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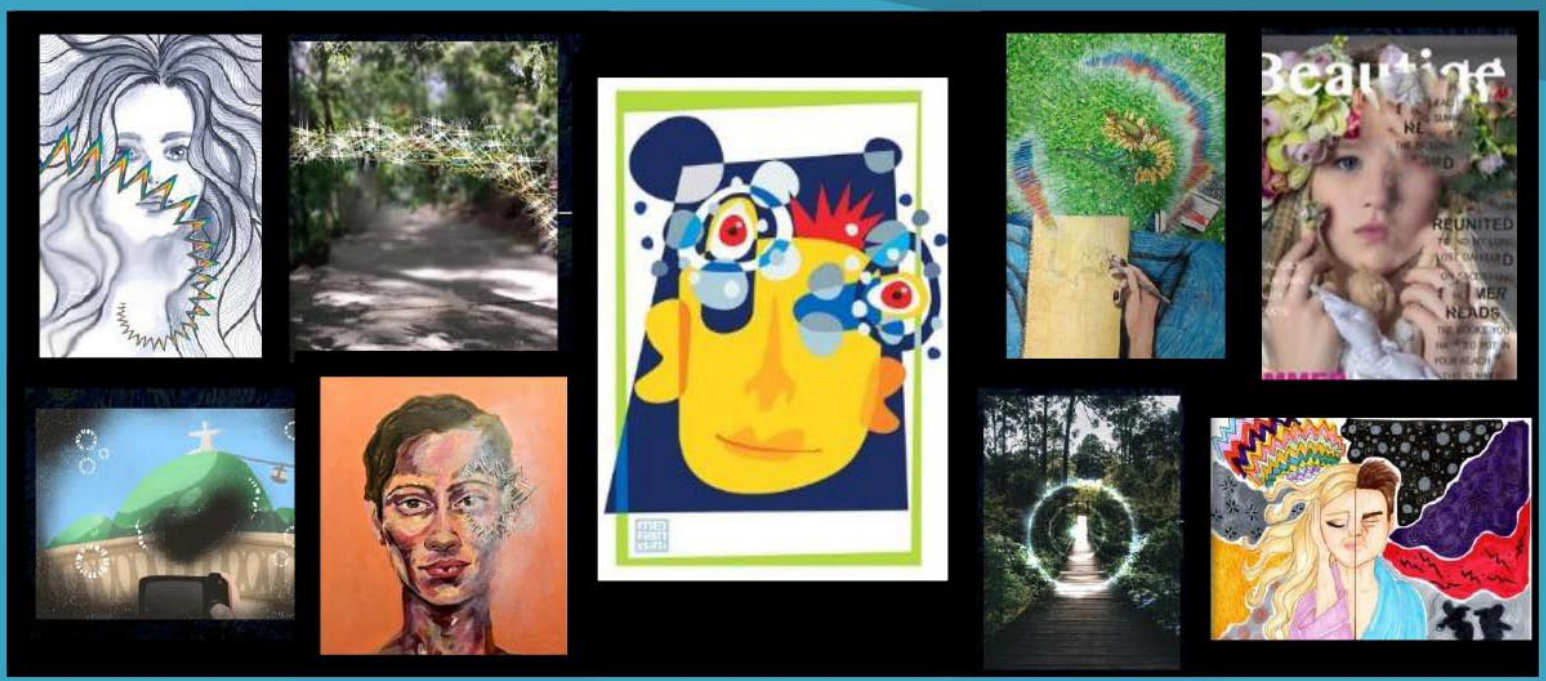
SOCIEDADE BRASILEIRA DE CEFALEIA

Brazilian Headache Society



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Scientific Publication of the Brazilian Headache Society

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A revista Headache Medicine é uma publicação de propriedade da Sociedade Brasileira de Cefaleia, indexada no Latindex e no Index Scholar, publicada pela Sociedade Brasileira de Cefaleia, www.sbcefaleia.com.br. Os manuscritos aceitos para publicação passam a pertencer à Sociedade Brasileira de Cefaleia e não podem ser reproduzidos ou publicados, mesmo em parte, sem autorização da HM & SBCe. Os artigos e correspondências deverão ser encaminhados para a HM através de submissão on-line, acesso pela página www.headachemedicine.com.br - Distribuição gratuita para os membros associados, bibliotecas regionais de Medicina e faculdades de Medicina do Brasil, e sociedades congêneres

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Editorial

Migraine surgery

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Edited by
Mario Fernando Prieto Peres

The Brazilian Headache Society hereby states its position regarding migraine surgery, a procedure created by American plastic surgeon Bahman Guyuron and that has been reported over the past months in the Brazilian media. The premise of Guyuron's technique is that there are four trigger sites for headaches in patients with Chronic Migraines, namely: frontal, temporal, occipital and rhinogenic sites[1]. Guyuron suggests that there is a muscle component and a vascular component in these regions. The vascular component (vasodilation) compresses the nerve and causes pain (in the vein-artery-nerve complex), while the muscle component is contracted especially in the sites where nerves go through muscles, also known as X foramens, and promotes pain.[1]

There are numerous scientific studies on the subject, many with deficient methodology and other with more appealing methodology. Professor Rami Burstein (world renowned reference in the field of physiopathology of headaches), in an article evaluating a series of seven patients, showed that some individuals had improvements in post-traumatic headaches and persistent daily headaches since the beginning, while others were non-responsive (chronic migraine). The Professor himself questions if the procedure works or not, suggesting that it should be applied to experimental studies.[2]

A task force from the American Headache Society stated their concern on the subject as such: "Don't recommend surgical deactivation of migraine trigger points outside of a clinical trial. The value of this form of "migraine surgery" is still a research question. Observational studies and a small controlled trial suggest possible benefit. However, large multicenter, randomized controlled trials with long-term follow-up are needed to provide accurate estimates of the effectiveness and harms of surgery. Long term side effects are unknown but potentially a concern."[3-7]

The members believed that this term would make it easier for doctors and patients to recognize the procedures at hand. The idea of a surgical "solution" is inherently attractive to patients. Interest in surgical approaches to headaches has been motivated by the accidental improvement in headaches observed among patients that have undergone several "forehead rejuvenation" surgical procedures. These procedures are based on the premise that the contraction of facial and other muscles collides with branches of the trigeminal nerve.

The procedures are frequently referred to collectively as "headache deactivation surgery", though multiple locations and surgical procedures are involved. These include corrugator supercilii resection with fat grafting, "temporal liberation" procedures, involving dissection of the glabelar region, transection of the zygomaticotemporal branch of the trigeminal nerve and resection of the semispinalis capitis muscle with fat grafting to reduce pressure on the occipital nerve. Finally, some surgeons also conduct nasal septoplasty or try to address possible intranasal trigger sites.[3]

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However, there is limited evidence to support that such surgeries are effective or safe. Several randomized studies have been conducted, but there are methodological deficiencies. Moreover, most studies in the literature were conducted by the same group of surgeons proposing the procedure and published in a single subspecialty journal.[4-7]

Despite the lack of good quality evidence to balance the pros and cons of surgical treatments for headaches, these procedures are becoming more common. Recent research from the Plastic Surgery Society found that 18% of interviewees had conducted a headache surgery. Sixty percent of those that did not conduct the surgery said they were "interested if the patient was referred to them by a neurologist."[5]

The American Headache Society emitted a statement urging "patients, healthcare professionals and migraine treatment specialists themselves, to exercise caution in recommending or seeking such therapy". The statement continued declaring that "In our view, surgery for migraine is a last-resort option and is probably not appropriate for most sufferers. To date, there are no convincing or definitive data that show its long-term value. Besides replacing the use of more appropriate treatments, surgical intervention also may produce side effects that are not reversible and carry the risks associated with any surgery. It also can be extremely expensive and may not be covered by insurance."[6] Given that the value of a headache migraine is still uncertain, the AHS and Choose Wisely Task Force believe that patients should only undergo this treatment in the context of procedures within clinical trials that seek to develop good quality evidence on the harms and benefits of treatment.

References

1. Guyuron B. Is migraine surgery ready for prime time? Thesurgical team's view. Headache 2015; 55:1464-1473.
2. Blake P, Nir R-R, Perry CJ, Burstein R. Tracking patients with chronic occipital headache after occipital nerve decompression surgery: A case series. Cephalalgia. 2019; 39: 556-563.
3. Gaul C, Holle D, Sandor PS, et al. The value of "migraine surgery." Overview of the pathophysiological concept and current evidence. Nervenarzt. 2010;81:463-470.
4. Guyuron B, Reed D, Kriegler JS, Davis J, Pashmini N, Amini S. A placebo-controlled surgical trial of the treatment of migraine headaches. Plast Reconstr Surg. 2009;124:461-468.
5. Kung TA, Pannucci CJ, Chamberlain JL, Cederna PS. Migraine surgery practice patterns and attitudes. Plast Reconstr Surg. 2012;129:623-628.
6. American Headache Society urges caution in using any surgical intervention in migraine Treatment. Position Statement of the American Headache Society. http://www.americanheadachesociety.org/american_headache_society_urges caution in using any surgical intervention in migraine treatment/ Accessed January 11, 2013.
7. Guyuron B, Kriegler JS, Davis J, Amini SB. Comprehensive surgical treatment of migraine headaches. Plast Reconstr Surg. 2005; 115:1-9.

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Views and Reviews

Headache in patients infected with the novel coronavirus (Covid-19): An integrative literature review

Cefaleia em pacientes infectados pelo novo coronavírus (Covid-19): uma revisão integrativa da literatura

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Mario Fernando Prieto Peres

Abstract

Introduction
The disease caused by the new coronavirus was named by the acronym Covid-19 which means "CO-rona VIrus Disease", while "19" refers to the year 2019, when the first cases in Wuhan, China, were identified.
Objective
Our objective was to identify the prevalence of headache and to know its clinical characteristics in COVID-19 patients, available in the literature.
Methods
Based on a literature search in the major medical databases and using the descriptors "headache and coronavirus", "headache and 2019-nCoV", "headache and SARS- CoV-2", "headache and coronavirus and 2019-nCoV" and "headache and coronavirus and SARS-CoV-2" we include articles published between January 2019 and April 2020. We found 94 articles, but only 13 met the inclusion criteria.
Results
In 13 articles analyzed in this review, a total of 3,105 Chinese patients (51.6% men and 48.4% women) had laboratory diagnoses of COVID-19. In 240 (7.7%) patients, headache was an associated symptom of COVID-19, but in only 52 (21.7%) of them there was some information about the characteristics of this headache.
Conclusions
COVID-19 patients have several clinical manifestations, including headache that is nonspecific with a prevalence of 7.7%.

Resumo

Introdução
A doença causada pelo novo vírus Corona foi batizada com o acrônimo COVID-19, que significa "Doença de Corona VIrus", enquanto "19" refere-se ao ano de 2019, quando foram identificados os primeiros casos em Wuhan, na China.
Objetivo
Nosso objetivo é identificar a prevalência da cefaleia e conhecer suas características clínicas em paciente com COVID-19, disponíveis na literatura.
Método
Com base em uma pesquisa bibliográfica nas principais bases de dados médicos e utilizando os descritores "headache and coronavirus", "headache and 2019- nCoV", "headache and SARS-CoV-2", "headache and coronavirus and 2019-nCoV" and "headache and coronavirus and SARS-CoV-2" incluímos artigos publicados entre janeiro de 2019 e abril de 2020. Foram encontrados 94 artigos, mas apenas 13 preencheram os critérios de inclusão.
Resultados
Em 13 artigos analisados nesta revisão, um total de 3.105 pacientes chineses (51,6% homens e 48,4% mulheres) tiveram diagnóstico laboratorial de COVID-19. Em 240 (7,7%) pacientes, a cefaleia foi um sintoma associado ao COVID-19, mas em apenas 52 (21,7%) deles havia alguma informação sobre as características dessa cefaleia.
Conclusão
Os pacientes com COVID-19 apresentam várias manifestações clínicas, inclusive cefaleia que é inespecífica e com uma prevalência de 7,7%.

Keywords:
Headache
Coronavirus
Covid-19
2019-nCoV
SARS-CoV-2

Palavras-chave:
Cefaleia
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Introduction

The disease caused by the novel coronavirus (2019-nCoV) was named by the acronym COVID-19 which means "COrona VIrus Disease", while "19" refers to the year 2019, when the first cases in Wuhan, China, were identified. The virus that causes this disease, a beta coronavirus, is called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) and it is the same virus that causes Severe Acute Respiratory Syndrome (SARS), identified in 2002, and Middle East Respiratory Syndrome (MERS), identified in 2012. Transmission of 2019-nCoV from humans to humans has been confirmed in China and the USA and occurs mainly with the contact of respiratory droplets from infected patients[1].

In December 2019, in China, a novel coronavirus was identified as the cause of a severe acute respiratory syndrome and received worldwide attention. It is a new emerging zoonotic agent that results in a severe syndrome that, in some patients, leads to the need for intensive respiratory treatment with specialized management in intensive care units[2].

In January 2020, the World Health Organization (WHO) declared the outbreak in China as a public health emergency of international interest. In March 2020, with the spread of the virus in different countries, the infection caused by SARS-CoV-2 was considered a pandemic and called COVID-19. In early April, WHO recorded more than 1 million cases of patients infected with SARS-CoV-2 worldwide and more than 65,000 deaths caused by the pandemic worldwide. In Brazil, at the time of writing this manuscript, there are more than 18,000 cases of infection and more than 1,000 deaths[3].

According to a Chinese study, the main clinical symptoms of patients with COVID-19 are fever (88.7%), cough (67.8%), fatigue (38.1%), sputum production (33.4%), dyspnoea (18.6%), sore throat (13.9%) and headache (13.6%). Gastrointestinal symptoms, such as diarrhea (3.8%) and vomiting (5.0%) are less frequent[4]. Elderly and people with underlying diseases are susceptible to infection and more predisposed to severe outcomes, which may be associated with acute respiratory distress syndrome (ARDS) and the cytokine storm[5,6].

Although headache is one of the clinical manifestations of COVID-19, this symptom is still poorly characterized. In this context, our objective was to identify the prevalence of headache and to know its clinical characteristics in a patient with COVID-19, available in the literature.

Methods

This study was an integrative and retrospective review of the articles on headache as a symptom of COVID-19 published in the last 16 months. The research was performed in the online databases Literatura Latino-Americana e do Caribe em Ciências da Saúde (LiLacs), Scientific Electronic Library Online (SciELO), Chinese National Knowledge Infrastructure (CNKI) and Medical Literature and Retrivial System onLine (MEDLINE/PubMed®), from January 2019 to April 2020, given the current status of the pandemic by SARSCov-19. We have used the descriptors "headache and coronavirus", "headache and 2019-nCoV", "headache and SARS-CoV-2", "headache and coronavirus and 2019-nCoV" and "headache and coronavirus and SARSCoV-2".

Articles written in all languages were included. Editorials, comments, letters to the editor, review articles, articles that were not fully available or those that did not have accurate information were excluded. To ensure the validity of these articles, the selected studies were analyzed in detail, by all authors, for the presence of headache in patients with COVID-19.

In our search, we found a total of 94 articles, but with the elimination of repeated articles, only 49 remained.

After reading the abstracts, we excluded articles that did not describe headache with associated symptom (36 articles). Only 13 articles describing case series were included and made up this review, totaling 3,105 patients (Figure 1).

Figure 1. Flowchart of search and selection of studies

Data were analyzed based on demographic and clinical characteristics and are presented as percentages. The percentage is always related to the total number of patients whose information was available for the specific issue.

Results

In 13 articles analyzed in this review, a total of 3,105 Chinese patients (51.6% men and 48.4% women) had laboratory diagnoses of COVID-19. In 7.7% (240/3,105) patients, headache was an associated symptom of COVID-19, but in only 21.7% (52/240) of them there was some information about the characteristics of this headache, as shown in Table 1.

Discussion

Coronaviruses are a large class of viruses that exist widely in nature and the newly discovered 2019-nCoV is the seventh coronavirus currently known to infect humans and also responsible for the current

pandemic that started in China[20].

To the best of our knowledge, this is the first study to assess headache characteristics in patients with COVID-19. We found that headache was an initial symptom of the disease in 3,105 pacients with this disease. Its prevalence has been reported in most studies, but its semiological characteristics have rarely been addressed.

According to the International Classification of Headache Disorders, 3rd edition (ICHD- 3)[21], headache attributed to systemic viral infection is characterized by its temporal relation to onset of viral infection and significant improvement or resolution in parallel with the improvement or resolution of systemic viral infection. Headache is usually diffuse and of moderate to severe intensity (Table 2).

Possibly, the neuroinvasive predisposition characteristic of coronoviruses is an explanation for patients with COVID-19 to develop headache. Genomic analysis shows that SARS-CoV-2 shares a highly homologous sequence with SARS-CoV-1 and MERSCoV, in addition to a similarity of receptors in human cells. This can affect the respiratory tract and also the central nervous system, especially the thalamus and brain stem[20].

Headache was observed in patients of all age groups, both in adults[7-13], as in children[6]. It is important to note that headache is a characteristic symptom of pneumonia caused by coronavirus and not exclusive to COVID-19, and does not behave as a differential symptom between these viral infections[13].

Table 1. Clinical characteristics of headache in 3,105 patients with coronavirus disease 2019 (Covid-19) in the period from January 2019 to April 2020 in China.

Published studies	Number of patients	Age (years)		Sex	Headache prevalence		Headache prevalence
		Average	Variation		n	%	
Tian et al., 2020[7]	262	47.5	1–94	M=127; F=135	17	6.5	Mild to moderate intensity in 93.5% of patients and it appeared at the beginning of the disease
Xu et al., 2020[8]	62	41.0	19-65	M=35; F=27	21	34.0	71.4% of patients and it appeared at the beginning of the disease
Huang et al., 2020[9]	41	49.0	18-65	M=30; F=11	3	7.3	NR
Liu et al., 2020[10]	30	35.038	21-59	M=10; F=20	16	53.3	It appeared at the beginning of the disease
Cheng et al., 2020[11]	1,078	46.0	0.25-94	M=573; F=505	22	2.0	NR
Wang et al., 2020[12]	31	7.1	0.5-17	M=15; F=16	3	9.7	NR
Li et al., 2020[13]	54	51.5	25-82	M=22; F=32	?	Rare	NR
Chen et al., 2020[14]	99	55.5313.1	21-82	M=67; F=32	8	8.0	NR
Liu et al., 2020[15]	137	55.0316.0	20-82	M=61; F=76	13	9.5	NR
Mi et al., 2020[16]	10	68.4318.5	34-87	M=2; F=8	1	10.0	NR
Jin et al., 2020[17]	651	NR	NR	M=331; F=320	67	10.3	It was more frequent in patients with gastrointestinal symptoms (21.6% versus 8.8%)
Ding et al., 2020[18]	5	50.239.8	39-66	M=2; F=3	2	40.0	NR
Zhang et al., 2020[19]	645	NR	NR	M=328; F=317	67	10.4	It was more frequent in patients with abnormal pulmonary imaging findings (11.3% versus 2.8%)

Legend: M – male; F – female; NR – not reported.

Table 2. Diagnostic criteria of ICHD-3 for headache attributed to systemic viral infection.

A. Headache of any duration fulfilling criterion C
B. Both of the following:
1. systemic viral infection has been diagnosed
2. no evidence of meningitic or encephalitic involvement
C. Evidence of causation demonstrated by at least two of the following:
1. headache has developed in temporal relation to onset of the systemic viral infection
2. headache has significantly worsened in parallel with worsening of the systemic viral infection
3. headache has significantly improved or resolved in parallel with improvement in or resolution of the systemic viral infection
4. headache has either or both of the following characteristics:
a. diffuse pain
b. moderate or severe intensity
D. Not better accounted for by another ICHD-3 diagnosis

In the studied cases of COVID-19, headache was usually associated with other typical symptoms of the disease, such as gastrointestinal symptoms. When the patient experienced nausea, vomiting and diarrhea, headache was more frequent, probably due to the higher fever and hydroelectrolytic imbalance[17].

We found in the 13 studies a prevalence of headache equal to 7.7% (240 out of 3,105 patients), ranging from 2.0% to 53.3%. A factor that may determine a higher prevalence of headache in COVID-19 patients is pneumonia, considered a predictive factor for severe subtypes of the disease. We observed that in patients with changes in pulmonary radiological images there was a higher prevalence of headache when compared to patients with normal exams[19].

The symptoms of COVID-19 are nonspecific, making the initial clinical presentation indistinguishable from other viral respiratory diseases. Initially, there is a predominance of systemic manifestations, such as fever, fatigue, myalgia and asthenia[10]. However, the headache that can also appear at the beginning of the disease should not be neglected, but contribute to the diagnosis, especially in those patients with a positive epidemiological history.

This review had some limitations. All patients were from China, so some articles found were written in Chinese and needed to be translated[10-13]. In addition, as it is pandemic, new studies were published almost daily and described the headache incompletely. However, we believe that these findings are consistent with the clinical manifestations of this disease.

Conclusion

COVID-19 patients have several clinical manifestations, including headache that is nonspecific with a prevalence of 7.7%.

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References

1. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak - an update on the status. Mil Med Res 2020 Mar;7(1):11.
2. Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez- Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis 2020;13:101623.
3. World Health Organization (WHO). Coronavirus disease (COVID-2019) situation reports. Available in: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation- reports/> Accessed on: April 10, 2020.
4. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med 2020;28.
5. BRASIL. Ministério da Saúde. Protocolo de manejo clínico do coronavírus (covid-19) na atenção primária à saúde. Secretaria de Atenção Primária à Saúde. Brasília. Março, 2020.
6. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069.
7. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z et.al. Characteristics of COVID-19 infection in Beijing. J Infect 2020;80(4):401-406.
8. Xu WX, Wu XX, Jiang XG, Xu KJ, Ying LJ,Ma CL et.al. Clinical findings in a group of patients infected with the 2019 novel Coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606.
9. 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.
10. Liu M, He P, Liu HG, Wang XJ, Li FJ, Chen S, et. al. Clinical characteristics of 30 medical workers infected with new coronovirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43(3):209-214.
11. Cheng JL, Huang C, Zhang GJ, Liu DW, Li P, Lucy CY, et al. Epidemiological characteristics of novel coronavirus pneumonia in Henan. Zhonghua Jie He He Hu Xi Za Zhi 2020;43(4):327-331.
12. Wang D, Ju XL, Xie F, Lu Y, Li F, Huang H, et al. Clinical analysis of 31 cases of 2019 novel coronavirus infection in children from six provinces (autonomous region) of northern China. Zhonghua Er Ke Za Zhi 2020;58(4):E011.
13. Li YY, Wang WN, Lei Y, Zhang B, Yang J, Hu JW, et al. Comparison of the clinical characteristics between RNA positive and negative patients clinically diagnosed with 2019 novel coronavirus pneumonia. Zhonghua Jie He He Hu Xi Za Zhi 2020;43(5):427-430.
14. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2002;395(10223):507-513.
15. Liu K, Fang YY, Deng Y, Liu W, Wang MF, Ma JP, et al. Clinical characteristics of novel coronavirus cases in tertiary hospitals in Hubei Province. Chin Med J (Engl) 2020;133(9):1025-1031. doi: 10.1097/CM9.0000000000000744. [Epub ahead of print].
16. Mi B, Chen L, Xiong Y, Xue H, Zhou W, Liu G. Characteristics and early prognosis of COVID-19 infection in fracture patients. J Bone Joint Surg Am 2020;102(9):750-758. doi: 10.2106/JBJS.20.00390. [Epub ahead of print].
17. Jin X, Lian JS, Hu JH, Gao J, Zheng L, Zhang YM, et al. Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020;69(6):1002-1009
18. Ding Q, Lu P, Fan Y, Xia Y, Liu M. The clinical characteristics of pneumonia patients co- infected with 2019 novel coronavirus and influenza virus in Wuhan, China. J Med Virol 2020 Mar 20. doi: 10.1002/jmv.25781. [Epub ahead of print].
19. Zhang X, Cai H, Hu J, Lian J, Gu J, Zhang S, et al. Epidemiological, clinical characteristics of cases of SARSCoV-2 infection with abnormal imaging findings. Int J Infect Dis 2020;94:81-87.
20. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020 Feb 27. doi: 10.1002/jmv.25728. [Epub ahead of print].
21. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition. Cephalalgia 2018;38(1):1- 211.

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Original

The Migraine Tree: a shared tool for migraine information

A Árvore da Migrânea: uma ferramenta compartilhada para informação sobre migrânea

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Keywords:
Migraine
Awareness
Education

Palavras-chave:
Migrânea
Conscientização
Educação

Abstract

Migraine awareness is a critical step in minimizing the disease burden. The Migraine Tree is a web structure designed by a Canadian team to inform people living with migraine and give them the knowledge they need to understand their disease and make daily decisions. This article summarizes the reasons for the creation of the Migraine Tree, its design and underlying principles and proposes future collaborations for translation in other languages.

Resumo

A conscientização sobre a migrânea é uma etapa crítica para minimizar a carga da doença. A Árvore da Migrânea é uma estrutura online projetada por uma equipe canadense para informar as pessoas que vivem com migrânea e fornecer o conhecimento necessário para entender sua doença e tomar decisões diárias. Este artigo resume os motivos da criação da árvore da migrânea, seu design e princípios subjacentes e propõe futuras colaborações para tradução em outros idiomas.

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Introduction

The Migraine Tree is a web structure designed by a Canadian team to inform people living with migraine and give them the knowledge they need to understand their disease and make daily decisions. This article summarizes the reasons for the creation of the Migraine Tree, its design and underlying principles and proposes future collaborations for translation in other languages.

A need for therapeutic education tools

Therapeutic education has been recommended to manage chronic diseases[1]. A World Health Organization report in 1998 summarized its principles and benefits. People living with migraine make numerous decisions every day related to their condition and need the knowledge to make choices that will allow them to function and avoid negative consequences. A systematic review of therapeutic education for migraine found positive outcomes on quality of life, headache related disability, depression and headache frequency[2].

The amount of information on migraine that has to be explained to patients is overwhelming. It cannot be synthetized in a busy clinic visit. Physicians may not have the time or communication skills to effectively counsel patients[3]. Education sessions have been found to be effective to improve outcomes and limit visit to the emergency department, but organizing and funding such sessions is not always possible[4]. The amount of misleading information available online is significant. People looking for reliable information can be bewildered by the numerous promises of cures and quick fixes. On the other side, scientific websites and blogs sometimes have too much unclassified information, making it difficult to find the topic needed. Every person with migraine has different needs. Attacks, symptoms, triggers and response to therapy vary. Having access to relevant, easy to understand information is crucial for migraine management. Some resources are also written in a language for health care providers and do not necessarily address people's needs and concerns.

The Migraine Tree structure and design

The Migraine Tree is an original idea of Dr Elizabeth Leroux, a headache neurologist from Canada. After years of involvement in headache care and counselling, and previous web experiences with Migraine Quebec, she realized that a structure could help patients and health care providers to find what they need, contribute to a better understanding of the global approach and also have an educational value for health care providers not familiar with migraine management.

It was very important to choose a positive symbol for the structure. The Tree was chosen as a symbol of growth. Every culture, every country is familiar with trees. Trees assemble in forests, communities. They are resilient, they can lose their leaves and then grow new ones. They can bear flowers and fruits. Every person with migraine is part of a forest and can grow as new skills are learned.

The Migraine Tree uses a structure linking the network of the roots to the trunk and then to another network of branches. The structure was presented to patients during a focus group for feedback and the structure was found to be easy to use and understand. One interesting points the patients provided was that the the word «alternative therapies» was not used. This was a mindful decision, as opposing alternative and traditional medicine was not thought to be beneficial to patients. For example, some supplements have been shown to be effective for migraine prevention and acupuncture is also supported by evidence.

For some options at the Leaf level, two pages exist on a single topic: the WHY focuses on the rationale and proof of effectiveness. The HOW presents practical tips to use the treatment.

The Migraine Tree visual design was accomplished through a graphic design contest led by 3aLogic, a company based in Quebec. The final design was chosen for its simplicity and colored in green and blue, in order to offer a soothing image. Images accompanying the texts were acquired in majority from the 123RF database and paid for by Migraine Canada. The team valued positivity, diversity and even humor to give an encouraging vibe to the readers. In the team's experience, people with migraine do not like to see images of pain and suffering repeatedly, as is unfortunately the case in the media.

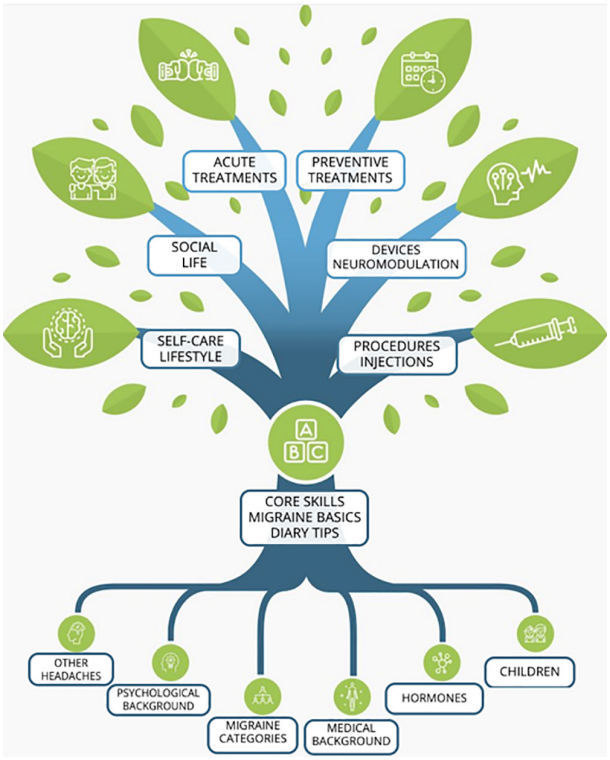

Figure 1. The Migraine Tree.

Table 1. The different levels of the Migraine Tree.

Level	Definition	Examples
Roots	The medical background and diversity of people with migraine.	Medical and psychological comorbidities
		Hormonal factors
		Hormonal factors
		Other headaches
Trunk	information that is relevant for most people with migraine at the beginning of their journey to improvement	Causes of migraine
Use of a diary		
Research and placebo response		
Branches	Treatment approaches are presented on an equal level.	Behavioral approaches, acute and preventive medications, neuromodulation
Leaves	Details on approaches, skills and treatments.	Individual medications, devices, skills

is the excess of distracting ads that may bother people with migraine who are photosensitive. It can be used in the clinic for teaching, the health care provider familiar with the pages being able to point out which topics are of interest from a particular patients.

The writing of the content

Topics were chosen and structured by Dr Leroux. Due to the large numbers of pages needed (close to 140), a team of Canadian writers was assembled. All writers were volunteers and agreed to decline authorship on the texts they provided. The guidelines of the Sick Kids Hospital from Toronto were used to determine format (PDF). The format chosen for most pages is a Question and Answer, that makes browsing for specific information easier. Questions were inspired from the clinical work of the health care providers who contributed. A checklist format has also been used, especially for the HOW pages. The pages have been limited to 600 to 900 words to avoid reading fatigue. The tone, format and style of pilot pages were reviewed by volunteer patient editors to provide guidance to the writers. Writers were instructed to write in an accessible and friendly way. They were encouraged to describe the typical challenges met by patients and choose words to empower them as much as possible. Some articles are more complex and may not be accessible to all readers but could benefit readers with higher literacy or scientific background.

In order to optimize search engine optimization (SEO), internal and external links were included in the pages. Key words and tags were selected. Scientific references were imported from Pubmed, prioritizing recent review articles.

A branch of the tree (Social Life) is still to be written by patients. This branch focuses on social impact of migraine and how to deal with relationships, school, and the workplace. Input from patients will be solicited through Migraine Canada in 2020. Engaging the patient community is extremely important.

Building a Migraine Tree community, sharing with other countries

The Migraine Tree was created in a spirit of sharing. The need for patient information of migraine is universal. Migraine is a common disease in all countries. Numerous resources are available in the English language, with the United Kingdom and the United States leading the way with well-organized and financially sustainable associations. For other languages though, resources are scarce. Headache associations don't always have the resources necessary to build elaborate educational tools. Reinventing the website wheel for each country, each association, would be time consuming for busy health care providers and volunteers alike. One of the goals of the team was to save time to other patient associations. In order to facilitate sharing, all the pages of the Migraine Tree are archived in a DropBox. Folders and pages all have an ID number. This archive is easy to share for translation.

Another important aspect of the Migraine Tree is its sustainability. As it is based on a hierarchical ensemble of numerated articles, it can be maintained relatively easily as knowledge progresses. Each article could be improved by requesting feedback from patients. As long as there is no duplication, new leaves can be added or even replace a similar leaf with a better version that can then be translated in other languages, a bit like the articles of the Wikipedia encyclopedia. Pages containing country-specific data would need to be adapted (lists of medications, coverage comments).

In order to improve the Migraine Tree, feedback from users should be gathered in the future, both from health care providers and patients.

Conclusion

The Migraine Tree is a new online structure offering people with migraine a wealth of reliable information in a format that is easy to browse. Future collaborations could be developed with other countries to make this information accessible to more people.

References

1. Ofman JJ, Badamgarav E, Henning JM, Knight K, Gano AD, Jr., Levan RK, et al. Does disease management improve clinical and economic outcomes in patients with chronic diseases? A systematic review. Am J Med. 2004;117(3):182-92.
2. Kindelan-Calvo P, Gil-Martinez A, Paris-Alemany A, PardoMontero J, Munoz-Garcia D, Angulo-Diaz-Parreno S, et al. Effectiveness of therapeutic patient education for adults with migraine. A systematic review and meta-analysis of randomized controlled trials. Pain medicine (Malden, Mass). 2014;15(9):1619-36.
3. Fortin AHt. Communication skills to improve patient satisfaction and quality of care. Ethn Dis. 2002;12(4):S3-58-61.
4. Lagman-Bartolome AM, Lawler V, Lay C. Headache Education Active-Waiting Directive: A Program to Enhance Well-Being During Long Referral Wait Times. Headache. 2018;58(1):109-17.

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Original

Migraine aura: results from an art contest

Aura da enxaqueca: resultados de um concurso de arte

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Abstract

Introduction
Migraine is a common primary headache and a major cause of disability. In at least a third of migraine attacks, the headache is preceded or accompanied by aura, and the visual manifestation is the most frequent phenotype. Migraine with aura is underdiagnosed and undertreated. So, a detailed aura iconography is important for better recognition, prevention, and treatment of migraine with aura.
Objective
A visual aura art contest was performed by ABRACES (Brazilian Association of Cluster Headaches and Migraines) in order to provide new images for raising awareness among the population and professionals and decreasing the gap between diagnosis and treatment.
Methods
The contest involved a free subscription of drawings, paintings, and digital art that expressed realistic results of a visual aura of migraine and answering a questionnaire. The awards were separated into two categories (painting/drawing and digital art/photography) and amounted up to R$5,000.
Results
There were 139 participants (76% women). The most common visual aura's characteristic was colorful points, and the less frequently was golden. The duration of visual aura was 110.6±450.5 min (1- 3,600 min). 36.7% of the subscribers have only one kind of visual aura, and 33.8% answered that have more than one kind. 46.5% said that their visual aura almost never occurs without pain after or while aura, and 19% reported that their visual aura always occurs without a headache.
Conclusion
Art contests are useful tools for disease awareness. Further actions in disseminating aura images may help migraine aura underdiagnosis and undertreatment.

Keywords:
Migraine
Aura
Contest

Resumo

Introdução
A enxaqueca é uma cefaleia primária comum e uma das principais causas de incapacidade. Em pelo menos um terço dos ataques de enxaqueca, a cefaleia é precedida e/ou acompanhada por aura e a manifestação visual é o fenótipo mais frequente. Enxaqueca com aura, um subtipo de enxaqueca, é subdiagnosticada e subtratada. Portanto, uma iconografia detalhada da aura é importante para um melhor reconhecimento, prevenção e tratamento da enxaqueca com aura.
Objetivo
Um concurso de arte de aura visuais foi realizado pela ABRACES (Associação Brasileira de Dores de Cabeça e Enxaqueca), para que mais imagens possam ser usadas para aumentar a conscientização da população e dos profissionais, otimizando o diagnóstico e o tratamento.
Métodos
O concurso envolveu inscrição gratuita de desenhos, pinturas, e arte digital e fotografia que expressavam resultados realistas de uma aura visual de enxaqueca e preenchimento de um questionário. Os prêmios foram separados em duas categorias (pintura/desenho e arte digital/fotografia), numa quantia até R$ 5.000.
Resultados
Foram 139 participantes, 24% homens e 76% mulheres. A mais prevalente característica da aura visual foi a presença de pontos coloridos e menos frequentemente dourados. A duração média foi de 110,6 minutos (450,5 de desvio padrão), mediana de 20 minutos, mínimo de 1 minuto e máximo de 3600 minutos. 36,7% dos participantes possuem apenas um tipo de aura visual e 33,8% responderam que possuem mais de um tipo. 46,5% disseram que sua aura visual quase nunca ocorre sem dor após ou durante a aura e 19% relataram que sua aura visual sempre ocorre sem dor de cabeça.
Conclusão
Concursos de arte são ferramentas úteis para a conscientização de doenças. Outras ações na disseminação de imagens da aura podem ajudar no subdiagnóstico e subtratamento da aura da enxaqueca.

Palavras-chave:
Enxaqueca
Aura
Concurso

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Introduction

Migraine is a common primary headache and a major cause of disability[1]. It is characterized by recurrent episodes of headache often associated with nausea, vomiting, photophobia and phonophobia. The annual prevalence in general population is an average of 12%, and it is more frequent in 25 to 55 years old individuals and women population[2]. Patients have episodic attacks separated by interictal phases. The attack is an interplay between genetic[3] and environmental factors, possibly resulting in a dysfunctional state and structure alteration of the brain[4,5].

In at least a third of migraine attacks, the headache is preceded and/or accompanied by reversible neurologic symptoms, named aura. This condition is classified as migraine with aura, a subtype of migraine disorder. In early descriptions, aura is linked to migraine since 1870, when Elliott showed the idea of migraine as a disorder characterized by aura, and associated with creativity, intellect, and visual disturbance.

According to Headache Classification Committee of the International Headache Society (IHS)[6], aura is described as one or more of visual, sensitive, speech, motor, brainstem or retinal symptoms. Positive and/or negative visual manifestation is the most frequent phenotype, present in 98% of the patients[7]. Prevalent symptoms are flashes of bright light, foggy/blurred vision, zigzag or jagged lines, scotoma and phosphenes; and less frequent are more complex perception, such as misperception of distance, fractured vision, dysmorphopsias, tunnel vision, hemianopsia, curved or circular lines, among others[8]. Since visual auras varies in form, severity and duration both among patients and within each patient[9], the anatomical location, extent and probably nature of the underlying occipital dysfunction must vary.

Migraine with aura are underdiagnosed and undertreated, partially because of misdiagnosis[10]. The consequences are chronic migraine, decreased quality of life and work productivity[11–13]. A detailed aura iconography is important for better recognition, prevention and treatment of migraine with aura.

An aura art contest was performed by ABRACES (Brazilian Association of Cluster Headaches and Migraines), so more images can be used for raising awareness of population and professionals, decreasing the gap between diagnosis and treatment.

Methods

The Art Contest Migraine Visual Aura by ABRACES involved free subscription of drawings, paintings, digital art and photography that expressed realistic results of a visual aura of migraine. The applications were open to September 22th until October 6th, 2019. The awards were separated in two categories (painting/drawing and digital art/photography) and were equivalent to up to R$ 5.000.

The participants were people that have migraine with visual aura or people with artistic skills that asked somebody who has.

Visual aura was characterized as a disturbance of visual perception that occurs before the start of a migraine (or during), in a gradual way, lasting five minutes to one hour and completely reversible.

Some questions were ascertained, such as: "how did you hear about the contest?", "are you submitting this work to someone else?", "how long does your aura take on average (in minutes)?", "do you have more than one type of aura?", "does your visual aura occur without a headache?" and "what are the characteristics of your visual aura?".

Double data and data not properly filled were excluded to analyzing the results.

Statistical analysis

Categorical variables are presented as percentages and absolute number and continuous variables are presented as means with standard deviation, median, maximum and minimum data.

Results

There were 139 participants in the contest. It was composed by 24% men and 76% women.

Most of participants heard about the contest by social medias: Instagram (38%) and Facebook (38%), 9% from google, 9% from ABRACES website, 5% from other vehicle of information and 1% from interview. The great majority submitted their own art expressing their visual aura.

Figure 1 detailed the prevalence of the characteristics of the visual aura. The most common was presence of points and colorful and the less common was golden. 20% of the participants answered that their visual aura has others features not mentioned.

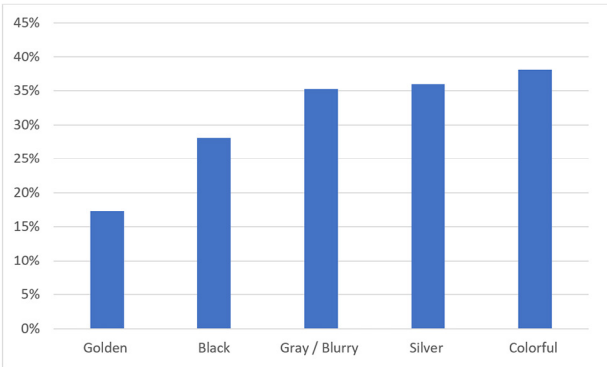

Figure 1. Percentage of visual disturbances reported by contest participants Type of color

The mean duration of visual aura was 110.6 minutes (450.5 of standard

deviation), median of 20 minutes, minimum of 1 minute and maximum of 3600 minutes.

About the predominance of the pattern of visual aura, 36.7% of the subscribers have only one kind of visual aura and 33.8% answered that have more than one kind. Besides visual aura, 6% of the participants also present loss of strength in one half of the body, 9% have difficulty of speaking and 14.4% show tingling of in a half of face or body (Figures 2 and 3).

About the relation with headache, 8 participants did not fill the field. From 131 of the participants that answered, 46.5% said that their visual aura almost never occurs without pain after or while aura and 19% reported that their visual aura always occurs without a headache (Figures 4, 5 and 6).

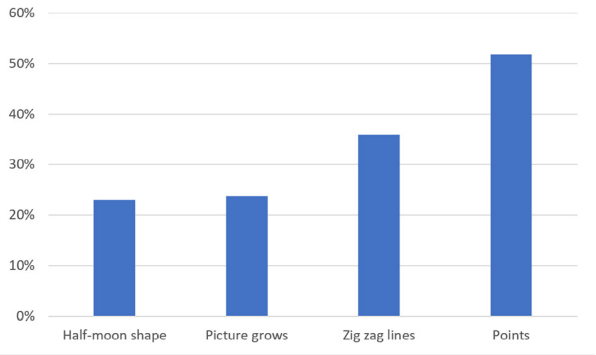

Figure 2. Percentage of visual aura types.

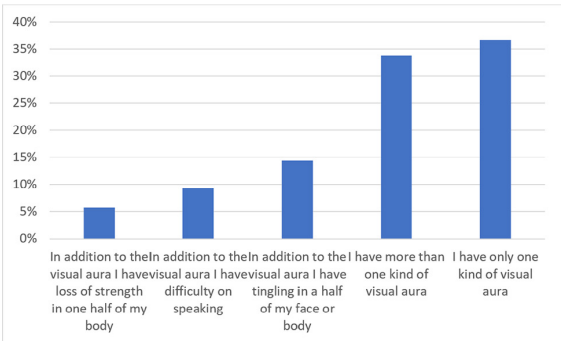

Figure 3. Percentage of visual auras, non-visual auras, with one type of visual auras or more than one visual aura.

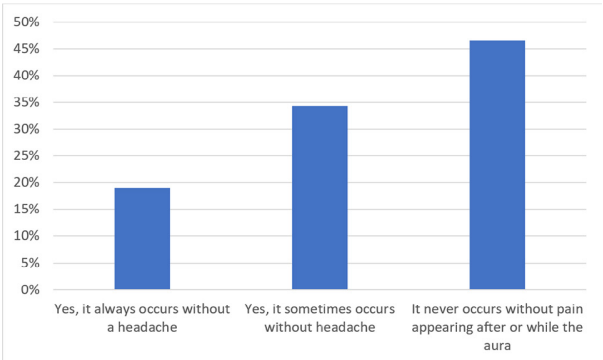

Figure 4. Visual aura occurring with or without headache.

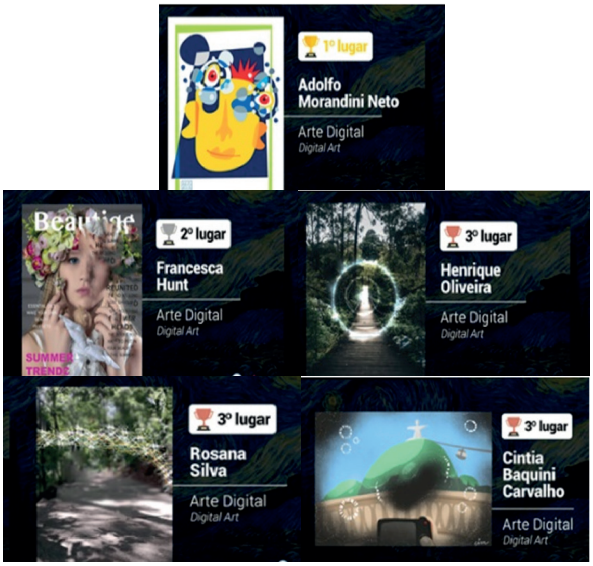

Figure 5. Winners of the contest for the category digital art

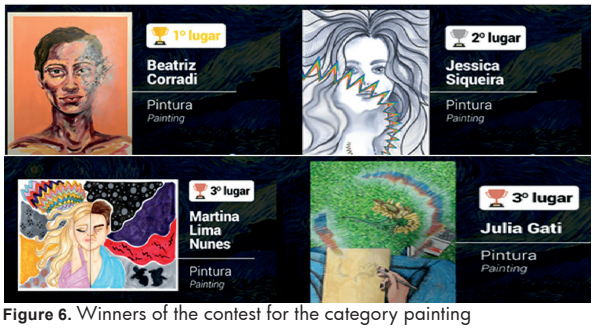

Figure 6. Winners of the contest for the category painting

Discussion

The visual aura contest attracted a significant number of participants who contributed with representations of migraine auras. This helped us in generating new iconography of migraine aura and therefore will be of help in increasing awareness of this underdiagnosed condition. Art contests are a useful tool for awareness campaigns. The images uploaded were from a great variety of visual auras.

Aura features reported by the participants were like the ones described in previous papers[8,14].

Further spread of the images is planned, a book with aura images is under development and hopefully will published soon. The same images could be uploaded and disseminated via social media and website / search engine such as Google. Indeed Health information is one of the most frequently searched topics on the Internet[15].

Availability of aura images to the general public may increase aura diagnosis, improving the access to migraine or other headache sufferers because recognition of visual patterns by patients is likely to occur.

Conclusion

Art contests are useful tools for disease awareness. Further actions in disseminating aura images may help migraine aura underdiagnosis and undertreatment.

References

1. Global, regional, and national incidence, prevalence, andye-ars lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet (London, England). 2015;386(9995):743-800. doi:10.1016/ S0140-6736(15)60692-4
2. Merikangas KR. Contributions of epidemiology to our understanding of migraine. Headache. 2013;53(2):230-246. doi:10.1111/head.12038
3. Anttila V, Winsvold BS, Gormley P, et al. Genome-wide meta-analysis identifies new susceptibility loci for migraine. Nat Genet. 2013;45(8):912-917. doi:10.1038/ng.2676
4. Hougaard A, Amin FM, Ashina M. Migraine and structural abnormalities in the brain. Curr Opin Neurol. 2014;27(3):309-Figure 4. Visual aura occurring with or without headache. 314. doi:10.1097/WCO.0000000000000086.
5. May A. Understanding migraine as a cycling brain syndrome: reviewing the evidence from functional imaging. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2017;38(Suppl 1):125-130. doi:10.1007/s10072-017-2866-0
6. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018;38(1):1-211. doi:10.1177/0333102417738202
7. Russell MB, Olesen J. A nosographic analysis of the migraine-aura in a general population. Brain. 1996;119 (Pt 2):355-361. doi:10.1093/brain/119.2.355
8. Viana M, Sances G, Linde M, et al. Clinical features of migraine aura: Results from a prospective diaryaided study. Cephalalgia. 2017;37(10):979-989. doi:10.1177/0333102416657147
9. Hansen JM, Goadsby PJ, Charles AC. Variability of clinical features in attacks of migraine with aura. Cephalalgia. 2016;36(3):216-224. doi:10.1177/0333102415584601
10. Miller S, Matharu MS. Migraine is underdiagnosed and undertreated. Practitioner. 2014;258(1774):2-3,19-24.
11. Blumenfeld AM, Varon SF, Wilcox TK, et al. Disability, HRQoL and resource use among chronic and episodic migraineurs: results from the International Burden of Migraine Study (IBMS). Cephalalgia. 2011;31(3):301-315. doi:10.1177/0333102410381145
12. Bigal ME, Serrano D, Reed M, Lipton RB. Chronic migraine in the population: burden, diagnosis, and satisfaction with treatment. Neurology. 2008;71(8):559-566. doi:10.1212/01.wnl.0000323925.29520.e7
13. Buse DC, Manack AN, Fanning KM, et al. Chronic migraineprevalence, disability, and sociodemographic factors: resultsfrom the American Migraine Prevalence and Prevention Study. Headache. 2012;52(10):1456-1470. doi:10.1111/j.1526-4610.2012.02223.x
14. Queiroz LP, Friedman DI, Rapoport AM, Purdy RA. Characteristics of migraine visual aura in Southern Brazil and Northern USA. Cephalalgia. 2011;31(16):1652-1658. doi:10.1177/0333102411430263
15. Reuters. Consumer-targeted internet investment: online strategies to improve patient care and product positioning. Reuters Bus Insight Rep 2003; May.

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Original

Plasma ACE activity after aerobic exercise training is related to sleep in migraine patients: A secondary, per protocol analysis

Atividade da ECA após treinamento físico aeróbio é correlacionada com sono em pacientes com migrânea: uma análise secundária por protocolo

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Keywords:
Physical Activity
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Chronic Pain
Headaches Disorders
Migraine
Sleep

Palavras-chave:
Atividade Física
Terapia por Exercício
Enzima conversora da angiotensina
Dor crônica
Cefaleias
Migrânea
Sono

Abstract

Angiotensin converting enzyme-1 (ACE) has been implicated in sleep regulation and nociception. In a secondary, per-protocol analysis, we investigated the effect of a 12-week aerobic exercise program on plasma ACE activity (primary outcome variable), migraine clinical outcomes, and psychometric scores between migraine and control, non-headache participants. Fifty-nine participants (migraine: n=31 and control: n=28) gave signed consent form and were per-protocol analyzed. At baseline, there were no differences between groups for ACE activity. After the intervention period, the ACE activity increased in the migraine exercise group compared to control waitlist group [mean difference (95% CI) = 33.8 $nM.min^{-1}.mg^{-1}$ (1.0, 66.5), p = 0.02]. Among patients, the migraine exercise group showed greater numeric reduction in the number of sleep deprivation-triggered attacks compared to migraine waitlist group (-21 vs -8, respectively), and lower insomnia scores [mean difference (95% CI) = -0.625 (-996, -254), p = 0.001]. There was an inverse correlation between BECK-II insomnia domain scores and ACE activity (r = -0.53, p = 0.035). This study suggests that aerobic exercise training increases plasma ACE activity with possible implication on sleep regulation in migraine patients.

Resumo

A enzima conversora de angiotensina-1 (ECA) está implicada na regulação do sono e nocicepção. Em uma análise secundária por protocolo, objetivamos investigar o efeito de um programa de exercícios aeróbicos de 12 semanas na atividade da ECA plasmática (variável de resposta primária), variáveis clínicas e escores psicométricos entre participantes com migrânea e controle sem nenhum tipo de cefaleia. Cinquenta e nove participantes (enxaqueca: n = 31 e controle: n = 28) assinaram o termo de consentimento e foram analisados por protocolo. No período basal, não houve diferenças entre os grupos para a atividade da ECA. Após o período de intervenção, a atividade da ECA aumentou no grupo de exercícios com migrânea em comparação ao grupo de lista de espera de controle [diferença média (IC95%) = 33,8 nM.min – 1.mg – 1 (1,0, 66,5), p = 0,02]. Entre os pacientes, o grupo exercício mostrou maior redução numérica no número de ataques desencadeados por privação do sono em comparação com o grupo controle (-21 vs -8, respectivamente) e menores escores médios do domínio de insônia BECK-II [diferença média (95% CI) = -0,625 (-996, -254), p = 0,001]. Houve uma correlação inversa entre os escores de insônia e a atividade da ECA (r = -0,53, p = 0,035). Este estudo sugere que o exercício aeróbico regular aumenta a atividade da ECA no plasma com possível implicação na regulação do sono em pacientes com migrânea.

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Introduction

Aerobic exercise training exerts prophylactic effects on migraine[1,2], and also promotes anxiolytic effects[2] in this population. In spite of ample theoretical explanations for the preventive effects of exercise for migraine, the mechanisms underlying the therapeutic effects of aerobic exercise are still elusive.

Angiotensin-I-converting enzyme (ACE), a key protease of the renin angiotensin system (RAS), has been implicated in migraine pathophysiology by mechanisms still not understood[3–5]. ACE cleavages angiotensin-I into angiotensin-II (AngII), a potent vasoconstrictor which also orchestrates several physiological adjustments and adaptations in response to acute and chronic physical exercise[6,7]. The RAS is operative in stress sensitivity[8] and sleep regulation[9], which are associated with migraine triggers[10], and pain perception[11]. Thus, it is plausible to hypothesize the participation of this signaling system in the clinical response to regular aerobic exercise and the mechanisms related to common migraine triggers such as stress and sleep deprivation.

Considering the participation of ACE in other pathological states such as hypertension, heart failure, diabetes, and chronic kidney disease, and the health-related effects of aerobic exercise training counterpointing an exaggerated RAS tone observed in these conditions[6,7], we hypothesized that migraine patients would exhibit higher plasma ACE activity and that aerobic exercise training would reduce plasma ACE activity in this population. Secondarily, we hypothesized that there would be correlations between changes in ACE and clinical outcomes, as well as with migrainerelated triggers and psychometric variables associated with ACE physiology.

Therefore, we compared plasma ACE activity between patients with migraine and healthy, nonheadache individuals, and investigate the influence of aerobic exercise training on this protease activity. We further exploited possible correlations between exercise training-induced changes in ACE activity, psychometric scores (i.e., stress, sleep, etc.) and clinical outcomes (e.g., days with headaches and migraine triggers). These data were preliminary presented at the 5th European Headache and Migraine Trust International Congress, held in Glasgow in September 2016.

Methods

Study Design

This is secondary, per-protocol analysis of a randomized controlled trial aimed at testing the effect of a 12-week aerobic exercise program on clinical outcomes[2]. We analysed the plasma ACE activities, clinical outcomes and psychometric scores, as well as tested the correlations between these variables. Participants were randomly assigned to receive intervention with aerobic exercise training (exercise groups) or enter a waitlist (waitlist groups). Simple randomization (1:1) was performed using an online number generation software.

Study's protocol was composed by 7 clinical visits scheduled every 4 weeks, including the screening, neurological examination, and delivery of headache diaries (Visit 0), and revaluations for checking the headache diagnosis and diaries (visits 1-6). The baseline period was set as the 4-week period between visits 0 and 1. Blood sampling and psychometric interview were scheduled in the samevisit, between visits 1 and 2, and were followed by the 12-week intervention period. The last 4 weeks of the intervention period (between visits 5-6) was set as "post-intervention" period for clinical analyses. Test-retest visits for blood collection and psychometric interviews were scheduled in the same order. All women were at the follicular phase of the menstrual cycle at the blood sampling visit. Retest visits for blood sampling were performed between 2-5 days after the last exercise session, or 48h after the last exercise session within the same phase of the menstrual cycle as undertaken at baseline. For all test-retest visits, participants were instructed to breakfast regularly, but to abstain from coffee. All patients were within the interictal period during all test-retest measurements.

The study's protocol complied with the 1964 Helsinki declaration on human research and was approved by the UNIFESP`s Research Ethical Committee, registered under #081511, and all participants gave written informed consent. This study was also registered in the National Institute of Health (www.ClinicalTrials.gov) under #NCT01972607.

Participants

We recruited patients from the Headache Unit of Hospital São Paulo and a headache tertiary clinic, and healthy individuals from the local community through printed and electronic media advertisements between March 2012 and March 2015. Participants were screened and evaluated by a neurologist. In this analysis, we added 9 participants to the primary analysis sample, 7 chronic migraine patients and 2 healthy controls.

Inclusion criteria were: individuals of both sex, aged between 18 and 65 years, non-headache individuals (defined as controls), and patients with episodic and chronic migraine with/without aura, according to the 2nd version of the International Classification of Headache Disorders[12]. Patients should not be under any prophylactic treatment for migraine (except for using abortive medication during attacks) or taking any other prescribed drug or dietary supplement. Participants should be physically inactive (≤1 day/week of leisuretime physical activity the previous 12 months). Exclusion criteria were: starting any non-pharmacological or pharmacological treatment during the study period, or presenting any other disease such as cardiovascular, pulmonary, metabolic, musculoskeletal, rheumatic, or neurological disorder, including another primary or secondary headache; smoking, alcohol, or drug abuse, and disagreement to continue the protocol.

Intervention

All exercise sessions were supervised by experienced exercise

physiologists. The 12- week program of aerobic exercise training was conducted at the Center for Studies in Psychobiology and Exercise, São Paulo, Brazil. It comprised 40-minute sessions of walking or jogging on treadmill, performed 3 times per week at treadmill speed ($m.min^{-1}$), heart rate, and rate of perceived effort corresponding to the ventilatory threshold. The ventilatory threshold was determined during maximal cardiopulmonary exercise test as described in a previous study[2].

Headache Diary

The headache diary retrieved data on days with migraines, migraine frequency, number of acute medication used, and commonly reported migraine attack triggers: stress/irritability, oversleep, sleep deprivation, alcohol, fasting, odorants and photic stimuli, foods, menstruation, fatigue, weather, neck/back pain, or nonidentifiable.

Psychometric Questionnaire

Participants filled the psychometric questionnaires at the Psychobiology Department before the blood collection. Depression scores were assessed by Beck Depression Inventory-II (BECK-II). Beck-II questionnaire has been validated and translated into Brazilian Portuguese.

ACE Activity Assays

Blood samples were collected between 8:00AM and 10:00AM at the Psychobiology Department after questionnaire filling, by venepuncture of the antecubital vein in cooled heparinized vacutainers (BD Vacutainer®, Franking Lakes, NY, USA). Samples were immediately centrifuged for 10 minutes at a 3,400g at 4°C. Plasma was separated, aliquoted in 2 mL vials, and stored at -80°C until analysis. All samples were analysed within 6 months after blood collection.

ACE activity was determined spectrofluorimetrically using fluorescence resonance energy transfer (FRET) peptides. The FRET peptides Abz-FRK(Dnp)P-OH (Aminotech Pesquisa e Desenvolvimento, Brazil) was used, as described by Carmona et al 2006 [13]. Briefly, ACE activity assays were performed in a Tris-HCl 100 mM pH 7.0 buffer containing NaCl 100 mM and ZnCl2 10 mM. Lisinopril (Sigma, USA) was used as ACE inhibitor to ensure substrate specificity. The reactions were continuously followed in a Gemini XS fluorimeter (Molecular Devices Company, Sunnyvale, CA, USA) that measured the fluorescence at lex = 320nm and lem = 420 nm (Abz group) and lex = 360 nm and lem =440 nm.

All measurements were performed in duplicate and proteases activity values were reported as nanomolar of substrate hydrolyzed per minute per milligram of protein ($nM.min^{-1}.mg^{-1}$).

Outcome Variables

The primary outcome variable was ACE activity. Secondary outcome variables were changes in days with headaches, migraine frequency, psychometric scores, and attacks trigger factors.

Statistical Analysis

Between- and within-groups comparisons (4 groups x 2 times) for ACE activity, anthropometric variables, and psychometric scores were performed by repeated-measure ANOVA with Bonferroni's *post hoc* corrections for multiple pairwise comparisons. Comparisons between migraine groups (2 groups x 2 time points) for clinical variables were performed by repeated-measure ANOVA with Bonferroni's adjustments for multiple pairwise comparisons. Differences between pre-post intervention values (delta values) for proteases activity were calculated by univariate ANOVA with Bonferroni's corrections for pairwise comparisons.

For the trigger factors analyses, we performed descriptive statistics of the trigger's prevalence in the patients' sample. Correlations were calculated by Pearson's correlation coefficients or Spearman's correlation coefficients, depending on variables distribution features. The SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY) was used for statistical analyses. A $p < 0.05$ was accepted as statistically significant.

Results

Fifty-eight participants were randomized, concluded the study, and were per protocol- analyzed. Participants characteristics' are reported in Table 1. For days with migraine and migraine attacks frequency, there were no statistically significant differences between migraine groups at baseline (Table 1). There was a significant group vs time interaction [$F(1,29) = 8.921$, $p = 0.006$, $\eta2 = 0.56$] for days with migraine. Migraine exercise group showed a significant reduction in days with headaches [mean difference (95% CI) = -5.0 (-8.5, -1.4); $p = 0.007$], without significant changes observed in the migraine waitlist group [mean difference (95% CI) = 2.2 (-1.2, 5.7); p = 0.19)]. No significant group vs time interaction was observed for migraine attacks frequency [$F(1, 29) = 1.389$, $p = 0.248$, $\eta2 = 0.06$].

For plasma ACE activity, repeated-measure ANOVA's pairwise comparisons showed no differences between groups at baseline (Figure 1), while there was a group vs time interaction [$F(3, 54) = 3.324$, $p = 0.026$, $\eta2 = 0.42$]. Bonferroni-adjusted pairwise comparisons showed increased ACE activity in migraine exercise group compared to control waitlist group after the intervention period [mean difference (95% CI) = 33.8 $nM.min^{-1}.mg^{-1}$ (1.0, 66.5), p = 0.02]. One-way ANOVA univariate test using the delta values expressed as percentage change from baseline showed significant between-group effects [$F(3, 54) = 3.223$, p = 0.03, $\eta2 = 0.41$], with ACE activity in migraine exercise group [mean difference (95% CI) = 47.3 % (21.3 %, 75.5 %)] significantly higher than the control waitlist group [mean difference (95% CI) = -9.1% (-41.1 %, 19.3 %)]; $p = 0.039$] (Figure 1). There were no correlations between ACE activity and days with migraine, neither at baseline (r = -0.83, p = 0.657) nor for changes after the intervention period (r = -0.156, $p = 0.409$). $p < 0.001$, $\eta2 = 0.27$]. Bonferroni-adjusted pairwise comparisons

Table 1. Participants anthropometric and clinical characteristics. Data are expressed as mean±SD

	Groups			
	Control Waitlist	Control Exercise	Migraine Waitlist	Migraine Exercise
Age (yrs)	35.3±9.5	34.4±11.5	36.2±10.2	39.8±13.5
BMI (kg/cm²)	26.2±3.4	25.6±3.6	26.4±5.4	27.2±4.1
Sex				
Female	11	11	12	12
Male	4	4	3	3
Diagnosis				
MwoA	-	-	7	5
MwA	-	-	4	8
CM	-	-	4	3
Time with Disease (yrs)	-	-	15.9±8.9	18.5±11.9
Days with Headaches (/month)	-	-	9.0±5.9	12.3±8.0
Acute Medication (/month)	-	-	7.4±6.3	9.4±9.9
SBP (mmHg)	112.5±2.8	114±2.5	110±2.7	115.6±2.5
DBP (mmHg)	74.1±1.7	75±1.5	69.6±1.6	72.6±1.5
VO_{2Peak}	34.0±7.5	33.0±6.8	31.5±6.7	31.5±6.7

MwoA: Migraine without aura; MwA: Migraine with aura; CM: Chronic migraine; SBP: Sitolic Blood Pressure; DBP: Diatolic Blood Pressure; VO_{2Peak}: Peak Oxygen Uptake (Measure of cardiorespiratory fitness).

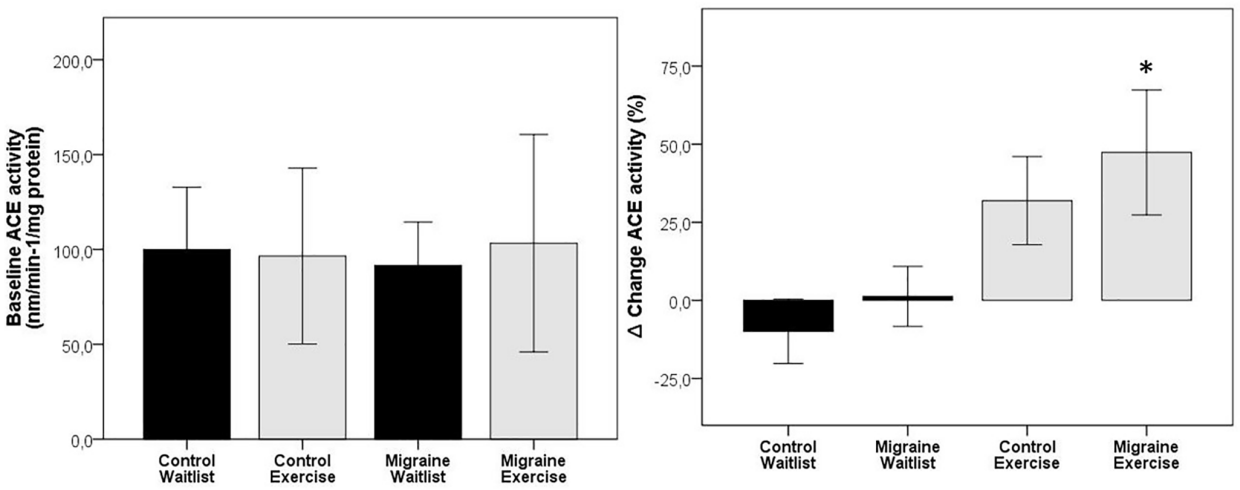

Figure 1. Plasma angiotensin-converting enzyme activity at baseline and percentage change after intervention. Data are expressed as mean±SE. *: $p < 0.05$, compared with control waitlist

showed that the migraine waitlist group had higher baseline BECK-II total score than the control waitlist [mean difference (95% CI) = 11.9 (4.6, 19.1); $p < 0.001$], control exercise [mean difference (95% CI) = 12.5 (5.7, 19.3); $p < 0.001$], and migraine exercise [mean difference (95% CI) = 7.0 (.56, 13.6); $p = 0.027$] groups (Figure 2). For the BECK-II insomnia domain, repeated-measure ANOVA showed a main effect of time [$F(1, 58) = 9.444$, $p = 0.003$, $\eta 2 = 0.17$]. Bonferroni-adjusted pairwise comparisons showed that the migraine exercise group had higher baseline BECK-II insomnia score than the control exercise group [mean difference (95% CI) = 0.409 (0.007, 0.901); $p < 0.001$], and was the only group with significant changes after intervention period [mean difference (95% CI) = -0.625 (-996, -254), $p = 0.001$] (Figure 2). No significant main effects of time or group, neither interaction was observed for BECK-II irritability domain.

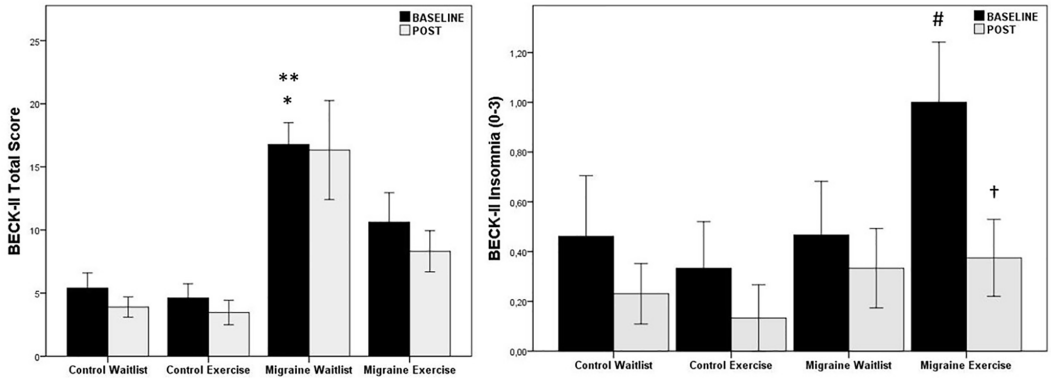

Figure 2. Beck II inventory scores (total and insomnia domain) at baseline and after intervention. Data are expressed as mean±SE. *: $p < 0.05$, compared with migraine exercise group; **: $p < 0.001$, compared with control exercise and control waitlist groups; #: $p < 0.001$, compared with control exercise group; †: $p < 0.01$, compared with baseline.

Because triggers prevalence varied both within and between subjects over the study period, we only conducted a descriptive analysis of triggers. The most common triggers were stress/irritability, sleep deprivation, and fasting (Figure 3). The migraine exercise group showed a greater numeric reduction than migraine waitlist group for sleep-deprivation (-21 vs -8 attacks, respectively) and stress/irritability triggers (-20 vs -13, respectively) (Figure 3). In order to explore the relation of major triggers in this sample with ACE activity, we compute the correlations of BECK-II subdomains as potential triggers correlates, that is, the BECK-II insomnia domain for sleep deprivation trigger, and the irritability domain for stress/irritability trigger. There was an inverse correlation between changes (delta values) in BECKII insomnia domain scores and ACE activity ($r = -0.53$, $p = 0.035$), while there was no correlation between ACE activity and BECK-II irritability domain scores ($r= 0.022$, $p = 0.883$).

Discussion

This study aimed at measuring the effect of a 12- week supervised moderate aerobic exercise training on plasma ACE activity and whether there would be any correlations with clinical outcomes. To the best of our knowledge, this is the first study to report a stimulatory effect of regular aerobic exercise on plasma ACE activity in migraine patients (nearly 50% increase), and a correlation between plasma ACE activity and sleep quality scores. Contrary to our hypothesis, we found no baseline ACE activity differences between migraine and control groups.

Clinical studies have found elevated circulating ACE activity in migraine patients in the interictal period[3] and increased plasma AngII and aldosterone in patients experiencing salt-induced migraine attacks[14]. At molecular level, an immunocytochemical investigation has uncovered the presence of an angiotensinergic system in the trigeminal ganglia of humans and rats [5], suggesting a role for this signaling system in migraine pathophysiology. At genetic level, a meta-analysis found no association between ACE I/D polymorphism and migraine, albeit in the Turkish population ACE II polymorphism – which is characterized by lower ACE expression than DD polymorphism - was associated with reduced risk for migraine[4]. Furthermore, ACE inhibitors or AngII receptor antagonists are common prophylactic drugs prescribed for migraine [15,16].

As such, we expected that migraine patients would exhibit higher baseline ACE activity that could be reversed by aerobic exercise training with clinical implications, as observed in other pathological conditions such as hypertension[17], heart failure[18], or chronic kidney disease[6,18], wherein there is a noticeable exaggerated RAS activity. Our results indicate that the relationship between ACE and migraine and its response to exercise is not as simplistic as hypothesized. Possible explanations to our data may lie in the etiological mechanisms of migraine, ACE response to exercise, and the complex, less known ACE actions on pain and sleep physiology.

The response of ACE or AngII to exercise vary in the population, with studies showing increase, decrease or no change following either acute or chronic exercise[6,7]. Increased resting, interictal ACE activity in migraine reported in a previous study was interpreted as a compensatory mechanism over vasoactive/algogenic molecules involved in migraine pathophysiology such as nitric oxide (NO) and calcitonin gene-related peptide (CGRP)[3]. In fact, there are evidences corroborating this hypothesis, showing an inhibitory effect of ACE on NO[19] and CGRP[20] production. A recent study showed an abnormal cardiovascular response following the administration of the NO donor nitroglycerin in migraine patients, suggesting heightened sensitivity to NO in this population[21]. Moreover, aerobic exercise is one of the more effective natural inducers of NO release - which in turn has been also credited as the cause of exerciseprovoked migraine attacks[22]. Thus, theoretically, this higher ACE activity response to exercise training found here could represent a migraine-specific compensatory mechanism to counteract exercise-induced exaggerated NO actions in migraine patients.

The RAS system has been implicated in pain[11,23,24] and sleep[25] physiology. Preclinical and clinical studies suggest a dual action of the RAS in pain perception, partly depending on whether its actions are mediated by angiotensin type-1 (AT1) or type-2 (AT2) receptors[11].

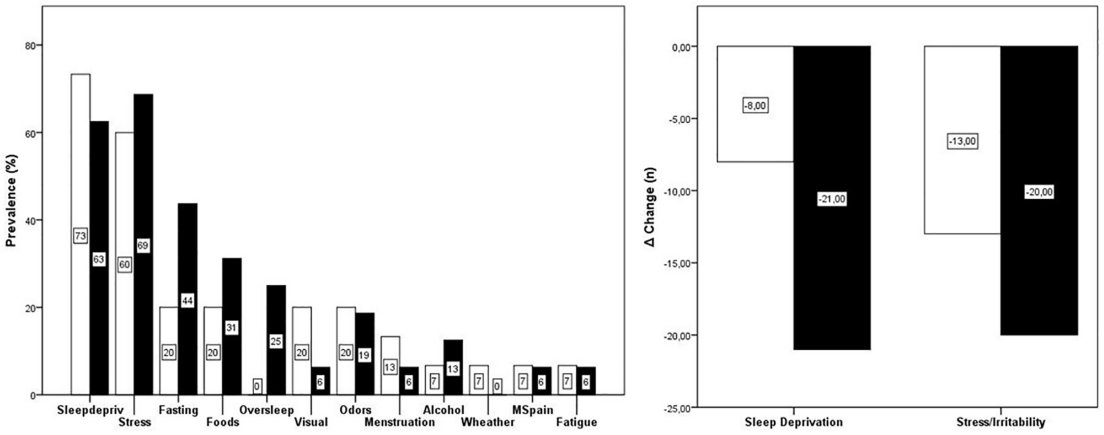

Figure 3. Prevalence of triggers (%) and changes in the number of trigger-related attacks for sleep and stress/irritability (numeric changes from group's sum).

It seems that through AT1 receptors, ACE-AngII can promote algogenic effects in several models of neuropathic and nociceptive pain by activating downstream signaling cascades culminating in pro-inflammatory cytokines upregulation, such as interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-a)[11]. As pro-inflammatory cytokines are associated with migraine[26], this could be a putative mechanism through which ACE activity inhibitors or AT1 receptors antagonists are efficacious for migraine prophylaxis[11,16].

On the other hand, mounting evidence have suggested opposite effects of ACE-AngII on pain through AT2 receptors-dependent and -independent mechanisms centrally and in the periphery[11]. As reviewed by Bali et al.[11], microinjections of AnII administered in the ventrolateral periachedutal gray matter (PAG) attenuates nociception in pain paradigms such as tail flick test and incision allodynia; intracerebroventricular administration of AngII promotes increases of tail flick and thermoalgesic stimuli latencies in rats; spontaneous hypertensive rats, which exhibit high RAS tone, have decreased pain sensitivity, while peripheral administration of AnII in normal rats decrease pain sensitivity. A higher RAS tone seems to mediate higher pain tolerance in hypertensive patients, as enalapril and losartan were shown to induce a lower dental pain tolerance in these patients[24].

The mechanisms by which ACE-AngII exerts hypoalgesic effects is believed to involve its stimulatory action of AngII on β-endorphin release, the participation of ACE in kinins degradation such as the potent algogenic mediators bradykinin and substace P (besides NO and CGRP aforementioned), and the formation of other peptides derived from AngII with centrally-mediated antinociceptive actions[11,23].

The correlation between improved insomnia score and changes in ACE activity following exercise training may involve also the interaction between physical exercise and RAS in sleep regulation. Regular aerobic exercise has been associated with improved sleep[27], and is considered a synchronizer of human circadian rhythms, partly by modulating melatonin secretion[28,29]. The RAS is believed to exerts stimulatory effects on melatonin production[9]. Angiotensin, ACE, AngII, and AT1 receptors are present in the pineal gland of rats, and pineal gland forms AngII at a higher rate than other brain areas. Furthermore, oral administration of losartan, an AT1 antagonist, reduces by 35% the melatonin secretion, while pineal gland cultures treated with this drug yielded a 67.6% reduction in melatonin secretion in rats[25]. Conversely, reduction in ACE specific activity and mRNA relative levels was observed in the hypothalamus and brainstem of rats under the paradoxal sleep deprivation paradigm[30].

Considering the prominent role of melatonin in migraine pathophysiology[31], and its modulation by the RAS[9], along with the influence of physical exercise on both hormonal signaling systems[6,7,28,29], it is admissible to speculate on a possible causal relation with regard the significant inverse correlation between BECK II insomnia score and plasma ACE activity in migraine patients following aerobic exercise training.

At this point, it is worth mentioning some aspects of ACE biochemistry in the body that should be considered when interpreting the data here. ACE et al. can be found in either plasma soluble or membrane bound forms, with tissue-specific production[30]. As underscored by Visniauskas et al.[30], as a cytoplasmatic membrane anchored enzyme, ACE turnover may vary in tissues and suffer influence of other peptidases, as well as its catalytic effects may be dissociated from AngII formation. Agreeably, the antihypertensive effects of ACE inhibition have long been seen to fail to correlate with plasma ACE inhibition[32]. Moreover, aerobic exercise can stimulate ACE-independent AngII production[33]. Nonetheless, our data cannot be extrapolated to assume that plasma ACE reflect the actions of ACE-AngII on pain and sleep processes in the brain.

The limitations of this study are as follows: this is a post hoc analysis from a clinical trial, therefore, the primary outcome in this analysis was not the original primary outcome. This per-protocol analysis also included 7 chronic migraine patients excluded from primary analysis. Also, the findings here cannot be generalized to the whole migraine population, as the data are underpowered, and the sample´s clinical characteristics are different regarding exercise-trigger attacks. For example, the fact that migraine participants showed no exercisetrigger attack, which is commonly observed

in this population[10], and voluntarily sought for exercise as a therapeutic option for migraine may constitute selection biases.

In conclusion, this study found a stimulatory effect of regular aerobic exercise on plasma ACE activity in migraine patients, which was inversely correlate with improved insomnia scores. Further studies should explore the participation of the RAS, and the relation of other ACE-derived peptides following exercise in migraine patients in a larger cohort. Clinical aspects of migraine such as trigger profile and its relationship with these molecules could also provide insights for the participation of RAS in multiple behavioral and homeostatic features of migraine.

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References

1. Peres M, Mercante J, Belitardo de Oliveira A. Non-Pharmacological Treatment for Primary Headaches Prevention and Lifestyle Changes in a Low-Income Community of Brazil: A Randomized Clinical Trial. Headache: The Journal of Head and Face Pain. 2019;59(1):86–96.
2. Oliveira AB, Ribeiro RT, Mello MT, Tufik S, Peres MFP. Anandamide Is Related to Clinical and Cardiorespiratory Benefits of Aerobic Exercise Training in Migraine Patients: A Randomized Controlled Clinical Trial. Cannabis and Cannabinoid Research. 2019;4(4):275–84.
3. Fusayasu E, Kowa H, Takeshima T, Nakaso K, Nakashima K. Increased plasma substance P and CGRP levels, and high ACE activity in migraineurs during headache-free periods. Pain. 2007;128(3):209–14.
4. Wan D, Wang C, Zhang X, Tang W, Chen M, Dong Z, et al. Association between angiotensin- converting enzyme insertion/deletion polymorphism and migraine: a meta-analysis. International Journal of Neuroscience. 2016;126(5):393–9.
5. Imboden A, Patil J, Nussberger J, Nicoud F, Hess B, Ahmed N, et al. Endogenous angiotensinergic system in neurons of rat and human trigeminal ganglia. Regul Pept. 2009;154(1–3):23–31.
6. Goessler K, Polito M, Cornelissen V. Effect of exercise training on the renin-angiotensin- aldosterone system in healthy individuals: a systematic review and meta-analysis. Hypertension research : official journal of the Japanese Society of Hypertension. 2016;39(3):119–26.
7. Rush J, Aultman C. Vascular biology of angiotensin and the impact of physical activity. Appl Physiol Nutr Metab [Internet]. 2008;33(1):162–72.
8. Müller H, Kröger J, Jöhren O, Szymczak S, Bader M, Dominiak P, et al. Stress sensitivity is increased in transgenic rats with low brain angiotensinogen. Journal of Endocrinology. 2010;204(1):85–92.
9. Campos LA, Cipolla-neto J, Amaral FG, Michelini LC, Bader M, Baltatu OC. The Angiotensin- Melatonin Axis. International Journal of Hypertension. 2013;2013:1–7.
10. Pellegrino ABW, Davis-Martin RE, Houle TT, Turner DP, Smitherman TA. Perceived triggers of primary headache disorders: A meta-analysis. Cephalalgia. 2017;38(6):1188–98.
11. Bali A, Singh N, Jaggi A. Renin-angiotensin system in pain: existing in a double life? J Renin Angiotensin Aldosterone Syst. 2014;15(4):329–40.
12. Headache Classification Sub-Committee of the International Headache Society. The International Classification of Headache Disorders. Cephalagia, 2004, 24:9-160.
13. Carmona A, Schwager S, Juliano M, Juliano L, Sturrock E. A continuous fluorescence resonance energy transfer angiotensin I-converting enzyme assay. Nature Protocols. 2006;1(4):1971–6.
14. Brainard J. Angiotensin and Aldosterone Elevation in Saltinduced Migraine. Headache: The Journal of Head and Face Pain. 1981;21(5):222–6.
15. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology [Internet]. 2012;78(17):1337–45.
16. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic Treatment of Migraine With an Angiotensin II Receptor Blocker. JAMA. 2003 Jan 1;289(1):65–9.
17. Ghiadoni L, Taddei S, Virdis A. Hypertension and Endothelial Dysfunction: Therapeutic Approach. Current Vascular Pharmacology. 2011;10(1):42–60.
18. Haack K, Zucker I. Central Mechanisms for Exercise Training-Induced Reduction in Sympatho- Excitation in Chronic Heart Failure. Autonomic Neuroscience [Internet]. 2015;0:44–50.
19. Ancion A, Tridetti J, Nguyen Trung M-L, Oury C, Lancellotti P. A Review of the Role of Bradykinin and Nitric Oxide in the Cardioprotective Action of Angiotensin-Converting Enzyme Inhibitors: Focus on Perindopril. Cardiology and Therapy. 2019;8(2):179–91.
20. Krämer HH, Schmidt K, Leis S, Schmelz M, Sommer C, Birklein F. Angiotensin converting enzyme has an inhibitory role in CGRP metabolism in human skin. Peptides. 2006;27(4):917– 20.
21. van Oosterhout WPJ, Schoonman GG, Saal DP, Thijs RD, Ferrari MD, van Dijk JG. Abnormal cardiovascular response to nitroglycerin in migraine. Cephalalgia [Internet]. 2019;0(0):1–12.
22. Hindiyeh NA, Krusz JC, Cowan RP. Does Exercise Make Migraines Worse and Tension Type Headaches Better? Curr Pain Headache Rep. 2013;17:380.
23. Pelegrini-da-Silva A, Rosa E, Guethe LM, Juliano MA, Prado WA, Martins AR. Angiotensin III modulates the nociceptive control mediated by the periaqueductal gray matter. Neuroscience [Internet]. 2009;164(3):1263–73.
24. Guasti L, Zanotta D, Diolisi A, Garganico D, Simoni C, Gaudio G, et al. Changes in pain perception during treatment with angiotensin converting enzyme-inhibitors and angiotensin II type 1 receptor blockade. Journal of Hypertension. 2002;20(3):485–91.
25. Baltatu O, Afeche SC, José dos Santos SH, Campos LA, Barbosa R, Michelini LC, et al. Locally synthesized angiotensin modulates pineal melatonin generation. Journal of neurochemistry [Internet]. 2002 Jan;80(2):328–34.
26. Oliveira AB, Bachi ALL, Ribeiro RT, Mello MT, Tufik S, Peres MFP. Unbalanced plasma TNF-a and IL-12/IL-10 profile in women with migraine is associated with psychological and physiological outcomes. Journal of Neuroimmunology. 2017;313:138–44.
27. Rubio-Arias JÁ, Marín-Cascales E, Ramos-Campo DJ, Hernandez A v., Pérez-López FR. Effect of exercise on sleep quality and insomnia in middle-aged women: A systematic review and meta- analysis of randomized controlled trials. Maturitas. 2017;100:49–56.
28. Knight J a, Thompson S, Raboud JM, Hoffman BR. Light andexercise and melatonin production in women. American journal of epidemiology. 2005;162(11):1114–22.
29. Buxton OM, Lee CW, L'Hermite-Baleriaux M, Turek FW, van Cauter E. Exercise elicits phase shifts and acute alterations of melatonin that vary with circadian phase. American journal of

physiology Regulatory, integrative and comparative physiology [Internet]. 2003 Mar [cited 2014 Mar 19];284(3):R714-24.
30. Visniauskas B, Oliveira V, Carmona A, D'Almeida V, de Melo R, Tufik S, et al. Angiotensin I- converting enzyme (ACE) activity and expression in rat central nervous system after sleep deprivation. Biol Chem. 2011;392(6):547–53.
31. Peres MF, Valença MM, Amaral FG, Cipolla-Neto J. Current understanding of pineal gland structure and function in headache. Cephalalgia. 2019;0(0):1–10.
32. Waeber B, Nussberger J, Juillerat L, Brunner HR. Angiotensin converting enzyme inhibition: discrepancy between antihypertensive effect and suppression of enzyme activity. Journal of Cardiovascular Pharmacology. 1989;14(Suppl 4):S53-9.
33. Aldigier JC, Huang H, Dalmay F, Lartigue M, Baussant T, Chassain, A. P., Leroux-Robert C, et al. Angiotensin-Converting Enzyme Inhibition Does Not Supress PLasma Angiotensin II Increase During Exercise in Humans. Journal of Cardiovascular Pharmacology. 1993;21:289–95.

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Original

Sociodemographic characteristics of patients with chronic headache

Características sociodemográficas dos pacientes portadores de cefaleia crônica

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Abstract

Introduction
Headache is an entity characterized by a painful process in the cephalic segment and may originate from cranial or facial structures, being considered a common medical complaint. The chronification process of the pain can present a decrease in quality, the functional capacity and the patient's and labor environment, and also as well as affect their interpersonal relationships, since the chronic cephalalgic process can lead the patient to moments of social isolation, mood swings, depression.
Methods
The research was conducted through a retrospective cross-sectional study, performing the analysis of medical records of patients seen at the Unifacisa's outpatient neurology School Clinic complaining of chronic headache, from February 1st to August 31, 2019.
Results
With the analysis of the medical records, 684 attendances were obtained, where 30 of the patients treated had the diagnosis of chronic headache, 29 women and 01 man. These patients received the following diagnoses: 18 (60%) patients with chronic migraine without aura, 4 (13.3%) patients with chronic migraine with aura, 12 (40%) patients with chronic daily medication overuse headache, 9 (30%) patients with chronic tensiontype headache (CTTH), 1 (3.3%) patient with basilar migraine, 2 (6.6%) patients with secondary headache.
Conclusion
Although a small number of chronic headache patients were obtained, yet we realize that it is the migraine that leads to a greater demand for specialized medical care. In addition, as expected due to the latest research, a significant number of patients with headache due to excessive use of common painkillers.

Resumo

Introdução
Cefaleia é uma entidade caracterizada por um processo doloroso no segmento cefálico, podendo ter origem em estruturas cranianas ou faciais, sendo considerada a queixa médica mais comum. O processo de cronificação da dor pode apresentar uma diminuição na qualidade, da capacidade funcional e laboral do paciente, assim como, também, afetar nas suas relações interpessoais, haja visto que o processo cefalálgico crônico pode levar o paciente a momentos de isolamento social, mudanças de humor, depressão.
Métodos
A pesquisa foi realizada através de um estudo transversal retrospectivo, realizando a análise de prontuários de pacientes atendidos no ambulatório de neurologia da Clínica Escola da Unifacisa com queixa de cefaleia crônica, de 1° de Fevereiro a 31 de Agosto, de 2019.
Resultados
Com a análise dos prontuários, obtevese a quantidade 684 atendimentos, onde 30 dos pacientes atendidos tinha o diagnóstico de cefaleia crônica, sendo 29 mulheres e 01 homem. Estes pacientes, receberam os seguintes diagnósticos: migrânea crônica sem aura 60%, migrânea crônica com aura 13,3%, cefaleia crônica diária por uso excessivo de analgésicos 40 %, cefaleia do tipo tensional crônica (CTT) 30%, enxaqueca basilar 3,3%, cefaleia secundária 6,6%.
Conclusão
Apesar de ter sido obtido um número pequeno de pacientes com cefaleia crônica, ainda assim, percebemos que são as migrâneas que levam a uma maior procura por atendimento médico especializado. Além disso, constatou-se, como esperado devido as mais recentes pesquisas, um número expressivo de pacientes portadores de cefaleia por uso excessivo de analgésicos comuns.

Keywords:
Chronic Headache
Migraine
Painkillers

Palavras-chave:
Transtornos da Cefaleia
Transtornos de Enxaqueca
Analgésicos

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Introduction

Headache is an entity characterized by a painful process in the cephalic segment, may originate from cranial or facial structures, being considered a common medical complaint[1,2]. This may also occur episodically or chronically and may be classified in primary or secondary.

Chronic headache may be associated with several reasons, one of them being the abusive use of painkillers. Abusive use is characterized by the use of simple analgesics for 15 days or more in a month or, for triptans, ergotamines, opioids, caffeine and combined painkillers for 10 or more days in a month[3-5].

In addition, one can list as risk factors for the painfull process chronification in the cephalic region: ineffective treatment of headache, obesity, psychiatric disorders, being female, low education, daily stresses[6]. In this perspective, besides the clinical diagnosis of headache type, it is of extreme importance to identify the potential comorbidities that are chronifying factors, aiming at treating them and thus avoiding the aggravation of chronification.

Thus, it was noted the need to analyze the epidemiological profile of patients attended at the Unifacisa's outpatient neurology clinic. Mainly to determine if the demand for attendance occurs by following the global epidemiological pattern or another, as well as generating knowledge about the patients' own profile attended in this service.

Material and Methods

The research was conducted through a retrospective cross-sectional study, performing the analysis of medical records of patients seen at the Unifacisa's outpatient neurology School Clinic complaining of chronic headache, from February 1st to August 31, 2019, following the classification criteria of the International Classification of Headaches Disorders (ICHD-3). All patients were included, regardless of gender or age, that met criteria for chronic headache, whether primary or secondary, being excluded all patients who had headache but did not meet the ICHD-3 chronification criterion or had not yet received a diagnosis of headache.

Results

With the analysis of the medical records from February to August 2019, 684 attendances were obtained, where 30 of the patients treated had the diagnosis of chronic headache, 29 women and 1 man. As for the profession, most were health care professionals, teachers and students. These patients received the following diagnoses: 18 (60%) patients with chronic migraine without aura, 4 (13.3%) patients with chronic migraine with aura, 12 (40%) patients with chronic daily medication overuse headache, 9 (30%) patients with CTTH, 1 (3.3%) patient with basilar migraine, 2 (6.6%) patients with secondary headache. Some of these patients received a diagnosis combination of chronic migraine or CTTH plus a chronic daily headache due to excessive painkillers.

Discussion

Chronic headache is defined when an individual who has a cephalalgic process that happens for at least 15 days in a month in 3 or more months in the year and may, in the case of migraine processes, meet chronification criteria with only 8 days of pain per month at 3 or more months in the year[4-5,8].

It is also possible to subdivide the main etiologies of chronic headache: Transformed Migraine (TM), Chronic Tension-Type Headache (CTTH), New Daily Persistent Headache and continuous hemicranial (CH)[8].

One of the main causes of the chronic headache process is the abusive use of common painkillers or symptomatic drugs such as triptans, ergotamines, opioids, and it is estimated that 50% of patients who have a headache self-medicate. What leads to an estimate in Latin America that 55-70% of patients that look for specialized centers due to headache, receive the diagnosis of medication overuse headache[5].

According to the World Health Organization's Global Burden of Disease, migraine is the second leading cause of disability among all diseases, falling behind only mental disorders. Among people with migraine, within one year, 25% presented the same in episodic form, while 40% will oscillate between chronic and episodic[5].

"Episodic tension-type headache is the most common of primary headaches, with peak prevalence in the fourth decade. In Brazil, the annual prevalence of migraine is 15.8%, affecting about 22% of women and 9% of men, with peak prevalence between 30 and 50 years. Migraine without aura (75% of cases) is more frequent than with aura (25% of cases)". (Speciali et al. 2018)

Due to the incapacitating process of chronic headaches, individuals affected by this disease tend to have, besides the loss of capacity or productivity, problems of a personal and social nature, generated by the painful process that tends to cause isolation, depression, seclusion[6-8].

Conclusion

Although a small number of chronic headache patients were obtained, since headache is one of the major medical complaint and the highest prevalence of CTTHs in the general population, yet we realize that it is the migraine that leads to a greater demand for specialized medical care. Therefore, it is evident how migraines compromise both the functionality of the individual, as well as the quality of life. Moreover, the high and disproportionate prevalence of females over males, evading epidemiological patterns for headache, is supposed

to be due to lower male demand for medical appointments, as well as fewer referrals from primary health care to more specialized centers. In addition, as expected due to the latest research, a significant number of patients with medication overuse headache. Thus, it becomes evident the importance of the early diagnosis clinical treatment, in addition to optimal drug treatment and population's awareness of the use of painkillers in order to reduce the prevalence of headaches caused by their abuse.

The small number of chronic headache care, about 4.32%, was attributed to Unifacisa's school clinic care model. It is in a metropolitan region and is a reference for the specialized care of the surrounding city areas where there is often inadequate screening and the complaints of headaches are not referenced appropriately.

Thus, it is noted that the need to better track patients with complaints of headache and make the service more visible so that more and more patients can reach the most specialized centers and receive the most appropriate service for their complaints, thus reducing headaches related comorbidities.

References

1. Nitrini RA, Bacheschi LA. Neurologia Que Todo Médico Deve Saber. 3rd. São Paulo: Atheneu; 2015. 289-306p. Brazilian Portuguese.
2. Puledda F, Messina R, Goadsby PJ. An update on migraine: current understanding and future directions. Journal of Neurology. 2017; 264(9): 2031–2039.
3. Diener HC, Holle D, Dresler T, Gaul C. Chronic headache due to overuse of analgesics and anti-migraine agents. Deutsches Aerzteblatt Online. 2018; 115: 365–70.
4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38(1): 1– 211.
5. Kowacs F, Roesler CAP, Piovesan ÉJ, Sarmento EM, Campos HC, Maciel Júnior JA, et al. Consensus of the Brazilian Headache Society on the treatment of chronic migraine. Arquivos de Neuro-Psiquiatria. 2019; 77(7): 509–520.
6. May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nature Reviews Neurology. 2016; 12(8): 455–464.
7. Del Monaco R. Migraña y (des)encuentros: encierros y relaciones vinculares a partir de dolores de cabeza crónicos. Cuadernos de antropología social. 2015 July 30; 41: 109-127. Spanish.
8. Cho S, Song T, Chu MK. Outcome of Chronic Daily Headache or Chronic Migraine. Curr Pain Headache Rep 20, 2 (2016). https://doi.org/10.1007/s11916-015-0534-8
9. Speciali JG, Kowacs F, Jurno ME, Bruscky IS, Carvalho JJF, Fantini FGMM, et al. Protocolo Nacional Para Diagnóstico E Manejo Das Cefaleias Nas Unidades De Urgência Do Brasil - 2018. Academia Brasileira De Neurologia (Departamento Científico De Cefaleia) & Sociedade Brasileira de Cefaleia. 2018. https://sbcefaleia.com.br/images/file%205.pdf . Brazilian Portuguese.

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Thesis

Peripheral projections of the trigeminovascular system as antimigraine target

Projeções periféricas do sistema trigeminovascular como alvo anti-enxaqueca

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Calcitonin gene-related peptide (CGRP) is a key neuropeptide, highly expressed in the central and peripheral trigeminovascular system, involved in craniofacial nociceptive modulation.[1] In migraine patients, CGRP infusion generates migraine-like headaches[2], and during spontaneous attacks this peptide is released in the extracerebral circulation[3]. The treatment of choice currently available for terminating migraine attacks are the triptans, 5-HT1B/1D receptor agonists, of which some also display affinity for the 5-HT1F receptor.[4] These drugs have the ability to decrease elevated CGRP levels by inhibiting further release from trigeminal perivascular afferents and consequently decrease nociceptive transmission from the periphery to the central nervous system.[3] However, due to their coronary vasoconstrictor potential, they are contraindicated in patients with cardiovascular diseases. This concern has resulted in the development of novel drugs devoid of vascular side-effects, such as monoclonal antibodies targeting CGRP or its receptor. Moreover, these drugs have shown that migraine attacks can be prevented exclusively via peripheral blockade of CGRP. This thesis focused on the pharmacological modulation of the peripheral CGRPergic projections of the trigeminovascular system.

We investigated in rodents the modulation of trigeminal CGRP release by lasmiditan, a highly selective 5-HT1F receptor agonist (ditan), and comparatively studied sumatriptan. CGRP release was diminished similarly by both drugs in all the trigeminovascular system components (dura mater, trigeminal ganglion and trigeminal nucleus caudalis) ex vivo. In vivo, lasmiditan or higher doses of sumatriptan significantly attenuated endogenous CGRP release, but not exogenous CGRP effects. These findings suggest that selective 5HT1F receptor activation (by lasmiditan) is sufficient to presynaptically inhibit CGRP release in peripheral and central trigeminal nerve terminals, and, consequently, attenuate nociceptive transmission in the trigeminovascular system.[5] Since activation of 5HT1F receptors is not associated with coronary vasoconstriction, lasmiditan may represent a cardiovascular safety advantage over the vasoactive triptans.

In addition to the trigeminovascular CGRP release inhibition by lasmiditan, further (antimigraine) mechanisms of action described with previous 5HT1F receptor agonists include modulation of glutamate release from sensory fibers.[6] The co-localization of 5HT1F receptors and glutamate in the vestibular nuclei of rats, suggests that the 5HT1F receptor might also modulate glutamate release in CNS structures.[7] Moreover, since glutamate receptor antagonism prevents the initiation of cortical spreading depressions (CSDs), a key pathogenic event in migraine with aura, 5-HT1F receptor agonism could attenuate CSDs via a central inhibition of glutamate. Therefore, after taking into account these additional mechanisms, future experiments are needed to determine whether lasmiditan can: (I) inhibit glutamatergic neurons in the central nervous system, or (II) attenuate CSDs initiation and its associated hyperaemia; and if all or none of these mechanisms are associated with ts clinical antimigraine efficacy.

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References

1. Hendrikse ER, Bower RL, Hay DL and Walker CS. Molecularstudies of CGRP and the CGRP family of peptides in the central nervous system. Cephalalgia. 2019; 39: 403-19.
2. Hansen JM, Hauge AW, Olesen J, et al. Calcitonin generelated peptide triggers migraine-like attacks in patients with migraine with aura Cephalalgia. 2010; 30: 1179-86
3. Goadsby PJ and Edvinsson L. The trigeminovascular system and migraine: Studies characterizing cerebrovascular and neuropeptide changes seen in humans and cats. Ann Neurol 1993; 33: 48–56.
4. Rubio-Beltrán E, Labastida-Ramirez A, Haanes KA et al. Characterization of binding, functional activity, and contractile responses of the selective 5-HT1F receptor agonist lasmiditan. Br J Pharmacol 2019; 176: 4681-4695.
5. Labastida-Ramirez A, Rubio-Beltrán E, Haanes KA et al. Lasmiditan inhibits calcitonin gene-related peptide release in the rodent trigeminovascular system. Pain 2020;161(5):1092- 1099, doi: 10.1097/j.pain.0000000000001801.
6. Ma QP. Co-localization of 5-HT1B/1D/1F receptor and gltamate in trigeminal ganglia in rats. Neuroreport 2001; 13: 1589-91
7. SK A, Khalmuratova R, Jeon SY et al. Colocalization of 5-HT1F receptor and glutamate in neurons of the vestibular nuclei in rats. Neuroreport 2009; 20: 111-5