinogen levels can predict poorer overall and cancer-specific survival in patients with prostate cancer[23]. By contrast, Hong et al.[19] found that there was no difference between fibrinogen levels in patients with prostate cancer compared with others. That study showed higher fibrinogen levels in patients with advanced prostate cancer than in patients with organ-confined disease, without a significant difference. We found no difference in fibrinogen levels between the groups.

There are some limitations to this study. It includes only one data center, the coagulation parameters (fibrinogen, D-dimer) were not checked again after first measuring the levels, and other hemostatic system factors were not analyzed. The stage of patients with prostate cancer was not homogenous. Finally, conditions such as trauma and inflammatory process, which may affect coagulation parameters, could not be eliminated. Despite these limitations, to the best of our knowledge, this is the largest series from Turkey to investigate the relationship between coagulation parameters and prostate cancer.

In conclusion, patients with prostate cancer presented higher plasma D-dimer levels than the others. Plasma D-dimer level may be a diagnostic marker for prostate cancer if further studies support our findings. Well designed, multicentre, prospective studies are needed to define the relationship between prostate cancer and the coagulation system.

Author's contribuition

The authors contributed equality for writing, datacollection and supervision.

RESUMO

OBJETIVO: *O câncer de próstata é uma das neoplasias mais comuns em homens. Os principais fatores de risco para a ativação da coagulação e trombose são malignidade e idade mais avançada. O risco de trombose pode estar associado ao aumento do nível dos marcadores de coagulação, tais como o fibrinogênio e D-dímero. O objetivo deste estudo é avaliar a relação entre os marcadores de coagulação e o câncer de próstata.*

METODOLOGIA: *Este estudo prospectivo incluiu os pacientes que foram submetidos à biópsia de próstata transretal guiada por ultrassonografia e que passaram por cirurgia da próstata entre janeiro de 2015 e janeiro de 2016. Os níveis no plasma de antígeno prostático específico (PSA), PSA livre (fPSA), porcentagem de fPSA, D-dímero e fibrinogênio foram medidos antes dos procedimentos. Os pacientes foram divididos em dois grupos de acordo com os resultados de patologia. Os pacientes com hiperplasia benigna da próstata foram colocados no grupo 1 e os pacientes com câncer de próstata no grupo 2.*

RESULTADOS: *No total, 76 pacientes foram incluídos neste estudo. Houve um total de 53 pacientes no grupo 1 e 23 pacientes no grupo 2. A idade média dos pacientes e os níveis de PSA, fPSA, fibrinogênio e D-dímero foram, respectivamente, 65.33 ± 7.47 anos, 8.21 ± 4.59, 1.41 ± 0.74 ng/ml, 309.75 ± 80.46 mg/dl e 0.42 ± 0.39 µg/ml no grupo 1. No grupo 2, a idade média dos pacientes e os níveis de PSA, fPSA, fibrinogênio e D-dímero foram, respectivamente, 66.08 ± 6.7 anos, 145.69 ± 509.35, 7.32 ± 15 ng/ml, 312.16 ± 69.48 mg/dl, 1.09 ± 2.11 µg/ml. Biópsia da próstata e cirurgia transuretal foram realizadas em 64 (%84,21) e 12 (%15,79) pacientes, respectivamente.*

CONCLUSÃO: *O presente estudo demonstrou que os níveis de D-dímero no plasma foram maiores em pacientes com câncer de próstata. Novos estudos com um maior número de pacientes são necessários para definir a relação entre câncer de próstata e distúrbios de coagulação.*

PALAVRAS-CHAVE: *Neoplasias da próstata. Trombofilia. Biomarcadores tumorais/sangue. Produtos de degradação da fibrina e do fibrinogênio.*

REFERENCES

1. Sungur M, Caliskan S. Awareness of prostate cancer diagnosis and management among Turkish males: a cross sectional study from Çorum. Aging Male. 2019:1-4.
2. Alghamidi IG, Hussain II, Alghamdi MS, El-Sheemy MA. The incidence rate of prostate cancer in Saudi Arabia: an observational descriptive epidemiological analysis of data from the Saudi Cancer Registry 2001–2008. Hematol Oncol Stem Cell Ther. 2014;7(1):18-26.
3. Lyman GH, Khorana AA. Cancer, clots and consensus: new understanding of an old problem. J Clin Oncol. 2009;27(29):4821-6.
4. Kohli M, Fink LM, Spencer HJ, Zent CS. Advanced prostate cancer activates coagulation: a controlled study of activation markers of coagulation in ambulatory patients with localized and advanced prostate cancer. Blood Coagul Fibrinolysis. 2002;13(1):1-5.
5. Caine GJ, Ryan P, Lip GY, Blann AD. Significant decrease in angiopoietin-1 and angiopoietin-2 after radical prostatectomy in prostate cancer patients. Cancer Lett. 2007;251(2):296-301.
6. Wen J, Yang Y, Ye F, Huang X, Li S, Wang Q. The preoperative plasma fibrinogen level is an independent prognostic factor for overall survival of breast cancer patients who underwent surgical treatment. Breast. 2015;24(6):745-50.
7. Ay C, Dunkler D, Pirker R, Thaler J, Quehenberger P, Wagner O. High D-dimer levels are associated with poor prognosis in cancer patients. Haematologica. 2012;97(8):1158-64.
8. Ghafoori M, Velayati M, Aliyari Ghasabeh M, Shakiba M, Alavi M. Prostate biopsy using transrectal ultrasonography; the optimal number of cores regarding cancer detection rate and complications. Iran J Radiol. 2015;12(2):e13257.
9. Kocan H. Factors affecting the diagnosis of prostate cancer through 12 quadrant guided prostate biopsy. Aging Male. 2019:1-6.
10. Mochtar CA, Atmoko W, Umbas R, Hamid ARAH. Prostate cancer detection rate in Indonesian men. Asian J Surg. 2018;41(2):163-9.
11. Mottet N, van den Bergh RCN, Briers E, Cornford P, De Santis M, Fanti S, et al. EAU Guidelines on Prostate Cancer. 2018. [cited 2019 Aug 12]. Available from: https://uroweb.org/guideline/prostate-cancer/
12. Hanna DL, White RH, Wun T. Biomolecular markers of cancer-associated thromboembolism. Crit Rev Oncol Hematol. 2013;88(1):19-29.
13. Bick RL. Coagulation abnormalities in malignancy: a review. Semin Thromb Hemost. 1992;18(4):353-72.
14. Constantini V, Zacharski LR. Fibrin and cancer. Thromb Haemost. 1993;69(5):406-14.
15. Ay C, Vormittag R, Dunkler D, Simanek R, Chiriac AL, Drach J, et al. D-dimer and prothrombin fragment 1+2 predict venous thromboembolism in patients with cancer: results from the Vienna Cancer and Thrombosis Study. J Clin Oncol. 2009;27(25):4124-9.
16. Thurner EM, Krenn-Pilko SK, Langsenlehner U, Stajokovic T, Pichler M, Gerger A, et al. The association of an elevated plasma fibrinogen level with cancer-specific and overall survival in prostate cancer patients. World J Urol. 2015;33(10):1467-73.
17. Sahni A, Simpson-Haidaris PJ, Sahni SK, Vaday GG, Francis CW. Fibrinogen synthesized by cancer cells augments the proliferative effect of fibroblast growth factor-2 (FGF-2). J Thromb Haemost. 2008;6(1):176-83.
18. Khoury JD, Adcock DM, Chan F, Symanowski JT, Tiefenbacher S, Goodman O, et al. Increases in quantitative D-dimer levels correlate with progressive disease better than circulating tumor cell counts in patients with refractory prostate cancer. Am J Clin Pathol. 2010;134(6):964-9.
19. Hong SK, Ko DW, Park J, Kim IS, Doo SH, Yoon CY, et al. Alteration of antithrombin III and D-dimer levels in clinically localized prostate cancer. Korean J Urol. 2010;51(1):25-9.
20. Ryu JA, Bang Oy, Lee GH. D-dimer levels and cerebral infarction in critically ill cancer patients. BMC Cancer. 2017;17(1):591.
21. Çalışkan S, Sungur M. Fibrinogen and D-dimer levels in prostate cancer: preliminary results. Prostate Int. 2017;5(3):110-2.
22. Perisandis C, Psyrri A, Cohen EE, Engelman J, Heinze G, Perisandis B, et al. Prognostic role of pretreatment plasma fibrinogen in patients with solid tumors: a systematic review and meta-analysis. Cancer Treat Rev. 2015;41(10):960-70.
23. Song H, Kuang G, Zhang Z, Ma B, Jin J, Zhang Q. The Prognostic value of pretreatment plasma fibrinogen in urological cancers: a systematic review and meta-analysis. J Cancer. 2019;10(2):479-87.

ORIGINAL ARTICLE

Comparison of the effect of two internal fixation methods for proximal clavicle fractures

Haining Xu[1]
Yan Nie[1]
Lifang Han[1]
Liang Li[1]
Haitao Sui[1]

1. Department of Orthopaedics, Dongying People's Hospital, Dongying, Shandong 257091 China.

http://dx.doi.org/10.1590/1806-9282.66.5.654

SUMMARY

OBJECTIVE: *To compare the effect of two internal fixation methods in the treatment of proximal clavicle fractures.*

METHODS: *Fifty patients with proximal clavicle fractures received surgical treatment. They were divided into a clavicular T-plate group and a double mini-plates group. The duration of the operation, blood loss during the operation, fracture healing time, and incision infection were evaluated between the two groups.*

RESULTS: *Operation time (t=2.063, P=0.058), intraoperative bleeding (t=1.979, P=0.062), and fracture healing time (t=1.082, P=0.066) were not statistically significant in the two groups. The patients were followed up for 12-18 months; one patient in the T-plate group had early removal of nails, but no clinical symptoms. At the 2-month follow-up, the ASES score in the double mini-plates group was significantly better than in the T-plate group (P<0.001); but at the 6-month follow-up, 1-week before removal of internal fixation and the final follow-up, the two groups had no significant differences (P>0.05).*

CONCLUSIONS: *Both internal fixations have similar clinical results in the duration of operation, blood loss during the operation, and fracture healing time. The double mini-plates fixation presents advantages by reducing complications and speeding fracture healing; thus it is a more effective method to treat proximal clavicle fractures.*

KEYWORDS: *Clavicle/injuries. Fracture fixation. Fracture fixation, internal. Orthopedic procedures/methods.*

INTRODUCTION

Proximal clavicle fractures represent one-third of all fractures involving the medial clavicle, accounting for 9.3% of the clavicle fractures. They are relatively rare in clinical practice, and more common in cases of larger direct violence. Non-surgical treatment may lead to deformed appearance, limited function, and other adverse consequences; thus the treatment effect is often not ideal. In recent years, scholars have carried out surgery for the treatment of proximal clavicle fracture[s1], but considering the complex characteristics of anatomical structures such as important nerves, blood vessels, organs, and so on in the dorsal side of the proximal clavicle, and no anatomical plate has been designed for the proximal clavicle. At present, there is no optimal internal fixation option for such fractures.From July 2014 to June 2019, fifty patients with proximal clavicle fractures treated by vertical internal fixation with T-plate and double mini plates

DATE OF SUBMISSION: 06-Nov-2019
DATE OF ACCEPTANCE: 30-Dec-2019
CORRESPONDING AUTHOR: Haitao Sui
Department of Orthopaedics, Dongying People's Hospital, n.317, Dongcheng South First Road, Dongying, Shandong, China - 257091
E-mail: jiawei20100303@163.com

were analyzed retrospectively in this study. By comparing the operation time, intraoperative hemorrhage, fracture healing time, and postoperative complications between the two groups, the differences in the functional recovery of the shoulder joint in different stages were analyzed. The report is as follows.

METHODS

Subjects

A total of 50 cases, 32 males and 18 females, aged from 22 to 62 (41.4 ± 23.5) years, were included in this study. According to the method of internal fixation, they were divided into a T-plate group (24 cases) and a double mini plates group (26 cases).

Clinical signs

Swelling of the proximal clavicle, obvious tenderness, palpable bone friction, and abnormal activity.

Imaging examination

CT three-dimensional reconstruction of imaging examination can provide the three-dimensional relationship between the proximal clavicle fracture and the displaced three-dimensional plane. Routine CT three-dimensional reconstruction examination before the operation can be the first choice for the diagnosis of proximal clavicle fracture and helps us prepare well before the operation and choose a more reasonable operation method[2].

Operative method

The anesthesia approach for the operation is brachial plexus anesthesia or general anesthesia, and a beach chair position is used. The operation incision cuts the skin and subcutaneous tissues along the surface of the proximal clavicle to the end of the sternum, exposing the sternoclavicular joint, peeling off the periosteum above the fracture site, fully exposing the broken end of the fracture, cleaning up the embedded soft tissue at the broken end, exposing the broken end of the medial clavicle fracture, and reducing the sternoclavicular joint under direct vision; if necessary, it can be bound with absorbable non-invasive suture or Kirschner wire Temporary fixing. T-shaped plate group: after the fracture is reduced satisfactorily, the T-shaped plate is molded and placed at the far and near end of the fracture. 2-3 screws are attached to the near end of the fracture, and 3-4 screws are attached to the far end of the fracture for fixation. The screws should not enter the space of the sternoclavicular joint. In the double mini plates group, two pre-bent 2.0mm or 2.5mm mini plates were implanted above and in front of the clavicle after a satisfactory reduction of the fracture.

Postoperative treatment

The patients in the two groups had their shoulder joints suspended by a wrist band. One day after the operation, functional exercises such as forearm rotation, elbow flexion and extension, pendulum-like activities were performed; one week after the operation, patients were encouraged to perform functional exercises such as upper limb abduction and shoulder shrug; four weeks after the operation, appropriate lifting activities were performed and the range of activities was gradually increased; six weeks after the operation, normal shoulder non-weight bearing activities were resumed.

Evaluation index

The operative time, intraoperative hemorrhage, fracture healing time, and postoperative complications of the two groups were analyzed. The differences in shoulder pain and functional recovery were evaluated by the American Shoulder and Elbow Surgeons (ASES)[3] Standard at 2 months, 6 months, and 1 week before internal fixation removal and the last follow-up.

Statistical analysis

SPSS 19.0 software was used for statistical analysis. The measured data were expressed by mean±standard deviation, and the mean index determined between the two groups was compared by students t-test; the comparison of the data was by the chi-square test, and $P < 0.05$ was considered as statistically significant.

RESULTS

The general characteristics of patients included in this study are summarized in Table 1. The causes of injury were: direct violence in 38 cases, indirect violence in 12 cases. The Craig III group of fractures were: 21 cases of type II, 12 cases of type III, and 17 cases of type V. The time from injury to operation was 2-7 days. According to the method of internal fixation, patients were divided into a T-plate group (24 cases) and a double mini plate group (26 cases). There was no significant difference between the two groups ($P > 0.05$).

Follow-up

Fifty patients in both groups were followed up for 12 to 18 months. All achieved bone healing.

Observation index

Table 2 shows the operation time, intraoperative blood loss, fracture healing time, and ASES score of each period of the two groups. Bone healing was achieved at the last follow-up.

Postoperative complications

There were no complications such as wound infection, fracture around the steel plate, and fracture of steel plate in both groups. In the T-plate group, 1 case (1 / 24) had screw loosening but no clinical symptoms; in the double mini plate group, there were no complications; there was a significant difference in the incidence of complications between the two groups ($P < 0.05$).

Typical cases

Case one, male, 39 years old, was treated with T-plate fixation for a closed fracture of the left distal clavicle (Craig III group III). CT before operation showed a clavicle fracture and displacement (Figure1A). X-ray at 6 months after the operation showed fracture reduction and good internal fixation (Figure1B). Case two, male, 32 years old, was treated with two mini plates to fix a closed fracture of the left distal clavicle (Craig III group V). CT before operation showed a clavicle fracture and displacement (Figure1C). X-ray at 6 months after the operation showed fracture reduction and good internal fixation (Figure1D). Case three, male, 45 years old, was treated with two mini plates to fix a closed fracture of the left distal clavicle (Craig III group II). Before the operation, CT showed a fracture and displacement of the clavicle (Figure1E). X-ray at 6 months after the operation showed fracture reduction and good internal fixation (Figure1F).

DISCUSSION

Our study found that the functional recovery of the double mini plate group was significantly better than that of the T-plate group. In the double mini plate group, not only the fixation of at least 3 screws is done at the distal and proximal ends of the fracture, but also the smaller size of the mini plates avoids the potential risk of skin bursting, which creates conditions for early rehabilitation exercises and recovery of shoulder joint function after the operation. In this study, there were no complications in the double mini plate group, indicating that the failure rate of the internal fixation and reduced loss rate were significantly smaller.

In view of the anatomic structure of the subclavian artery, subclavian vein, external jugular vein, 4-8 nerves and 1-2 nerves in the chest, conservative treatment is generally adopted for proximal clavicle fractures, but the traditional "8" bandage or sling leads to shoulder dysfunction in the long-term conservative treatment of proximal clavicle fractures. Even if functional exercise is encouraged, there will be a certain

TABLE 1. GENERAL CHARACTERISTICS OF PATIENTS INCLUDED IN THIS STUDY

Group	n	Gender		Age(years)	Craig III			Causes of injury	
		Male	Female		II	III	V	direct	indirect
T-plate	24	18	6	44.2±26.1	10	6	8	18	6
double mini plate	26	19	7	43.7±33.9	11	6	9	20	6
t/χ^2		2.647		2.086		1.064		1.826	
P		0.586		0.692		0.248		0.326	

TABLE 2. COMPARISON OF THE OBSERVATION INDEX BETWEEN THE TWO GROUPS

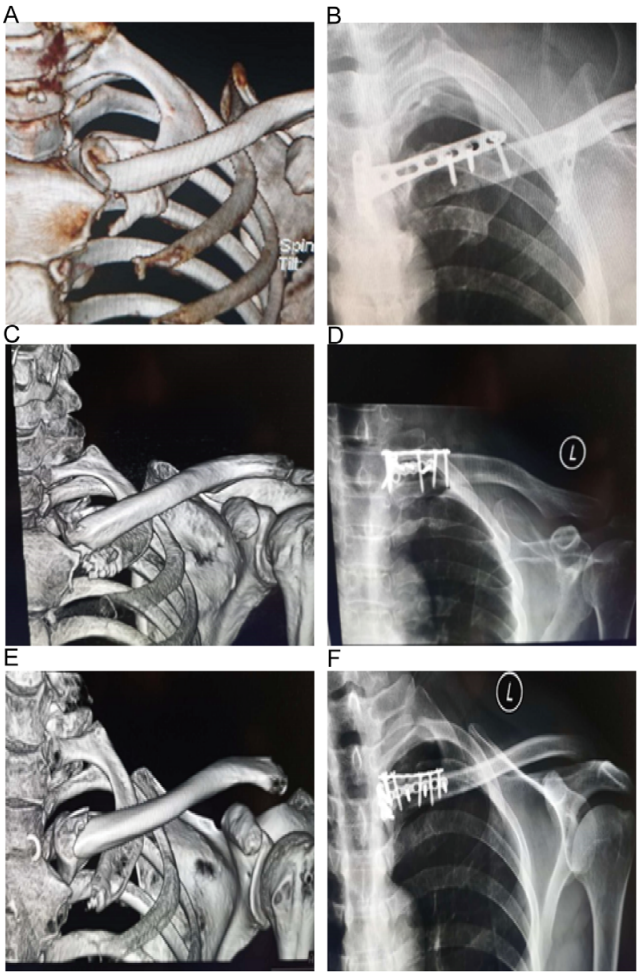
		T-plate group	Double mini plate group	t/χ^2	P
Operation time (min)		42.1 ± 11.4	43.2 ± 12.1	2.063	0.058
Intraoperative blood loss (ml)		22.6 ± 11.8	23.1 ± 10.6	1.979	0.062
Fracture healing time (month)		5.3 ± 1.2	5.1 ± 1.6	1.082	0.066
Score of ASES	Time A	68.0±2.1	76.5±6.4	2.686	0.027
	Time B	84.3±3.4	88.4±5.9	1.086	0.214
	Time C	90.1±2.6	91.2±2.6	1.045	0.268
	Time D	90.2±2.7	91.3±2.4	1.026	0.296

Note: Time A: Two months after operation; Time B: Six months after operation; Time C: One week before removal of internal fixation; Time D: Last follow –up.

degree of fracture healing[4]. Throckmorton et al.[5] followed up the conservative treatment of proximal clavicle fractures, and about 53% of the patients had pain symptoms. Therefore, conservative treatment has been gradually replaced by surgical treatment. More and more scholars believe that open reduction and internal fixation is the better choice for the treatment of proximal clavicle fractures. Because there is no specially designed steel plate for the special anatomic characteristics of the proximal clavicle, there are little methods to fix fractures of the proximal clavicle. Bourghli and Fabre[6] reported that Kirschner wire was used to fix the proximal clavicle fracture, and good surgical results were achieved. Bartonícek et al.[7] reported that the proximal clavicle fracture was fixed with steel wire, and no dysfunction was left after the operation. Sidhu et al.[8] reported that patients with such fractures were fixed with distal clavicular plates on the same side, and the results showed that the fractures were completely healed. Although the extensive use of internal fixation has effectively improved the healing rate of the proximal clavicle fracture and functional recovery of patients, there is still no small controversy on the selection of the method for internal fixation[8].

Although the steel plate and screws of the micro steel plate system are small, they can be fixed using multiple 2.0mm or 2.5mm screws in different directions to make the stability control more reliable. Double mini steel plates were placed vertically on two 90 ° planes to form a beam structure, which also increased the fixation firmness of the diamond frame structure near the clavicle[9]. After anatomic reduction of the proximal clavicle fracture, two micro plates were placed vertically at the top and the front, and the distal and proximal clavicle fractures could be fixed with at least three screws. There is no interference and no involvement of the sternoclavicular joint, so patients can exercise shoulder joint function early after the operation. Stable fixation also provided favorable conditions for early functional exercise. The ASES score was better than that of the T-plate group at the 2 months follow-up. In this study, there were no complications such as screw loosening, fracture around the plate, and nonunion in the double mini plate group. Therefore, the author believes the following points should be paid attention to in the treatment of proximal clavicular fracture with double mini plate technology: (1) operate gently during reduction to avoid further comminution of fracture in patients with osteoporosis; (2) in order to prevent the loss of clavicle length and rotation deformity, realize an anatomical reduction of fracture in the sternoclavicular joint. At the same time, avoid too much incision and separation to affect the stability of the sternoclavicular joint; (3) pre-bend the mini steel plate properly to make it more attached to the clavicle; (4) screw at least three screws into the proximal end of the fracture for fixation; (5) pay attention to the angle when screwing in to prevent the screw from entering the sternoclavicular joint space.

FIGURE 1



CONCLUSION

Both internal fixation methods have similar clinical results in the duration of operation, blood loss during the operation, and fracture healing time. The double mini-plates fixation provides advantages regarding a reduction of complications and faster fracture healing; therefore, this is a more effective method to treat proximal clavicle fractures.

Conflict of interest

The authors declare no conflicts of interest.

Author Contributions

All authors contributed to the data analysis, drafting and revision of the article, gave final approval of the version to be published, and agreed to be accountable for all aspects of the work.

Haining Xu and Yan Nie contributed equally to the work.

RESUMO

OBJETIVO: *Comparar o efeito de dois métodos de fixação interna no tratamento de fraturas da clavícula proximal.*

MÉTODOS: *Cinquenta pacientes com fraturas da clavícula proximal receberam tratamento cirúrgico. Eles foram divididos em um grupo de placa T clavicular e um grupo de miniplacas duplas. A duração da operação, perda de sangue durante a operação, tempo de cura da fratura e infecção na incisão foram avaliados nos dois grupos.*

RESULTADOS: *O tempo de operação (t=2,063, P=0,058), perda de sangue durante a operação (t=1,979, P=0,062) e tempo de cura das fraturas (t=1,082, P=0,066) não foram estatisticamente significativos nos dois grupos. Os pacientes foram acompanhados por 12-18 meses; um dos pacientes do grupo da placa T teve retirada antecipada dos parafusos, mas não apresentou sintomas clínicos. Aos dois meses de acompanhamento, a pontuação ASES no grupo de miniplacas duplas foi significativamente melhor do que a do grupo de placas T (P<0,001). Porém, no acompanhamento de seis meses, uma semana antes da remoção da fixação interna e do acompanhamento final, os dois grupos não apresentavem diferenças significativas (P>0,05).*

CONCLUSÃO: *Ambas técnicas de fixação interna têm resultados clínicos semelhantes quanto a duração da operação, perda de sangue durante a operação e tempo de cura da fratura. A fixação de miniplacas duplas apresenta vantagens quanto a redução das complicações e cura mais rápida da fratura, sendo, portanto, um método mais eficaz para tratar fraturas da clavícula proximal.*

PALAVRAS-CHAVE: *Clavícula/lesões. Fixação de fratura. Fixação interna de fraturas. Procedimentos ortopédicos/métodos.*

REFERENCES

1. Salipas A, Kimmel LA, Edwards ER, Rakhra S, Moaveni AK. Natural history of medial clavicle fractures. Injury. 2016;47(10):2235-9.
2. Wang Y, Jiang J, Dou B, Zhang P. Inverted distal clavicle anatomic locking plate for displaced medial clavicle fracture. Arch Orthop Trauma Surg. 2015;135(9):1241-5.
3. King GJ, Richards RR, Zuckerman JD, Blasier R, Dillman C, Friedman RJ, et al. A standardized method for assessment of elbow function. Research Committee, American Shoulder and Elbow Surgeons. J Shoulder Elbow Surg. 1999;8(4):351-4.
4. Rieser GR, Edwards K, Gould GC, Markert RJ, Goswami T, Rubino LJ. Distal-third clavicle fracture fixation: a biomechanical evaluation of fixation. J Shoulder Elbow Surg. 2013;22(6):848-55.
5. Throckmorton T, Kuhn JE. Fractures of the medial end of the clavicle. J Shoulder Elbow Surg. 2007;16(1):49-54.
6. Bourghli A, Fabre A. Proximal end clavicle fracture from a parachute jumping injury. Orthop Traumatol Surg Res. 2012;98(2):238-41.
7. Bartonícek J, Fric V, Pacovský V. Displaced fractures of the medial end of the clavicle: report of five cases. J Orthop Trauma. 2010;24(4):e31-5.
8. Sidhu VS, Hermans D, Duckworth DG. The operative outcomes of displaced medial-end clavicle fractures. J Shoulder Elbow Surg. 2015;24(11):1728-34.
9. Kim KC, Shin HD, Cha SM. Surgical treatment of displaced medial clavicle fractures using a small T-shaped plate and tension band sutures. Arch Orthop Trauma Surg. 2011;131(12):1673-6.

ORIGINAL ARTICLE

Mucosal bacterial vaccines in clinical practice – a novel approach to an old problem?

João Neiva Machado[1]
José Coutinho Costa[1]
Teresa Costa[1]
Cidália Rodrigues[1]

1. Unidade de Pneumologia – Universidade e Centro Hospitalar de Coimbra, Coimbra, Portugal.

http://dx.doi.org/10.1590/1806-9282.66.5.659

SUMMARY

OBJECTIVES: *To evaluate the efficacy of mucosal bacterial vaccines (MBV) in reducing the number of exacerbations in patients with chronic respiratory disease.*

METHODS: *A prospective cohort study of patients followed at the Pneumology Unit of the University and Hospital Centre of Coimbra, with frequent infectious exacerbations (3 or more) despite the best therapeutic strategies employed. MBV was used as additional therapy. The number of exacerbations 1 year before therapy and 1 year after it were analyzed.*

RESULTS: *A sample of 11 individuals, 45.5% male, mean age 62.5 years. Eight patients had non-cystic fibrosis bronchiectasis, 2 COPD (1 on long-term oxygen therapy), and 1 patient with Mounier Kuhn's syndrome. Three patients were on azithromycin, 1 on inhaled colistin, and 2 on inhaled tobramycin. Out of the 11 patients, one presented complication (fever), which led to a suspension of therapy (excluded from results). Of the 10 patients who completed treatment, 5 had bacterial colonization and were submitted to a custom vaccine. The remaining 6 completed the standard composition. The average of infectious exacerbations in the previous year was 4.3 (0.7 with hospitalization). In the year after therapy, the mean number was 1.5 (0.5 with hospitalization).*

CONCLUSION: *The results obtained in this study favor the use of bacterial immunostimulation to reduce the frequency of RRIs in patients with chronic respiratory disease.*

KEYWORDS: *Bacterial vaccines. Administration, sublingual. Respiratory tract infections. Respiratory tract diseases.*

INTRODUCTION

Antibiotic resistance has been a focus of concern of public health care, and the problem is such that the World Health Organization (WHO) implemented a Global Action Plan in 2015 to tackle it, which includes increasing investment in new medicines, diagnostic tools, vaccines, and other interventions[1].

Approximately 65% of the agents causing human infections form bacterial biofilms that favor chronic infections[1], and the frequent use of antibiotics favors the risk of antibiotic resistance[2]. Recurrent respiratory infections (RRI) are characterized by at least three episodes of fever, locoregional inflammation, cough, asthma, and wheezing without severe impairment of respiratory functions yearly[3]. This syndrome is frequent, therefore RRIs are a major health-care problem associated with significant morbidity and mortality. They are also associated with the spread of resistance to antibiotics in patients with deficient humoral and cellular immune functions, such as primary and secondary immunodeficiencies and chronic obstructive

DATE OF SUBMISSION: 15-Dec-2019
DATE OF ACCEPTANCE: 28-Dec-2019
CORRESPONDING AUTHOR: João Pedro Neiva Machado
Quinta dos Vales, São Martinho do Bispo, Coimbra, Portugal - 3041-801
E-mail: joaoneivamachado@gmail.com

pulmonary disease[4]. Immunostimulant agents of bacterial origin have been used as an adjunct treatment in these patients because of their immunomodulatory properties, increasing immune responses and boosting the innate immune system. For example, several studies have shown that the oral administration of bacterial immune stimulants ameliorates RRI in adults and children by reducing the number, duration, and severity of infectious clinical episodes[5]. Unfortunately, antigens delivered orally are easily degraded during the passage through the acidic environment of the stomach, while antigens delivered intranasally have the demonstrated potential to migrate through the olfactory bulb to the brain, thereby reducing vaccine safety. The sublingual route has been used for many years as a noninvasive and effective immunotherapy for the treatment of allergies to a variety of allergens and, recently, the sublingual administration of bacterial preparations has been proposed as a safer and effective immunotherapy to stimulate strong and long-lasting systemic and mucosal antigen-specific humoral and cell-mediated immunity[6]. Moreover, the induction of immunological memory to a specific pathogen is critical to maintaining long-lasting immune surveillance upon vaccination using the sublingual immunization strategy[7-11].

These bacterial preparations also present a higher likelihood to generate the necessary B and T cell responses for optimal protection at the point of entry of infectious agents, in addition to promoting the levels of systemic immunity generally achieved by conventional injected vaccines[8].

Mucous membranes are the main route of entry of infectious and environmental agents. Mucosal anti-infective vaccines are combinations of inactivated whole bacteria or fungi or of bacterial lysates that stimulate the immune system, which according to numerous studies, reduce the number of reinfections by the same pathogens and others. The mechanisms underlying this collateral benefit may be due in large part to "trained immunity" rather than the specific wing, which has also been found to contribute to the protective effect[2].

For mucosal vaccines to be effective, it is desirable that secretory IgA antibody (the hallmark of immune responses at mucosal surfaces) responses should persist, or at least be very rapidly recallable in the face of a pathogenic attack to forestall infection at the mucosal surface. However, it appears that secretory IgA (S-IgA) antibodies do not always persist for long after the removal of the inducing antigenic stimulus, meaning that these vaccines require repetitive stimulation to reach their full potential[12].

Therapeutic interventions with mucosal anti-infectious vaccines have different advantages over conventional parenteral vaccines: a) they carry out their effects directly at the mucosal infection site and can prevent infection and colonization by pathogens[3]; b) mucosal immunization may result in the secretion of antibodies in other, more distant mucous membranes, and also systemically[13]; c) they do not require medical personnel for administration and can be used in mass vaccinations and disease prevention campaigns, and d) they are painless and simple to administer. Also, taking into account that gram-positive bacteria stimulate the production of IL-12 and that gram-negative bacteria stimulate the production of IL-10 by monocytes, the combination of gram-positive and gram-negative bacteria in infectious mucosal vaccines seems to provide a synergistic immunologic response that could be greater depending on the pathology involved[14]. These preparations for mucosal administration with completely inactivated bacteria are presented to the immune system in a more natural way, maximizing their full potential as immunogens[15] stimulating different immune mechanisms, which have been proven to be very important for complete cellular activation, such as phagocytosis[16].

Besides these advantages, formulations for sublingual immunotherapy have a lower cost of manufacture since non-sterile products can be delivered by this route and endotoxic shock is not a concern[17].

In the present study, we evaluated prospectively whether the daily administration of a polyvalent bacterial preparation via the sublingual route could reduce the number of infectious exacerbations of patients with RRIs.

METHODS

This prospective cohort study aimed to assess whether the daily sublingual administration (4.5 - 6 months, depending on manufacturer instructions) of a polyvalent bacterial preparation could impact on the clinical outcome of patients with RRIs. The study was conducted between January 2016-January 2019, including the treatment and follow-up period. We used a convenience sample of 11 patients affected by RRIs and followed-up at the subspecialty (patients with chronic obstructive diseases and/or

respiratory failure) Pneumology consultation of the Pneumology Unit of the University and Hospital Center of Coimbra.

All patients had suffered RRIs during the 12 months prior to the study and were required to meet the following criteria: 3 or more respiratory infections in the previous 12 months; chronic pulmonary disease (COPD, bronchiectasis, other); recurrent need for oral and/or intravenous antibiotic courses and/or hospitalizations to clear infections in the previous 12 months. The exclusion criteria were: treatment with immunosuppressants (prednisone 10mg/day or equivalent), immunostimulants, gamma globulins within the previous 12 months; patients who had laboratory or clinical criteria for lymphoproliferative disorders or non-respiratory chronic infections. All patients eligible started the immunizations with Bactek® (Immunotek) or Vacinas Bacterianas Diater® when they had asymptomatic clinical status.

Bacterial preparations Bactek® (Inmunotek Laboratories, Madrid, Spain) and Vacinas Bacterianas Diater® (Diater Laboratories, Madrid, Spain) are commercially available polyvalent bacterial preparations. Bactek® contains different species of inactivated bacteria at 10^9 bacteria/ml which are frequently present in the respiratory tract: *S. aureus* (15%), *S. epidermidis* (15%), *S. pneumoniae* (60%), *Klebsiella pneumoniae* (4%), *Branhamella catarrhalis* (3%), and *Haemophilus influenzae* (3%). Vacinas Bacterianas Diater® contains *S. pyogenes* (25%), *S. pneumoniae* (25%), *Klebsiella pneumoniae* (25%), and *Haemophilus influenzae* (25%). We established the composition of the patient bacterial preparation based on the most common bacteria causing respiratory infections, combined with sputum analysis, to address for either colonization or the most common infectious pathogen. We found 5 patients had bacterial colonization; they were submitted to a custom vaccine composition with a higher percentage of the colonizing agent (minimum of 10% in the composition) associated with at least 50% of the standard composition.

The preparation was delivered sublingually, two sprays, each day, for 4,5 to 6 months.

Patients were assessed every 3-6 months and every time they had respiratory tract symptoms. RRIs were defined by the presence of diagnostic symptoms for at least 48–72 h. Multiple illnesses were counted only if the patient had been without symptoms for at least 72 h between the end of one episode and the beginning of another.

The clinical status and total number of infectious respiratory episodes that had occurred in the year previous to immunization were recorded for each patient by their attending physician during the 12 months that followed immunization. The number of infectious respiratory episodes prior and after the treatment was considered the main variable for the clinical outcome. Patients were treated with antibiotics for controlling their RRIs at physician criteria.

The study was conducted according to the declaration of Helsinki. Data were obtained through a chart review and analyzed using SPSS® v23. Data were presented as mean and standard deviation (SD) for continuous variables and percentages for categorical variables. Data analysis demonstrated a non-normal distribution, and non-parametric tests (Wilcoxon signed-rank test and Mann-Whitney U test) were therefore employed in the statistical analysis. The significance level of 0.05 was used.

RESULTS

The sample contained 11 patients, 45.5% (n=5) males, with a mean age of 62.5 years (±9.8). Their clinical characteristics are presented in table 1. One COPD patient (#6) and one NCFB (#10) were on long-term oxygen therapy. Three patients were or used to be on long-term therapy with azithromycin (#5, #9 and #11), 1 patient was on inhaled colistin (#10), and 2 on inhaled tobramycin (#3 and #4). Out of the 11 patients, only one (patient with NCFB) presented a possible complication (fever), which led to the suspension of therapy at the end of the first month its exclusion from the results (table 2). Of the 10 patients who completed the treatment, 5 had bacterial colonization, all of them with *Pseudomonas aeruginosa*, and one also with *Haemophilus influenzae*; they were submitted to a custom vaccine composition (table 2). The remaining patients completed the standard composition.

The mean respiratory infectious episodes in the previous year were 4.3 (±1.3). Clinical assessment throughout the study showed a significant reduction of the total number of respiratory tract infection episodes after the treatment compared with the number of RRIs scored throughout the 12 months prior to the treatment ($Z=-2.871$; $p = 0.004$) (figure 1). There was no statistically significant difference regarding the laboratory manufacturing the vaccines ($U=8.000$; $p>0.05$). Anecdotally, four patients reported major clinical improvement with therapy.

DISCUSSION

In this pilot study, we observed a remarkable reduction in the frequency of respiratory tract infectious episodes in a cohort of patients with RRIs treated with mucosal bacterial vaccines over a 12-month period after initiation of therapeutic immunization, in comparison to the number of RRIs prior to the treatment and using personalized formulations based on previous sputum bacterial results, aiming to achieve better clinical outcomes by exploring the advantages of the personalized therapy that these vaccines offer. Our results agree with other studies showing an association between immunization with polyvalent bacterial preparations and clinical improvement of infectious respiratory diseases[5-7,9-11].

Several clinical studies have shown that the oral administration of a polyvalent bacterial preparation in patients with COPD is capable of improving impaired immune functions, such as alveolar macrophage activity and interferon-gamma production[10]. The preparations used by our patients differ from others in their formulation, concentration, and/or route of administration (sublingual), and delivers whole inactivated bacteria instead of the most common bacterial lysates.

The mechanisms behind the efficacy of this novel approach, despite not fully understood, are being studied in order to clarify all its potential. For example, a prospective observational clinical study evaluated the clinical and immunological effects of the treatment with sublingual vaccines of bacterial combinations in antigen-specific responses to bacteria responsible

TABLE 1. CLINICAL CHARACTERISTICS OF THE PATIENTS (N=11). VALUES REPRESENT FREQUENCIES OTHERWISE STATED IN CONTRARY

Patient	Diagnosis	Episodes before vaccination (total)	Episodes before vaccination without hospital stay	Episodes before vaccination with hospital stay	Episodes after vaccination (total)	Episodes after vaccination without hospital stay	Episodes after vaccination with hospital stay
1	NCFB	5	4	1	1	1	0
2	NCFB	3	3	0	2	1	1
3	NCFB	3	3	0	1	1	0
4	COPD	6	4	2	1	1	0
5	Mounier Kuhn's Syndrome	6	6	0	4	3	1
6	NCFB	5	4	1	2	2	0
7	NCFB	3	3	0	-	-	-
8	NCFB	3	3	0	1	1	0
9	NCFB	6	4	2	1	1	0
10	NCFB	3	2	1	1	1	0
11	COPD	3	3	0	1	1	0

NCFB (Non Cystic Fibrosis Bronchiectasis); COPD (Chronic obstructive pulmonary disease

TABLE 2. MUCOSAL BACTERIAL VACCINATION INFORMATION

Patient	Diagnosis	Formulation	Duration of therapy (months)	Complications
1	NCFB	100% Polibacterial	6	0
2	NCFB	100% Polibacterial	6	0
3	NCFB	100% Polibacterial	4,5	0
4	COPD	100% Polibacterial	4,5	0
5	Mounier Kuhn's Syndrome	100% Polibacterial	4,5	0
6	NCFB	100% Polibacterial	4,5	0
7	NCFB	50% Polibacterial + 50% PA	1*	Fever
8	NCFB	50% Polibacterial + 50% PA	6	0
9	NCFB	50% Polibacterial + 50% PA	6	0
10	NCFB	50% Polibacterial + 50% PA	4,5	0
11	COPD	75% Polibacterial + 10% HI + 15% PA	4,5	0

NCFB (Non Cystic Fibrosis Bronchiectasis); COPD (Chronic obstructive pulmonary disease); PA (Pseudomonas aeruginosa); HI (Haemophilus influenzae)

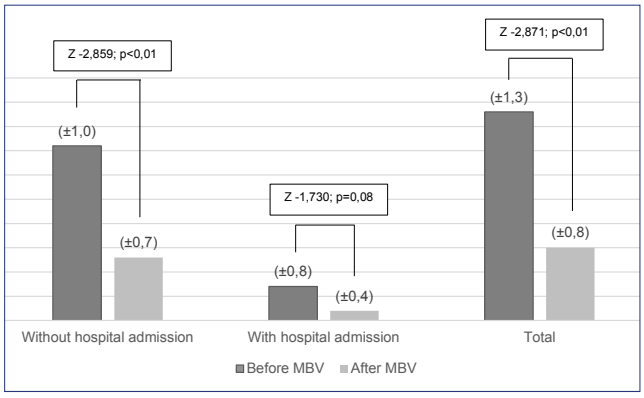
*Did not complete treatment

for respiratory tract infections[6]. Daily immunization with a multivalent bacterial sublingual preparation over a period of 6 months was studied in a cohort of 17 patients with RRIs, and the number of respiratory infections in immunized patients decreased significantly compared to the previous year. Besides, an increase in the proliferative capacity of CD4 + and CD8 + T lymphocytes specific for influenza virus antigen after 6 months of treatment (not contained in the vaccine) was evidenced[6].

Another study described the clinical evolution of 88 patients, diagnosed with recurrent tonsillitis and chronic inflammation[18]. The authors observed that the majority of the patients (82%) who received immunotherapy experienced clinical improvement, avoiding tonsillectomy, whereas in the other group the percentage of patients was 51%. It is emphasized that purified components from bacteria or bacterial lysates selectively activate specific Toll-Like Receptors (TLR), leading to shared and unique responses in innate immune cells, whereas whole bacteria contain multiple agonists for multiple TLR, eliciting a potent and robust response. None of the patients reported any local (at the site of administration) or systemic side effects[18].

A prospective observational study conducted on 50 patients with inflammatory diseases (RA, systemic lupus erythematosus, and mixed connective tissue disease), most of whom were undergoing treatment with biological and/or non-biological disease-modifying anti-rheumatic drugs and glucocorticoids at low doses, and who presented recurrent urinary and/or respiratory infections, evaluated treatment with two different polybacterial sublingual formulations

FIGURE 1. EPISODES OF RESPIRATORY INFECTIONS 1 YEAR BEFORE AND 1 YEAR AFTER TREATMENT (MEAN - SD)



MBV (Mucosal bacterial vaccination)

depending on the type of infection[19]. Vaccines were administered in cycles of 3 months per year and the clinical response was recorded at 6 months and a year. The paired comparison of the number of infectious events in both groups showed a significant decrease in the rate of repeated urinary tract infections and in the rate of recurrent respiratory infections in the previous year compared to the year after the vaccine[19].

Overall, these preparations have shown very good safety profiles, even in immunosuppressed patients[19,20]. In our study, only one patient had what could in theory be a side effect from the therapy leading to discontinuation (fever), out of precaution. Despite this, all other patients tolerated very well the sublingual administration.

Another concern is the duration of the protective effect since it is known that these therapies require repetitive stimulation. One study demonstrated that the sublingual administration could induce persistent systemic and mucosal immune responses up to 4 months after the last immunization[21].

The clinical experience with mucosal bacterial vaccines has been increasing not only in the prevention of RRIs but also in recurrent urinary tract infections (RUTI), providing valuable information on how to expand its beneficial effects. In a retrospective observational study of 319 women affected by RUTIs that compared the clinical impact of the prophylactic treatment with a bacterial vaccine (Uromune®) and the currently accepted antibiotic therapy, the authors found that the group treated with Uromune® experienced a highly significant reduction in the number of infections and none had side effects[22].

The positive results obtained with this therapy are probably related to the fact that the sublingual mucosa is a good inductive site for generating a broad spectrum of mucosal and systemic immune responses, with a high degree of efficacy and persistence of the immune response in the respiratory and genitourinary tracts. Furthermore, it has been demonstrated that the sublingual administration of immunogens and whole bacteria activates dendritic cells and induces systemic dose-dependent immune responses, generating Th1, Th17, and IL-10 responses[23].

All things considered, our study demonstrates the effectiveness of a bacterial preparation administered through the sublingual route. We acknowledge that because this study has a very small population and not all the patients were immunized with the same preparation and even the same microorganisms

percentage, it is hard to reproduce. However, we were able to explore one of the advantages of these formulations (personalized formulation) to better suit the immunologic needs of our patients, which possibly helps explain the good results. We were able to reduce the total number of episodes (with statistical significance) and the number of episodes needing hospital stay (without statistical significance probably due to sample size). The data collected from clinical histories of patients provide clinically valuable information of the patients treated under "real-life" conditions. Considering the high prevalence and high cumulative cost of managing respiratory infections, as well as the frequent failure of conventional therapies, bacterial immunostimulation could be an effective management strategy to reduce costs, frequency, severity, and duration of such episodes in adults and children suffering from chronic respiratory tract infections.

CONCLUSION

Limitations of the present study include the relatively small number of patients recruited, in addition to the lack of a control group. To further progress our understanding, prospective studies involving larger groups of patients, with longer follow-up periods and conducted in a double-blind placebo-controlled manner, are required.

Author's contributions

João Neiva Machado: Conceptualization (Lead); Methodology (Lead); Writing-original draft (Lead); Writing-review & editing (Lead); José Coutinho Costa: Validation (Supporting); Visualization (Supporting); Writing-review & editing (Supporting); Teresa Costa: Methodology (Supporting); Supervision (Supporting); Validation (Supporting); Writing-review & editing (Supporting); Cidália Rodrigues: Conceptualization (Supporting); Supervision (Supporting); Validation (Supporting); Visualization (Supporting); Writing-review & editing (Supporting).

The authors declare that no sponsorship was received for the work. The authors declare no conflicts of interest.

RESUMO

OBJETIVO: *Avaliar a eficácia de vacinas bacterianas de mucosa (MBV) na redução do número de exacerbações de pacientes com doença respiratória crônica.*

MÉTODOS: *Um estudo de coorte prospectivo incluindo pacientes da Unidade de Pneumologia da Universidade e Centro Hospitalar de Coimbra, com exacerbações infecciosas frequentes (3 ou mais), apesar do uso das melhores estratégias terapêuticas. MBVs foram usadas como terapia adicional. O número de exacerbações 1 ano antes da terapia e 1 ano após ela foram analisados.*

RESULTADOS: *Amostra incluiu 11 indivíduos, 45,5% do sexo masculino, com média de idade de 62,5 anos. Oito pacientes apresentaram bronquiectasia não relacionada à fibrose cística, 2 DPOC (1 em oxigenoterapia prolongada) e 1 paciente com síndrome de Mounier-Kuhn. Três pacientes estavam sendo medicados com azitromicina, 1 com colistina inalada e 2 com tobramicina inalada. Dos 11 pacientes, um apresentou complicação (febre), o que levou à suspensão da terapia (excluído dos resultados). Dos 10 pacientes que completaram o tratamento, 5 apresentaram colonização bacteriana e receberam uma vacina personalizada. Os 6 restantes foram tratados com a composição padrão. A média de exacerbações infecciosas no ano anterior foi de 4,3 (0,7 com hospitalização). No ano após a terapia, o número médio foi de 1,5 (0,5 com hospitalização).*

CONCLUSÃO: *Os resultados obtidos neste estudo favorecem o uso de imunoestimulação bacteriana para reduzir a frequência de infecções respiratórias recorrentes em pacientes com doença respiratória crônica.*

PALAVRAS-CHAVE: *Vacinas bacterianas. Administração sublingual. Infecções respiratórias. Doenças respiratórias.*

REFERENCES

1. Martín-Rodríguez AJ, Quezada H, Becerril-Aragón G, Fuente-Nuñez C, Castillo-Juarez I, Maeda T, et al. Recent advances in novel antibacterial development. [cited 2019 Oct 3]. Available from: https://www.researchgate.net/profile/Alberto_Martin-Rodriguez/publication/301358410_Recent_Advances_in_Novel_Antibacterial_Development/links/57155b5a08ae8ab56695ac4c.pdf
2. Sánchez Ramón S, Manzanaresa M, Candelas G. Vacunas antiinfecciosas de mucosas en la profilaxis de infecciones recurrentes: más allá de las vacunas convencionales. Reumatol Clin. 2020;16(1):49-55.
3. Braido F, Tarantini F, Ghiglione V, Melioli G, Canonica GW. Bacterial lysate in the prevention of acute exacerbation of COPD and in respiratory recurrent infections. Int J Chron Obstruct Pulmon Dis. 2007;2(3):335-45.

4. Felmingham D, Feldman C, Hryniewicz W, Klugman K, Kohno S, Low DE, et al. Surveillance of resistance in bacteria causing community-acquired respiratory tract infections. Clin Microbiol Infect. 2002;8(Suppl 2):12-42.
5. Steurer-Stey C, Bachmann LM, Steurer J, Tramèr MR. Oral purified bacterial extracts in chronic bronchitis and COPD: systematic review. Chest. 2004;126(5):1645-55.
6. Alecsandru D, Valor L, Sánchez-Ramón S, Gil J, Carbone J, Navarro J, et al. Sublingual therapeutic immunization with a polyvalent bacterial preparation in patients with recurrent respiratory infections: immunomodulatory effect on antigen-specific memory CD4+ T cells and impact on clinical outcome. Clin Exp Immunol 2011;164(1):100-7.
7. Negri DR, Riccomi A, Pinto D, Vendetti S, Rossi A, Cicconi R, et al. Persistence of mucosal and systemic immune responses following sublingual immunization. Vaccine. 2010;28(25):4175-80.
8. Holmgren J, Czerkinsky C. Mucosal immunity and vaccines. Nat Med. 2005;11(4 Suppl):S45-53.
9. Passalacqua G, Canonica GW. Sublingual immunotherapy: update 2006. Curr Opin Allergy Clin Immunol. 2006;6(6):449-54.
10. Emmerich B, Emslander HP, Pachmann K, Hallek M, Milatovic D, Busch R. Local immunity in patients with chronic bronchitis and the effects of a bacterial extract, Broncho-Vaxom, on T lymphocytes, macrophages, gamma-interferon and secretory immunoglobulin A in bronchoalveolar lavage fluid and other variables. Respiration. 1990;57(2):90-9.
11. Cvoriscec B, Ustar M, Pardon R, Palecek I, Stipic-Markovic A, Zimic B. Oral immunotherapy of chronic bronchitis: a double-blind placebo-controlled multicenter study. Respiration. 1989;55(3):129-35.
12. Hapfelmeier S, Lawson MA, Slack E, Kirundi JK, Stoel M, Heikenwalder M, et al. Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. 2010;328(5986):1705-9.
13. Koetz K, Bryl E, Spickschen K, O'Fallon WM, Goronzy JJ, Weyand CM. T cell homeostasis in patients with rheumatoid arthritis. Proc Natl Acad Sci U S A. 2000;97(16):9203-8.
14. Hessle C, Andersson B, Wold AE. Gram-positive bacteria are potent inducers of monocytic interleukin-12 (IL-12) while gram-negative bacteria preferentially stimulate IL-10 production. Infect Immun. 2000;68(6):3851-6.
15. Kang SS, Yang JS, Kim KW, Yun CH, Holmgren J, Czerkinsky C, et al. Anti-bacterial and anti-toxic immunity induced by a killed whole-cell-cholera toxin B subunit cholera vaccine is essential for protection against lethal bacterial infection in mouse pulmonary cholera model. Mucosal Immunol. 2013;6(4):826-37.
16. Ip WK, Sokolovska A, Charriere GM, Boyer L, Dejardin S, Cappillino MP, et al. Phagocytosis and phagosome acidification are required for pathogen processing and MyD88-dependent responses to Staphylococcus aureus. J Immunol. 2010;184(12):7071-81.
17. Muñoz-Wolf N, Rial A, Saavedra JM, Chabalgoity JA. Sublingual Immunotherapy as an alternative to induce protection against acute respiratory infections. J Vis Exp. 2014;(90). doi: 10.3791/52036.
18. García González LA, Arrutia Díez F. Mucosal bacterial immunotherapy with MV130 highly reduces the need of tonsillectomy in adults with recurrent tonsillitis. Hum Vaccin Immunother. 2019;15(9):2150-3.
19. Hernández Llano K, Sánchez-Ramón S, Ochoa Grullon J, Macarron P, Morado C, Martínez-Prada C, et al. Sublingual vaccine: new challenge in the prevention of recurrent infections in autoimmune diseases. Ann Rheum Dis. 2017;76(suppl. 2):990.
20. Ochoa-Grullón J, Candelas G, Macarrón P. Polybacterial sublingual vaccines in actively immunosuppressed patients with systemic autoimmune disease. In: European Congress of Immunology, Berlin, Germany; 2015.
21. Negria DR, Riccomi A, Pinto D, Vendetti S, Rossi A, Cicconi R, et al. Persistence of mucosal and systemic immune responses following sublingual immunization. Vaccine. 2010;28(25):4175-80.
22. Lorenzo-Gómez MF, Padilla-Fernández B, García-Criado FJ, Mirón-Canelo JA, Gil-Vicente A, Nieto-Huertos A, et al. Evaluation of a therapeutic vaccine for the prevention of recurrent urinary tract infections versus prophylactic treatment with antibiotics. Int Urogynecol J. 2013;24(1):127-34.
23. Benito-Villalvilla C, Cirauqui C, Diez-Rivero CM, Casanovas M, Subiza JL, Palomares O. MV140, a sublingual polyvalent bacterial preparation to treat recurrent urinary tract infections, licenses human dendritic cells for generating Th1, Th17, and IL-10 responses via Syk and MyD88. Mucosal Immunol. 2017;10(4):924-35.

ORIGINAL ARTICLE

Reduced bone mineral content and density in neurofibromatosis type 1 and its association with nutrient intake

Marcio Leandro Ribeiro de Souza[1]
Ann Kristine Jansen[1]
Luiz Oswaldo Carneiro Rodrigues[1]
Darlene Larissa de Souza Vilela[1]
Adriana Maria Kakehasi[1]
Aline Stangherlin Martins[1]
Juliana Ferreira de Souza[1]
Nilton Alves de Rezende[1]

1. Universidade Federal de Minas Gerais, Belo Horizonte, MG Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.666

SUMMARY

BACKGROUND: *Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disease characterized by multisystem involvement including low bone mineral density (BMD).*

OBJECTIVE: *To assess the bone phenotype of individuals with NF1 and verify its association with nutrient intake.*

METHODS: *Twenty-six adults with NF1 underwent bone phenotype assessments using dual-energy X-ray absorptiometry (DXA) and food intake evaluations. They were compared to 26 unaffected matched control patients. Weight, height, and waist circumference (WC) were measured. DXA provided total body, spine, and hip BMDs and bone mineral content (BMC) for all patients. Food intake was evaluated for energy, macro- and micro-nutrients.*

RESULTS: *Height (1.68 ± 0.1; 1.61 ± 0.1 cm; P = 0.003) and BMC (2.3 ± 0.4; 2.0 ± 0.5 kg; P = 0.046) were lower in the NF1 group. Individuals with NF1 also presented lower total body and spine BMDs (g/cm2) (1.1 ± 0.1, 1.0 ± 0.1, P = 0.036; 1.0 ± 0.1, 0.9 ± 0.1; P = 0.015, respectively). The frequency of total body bone mass below the expected level for patients' ages was higher in the NF1 group (7.7%; 34.6%, P = 0.016). There were no differences in energy consumption. No correlations between BMC and BMD with nutrient intake were observed in the NF1 group.*

CONCLUSIONS: *The NF1 group presented lower BMCs and BMDs. Although a lower consumption of calcium, iron, and vitamin A, and a higher intake of sodium and omega-6 were observed, there was no relationship between bone phenotype and nutrient intake.*

KEYWORDS: *Neurofibromatosis 1. Nutrients. Eating. Bone density. Bone development.*

INTRODUCTION

Neurofibromatosis type 1 (NF1) is the most prevalent in a group of three genetic diseases called Neurofibromatoses. It is caused by inherited or *de novo* mutations on chromosome 17, resulting in reduced neurofibromin synthesis, which subsequently reduces tumor suppression[1]. The diagnostic criteria for NF1

DATE OF SUBMISSION: 01-Nov-2019
DATE OF ACCEPTANCE: 29-Dec-2019
CORRESPONDING AUTHOR: Marcio Leandro Ribeiro de Souza
Rua dos Guajajaras, 1470 / sala 1702, Belo Horizonte, MG, Brasil - 30180-101
E-mail: marcionutricionista@yahoo.com.br

are clinical and established by the National Institute of Health (NIH) Consensus[2]. The most common clinical features of NF1 are *café au lait* spots, dermal and plexiform neurofibromas, Lisch nodules, axillary and/or inguinal freckling, and some typical bone dysplasia[1,3]. NF1 can also exhibit multisystemic involvement, including bone disorders[1,3,4].

Some studies have shown a reduction of bone mineral density (BMD) and an increase of osteoporosis and osteopenia in individuals with NF1, although the mechanism responsible for these alterations is not well known[4]. Some experimental studies suggest that neurofibromin plays a central role in these alterations since it adversely regulates the function of *Ras* proteins and controls cell proliferation, differentiation, and apoptosis in bone tissue[5-8]. The majority of studies evaluating BMD in NF1 were performed in children, demonstrating a reduction of bone mass in this population when compared with healthy controls[8]. The few studies conducted in adults also confirm these changes[9-11].

Poor nutrition and insufficient intake of nutrients related to bone metabolism are also part of the risk factors for the development of osteopenia and osteoporosis[12]. Nutritional studies in NF1 are scarce and have only recently begun. Previously, our group published a cross-sectional study of 60 adults with NF1 and showed that NF1 individuals had an unhealthy diet, rich in fats and sodium and lacking in fiber and micronutrients, especially magnesium, vitamin D, calcium, and pyridoxine[13].

A recent search of the MEDLINE, SCOPUS, Lilacs, and SciELO databases did not identify any studies involving the bone characteristics of Brazilian adults with NF1, and no studies were found that researched the association of bone status with nutrient consumption. Thus, using gold-standard methodologies for bone evaluation, the present study aimed to investigate bone phenotypes in individuals with NF1 and verify its associations with nutrient intake.

METHODS

Ethical Statement

This study complies with the Declaration of Helsinki and was approved by the Research Ethics Committee of our institution under protocol number CAAE-03005812.6.0000.5149. All subjects provided written informed consent before admission to the study. The study protocol did not interfere with any medical procedures.

Sample

This case-control study included NF1 individuals >18 years old who were evaluated in a Brazilian Neurofibromatosis Outpatient Reference Center. Patients were excluded based on: musculoskeletal limitations, the presence of diseases that required a specific diet or food consumption, neoplasms, hypothyroidism, weight loss ≥10% in the last six months, and use of medications that might compromise nutritional assessments or BMD. We also excluded men >50 years old and postmenopausal women because they have a high risk of osteoporosis. The NF1 group was compared to unaffected controls (1:1) and matched by sex, age, body mass index (BMI), and physical activity levels evaluated by the International Physical Activity Questionnaire (IPAQ) short version. The control group included individuals with similar socioeconomic characteristics (income and education level), such as neighbors, friends, or relatives who do not live in the same household. After performing a pre-test with ten individuals from each study group, a power calculation was performed, and it was determined that to attain a test power of 80%, a minimum of 24 individuals in each group was required.

Data Collection

Bone characteristics were assessed by dual-energy X-ray absorptiometry (DXA), using the Discovery W Hologic® device (Bedford, MA, USA), software version 3.3.0. A qualified professional interpreted the results. Total body measurements lasted six minutes and were performed with the individuals lying in a supine position after removing all metal fittings as recommended by the manufacturer. For spine analyses, individuals remained lying down, with their legs supported by a box that aligned their pelvises and the lower portions of their lumbar spines. In the femoral analyses, individuals were placed in a supine position with their feet strapped to a triangular support allowing internal rotation of the hip[12,14]. All these placements followed the manufacturer's guidelines. The room was equipped with air conditioning and the room temperature was maintained constant during all the measurements.

Anthropometric measurements were also evaluated to characterize our population and included: weight, height, body mass index (BMI), and waist circumference (WC). These measurements followed the protocol proposed by the World Health Organization (WHO)[15,16]. The BMI categories used in this study were: normal weight (BMI 18.5–25 kg/m^2),

underweight (BMI < 18.5 kg/m²), and overweight (BMI ≥ 25.0 kg/m²)[15].

Food intake was obtained using three self-reported 24 h dietary recall surveys (24HR) on three non-consecutive days (2 days during the week and, as a non-typical day, 1 day during the weekend), in accordance with the recommendations of the Institute of Medicine[17], which proposes that at least two 24HRs be used for similar studies. The interviewer had been trained in how to record portion sizes and the subjects provided detailed descriptions of all consumed food and drink, as well as the cooking methods, ingredients, and the use of salt and oil during their preparation. Potential confounding variables were evaluated by questioning the subjects regarding food quantities, added ingredients, and the brands that they consumed.

The amounts of each nutrient consumed were converted into grams. Any consumption of dietary supplements reported by a participant was also included in the nutrient analysis. The mean 3-day values were used in our analyses. Energy, macro- and micronutrients were evaluated in our study.

Statistical Analyses

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS®) version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to evaluate normality and determine the appropriate statistical test. Qualitative variables were described using absolute and relative (percentage) frequencies. Grouped comparisons of qualitative variables were performed using McNemar's or chi-squared tests. Quantitative variables with a normal distribution were expressed as mean and standard deviation and compared using the paired Student's *t*-test. Quantitative variables that were not normally distributed were presented as medians with minimum and maximum values and compared using the nonparametric Wilcoxon test. Correlations were evaluated using Pearson's test for normal distributions or Spearman's correlation for non-normal distributions. *P*-values <0.05 were considered statistically significant.

RESULTS

Twenty-nine individuals with NF1 were included in this study, and three were excluded (one 51-year-old man with hypothyroidism, and two postmenopausal women: 55 and 57 years old). The remaining 26 subjects were comprised of 12 women (46.2%) and 14 men (53.8%). The NF1 group was compared to 26 unaffected controls, matched by sex, age, BMI, and physical activity levels.

Demographic, anthropometric, and bone characteristics data are listed in Table 1. There were no differences for age, weight, BMI, and WC (*P*=0.316, *P* = 0.175, *P*=0.768 and *P*=0.807, respectively). Statistically, the NF1 group was shorter in stature (*P*=0.003). For bone parameters, BMCs were lower in the NF1 group compared to the controls (*P*=0.046). In addition, the NF1 group had lower total body (*P*=0.036) and spine (*P*=0.015) BMDs (g/cm²) and lower total body (*P*=0.049) and spine (*P*=0.025) Z-scores. For the total body, the prevalence of subjects with bone mass below the expected level for their ages was higher in the NF1 group (34.6%) compared to the controls (7.7%) (*P*=0.016). No differences were observed in hip parameters.

Comparing nutrient intakes (Table 2), there were no differences in energy and macronutrient (carbohydrate, protein, and fat) consumption, except for polyunsaturated fats (*P*=0.013), especially omega-6 (*P*=0.008). The NF1 group also consumed higher amounts of sodium (*P*=0.018) and lower amounts of calcium (*P*=0.038), iron (*P*=0.042), and vitamin A (*P*=0.038).

Figure 1 presents the correlations between BMC and total BMD with nutrient intake parameters. In the control group, BMC and total BMD presented a positive weak correlation with carbohydrate intake. In the NF1 group, there was no association between BMC and BMD with nutrient intake.

DISCUSSION

In our study, individuals with NF1 showed lower BMCs and BMDs for their total body and spine and a higher prevalence of bone mass below the expected level for their age in their total body. No previous studies were found verifying the association between bone parameters and nutrient intake in NF1 individuals.

Lower BMDs in adults with NF1 have been demonstrated in other studies. Lammert et al.[11] evaluated 104 adults with NF1 aged 20 to 80 years. Using quantitative ultrasonography, they found lower BMDs in adults with NF1 when comparing their results to reference values for a population not affected by the disease (no control group was used). In another study using DXAs with 26 NF1 subjects aged 24–73 years, the authors found lower BMDs and BMCs in the NF1

TABLE 1. DEMOGRAPHIC, ANTHROPOMETRIC, AND BONE CHARACTERISTICS FOR EACH GROUP

Parameters	Control (n = 26)	NF1 (n = 26)	P-value*
Age (years)	32.92 (6.14)	34.31 (6.05)	0.316
Weight (kg)	69.08 (14.11)	62.54 (16.99)	0.175
Height (m)	1.68 (0.08)	1.61 (0.10)	0.003
BMI (kg/m^2)	24.28 (3.64)	23.88 (4.83)	0.768
Waist circumference (cm)	82.37 (11.43)	81.39 (14.62)	0.807
BMC (kg)	2.29 (0.43)	2.03 (0.47)	0.046
TOTAL BODY			
BMD total body (g/cm^2)	1.10 (0.10)	1.04 (0.10)	0.036
BMD total body – Z-score	- 0.75 (0.93)	- 1.35 (1.12)	0.049
Categorization – n (%)			0.016
Normal bone mass	24 (92.3)	17 (65.4)	
Bone mass below the expected level for age	2 (7.7)	9 (34.6)	
SPINE			
BMD spine (g/cm^2)	1.00 (0.08)	0.91 (0.14)	0.015
BMD spine – Z-score	- 0.69 (0.92)	- 1.39 (1.24)	0.025
Categorization – n (%)			0.070
Normal bone mass	24 (92.3)	18 (69.2)	
Bone mass below the expected level for age	2 (7.7)	8 (30.8)	
HIP (femoral neck)			
BMD Hip (femoral neck) (g/cm^2)	0.85 (0.15)	0.77 (0.12)	0.106
BMD Hip (femoral neck) – Z-score	- 0.26 (1.16)	- 0.74 (0.96)	0.165
Categorization – n (%)			1.000
Normal bone mass	24 (92.3)	23 (88.5)	
Bone mass below the expected level for age	2 (7.7)	3 (11.5)	
HIP (total femoral)			
BMD Hip (total femoral) (g/cm^2)	0.94 (0.13)	0.90 (0.13)	0.309
BMD Hip (total femoral) – Z-score	- 0.32 (0.91)	- 0.56 (0.97)	0.409
Categorization – n (%)			0.705
Normal bone mass	26 (100)	23 (88.5)	
Bone mass below the expected level for age	0	3 (11.5)	

Note: NF1: Neurofibromatosis type 1; SD: standard deviation; BMI: body mass index; BMC: bone mineral content; BMD: bone mineral density; kg: kilogram; g: gram; m: meter; cm: centimeter; *Quantitative values are expressed as mean (SD) and compared using paired Student´s t-test. Categorical values are expressed as n (%) and compared using McNemar's or chi-squared tests.

group compared to controls[10]. Illés et al.[9] showed lower spine BMDs than expected for their age in 12 individuals with NF1, ranging from 7.6 to 42.7 years, assessed by Z-scores using DXA, but these results were not compared to a control group.

In our study, there was no difference in hip BMDs (total or femoral). A statistical difference was only found for the spine and total body BMDs. This result follows the trend of bone metabolism in young individuals in whom the lumbar spine shows precocious bone loss since this is a region with more trabecular bone. In the femur, with a predominance of cortical bone, this loss is slower[18].

Our hypotheses to explain the lower bone mass in NF1 are summarized in Figure 2 and will be discussed in sequence. These bone changes in NF1 may be related to the deficiency of neurofibromin and, consequently, greater activation of Ras proteins, which control cell proliferation, differentiation, and apoptosis in bone tissue. In mice with NF1, the activity of osteoclasts was higher due to an increase in Ras activation[5-8]. The Ras pathway may be associated with bone alterations in NF1, since in other RASophaties, such as Costello's Syndrome, bone mineral density is also reduced[19].

Another possible explanation for the lower BMCs and BMDs may be related to calcidiol (25-OH-D3) levels. Vitamin D plays an important role in bone health, since reduced levels of this vitamin decrease intestinal calcium absorption, elevate parathyroid hormone, and increase bone resorption[20]. Vitamin D levels were not investigated in our study.

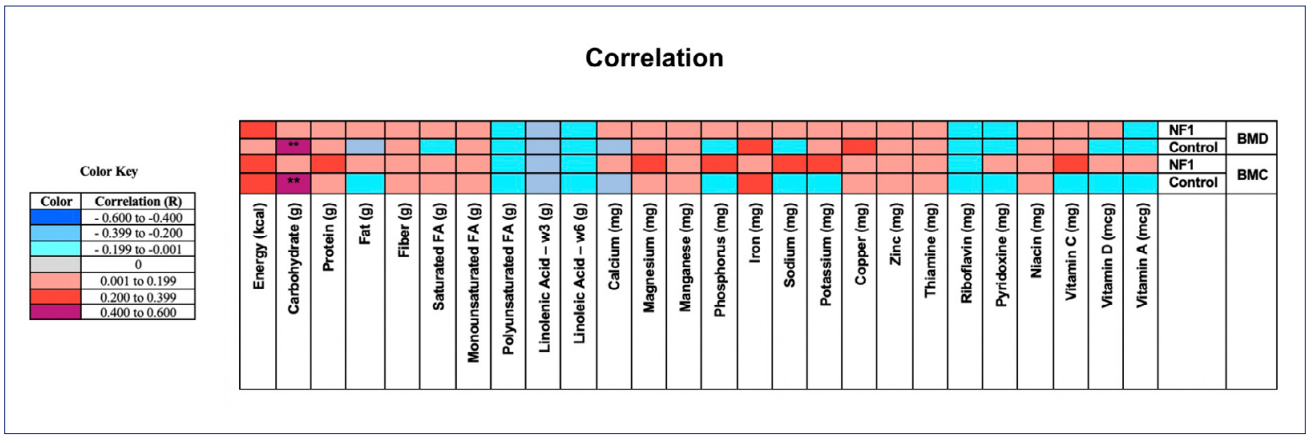
Poor nutrition and insufficient intake of nutrients related to bone metabolism are part of the risk factors for the development of osteopenia and osteoporosis[12].

TABLE 2. NUTRIENT INTAKE: ENERGY, MACRO- AND MICRO-NUTRIENT CONSUMPTION FOR EACH GROUP

Parameters	Control (n = 26)	NF1 (n = 26)	P-value
Energy (kcal)	2,104.4 (1,177.4 – 3,344.3)	2,202.6 (1,257.2 – 3,000.0)	0.240#
Energy (kcal/kg/d)	29.6 (16.0 – 69.0)	35.9 (20.6 – 67.5)	0.069*
Carbohydrate (g)	227.8 (106.6 – 392.0)	240.4 (138.9 – 392.3)	0.439#
Carbohydrate (g/kg/d)	3.5 (1.7 – 8.0)	4.1 (1.9 – 8.4)	0.205#
Protein (g)	91.8 (31.8 – 134.0)	88.1 (50.7 – 179.3)	0.874#
Protein (g/kg/d)	1.4 (0.5 – 2.9)	1.5 (0.8 – 2.9)	0.317#
Fat (g)	81.3 (36.5 – 144.9)	90.9 (50.1 – 163.5)	0.172#
Fat (g/kg/d)	1.2 (0.5 – 2.9)	1.4 (0.7 – 3.0)	0.096*
Fiber (g)	18.8 (10.3 – 42.1)	19.8 (8.1 – 44.1)	0.978#
Saturated FA (g)	30.6 (11.2 – 56.7)	30.3 (16.7 – 55.5)	0.981#
Monounsaturated FA (g)	31.9 (11.2 – 47.9)	31.0 (17.1 – 48.5)	0.502#
Polyunsaturated FA (g)	22.2 (9.9 – 43.6)	29.5 (9.2 – 55.1)	0.013#
Linolenic Acid (w3) (g)	2.8 (1.0 – 4.6)	3.3 (1.1 – 6.6)	0.120#
Linoleic Acid (w6) (g)	19.1 (7.6 – 36.8)	26.5 (8.0 – 48.3)	0.008#
Cholesterol (mg)	321.3 (138.1 – 652.0)	296.1 (133.1 – 630.6)	0.319#
Calcium (mg)	623.2 (159.1 – 2,563.8)	439.0 (133.4 – 1,364.2)	0.038*
Magnesium (mg)	244.0 (84.0 – 480.0)	233.2 (145.3 – 369.0)	0.857#
Manganese (mg)	2.6 (1.3 – 7.1)	2.2 (1.3 – 5.3)	0.280*
Phosphorus (mg)	1,164.0 (569.3 – 2,545.3)	1,108.4 (634.0 – 2,248.2)	0.474#
Iron (mg)	10.2 (5.3 – 18.7)	8.8 (5.3 – 12.2)	0.042#
Sodium (mg)	3,010.1 (1,696.0 – 5,570.2)	3,849.9 (1,678.7 – 9,017.2)	0.018#
Potassium (mg)	2,465.4 (772.9 – 4,562.6)	2,502.3 (1,408.9 – 3,923.9)	0.912#
Copper (mg)	0.9 (0.5 – 1.7)	0.9 (0.5 – 3.4)	0.980*
Zinc (mg)	11.4 (4.0 – 18.8)	9.7 (5.5 – 21.7)	0.362#
Thiamine (mg)	1.4 (0.6 – 4.5)	1.3 (0.7 – 10.0)	0.799*
Riboflavin (mg)	1.1 (0.5 – 3.5)	1.0 (0.5 – 3.1)	0.525*
Pyridoxine (mg)	0.8 (0.2 – 2.3)	0.9 (0.3 – 1.8)	0.836#
Niacin (mg)	19.9 (6.1 – 43.8)	20.2 (5.2 – 51.6)	0.509#
Vitamin C (mg)	58.7 (9.7 – 1003.7)	70.7 (3.6 – 310.3)	0.638*
Vitamin D (mcg)	3.2 (0.9 – 13.4)	2.7 (0.9 – 18.5)	0.517*
Vitamin A (mcg)	541.4 (154.5 – 1,357.4)	402.2 (183.2 – 2,250.5)	0.038*

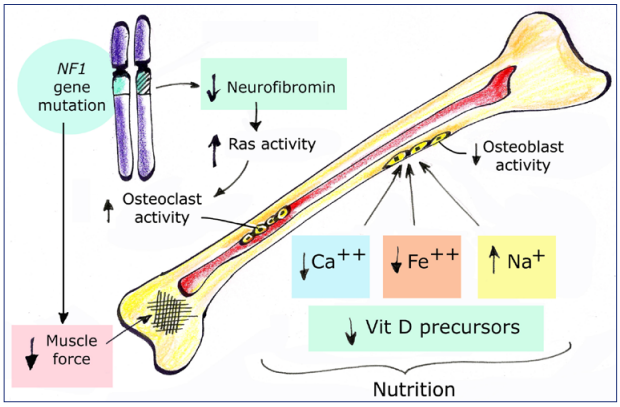
Note: All values are expressed as median (minimum-maximum); NF1: Neurofibromatosis type 1; FA: fatty acid; kg: kilogram; kcal: kilocalories; d: day; g: gram; mg: milligram; mcg: microgram; #: paired Student´s test; *: Wilcoxon test.

FIGURE 1. CORRELATIONS BETWEEN BONE MINERAL CONTENT AND TOTAL BODY BONE MINERAL DENSITY WITH NUTRIENT INTAKE



Note: NF1: Neurofibromatosis type 1; BMC: bone mineral content; BMD: total body bone mineral density; FA: fatty acid; kcal: kilocalorie; g: gram; mg: milligram; mcg: microgram; Pearson correlation for normal distributions and Spearman correlation for non-normal distributions. **: p<0.05.

FIGURE 2. POSSIBLE HYPOTHESES TO EXPLAIN THE LOWER BONE MASS IN NF1



NF1: Neurofibromatosis type 1; Ca: calcium; Fe: iron; Na: sodium; Vit D: vitamin D.

In our study, the NF1 group consumed less calcium, iron, and vitamin A, and higher amounts of sodium and omega-6: nutrients related to bone health. No differences were observed for energy and macronutrient intake, except for polyunsaturated fatty acid consumption. Other nutrients involved in bone health such as magnesium, manganese, phosphorus, potassium, vitamin D, zinc, and B-vitamins did not show differences between the two groups.

The median calcium intake for the NF1 group was approximately 439 mg in our study, below the recommended dietary intake level (700 to 1,200 mg) for preventing osteopenia and osteoporosis[12]. Iron intake was also lower in individuals with NF1, and this mineral is used as a cofactor for enzymes involved in bone matrix synthesis (activation of lysyl hydroxylase) and in the synthesis of 25-hydroxy-cholecalciferol hydroxylase, which is responsible for the activation of vitamin D[21,22].

Sodium intake was higher in subjects with NF1. High sodium intake may increase urinary calcium excretion, temporarily reducing serum calcium, resulting in increased parathyroid hormone and, consequently, increased bone resorption[23]. A higher intake of polyunsaturated fatty acids in the NF1 group, especially linoleic acid (omega-6) were also observed, probably due to the high consumption of vegetable oils, such as soybean oil. In humans with a Western dietary pattern, arachidonic acid, or its precursor linoleic acid, makes a significant contribution to the fatty acids present in the membrane phospholipids of cells involved in inflammation, which may be associated with bone diseases[24,25].

Thus, in association with the genetic effects in NF1, dietary intake of nutrients could also have a role in the reduced spine and total body BMDs described in our study. However, even with the decrease in consumption of certain nutrients, it is important to note that no correlations between BMC with nutrient intake were found in the NF1 group. Even without any statistical associations, healthy nutrition and adequate intake of calcium, vitamin D, and protein are usually included in all recommendations or guidelines for maintaining bone health and delaying or preventing osteopenia and osteoporosis[12].

Our study has some limitations. Current food consumption may not represent the subjects' consumption over the last few years, which is important since it is known that osteopenia/osteoporosis are slow-developing diseases. The external validity of this study must be viewed with caution, as the socio-economic characteristics and place of residence must be considered when extrapolating results to other nutritional studies in different countries. Randomization would be useful in improving the external validity of similar studies. Despite these limitations, this was the first study of bone characteristics in Brazilian adults with NF1. This was also the first study that evaluated the association between nutrient intake and bone parameters in NF1 individuals, although further controlled studies are needed to validate our results.

CONCLUSIONS

Individuals with NF1 presented lower BMCs and lower BMDs in their spines and total body when evaluated by DXA. Lower consumption of calcium, iron, and vitamin A, and higher intakes of sodium and omega-6, all nutrients related to bone health, have also been observed in the NF1 group. However, no association between bone phenotypes and nutrient intake were found in our study. Further investigations including nutrition and bone characteristics in individuals with NF1 may help explain the mechanisms involved.

Conflicts of interest

All authors have no conflicts of interest.

Funding

The authors received financial support from three Brazilian government funding agencies: CAPES, National Council of Technological and Scientific Development – CNPq (#471725/2013-7), and FAPEMIG (#APQ-00928-11; #PPM-00120-14). The funding sources did not influence in the design, analysis, writing, or decision to publish this study.

Author Contributions

All authors (MLRS, AKJ, LORC, DLVS, AMK, ASM, JFS e NAR) conceived, planned, and performed the work leading to the report and interpreted the results. They also wrote, reviewed, and approved the final version.

RESUMO

INTRODUÇÃO: *A Neurofibromatose tipo 1 (NF1) é uma doença genética autossômica dominante caracterizada por envolvimento neurocutâneo e multissistêmico, incluindo baixa densidade mineral óssea (DMO).*

OBJETIVOS: *Avaliar características ósseas em indivíduos com NF1 e verificar associação com a ingestão de nutrientes.*

METODOLOGIA: *26 adultos com NF1 submeteram-se a avaliação dos parâmetros ósseos usando absorciometria com raios-X de dupla energia (DXA), além da avaliação da ingestão alimentar. O grupo NF1 foi comparado e pareado com 26 indivíduos sem a doença. Peso, estatura e circunferência da cintura foram avaliados. DXA forneceu o conteúdo mineral ósseo (CMO) e a DMO do corpo total, coluna e fêmur. A ingestão de calorias, macronutrientes e micronutrientes foi avaliada.*

RESULTADOS: *O grupo NF1 apresentou redução da estatura (1,68 ± 0,1; 1,61 ± 0,1 cm; P=0,003) e do CMO (2,3 ± 0,4; 2,0 ± 0,5 kg; P=0,046). Indivíduos com NF1 também apresentaram redução da DMO de corpo total e coluna (g/cm2) (1,1 ± 0,1, 1,0 ± 0,1, P=0,036; 1,0 ± 0,1, 0,9 ± 0,1; P=0,015, respectivamente). A frequência de indivíduos com massa óssea abaixo do esperado para a idade foi maior no grupo NF1 (7,7%; 34,6%, P=0,016). Não houve diferenças no consumo energético. Não houve correlação entre CMO e DMO com a ingestão de nutrientes no grupo NF1.*

CONCLUSÕES: *O grupo NF1 apresentou redução do CMO e da DMO. Apesar de menor consumo de cálcio, ferro e vitamina A, e maior consumo de sódio e ômega-6, não foi observada relação entre o fenótipo ósseo e a ingestão de nutrientes.*

PALAVRAS-CHAVE: *Neurofibromatose 1. Nutrientes. Ingestão de alimentos. Densidade óssea. Desenvolvimento ósseo.*

REFERENCES

1. Rodrigues LO, Batista PB, Goloni-Bertollo EM, Souza-Costa D, Eliam L, Eliam M, et al. Neurofibromatoses: part 1 - diagnosis and differential diagnosis. Arq Neuropsiquiatr. 2014;72(3):241-50.
2. National Institutes of Health Consensus Development Conference Statement: neurofibromatosis. Bethesda, Md., USA, July 13-15, 1987. Neurofibromatosis. 1988;1(3):172-8.
3. Riccardi VM. Neurofibromatosis type 1 is a disorder of dysplasia: the importance of distinguishing features, consequences and complications. Birth Defects Res A Clin Mol Teratol. 2010;88(1):9-14.
4. Batista PB, Bertollo EM, Costa DS, Eliam L, Cunha KS, Cunha-Melo JR, et al. Neurofibromatosis: part 2: clinical management. Arq Neuropsiquiatr. 2015;73(6):531-43.
5. Yang FC, Chen S, Robling AG, Yu X, Nebesio TD, Yan J, et al. Hyperactivation of p21ras and PI3k cooperate to alter murine and human neurofibromatosis type 1-haploinsufficient osteoclast functions. J Clin Invest. 2006;116(11):2880-91.
6. Wu X, Estwick SA, Chen S, Yu M, Ming W, Nebesio TD, et al. Neurofibromin plays a critical role in modulating osteoblast differentiation of mesenchymal stem/progenitor cells. Hum Mol Genet. 2006;15(19):2837-45.
7. Stevenson DA, Yan J, He Y, Li H, Liu Y, Zhang Q, et al. Multiple increased osteoclast functions in individuals with neurofibromatosis type 1. Am J Med Genet A. 2011;155A(5):1050-9.
8. Poyrazoğlu HG, Bas VN, Arslan A, Bastug F, Canpolat M, Per H, et al. Bone mineral density and bone metabolic markers´ status in children with neurofibromatosis type 1. J Pediatr Endocrinol Metab. 2017;30(2):175-80.
9. Illés T, Halmai V, Jonge T, Dubousset J. Decreased bone mineral density in neurofibromatosis-1 patients with spinal deformities. Osteoporos Int. 2001;12(10):823-7.
10. Kuorilehto T, Pöyhönen M, Bloigu R, Heikkinen J, Väänänen K, Peltonen J. Decreased bone mineral density and content in neurofibromatosis type 1: lowest local values are located in the load-carrying parts of the body. Osteoporos Int. 2005;16(8):928-36.
11. Lammert M, Kappler M, Mautner VF, Lammert K, Störkel S, Friedman JM, et al. Decreased bone mineral density in patients with neurofibromatosis 1. Osteoporos Int. 2005;16(9):1161-6.
12. Compston J, Cooper A, Cooper C, Gittoes N, Gregson C, Harvey N, et al; National Osteoporosis Guideline Group (NOGG). UK clinical guideline for the prevention and treatment of osteoporosis. Arch Osteoporos. 2017;12(1):43.
13. Souza ML, Jansen AK, Martins AS, Rodrigues LO, Rezende NA. Nutrient intake in neurofibromatosis type 1: a cross-sectional study. Nutrition. 2015;31(6):858-62.
14. Lewiecki EM, Binkley N, Morgan SL, Shuhart CR, Camargos BM, Carey JJ, et al; International Society for Clinical Densitometry. Best practices for dual-energy X-ray absorptiometry measurement and reporting: International Society for Clinical Densitometry Guidance. J Clin Densitom. 2016;19(2):127-40.
15. World Health Organization. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995;854:1-452.
16. World Health Organization. Waist circumference and waist-hip ratio. Report of a WHO Expert Consultation. Geneva: World Health Organization; 2011. 47p.
17. Institute of Medicine (US) Subcommittee on Interpretation and Uses of Dietary Reference Intakes; Institute of Medicine (US) Standing
18. Committee on the Scientific Evaluation of Dietary Reference Intakes. DRI dietary reference intakes: applications in dietary assessment. Washington: National Academy Press; 2000. 306p.
19. Corrêa PHS. Medida da densidade mineral óssea em dois sítios. Arq Bras Endocrinol Metab. 2003;47(1):3-4.
20. Stevenson DA, Schwarz EL, Carey JC, Viskochil DH, Hanson H, Bauer S, et al. Bone resorption in syndromes of the Ras/MAPK pathway. Clin Genet. 2011;80(6):566-73.
21. Wacker M, Holick MF. Vitamin D: effects on skeletal and extraskeletal health and the need for supplementation. Nutrients. 2013;5(1):111-48.
22. Zofková I, Nemcikova P, Matucha P. Trace elements and bone health. Clin Chem Lab Med. 2013;51(8):1555-61.
23. Higgs J, Derbyshire E, Styles K. Nutrition and osteoporosis prevention for the orthopaedic surgeon: a wholefoods approach. EFORT Open Rev. 2017;2(6):300-8.
24. Park SM, Joung JY, Cho YY, Sohn SY, Hur KY, Kim JH, et al. Effect of high dietary sodium on bone turnover markers and urinary calcium excretion in Korean postmenopausal women with low bone mass. Eur J Clin Nutr. 2015;69(3):361-6.
25. Innes JK, Calder PC. Omega-6 fatty acids and inflammation. Prostaglandins Leukot Essent Fatty Acids. 2018;132:41-8.

ORIGINAL ARTICLE

Comparison of serum NEDD-9, CA 15-3, and CEA levels and PET metabolic parameters in breast cancer patients with 18 F-FDG PET / CT

Esra Arslan[1]
Hale Aral[2]
Tamer Aksoy[1]
Çiğdem Usul Afşar[3]
Senem Karabulut[4]
Fadime Didem Can Trabulus[5]
Rıza Umar Gürsu[6]
Tevfik Fikret Çermik[1]

1. University of Health and Sciences, Istanbul Training and Research Hospital, Department of Nuclear Medicine, Istanbul, Turkey.
2. University of Health and Sciences, Istanbul Training and Research Hospital, Department of Biochemistry, Istanbul, Turkey.
3. Acibadem Bakirkoy Hospital, Department of Internal Medicine and Medical Oncology, Medical Faculty, Acıbadem Mehmet Ali Aydınlar University.
4. Department of Medical Oncology, Institute of Oncology, Istanbul University.
5. University of Health and Sciences, Istanbul Training and Research Hospital, Department of Surgery, Istanbul, Turkey.
6. University of Health and Sciences, Istanbul Training and Research Hospital, Department of Medical Oncology, Istanbul, Turkey.

http://dx.doi.org/10.1590/1806-9282.66.5.673

SUMMARY

OBJECTIVE: *Analyze the over expression of neural precursor cell expressed developmentally down-regulated protein 9 (NEDD-9) deregulated associated with a poor prognosis in various carcinomas. Our objective was to investigate the relationship between the levels of NEDD-9, CA 15-3, and CEA and PET (SUVmax, MTV40, TLG40) with the clinical parameters of patients with breast cancer (BC).*

METHODS: *One hundred and eleven patients (82 BC patients who underwent 18F-FDG PET/CT and 29 healthy controls) were evaluated. SUVmax, MTV, and TLG of the primary tumor were compared with the molecular and histopathological subtypes. 18F-FDG, MTV, and TLG were evaluated based on the clinical data, i.e., nodal involvement, distant metastasis, ER and PR status, Ki-67, serum levels of NEDD-9, CA15-3, and CEA. We compared the NEDD-9 in the BC and healthy control groups.*

RESULTS: *The mean ± SD of SUVmax in the 82 patients was 13.0 ± 8.6. A statistically significant relationship (p = 0.022) was found between the molecular subtypes and 18F-FDG uptake. The relationship between 18F-FDG uptake and TLG measured in patients <50 years, ER-PR negativity, and HER2 positivity were statistically significant (p=0.015, 0.007, 0.046, and 0.001, respectively). MTV40, TLG40, and CA 15-3 in metastatic patients were statistically significant (p=0.004, 0.005, and 0.003, respectively). NEDD-9 in the BC group was significantly higher than in the healthy group (p=0.017). There was a positive correlation between SUVmax and Ki67 and CA 15-3; MTV40 and CEA; CA 15-3, CEA, SUVmax, and MTV40; a negative correlation was found between CEA, TLG40, and age.*

CONCLUSION: *The use of SUVmax, MTV40, and TLG40 parameters with NEDD-9 and tumor markers has been shown to provide a high diagnostic, predictive, and prognostic value for the management of BC. This is considered to be the basis of interventions focused on the treatment objectives related to NEDD-9.*

KEYWORDS: *Breast neoplasms. Fluorodeoxyglucose F18. Adaptor proteins, signal-transducing. Carcinoembryonic antigen.*

DATE OF SUBMISSION: 09-Nov-2019
DATE OF ACCEPTANCE: 29-Dec-2019
CORRESPONDING AUTHOR: Esra Arslan
Istanbul Egitim ve Arastirma Hastanesi, Nukleer Tıp Kliniği, Org. Nafiz Gurman Caddesi, Samatya, Kocamustafapasa, Fatih, Istanbul, Turkey
Tel: +90 212 459-6455 / Fax: +90 212 632-6329
E-mail: dresraarslan@gmail.com

INTRODUCTION

The Cas protein family plays a role in the management of cell survival, proliferation, and migration.[1] The "Neural precursor cell expressed developmental downregulated 9" (NEDD-9) initiates a process resulting in differentiation, proliferation, and migration by revealing the potential tumorigenesis of cells.[2] NEDD-9 overexpression is associated with poor prognosis, shortened survival in breast carcinomas (BC) and many other types of cancer. NEDD-9 overexpression has been reported to be strongly correlated with cancer metastasis due to its regulatory property on cell migration.[3-5]

Carcinoembryonic antigens (CEA) and carbohydrate antigens 15-3 (CA 15-3) are used in BC follow-up; however, their prognostic value is limited regarding its sensitivity and specificity.[6] The American Society of Clinical Oncology does not recommend them for the diagnosis, screening, staging, and treatment follow-up of BC.[7] ^{18}F-fluoro-2-deoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is recommended for the staging, prognosis, and follow-up of BC.[8] In several studies, the maximum standardized uptake (SUVmax) levels, tumor characteristics and total metabolic tumor volume (MTV), lesion glycolysis (TLG) have demonstrated potential prognostic value.[9,10]

We aim to investigate the potential predictive, diagnostic, prognostic, and clinical value of NEDD-9, CA15-3, and CEA, along with PET parameters (SUVmax, MTV, TLG) in BC.

METHODS

Patients

We included eighty-two BC patients who underwent ^{18}F-FDG PET/CT and 29 healthy subjects, with a total 111 subjects enrolled in this study. For our prospective study, the local ethics committee approval has obtained (2018/1380). Verbal and written informed consent was obtained from patients.

Histological Analysis

BC histopathological analysis was performed on tissue samples prior to ^{18}F-FDG PET/CT or breast-conserving surgery following ^{18}F-FDG PET/CT. The Scarff Bloom Richardson (SBR) classification system was used for staging. Receptors found positive for ER and PR showed 10% or more in immunohistochemical staining in positive tumor cells.

Scoring for HER2;

- Score 0: negative immunostaining,
- Score 1: poor staining/staining lesser than 30%,
- Score 2: Uniform/complete membranous staining, even if weak staining,
- Score 3: Uniform staining of at least 30%.

Cut-off value Ki-67 determined at 15% by using immunohistochemical and gene expression profiling methods for the differentiation of Luminal subtypes in routine practice and <15% was considered low, and ≥ 15% high.[11]

Molecular subgroups;

1. Luminal A: ER (+) and/or PR (+), HER2 (-) & Low Ki-67 (<15%),
2. Luminal B: ER (+) and/or PR (+), HER2 (+), or HER2 (-) & High Ki-67 (≥15%),
3. Triple negative/basal: ER (-), PR (-), HER2 (-),
4. HER2 Type: ER (-), PR (-), HER2 (+).

18F-FDG PET/CT Imaging

Glucose levels lower than 150 mg/dl at least six hours of fasting were admitted. 3.7-5.3 MBq/kg ^{18}F-FDG IV injection was administered. After 45 to 60 minutes after IV injection, imaging was obtained from the vertex-mid thigh (mCT 20 ultra HD LSO PET/CT, Siemens Molecular Imaging, Hoffmann Estates, Illinois, USA).

Maximum standard uptake (SUVmax) was calculated by "volume-of-interest (VOI)" on the most active-looking slice of ^{18}F-FDG positive lesions. SUVmax was calculated according to the formula: Maximum activity inside the ROI (MBq/gr), injected ^{18}F-FDG dosage (MBq/kg body mass). Metabolic tumor volume (MTV40) and tumor lesion glucose (TLG40) was calculated by the standard methods.

Based on the PET/CT parameters, histopathological-molecular characteristics, receptor properties, nodal involvement and distant metastasis, NEDD-9 was evaluated and reported along with CA15-3 and CEA. The NEDD-9 expression was compared between the BC and healthy control groups.

Biochemical analysis

CEA and CA 15-3 measured by electrochemiluminescence, Roche, Cobas 6000 model (Tokyo, Japan) immunological autoanalyzer system with chemiluminescent test kits. NEDD-9 expression obtained by enzyme-linked immunosorbent assay anti-NEDD-9 antibodies (INOVA, San Diego, Calif., USA).

Statistical analysis

Data were analyzed by SPSS software (v21.0; IBM, Armonk, NY, USA). The normalization of data distribution was evaluated by the Kolmogorov-Smirnov test. The Mann Whitney and Kruskal Wallis tests were used for comparing the variables; the correlation analysis was evaluated by the Pearson test. The Chi-Square test was used to evaluate categorizable variables. Results were considered statistically significant when P <0.05.

RESULTS

The Mean±SD age was 55.0±12.5 years in the BC group, and 50.3±11.3 years in the control group (p = 0.078). A total of 51.2% in the BC group and 44.8% in the control group were in the menopause period (p = 0.554). ^{18}F-FDG uptake was observed in all tumors (n = 82). The mean SUVmax was 13.0 ± 8.6 (median= 11.6, range=2.1-48.4). The molecular subtype classification was as follows: 13 (15.9%) identified luminal A; 50 (61.0%) luminal B; 10 (12.2%) triple-negative; and 9 (11.0%) HER2 type. The relationship between ^{18}F-FDG uptake and molecular subtype classification was evaluated; the mean SUVmax in luminal A was 9.4±6.5, 12.1±6.9 in luminal B, 16.7±12.9 in triple-negative, and 19.2 ± 10.4 in the HER2 type. A statistically significant relationship was found between the molecular subtypes and SUVmax (p = 0.022).

Invasive ductal carcinoma was in found 73.2% (n = 60), invasive lobular carcinoma in 9.8% (n = 8), mucinous in 6.1% (n = 5), apocrine in 4.9% (n = 4), micropapillary in 3.7% (n = 3), neuroendocrine in 1.2% (n = 1), and mixed type in 1.2% (n= 1). No statistically significant difference was found between histopathological types and ^{18}F-FDG uptake.

The clinical features of patients were evaluated according to 18F-FDG uptake, MTV40, and TLG40. The mean±SD of TLG40 (244.1 ± 444.3) in the group below 50 years (n = 32) was not found to be significantly higher than the mean±SD of TLG40 (122.3±276.5) in those older than 50 years (n = 50) (p = 0.015). A total of 76.8% (n = 63) of tumors were ER(+), 61.0% (n = 50) were PR(+), and 20.7% (n=17) were HER2(+). 18F-FDG uptake was associated with negative ER-PR and positive HER2; the association was statistically significant (p = 0.007, 0.046, and 0.001, respectively). Ki-67 expression was high (≥ 15%) in 70 cases (85.4%) and low (<15%) in 12 cases (14.6%). SUVmax, MTV, and TLG40 did not show any statistically significant difference compared to Ki-67 (Table 1).

A total of 65.9% of patients (n= 54) presented LN involvement but there was no correlation with

TABLE 1. MEAN±SD SUVMAX, MTV40, TLG40, NEDD-9, CA 15-3 AND CEA VALUES CHANGE ACCORDING TO THE CLINICAL AND HISTOPATHOLOGICAL CHARACTERISTICS OF THE PATIENTS

	n (%)	SUVmax (Mean±SD)	p-value	MTV40 (Mean±SD)	p-value	TLG40 (Mean±SD)	p-value	NEDD-9 (ng/ml) (Mean±SD)	p-value	CA 15-3 (U/ml) (Mean±SD)	p-value	CEA (ng/ml) (Mean±SD)	p-value
Age													
< 50 ≥ 50	32 (39.0%) 50 (61.0%)	14.4±8.7 12.2±8.4	0.201	37.6±67.9 14.7±17.8	0.126	244.1±444.3 122.3±276.5	0.015*	1.8±1.3 2.2±1.9	0.467	22.6±35.9 22.1±23.2	0.618	13.28±36.06 5.18±16.22	0.768
ER													
Negative Positive	19 (23.2%) 63 (76.8%)	17.9±11.6 11.6±6.9	0.007*	22.2±37.3 24.0±48.1	0.725	247.1±532.8 146.6±281.1	0.054	2.3±1.7 2.0±1.7	0.323	26.3±29.7 21.1±28.4	0.302	1.8±1.2 10.3±29.3	0.031*
PR													
Negative Positive	32 (39.0%) 50 (61.0%)	15.5±10.4 11.5±6.8	0.046*	19.2±30.2 26.5±53.4	0.736	183.6±416.0 161.1±312.4	0.151	2.3±2.1 1.9±1.4	0.714	23.2±23.8 21.7±31.5	0.172	5.8±20.1 9.9±29.2	0.084
HER2													
Negative Positive	65 (79.3%) 17 (20.7%)	11.7±8.2 18.0±8.4	0.001*	25.2±49.9 17.5±23.4	0.868	166.0±383.2 184.8±217.2	0.124	2.1±1.8 1.8±1.3	0.762	20.5±21. 0 29.3±48.0	0.331	5.5±15.1 19.2±48.3	0.556
Ki-67													
< 15% ≥ 15%	12 (14.6%) 70 (85.4%)	9.7±7.2 13.6±8.7	0.117	18.6±19.2 24.5±48.8	0.641	135.2±163.4 175.8±377.7	0.582	1.6±1.3 2.1±1.7	0.265	25.3±25.0 21.8±29.3	0.491	15.1±33.4 7.2±24.5	0.546
Nodal involvement													
Absent Present	28 (34.1%) 54 (65.9%)	11.3±5.5 14.0±9.7	0.423	14.9±14.6 28.1±54.9	0.766	112.6±121.5 199.5±426.0	0.571	2.3±2.0 1.9±1.5	0.363	20.3±18.9 23.3±32.6	0.938	4.2±7.5 10.5±31.4	0.880
Organ metastasis													
Absent Present	55 (67.1%) 14 (17.1%)	12.8±8.8 16.3±9.7	0.148	18.1±40.7 53.2±69.7	0.004*	100.5±125.1 504.1±749.6	0.005*	2.2±1.8 1.5±1.3	0.152	17.9±17.7 41.3±54.1	0.003*	3.3±5.6 25.5±52.2	0.052*

*= p<0.05 statistically significant.

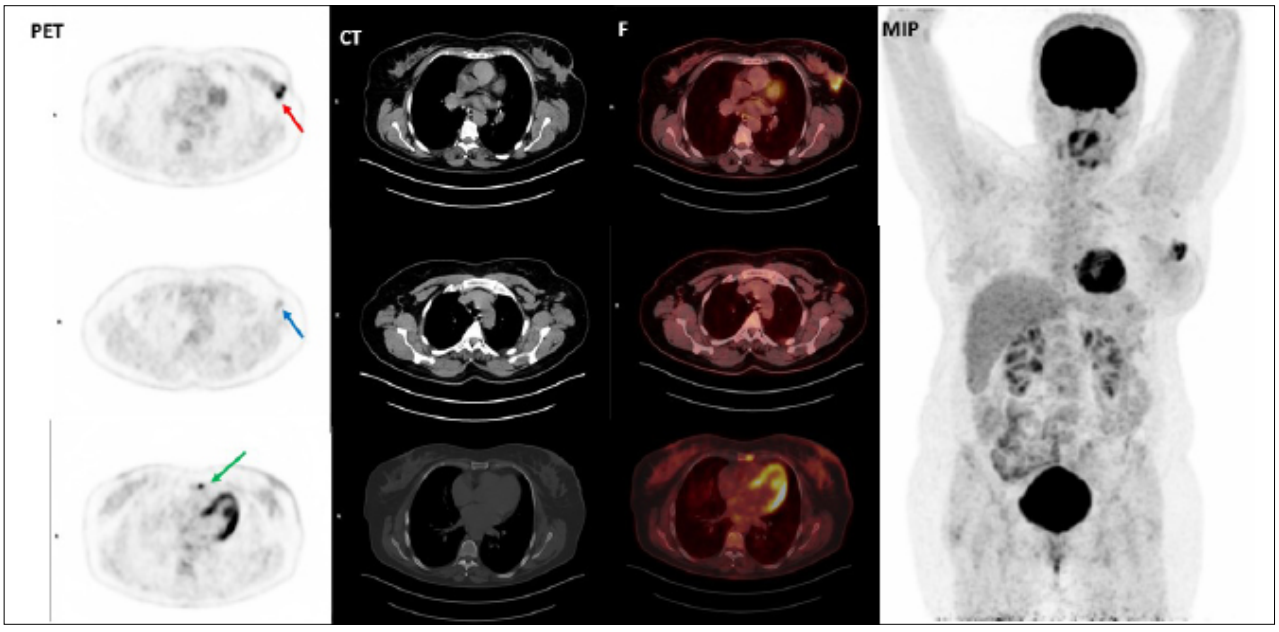
SUVmax, MTV40, and TLG40 (Table 1). Distant metastasis detected in 14 cases (17%). In 13.4% (n= 11) there was bone-bone marrow metastasis (Figure 1), in 1.2% (n= 1) multiple variable metastasis, in 1.2% (n= 1) liver, and in 1.2% (n = 1) lung. No statistically significant difference was found (p= 0.148) in SUVmax between groups with/without distant metastasis; MTV40 and TLG40 in patients with distant metastasis were significantly higher than in those without it (p-values= 0.004 and 0.005, respectively) (Table1). The mean serum NEDD-9 was 2.05 ± 1.69 ng/ml in BC and 1.44 ± 0.88 ng/ml in healthy controls. NEDD-9 was significantly higher in BC compared to the healthy controls (p= 0.017). The clinical features of BC were evaluated according to the NEDD-9, CA 15-3, and CEA values; no statistically significant relationship between NEDD-9 and receptor status (ER, PR, HER2), Ki67, LN, or distant metastasis was found (p> 0.05). CA 15-3 in metastatic BC was found to be statistically significantly higher than in those without organ metastasis (p = 0.003) (Table 1).

The correlations between SUVmax, MTV40, and TLG40 and NEDD-9, CA 15-3, and CEA are presented in Table 2. There was a statistically significant correlation between SUVmax and Ki-67, CA 15-3, and a negative correlation between SUVmax and CEA. A statistically significant correlation was found between MTV40 and CEA. A statistically significant negative correlation was found between TLG40 and mean age, and a positive correlation between CA 15-3, CEA, SUVmax, and MTV.

DISCUSSION

The oncogenic characteristics associated with NEDD-9 have been highlighted in many studies. The metastatic inducing effect of NEDD-9 is present in many cancers, including BC.[12,13] ^{18}F-FDG PET/CT has been shown to provide useful BC staging and follow-up. In BC, there are limited data regarding the combination of NEDD-9, PET/CT parameters for combined diagnostic and prognostic potentials. Ueda et al.[14] evaluated 152 BC cases preoperatively with ^{18}F-FDG PET/CT; they analyzed high SUVmax with tumor size, grade, nuclear type, LN metastasis, histopathological subtype, negative ER - PR and positive HER2 expression and their statistically significant correlation with poor prognosis in BC. Studies have shown ^{18}F-FDG uptake in BC might be statistically different according to the histopathological subtype, molecular grading, ER - PR receptor expression, LN involvement, and distant metastasis. ^{18}F-FDG PET/CT provides insufficient benefits, especially in LN and distant organ metastasis.[8,15] A meta-analysis of 23 studies

FIGURE 1. 53 YEARS OLD F, LEFT BREAST LOCALISED ER(-),PR(-),HER2(-) TRIPLE NEGATIVE (LUMINAL C) INVASIVE DUCTAL TYPE CARCINOMA (PET: POSITRON EMISSION TOMOGRAPHY, CT: COMPUTED TOMOGRAPHY, F: FUSION, MIP: MAXIMUM INTENSITY PROJECTION), KI 67: 50%, PRIMARY TUMOR AXIAL DIAMETER: 2.61 cm, PRIMARY TUMOR SUV MAX: 9.24, PRIMARY TUMOR SUVMEAN: 5.41, PRIMARY TUMOR MTV40(%): 6.62, TLG40: 35.8, AXILLARY LN METASTASIS(+),BONE METASTASIS(+), SERUM NEDD 9 LEVEL: 6.954 ng/ml,SERUM CA15.3 LEVEL:69.8 (U/ml), SERUM CEA LEVEL:2.59 (ng/ml).



published by Liu et al.[15] concluded that the ^{18}F-FDG PET/CT method has low metastatic sensitivity but high specificity, whereas conventional methods such as MRI were more effective in detecting metastasis. Robertson et al.[16] emphasized that 18F-FDG uptake has very low sensitivity for LN detection.

In our study, statistically significant differences were found between the molecular subtypes and SUVmax, and ER - PR negativity, HER2 positivity, and increased 18F-FDG uptake were significantly correlated. However, we did not find statistical significance in SUVmax between non-metastatic and LN involvement/distant metastatic BC.

MTV and TLG parameters from ^{18}F-FDG PET/CT provide information not only on the severity of 18F-FDG uptake but the volume and metabolic activity of the tumor. Son et al.[17] concluded that MTV is a useful prognostic factor for metastatic BC. Marinelli et al.[18] found the MTV of 47 triple-negative BC (TNBC) patients, MTV is a strong prognostic factor for TNBC. Based on the study of 135 IDC patients, Yoo et al.[19] concluded that TLG is predictive of ALN metastasis. Based on 85 BC patients, Koizumi et al.[20] reported that TLG is predictive of bone metastasis detection. In our study, we did not find any statistical correlation between SUVmax and distant organ metastasis; but the MTV40 and TLG40 calculated in distant metastatic patients were significantly higher than those without metastasis.

NEDD-9 overexpression revealed a complex signaling mechanism that provides a basis for migration, invasion, morphological transformation and proliferation, number of aggressive tumor characteristics, and metastasis-related studies in different tumors.[3,4] Kong et al.[5] noted that NEDD-9 expression was increased in TNBC patients. Štajduhar et al.[21] showed, based on 40 non-metastatic tissue samples and 40 metastatic samples from BC, increased NEDD-9 expression in ALN metastasis. Hata et al.[22] reported a high NEDD-9 expression in bone metastatic BC. Loskutov et al.[23] noted that NEDD-9 inhibition significantly reduced tumor growth and metastasis in BC xenograft models. In a meta-analysis of 13 studies, 1179 cases and 493 controls, Fu and Li[24] concluded that CA15-3 and CEA are potential markers for BC and can be used for tumor staging and follow-up. In many published data, these were reported to be beneficial in poor prognosis, metastasis, and treatment follow-up.[25] In our study, NEDD-9 was found to be statistically significantly higher in BC compared to healthy controls. The CA 15-3 of a distant metastatic group was significantly higher than in one without metastasis. A statistically significant positive correlation was found between SUVmax and CA 15-3; a negative correlation was found between CEA and SUVmax. A statistically significant correlation was found between MTV and CEA. A statistically significant correlation was found between TLG and CA 15-3, CEA, SUVmax, and MTV.

TABLE 2. CORRELATION ANALYSIS AMONG WITH CLINICAL, PATHOLOGICAL, BIOCHEMICAL FEATURES AND PET PARAMETERS IN PATIENTS GROUP

	SUVmax	MTV40	TLG40			
	r	p	R	p	R	P
Age						
	- 0.169	0.128	- 0.120	0.282	- 0.227	0.040*
LN diameter						
	0.059	0.676	0.140	0.317	0.185	0.185
Ki-67						
	0.285	0.010*	- 0.009	0.937	0.154	0.168
NEDD-9						
	- 0.020	0.859	- 0.127	0.255	- 0.141	0.206
CA 15-3						
	0.299	0.006*	0.200	0.071	0.321	0.003*
CEA						
	- 0.021	0.849	0.301	0.006*	0.281	0.010*
SUVmax						
	-	-	0.128	0.250	0.512	0.000*
MTV40						
	-	-	-	-	0.853	0.000*

*= p<0.05 statistically significant.

Increases in NEDD-9 expression in BC and SUVmax are due to significant changes in molecular subtypes and receptor status; the relationship between metastasis and MTV40 and TLG40, using NEDD-9 and ^{18}F-FDG PET/CT metabolic parameters together, can contribute to BC staging. The correlation of CA 15-3 and CEA with ^{18}F-FDG PET/CT metabolic parameters may provide diagnostic, predictive, and prognostic value. We conclude that the use of SUVmax, MTV40, and TLG40 in combination with NEDD-9 and tumor markers will enhance BC management and provide a basis for NEDD-9-related treatment and target-oriented interventions.

Conflicts of interest

None.

Funding sources

None.

Author contribution form

	Esra Arslan	Hale Aral	Tamer Aksoy	Çiğdem Usul Afsar	Senem Karabulut	Fadime Didem Can Trabulus	Riza Umar Gursu	Tevfik Fikret Cermik
Idea/concept	40%	20%	10%	5%	5%	5%	5%	10%
Design	30%	30%	10%	5%	5%	5%	5%	10%
Check	20%	20%	20%	5%	5%	5%	5%	20%
Source and fund providing	30%	30%	10%	5%	5%	5%	5%	10%
Data collecting and/or processing	30%	20%	20%	5%	5%	5%	5%	10%
Analysis-comment	30%	30%	10%	5%	5%	5%	5%	10%
Literature screening	20%	20%	20%	5%	5%	5%	5%	20%
Article writing	60%	10%	5%	5%	5%	5%	5%	5%
Critical examination	20%	10%	10%	10%	10%	5%	5%	30%

RESUMO

OBJETIVO: *Analisar a associação da superrexpressão das células NEDD-9 ao prognóstico negativo em vários tipos de carcinoma. Nosso objetivo foi investigar a relação entre os níveis de NEDD-9, CA 15-3 e CEA e PET (SUVmax, MTV40, TLG) e os parâmetros clínicos em pacientes com câncer de mama (CM).*

MÉTODOS: *Cento e onze pacientes (82 pacientes de CM submetidos a 18F-FDG PET/TC e 29 controles saudáveis) foram avaliados. SUVmax, MTV, e TLG do tumor primário foram comparados nos subtipos molecular e histopatológico. A captação de 18F-FDG, MTV, e TLG foi avaliada com base em dados clínicos (envolvimento nodal, metástase distante, status de ER e PR, Ki-67, níveis séricos de NEDD-9, CA15-3 e CEA). Foi comparada a NEDD-9 do grupo de CM e o controle saudável.*

RESULTADOS: *A média ± DP de SUVmax de 82 pacientes foi de 13,0 ± 8,6. Uma relação estatisticamente significativa (p=0,022) foi encontrada entre subtipos moleculares e captação de 18F-FDG. A relação entre captação de 18F-FDG e TLG medida em pacientes com idade <50 anos, ER-PR negativo e HER2 positivo foi estatisticamente significativa (p=0,015; 0,007; 0,046; e 0,001, respectivamente). MTV40, TLG40 e CA 15-3 em pacientes metastáticos foram estatisticamente significantes (p=0,004, 0,005 e 0,003, respectivamente). NEDD-9 no grupo BC foi significativamente maior do que no grupo saudável (p=0,017). Uma correlação positiva foi encontrada entre SUVmax e Ki67 e CA 15-3; MTV40 e CEA; CA 15-3, CEA, SUVmax e MTV40; uma correlação negativa foi encontrada entre CEA, TLG40 e idade.*

CONCLUSÃO: *O uso dos parâmetros SUVmax, MTV40 e TLG40 com NEDD-9 e marcadores tumorais demonstrou um alto valor diagnóstico, preditivo e prognóstico para o manejo do CM. Isso é considerado a base para intervenções focadas nos objetivos de tratamento relacionados às NEDD9.*

KEYWORDS: *Neoplasias da mama. Fluorodesoxiglicose F18. Proteínas adaptadoras, transdutoras de sinal. Antígeno carcinoembrionário.*

REFERENCES

1. Tornillo G, Defilippi P, Cabodi S. Cas proteins: dodgy scaffolding in breast cancer. Breast Cancer Res. 2014;16(5):443.
2. Shagisultanova E, Gaponova AV, Gabbasov R, Nicolas E, Golemis EA. Preclinical and clinical studies of the NEDD9 scaffold protein in cancer and other diseases. Gene. 2015;567(1):1-11.
3. Kozyreva VK, McLaughlin SL, Livengood RH, Calkins RA, Kelley LC, Rajulapati A, et al. NEDD9 regulates actin dynamics through cortactin deacetylation in an AURKA/HDAC6–dependent manner. Mol Cancer Res. 2014;12(5):681-93.
4. Afsar CU, Karabulut M, Karabulut S, Ozal ST, Cikot M, Serilmez M, et al. Clinical significance of serum NEDD9 levels in patients with pancreatic cancer. Biomolecules. 2018;8(4). doi: 10.3390/biom8040169.
5. Kong C, Wang C, Wang L, Ma M, Niu C, Sun X, et al. NEDD9 is a positive regulator of epithelial-mesenchymal transition and promotes invasion in aggressive breast cancer. PloS One. 2011;6(7):e22666.
6. Geng B, Liang MM, Ye XB, Zhao WY. Association of CA 15-3 and CEA with clinicopathological parameters in patients with metastatic breast cancer. Mol Clin Oncol. 2015;3(1):232-6.
7. Harris L, Fritsche H, Mennel R, Norton L, Ravdin P, Taube S, et al. American Society of Clinical Oncology 2007: update of recommendations for the use of tumor markers in breast cancer. J Clin Oncol. 2007;25(33):5287-312.
8. Arslan E, Çermik TF, Trabulus FDC, Talu ECK, Başaran Ş. Role of 18F-FDG PET/CT in evaluating molecular subtypes and clinicopathological features of primary breast cancer. Nucl Med Commun. 2018;39(7):680-90.
9. Arslan E, Aksoy T, Cermik T. The prognostic value of 18 FDG PET/CT metabolic tumor volume (MTV) in distant metastatic breast cancer. J Nucl Med. 2019;60(suppl. 1):1235.
10. Chen W, Zhu L, Yu X, Fu Q, Xu W, Wang P. Quantitative assessment of metabolic tumor burden in molecular subtypes of primary breast cancer with FDG PET/CT. Diagn Interv Radiol. 2018;24(6):336-41.
11. Cheang MC, Chia SK, Voduc D, Gao D, Leung S, Snider J, et al. Ki-67 index, HER2 status, and prognosis of patients with luminal B breast cancer. J Natl Cancer Inst. 2009;101(10):736-50.
12. Iida J, Dorchak J, Slavik J, Clancy R, Cutler ML, Shriver CD. NEDD9 promotes breast cancer metastasis by regulating mitochondrial functions. 2016 San Antonio Breast Cancer Symposium; December 6-10, 2016; San Antonio, Texas.
13. Gu Y, Lu J, Chen C, Zheng F. NEDD9 overexpression predicts poor prognosis in solid cancers: a meta-analysis. OncoTargets Ther. 2019;12:4213-22.
14. Ueda S, Tsuda H, Asakawa H, Shigekawa T, Fukatsu K, Kondo N, et al. Clinicopathological and prognostic relevance of uptake level using 18F-fluorodeoxyglucose positron emission tomography/computed tomography fusion imaging (18F-FDG PET/CT) in primary breast cancer. Jpn J Clin Oncol. 2008;38(4):250-8.
15. Liu T, Cheng T, Xu W, Yan WL, Liu J, Yang HL. A meta-analysis of 18 FDG-PET, MRI and bone scintigraphy for diagnosis of bone metastases in patients with breast cancer. Skeletal Radiol. 2011;40(5):523-31.
16. Robertson IJ, Hand F, Kell MR. FDG-PET/CT in the staging of local/regional metastases in breast cancer. Breast. 2011;20(6):491-4.
17. Son SH, Lee SW, Jeong SY, Song BI, Chae YS, Ahn BC, et al. Whole-body metabolic tumor volume, as determined by (18)F-FDG PET/CT, as a prognostic factor of outcome for patients with breast cancer who have distant metastasis. AJR Am J Roentgenol. 2015;205(4):878-85.
18. Marinelli B, Espinet-Col C, Ulaner GA, McArthur HL, Gonen M, Jochelson M, et al. Prognostic value of FDG PET/CT-based metabolic tumor volumes in metastatic triple negative breast cancer patients. Am J Nucl Med Mol Imaging. 2016;6(2):120-7.
19. Yoo J, Kim BS, Yoon HJ. Predictive value of primary tumor parameters using 18 F-FDG PET/CT for occult lymph node metastasis in breast cancer with clinically negative axillary lymph node. Ann Nucl Med. 2018;32(9):642-8.
20. Koizumi M, Motegi K, Umeda T. A novel biomarker, active whole skeletal total lesion glycolysis (WS-TLG), as a quantitative method to measure bone metastatic activity in breast cancer patients. Ann Nucl Med. 2019;33(7):502-11.
21. Štajduhar E, Sedić M, Leniček T, Radulović P, Kerenji A, Krušlin B, et al. Expression of growth hormone receptor, plakoglobin and NEDD9 protein in association with tumour progression and metastasis in human breast cancer. Tumor Biol. 2014;35(7):6425-34.
22. Hata K, Morita Y, Nakanishi M, Nishisyou T, Yoneda T. TGFβ target gene NEDD9 identified by gene profiling plays a critical role in breast cancer bone metastasis. Bone. 2011;48(1):S13.
23. Loskutov YV, Kozyulina PY, Kozyreva VK, Ice RJ, Jones BC, Roston TJ, et al. NEDD9/Arf6-dependent endocytic trafficking of matrix metalloproteinase 14: a novel mechanism for blocking mesenchymal cell invasion and metastasis of breast cancer. Oncogene. 2015;34(28):3662-75.
24. Fu Y, Li H. Assessing clinical significance of serum CA15-3 and carcinoembryonic antigen (CEA) levels in breast cancer patients: a meta-analysis. Med Sci Monit. 2016;22:3154-62.
25. Lee JS, Park S, Park JM, Cho JH, Kim SI, Park BW. Elevated levels of preoperative CA 15-3 and CEA serum levels have independently poor prognostic significance in breast cancer. Ann Oncol. 2013;24(5):1225-31.

ORIGINAL ARTICLE

Evaluation of the fibulin 5 gene polymorphism as a factor related to the occurrence of pelvic organ prolapse

Marcus Vinicius Barbosa de Paula[1]
Marcos Antônio de Farias Lira Júnior[1]
Vivian Costa e Silva Crocco Monteiro[2]
Ricardo Peres Souto[3]
César Eduardo Fernandes[4]
Emerson de Oliveira[5]

1. Mestrando, Departamento de Ginecologia e Obstetrícia, Faculdade de Medicina do ABC, Santo André, SP, Brasil.
2. Graduando, Departamento de Ginecologia e Obstetrícia, Faculdade de Medicina do ABC, Santo André, SP, Brasil.
3. Professor Assistente, Departamento de Morfologia e Psicologia, Faculdade de Medicina do ABC, Santo André, SP, Brasil.
4. Professor Titular, Departamento de Ginecologia e Obstetrícia, Faculdade de Medicina do ABC, Santo André, SP, Brasil.
5. Professor Assistente, Departamento de Ginecologia e Obstetrícia, Faculdade de medicina do ABC, Santo André,SP, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.680

SUMMARY

OBJECTIVE: *Pelvic organ prolapse (POP) is a very frequent situation in our population that may lead to a significant decrease in patients' quality of life. Currently, we are looking for predictive factors for the development of POPs; thus, this study seeks to evaluate whether the Fibulin 5 polymorphism (FBLN5) is associated with the occurrence of POP.*

METHODS: *This is a cohort study with postmenopausal women who were divided into groups by POP stage: POP stages 0 and I (control group) and POP stages III and IV (case group). Subsequently, analyses of genetic polymorphisms of FBLN5 were performed using the Restriction Fragment Length Polymorphism (RFLP) technique.*

RESULTS: *A total of 292 women were included in the study. Pregnancy, parity and vaginal delivery in the patients, as well as in data described in the literature, were related to the occurrence of POP in the univariate analysis. However, after binary logistic regression, home birth and age remained independent risk factors for POP. We found no association between the FBLN5 polymorphism and the occurrence of POP (p = 0.371).*

CONCLUSION: *There was no association between the FBLN5 polymorphism and the occurrence of POP in Brazilian women.*

KEYWORDS: *Female urogenital diseases. Pelvic organ prolapse. Extracellular matrix proteins.*

INTRODUCTION

Pelvic organ prolapse (POP) is a very prevalent disease in our population[1]. The absolute majority of women who suffer from this disease do not seek medical care for their symptoms[2]. Although POP is a disease without mortality, the morbidity is high, mainly in relation to the decrease in the quality of life of patients[1].

POP results from defects of the pelvic support system, whose main components are the urogenital

DATE OF SUBMISSION: 23-Nov-2019
DATE OF ACCEPTANCE: 08-Dec-2019
CORRESPONDING AUTHOR: Emerson de Oliveira
Av. Lauro Gomes, 2000, Vila Sacadura Cabral, Santo André, SP, Brasil - 09060-870
Tel: + 55 11 4993-5400
E-mail: emerson_oliveira@terra.com.br

muscles, vaginal fascia and connective tissue. Several risk factors have already been clearly related to the disease, of which the most well established are parity, previous pregnancies, vaginal and/or instrumentalized births and age[2,3].

Currently, in the field of medical science, we are looking for predictive factors for the development of diseases so that we can act preventively. The study of gene polymorphisms in POP has suggested the possibility of screening young women who are candidates for the development of the disease, thus allowing them to take certain actions throughout their life to minimize the occurrence of POP over time[4-6].

Gene polymorphisms consist of genetic differences between individuals with no pathological consequences. They arise from genetic variations in a portion of the population according to a given characteristic. These variations become a polymorphism when they have a prevalence of at least 1% of the population. They may occur in several characteristics of the population, for example, different blood types[5,6].

Polymorphisms of collagen metabolizing genes and extracellular matrix proteins linked to elastogenesis may be related to POP[4,7]. The extracellular matrix consists of a set of intercellular elements comprised of collagen, proteoglycans, glycoproteins and integrins secreted by the cells that permeate it. The extracellular matrix is responsible for the interaction between cells through the connections between cellular elements[8].

The synthesis of collagen fibers (comprised of collagen) is a complex and not yet fully understood process. Elastin monomers are secreted by fibroblasts and smooth muscle cells. Microfibrils form the framework where elastin is deposited on the edge of the growing fiber regulated by the enzyme lysyl oxidase (LOX).

Fibulin 5 is a crucial protein for elastogenesis[9,10]. The extracellular matrix of the fibulin 5 protein promotes adhesion between endothelial cells through integrins. The gene encoding this protein is located on chromosome 14q32[11]. The fibulin 5 protein is encoded by the FBLN5 gene and promotes endothelial cell adhesion. Mutations of fibulin 5 are related to degenerative diseases and POP[8,10].

This study evaluated the gene polymorphism of the Fibulin 5 fraction snp1, as well as its risk factors, to establish a correlation with the occurrence of POPs through the Restriction Fragment Length Polymorphism (RFLP) technique.

METHODS

Study design

This is a single-center prospective cohort study carried out between 2014 and 2016 of patients who were admitted to the Urogynecology and Vaginal Surgery Section of the Department of Obstetrics and Gynecology of the Faculdade de Medicina do ABC (FMABC) in Santo André, São Paulo, Brasil. The study observed the ethical guidelines of the Brazilian Health Council and followed the principles of the Declaration of Helsinki. The study was previously evaluated and approved by the Research Ethics Committee from FMABC (process number 554.670/2014). All patients were informed about the study and signed a consent form to participate.

Patients

Women with a clinical history compatible with post menopause (no menses for at least one year) were included. POP was determined through gynecological exam, following the classification proposed by the International Continence Society (ICS), American Society of Urogynecology (ASUG) and the Society of Gynecologic Surgeons (SGS)[12] (Figures 1, 2 and 3). Women with clinical diagnoses of stages III and IV of prolapse were included in the case group. The control group was comprised of women with prolapse stages 0 or I. The criteria for non-inclusion were refusal of blood collection and a history of prior vaginal surgery of any kind.

Weight and height were measured to calculate body mass index (BMI). Sociodemographic and clinical data (family history of genital dystopia, obstetric history, age at menopause, previous use of hormone therapy, constipation history, chronic cough and chronic diseases) were collected by a physician interview.

DNA extraction

Blood samples were collected with EDTA and centrifuged. A leukocyte-rich fraction was transferred to a new tube and stored at -20°C (-4°F). Genomic DNA was extracted from leukocytes using an illustra blood genomicPrep Mini spin kit (GE Healthcare), following the instructions from the supplier. DNA preparation was quantified by UV absorbance using a NanoVue Plus spectrophotometer (GE Healthcare).

Genetic analysis of polymorphism rs12586948

Amplification of the FBLN5 gene promoter including the polymorphism (rs 12586948) was conducted in a 10 µL reaction using approximately 100

ng of genomic DNA, PCR Master Mix (Promega) and primers described by Khadzhieva et al.[11]: R (5´-TACCTGAATGGAAGCCCTTG-3´) and F (5´-GCAGAATCTCAGGGCTAGGA-3´). The PCR protocol started with an initial stage of 94°C (201°F) for 5 min, followed by 45 cycles at three temperatures (94°C/201°F for 30 s, 55°C/131°F for 60 s, and 72°C/162°C for 60 s) and a final incubation at 37°C/97°F for 16 h. The amplified DNA was digested with an AluI restriction enzyme (Biolabs) and analyzed with 3.0% agarose electrophoresis. Genotypes were set by the observed pattern of digestion bands: a single band of 238 bp for homozygous GG, two bands of 238 bp and 196 bp and a single band of 196 bp for homozygous AA; the bands of 37 bp and 42 bp were not visible (Figure 1).

Statistical Analysis

An unpaired t-test was used to compare quantitative variables. The Shapiro-Wilk test was performed to obtain the normality of the quantitative data. Chi-square and Fisher´s exact tests compared the qualitative variables. Data analysis was carried out using GraphPad Prism 6 and SPSS version 23. Odd ratios (ORs) were used to estimate, after stratification of the groups, the influence of clinical characteristics

FIGURE 1

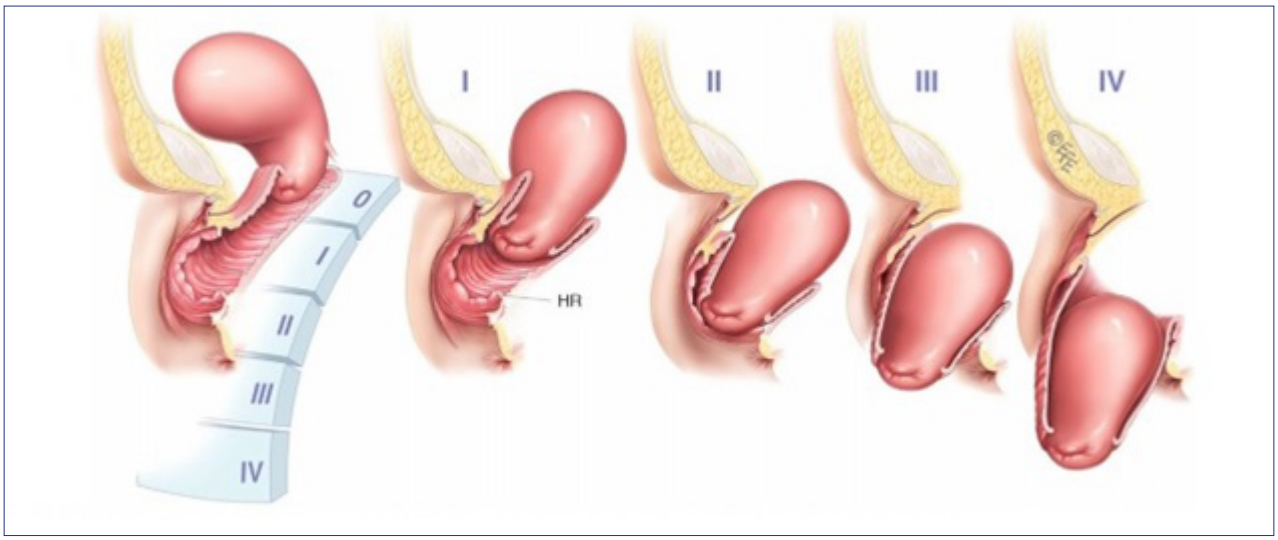


FIGURE 2

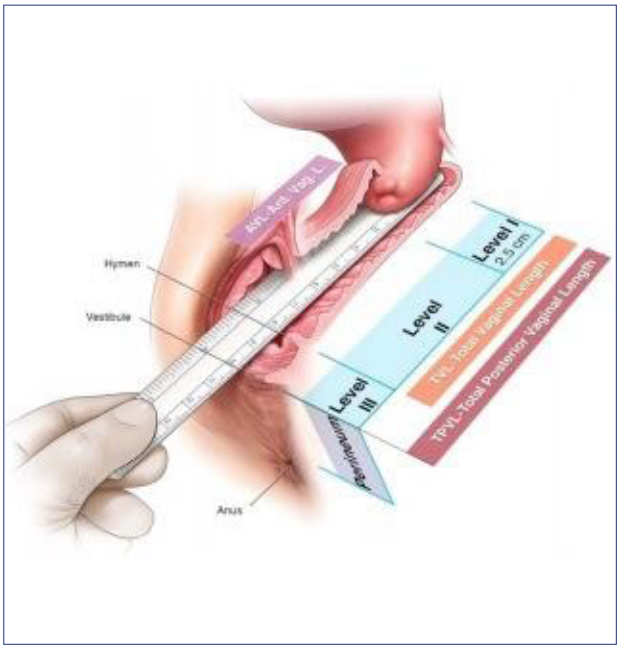
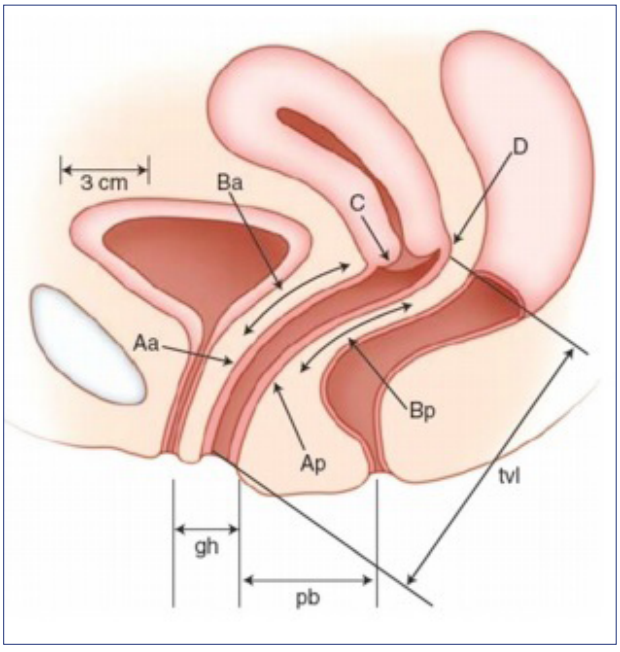


FIGURE 3



on the risk of POP, obtained from the binary logistic regression model. The assumed confidence interval was 95% (95% CDI), and the assumed significance level was 5% (p<0.05).

RESULTS

The study included 292 women with a mean age of 68.4 years in the case group and 57.8 years in the control group, with a statistically significant difference between the groups. Overall, the women were mostly Caucasian and had similar BMIs. Pregancy, parity and vaginal delivery of the patients, as well as those reported in the literature, were related to the occurrence of POP in the univariate analysis (Table 1). However, after binary logistic regression, home birth and age remained independent risk factors for POP occurrence (Table 2).

Hardy-Weinberg equilibrium was not observed between the groups (p = 0.01), and we found the following genotypes: 125 GG homozygotes, with 55 in the case group and 70 in the control group; and 74 with at least one A (AG + AA), with 27 in the case group and 47 in the control group. There was no significant difference in the presence of genotypes between cases and controls (p = 0.371) (Table 3).

TABLE 1. INCIDENCE OF RISK FACTORS FOR PELVIC ORGAN PROLAPSE

Variables	Case (n = 112) N, mean or %	Control (n = 180) N, mean or %	P
Age	68.4	57.8	< 0.0001
Caucasian	69.9%	64.8%	0.422
Non-Caucasian	30.1%	35.2%	
BMI	28.8	28.9	0.874
Age of menopause	48.8	46.6	0.07
Use of hormone replacement therapy	10.7%	18.1%	0.09
Smoking	13.1%	20.1%	0.15
Arterial hypertension	57.8%	49.4%	0.186
Diabetes mellitus	24.5%	23.7%	0.888
Dyslipidemia	25.4%	24.7%	0.889
Chronic cough	1.8%	6.8%	0.08
Constipation	14.3%	10.4%	0.35
Pregnancy	5.6	3.5	< 0.0001
Parity	4.8	2.9	< 0.0001
Vaginal deliver	4.1	2.3	< 0.0001
Cesarian birth	0.08	0.12	0.377
Weight of heaviest newborn	3516	3059	0.147
Episiotomy	8.3%	9.2%	> 0.999
Labor analgesia	3.7%	4.8%	0.768
Home birth	25,9%	3.05%	< 0.0001
Previous hysterectomy	15.2%	15.6%	> 0.999
Activities with great effort	22.5%	14.1%	0.077

Statistical test for values expressed as the mean: Student's t-te st; Statistical test for values expressed as percentages: Fisher's exact test; Statistical test for values expressed as the mean: Student's t-te st; Statistical test for values expressed as percentages: Fisher's exact test; Statistical Analysis with Student's T-Test or Fisher's Exact, as appropriate.

TABLE 2. MULTIVARIATE ANALYSIS WITH BINARY LOGISTIC REGRESSION OF POTENTIAL RISK FACTORS FOR POP

Covariable	Gross OR CI	P	Adjusted OR CI	p
Age ≥ 51	15.57 (4.73 – 51.2)	< 0.0001	11.89 (3.53 – 40)	< 0.0001
Pregnancies ≥ 3	2.02 (1.24 – 3.28)	0.004	0.656 (0.283 – 1.51)	0.325
Vaginal birth ≥ 3	3.12 (1.86 – 5.23)	< 0.0001	1.91 (0.7 – 5.22)	0.202
Parity ≥ 3	2.64 (1.62 – 4.31)	< 0.0001	2.01 (0.665 – 6.1)	0.216
Home birth	11.1 (4.14 – 29.7)	< 0.0001	9.645 (3.35 – 27.7)	< 0.0001

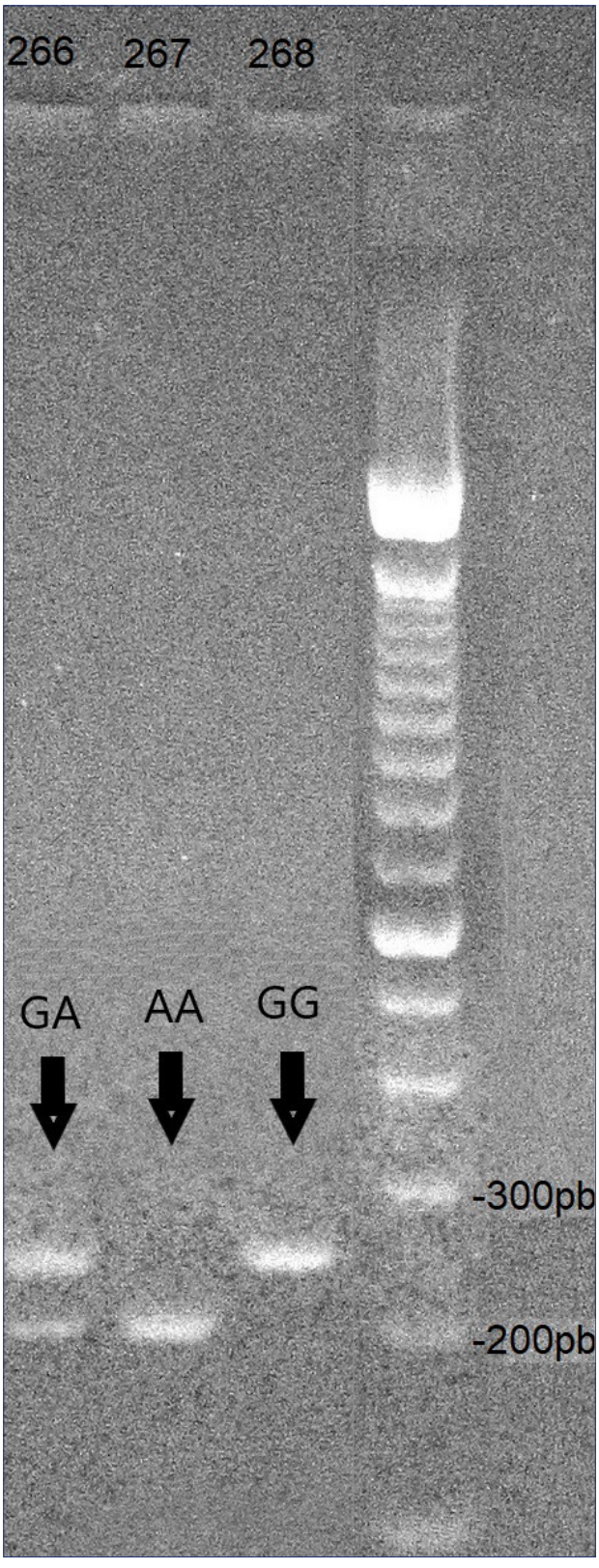
OR: Odds ratio; CI: Confidence Interval.

TABLE 3. GENOTYPIC OCCURRENCE BETWEEN CASES AND CONTROLS

Genotype	Case	Control	p
GG	55	27	0.371
AA + AG	70	47	

Statistical Analysis: Fisher's exact test

FIGURE ???



DISCUSSION

The study of polymorphisms is being developed in several diseases, including neoplasic ones. The possibility of identifying predictive factors for disease prevention strongly impacts treatment costs and can prevent disease in susceptible individuals.

Our group has been studying the impact of these polymorphisms on prolapse of pelvic organs and is being one of the pioneers in this line of research in Brasil. In many parts of the world, this same line is yielding a database that may help provide predictors for disease development. In Brasil, there are some groups with POP research studying the prevalence, impact and risk factors related to this disease.

Several studies around the world study the gene polymorphisms of collagen metabolization of different populations and different results are observed. Khadzhieva et al.[11] suggested that 4 of 11 fibulin 5 polymorphisms studied were related to POP, however the rs 12586948 were not correlated. The study of this group served as a basis for ours and thus we sought to assess whether the premise found by these authors also applied in our population. Therefore, we use the SNP RFLP method as the most common and reproducible polymorphism according to the study mentioned above[13].

Some studies suggest that decreasing fibulin protein expression 5 increases the risk of POP. Zhao and Zhou[1] detected a decrease or absence of fibulin 5 expression in uterosacral ligaments of women with POP. Choi et al.[14] analyzed the role of protein fibulin 5 in elastogenesis and concluded that it plays an important role in the quality of the genesis of elastic fiber. In line with the last two studies, Wieslander et al.[15] demonstrated that the absence of fibulin 5 in the vaginal wall of rats compromises the elastogenesis and increases local protease, related to the occurrence of POP. Also corroborated with these findings, the group by Söderberg et al.[16] which observed a lower expression of fibrin 5 mRNA in individuals with POP and the de Jung et al.[17] who observed a lower expression of fibulin 5 in hysterectomized patients with POP and concluded that the deficiency of this protein is an important factor in the genesis of the disease. Drewes et al.[18] inferred that postpartum remodeling of collagen depends on a balance between fiber synthesis and fiber degradation.

Thus, genetic defects that make fiber remodeling difficult can lead to POP in some women and thus justifies the interest of several researchers in the

line of research we have been working on. In Brasil, our study is pioneering and we found no association between polymorphism rs 12586948 and POP, ratifying Khadzieva et al.[11]. In addition, the risk factors for POP described in the literature were also evidenced in our study, as related and independent variables, such as home birth and age. The important factor is the heterogeneity of the Asian population compared to the Brazilian one. Therefore, the important miscegenation in our population and all the diversity that is peculiar to it may have made it difficult to point out factors in our study.

There is currently a growing discussion regarding birth methods in our society. Caesarean birth, so frequent in Brasil, has been restrained, either by the alarming number, either by the attempt to prioritize vaginal delivery, considered natural. The "Obstetric violence", a term coined suggesting the violation of parturient rights has been used as a focus for prioritizing vaginal delivery. The humanization of childbirth, a fact sought by all involved (whether the healthcare professional or patient) has in many cases been confused with the defense of home birth.

Given this situation, and because we observe a correlation of the increased risk of genital prolapse in patients with this polymorphism, this leads us to rethink about the thoughtless defense of vaginal delivery, especially home delivery. It is suggested that women with other types of polymorphisms may increase the chance of genital prolapse when undergoing home birth, as observed in the possibility of selection by the professional and the patient's method of delivery, given the risk associated with the presence of polymorphism. Despite the limitations, this study is important because it is the first in Brasil investigating and trying to demonstrate a relationship between Fibulin 5 polymorphism and POP, and it will certainly contribute to future meta-analyzes. Also, we believe it is necessary to increase the sample so that we can respond more safely to the question that motivated us in this study.

In conclusion, our data did not demonstrate any association between the Fibulin 5 polymorphism and POP occurrence but found a correlation between the risk factors as describe in the literature.

Acknowledgements

The authors thank FAPESP (Fundação de Amparo à Pesquisa do Estado de São Paulo) for financially supporting this research under contract 2014/01107-6.

Author Contributions

Marcus Vinicius Barbosa de Paula - main author, contribute to concept, investigation, research, methodology, analysis and writing the article; Marcos Antônio de Farias Lira Júnior - contribute to research, methodology, analysis and writing the article; Vivian Costa e Silva Crocco Monteiro - contribute to research, methodology analysis and writing the article; Ricardo Peres Souto - contribute to concept, supervision, methodology, analysis and editing the article; César Eduardo Fernandes - contribute to concept, formal analysis, methodology, project administration, supervision; Emerson de Oliveira - contribute to concept, research, supervision, methodology, analysis and editing the article.

RESUMO

OBJETIVOS: *O prolapso de órgãos pélvicos (POP) é uma situação muito frequente em nossa população que pode levar a uma diminuição significativa da qualidade de vida dos pacientes. Atualmente, buscam-se fatores preditivos para o desenvolvimento de POPs e, assim, este estudo correlaciona um polimorfismo de Fibulina 5 (FBLN5) com a ocorrência da doença.*

MÉTODOS: *Estudo de coorte com mulheres na pós-menopausa, divididas por grupos pelos estádios 0 e I do POP (grupo controle) e POP III e IV (grupo caso). Posteriormente, análises do polimorfismo genético de FBLN5 foram realizadas utilizando a técnica de Polimorfismo de Comprimento de Fragmentos de Restrição (RFLP).*

RESULTADOS: *Um total de 292 mulheres foi incluído no estudo. Gestação, paridade e parto vaginal, como bem descritos na literatura, foram relacionados à ocorrência de POPs na análise univariada. No entanto, após a regressão logística binária, o parto domiciliar e a idade permaneceram como fatores de risco independentes para os POPs. Não encontramos associação deste polimorfismo FBLN5 com a ocorrência de POP (p=0,371).*

CONCLUSÃO: *Não houve associação deste polimorfismo FBLN5 com a ocorrência de POPs em mulheres brasileiras.*

PALAVRAS-CHAVE: *Doenças urogenitais femininas. Prolapso de órgão pélvico. Proteínas da matriz extracelular.*

REFERENCES

1. Zhao BH, Zhou JH. Decreased expression of elastin, fibulin -5 and lysyl oxidase -like 1 in the uterosacral ligaments of postmenopausal women with pelvic organ prolapse. J Obstet Gynaecol Res. 2012;38(6):925-31.
2. Olsen AL, Smith VJ, Bergstrom JO, Colling JC, Clark AL. Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997;89(4):501-6.
3. Jelovsek JE, Maher C, Barber MD. Pelvic organ prolapse. Lancet. 2007;369(9566):1027-38.
4. Chin K, Wieslander C, Shi H, Balgobin S, Montoya TI, Yanagisawa H, et al. Pelvic organ support in animals with partial loss of fibulin-5 in the vaginal wall. PLoS One. 2016;11(4):e0152793.
5. Botstein D, White RL, Skolnick M, Davis RW. Construction of a genetic linkage map in man using restriction fragment length polymorphisms. Am J Hum Genet. 1980;32(3):314-31.
6. Risch N, Merikangas K. The future of genetic studies of complex human diseases. Science. 1996;273(5281):1516-7.
7. Budatha M, Roshanravan S, Zheng Q, Weislander C, Chapman SL, Davis EC, et al. Extracellular matrix proteases contribute to progression of pelvic organ prolapse in mice and humans. J Clin Invest. 2011;121(5):2048-59.
8. Abedin M, King N. Diverse evolutionary paths to cell adhesion. Trends Cell Biol. 2010;20(12):734-42.
9. Budatha M, Silva S, Montoya TI, Suzuki A, Shah-Simpson S, Wieslander CK, et al. Dysregulation of protease and protease inhibitors in a mouse model of human pelvic organ prolapse. PLoS One. 2013;8(2):e56376.
10. Yanagisawa H, Schluterman MK, Brekken RA. Fibulin-5, an integrin-binding matricellular protein: its function in development and disease. J Cell Commun Signal. 2009;3(3-4):337-47.
11. Khadzhieva MB, Kamoeva SV, Chumachenko AG, Ivanova AV, Volodin IV, Vladimirov IS, et al. Fibulin-5 (FBLN5) gene polymorphism is associated with pelvic organ prolapse. Maturitas. 2014;78(4):287-92.
12. Haylen BT, Maher CF, Barber MD, Camargo S, Dandolu V, Digesu A, et al. An International Urogynecological Association (IUGA) / International Continence Society (ICS) joint report on the terminology for female pelvic organ prolapse (POP). Int Urogynecol J. 2016;27(2):165-94.
13. Leaché AD, Oaks JR. The utility of single nucleotide polymorphism (SNP) data in phylogenetics. Annu Rev Ecol Evol Syst. 2017;48(1):69-84.
14. Choi J, Bergdahl A, Zheng Q, Starcher B, Yanagisawa H, Davis EC. Analysis of dermal elastic fibers in the absence of fibulin-5 reveals potential roles for fibulin-5 in elastic fiber assembly. Matrix Biology. 2009;28(4):211-20.
15. Wieslander CK, Rahn DD, McIntire DD, Acevedo JF, Drewes PG, Yanagisawa H, et al. Quantification of pelvic organ prolapse in mice: vaginal protease activity precedes increased MOPQ scores in fibulin 5 knockout mice. Biol Reprod. 2009;80(3):407-14.
16. Söderberg MW, Byström B, Kalamajski S, Malmström A, Ekman-Ordeberg G. Gene expressions of small leucine-rich repeat proteoglycans and fibulin-5 are decreased in pelvic organ prolapse. Mol Hum Reprod. 2009;15(4):251-7.
17. Jung HJ, Jeon MJ, Yim GW, Kim SK, Choi JR, Bai SW. Changes in expression of fibulin-5 and lysyl oxidase-like 1 associated with pelvic organ prolapse. Eur J Obstet Gynecol Reprod Biol. 2009;145(1):117-22.
18. Drewes PG, Yanagisawa H, Starcher B, Hornstra I, Csiszar K, Marinis SI, et al. Pelvic organ prolapse in fibulin-5 knockout mice: pregnancy-induced changes in elastic fiber homeostasis in mouse vagina. Am J Pathol. 2007;170(2):578-89.

REVIEW ARTICLE

Comparison of the effect of mesh-plug, Lichtenstein, transabdominal preperitoneal, and totally extraperitoneal hernia repair: A network meta-analysis

Yi-Hua Shi[1]
De-Shuang Xiao[1]
Ling-Bo Dai[1]
Qian Fang[1]

1. Department of General Surgery, The First People's Hospital of Wenling, Wenling, 234000, Zhejiang Province, China.

http://dx.doi.org/10.1590/1806-9282.66.5.687

SUMMARY

OBJECTIVE: *To compare Mesh-plug, Lichtenstein, transabdominal preperitoneal (TAPP), and totally extraperitoneal (TEP) repairs in regards to operation time, seroma, infection, and recurrence of inguinal hernia repair.*

METHODS: *Relevant literature was searched in the Cochrane Library, Pubmed, and Embase. Furthermore, the analysis of randomized controlled studies (RCTs) was performed using methods recommended by the Cochrane Collaboration. The main outcomes including operation time, seroma, infection, and recurrence were evaluated.*

RESULTS: *A total of 38 RCTs with 3255 patients were included in the meta-analysis. In addition, the comparison between Mesh-plug, Lichtenstein, TAPP, and TEP showed the differences were not significant regarding operation time, seroma, infection, and recurrence.*

CONCLUSIONS: *Meta-analysis suggests that Mesh-plug, Lichtenstein, TAPP, and TEP are comparable in the outcomes of hernia repair, such as operation time, seroma, infection, and recurrence.*

KEYWORDS: *Hernia, inguinal/surgery. Treatment outcome. Herniorrhaphy. Surgical mesh. Meta-Analysis.*

INTRODUCTION

Hernias are generally weaknesses or defects of the muscle fibers that occur through the abdominal wall and provide a body cavity for the protrusion of internal organs[1,2]. The most common of hernias, the inguinal hernia has been a common prevalent condition worldwide with an incidence of 5%-7%[3]. Inguinal hernias are more frequent in children[4]. Currently, surgical repair is the primary choice treatment for it, and approximately 20 million inguinal hernia repairs are performed worldwide annually[5], which brings about a significant cost and morbidity burden worldwide.

Moreover, an increasing number of patients have undergone laparoscopic hernia repairs, such as transabdominal preperitoneal (TAPP) repair and total extraperitoneal (TEP) repair. In comparison to open repair, the morbidity and postoperative pain scores

DATE OF SUBMISSION: 09-Dec-2019
DATE OF ACCEPTANCE: 29-Dec-2019
CORRESPONDING AUTHOR: Qian Fang
Department of General Surgery, The First People's Hospital of Wenling - Chuan an South Road, 333, Wenling, Zhejiang, China - 234000
Tel: +86 151 69572822
E-mail: fzx120424@tom.com

have decreased, but recovery has increased[6,7]. Previous studies only compare two methods[8-10], and no comprehensive comparison between all these methods has been performed until now.

Therefore, the objective of this meta-analysis was to compare four methods of hernioplasty, including Mesh-plug, Lichtenstein, TAPP, and TEP. The main goal was to assess if there were differences in terms of clinical outcomes (operation time, seroma, infection, and recurrence) to provide a reliable foundation for further clinical practice.

MATERIALS AND METHODS

Literature search

To make sure the data of the studies included was veritable and reliable, we systematically searched the literature published from January 1996 to January 2017 in the Cochrane Library, Pubmed, and Embase public databases. The search terms were "inguinal hernia OR groin hernia OR hernia of groin", "mesh-plug OR plug and patch OR perfix plug OR Rutkow-Robbins", Lichtenstein, "TEP OR totally extraperitoneal repair", "TAPP OR transabdominal preperitoneal repair", as well as "Randomized Controlled Trial". Only articles published in English were considered.

Selection criteria

The studies were considered eligible if they met the following criteria: (1) Published in English. (2) Randomized controlled trial (RCT) design. (3) Mesh-plug, TAPP, Lichtenstein, and TEP adopted in the trials, and the outcomes mainly included operation time, seroma, infection, and recurrence rate. Studies were excluded from analysis if the papers were reviews, reports, comments, or letters.

Data extraction and quality assessment

Primarily, each article was critically reviewed separately by two authors, and then the first author's name, the year of publication, country of origin, study year, the types and methods of interventions, the patients' number, demographic characteristics of the general population, and outcomes involved were extracted and analyzed. The quality of the trials was assessed using the Cochrane Collaboration's tool[11]. Whenever there were disagreements in the process, a consensus was reached through pannel discussion and communication with a third investigator.

Statistical analysis

Meta-analyses were performed using the aggregate data drug information system(ADDIS) (1.16.5) based on the Bayesian framework and using Markov Chain Monte Carlo (MCMC) to evaluate the data[12,13]. The variables were expressed as odds ratio (OR) or mean difference (MD), with their respective 95% confidence intervals (95% CI). The consistency test was analyzed by node-splitting analysis, and *the consistency* model was used if P>0.05; otherwise the inconsistency model was adopted[14]. The Brooks-Gelman-Rubin method was applied to assess the convergence of the model with a potential scale reduction factor (PSRF)[15]. PSRF less than 1.2 was acceptable.

RESULTS

Literature search

The literature search and reference analysis obtained 1079 potentially eligible studies (417 Pubmed, 521 on Embase, and 141 on Cochrane Library). After removing 314 duplicated articles, 642 irrelevant studies, 44 articles including reviews, reports, comments, or letters, and 41 records, finally, 38 RCTs with 8305 participants were included in the study.

Results of meta-analysis

The parameters of ADDIS were used in our study as follows: Number of chains: 4, Tuning iterations: 20000, Simulation iterations: 50000, Thinning interval: 10, Inference samples: 10000, Variance scaling factor: 2.5. The network construction of various indicators revealed that closed networks were formed between the studies included.

Operation time

The node-splitting analysis showed the network meta-analysis appeared consistent (P>0.05, 1.00<PSRF<1.01), and results from the consistency model revealed patients with the mesh-plug had shorter operation time compared to those who underwent the other three interventions, but the differences were not significant (Figure 1).

Seroma

The node-splitting analysis showed the network meta-analysis appears consistent (P>0.05, 1.00<PSRF<1.03). The meta-analysis with the consistency model illustrated that patients with mesh-plug had a higher incidence of postoperative seroma than

those who underwent other interventions; however, the differences were not significant (Figure 2).

Infection

The node-splitting analysis suggested the model had good convergency and stability (P<0.05, 1.00<PSRF<1.01). The meta-analysis on the *inconsistency* model showed the infection rate in patients in the TEP group was significantly lower than that in the LR (OR=0.39, 95% CI: 0.10-0.90, P=0.030). However, there was no difference between TEP and other interventions, including Mesh-plug and TAPP (both P>0.05).

Recurrence

The node-splitting analysis demonstrated the model had good convergency and stability (P>0.05, 1.00<PSRF<1.04). Figure 3 shows the recurrence of inguinal hernia with LR was decreased in comparison to other interventions, including mesh-plug, TAPP, and TEP, but the differences were not significant (all, P>0.05).

DISCUSSION

This study for the first time compared the differences of outcomes between mesh-plug, Lichtenstein, TAPP, and TEP inguinal hernia repairs based on 38 RCTs with network meta-analysis. There was no significant difference between them in aspects of operation time, seroma, infection, and recurrence, which provides a reliable foundation for further clinical practice.

Complications of inguinal hernia repair, including seroma formation and infection, have been the most common reasons for reoperation. Clinical experience indicates there is a higher frequency of seroma and wound hematoma in inguinal hernia patients with open repair. Schmedt et al.[16] have demonstrated that seroma is less frequent in cases of the Lichtenstein method compared to those with endoscopic surgery. Our meta-analysis showed that there were no differences in postoperative wound complications (seroma and infection) in the mesh, Lichtenstein, TAPP, and TEP groups. A Previous study reported that TEP requires a shorter operating time than open repair, including mesh and Lichtenstein[17]. Moreover, Dedemadi et al.[18] demonstrated that the operation time in the group of open tension-free repair is shorter than in the group of laparoscopic repair, whereas another study found no differences in the operation time

FIGURE 1. DIAGRAM OF PROBABILITY. THERE WERE NO SIGNIFICANT DIFFERENCES IN OPERATION TIME BETWEEN THE MESH-PLUG, LICHTENSTEIN, TAPP, AND TEP GROUPS.

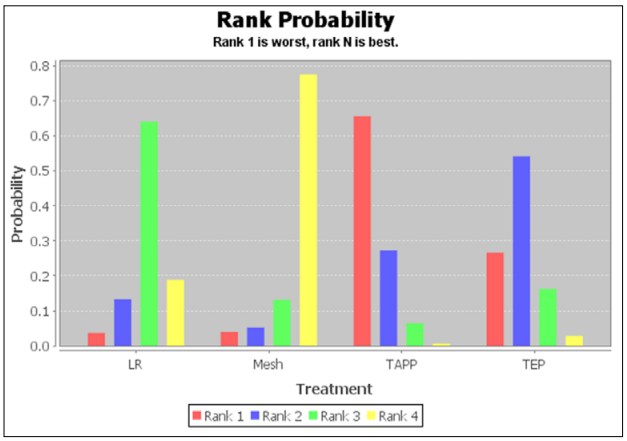


FIGURE 2. DIAGRAM OF PROBABILITY. THERE WERE NO SIGNIFICANT DIFFERENCES IN SEROMA BETWEEN THE MESH-PLUG, LICHTENSTEIN, TAPP, AND TEP GROUPS.

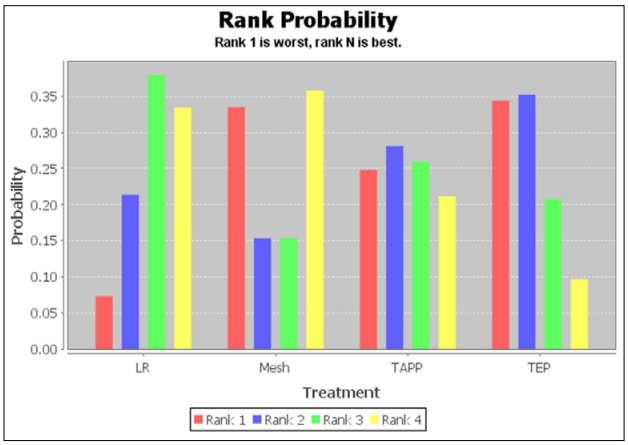
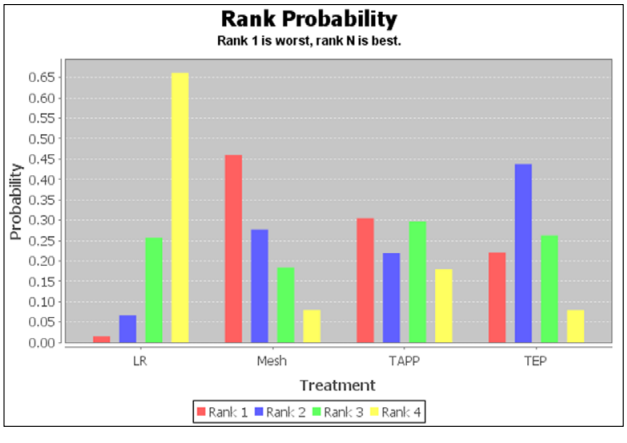


FIGURE 3. DIAGRAM OF PROBABILITY. THERE WERE NO SIGNIFICANT DIFFERENCES IN RECURRENCE BETWEEN THE MESH-PLUG, LICHTENSTEIN, TAPP, AND TEP GROUPS.



between the laparoscopic and Lichtenstein methods[19]. According to our results, there was no significant difference between the mesh-plug, Lichtenstein, TAPP, and TEP techniques in terms of operation time.

Recurrence, the most important aspect of clinical outcomes, is influenced by technical errors, such as improper fixation, deficiency of dissection, or inadequate repair of the hernia defect[20]. Previous experiences in the institute have shown that recurrence rates of patients after hernia repair are approximately 0~10%[9], and therefore, avoiding recurrence is becoming the primary issue of hernia repair. Memon et al.[7] have indicated a trend of increased recurrence after laparoscopic repair. Moreover, a meta-analysis showed the recurrence rate of laparoscopic repair (both TEP and TAPP) was higher than that of open repair[16]. However, in the present study, we found no differences in recurrence among Mesh, Lichtenstein, TAPP, and TEP techniques.

However, there were several limitations to the present study. For example, subgroup analysis was not performed due to the incomplete research data, and in order to analyze the role of each, we analyzed only four outcome indicators. Additionally, although ADDIS was easy to operate, the results could be limited because of the inability to program freely.

In summary, the results based on the network meta-analysis demonstrated that the differences in repair outcomes between Mesh, Lichtenstein, TAPP, and TEP were not significant in the treatment of inguinal hernias. However, to further verify the results, a large number of clinical randomized controlled studies are still needed.

Conflict of interest

None.

Funding

None.

Author Contributions

Conceptualization, Qian Fang; formal analysis, Yi-Hua Shi; writing (original draft preparation), De-Shuang Xiao; writing (review and editing), Ling-Bo Dai; supervision, Ling-Bo Dai; funding acquisition, Qian Fang.

RESUMO

OBJETIVO: *Comparar as abordagens de tampão com tela (mesh plug), Lichtenstein, transabdominal preperitoneal (TAPP) e totalmente extraperitoneal (TEP) em relação ao tempo de operação, seroma, infecção e recorrência no reparo de hérnias inguinais.*

MÉTODOS: *Estudos relevantes na literatura foram pesquisados nos bancos de dados Cochrane, PubMed e Embase. Além disso, a análise dos estudos clínicos controlados randomizados (RCTs) foi feita utilizando métodos recomendados pela Cochrane Collaboration. Os principais resultados, incluindo tempo de operação, seroma, infecção e recorrência, foram avaliados.*

RESULTADOS: *Um total de 38 RCTs com 3.255 pacientes foram incluídos na meta-análise. Além disso, a comparação entre mesh plug, Lichtenstein, TAPP e TEP mostrou que não havia diferenças significativas nos aspectos de tempo de operação, seroma, infecção e recorrência.*

CONCLUSÕES: *A meta-análise sugere que mesh plug, Lichtenstein, TAPP e TEP oferecem resultados comparáveis no reparo das hérnia inguinais em relação a tempo de operação, seroma, infecção e recorrência.*

PALAVRAS-CHAVE: *Hérnia inguinal/cirurgia. Resultado do tratamento. Herniorrafia. Telas cirúrgicas. Meta-análise.*

REFERENCES

1. Mahmoudvand H, Forutani S, Nadri S. Comparison of treatment outcomes of surgical repair in inguinal hernia with classic versus preperitoneal methods on reduction of postoperative complications. BioMed Res Int. 2017;2017:3785302.
2. Kingsnorth A, LeBlanc K. Hernias: inguinal and incisional. Lancet. 2003;362(9395):1561-71.
3. Pahwa HS, Kumar A, Agarwal P, Agarwal AA. Current trends in laparoscopic groin hernia repair: a review. World J Clin Cases. 2015;3(9):789-92.
4. Ein SH, Njere I, Ein A. Six thousand three hundred sixty-one pediatric inguinal hernias: a 35-year review. J Pediatr Surg. 2006;41(5):980-6.
5. Kalra T, Soni RK, Sinha A. Comparing early outcomes using non absorbable polypropylene mesh and partially absorbable composite mesh through laparoscopic transabdominal preperitoneal repair of inguinal hernia. J Clin Diagn Res. 2017;11(8):PC13-6.
6. Bittner R, Schwarz J. Inguinal hernia repair: current surgical techniques. Langenbecks Arch Surg. 2012;397(2):271-82.
7. Memon MA, Cooper NJ, Memon B, Memon MI, Abrams KR. Meta-analysis of randomized clinical trials comparing open and laparoscopic inguinal hernia repair. Br J Surg. 2003;90(12):1479-92.

8. Bobo Z, Nan W, Qin Q, Tao W, Jianguo L, Xianli H. Meta-analysis of randomized controlled trials comparing Lichtenstein and totally extraperitoneal laparoscopic hernioplasty in treatment of inguinal hernias. J Surg Res. 2014;192(2):409-20.

9. Li J, Ji Z, Li Y. Comparison of mesh-plug and Lichtenstein for inguinal hernia repair: a meta-analysis of randomized controlled trials. Hernia. 2012;16(5):541-8.

10. Wei FX, Zhang YC, Han W, Zhang YL, Shao Y, Ni R. Transabdominal preperitoneal (TAPP) versus totally extraperitoneal (TEP) for laparoscopic hernia repair: a meta-analysis. Surg Laparosc Endosc Percutan Tech. 2015;25(5):375-83.

11. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. [cited 2019 Oct 12]. Available from: https://handbook-5-1.cochrane.org/

12. Zhao J, Valkenhoef GV, De Brock B, Hillege H. ADDIS: an automated way to do network meta-analysis. [cited 2019 Oct 12]. Available from: https://www.rug.nl/feb/research/som-research-reports/som-research-reports-2012/12007-otherdef.pdf

13. Van Valkenhoef G, Tervonen T, Zwinkels T, De Brock B, Hillege H. ADDIS: a decision support system for evidence-based medicine. Decision Support Systems. 2013;55(2):459-75.

14. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment comparison meta-analysis. Stat Med. 2010;29(7-8):932-44.

15. Brooks SP, Gelman A. General methods for monitoring convergence of iterative simulations. J Comput Graphi Stat. 1998;7(4):434-55.

16. Schmedt CG, Sauerland S, Bittner R. Comparison of endoscopic procedures vs Lichtenstein and other open mesh techniques for inguinal hernia repair: a meta-analysis of randomized controlled trials. Surg Endosc. 2005;19(2):188-99.

17. Bringman S, Ramel S, Heikkinen TJ, Englund T, Westman B, Anderberg B. Tension-free inguinal hernia repair: TEP versus mesh-plug versus Lichtenstein: a prospective randomized controlled trial. Ann Surg. 2003;237(1):142-7.

18. Dedemadi G, Sgourakis G, Karaliotas C, Christofides T, Kouraklis G, Karaliotas C. Comparison of laparoscopic and open tension-free repair of recurrent inguinal hernias: a prospective randomized study. Surg Endosc. 2006;20(7):1099-104.

19. Eklund A, Rudberg C, Leijonmarck CE, Rasmussen I, Spangen L, Wickbom G, et al. Recurrent inguinal hernia: randomized multicenter trial comparing laparoscopic and Lichtenstein repair. Surg Endosc. 2007;21(4):634-40.

20. Fitzgibbons RJ Jr, Puri V. Laparoscopic inguinal hernia repair. Am Surg. 2006;72(3):197-206.

REVIEW ARTICLE

Ectopic ureter associated with Zinner's syndrome in a kidney recipient: case report and literature review

Korhan Tuncer[1]
Gizem Kilinc[1]
Ismail Sert[1]
Goksever Akpinar[1]
Cem Tugmen[1]

1. Department of General Surgery, Tepecik Training and Research Hospital, Izmir, Turkey

http://dx.doi.org/10.1590/1806-9282.66.5.692

SUMMARY

INTRODUCTION: *Zinner's Syndrome is a triad of mesonephric duct anomalies comprising unilateral renal agenesis, seminal vesicle cyst, and ejaculatory duct obstruction. In this study, we present a kidney recipient with ectopic ureter associated with Zinner's syndrome and a literature review.*

CASE PRESENTATION: *A 59-year-old male with a history of chronic kidney disease and left renal agenesis underwent deceased donor kidney transplantation. After securing optimal renal functions, the patient underwent abdominal computed tomography (CT) scan for the seroma that occurred under the incision. The final diagnosis was an ectopic distal ureter ending in the seminal vesicle cyst's wall and ipsilateral renal agenesis. The patient was discharged without any complications and the clinical follow up was uneventful.*

DISCUSSION AND CONCLUSION: *Congenital seminal vesicle disorders are usually associated with ipsilateral urinary duct anomalies stemming from the same embryonic structure. To our knowledge, this is the first case report that describes kidney transplantation in a patient with ipsilateral renal agenesis and ectopic ureter ending in the seminal vesicle cyst. In patients with renal agenesis, during the ipsilateral urinary tract anastomosis, the possibility of ectopic ureter should be kept in mind otherwise graft loss can occur with a high morbidity rate.*

KEYWORDS: *renal transplantation, seminal vesicle cyst, Zinner's syndrome*

INTRODUCTION

Zinner's Syndrome is a triad of mesonephric duct anomalies comprising unilateral renal agenesis, seminal vesicle cyst, and ejaculatory duct obstruction. Congenital seminal vesicle disorders are usually associated with ipsilateral urinary duct anomalies consisting of the same embryonic structure, named mesonephric duct (Wolfian duct)[1]. Ectopic ureter is described as a ureter opening to an area separate from the vesical trigone. Patients diagnosed with Zinner's Syndrome are usually asymptomatic, and symptomatic ones present prostatism, dysuria, and painful ejaculation. In this study, we present a kidney recipient with ectopic ureter associated with Zinner's syndrome and literature review.

DATE OF SUBMISSION: 02-Sep-2019
DATE OF ACCEPTANCE: 03-Dec-2019
CORRESPONDING AUTHOR: Gizem Kilinc
Department of General Surgery, Tepecik Education and Research Hospital – Street Number: 1140/1 Gate Number: 1
Postal Code: 35180 Izmir/Turkey
E-mail: drgizemkilinc@gmail.com

CASE PRESENTATION

A 59-year-old male with a history of chronic kidney disease and left renal agenesis underwent deceased donor kidney transplantation. Antithymocyte globulin (ATG) and corticosteroid were introduced as induction therapy; tacrolimus (FK506), mycophenolate mofetil, and corticosteroid were used as maintenance therapy. After securing the optimal renal functions, the patient underwent abdominal computed tomography (CT) scan for the seroma that occurred under the incision. Left renal agenesis and a lesion located on the left posterolateral side of the vesica with a 20 mm diameter and diverticular contrast filling excess was revealed in the CT scan. There was also a high-density tortuous lesion elongated up to the left seminal vesicle at the distal part of the left ureter. Pelvic magnetic resonance imaging (MRI) was obtained for a better analysis of these incidentally discovered structures. MRI showed that the left ureterovesical junction could not be seen because the distal portion of the left ureter ended inside of an almost 25 x 15 mm solid lesion, which was located next to the left seminal vesicle. This lesion was not filling up with contrast in the T2 phase images (Figure 1). Also, the cystic dilatation in the distal portion of the left ureter had intermediate signals in the T2 phase and high signals in T1 phase images (Figure 2). The final diagnosis was ectopic distal ureter ending in the seminal vesicle cyst's wall and ipsilateral renal agenesis. The patient was discharged without any complications and the clinical follow up was uneventful.

DISCUSSION

Congenital seminal vesicle disorders are usually associated with ipsilateral urinary duct anomalies stemming from the same embryonic structure. Ectopic ureter usually presents asymptomatically in males, therefore it is less frequent in males than in females (ratio 1:2.9). The ectopic region in men is often found in the seminal vesicle (37%) or posterior urethra (33%). Renal anomalies such as renal agenesis and dysgenesis are observed in 58% of cases of ectopic ureter[2]. Approximately two-thirds of seminal vesicle

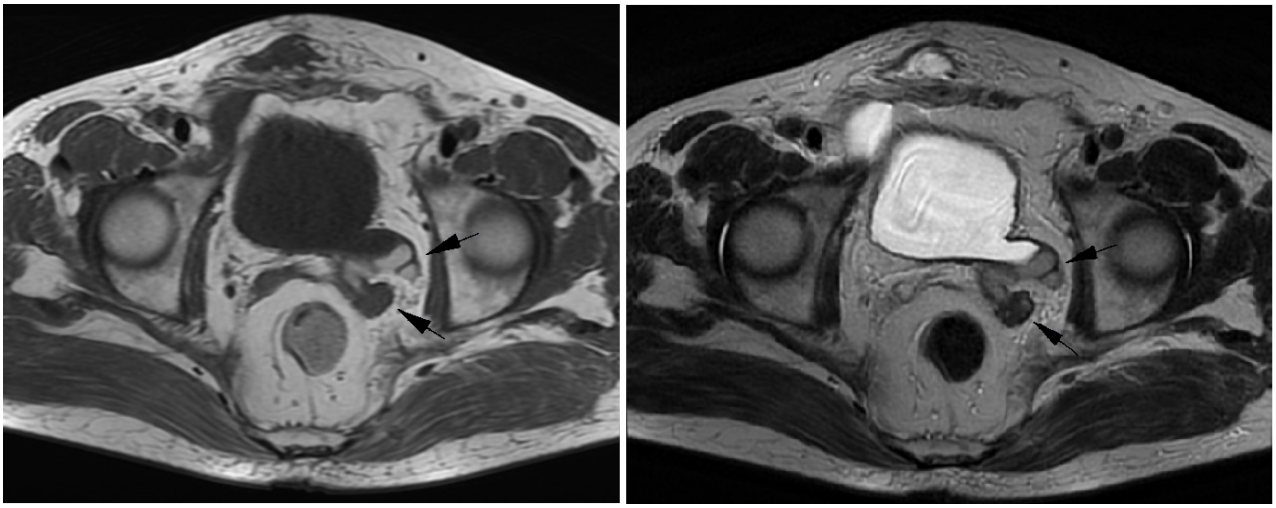


FIGURE 1.

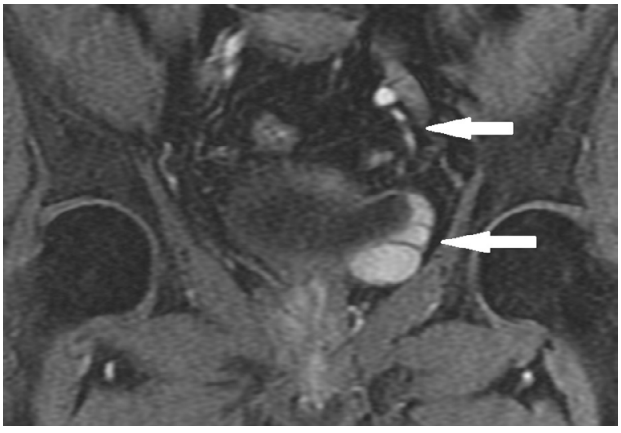


FIGURE 2.

cysts are associated with ipsilateral renal agenesis[3]. In this patient, the left distal ureter ended inside of the left seminal vesicle with a cystic dilatation. In the literature, many cases have been reported as Zinner's Syndrome with urinary and genital anomalies. Van den Ouden et al.[4] analyzed 52 patients with Zinner's Syndrome and found the most common symptoms were dysuria (37%), frequency (33%), perineal pain (29%), epididymitis (27%), pain following ejaculation (21%), and scrotal pain (13%). Also in this study, infertility was found in 9 patients (17%). In our case, renal agenesis was known in the patient's medical history, and the ectopic ureter and seminal vesicle cyst were incidentally revealed on the CT scan performed for the seroma. The patient was asymptomatic for years and had no fertility problems. In patients with renal agenesis, Zinner's Syndrome and ectopic ureter anomaly must be considered as a differential diagnosis. Endorectal ultrasonography, abdominopelvic CT scans, and Pelvic MRI can be used as diagnostic methods.

Uder et al.[5] reported 7 patients with seminal vesicle cysts associated with ipsilateral renal agenesis, and 5 of them were followed up for a mean period of 52 months (26-119 months, mean 52 months). Only one patient was defined as symptomatic with significant enlargement of the cyst causing compression of the bladder 10 years after the primary diagnosis. Another 4 patients were totally asymptomatic. Therefore, regular clinical follow-up was recommended for asymptomatic cases. In the literature, transurethral versus transrectal approaches and laparoscopic versus open surgery techniques were identified for symptomatic patients. It is observed that laparoscopic approaches provide a minimally invasive surgical treatment and less morbidity[6].

Malignancies of the ectopic ureter are rare in men and their differential diagnosis is difficult. In literature, malignancies related to ectopic ureter or seminal vesicle cysts are reported rarely. Narita et al.[2] reported a case in which left nephroureterectomy with total prostatectomy was performed due to transitional cell carcinoma of an ectopic ureter. Kim et al.[7] presented a case of squamous cell carcinoma due to the seminal vesicle cyst in a patient with Zinner's Syndrome. Okada et al.[8] reported a case of papillary adenocarcinoma due to ipsilateral renal agenesis associated with seminal vesicle cyst but did not describe an ectopic ureter. Also, Lee et al.[9] reported a case of mucinous adenocarcinoma present in a seminal vesicle cyst. Jaidane et al.[10] reported an adenocarcinoma of a ureter draining a dysplastic pelvic kidney and inserted in the cervix of a bicornuate uterus. Nakai et al.[11] performed total prostatectomy and ureterectomy to a case due to prostate cancer and left ectopic ureter opening to the seminal vesicle with left renal agenesis. In our case, we consider that more attention should be taken to secondary malignancies that may develop in patients who receive strong and long-term immunosuppressive treatment due to kidney transplantation.

In renal transplantation surgery, after the completion of vascular anastomoses, the continuity of the urinary system is ensured by ureteroneocystostomy or native ureteroureterostomy. Advanced urinary tract imaging before the transplantation is generally not necessary if the recipient is asymptomatic. Native ureteroureterostomy is usually done using a ureteric catheter, like Double J. The use of this procedure in distal urinary tract malformations may result in anuria and graft dysfunction. Shenoy et al.[12] reported a case of ureter anomaly leading to an ejaculatory canal detected after postoperative urinary leakage and hydronephrosis in a patient with VATER Syndrome who underwent renal transplantation and performed ureteroureterostomy. In our patient, the kidney was transplanted to the right iliac fossa, and urinary continuity was provided with ureteroneocystostomy. Patients with chronic renal failure due to renal agenesis must be examined for intact urinary tract before renal transplantation to decrease postoperative complications and graft dysfunctions.

CONCLUSION

Seminal vesicle cysts associated with ipsilateral renal agenesis or hypoplasia are a rare malformation and are usually detected accidentally. To our knowledge, this is the first case report that describes kidney transplantation in a patient with ipsilateral renal agenesis and ectopic ureter ending in the seminal vesicle cyst. However, this malformation is not a contraindication for renal transplantation. In patients with renal agenesis, during ipsilateral urinary tract anastomosis, the possibility of ectopic ureter should be kept in mind otherwise graft loss can occur with a high morbidity rate. Furthermore, we consider that asymptomatic cases should be closely followed up for secondary malignancies caused by immunosuppressive therapy.

Authors Contributions

Korhan Tuncer: Contributed to the concept, design, and data analysis of the manuscript; Gizem Kilinc: Contributed to the data analysis and translation of the manuscript; Cem Tugmen: Contributed to the concept, design, and supervision of the manuscript; Ismail Sert: Contributed to the translation and supervision of the manuscript; Goksever Akpinar: Contributed to the design and data analysis of the manuscript; All authors contributed to the final approval of the manuscript.

RESUMO

INTRODUÇÃO: *A Síndrome de Zinner é uma tríade de anomalias do ducto mesonéfrico que compreende agenesia renal unilateral, cisto da vesícula seminal e obstrução do ducto ejaculatório. Neste estudo, apresentamos um receptor de rim com ureter ectópico associado à Síndrome de Zinner e revisão da literatura.*

APRESENTAÇÃO DO CASO: *Homem de 59 anos com história de doença renal crônica e agenesia renal esquerda foi submetido a transplante de rim de doador falecido. Após função renal ideal, foi realizada tomografia computadorizada do abdome (TC) devido ao seroma sob incisão. O diagnóstico final foi um ureter distal ectópico que termina na parede do cisto da vesícula seminal e agenesia renal ipsilateral. O paciente recebeu alta sem complicações e o acompanhamento clínico ocorreu sem intercorrências.*

DISCUSSÃO E CONCLUSÃO: *Os distúrbios congênitos da vesícula seminal geralmente estão associados às anomalias do ducto urinário ipsilateral devido a uma mesma estrutura embrionária. Até onde sabemos, é o primeiro relato de caso que descreve o transplante renal em um paciente com agenesia renal ipsilateral e ureter ectópico terminado no cisto da vesícula seminal. Em pacientes com agenesia renal, durante a anastomose do trato urinário ipsilateral, deve-se ter em mente a possibilidade do ureter ectópico, caso contrário, poderá ocorrer perda do enxerto com alta taxa de morbidade.*

PALAVRAS-CHAVE: *transplante renal, cisto de vesícula seminal, síndrome de Zinner.*

REFERENCES

1. El Mortaji H, Elatiqi K, El Hammaoui H, Alj S, Fettouh A, Lakmichi A, et al. Zinner's syndrome: a case report. Prog Urol. 2018;28(10):464-5.
2. Narita S, Akao T, Tsuchiya N, Kumazawa T, Kakinuma H, Satoh S, et al. Transitional cell carcinoma in an ectopic ureter. Int J Urol. 2003;10(5):276-7.
3. Slaoui A, Regragui S, Lasri A, Karmouni T, El Khader K, Koutani A, et al. Zinner's syndrome: report of two cases and review of the literature. Basic Clin Androl. 2016;26:10.
4. van den Ouden D, Blom JH, Bangma C, Spiegeleer AH. Diagnosis and management of seminal vesicle cysts associated with ipsilateral renal agenesis: a pooled analysis of 52 cases. Eur Urol. 1998;33(5):433-40.
5. Uder M, Siemer S, Gohl D, Schneider G, Kramann B, Humke U. Seminal vesicle cysts associated with ipsilateral renal agenesis. Diagnosis, and long-term clinical course. Radiologe. 1998;38(9):766-73.
6. Kord E, Zisman A, Darawsha AE, Dally N, Noh PH, Neheman A. Minimally invasive approach for treatment of seminal vesicle cyst associated with ipsilateral renal agenesis. Urol Int. 2017;99(3):338-42.
7. Kim Y, Baek HW, Choi E, Moon KC. Squamous cell carcinoma of the seminal vesicle from zinner syndrome: a case report and review of literature. J Pathol Transl Med. 2015;49(1):85-8.
8. Okada Y, Tanaka H, Takeuchi H, Yoshida O. Papillary adenocarcinoma in a seminal vesicle cyst associated with ipsilateral renal agenesis: a case report. J Urol. 1992;148(5):1543-5.
9. Lee BH, Seo JW, Han YH, Kim YH, Cha SJ. Primary mucinous adenocarcinoma of a seminal vesicle cyst associated with ectopic ureter and ipsilateral renal agenesis: a case report. Korean J Radiol. 2007;8(3):258-61.
10. Jaidane M, Slama A, Bibi M. A tumor of an ectopic ureter mimicking uterine cervix adenocarcinoma: case report and brief review. Int Urogynecol J Pelvic Floor Dysfunct. 2009;20(11):1393-5.
11. Nakai Y, Tanaka M, Yoshikawa M, Tanaka N, Hirayama A, Fujimoto K, et al. Prostate cancer and left ectopic ureter opening to seminal vesicle with left renal agenesis: a case report. Hinyokika Kiyo. 2009;55(1):47-50.
12. Shenoy S, Hovsepian D, Brennan DC, Hudson MA, Howard TK, Flye MW. Anomalous ureteral insertion in VATER syndrome complicating renal transplantation. Clin Transplant. 1995;9(2):125-8.

REVIEW ARTICLE

Immunological aspects of coronavirus disease during pregnancy: an integrative review

Camila Radelley Azevedo Costa da Silva[1]
Lisiane Vital de Oliveira[2]
Lorenna Peixoto Lopes[1,2]
Wancler Albert Gomes dos Santos[3]
Isabela Karine Rodrigues Agra[1,2]

1. Faculdade de Medicina – Universidade Federal de Alagoas, Maceió, AL, Brasil.
2. Faculdade de Medicina – Centro Universitário CESMAC, Maceió, AL, Brasil.
3. Santa Casa de Misericórdia de Maceió, Maceió, AL, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.696

SUMMARY

OBJECTIVE: *To review the immunological aspects of the 2019 coronavirus disease (COVID-19) in pregnancy, based on the scientific evidence currently available.*

METHODS: *An integrative review was performed by two independent researchers, based on the literature available in the MEDLINE (via PubMed) and LILACS databases, using the descriptors "pregnancy" and "COVID-19". This search included articles published up until 14th April 2020 published in English, Spanish or Portuguese. After reading the articles available in their entirety, those related specifically to the immunological aspects of the disease in pregnancy were selected. We initially found a total of 62 articles; 52 were accessed in full-text, and 5 were finally selected.*

RESULTS: *Pregnant women are more affected by respiratory diseases possibly because of physiological, immune, and anatomical changes. Some studies highlight the important shift to a T-helper lymphocyte type 2 (Th2) immune response in pregnancy, as a potential contributor to the severity in cases of COVID-19. Additionally, the cytokine storm present in severe cases leads to an increased inflammatory state, which may deteriorate the clinical prognosis in this population. Therefore, pregnant women may represent a vulnerable group to COVID-19 infection, primarily due to the immune imbalance in the maternal-fetal interface.*

CONCLUSION: *Maternal immune response probably plays an important role in the pathophysiology of this infection, although some details remain unsolved. Although further studies are needed to deeply investigate the immunological aspects of the disease in pregnancy, our findings may provide insights into the possible immune mechanisms involved in the pathophysiology of COVID-19 in pregnancy.*

KEYWORDS: *Pregnancy. Immunity. COVID-19. Coronavirus infections. Pandemics.*

INTRODUCTION

In December 2019, a new type of coronavirus was identified as the cause of a pneumonia outbreak of unknown etiology in Wuhan, China[1]. The World Health Organization (WHO) has officially named the disease 2019 coronavirus disease (COVID-19) and the virus-related disorder "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2)[2,3]. Despite the efforts taken to control the pathogen, COVID-19 was considered a pandemic by the WHO on 11th March 2020.

DATE OF SUBMISSION: 25-Apr-2020
DATE OF ACCEPTANCE: 29-Apr-2020
CORRESPONDING AUTHOR: Isabela Karine Rodrigues Agra
Faculdade de Medicina da Universidade Federal de Alagoas (UFAL) - Campus A. C. Simões
Av. Lourival Melo Mota s/n, Tabuleiro dos Martins, Maceió, AL, Brasil - 57072-900
Tel: +55 82 3214-1858
E-mail: agraisabela@gmail.com

This new RNA coronavirus, which can be rapidly transmitted via airborne and interpersonal contact, can cause mild upper respiratory tract infection with fever, cough, and lower respiratory tract infection that can evolve to severe cases and life-threatening pneumonia with acute respiratory distress syndrome[4]. Despite having some similarities with other coronaviruses, SARS-CoV-2 is more contagious than other pathogens and currently, there is no effective target treatment for this virus[5].

Up until 14th April 2020, Brasil had reported 25,262 confirmed cases and 1,532 deaths from COVID-19, which corresponds to a lethality rate of 6,1%[6]. Most of the cases were concentrated in the Southeast region, followed by the Northeast and South regions. Among the Federated Units, São Paulo presented the largest number of confirmed cases of the disease[6]. The Brazilian epidemiological bulletin did not provide information specifically regarding the number of cases involving pregnant women; instead, it considered the inclusion of pregnant and post-partum women in high-risk groups[7].

The published data on COVID-19 during pregnancy are still limited, but it is well known that it represents a group of interest and a high-risk population during infectious respiratory disease outbreaks[8]. This may be due to physiological and mechanical modifications, such as increased oxygen consumption, edema of the respiratory mucosa, the elevation of the diaphragm, and altered pulmonary volumes[9,10]. These changes contribute to reduced total lung capacity at term and inability to clear pulmonary secretions effectively[11]. Besides that, these physiological modifications of the maternal organism may contribute to delay the COVID-19 diagnostics in pregnancy, since classic symptoms can be mistaken by gestational complaints.

Additionally to these mechanical alterations, immunological adaptations are necessary to ensure maternal tolerance to the fetus – such as the down-regulation of lymphocyte proliferation and activation –, contributing to transform pregnant women into a more vulnerable group[12]. External stimulation, especially virus infection, may cause serious disorders in this complex immune balance at the maternal-fetal interface and can be related to the unique aspects of SARS-CoV-2 infection in this specific group.

Therefore, in this review, we focused on the immunological aspects of COVID-19 during pregnancy and the great challenge that this infection represents to the immune system.

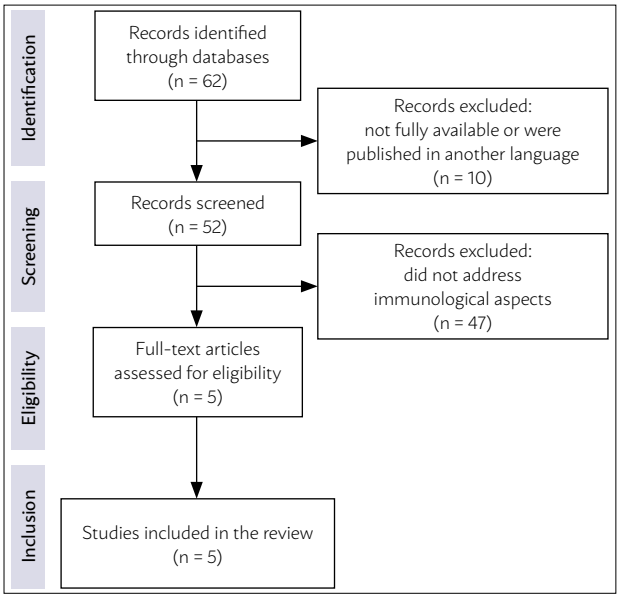
METHODS

This integrative literature review was conducted in the Medical Literature Analysis and Retrieval System on-line (Medline, through access to the PubMed) and in the Latin America and Caribbean Health Sciences Literature (Lilacs) databases. The descriptors – and their combination in Portuguese and English – used were "pregnancy" and "COVID-19", crossed using the Boolean operator "AND". This search was not restricted to any year of publication and included articles published up until 14th April 2020.

The inclusion criteria defined was to first select articles published in English, Spanish, or Portuguese. Initially, articles that were not available on the internet databases in its entirety or were written in languages other than those mentioned above were excluded. Then, after reading the full extent of the articles, those that did not address specifically to the immunological aspects of COVID-19 infection in pregnancy were also excluded. For that, two independent researchers executed the search strategy in the scientific databases, and if there were disagreements regarding the final inclusion, a third senior researcher was consulted.

This review was performed according to a standard protocol for systematic reviews, which was based on the methodological manuals of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). We initially found a total of 62 articles; 52 were accessed in full-text and, according to the inclusion and exclusion criteria adopted, 5 papers were finally selected. Figure 1 summarizes study selection.

FIGURE 1. PRISMA 2009 FLOWCHART FOR INCLUSION OF ARTICLES ON THE IMMUNOLOGICAL ASPECTS OF COVID-19 IN PREGNANCY.



RESULTS

The articles selected are shown in Table 1, which summarizes their information, methodologies, and main results.

DISCUSSION

Pregnancy is a unique immunological state, in which intricate processes take place physiologically in the maternal-fetal interface. When this fragile balance is disturbed by infections, this system can collapse. There is little evidence regarding the immune adaptation to SARS-CoV-2 infection in pregnancy, which highlights the importance of this review. There is still no robust publication, based on currently available scientific evidence, related to the specific immune aspects of COVID-19 in pregnant women. Therefore, we selected all studies relating to immunity, COVID-19, and pregnancy, in spite of the study design. All publications that were included correspond to narrative reviews, lacking details and methodological information about the selection of data.

Chen et al.[13] and Dashraath et al.[8] mentioned that pregnant women are known to be disproportionately affected by respiratory illness and cases involving this population are more associated with increased morbidity and mortality. As pregnancy progresses, its physiological adaptations – such as elevation of the diaphragm, compression of the thoracic cage, and altered pulmonary volumes – lead to shortness of breath, inability to clear pulmonary secretions effectively, and greater risk of severe infections in this group[8,13].

Additionally, Liu et al.[14] reported that, throughout pregnancy, the maternal immune system faces great challenges to establish and maintain tolerance to the allogeneic fetus, preserving the ability for protection against microbial agents. A successful pregnancy relies on the ability to maintain this balance. For that, it is well known that the female pregnant body has the skill to shift from a pro-inflammatory to an anti-inflammatory state depending on the pregnancy needs[17].

Therefore, Jiao[15] postulated that, at different stages of pregnancy, the hormone level and immune status are distinct. In early pregnancy, for example, the author suggested that the immune balance is still unstable, which can result in serious immune system disorder and internal environment imbalance in case of a viral infection, leading to abortion or abnormal fetal growth, similar to that described in other respiratory infections[18]. As the pregnancy progresses, the mother is constantly adjusting this immune balance, with theoretically less severity, according to this author[15].

Concerning this immunological adjustment, in healthy pregnancies, there is a physiological shift to

TABLE 1. PUBLICATIONS INCLUDED IN THIS INTEGRATIVE REVIEW

Author, Year	Study Design	Main Results
Dashraath et al.[8] 2020	Narrative Review	Pregnant women are known to be more affected by respiratory illness, which is associated with increased morbidity and mortality rates. In pregnancy, the physiological shift to a Th2 dominant environment contributes to overall infections by increasing maternal susceptibility to intracellular pathogens like viruses. Patients with SARS showed preferential activation of lymphocyte T-helper type 1 (pro-inflammatory) response. Authors postulated that transition to a lymphocyte T-helper type 2 environment in pregnancy, favoring the expression of anti-inflammatory cytokines, may result in milder cases of COVID-19 in pregnancy.
Chen et al.[13] 2020	Narrative Review	Pregnant women are more susceptible to the virus due to immune and anatomic alteration. Alterations in cellular immunity, such as down-regulation of lymphocyte proliferation and activation, are primarily aimed at adopting maternal immune tolerance to the fetus. Despite the limited sample sizes of the studies analyzed, the authors suggest a higher fatality rate in the pregnant population.
Liu et al.[14] 2020	Narrative Review	Pregnant women represent a uniquely vulnerable group in any infectious disease outbreak due to their altered physiology, compromised mechanical and immunological functions. The COVID-19 infection is associated with a cytokine-storm, which leads to an important increase of inflammatory mediators at the maternal-fetal interface. As a result, pregnant women may face severe morbidity and mortality.
Jiao[15] 2020	Narrative Review	Update on the issues that may be faced by different groups of pregnant populations: late, middle, and early pregnancy, as the maternal immune response varies during the different stages of pregnancy. In early pregnancy, the immune system is very sensitive and unstable, favoring more severe infections and serious immune fetal and maternal disorders. The author recommended first and second-trimester follow-ups to anticipate those risks.
Ashokka et al.[16] 2020	Narrative Review	Given the limited knowledge about this novel coronavirus, which has both similarities and differences to SARS-CoV-1 and MERS-CoV, the authors provided a general guide based upon currently available evidence. They also postulated that cytokine-storm, leading to an increase in levels of inflammatory mediators, is associated with disease severity and admission in ICU.

COVID-19: 2019 coronavirus disease; ICU: Intensive Care Unit; SARS: Severe Acute Respiratory Syndrome.

a pattern of cytokines produced by T-helper lymphocyte type 2 (Th2), characterized by anti-inflammatory substances, such as interleukin (IL) 4, IL-10, IL-13 and transforming growth factor-beta (TGF-beta)[19]. Dashraath et al.[8] reported that this shift to a Th2-dominant environment may contribute to overall infection morbidity by increasing maternal susceptibility to intracellular pathogens like viruses.

In COVID-19 infection, recent literature indicates that in severe cases there is a cytokine-storm, which is characterized by increased concentrations of important plasma mediators, such as IL-2, IL-7, IL-10, granulocyte-colony stimulating factor, interferon-alfa-inducible protein 10, and tumor of necrosis factor alfa, most of them related to an inflammatory response[14,20]. Liu et al.[14] declared that, based on the knowledge that the first and third trimesters of pregnancy constitute pro-inflammatory states, cytokine-storm induced by SARS-CoV-2 may induce a more severe inflammatory state in these women. Ashokka et al.[16] also found that cytokine-storms are known to be associated with disease severity and admissions at Intensive Care Units (ICU).

In contrast, Dashraath et al.[8] postulated that the physiological transition to a Th2 anti-inflammatory environment during pregnancy and other unidentified immune adaptations may serve as the predominant immune response to SARS-CoV-2, resulting in a lesser severe presentation of COVID-19 in this group. These findings are in consonance with the scarce current literature that affirms that, despite being placed in high-risk groups mainly due to precautionary measures, cases of COVID-19 among pregnant women may not present greater severity and worse clinical outcomes than the general population[21].

Overall, due to the lack of appropriate data about the effects of COVID-19 on the immune response during pregnancy, some aspects remain unsolved until proper evidence-based articles with a large number of cases are published.

CONCLUSION

The global attention related to the continuing of the COVID-19 pandemic and dissemination of this disease in the vulnerable population makes it even more important to discuss the peculiarities of this infection in pregnant women. The maternal immune response probably plays an important role in the pathophysiology of this infection, although some details remain unsolved.

Further studies are warranted to investigate the immunological aspects of COVID-19 in pregnancy. However, our findings may provide insights into possible immune mechanisms involved in the pathophysiology of COVID-19 in pregnancy.

Authors' contributions

Camila R. A. C. da Silva: Data management/analysis, manuscript writing; Lisiane V. de Oliveira: Data management/analysis, manuscript writing; Lorenna P. Lopes: Project development, data management/analysis, manuscript writing; Wancler A. G. Santos: Data management/analysis, manuscript editing; Isabela K. R. Agra: Project development, data management/analysis, manuscript editing.

RESUMO

OBJETIVOS: *Revisar o conhecimento atual sobre os aspectos imunológicos da infecção por coronavírus 2019 (COVID-19) na gravidez, com base nas evidências científicas recentes.*

MÉTODOS: *Uma revisão integrativa foi realizada por dois pesquisadores independentes, com base na literatura disponível nas bases de dados MEDLINE (via PubMed) e LILACS, utilizando os descritores "gravidez" e "COVID-19". Esta pesquisa incluiu artigos publicados até 14 de abril de 2020, publicados em inglês, espanhol ou português. Após a leitura integral dos artigos, foram selecionados aqueles relacionados especificamente aos aspectos imunológicos da doença na gravidez. Encontramos inicialmente um total de 62 artigos; 52 foram acessados em texto completo e 5 artigos foram finalmente selecionados.*

RESULTADOS: *As gestantes são sabidamente mais afetadas por doenças respiratórias, devido a alterações imunológicas e anatômicas fisiológicas. Alguns estudos destacam a importante mudança para uma resposta imune linfocitária T do tipo 2 (Th2) na gravidez, como potencial contribuinte para a gravidade nos casos de COVID-19. Além disso, a tempestade de citocinas apresentada em casos graves da doença leva a um aumento do estado inflamatório, que pode deteriorar o prognóstico clínico nessa população. Portanto, as mulheres grávidas podem representar um grupo vulnerável à infecção por COVID-19, principalmente devido ao desequilíbrio imunológico na interface fetal materna.*

CONCLUSÃO: *A resposta imune materna provavelmente desempenha um papel importante na fisiopatologia dessa infecção, apesar de alguns detalhes permanecerem sem solução. Embora sejam necessários mais estudos para investigar profundamente os aspectos imunológicos da doença na gravidez, nossos achados podem fornecer informações sobre possíveis mecanismos imunológicos envolvidos na fisiopatologia do COVID-19 na gravidez.*

PALAVRAS-CHAVES: *Gravidez. Imunidade. COVID-19. Infecções por coronavirus. Pandemias.*

REFERENCES

1. Anesi GL. Coronavirus disease 2019 (COVID-19): critical care issues. UpToDate 2020. [cited 2020 Apr 24]. Available from: https://www.uptodate.com/contents/coronavirus-disease-2019-covid-19-critical-care-issues
2. World Health Organization. Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. [cited 2020 Apr 24]. Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020
3. Wang L, Wang Y, Ye D, Liu Q. Review of the 2019 novel coronavirus (SARS-CoV-2) based on current evidence. Int J Antimicrob Agents. 2020;105948. doi:10.1016/j.ijantimicag.2020.105948.
4. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of 2019 novel coronavirus infection in China. N Engl J Med. 2020;382(18):1708-20.
5. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-74.
6. Brasil. Ministério da Saúde, Secretaria de Vigilância em Saúde. Situação epidemiológica da COVID-19: doença pelo coronavírus 2019. Boletim Epidemiológico 09 do Centro de Operações em Emergência em Saúde Pública. 2020. [cited 2020 Apr 20]. Available from: https://portalarquivos.saude.gov.br/images/pdf/2020/April/12/2020-04-11-BE9-Boletim-do-COE.pdf
7. Brasil. Ministério da Saúde. Secretaria de Atenção Especializada à Saúde. Protocolo de manejo clínico da Covid-19 na Atenção Especializada. Brasília: Ministério da Saúde; 2020. [cited 2020 Apr 20]. Available from: https://portalarquivos.saude.gov.br/images/pdf/2020/April/14/Protocolo-de-Manejo-Cl--nico-para-o-Covid-19.pdf
8. Dashraath P, Wong JLJ, Lim MXK, Lim LM, Li S, Biswas A, et al. Coronavirus disease 2019 (COVID-19) pandemic and pregnancy. Am J Obstet Gynecol. 2020; S0002-9378(20)30343-4. doi:10.1016/j.ajog.2020.03.021
9. Li N, Han L, Peng M, Lv Y, Ouyang Y, Liu K, et al. Maternal and neonatal outcomes of pregnant women with COVID-19 pneumonia: a case-control study. Clin Infect Dis. 2020;ciaa352. doi:10.1093/cid/ciaa352.
10. Qiao J. What are the risks of COVID-19 infection in pregnant women? Lancet. 2020;395(10226):760-2.
11. Gardner MO, Doyler NM. Asthma in pregnancy. Obstet Gynecol Clin North Am. 2004;31(2):385-413.
12. Hanssens S, Salzet M, Vinatier D. Immunological aspect of pregnancy. J Gynecol Obstet Biol Reprod. 2012;41(7):595-611.
13. Chen Y, Li Z, Zhang YY, Zhao WH, Yu ZY. Maternal health care management during the outbreak of coronavirus disease 2019. J Med Virol. 2020;10.1002/jmv.25787. doi:10.1002/jmv.25787.
14. Liu H, Wang LL, Zhao SJ, Kwak-Kim J, Mor G, Liao AH. Why are pregnant women susceptible to COVID-19? An immunological viewpoint. J Reprod Immunol. 2020;139:103122. doi:10.1016/j.jri.2020.103122.
15. Jiao J. Under the epidemic situation of COVID-19, should special attention to pregnant women be given? J Med Virol. 2020;10.1002/jmv.25771.
16. Ashokka B, Loh MH, Tan CH, Su LL, Young BE, Lye DC, et al. Care of the pregnant woman with COVID-19 in labor and delivery: anesthesia, emergency cesarean delivery, differential diagnosis in the acutely ill parturient, care of the newborn, and protection of the healthcare personnel. Am J Obstet Gynecol. 2020;S0002-9378(20)30430-0. doi:10.1016/j.ajog.2020.04.005.
17. Mor G, Aldo P, Alvero AB. The unique immunological and microbial aspects of pregnancy. Nat Rev Immunol. 2017;17(8):469-82.
18. Wong SF, Chow KM, Leung TN, Ng WF, Ng TK, Shek CC, et al. Pregnancy and perinatal outcomes of women with severe acute respiratory syndrome. Am J Obstet Gynecol. 2004;191(1):292-7.
19. Nelson-Piercy C. Respiratory disease. In: Handbook of obstetric medicine. 5th ed. Boca Raton: CRC Press; 2015. p.63-84.
20. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
21. Panahi L, Amiri M, Pouy S. Risks of novel coronavirus disease (COVID-19) in pregnancy: a narrative review. Arch Acad Emerg Med. 2020;8(1):e34.

REVIEW ARTICLE

Residual lesions in patients who underwent microsurgical clipping of cerebral aneurysms

Guilherme Brasileiro de Aguiar[1]
Matheus Kohama Kormanski[2]
Andrew Vinícius de Souza Batista[3]
Mario Luiz Marques Conti[4]
José Carlos Esteves Veiga[5]

1. Mestre, Neurocirurgião/Neurorradiologista Intervencionista e Professor, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FMSCSP), SP, Brasil.
2. Estudante de Medicina. Faculdade de Ciências Médicas da Santa Casa de São Paulo (FMSCSP), SP, Brasil.
3. Residente de Neurocirurgia, FAculdade de Ciências Médicas da Santa Casa de São Paulo (FMSCSP), SP, Brasil.
4. Doutor, Neurocirurgião/Neurorradiologista Intervencionista e Professor, Faculdade de Ciências Médicas da Santa Casa de São Paulo (FMSCSP), SP, Brasil.
5. Doutor, Professor Titular da Disciplina de Neurocirurgia da Faculdade de Ciências Médicas da Santa Casa de São Paulo (FMSCSP), SP, Brasil.

http://dx.doi.org/10.1590/1806-9282.66.5.701

SUMMARY

Microsurgical clipping is currently the main method of treating cerebral aneurysms, even with the improvement of endovascular therapy techniques in recent years. Treatment aims at complete occlusion of the lesion, which is not always feasible. Although appearing superior to endovascular treatment, microsurgical clipping may present varying percentages of incomplete occlusion. Such incidence may be reduced with the use of intraoperative vascular study. Some classifications were elaborated in an attempt to standardize the characteristics of residual lesions, but the classification criteria and terminology used in the studies remain vague and poorly documented, and there is no consensus for a uniform classification. Thus, there is also no agrément on which residual aneurysms should be treated. The aim of this study is to review the literature on residual lesions after microsurgery to treat cerebral aneurysms and how to proceed with them.

KEYWORDS: *Intracranial aneurysm. Cerebral angiography. Microsurgery. Treatment failure. Reoperation.*

INTRODUCTION

Microsurgical clipping remains the main therapeutic method used in brain aneurysms, despite the advancement in endovascular therapy techniques in recent years[1]. The aim of the treatment is to promote the complete occlusion of the lesions, thus avoiding future bleeding and preserving the flow of the artery involved. However, it is not always possible to guarantee total occlusion of the aneurysm, so the prevalence of residual lesions may be more than one-third of the cases in some studies. In the literature studied, we observed a great variability of this data, with values ranging from 1.6% to 42%[1-3].

Some factors are related to a higher incidence of residual lesions, such as the size and morphology of the aneurysm, its location and the relationship with the vessel, the number of clips used during the procedure, and the age of the patient[1,4]. In general, the incomplete treatment of aneurysms may be associated with ruptures of these lesions and a consequent increase in morbidity and mortality[2]. The objective of this study is to conduct a review of the literature regarding residual lesions after microsurgery for the treatment of cerebral aneurysms and how to proceed when faced with this finding.

DATE OF SUBMISSION: 14-Sep-2019
DATE OF ACCEPTANCE: 10-Oct-2019
CORRESPONDING AUTHOR: Guilherme Brasileiro de Aguiar
Faculdade de Ciências Médicas da Santa Casa de São Paulo, Departamento de Cirurgia - Disciplina de Neurocirurgia
Rua Dr. Cesário Motta Júnior, 61, Vila Buarque, SP, Brasil - CEP: 01221-020
Tel: +55 11 3367-7700
E-mail: guilhermebraguiar@yahoo.com.br

METHODS

This is a descriptive study of the literature available in the Medline/PubMed databases. For the search, we used the English terms "intracranial aneurysm", "microsurgical clipping", "cerebral angiography", and "aneurysm remnant". The papers considered relevant were included in this review, as well as the works referenced therein, in order to sensitize the method. Duplicated papers were discarded.

DISCUSSION

The follow-up of patients with cerebral aneurysmal disease treated by microsurgery or endovascular technique must include, ideally, imaging control to identify the presence and growth of residual lesions as well as the emergence of new aneurysms[5-7]. This care should be provided particularly for young patients, who have greater life expectancy[8].

The study by Dellaretti et al.[4], conducted with 90 patients treated by microsurgery, showed a likelihood of bleeding of residual necks of 0.38-0.79% per year [4], while the studies by David et al.[8] and Jabbarli et al.[1] reported a risk of 1.5% and 1.9% per year, respectively. In addition to the risk of bleeding, in the casuistry presented by Brown et al.[9], there was an increase in the size of residual lesions in 13.6% of the cases treated by microsurgery.

Thus, even in cases in which aneurysm clipping is considered complete in the intraoperative period and in the control angiography, long-term monitoring demonstrates there is a risk of lesion recurrence and spontaneous bleeding[2,10,11]. Sindou et al.[3] highlight the cases of aneurysms considered "giant" or of difficult access, for which the benefits of control examination outweigh the risks inherent to invasive diagnostic procedures. The time required for the follow-up of these patients, however, is still not well defined in the literature[1] and may be up to ten years.

Residual lesions should be evaluated based on imaging tests that allow for the best morphological characterization. Cerebral arteriography is the method of choice, despite the risks associated with the procedure[11-13]. In addition to confirming the complete occlusion of aneurysms, it is the main exam to assess the presence of residual necks, follow the growth of lesions, detect incorrect positioning of clips, as well as diagnose the presence of new aneurysms[14.15]. Angiotomography and magnetic resonance angiography use noninvasive techniques for evaluating the vascular anatomy of the brain, but are less reliable to detect residual necks than angiography and should not be used alone to rule out lesions in order to avoid false negatives[11.12].

Due to the morphological variety of aneurysms and formats of clips currently available, residual lesions may have different characteristics. Figure 1 outlines some possible presentations of residual necks due to incomplete clipping of the aneurysm, and Figure 2 shows the arteriographies of the three illustrative cases. Several systems have been developed over the years in an attempt to standardize the characteristics of residual lesions like these, but the classification criteria and the terminology used in different works

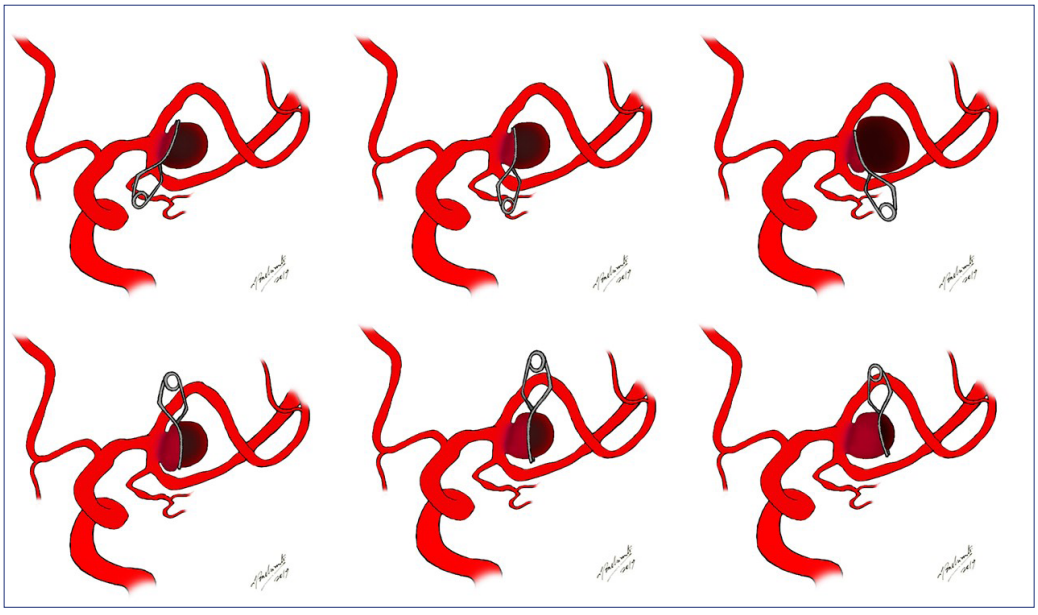


FIGURE 1. SCHEMATIC REPRESENTATION OF BIFURCATION ANEURYSM OF THE MIDDLE CEREBRAL ARTERY, SHOWING DIFFERENT POSSIBILITIES OF RESIDUAL LESIONS (ADAPTED FROM SINDOU ET AL[3] AND DAVID ET AL[8]).

remain vague and poorly documented[16]. The most famous and used system was developed by Sindou et al.[3], in 1998, and separates the morphology of residual lesions into five categories: I - less than 50% of the neck of the aneurysm; II - over 50% of the neck of the aneurysm; III - residual lobe in a multilobed aneurysmal sac; IV - residual sec smaller than 75%; V - residual sac bigger than 75%. The division proposed establishes that lesions classified as I and II benefit less from a new procedure, while lesions III to V should be considered for microsurgical or endovascular retreatment[3].

Another existing classification, proposed by David et al.[8], in 1999, divides the residual aneurysms into two possible morphologies. In the dog ear residua variant, which corresponded to 8 of the 12 residual necks obtained in this study, a small residual portion of the aneurysm can be seen between the vessel and the clip, presenting an annual risk of hemorrhage of up to 1.9%[8]. This would be the variant with a greater risk of in the short term. The other variant is the broad-based residua, in which the aneurysm encompasses a more extensive portion of the circumference of the vessel. Although no bleeding occurred in the lesions classified in the second subgroup, the study considered that the lesions of the broad-based residua type presented higher growth in comparison with the first variant[8].

More recent systems have been proposed in an attempt to standardize the nomenclature and classification criteria, but none is completely validated or reliable; thus, there is no consensus in the current literature[16].

In the studies analyzed, the prevalence of reported residual lesions ranged from 1.6% to 42%[1-3], which denotes great heterogeneity among the results. In the study by Sindou et al.[3], published in 1998, 246 patients were submitted to the surgical clipping of 305 intracranial lesions, resulting in a percentage of 5.9% residual lesions. A more recent study by Jabbarli et al.[1] showed a percentage of 18.2% in the first postoperative control angiography[1], corresponding to 112 incomplete clippings out of the 616 lesions treated. More recently, the use of intraoperative vascular study using indocyanine green and the routine use of intraoperative subtraction angiography in hybrid operating rooms has contributed to the reduction in cases of incomplete microsurgical treatment of aneurysms[17,18] and, although results are promising, such techniques are not available in most services.

From the advent of endovascular therapy for brain aneurysms, in the 1990s, the comparison between this new treatment modality and the microsurgical approach, previously established, became frequent[1,19]. One of the main divergent aspects between the techniques is precisely the rate of complete and permanent aneurysm occlusion.

In the ISAT (International Subarachnoid Aneurysm Trial)[20] study, published in 2005, 2,143 patients with

FIGURE 2

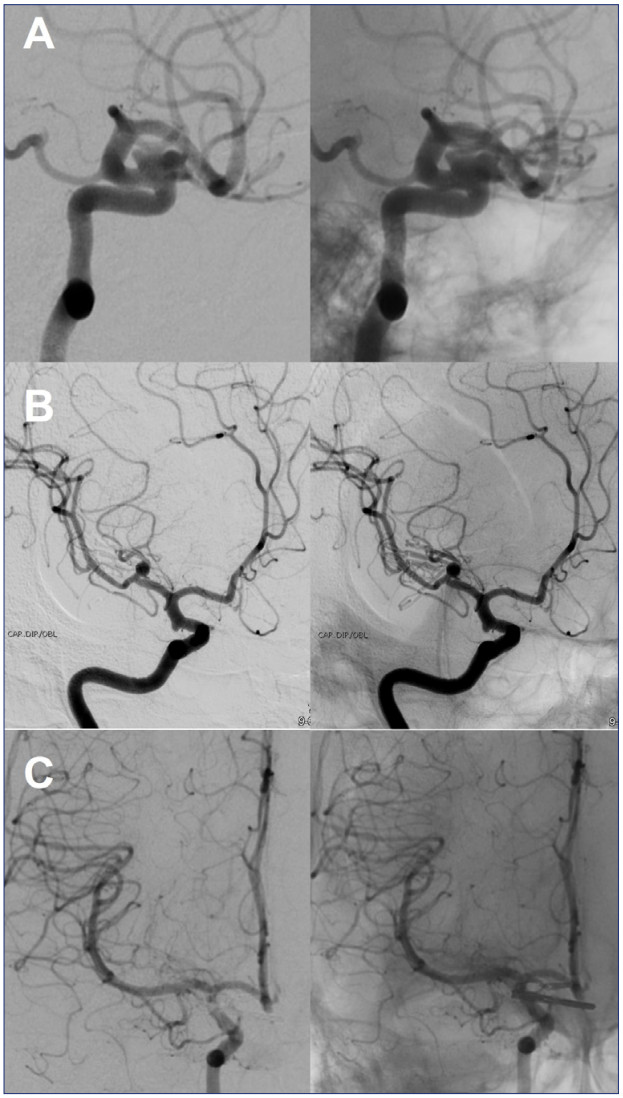


FIGURE 2. ARTERIOGRAPHY OF CAROTID ARTERIES OBTAINED AFTER MICROSURGICAL TREATMENT OF CEREBRAL ANEURYSMS, SHOWING RESIDUAL LESIONS. FIGURE A SHOWS THE INCOMPLETE CLIPPING OF THE OPHTHALMIC SEGMENT ANEURYSM OF THE INTERNAL CAROTID ARTERY; B SHOWS A RESIDUAL ANEURYSM IN THE M1 SEGMENT OF THE MIDDLE CEREBRAL ARTERY; C ILLUSTRATES A RESIDUAL LESION IN AN ANTERIOR INTERCONNECTING ANEURYSM COMPLEX (IMAGES WITH AND WITHOUT DIGITAL SUBTRACTION ARE REPRESENTED IN THE FIRST AND SECOND COLUMNS, RESPECTIVELY).

ruptured intracranial aneurysms were randomized to receive microsurgical or endovascular treatment. Among the cases submitted to endovascular therapy, follow-up angiographies showed 8% of residual necks, with 26% of subtotal occlusion, and 66% of total occlusion. The angiographies performed in patients post-microsurgical clipping, on the other hand, showed a rate of 6% of incomplete occlusions, 12% of subtotal occlusions, and 82% of complete occlusions.

In 2009, new data derived from the ISAT study were published regarding the long-term follow-up of patients[14]. With an average of nine years of angiography follow-up, the study showed a higher rate of rebleeding in patients submitted to endovascular therapy in comparison to those who underwent the surgical approach, although no statistical difference was found between the groups regarding post-treatment mortality from bleeding[14]. Curiously, the work by Yu et al.[21] indicates that the residual aneurysms after microsurgery have a greater tendency of bleeding than after endovascular treatment.

More recently, a meta-analysis published by Li et al.[19] that used four clinical trials and 23 observational studies on the two modalities of treatment showed greater benefits from microsurgical clipping for the complete occlusion of aneurysms and in reducing the risk of bleeding. Endovascular therapy showed positive results in patients with good preoperative status, but the technique was inferior to microsurgery in the main outcomes evaluated by the study[19].

The indications for the treatment of residual lesions - either after microsurgery or embolization - are still controversial and lack of evidence to justify the risks of a new approach[2]. However, due to the risk of hemorrhage, David's "dog-ear residua" lesions and Sindou's classes IV and V should be evaluated carefully for retreatment aiming at their complete occlusion. Lesions with less risk of rebleeding must be followed-up by imaging exams.

FINAL CONSIDERATIONS

The literature regarding the treatment of intracranial aneurysms and the management of residual necks proved to be heterogeneous and inconclusive in several aspects, especially with regard to the monitoring, classification, and approach of residual lesions. Despite these differences, the revision of studies allows us to affirm that vascular studies based on neuroimaging methods are mandatory for follow-up after microsurgery to evaluate the complete occlusion of the lesions and the emergence of new aneurysms. The rates of incomplete occlusion are variable but, in general, low. The treatment is indicated for residual lesions with a higher chance of rupture. For lesions of lower risk, a series of follow-up imaging exams is recommended.

Statement of conflict of interests

All the authors declare complete and total exemption from any conflict of interest with any commercial product, equipment, or company.

Authors' contributions

Guilherme Brasileiro de Aguiar: Concept, methodology design, collection of data, drafting of the manuscript; Matheus Kohama Kormanski: Concept, methodology design, collection of data, drafting of the manuscript; Andrew Vinícius de Souza Batista: Concept, methodology design, collection of data, drafting of the manuscript; Mario Luiz Marques Conti: Concept, revision of the text; José Carlos Esteves Veiga: Concept, methodology design, revision of the text.

RESUMO

A clipagem microcirúrgica é, atualmente, o principal método de tratamento dos aneurismas cerebrais, mesmo com o aprimoramento das técnicas de terapia endovascular nos últimos anos. O tratamento visa à oclusão completa da lesão, o que nem sempre é factível. Apesar de parecer superior ao tratamento endovascular, a clipagem microcirúrgica pode apresentar porcentagens variadas de oclusão incompleta. Tal incidência pode ser reduzida com utilização de estudo vascular intraoperatório. Algumas classificações foram elaboradas na tentativa de padronizar as características das lesões residuais, mas os critérios de classificação e a terminologia utilizados nos trabalhos mantêm-se vagos e pobremente documentados, não havendo consenso para uma classificação uniforme. Dessa forma, não há também concordância sobre quais aneurismas residuais devam ser submetidos a tratamento. O objetivo do presente estudo é realizar uma revisão da literatura a respeito das lesões residuais após microcirurgia para tratamento dos aneurismas cerebrais e como proceder diante dessas.

PALAVRAS-CHAVE: *Aneurisma intracraniano. Angiografia cerebral. Microcirurgia. Falha de tratamento. Reoperação.*

REFERENCES

1. Jabbarli R, Pierscianek D, Wrede K, Dammann P, Schlamann M, Forsting M, et al. Aneurysm remnant after clipping: the risks and consequences. J Neurosurg. 2016;125(5):1249-55.
2. Johnston SC, Dowd CF, Higashida RT, Lawton MT, Duckwiler GR, Gress DR. CARAT Investigators. Predictors of rehemorrhage after treatment of ruptured intracranial aneurysms: the Cerebral Aneurysm Rerupture After Treatment (CARAT) study. Stroke. 2008;39(1):120-5.
3. Sindou M, Acevedo JC, Turjman F. Aneurysmal remnants after microsurgical clipping: classification and results from a prospective angiographic study (in a consecutive series of 305 operated intracranial aneurysms). Acta Neurochir (Wien). 1998;140(11):1153-9.
4. Dellaretti M, Silva Martins WC, Dourado JC, Faglioni Junior W, Quadros RS, de Souza Moraes VV, et al. Angiographic and epidemiological characteristics associated with aneurysm remnants after microsurgical clipping. Surg Neurol Int. 2017;8:198.
5. Tsutsumi K, Ueki K, Morita A, Usui M, Kirino T. Risk of aneurysm recurrence in patients with clipped cerebral aneurysms: results of long-term follow-up angiography. Stroke. 2001;32(5):1191-4.
6. Akyüz M, Tuncer R, Yilmaz S, Sindel T. Angiographic follow-up after surgical treatment of intracranial aneurysms. Acta Neurochir (Wien). 2004;146(3):245-50.
7. Suzuki MT, Aguiar GB, Jory M, Conti ML, Veiga JC. De novo basilar tip aneurysm. Case report and literature review. Neurocirugia (Astur). 2011;22(3):251-4.
8. David CA, Vishteh AG, Spetzler RF, Lemole M, Lawton MT, Partovi S. Late angiographic follow-up review of surgically treated aneurysms. J Neurosurg. 1999;91(3):396-401.
9. Brown MA, Parish J, Guandique CF, Payner TD, Horner T, Leipzig T, et al. A long-term study of durability and risk factors for aneurysm recurrence after microsurgical clip ligation. J Neurosurg. 2017;126(3):819-24.
10. Thornton J, Bashir Q, Aletich VA, Debrun GM, Ausman JI, Charbel FT. What percentage of surgically clipped intracranial aneurysms have residual necks? Neurosurgery. 2000;46(6):1294-8.
11. Uricchio M, Gupta S, Jakowenko N, Levito M, Vu N, Doucette J, et al. Computed tomography angiography versus digital subtraction angiography for postclipping aneurysm obliteration detection. Stroke. 2019;50(2):381-8.
12. Dündar TT, Aralaşmak A, Özdemir H, Seyithanoğlu MH, Uysal Ö, Toprak H, et al. Comparison of TOF MRA, contrast-enhanced MRA and subtracted CTA from CTP in residue evaluation of treated intracranial aneurysms. Turk Neurosurg. 2017. doi: 10.5137/1019-5149.JTN.21113-17.2.
13. Thaker NG, Turner JD, Cobb WS, Hussain I, Janjua N, He W, et al. Computed tomographic angiography versus digital subtraction angiography for the postoperative detection of residual aneurysms: a single-institution series and meta-analysis. J Neurointerv Surg. 2012;4(3):219-25.
14. Molyneux AJ, Kerr RS, Birks J, Ramzi N, Yarnold J, Sneade M, et al; ISAT Collaborators. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. Lancet Neurol. 2009;8(5):427-33.
15. Murphy M, Bell D, Worth RD, Jehle KS, Critchley GR, Norris JS. Angiography postclipping and coiling of cerebral aneurysms. Br J Neurosurg. 2005;19(3):225-8.
16. Kotowski M, Farzin B, Fahed R, Guilbert F, Chagnon M, Darsaut TE, et al. Residual cerebral aneurysms after microsurgical clipping: a new scale, an agreement study, and a systematic review of the literature. World Neurosurg. 2019;121:e302-21.
17. Doss VT, Goyal N, Humphries W, Hoit D, Arthur A, Elijovich L. Comparison of intraoperative indocyanine green angiography and digital subtraction angiography for clipping of intracranial aneurysms. Interv Neurol. 2015;3(3-4):129-34.
18. Sharma M, Ambekar S, Ahmed O, Nixon M, Sharma A, Nanda A, et al. The utility and limitations of intraoperative near-infrared indocyanine green videoangiography in aneurysm surgery. World Neurosurg. 2014;82(5):e607-13.
19. Li H, Pan R, Wang H, Rong X, Yin Z, Milgrom DP, et al. Clipping versus coiling for ruptured intracranial aneurysms: a systematic review and meta-analysis. Stroke. 2013;44(1):29-37.
20. Molyneux AJ, Kerr RS, Yu LM, Clarke M, Sneade M, Yarnold JA, et al; International Subarachnoid Aneurysm Trial (ISAT) Collaborative Group. International subarachnoid aneurysm trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised comparison of effects on survival, dependency, seizures, rebleeding, subgroups, and aneurysm occlusion. Lancet. 2005;366(9488):809-17.
21. Yu LB, Fang ZJ, Yang XJ, Zhang D. Management of residual and recurrent aneurysms after clipping or coiling: clinical characteristics, treatments, and follow-up outcomes. World Neurosurg. 2019;122:e838-46.

COMMENTARY

Manipulating miR-125a-5p to regulate cancer stem cells phenotype and epithelial to mesenchymal transition in glioblastoma

Yeqin Sha[2]
Daoyun Lei[1]
Lianping He[2]

1. Jiangsu University, Jiangsu, Zhenjiang 212013, China.
2. Department of Immunology, Nanjing medical university, Nanjing, Jiangsu 211166, China.

Yeqin Sha and Daoyun Lei contributed to this work.

http://dx.doi.org/10.1590/1806-9282.66.5.706

Dear Editor,

We read the study by Zhu X-D et al.[1] with great interest. The study demonstrated that miR-125a-5p could inhibit cancer stem cell phenotype and epithelial to mesenchymal transition in glioblastoma. The author concluded that miR-125a-5p might be a novel therapy target for glioblastoma. This study disclosed the involvement of miRNA in the progression of glioblastoma, providing potential approaches for glioblastoma treatment and prevention. Considering the high prevalence and lethality of glioblastoma in the population, it is of great clinical significance to explore novel therapeutic targets for glioblastoma treatment. However, in our opinion, more studies should be conducted so that the conclusion could be more convincing.

To begin with, different study groups have identified that lots of miRNAs play a vital role in glioblastoma pathogenesis[2] and epithelial to mesenchymal transition[3]. Therefore, the bioinformatics method is a better way of finding different expressions of miRNAs between glioblastoma tissues and adjacent normal tissues. Additionally, the results of scratch wound-healing motility assays and transwell migration assays should be displayed to confirm that miR-125a-5p may suppress migration and invasion of glioblastoma.

Although a large number of studies have revealed that miRNAs have different functions in the pathogenesis of various diseases, few miRNAs have been actually applied as a therapy target. The main advantage of the use of miRNAs as a therapy target is that they might influence different physiological and pathological conditions, including chronic inflammation and other non-tumor pathologies[4]. Therefore, further animal studies should be conducted to confirm the overall effect of miR-125a-5p on epithelial to mesenchymal transition in glioblastoma.

REFERENCES

1. Zhu X-D, Gao Z-J, Pang Q, Zheng G-D. miR-125a-5p inhibits cancer stem cells phenotype and epithelial to mesenchymal transition in glioblastoma. Rev Assoc Med Bras. 2020;66(4);445-451.
2. Ahir BK, Ozer H, Engelhard HH, Lakka SS. MicroRNAs in glioblastoma pathogenesis and therapy: a comprehensive review. Crit Rev Oncol Hematol. 2017;120:22-33.
3. McCubrey JA, Fitzgerald TL, Yang LV, Lertpiriyapong K, Steelman LS, Abrams SL, et al. Roles of GSK-3 and microRNAs on epithelial mesenchymal transition and cancer stem cells. Oncotarget. 2017;8(8):14221-50.
4. Wang H, Peng R, Wang J, Qin Z, Xue L. Circulating microRNAs as potential cancer biomarkers: the advantage and disadvantage. Clin Epigenetics. 2018;10:59.

DATE OF SUBMISSION: 24-Oct-2019
DATE OF ACCEPTANCE: 08-Nov-2019
CORRESPONDING AUTHOR: Lianping He
101 Longmian Avenue, Department of Immunology, Nanjing Medical University, Nanjing, Jiangsu, China - 211166
Tel. / Fax: +86 553 2871221
E-mail: lianpinghe@126.com

Addendum

http://dx.doi.org/10.1590/1806-9282.66.5.707

As a complement for the material regarding the "**Investigating gender differences for effectiveness and side effects of varenicline during smoking cessation treatment**" , with DOI number: http://dx.doi.org/10.1590/1806-9282.66.2.146 published in Journal of the Brazilian Medical Association, 2020;66(02), page 146, we are sending you the Disclosures and Acknowledgments below to be included.

Disclosures and Acknowledgments

Financial Support: Pfizer provided medication (varenicline) and financial support for equipment (computer and CO monitor).

Contributors Statement: VC designed the study, edited and critically reviewed the manuscript, and approved the final version of the manuscript. PDG designed the study, edited and critically reviewed the manuscript, and approved the final version of the manuscript. JMCM designed the study, edited and critically reviewed the manuscript, and approved the final version of the manuscript. AM designed the study, edited and critically reviewed the manuscript, and approved the final version of the manuscript.

Conflict of Interest Statement: Dr. Castaldelli-Maia is a grantee of Pfizer Independent Grant for Learning and Change (IGLC) managed by Global Bridges (Healthcare Alliance for Tobacco Dependence Treatment), hosted by the Mayo Clinic, to support free smoking cessation treatment training in addiction/mental health care units in Brazil (grant IGLC 13513957, PI: Castaldelli-Maia) and Portugal (grant IGLC 25629313, PI: Castaldelli-Maia), which have no relationship with the present study. All other authors have no conflict of interest.

Acknowledgment: None