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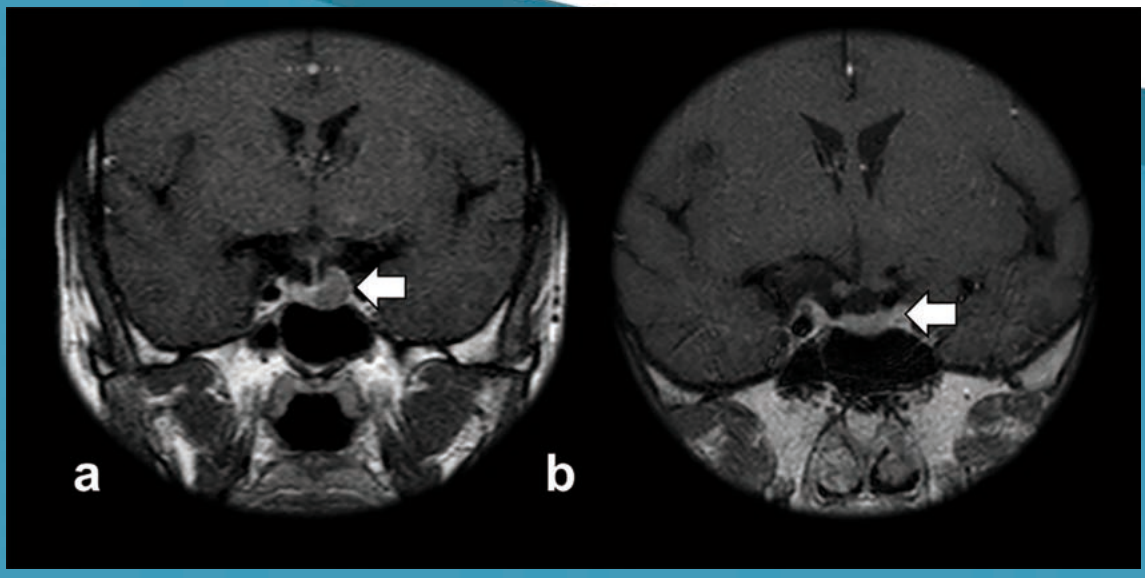

Headache Medicine

Scientific Publication of the Brazilian Headache Society

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CONSELHO EDITORIAL

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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Tenth year of Headache Medicine Journal, 25 years of Brazilian publications in the headache field

It is surprising to look back and realize that Headache Medicine, the Journal of the Brazilian Headache Society, is now in its tenth year. Not only that, but also the fact that the Brazilian Headache Society through our journals, Headache Medicine, formerly known as "Migraneas & Cefaleias", has been publishing scientific articles since 1994. This attests to the Brazilian tradition in the field.

Nonetheless, we now live in a new era of online journals, completely different submission processes, alternative metrics to academic scientific citations, so it is high time to put our Journal and the supportive Brazilian Headache Society in its deserved place among outstanding international journals in the field of Neurology. It is time for us to become truly International, to be part of all main indexation databases. We have grown up and are gradually moving in this direction.

The editorial board has been renewed, with the exceptional cooperation of outstanding researchers from the United States, Asia, Europa and Latin America.

Mario Peres has joined Marcelo Valença as joint editor-in-chief, and a new board of associate editors has been selected to cover different areas in headache science, such as, Procedures, Women and headaches, Clinical trials, Orofacial pain, Theses, Non-pharmacological treatments, Secondary headaches, Intracranial hypotension and hypertension, Trigemino-autonomic cephalgias and Headaches in children.

A number of new sections have been introduced including controversies, expert opinions, images and video, and advocacy. Professor Wilson Luiz Sanvito, our editor emeritus, will contribute with his thoughtful articles, and Professor Silva-Neto, the scientific editor, the liaison member with the editorial board and the editors-in-chief. The contributions of previous editors need to be duly recognized for, we would not be around today without their invaluable efforts.

We hope everyone contributing to Headache Medicine will never regret it. We trust that all the studies or articles already published or due to appear in forthcoming editions will make us proud to be part of this dynamic scientific community.

Our journal Headache Medicine and the Brazilian Headache Society have been recognized by the American Headache Society and its outstanding journal Headache (The Journal of Head and Face Pain). A new supplement on Brazilian Headache Medicine is on course to be launched soon, similar to previous ones in 2007 and 2015.[1,2] A virtual section has been added to the Headache Journal website on Brazilian headache medicine since 2012.[3] Also, Toolboxes, translated to Brazilian Portuguese,[4] can be found on this website, a section dedicated to patient education on a specific topic, a clear indication of the prestige in which our society is held. This indicates that our work and prestige as headache specialists have been recognized, as have our efforts in contributing to the progress of Headache Medicine worldwide.

Mario Fernando Prieto Peres
Marcelo Moraes Valença

Editors-in-Chief, Headache Medicine

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ID-Migraine is a sensitive tool for screening migraine among patients with multiple sclerosis

ID-Migraine é uma ferramenta sensível para identificação de enxaqueca em pacientes com esclerose múltipla

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ABSTRACT

Introduction: Migraine and multiple sclerosis (MS) have been described as comorbidities. While other types of headaches can be seen in patients with MS, it is migraine that usually adds to the burden of patients suffering from an already disabling and chronic neurological disease. Migraine is more prevalent in patients with MS than in the general population, and can be worsened by certain treatments that are used to control MS. ID-migraine is a tool to screen migraine in a population. It consists of only three self-reported questions, and shows good sensitivity, specificity and reliability. The aim of the present study was to assess the role of ID-migraine as a potential tool for screening migraine in patients with MS. **Method:** Patients diagnosed with MS for at least one year were invited to answer ID-migraine. Demographic data and information on MS therapy were obtained at the same time. **Results:** Sixty-two patients participated in the study. There were 16 men and 46 women, of average age 35 years. Migraine was identified in 51.5% of them and 18% reported having the characteristics of chronic migraine. ID-migraine showed 93% sensitivity and specificity for migraine in this population. The medication most frequently associated with worsening of previous migraine was interferon beta 1-a (27.4% of the cases). **Conclusion:** ID-migraine was shown to be a potential tool for identifying migraine in patients with MS. However, the high prevalence of migraine in this population may have constituted a selection bias, since most patients without headache may not have felt inclined to participate in this voluntary investigation. The results from this pilot study will be expanded and investigated in more detail in a large national study.

Keywords: Migraine; Headache; Multiple Sclerosis; Interferon.

RESUMO

Introdução: Enxaqueca e esclerose múltipla (EM) têm sido descritas como comorbidades. Enquanto outros tipos de cefaleia podem ser vistos em pacientes com EM, é a enxaqueca que geralmente completa a incapacidade de um paciente que já sofre de uma doença neurológica crônica e incapacitante. Enxaqueca é mais prevalente em pacientes com EM do que na população geral e pode piorar quando certos tratamentos são utilizados para o controle da EM. ID-Migraine é uma ferramenta utilizada para avaliar enxaqueca em populações. Consiste em apenas três questões auto relatadas, mostrando boa sensibilidade, especificidade e confiabilidade. O propósito do presente estudo foi avaliar o papel de ID-Migraine como potencial ferramenta para determinação de casos de enxaqueca em pacientes com EM. **Método:** Pacientes diagnosticados com EM por pelo menos um ano foram convidados a responder ID-Migraine. Dados demográficos e informações sobre tratamento da EM foram obtidos na mesma ocasião. **Resultados:** Sessenta e dois pacientes participaram deste estudo. Foram 16 homens e 46 mulheres, com média de idade de 35 anos. Enxaqueca foi identificada em 51,5% deles, sendo que 18% relataram características de enxaqueca crônica. ID-Migraine mostrou 93% sensibilidade e especificidade para esta população enxaquecosa. A medicação mais frequentemente associada com piora de enxaqueca previamente existente foi a interferona beta 1-a (27,4% dos casos). **Conclusão:** ID-Migraine mostrou-se uma opção para identificação de casos de enxaqueca em pacientes com EM. No entanto, a alta prevalência de enxaqueca na população estudada pode refletir um viés de seleção, uma vez que muitos pacientes sem cefaleia podem não ter se sentido dispostos a participar da investigação. Os resultados deste estudo piloto serão expandidos e investigados com maiores detalhes em um amplo estudo nacional.

Descritores: Enxaqueca; Migrânea; Cefaleia; Esclerose Múltipla; Interferona

INTRODUCTION

Patients with multiple sclerosis (MS) are consistently reported as having higher prevalence of headaches, particularly migraine[1]. The reason for this finding is yet to be clarified, but the predominance of inflammatory cytokines and adverse events from medications rate highly among the potential causes of increased prevalence of headache among MS cases[2]. In addition, demyelinating lesions in and around the periaqueductal grey area may be associated to (often-intractable) headaches in patients with MS[3,4]. Adverse events relating to MS therapy may also account for the onset or worsening of migraine[5,6].

ID-Migraine is a simple three-item questionnaire that is used for screening migraine cases in primary care. However, it has only rarely been used in MS clinics[7]. It has been validated in several languages, including Brazilian Portuguese[8]. Only one previous study investigated the potential use of ID-Migraine among patients with MS[9]. In this previous Italian study, ID-Migraine showed high sensitivity (91%) and specificity (94%) for identifying migraine in 144 patients with MS. The present investigation was a pilot study with the aim of expanding these data, through including a population of Brazilian patients with MS in which ID-migraine was used.

METHOD

This was a cross-sectional study carried out in three university MS centers. Patients with MS attending regular consultations at these centers were invited to reply to an online questionnaire that sought ID-migraine responses. Cases of episodic and chronic migraine were diagnosed in accordance with thecriteria of the International Headache Society (ICDH-3)[10].Details of these patients' MS therapy were recorded. All information was obtained online without identification of patients.No healthcare professional had any influence on the responses that patients gave. Only patients with at least one year of confirmed diagnoses of MS were included in the study. The results are presented mainly in a descriptive manner.

RESULTS

Sixty-two patients entered this pilot study. The group consisted of 16 men and 46 women, of average age 35 years. All of them had had a diagnosis of MS for at least one year. Migraine was identified in 51.5% of these patients. Among these individuals, 69% reported having aura occasionally, but most attacks were migraine without aura. Eighteen percent of the patients with migraine fulfilled the diagnostic criteria of chronic migraine.

ID-Migraine identified 10 men and 20 women as migraineurs in this study. Using the ICDH-3 criteria, eight men and 20 women had all the necessary items for diagnosing migraine.Thus, ID-Migraine presented 93% specificity. The questionnaire showed 100% sensitivity, since no cases of migraine were identified using the ICDH-3 criteria and not through ID-Migraine.

Thirty-one patients in this study reported having had migraine episodes before they received the diagnosis of MS, while only one person started having migraine after being diagnosed with MS. Onset or worsening of migraine due to MS therapy was observed in 20 patients (62.5%). Interferon beta 1-a led to worsening of migraine in 27.4% of the patients, irrespectively of the mode of administration of this drug (subcutaneously or intramuscularly).

DISCUSSION

This pilot study showed that ID-Migraine is a sensitive and specific tool for screening migraine in populations of patients with MS. If we apply this questionnaire in our MS centers, we may be able to identify a large group of patients in need of special attention to their headache. MS clinics tend to concentrate efforts on maintaining good neurological function, appropriate mobility, visual ability, adequate coordination and sphincter function, cognition, control of neuropathic pain (such as trigeminal neuralgia), but without any specific programs for attending to primary headaches. Since migraine can negatively influence patients' quality of life, mood, sleep and cognition[11], it is important to address migraine in patients with MS.

The very high prevalence of migraine in this population (51.5%) may have been biased by the online tool that was used for screening. It is plausible that only individuals who suffer from headache might feel inclined to reply to an online survey on headache. However, other studies have reported migraine in 50% of patients with MS[2,4] and the results obtained here may just reflect the same prevalence in Brazilian patients. In fact, the only other previous study using ID-Migraine to screen patients with MS showed that 53.5% of the patients had a diagnosis of migraine.

Interferon beta 1-a was associated with worsening of migraine in these patients. This finding has been systematically reported by other authors[5,6,12] and often directs neurologists caring for patients with MS not to prescribe interferon beta 1-a whenever there is a concomitant history of migraine. More recently, other drugs have been described as headache triggers[13], but the population of this pilot study did not allow for further assessments.

CONCLUSION

ID-migraine was a sensitive tool for identifying migraine in patients with MS and its use can be implemented in MS units. As previously described by several groups, interferon beta may worsen migraine symptoms.

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Systematic review of the beneficial effects of thrombin and vitamin K inhibitors on migraine treatment

Revisão sistemática dos efeitos benéficos dos inibidores de trombina e de vitamina K no tratamento da enxaqueca

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ABSTRACT

Background: Prophylactic migraine therapy includes beta-blockers, anticonvulsants, tricyclic antidepressants and calcium channel modulators. These drugs have been serendipitously identified as agents capable of migraine control. In order to reduce drug intake, interactions and potential adverse events, patients who have high blood pressure and migraine are often prescribed beta-blockers or calcium channel antagonists. Patients with epilepsy and migraine can use anticonvulsants, those with depression and migraine can be treat with antidepressants, and those with heart arrhythmia or recurrent vertigo and concomitant migraine can benefit from use of calcium channel antagonists. The beneficial effects of vitamin K or thrombin inhibitors on migraine attacks were first described decades ago, and there may be a place for these drugs in migraine prophylaxis. **Objective:** To investigate the potential beneficial effects of this class of anticoagulants regarding prevention of migraine attacks. **Method:** Systematic review of the literature including papers with patients' results. **Results:** A search of the literature yielded 16 papers with data on patients using inhibitors of vitamin K or thrombin for thromboembolic conditions. Articles typically reported on single cases or small case series. In all but one of these reports, the effect of the drug was remarkable in decreasing migraine severity. **Conclusion:** Although the level of recommendation is low due to the lack of proper clinical trials, vitamin K or thrombin inhibitors may be useful for migraine management in patients who also require anticoagulation. For these individuals, use of this class of anticoagulants could avoid adding extra drugs for migraine management.

Keywords: Vitamin K, Migraine, Treatment

RESUMO

Introdução: O tratamento profilático da enxaqueca inclui betabloqueadores, anticonvulsivantes, antidepressivos tricíclicos e modulares dos canais de cálcio. Estas drogas foram identificadas de forma casual como agentes capazes de controlar enxaqueca. Os efeitos benéficos dos inibidores da vitamina K ou da trombina na prevenção de crises de enxaqueca foi inicialmente descrito há muitas décadas, podendo haver lugar para estas medicações na profilaxia. O objetivo desta revisão foi a investigação dos potenciais efeitos benéficos desta classe de anticoagulantes como preventivos de crises de enxaqueca. **Método:** Revisão sistemática da literatura usando como termos de busca "heparin" OR "warfarin" OR "coumarol" OR "thrombin" AND "migraine" nas seguintes bases de dados: Medline, PubMed, LILACS, SciELO e Google Scholar. **Resultados:** A busca sistemática resultou em 16 artigos com dados sobre pacientes que usavam inibidores da vitamina K ou da trombina para condições tromboembólicas. Os artigos relataram casos isolados ou pequenas séries de casos. Em todos, exceto um artigo, o efeito destas drogas foi ótimo na redução da gravidade da enxaqueca. **Conclusão:** Embora o nível de recomendação seja baixo pela falta de estudos clínicos apropriados, inibidores da vitamina K ou da trombina podem ser úteis no controle da enxaqueca de pacientes que necessitam anticoagulação. Para estas pessoas, o uso desta classe de anticoagulantes poderia evitar a adição de drogas extras para o controle da enxaqueca.

Descritores: Enxaqueca; Migrânea; Warfarina; Acenocoumarol; Vitamina K; Trombina

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INTRODUCTION

Migraine is a common neurological disorder characterized by episodic attacks and by a chronic phase, both of which can be disabling.[1] In addition to cortical, thalamic and hypothalamic dysfunction, the cascade of reactions led by the trigeminovascular system requires adequate management and therapeutic interventions.[1] In subjects who do not tolerate or do not respond well to acute treatments, continuous use of a prophylactic drug is the best option. Interestingly, these prophylactic agents have mostly been identified by chance: while undergoing treatment for another disease with a certain drug, patients reported reduced numbers and lower intensity of migraine attacks. Beta-blockers, anticonvulsants, tricyclic antidepressants and calcium channel modulators have all been identified as potential prophylactic therapies for migraine. These are now approved and recommended for migraine prevention, with evidence supporting their use.[2]

It is only logical that patients who can benefit from the same drug to treat two diseases should receive this drug when they have no contraindication for this minimalistic approach. Therefore, patients who have high blood pressure and migraine can benefit from beta-blockers or calcium channel antagonists, and those with epilepsy and migraine can use anticonvulsants. Likewise, individuals with depression and migraine can be treat with antidepressants, while subjects with heart arrhythmia or recurrent vertigo and concomitant migraine can benefit from use of calcium channel antagonists. Following the same line of thought, migraineurs requiring anticoagulation can benefit from vitamin K or thrombin inhibitors, according to the theory and results presented in papers published over the last 55 years. Following an initial investigation on the potential role of basophil granulocytes in migraine.[3] heparin became a matter of interest in the physiopathology of migraine attacks. Thonnard-Neumann published a series of papers discussing the potential role of heparin in migraine[4, 5] after an initial case-control open trial.[6] Other papers followed but the subject is yet far from clear. The objective of the present review was to assess the potential beneficial effects of this class of anticoagulants on prevention of migraine attacks.

METHOD

This study was a systematic review and did not require approval from an Ethics Committee, since the authors only accessed published data. The present review followed the guidelines of the *Preferred Reporting Items for Systematic Review and Meta-Analysis* (PRISMA) protocol.[7]

The search terms were "heparin" OR "warfarin" OR "coumarol" OR "thrombin" AND "migraine" in the following databases: Medline, PubMed, LILACS, SciELO and Google Scholar. The term "headache" as an alternative to "migraine" generated thousands of unrelated papers and was, therefore, not used in the search. The search was not limited by date and only papers presenting data on patients were selected. Only articles that used the English language in title, key words and abstract were included. Abstracts from conferences and journal editorials were not included in this review. References from selected articles were further used in the search for other potential papers.

The authors individually searched for papers following the set criteria for inclusion and exclusion and, after two meetings, decided which articles should be included. The results from this systematic review are presented essentially in descriptive form with no meta-analyses or statistical assessment of the results.

RESULTS

The initial search generated 163 papers. After reading the titles of these papers and their abstracts, 16 articles were selected for this review. One article, published in 1974[8] had no authors listed and no abstract. It could not be retrieved and was, therefore, excluded, despite its potential interesting title. One case report from Sweden[9] was also excluded, although it had been identified as a reference to other authors. This paper is in Swedish and the search in the original journal rendered no results for that particular article.

There were 11 case reports from eight different countries (UK,[10], Holland,[11, 12] Brazil,[13] South Africa,[14] Italy,[15-17] Taiwan,[18] Canada,[19] USA[20]), one retrospective cohort from Holland,[21] one prospective cohort (from USA),[22] one open crossover trial from Holland,[23] two case control studies (USA,[4] Spain,[24]). Data were typically obtained from isolated cases or small series of patients. The results from 15 studies suggested that heparin, warfarin and coumarin derivatives can be very effective in reducing the intensity and/or frequency of migraine attacks. One of the studies did not obtain the same good result when comparing acenocoumarol to propranolol in migraine prophylaxis.[23] An International Normalized Ratio (INR) of around 2.5 was sufficient to induce improvement in migraine, thus indicating that full anticoagulation is not necessary to alleviate the headache. A summary of the papers with data on patients is presented in Table 1.

DISCUSSION

Serendipitous discoveries have been a characteristic of many drugs used in migraine prophylaxis. The present review showed that potent anticoagulants that are vitamin K inhibitors have shown remarkable beneficial effects in migraineurs. All studies have the same conclusion and it would be of great interest to prospectively study large cohorts of patients (who happen to have migraine) and need to be treated with vitamin K inhibitors.

Thrombin is a serine protease involved in a cascade of coagulation and inflammation via the proteinase-activated receptors (PARs).[25] Pro-inflammatory mediators are released through activation of PAR1, while the activation of PAR2 induces the release of substance P and calcitonin-gene-related peptide (CGRP).[26-28] The aberrant activity of serine proteases, including thrombin, can be identified in many neurological conditions,

Table 1. Summarized results from articles reported on migraine patients using vitamin K or thrombin inhibitors.

Author	Year	Ref	Country	Method	Result
Thonnard-Neumann	1973	4	USA	Case-control (n=20 migraine; 21 control)	5,000 U of heparin intravenously leading to a substantial reduction in severity and frequency of migraine attacks in 16 out of 20 migraine patients.
Suresh et al	1994	10	UK	Case report (n=1)	6mg/day warfarin prescribed to a 71 year-old woman (DVT) led to migraine control. Withdrawal resulted in migraine returning to basaline pattern. Patient was treated blindly with warfarin-placebo and only warfarin improved her headache attacks
van Puijenbroek	1996	11	Holland	Case report (n=1)	3-4mg/day acenocoumarol led to a dramatic reduction of migraine attacks in a 68 year-old woman. Migraines returned after drug was withdrawn and was well controlled again after re-starting acenocoumarol
Fragoso	1997	13	Brazil	Case report (n=2)	Two patients with remarkable improvement on the intensity and frequency of their migraine attacks after taking 5mg/day of warfarin (INR kept at 2.5).
Morales-Asin et al	2000	24	Spain	Case-control (66 migraine; 100 non-migraine headache)	Remarkable improvement on migraine during the use of acenocoumarol. More severe migraine had better response to this treatment
Rahimtoola et al	2001	21	Holland	Retrospective analyses (n=32 warfarin; n=60 aspirin)	Coumarin treatment was clearly associated with a reduction of migraine attacks and severity in comparison with low-dose aspirin treatment
Wammes-van der Heijden et al	2004	12	Holland	Case report (n=4)	Patients with migraine and thromboembolic predisposition improved of their headache during acenocoumarol therapy
Wammes-van der Heijden et al	2005	23	Holland	Open crossover study using propranolol or acenocoumarol (n=12)	No beneficial effect of propranolol or acenocoumarol could be established after 12 weeks
Asherson et al	2007	14	South Africa	Case report (n=1)	Patient with anti-phospholipid syndrome undergoing therapy with warfarin had dramatic improvement in migraine
Maggioni et al	2012	15	Italy	Case report (n=1)	Complete remission of migraine in a woman undergoing warfarin therapy. Migraines returned after drug was withdrawn and was well controlled again after re-starting warfarin
Russo et al	2013	16	Italy	Case report (n=1)	Patient undergoing therapy with warfarin had total remission of migraine pain but remained with aura
Mohanty et al	2015	22	USA	Prospective (n=40 migraine; n=85 control)	Migraine symptoms substantially decreased in 38 patients using warfarin
Kung et al	2015	18	Taiwan	Case report (n=1)	Dabigratan 110mg twice a day controlled migraine-like visual aura without headache
Maggioni et al	2015	17	Italy	Case report (n=1)	Complete remission of migraine with aura on warfarin. Return of symptoms within 3 weeks of switching to apixaban. Resolution of symptoms once again when warfarin was reintroduced
Nilsson et al	2017	19	Canada	Case report (n=1)	Complete remission of migraine with aura on warfarin. Return of symptoms within 3 weeks of switching to apixaban. Resolution of symptoms once again when warfarin was reintroduced
Beh	2018	20	USA	Case report (n=1)	Patient with vestibular migraine who improved when warfarin was associated to his previous topiramate therapy

including hemorrhagic, hypoxic, oncogenic, traumatic and infectious injuries.[29] Expressed in astrocytes, microglia and neurons, PAR1 has been described as a well-positioned receptor to play a central role mediating the complex inflammatory cascades within the central nervous system,[29,30] It is, therefore, perfectly plausible that thrombin might be involved in the inflammatory trigeminovascular cascade of events in migraine.

This review is not without limitations. The results are essentially based on case reports with the bias of publication of positive results. There may be migraineurs with no benefit at all from these drugs whose cases are never going to be reported. Even the larger series of patients and the prospective cohort identified by the reviewers typically reported on insufficient numbers of cases assessed in open studies. At present, it is only possible to give a low (Code C) or very low (Code D) recommendation for this therapy as a migraine prophylactic alternative. As a reminder, Code C means that there are only a few studies with severe limitations, while Code D, in essence, denotes a recommendation from experts.[31]

In order to improve the personal and societal impact of migraine, patients need to receive appropriate treatments and continuity of care.[32] Adherence to therapy is of essence and the fewer the numbers of drugs and daily doses a patient has to use, the higher the chances are that he/she will follow medical recommendations.[33,34] Patients who suffer from migraine and require anticoagulant therapy for any other reason might achieve improvement of their migraine through use of vitamin K and thrombin inhibitors, even when the target INR is relatively low. However, this recommendation is limited by the low level of evidence presented by the data in the medical literature. Prospective observational cohorts among patients who suffer from migraine and receive anticoagulant therapy for any other disease could be the next step in this investigation.

CONCLUSION

The present systematic review showed that vitamin K or thrombin inhibitors have a potential beneficial effect regarding prevention of migraine attacks. Careful interpretation of the results is recommended since most published data come from small series or single cases.

Role of authors:

Eduardo de Almeida Guimaraes Nogueira – recently graduated medical doctor, coordinated the study and prepared the final table of results.

Angela dos Anjos Couto - medical student in training for systematic reviews, had an active participation in the literature search and selection of papers

Beatriz Moraes Grossi - medical student in training for systematic reviews, had an active participation in the literature search and selection of papers

Gabriela Dias Nunes - medical student in training for systematic reviews, had an active participation in the literature search and selection of papers

Taliê Zanchetta B. Hanada - medical student in training for systematic reviews, had an active participation in the literature search and selection of papers

Yara Dadalti Fragoso - designed and supervised the study, wrote the final paper and is ultimately responsible for data collection and analyses.

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Aerobic exercise training for migraine prevention: A trigger-based analysis

Treinamento físico aeróbico na prevenção da migrânea: Uma análise de fatores desencadeantes

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ABSTRACT

Background: Although aerobic exercise has been recommended for migraine management, no study has yet explored the effects of regular aerobic exercise on migraine triggers profile. **Objective:** To evaluate the effects of a 12-week aerobic exercise intervention on migraine triggers profile. **Methods:** We conducted a secondary, post hoc analysis of a randomized, controlled clinical trial. Triggers were recorded in a paper-based headache diary with a formal list including 8 common migraine triggers. Results: Twenty-five patients concluded the protocol and were analysed (exercise: n = 12; waitlist: n = 13). In the whole cohort, the most common triggers were stress/irritability (60 %), sleep deprivation (60 %), fasting (28 %), and foods (28 %). Most patients (52 %) had ≥ 3 triggers. The exercise group showed a higher baseline proportion of patients with ≥ 3 triggers (69 %) compared to waitlist group (25 %) (p = 0.041). After intervention period, there was no difference in the proportion of patients with ≥ 3 triggers between waitlist (16.6 %) and exercise (30 %) groups (p = 0.502). The exercise group showed greater numeric reductions (from group's sum) than waitlist group for triggers stress/irritability (-14 vs -9), fatigue (-12 vs -6), and menstruation (-9 vs -5). This seemed to reflect the reduced number of attacks in the exercise group [mean (CI95 %): -2.5 (-3.7, -1), p = 0.002] vs waitlist [0.9 (2.4, -0.8), p = 0.341]. **Conclusion:** Tracking migraine triggers during exercise interventions may help to unravel specific clinical effects of regular exercise. Trial registration: #NCT01972607.

Keywords: Physical Activity, Exercise, Stress, Treatment, Triggers.

RESUMO

Embora o exercício aeróbico seja recomendado no tratamento da migrânea, nenhum estudo seu efeito no padrão de fatores desencadeantes das crises, os chamados "gatilhos". O objetivo desse estudo foi avaliar se um programa de exercícios aeróbicos de 12 semanas afeta o perfil de gatilhos reportados pelos pacientes. Foi realizada uma análise secundária post hoc de um estudo controlado e randomizado. Os gatilhos foram registrados em diário da dor impresso contendo uma lista de 8 gatilhos frequentemente reportados na literatura. Vinte e cinco participantes concluíram o protocolo e foram analizados. Na amostra total, os gatilhos mais comuns foram estresse/irritabilidade (60 %), privação do sono (60 %), jejum (28 %) e alimentos (28 %). A maioria dos pacientes (52 %) reportaram ≥ 3 gatilhos. O grupo exercício mostrou maior proporção de pacientes com ≥ 3 gatilhos (69 %) no período pré intervenção em comparação com o grupo controle (25 %) (p = 0.041). Após intervenção, essa diferença não foi observada (exercício = 30 % vs controle = 16.6, p = 502). O grupo exercício mostrou maior redução numérica (dados de soma dos gatilhos por grupo) em comparação com o grupo controle para os gatilhos estresse/irritabilidade (-14 vs -9), fadiga (-12 vs -6) e menstruação (-9 vs -5). Esse efeito refletiu redução no número dos ataques no grupo exercício [média (IC 95 %): -2.5 (-3.7, -1), p = 0.002] vs grupo controle [0.9 (2.4, -0.8), p = 0.341]. O registro no padrão de gatilhos durante intervenções com exercícios pode auxiliar no rastreio de efeitos clínicos específicos ainda não estudados. Registro do estudo clínico: NCT01972607.

Descritores: Atividade Física, Exercício Físico, Migrânea, Fatores Desencadeantes, Estresse.

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INTRODUCTION

Growing body of evidence has strengthened the therapeutic benefits of regular physical activity for the management of migraine[1]. In particular, aerobic exercise performed at moderate intensity and practiced 3 times per week is accounted for reducing around 30-40 % the number of migraine attacks/days with migraine2–4), with therapeutic effects comparable to preventive medication[5,6]. Other health outcomes such as perceived stress, mood, and well-being may also improve by adopting aerobic exercise as an adjunct treatment for migraine[2,7,8]. However, there are still other unexplored effects of aerobic exercise on clinical aspects of migraine, such as the triggers profile of patients.

Many patients perceive a myriad of internal or external stimuli as precipitants of migraine attacks, the so-called triggers[9–13]. A recent meta-analysis showed that nearly 90% of headache patients report at least one consistent trigger[9]. The most common triggers reported by patients include stress, sleep deprivation, fasting, certain foods, menstruation, to name a few[9]. While physical exercise is also considered a trigger by around 20-40 % of patients[14,15], many evidences from clinical and epidemiological studies strengthen the recommendation of regular aerobic exercise, and the current understanding is that the protective effect outweighs possible harmful triggered during exercise[1,16]. In fact, exercise imposes a challenge to homeostasis at molecular and physiological levels in several neurobehavioral and physiological processes, it could interact with mechanisms thought to be involved in migraine triggers, such as sleep, stress response, hydration, hypoglycaemia, and so forth to either worse/precipitate the attacks or prevent them[1,17].

In this sense, exploring the patient´s trigger pattern while engaging in an exercise training program may have clinical and behavioural implications, and even affect exercise prescription recommendation for this population. Therefore, it is necessary to understand better the relationship between aerobic exercise and migraine under the perspective of triggers factors. To our knowledge, no study has yet evaluated the response of regular aerobic exercise on the triggers' profile of migraine patients. Thus, the scope of this study was to evaluate the trigger profile of a migraine patient cohort following a 12-week aerobic exercise program. Because there is inter-person variability for triggers, we did not set any a priori hypothesis. We rather conducted an exploratory data analysis, then provided contextual interpretation based on current literature.

METHODS

Study Design

This study consists of a secondary, post hoc, per-protocol analysis of an open-label, randomized controlled clinical trial aiming to assess clinical outcomes in migraine patients following a 12-week aerobic exercise program[2]. We retrospectively analysed the triggers recorded in the headache diary of patients.

The study protocol was approved by the Research Ethics Committee of the Sao Paulo Federal University, and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All participants gave their informed consent prior to their inclusion in the study. The trial has been registered in the National Institute of Health (www.ClinicalTrials.gov) under #NCT01972607. The study complies with the CONSORT's Statement on data reporting for non-pharmacological trials[18].

Participants

Participants were recruited and screened in the Neurology Department of the Sao Paulo Federal University. The inclusion criteria were: subjects of both sexes, between 18 and 65 years, physically inactive the previous 12 months (defined as ≤ 1 day/week of leisure-time physical activity). Exclusion criteria were: patients taking any prescribed medication or dietary supplements; practicing mind-body activities (e.g., yoga, tai chi, etc.); pregnancy; clinical history of cardiovascular, pulmonary, metabolic, rheumatic, musculoskeletal, psychiatric, or other neurological disease. All participants had a neurological and cardiological examination before inclusion in study.

Migraine Triggers Assessment

Clinical data were retrieved from paper-based headache diary. Besides the data on migraine frequency, the diary had a formal list including eight common migraine triggers: "stress/irritability", "sleep deprivation", "oversleep", "fasting", "foods", "odours", "photic stimuli", "alcohol", and "other" for non-listed factors. If there were no identifiable triggers, patients were instructed to let the option for description blank.

Statistical Analyses

Descriptive statistics and comparison between groups for participants' characteristics were calculated by independent t-test (normal distribution assumed). Within-group differences for migraine frequency (continuous variable) pre-post intervention were computed by paired t-test. These data are shown as mean and 95 % confidence interval. For triggers/clinical variables analyses, the pre- and post-intervention periods were set as the 4 weeks prior the 12-week intervention period and the last 4 weeks of this intervention period, respectively.

Descriptive statistics for trigger profile are expressed as either group or whole cohort percentage, or group's sum. Comparisons in the proportion of triggers/patient pre and post intervention were calculated by two-sided Exact Fisher's test. Data were computed in the SPSS software (IBM, Version 19.0, Chicago, IL). A p value < 0.05 was considered statistically significant.

RESULTS

Twenty-five participants were per-protocol analysed. Table 1 shows participants clinical and anthropometrical characteristics. In the whole cohort, 92 % of patients (23 out of 25 patients) reported at least one trigger during the intervention period. The most common triggers were stress/irritability (15/25 patients, or 60%), sleep deprivation (15/25 patients, or 60%), fasting (7/25 patients, or 28 %), food (7/25 patients, or 28 %), and odours (5/25 patients, or 20%). The groups' trigger profile are shown in the Figure 1. Most patients (13/25, or 52%) ascribed ≥ 3 triggers to their attacks in the baseline period.

Table 1. Participants' characteristics. Data expressed as mean 3 standard deviation, or group' percentage.

Variables	Waitlist	Exercise
Age (years)	34.2±9.0	37.4±13.8
Body Mass (kg)	69.6±18.9	72.9±15.7
Height (m)	1.63±0.1	1.64±0.05
BMI (kg/m^2)	25.9±6.03	27.0±4.5
Sex:		
Male, n(%)	3(25)	2(15.4)
Female, n(%)	9(75)	11(84.6)
Time living with migraine (yrs.)	15.6±8.5	18.2±13.3
Days w/ Migraine (n/month)	7.6±.4	8.9±3.6
Attacks Frequency (n/month)	5.1±2.5	6.3±3

The exercise group showed a higher baseline proportion of patients with ≥ 3 triggers (69 %) compared to waitlist group (25 %) (p = 0.041) (Figure 2). After intervention period, the exercise group showed reduced migraine attack frequency compared to waitlist group [mean (CI 95 %): exercise = -2.5 (-3.7, -1), p = 0.002 vs waitlist = 0.9 (2.4, -0.8), p = 0.341], while there was no difference in the proportion of patients with ≥ 3 triggers between waitlist (16.6 %) and exercise (30 %) groups (p = 0.502) (Figure 2). The exercise group showed greater numeric reductions (i.e., "Δ" values computed from group's sum) than waitlist group for the triggers stress/irritability (-14 vs -9), fatigue (-12 vs -6), and menstruation (-9 vs -5) (Figure 3).

Figure 4 illustrates the flow of migraine triggers for each group across time from baseline to post intervention period. Triggers that were not reported by patients in any period of intervention were designated "no trigger".

DISCUSSION

To our knowledge, this is the first study to evaluate the triggers profile of migraine patients following exercise training. In this secondary analysis, we tracked back the triggers' profile of a migraine patient cohort enrolled in a randomized control trial testing the efficacy of aerobic exercise training for migraine prevention. We intended to identify possible changes in the pattern of trigger profile following the aerobic exercise training protocol.

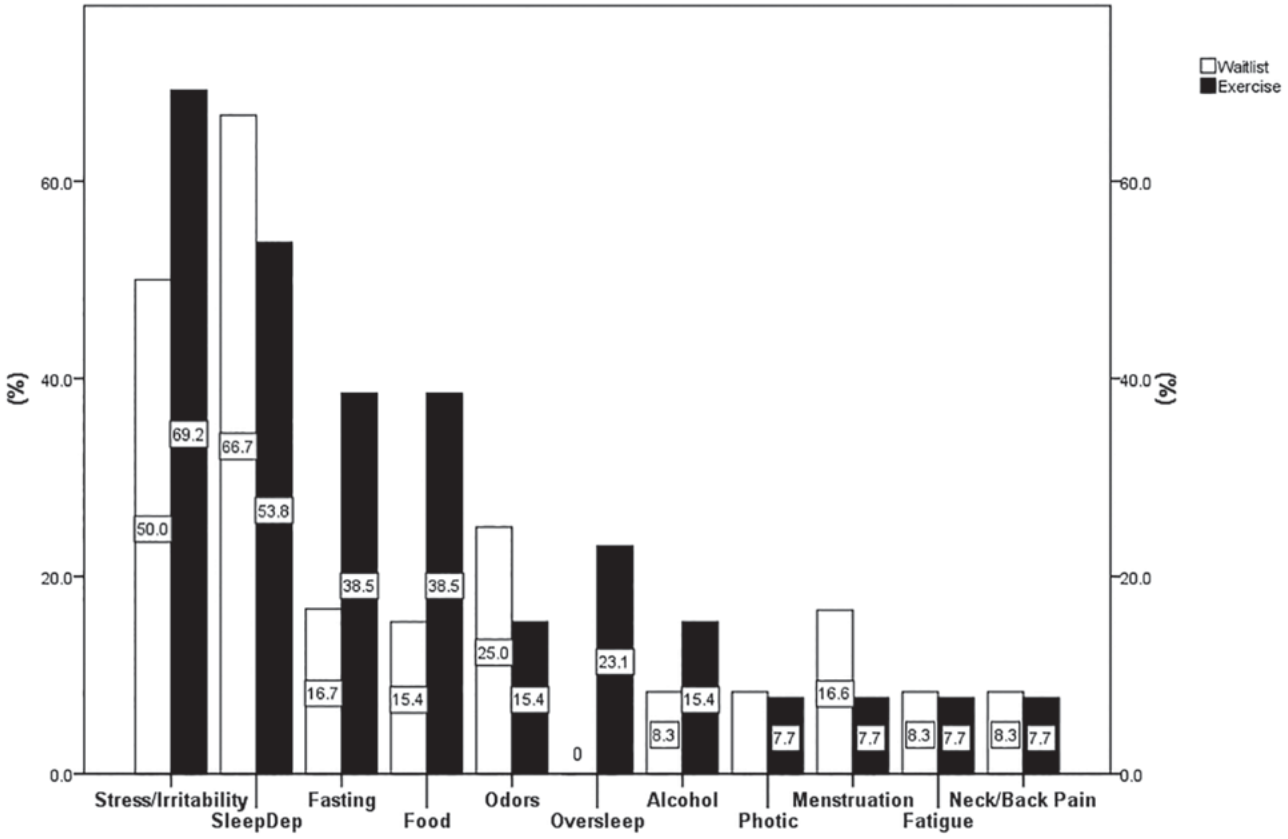

Figure 1. Trigger profile observed in waitlist and exercise groups.

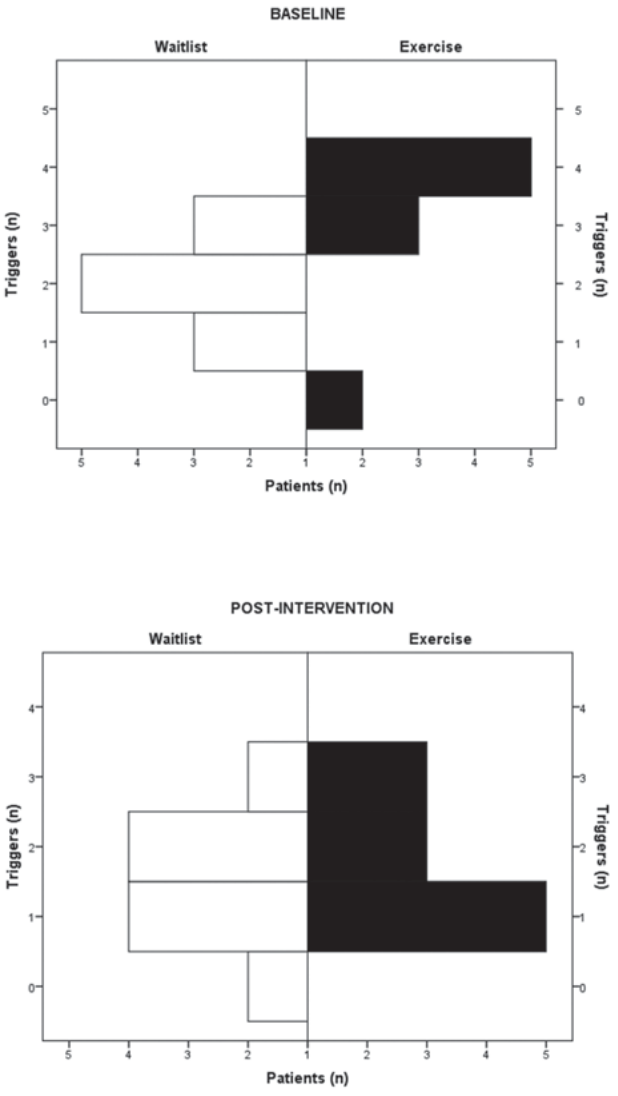

Figure 2. Triggger profile before and after exercice.

We confirmed previous studies showing a high percentage of patients reporting at least one trigger (over 90 %)[9], as well as we replicated the data showing perceive stress, sleep deprivation, and fasting (skipping meals) as the most common triggers[9–13]. We found that the higher proportion of patients with ≥ 3 triggers in the exercise group compared to waitlist group at baseline equalized the waitlist group after intervention period (Figure 2), probably reflecting the reduction in the number of migraine attacks across time with exercise training. This also seemed to be the case regarding the greater numeric reduction for most triggers in the exercise group (Figure 3). Moreover, this larger numeric reduction for some triggers in the exercise group could be due to a greater sample size in this group.

While regular aerobic exercise may reduce migraine frequency[1,3], between 1/4 and 1/3 of migraine patients report physical exercise as a consistent trigger[14,15]. Surprisingly, there was no reported physical exercise-triggered attack in this study. Some explanations to this finding may be the fact that all participants were willing to participate in an exercise program, the exercise intensity was gradually increased up to the level prescribed (moderate intensity around 70% of the age-predicted maximum heart rate) based on cardiorespiratory parameters, and all exercise sessions were supervised.

It is relevant to understand the relation of triggers with physical exercise, since there is no specific exercise prescription recommendation for migraine patients with regard to their personal trigger profile, or whether or not the surge of new popular exercise modalities could be deleterious for the migraine patient. For example, new popular exercise modalities that rapidly gain adepts worldwide such as high intensity interval training[19] or training in a fasted state[20], can be challenging for a migraine patient and is impractical to be recommended. On the other hand, in face of positive metabolic and cardiovascular benefit of these exercise modalities, one could question whether a progressive introduction of such exercise types would benefit clinical aspects of migraine, including the trigger pattern. Such trigger

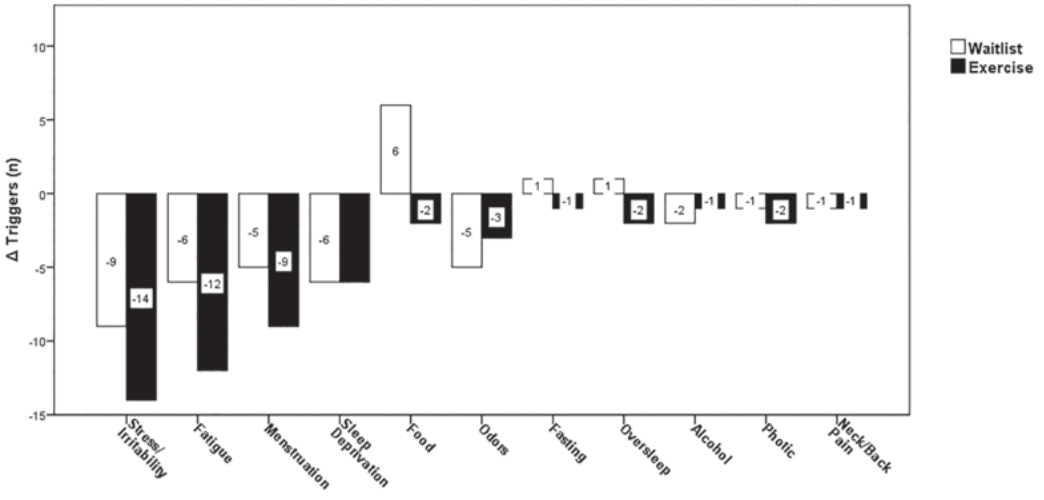

Figure 3. Change in common migraine triggers after intervention period.

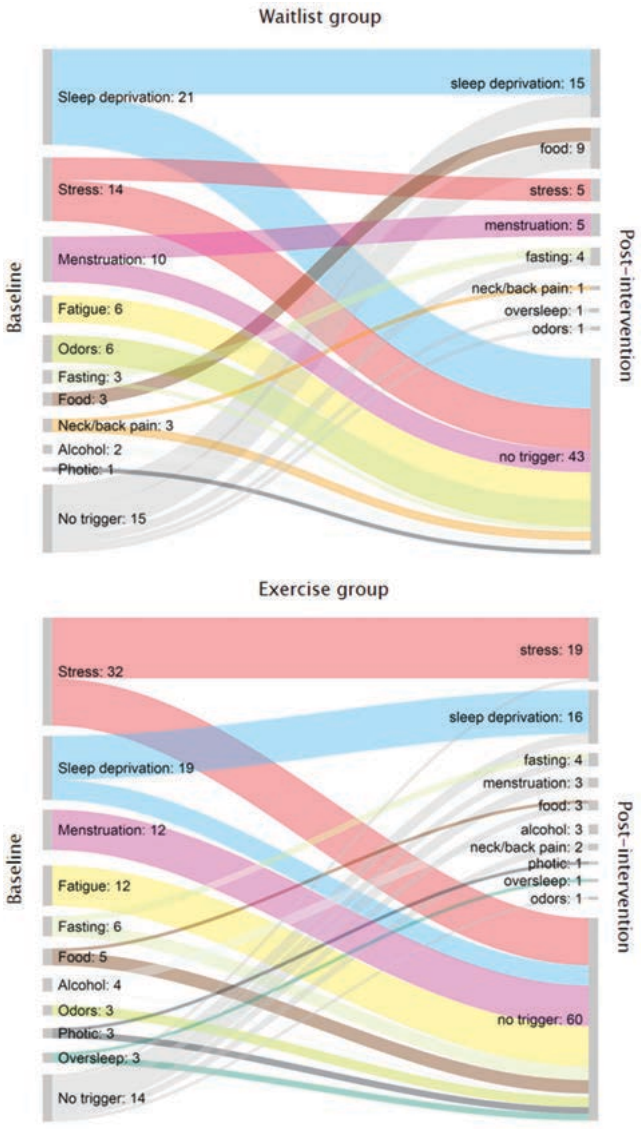

Figure 4. Flow of migraine triggers for each group across time from baseline to post intervention period.

analysis, in clinical practice, could help patients to detect either positive or potentially harmful effects of regular physical activity interacting with subjective triggers. In the future, further studies could establish specific exercise prescription recommendations for this population.

Although the data here do not allow us to draw conclusion for specific effects of exercise training on the pattern of migraine triggers, regular aerobic exercise training mediates several neurdocrine, neuroimmune, and neuromodulatory processes, which could be accounted for the greater reduction in triggers such as stress/irritability, sleep deprivation, menstruation, neck pain, and fatigue in the intervention group. For example, regular exercise is thought to promote anti-inflammatory effects[21], regulate the hypothalamic-pituitary-adrenal axis mediating habituation of stress response[22–24], which are akin with the recent evidence of exercise-mediate anxiolysis and lower pro-inflammatory cytokines in migraine women[7]. Also, aerobic exercise may improve sleep quality, and therefore could prevent sleep deprivation-triggered attacks, by changing melatonin production[25,26], which in its turn represent a endogenous molecule thought to play a role in the pathomechanisms of migraine disorders[27]. A recent study showed that aerobic exercise helped to reduce neck pain in a particular subpopulation of patients presenting with both migraine and tension-type headaches[28]. Less attacks due to fatigue could reflect improvement in oxidative energy metabolism following exercise training through changes in mitochondrial function, which has been also linked to migraine pathophysiology[29,30].

There was a large difference in non-identifiable triggers between groups (20 attacks). It is likely that interference from attention and care delivered by researchers to the exercise group during the exercise sessions may have rendered participants more aware of their triggers by speaking with researchers about their personal clinical features.

Limitations and Strengths

There are limitations in this study, which hamper one to generalise our findings. The study is comprised of a small sample of patients interested in adopting aerobic exercise training as a non-pharmacological approach to manage their migraine. This constitute selection bias and, thus, this sample do not represent the general migraine population. Furthermore, this is a secondary, per-protocol analysis, which means that the analyses were designed after randomization. The strengths of this study lie on the trigger data collected through paper-based diary throughout the study period, and a supervised exercise program design.

Taking into account multiple neurophysiological and biochemical processes affected by physical exercise, and possible relation to migraine triggers mechanisms, further studies are needed to elucidate particular clinical responses of aerobic exercise training in a more representative sample.

CONCLUSIONS

The preventive effect of regular aerobic exercise may reflect on the triggers pattern of patients. Mostly by reducing the number of triggers, and the more frequent ones. Tracking the patient triggers profile during exercise training interventions may unravel specific clinical data, and further advance the understanding of the relationship between exercise and migraine. The implications on exercise prescription should be further explored in the future.

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Cerebral energetic metabolism of individuals with migraine through ^{31}P-MRS: A systematic review

Metabolismo energético cerebral de indivíduos com migrânea através da ^{31}P-MRS: Uma revisão sistemática

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ABSTRACT

Introduction: Migraine has a neurological origin and is characterized by failure of central modulation leading to neuronal hyperexcitability. Among the factors related to such excitability is the mitochondrial dysfunction that has been considered since the 1980s. **Objective:** To investigate changes in the cerebral energetic metabolism of individuals with migraine through phosphorus magnetic resonance spectroscopy (^{31}P-MRS). **Methods:** It was searched articles on Pubmed, Web of Science and Science Direct betweenof June, 2018 and February, 2019. There was no restriction regarding the year of publication and language. The combination of the descriptors used for this systematic review was: Migraine AND Magnetic resonance spectroscopy [MESH]. The inclusion criteria chosen were: original articles using ^{31}P-MRS in individuals diagnosed with migraine (with and/or without aura); studies with adults between 18 and 60 years of age diagnosed with episodic or chronic migraine; with control group of individuals without migraine and without pathologies or conditions that would interfere in the results. **Excluded were articles:** incomplete or unpublished; animal studies; and research protocol articles. **Results:** Of the 319 articles found, nine were selected. The sample totaled 216 individuals with migraine (53.7% without aura) and 233 healthy individuals in the control group. It was verified a reduction of phosphocreatine, phosphorylation potential, Mg^{2+} and ATP, whereas it was observed increase of inorganic phosphate and ADP. **Conclusion:** There are alterations in cerebral energetic metabolism in individuals with migraine, revealing mitochondrial dysfunction. However, it is needed more studies with higher quality and analysis of the relationships with the socio-demographic and clinical variables.

Keywords: Migraine; Phosphorus Magnetic Resonance Spectroscopy; ^{31}P-MRS; Brain Energy Metabolism; Mitochondrial Dysfunction.

RESUMO

Introdução: A migrânea tem origem neurológica e é caracterizada por falha na modulação central, levando à hiperexcitabilidade neuronal. Entre os fatores relacionados a essa excitabilidade está a disfunção mitocondrial considerada desde os anos 80. **Objetivo:** Investigar alterações no metabolismo energético cerebral de indivíduos com enxaqueca por espectroscopia de ressonância magnética com fósforo (^{31}P-MRS). **Métodos:** Foram pesquisados artigos no Pubmed, Web of Science e Science Direct entre junho de 2018 e fevereiro de 2019. Não houve restrição quanto ao ano de publicação e idioma. A combinação dos descritores utilizados para esta revisão sistemática foi: *Migraine* AND *Magnetic resonance spectroscopy* [MESH]. Os critérios de inclusão escolhidos foram: artigos originais utilizando ^{31}P-MRS em indivíduos com diagnóstico de migrânea (com e/ou sem aura); estudos com adultos entre 18 e 60 anos diagnosticados com enxaqueca episódica ou crônica; com grupo controle de indivíduos sem migrânea e sem patologias ou condições que interferissem nos resultados. **Foram excluídos os artigos:** incompletos ou inéditos; estudos em animais; e artigos de protocolo de pesquisa. **Resultados:** Dos 319 artigos encontrados, nove foram selecionados. A amostra totalizou 216 indivíduos com migrânea (cerca de 53,7% sem aura) e 233 indivíduos saudáveis no grupo controle. Verificou-se uma redução de fosfocreatina, potencial de fosforilação, Mg^{2+} e ATP, enquanto se observou um aumento de fosfato inorgânico e ADP. **Conclusão:** Existem alterações no metabolismo energético cerebral em indivíduos com migrânea, revelando disfunção mitocondrial. Porém, são necessários mais estudos com maior qualidade e análise das relações com as variáveis sociodemográficas e clínicas.

Descritores: Enxaqueca; Espectroscopia de Ressonância Magnética de Fósforo; ^{31}P-MRS; Metabolismo da Energia Cerebral; Disfunção Mitocondrial.

INTRODUCTION

According to the World Health Organization (WHO),[1] 50 to 75% of individuals between 18 and 65 years old presented at least one headache crisis per year in the world, 30% of them with reports of migraine attacks. Still according to the WHO, 1.7% to 4% of adults in the world population present chronic headache (≥ 15 days/month).[1]

Migraine has a neurological origin and is characterized by a failure in central modulation that leads to neuronal hyperexcitability,[2] it has moderate to severe pain intensity, usually with pulsatile character, presenting predominantly in hemicranial form, with a duration of 4 to 72 hours.[3]

The relationship between migraine and mitochondrial dysfunction has been considered since the 1980s.4 Changes in mitochondrial functionality would lead to high intracellular Ca^{2+} penetration, phosphorylation deficiency, and excessive free radical production causing energy failure in neurons and astrocytes, triggering, among other factors, the Cortical Spreading Depression involved with migraine.[5]

In addition, mitochondrial impairments are presented in muscle biopsy of individuals with migraine, as well as, therapeutic strategies focused on the improvement of mitochondrial metabolism are effective in the treatment of migraine, such as riboflavin, coenzyme Q10, magnesium, etc.[5]

In this context, phosphorus magnetic resonance spectroscopy (^{31}P-MRS) is a non invasive technique used to investigate cerebral energetic metabolism in vivo6 Mitochondrial functionality is verified through the intracellular levels of adenosine diphosphate (ADP), phosphocreatine (PCr), inorganic phosphate (Pi), phosphorylation potential (PP), pH and Mg^{2+} factors that are indispensable for creatine kinase balance. [7,8]

Despite this context, there is still no consensus of the possible mechanisms related to changes in the energy metabolism of individuals with migraine, such as whether this relationship actually exists at the brain level, whether mitochondrial dysfunction would be related to the onset of migraine or it would be the consequence.

Thus, this systematic review aimed to investigate changes in cerebral energetic metabolism of individuals with migraine through ^{31}P-MRS, with the hypothesis that individuals with migraine would have altered rates of ADP, PCr, Pi and Mg^{2+} when compared with a control group, suggesting dysfunction in mitochondrial activity.

METHODS

The study is a Systematic Review developed between June, 2018 and February, 2019, registered in PROSPERO as CRD42018112763. The review was carried out to answer the reasearch guiding question: Are there changes in cerebral energy metabolism in individuals with migraine? In order to answer this question, the acronym PICOS was used to guide the review (P: Individuals with Migraine, I: ^{31}P-MRS, C: individuals without migraine, O: Alterations in cerebral energy metabolism, S: Transversal studies).

Searches were performed on Pubmed and ScienceDirect by combining the descriptors: Migraine AND Magnetic Resonance Spectroscopy [MESH]. It was selected articles without restriction of year of publication and language. The search and selection of articles according to the eligibility criteria was described in the flowchart based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA)9 model (Figure 1).

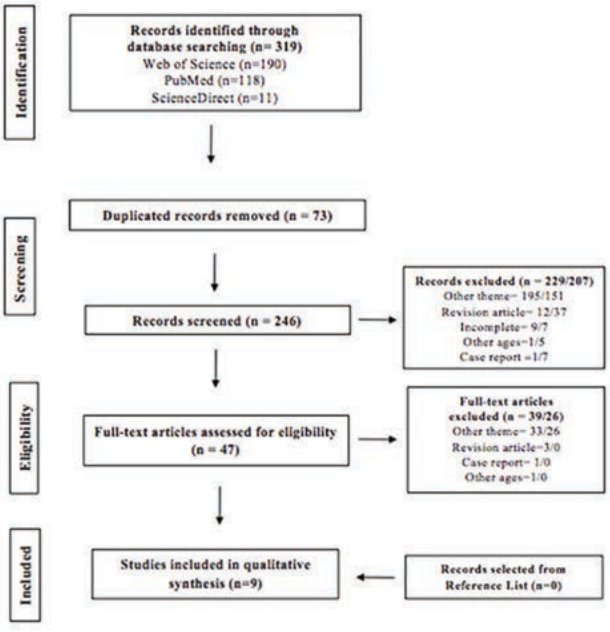

Figure 1. Flowchart of articles selection. Source: Research Data.

The inclusion criteria chosen were: original articles using phosphorus magnetic resonance spectroscopy (^{31}P-MRS) in individuals diagnosed with migraine (with and/or without aura); studies with adults between 18 and 60 years of age diagnosed with episodic or chronic migraine; with control group of individuals without migraine and without pathologies or conditions that would interfere in the results. Excluded were articles: incomplete or unpublished; animal studies; and research protocol articles.

The search and selection of the articles according to the eligibility criteria was done independently by two evaluators (MD and LN), in case of disagreement, they discussed and entered into a consensus. When the disagreement between the two initial evaluators remained, the third evaluator (RM) decided whether or not to include the article in question. At the end of the selection, the eligibility of the studies included in the reference list of the selected articles was verified. The flowchart used, which presents in detail the selection process, follows the model PRISMA[34] (Figure 1).

The selected articles were evaluated according to the Strengthening the Reporting of Observational Studies in Epidemiology Statement - STROBE Statement[10] by the evaluators (MD and LN) independently. There was agreement of 43.6% among the evaluators in the title and abstract reading stage. In the article reading phase, there

was an initial agreement of 61.5% and, after discussion, the decision resulted in 9 articles.

The selected studies presented different methods and variables, making it impossible to carry out quantitative analyzes of the studies. Therefore, results such as age, gender, diagnosis, medication, pain intensity, frequency of attacks, imaging techniques and main results were extracted and expressed in tables for qualitative data analysis.

RESULTS

The search culminated in 319 articles, among which nine studies were selected according to the eligibility criteria of the review. The selected studies presented moderate quality in the writing of the article according to STROBE reaching the average score of 14.6 (66.4%), with a mean of 64,1% of agreement (Table 1).

Regarding the characterization of the subjects, the sample totaled 216 individuals with migraine and 233 healthy individuals in the control group. Among the individuals with migraine, it was observed predominance of female (about 78.2%), adults in middle age, diagnosis of migraine without aura (about 53.7%) and no medication at the time of the imaging (Table 2).

The studies used devices with varied magnetic field strength, between 1.5 and 3T (Table 3). There were prevalence of individuals in the interictal period (88.5%), and the occipital area was chosen in the majority of studies for ^{31}P-MRS analysis,[8,10-15] although it was not the only region.

Regarding the results obtained through ^{31}P-MRS, there was a reduction of PCr,[10,11,16] Phosphorylation potential,[8,16] Mg^{2+}, [8,11-13] and ATP,[8,12] whereas there was an increase in Fi[8,16] and ADP[8,16]. In addition, there was a reduction in Pcr/Pi and Pcr/TP (TP: total phosphorus) in the ictal phase; on the other hand, in the ictal and interictal phase there was an increase in Pi/TP[14] and ↑pMg at ictal stage,[17] suggesting mitochondrial dysfunction. Other studies did not find statistical diferences in terms of PCr/Pi, PCr/ATP, Pi/ATP and pH.[18,15]

DISCUSSION

The findings of the review support the initial hypothesis that suggests the existence of a dysfunction in cerebral energetic metabolism of individuals with migraine. The reduced energy potential observed in individuals with migraine was assumed to result from reduced mitochondrial reserve, which is a biochemical substrate for susceptibility to migraine attacks.[11]

At rest, ATP is the result of the balance between its use and synthesis. ATP is almost exclusively the product of mitochondrial oxidative phosphorylation, requiring glucose and oxygen as a supply. Changes in PCr leads to an imbalance between the synthesis and delivery of ATP, since ADP is refosphorylated by the creatine kinase reaction, converting PCr to creatine.[16] On the other hand, Mg^{2+} is important because it binds to ATP so that the ATP can be active, necessitating ideal levels of Mg^{2+},[16] which has not been seen in individuals with migraine.

Mitochondrial dysfunctions and disturbances in magnesium metabolism at the cerebral and systemic level would lead to a neuronal hyperexcitability already observed in individuals with migraine.[11] Magnesium is an important component in the human metabolism, it is an essential cofactor for more than 300 biochemical reactions.[19] These reactions include cellular energy production and storage stabilization of mitochondrial membranes[20-22]

The Mg^{2+} has membrane stabilizing properties and is fundamental in the function of several ATPases, especially in the Na^+/K^+ ATPase that controls the Na^+ pump. Neuronal hyperexcitability would be a result of the reduction of Mg^{2+} levels that would justify the appearance of Cortical Spreading Depression and the increased sensitivity to the factors that trigger migraine. In addition, Mg^{2+} regulates brain excitation and/or inhibition by potentiating the gamma-aminobutyric acid (GABA) receptors, thus the reduction of Mg^{2+} would lead to hyperexcitability by reducing the inhibitory function of GABA.[23,24]

The reduction of free Mg^{2+} induces the increase of ADP, essential in the regulation of mitochondrial ATP production. High levels of ADP, in turn, induce high rates of oxidation in an attempt to return to homeostasis.[12] Despite the repercussion of Mg^{2+}, Lodi et al.,[12] based on their findings, argue that therapies that increase the efficiency of the production of Mitochondrial ATP would be more advantageous than treatments based on the administration of magnesium.

Because of the importance of Mg^{2+} for energy production, it may have a special role in the pathogenesis of migraine. Nevertheless, it is seen that Mg^{2+} medication is useful in some cases of migraine[25-29]

The predominance of the adoption of the occipital region for analysis through ^{31}P-MRS would be in the fact that it has regional cerebral metabolic oxygen rate higher when compared to other cortical areas. Likewise, the regional cerebral metabolic glucose rate is higher in the occipital white matter and visual cortex than in other areas, and the latter one remains without metabolic changes with age.[30,31]

The reason to some studies not verify alterations on cerebral energetic metabolism could be the brain region choosen to investigate. Changes in energy metabolism in migraineurs have been shown in muscle and platelets[6,32-34] defending a generalized character of energetic metabolism alteration in individuals with migraine that would unlikely exclude the brain.

Some studies found relations between energy metabolism in complicated types of migraine, such as prolonged aura, stroke migraine or hemiplegic migraine[6,11,12,18,34,35] Therefore, rather than influencing the susceptibility to developing a migraine attack, changes in energy metabolism would determine the clinical characteristics of an attack.[18] Probably because of that, some treatments with magnesium do not show good results in the relieving migraine attacks.[36-38]

Another assumption is that the energetic metabolism alterations verified in some individuals diagnosed with typical or classical migraine could be signals to a possible

Table 1. Evaluation of the selected articles in accordance with the STROBE Statement.

Authors (year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	Total	Percentage of Agreement (%)
Montagna et al. (1994)[10]	N/Y	N/N	N/Y	Y/N	N/Y	N/Y	Y/Y	Y/N	Y/N	N/N	N/N	N/N	Y/Y	Y/Y	Y/N	Y/Y	N/N	Y/Y	N/N	Y/Y	N/Y	N/N	10/11	59.1
Reyngoudt et al. (2011)[7]	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	Y/Y	Y/N	N/N	N/N	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/N	Y/Y	N/N	Y/Y	Y/Y	Y/Y	15/17	81.8
Boska et al. (2002)[11]	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	Y/N	N/Y	N/N	Y/Y	Y/Y	Y/N	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/N	Y/Y	Y/N	N/N	16/16	72.7
Lodi et al. (2000)[12]	Y/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	Y/Y	Y/N	Y/Y	N/N	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	Y/Y	N/N	Y/Y	Y/N	Y/Y	18/18	81.8
Ramadan et al. (1989)[13]	N/Y	Y/Y	Y/Y	Y/Y	N/Y	N/Y	Y/Y	Y/N	N/N	N/N	Y/N	Y/N	Y/Y	Y/Y	Y/Y	N/Y	Y/N	Y/Y	N/Y	Y/Y	Y/Y	Y/N	15/15	54.5
Welch et al. (1989)[14]	N/Y	Y/Y	N/Y	Y/Y	N/Y	N/N	N/Y	Y/Y	N/N	N/N	Y/Y	Y/N	Y/Y	Y/Y	Y/N	N/Y	Y/N	Y/Y	Y/N	Y/N	Y/N	Y/N	14/13	45.4
Halvorson et al., (1992)	Y/Y	Y/Y	N/Y	Y/Y	N/N	N/N	Y/Y	Y/N	Y/N	N/N	N/Y	Y/Y	N/N	N/N	Y/Y	Y/Y	N/N	Y/Y	N/N	Y/Y	Y/N	N/N	12/11	77.3
Schulz et al., 2007	Y/Y	Y/Y	Y/Y	Y/N	N/Y	Y/Y	Y/N	Y/N	Y/N	N/Y	Y/Y	Y/Y	N/Y	Y/Y	Y/Y	Y/Y	Y/N	Y/Y	Y/N	Y/N	Y/N	Y/Y	19/15	50.0
Welch et al. (1988)	Y/Y	Y/Y	N/Y	Y/N	N/N	N/N	Y/Y	Y/N	Y/N	N/N	Y/N	Y/N	N/Y	Y/Y	Y/N	Y/Y	Y/N	Y/Y	N/Y	Y/Y	Y/Y	Y/Y	16/12	54.5

Source: Research Data. 1: Title and abstract; 2: Background/rationale; 3: Objectives; 4: Study design; 5: Setting; 6: Participants; 7: Variables; 8: Data sources/ measurement; 9: Bias; 10: Study size; 11: Quantitative variables; 12: Statistical methods; 13: Participants; 14: Descriptive data; 15: Outcome data; 16: Main results; 17: Other analyses; 18: Key results; 19: Limitations; 20: Interpretation; 21: Generalisability. 22: Funding; Y= Yes; N= No

Table 2. Characteristics of the individuals in the selected studies.

Authors (year)	Subjects	Sex	Age	Migraine Type	Migraine Duration	Pain Intensity	Attacks Frequency	Medication
Montagna et al. (1994)[9]	40 (E:22; C:18)w	E: 19F; C: 19F.	E: 34.0 ± 10.0; C: 34.0 ± 18.0	MwoA (22)	19.0 ± 10.0 anos	X	3.6 ± 1.8 attacks/ month	Without medication
Reyngoudt et al. (2011)[7]	45 (E: 19; C:26)	E: 18F; C: 15F	E:32.3 ± 12.1; C: 27.6 ± 10.9	MwoA (19)	X	X	X	Without prophylactic medication
Boska et al. (2002)*[11]	78 (E: 38; C: 40)	E: 32F; C: 27F	E: MWA (40.9 ± 8.4), MwoA (35.7 ± 9.5); C: 37.5 ± 11.3.	MWA (19), MwoA (19)	X	X	X	Without medication
Lodi et al. (2000)*[12]	94 (E:58; C: 36)	E: 40F; C: ?	E: MWA (23.0 ± 2.0), MwoA (32.0 ± 2.0); C: 36.0 ± 3.0.	MWA (37), MwoA (21)	MWA: 11.0 ± 2.0 anos; MwoA: 18.0 ± 2.0 anos.	X	X	Without medication
Ramadan et al. (1989)[13]	44 (E: 19; C: 25)	E: 17F; C: 15F	E: MWA (37.1 ± 13.2) MwoA (34.3 ± 9.7); C: 43.4 ± 18.2	MWA (8), MwoA (11)	X	X	X	Individuals did not use analgesics 4 hours before the imaging. Some used prophylactic medication.
Welch et al. (1989)[14]	47 (E: 20; C: 27)	E: 18F; C: 17F	E: MWA (37.1 ± 13.2) MwoA (37.2 ± 12.0); C: 45.1 ± 17.6.	MWA (8), MwoA (12)	X	X	X	Individuals did not use analgesics 4 hours before the imaging. Some used prophylactic medication.
Halvorson et al., (1992)*	28 (E: 10; C: 18)	X	X	X	X	X	X	X
Schulz et al., (2007)*	26 (E: 10; C: 16)	E: 7F; C: 8F	E: 42.7 ± 13.7; C: 39.0 ± 15.0	MWA (10)	≤1h (6); >1h≤24h (2); >24h ≤7days(1); >7h (1)**	X	≥1 attacks/ month (3); <1 attacks/ month (7)	X
Welch et al. (1988)	47 (E: 20; C: 27)	E: 18F; C: 17F	E: MWA (37.1 ± 13.2) MwoA (37.2 ± 12.0); C: 45.1 ± 17.6.	MWA (8), MwoA (12)	X	X	X	Individuals did not use analgesics 4 hours before the imaging. Some used prophylactic medication.

Source: Research Data. 1: Title and abstract; 2: Background/rationale; 3: Objectives; 4: Study design; 5: Setting; 6: Participants; 7: Variables; 8: Data sources/ measurement; 9: Bias; 10: Study size; 11: Quantitative variables; 12: Statistical methods; 13: Participants; 14: Descriptive data; 15: Outcome data; 16: Main results; 17: Other analyses; 18: Key results; 19: Limitations; 20: Interpretation; 21: Generalisability. 22: Funding; Y= Yes; N= No

progression to a complicated migraine. Knowing the suscetibility to future migraine stroke episode or a progression to a prolonged aura crisis or another type of complicated migraine would help to plan a more specific treatment for each situation. In this way, with more studies at the field, the [31]-RMS could became a search tool to determine individuals at risk to develop a complicated migraine.

This review presented some limitations, such as the necessity to consider subgroups of interest in the articles with various subgroups of complicated migraine. In some articles, it was not possible to find all the information that was intended (age, gender, medication, duration, frequency neither intensity of pain). Furthermore, it was not possible to apply a specific tool of assessment risk of bias neither to develop a meta-analysis due to the variability of the results.

Despite the similarities of the conclusions obtained with the selected articles, it is necessary to carry out more

Table 3. Characteristics of selected studies.

Authors (year)	Ictal/interictal condition	^{31}P-MRS Instrument	Region	Results	Conclusions
Montagna et al. (1994)[9]	Interictal	1.5T, Signa	Occipital lobes	↓PCr; ↑Pi; ↑ADP; ↑V/Vmáx; ↓PP	Presence of unstable metabolic status in brain cells, indicating a defect in the energy metabolism of individuals with migraine without aura.
Reyngoudt et al. (2011)[7]	Interictal	3T, Siemes	Medial occipital lobe	↓PCr; ↑Pi; ↓ATP; ↑ADP; ↓PP; ↓Mg^{2+}	Disturb in the energetic metabolism of individuals with migraine. The reduction of ATP indicates a possible participation of mitochondria in the pathophysiology of migraine.
Boska et al. (2002)*[11]	Interictal	3T, Magnex-SMIS	Calcarine cortex, temporal gyri, occipital gyri, frontal gyri, frontal forceps, genu of corpus callosum, occipital cortex	MwoA: ↑PDE in most brain regions, ↑Mg^{2+} in posterior brain regions. MWA: ↓PCr in anterior brain regions, ↓ Mg^{2+} in posterior brain regions, but no consistent changes in PME, PDE, Pi, or pH.	No substantial alteration of energy metabolism, but the disturbances in Mg^{2+} homeostasis may contribute to brain hyperexcitability
Lodi et al. (2000)*[12]	Interictal	1.5T, Signa	Occipital lobes	↓Cytosolic free Mg^{2+}, ↓free energy released by the reaction of ATP hydrolysis.	There is mitochondrial dysfunction in individuals with migraine secondary to bioenergetics déficit.
Ramadan et al. (1989)[13]	Ictal (10); Interictal (9)	1.89T, Bruker	Frontal, frontotemporal, parieto-occipital, occipital cortex	↓Mg^{2+}, especially between controls and migraineurs measured during an attack. No changes in pH.	Low brain Mg^{2+} is important in migraine pathofhysiology.
Welch et al. (1989)[14]	Ictal (11); Interictal (9)	1.89T, Bruker	Frontal, frontotemporal, parieto-occipital, occipital cortex	Ictal: ↓PCr/Pi; ↓PCr/TP; ↑Pi/TP Interictal: ↑Pi/TP	Energy phosphate metabolism is altered during a migraine attack.
Halvorson et al., (1992)	Ictal (10); Interictal (10)	1.89T, Bruker/ Oxford Research	X	Increased variability of pMg among migraineurs. ↑pMg at ictal stage.	Increased variability of pMg concrntration. The difference between the means of ictal and interictal period was statistically significant.
Schulz et al., (2007)*	Interictal	2T, Bruker	Level of the basal ganglia (white and grey matter)	Non-significant differences between control and migraine with non-motor aura in terms of PCr/Pi , PCr/ATP, Pi/ATP and pH	Energy metabolism alterations may not initiate a migraine attack but may be involved you the clinical manifestation of aura.
Welch et al. (1988)	Ictal (11); Interictal (9)	1.89T, Bruker	Frontal, frontotemporal, parieto-occipital, occipital cortex	Non-significant pH differences between control and migraine at ictal neither interictal phases.	The pain of migraine is unlikely to be caused by cerebral vasodilatation induced by prodromal ischemic brain acidosis neither other pH alterations.

Source: Research Data. PCr: Phosphocreatine; Fi: Inorganic phosphate; ADP: Adenosine diphosphate; V/Vmáx: Rate of ATP synthesis; PP: Phosphorylation potential; ATP: Adenosine triphosphate; MwoA: Migraine without aura; MWA: Migraine with aura; PDE: phosphodiester concentration, PME: phosphomonoester concentration; TP: total phosphorus. *Only the group with migraine (with and/or without aura) and the control group was considered

studies in the area with higher quality and control of the intervening variables like the medication, not only during the imaging, but also in the routine of the individuals. Likewise, it is important to carry out analyzes regarding the relations of ^{31}P-MRS results with sociodemographic and clinical variables such as differences between sexes and age; duration of migraine history, pain intensity, frequency of attacks and medication.

In addition, there has been a dearth of recent studies, which are important, given socioeconomic and cultural differences throughout the years, so that nowadays greater knowledge of the disease, modification of the eating and physical habits profile and greater exposure to medicines may change the results.

From the results verified in the selected studies, there are alterations in cerebral energetic metabolism in individuals with migraine, revealing the importance of considering mitochondrial dysfunction as a component in the pathophysiology of this disease. More studies in the area with higher quality, control of intervening variables and analysis of the relationships with the socio-demographic and clinical variables of the affected individuals are necessary.

CONFLICT OF INTEREST AND FINANCIAL SUPPORT

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ARTICLE HIGHLIGHTS

- There are alterations in cerebral energetic metabolism in individuals with migraine;
- A mitochondrial dysfunction should be considered as a component in the pathophysiology of migraine;
- Energetic metabolism alterations verified in some individuals diagnosed with typical or classical migraine could be signals to a possible progression to a complicated migraine in the future.
- Treatments acting on energetic metabolism, such as magnesium, coenzyme Q10 or riboflavine might be beneficial in the migraine prophylaxis.
- More studies in the area with higher quality, control of intervening variables and analysis of the relationships with the socio-demographic and clinical variables of the affected individuals are necessary.

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Melatonin reverts CGRP expression induced by capsaicin

Melatonina reverte a expressão de CGRP induzida pela capsaicina

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ABSTRACT

Introduction: CGRP, a neuropeptide synthetized and released in the central nervous system and potent vasodilator, has been implicated in migraine physiopathology. Because of that, there are CGRP targeted therapies that decrease CGRP levels. Melatonin, a pineal gland secretion, has already proved its analgesic effect. We aimed to study CGRP expression in an animal model comparing capsaicin, CGRP and melatonin. **Methods:** We used in our study male animal rats and separated them into groups based in the kind of received solution (control group, capsaicin only and melatonin plus capsaicin). It was prepared brain stem slices and measured the CGRP levels in the trigemino nucleus caudalis (TNC). **Results:** Capsaicin group (N = 5) presented low intensity of GCRP expression and animals that received capsaicin plus melatonin (N = 5) showed high intensity of CGRP expression compared to capsaicin group. **Conclusion:** Melatonin decreases CGRP in an experimental model in rats induced by capsaicin, reducing its inflammatory action in cerebral vessels.

Keywords: Melatonin, CGRP, Animal Model.

RESUMO

Introdução: CGRP, um peptídeo produzido e liberado no sistema nervoso central e potente vasodilatador, tem sido implicado na fisiopatologia da Migrânea. Devido a isso, tem surgido diversas terapias direcionadas ao CGRP que reduzem seus níveis. A melatonina, substância produzida pela glândula pineal, já possui seu efeito analgésico comprovado. Nós objetivamos estudar a expressão do CGRP em um modelo animal comparando capsaicina, CGRP e melatonina. **Métodos:** Foi utilizado em nosso estudo ratos machos adultos e estes foram separados em grupos baseados na solução que recebiam (grupo controle, apenas capsaicina e melatonina mais capsaicina). Foram preparadas fatias dos cérebros dos animais e então medidos os níveis de CGRP no núcleo caudal trigeminal. **Resultados:** Grupo da Capsaicina (N = 5) apresentou baixa intensidade da expressão de CGRP, enquanto aqueles animais que receberam capsaicina mais melatonina (N = 5) mostraram altos níveis de expressão de CGRP quando comparados ao grupo do CGRP. **Conclusão:** No nosso estudo experimental com ratos induzidos por capsaicina notou-se que a melatonina reduz os níveis de CGRP, diminuindo a ação inflamatória nos vasos cerebrais.

Descritores: Melatonina, CGRP, Modelo Animal.

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INTRODUCTION

CGRP (Calcitonin Gene-Related Protein) is a 37-amino acid neuropeptide that belongs to a family of structurally related peptides (e.g. calcitonin, amylin, adrenomodulin). This neuropeptide is synthesized and released from sensory nerves in the central nervous system and gastrointestinal system, where it acts as a potent vasodilator[1,2].

It has been implicated in the mechanisms of migraine, acting along trigeminovascular pathways as a vasodilator and nociceptive initiator[3].

CGRP targeted therapies have been studied for both acute (gepants) and preventive (anti-CGRP monoclonal antibodies) treatment[4].

Decrease CGRP levels contribute to migraine treatment. Other strategies may also improve migraine control by reducing CGRP levels, such as the use triptans, coenzyme Q10, serotonin reuptake inhibitors, exercise, acupuncture and some kinds of food, such as grape pomace, cocoa and ginger extracts[4-9].

Melatonin is the primary secretory product of the pineal gland, an indoleamine derivate of the essential amino acid tryptophan[9]. It has been extensively linked to migraine pathophysiology, due to its capacity of membrane stabilization, anti-inflammatory properties, modulation of serotonin, inhibition of dopamine release, gamma amino butyric acid (GAMA) and glutamate neurotransmission, scavenging toxic free radicals and cerebrovascular regulation[10,11]. Besides, melatonin plays important roles in antinociceptive mechanisms. It has been reported that patients suffer less pain and prolonged latencies thresholds during nighttime. These observations were attributed to high melatonin levels through night and its analgesic effect[12].

Melatonin has been studied as a prophylaxis headache treatment in cluster headache and migraine, but its underlying mechanisms has yet to be determined[11]. We aimed to study the pattern of CGRP expression in an experimental model of headache, comparing capsaicin, melatonin and CGRP levels.

METHODS

Animals

The ethical committee of the Universidade Federal de São Paulo (UNIFESP) approved all experimental protocols. All efforts were made to minimize animal suffering following the proposal of International Ethical Guideline for Biomedical Research[13]. Wistar adult male rats (250–300 g) housed under environmentally controlled conditions in a 12 hours light/dark cicle and granted free access to food and water were used. These animals were separated into four groups.

Groups

VEI (n = 5): animals that received vehicle solution only; CAP (n = 5): animals that received capsaicin solution (200 nM) only; and CAP + MEL (n = 5) animals that received capsaicin solution (200 nM) and intraperitoneal melatonin (Sigma, 10 mg/kg) 20 min after capsaicin injection.

Drugs

Capsaicin solution was prepared with 3.05 mg capsaicin (Merck) per 1 ml of vehicle (saline–ethanol–Tween 80, 8:1:1) and diluted 1:50 (200 nM) with saline. Vehicle was diluted 1:50 in saline.

Surgical procedures

Capsaicin stimulation

For this procedure, all rats were anesthetized with pentobarbital (40 mg/kg i.p.) and a surgical opening was made in the region between the scalp and C1 (first cervical vertebra). An amount of 10 ml of capsaicin solution (see "Drugs") was injected into the cisterna magna (over 15 min) using a Hamilton syringe with the aid of a stereotaxic frame[14]. To avoid capsaicin outflow, the needle was only removed 10 min after injection.

Perfusion and immuno-histochemistry

The rats were anesthetized with pentobarbital overdose (120 mg/kg) after two hours infusion, followed by perfusion via the ascending aorta with 0.1 M phosphate saline buffer (PBS, 200 ml, pH 7.4) and 4% paraformaldehyde (200 ml) in 0.1 M phosphate buffer (PB, pH 7.4). Brain stem with attached cervical cord was stored overnight in the same fixative and then placed in a cryoprotectant (30% sucrose in 0.1 M PB, pH 7.4). Coronal serial sections (40 ml) were prepared on a cryostat microtome at -20ºC and collected in PBS with sodium azide (0.1%) to Nissl staining and immuno-histochemistry. Sections were rinsed three times 5 min in PBS, pre-treated with 0.3% H2O2 in PBS for 15 min, rinsed three times 5 min in PBS and pre-incubated in 10% bovine serum albumin (Calbiochem) and 2% normal serum (Vector) in PBS for 2 hours at room temperature. Sections were incubated for 48 hours at 4ºC in PBS solution containing 2% BSA, 2% normal serum and 0.3% Triton X-100 in PBS. Following three washes in PBS, the sections were incubated in a PBS solution contained biotinylated rabbit IgG (1:200) (Vector) for 2 h at room temperature. Sections were rinsed three times 5 min in PBS and incubated with the avidin–biotin–peroxidase complex (Vector) in PBS for 1 h and 30 min at room temperature. Sections were rinsed twice 5 min in PBS and 5 min in Tris–HCl (pH 7.6) and revealed with 0.06% 3,30-diaminobenzidine tetrahydrochloride (Sigma) and with 0.002% H2O2. Sections were then mounted in slides and dehydrated through alcohol to xylene and coverslipped with Entellan (Merck).

Nissl staining

Brain stem slices (40 ml) were hydrated in alcohol solutions of decreased concentration followed by

staining in 0.5% cresyl Violet acetate (Sigma) diluted in 0.1 M acetate buffer pH 4.0. Slices were dehydrated, coverslipped and analyzed by light microscopy optic Zeiss Axiolab.

Quantifications

The CGRP expression sections in TNC layer I/II were counted at 0 to - 1 mm caudal to obex. Representative images of the brainstem slices were digitalized using the Image 1.61 system. The images were transformed into black and White. The image analysis were performed in the anterior region of the TNC, which presented the same area analyzed in all the cuts. It was quantified the optic density from the negative obteined of the images, through the grayscale analysis of the Image Tool program in "pixels" unit. The white color "pixels" were quantified and the results were expressed as mean 3 standard deviation.

Statistical analysis

Data were analyzed using one-way analyses of variance (ANOVA) followed by Tukey's Q test. A value of $p < 0.05$ was accepted as significant.

RESULTS

The studied groups presented difference in the CGRP expression analyzed through the densitometry. Control group that received vehicle into the cisterna magna showed high intensity of CGRP expression (VEI: 733,95 3 144,08) in TNC (layer I/II). In contrast, we observed that animals submitted to trigeminal stimulation of intracisternal capsaicin presented low intensity of CGRP expression (CAP: 295,1 3 49,93). This number is significantly different when we compare CAP x VEI ($p < 0.001$). On the other hand, animals that received intraperitoneal melatonin 20 min before the capsaicin stimulation presented high intensity of CGRP expression (CAP + MEL: 584,02 3 133,59) when compared to animals that received capsaicin only ($p < 0.05$) and similar to VEI group.

The results of immunohistochemical and quantification through CGRP expression optic density were observable in figures 1, 2 and 3.

DISCUSSION

We found in this experimental study direct relation of the levels of Melatonin and Capsaicin in rats model, which were exposed to capsaicin and melatonin injection. After that, it was measured the CGRP density and it showed decrease of its density when associated to capsaicin. However, when we measure melatonin and capsaicin both together, its levels increase and almost normalize. A similar study, has already evidenced data about the relation of melatonin and pineal gland in neurovascular headaches' pathophysiology[15].

Melatonin reverts CGRP alteration induced by capsaicin due to the inhibition of CGRP-induced increase

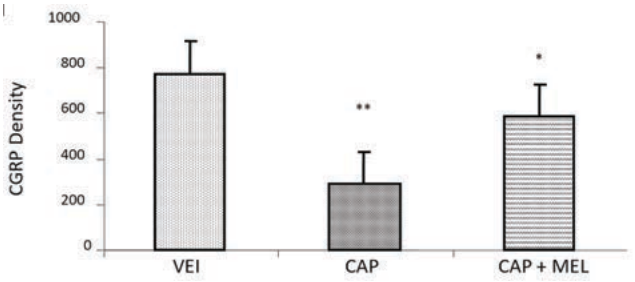

Figure 1. Photomicrographs of CGRP expression in TNC (layer I/II). A: Tissue from animal that received vehicle. B: Tissue from capsaicin-injected animal. C: Tissue from animal that received capsaicin and melatonin. Detail shows the area used to quantify by optic density. x200, scale bar 55 Qc.

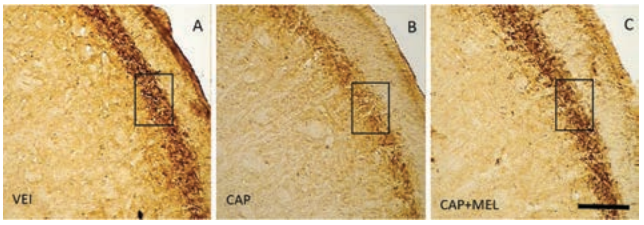

Figure 2. Photomicrographs of CGRP expression in TNC (layer I/II). A: Tissue from animal that received vehicle. B: Tissue from capsaicin-injected animal. C: Tissue from animal that received capsaicin and melatonin. Detail shows the area used to quantify by optic density. x200, scale bar 55 Qc. A', B' and C' represents the negative of the cut images used for quantification by density optic.

in adenylate cyclase. It has already been proposed that CGRP and melatonin may share an active role in the maintenance of arterial tone in cerebral vasculature. Several studies have demonstrated that melatonin causes constriction of rat cerebral arteries[16-18].

We hypothesized melatonin could revert capsaicin effect owing to its ability of avoiding capsaicin. These data are in accordance with previous studies showing melatonin is able to produce a significant inhibition against the neurogenic pain caused by capsaicin. It has been reported the melatonin antinociceptive effect by central administration of it, showing its high lipid solubility, capacity to penetrate the blood-brain-barrier and produce a significant inhibition against the neurogenic pain by activating supraspinal sites. In another study, it was presented that melatonin has the ability of avoid capsaicin effect of initiation and limit the development of "central sensibilization"[19].

Clinical implications

It is an exciting moment to migraine specialists and patients. There is one approved CGRP receptor antagonist and some others being studied. Thus, some doubts about it and its interaction to other established drugs will need to be answered in the next years. Melatonin has been showed as a potential candidate for migraine treatment, including a Brazilian study that

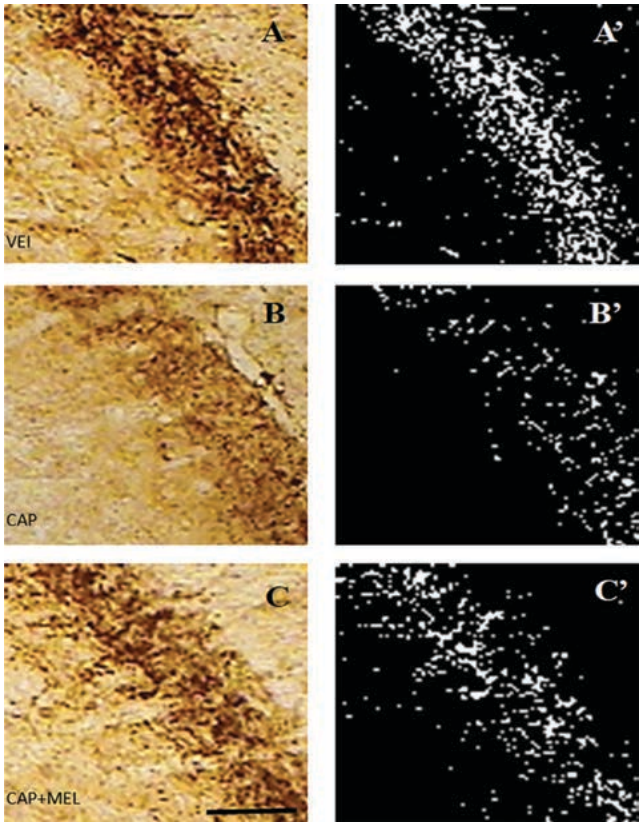

Figure 3. Quantification of CGRP expression through optic density in rats that received: VEI – vehicle (n = 5); CAP – rats that received capsaicin (n = 5); CAP + MEL – rats that received capsaicin and melatonin (n = 5). Rats were killed 60 min after injection. Cells were counted in 40 Qm sections sampled in the TNC layers I and II at 0 to – 1 mm caudal to the obex (3 secctions). *p < 0.05 compared with capsaicin-treated animals; **p <0.001 compared with vehicle only.

found significant headache response with melatonin as a migraine prevention[20].

Our study brings new questions and challenges to headache societies: may migraine patients taking melatonin still respond to CGRP antagonists? Is the decrease of CGRP the real explanation for melatonin improvement in headache disorders? Or do these drugs have synergistic effect?

Melatonin has been associated to CGRP decreased in patients with pure menstrual migraine[21]. It was investigated the melatonin capability of reduce inflammation through decreasing CGRP and inducible nitric oxide synthase. At the beginning of the 2000s, it was proposed that melatonin could inhibit CGRP vasodilatation effect and increases cAMP in rats' arteries[22].

LIMITATIONS

CGRP should be measured in other brain structures besides trigeminal nucleus caudalis, such as trigeminal ganglion, cerebral ventricles, meningeal afferents and even medullary components of the TNC, as well as structures outside the central nervous system (CNS), like skin[23], gastrointestinal tract, lymphocytes[24] and thymus[25].

CONCLUSION

Melatonin decreases CGRP in an experimental model in rats induced by capsaicin, reducing its inflammatory action in cerebral vessels.

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Of the available triptans, which should be chosen and how should they be used?

Dos triptanos disponíveis, quais devem ser escolhidos e como devem ser usados?

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ABSTRACT

There is a plethora of articles dealing with the use of triptans to treat migraine, but so far no unanimity exists regarding the optimal form of using this group of drugs in a patient with recurrent attacks of migraine. Although all of them may exert their pharmacological effects through a known specific mechanism of action, i.e. agonist effects on serotonin 5-HT (1B/1D) receptors, distinct differences exist. The author comment a few facts on the prescription of triptans and possible adverse effects, depending on the clinical scenario. Thus, even though an enormous amount of information has accumulated over the last few decades on triptans, several questions remain to be answered, and research priorities need to be addressed.

Keywords: Triptans, Adverse Effect, Migraine, Prescription.

RESUMO

Há uma infinidade de artigos que tratam do uso de triptanos no tratamento da enxaqueca, mas até agora não existe unanimidade em relação à forma ideal de usar esse grupo de medicamentos em um paciente com ataques recorrentes de enxaqueca. Embora todos eles possam exercer seus efeitos farmacológicos através de um mecanismo de ação específico conhecido, isto é, efeitos agonistas nos receptores da serotonina 5-HT (1B/1D), existem diferenças distintas. Os autores comentam alguns fatos sobre a prescrição de triptanos e possíveis efeitos adversos, dependendo do cenário clínico. Assim, embora uma quantidade enorme de informações tenha se acumulado nas últimas décadas sobre triptanos, várias questões ainda precisam ser respondidas e as prioridades de pesquisa precisam ser abordadas.

Descritores: Triptanos, Efeito Adverso, Enxaqueca, Prescrição.

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There is a plethora of articles dealing with the use of triptans to treat migraine, but so far no unanimity exists regarding the optimal form of using this group of drugs in a patient with recurrent attacks of migraine. Although all of them may exert their pharmacological effects through a known specific mechanism of action, i.e. agonist effects on serotonin 5-HT (1B/1D) receptors, distinct differences exist.

Rapoport and coworkers[1] suggested a few strategies to be adopted when choosing a triptan. They pointed out that some patients prefer a form of treatment that works quickly, some consider as satisfactory treatment triptans that provide complete relief of the pain, while others expect consistent effects as the most important result of triptan treatment. In addition, adverse effects are not tolerated by some migraineurs.[1,2]

Almas and coleagues[3] reported that eletriptan provides consistent migraine relief with an 80-mg dose. Some of these individuals reported failure with a lower dose of 40 mg. This is of major importance since the failure of triptan treatment may be caused by the use of subtherapeutic doses. However, 80 mg is the maximum daily dose allowed and a subsequent intake of eleptriptan must be avoided to prevent serious adverse effects. Nevertheless, only 18.6% and 8% of the patients achieved pain-free status at 2 hours or 24 hours sustained headache response, respectively, on all three sequential treated attacks.[3] Although this is an excellent clinical outcome in terms of current treatment of migraine attacks, it is far from the ideal goal of a foreseeable 100% effective antimigrainous drug.

Seven triptans are currently being used in clinical practice (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan and zolmitriptan)[1, 2]. The relevant literature is controversial regarding the most successful triptan in the treatment of migraine attacks. A number of specific advantages are claimed for some of them as compared with the others. Thus, among the available triptans, which one should be chosen to treat a given patient is still a moot point. In part, this is also due to the different ways in which triptans are tested for their efficacy and possible adverse effects.

Different study end-points are evaluated during trials using triptans.[4] Even though an attempt is always made to attenuate bias during clinical trials, it is virtually impossible to eliminate completely. The 'negative result' bias and the supposed influence of pharmaceutical companies over the publication of favorable results of a given drug produced by them must be considered when interpreting study outcomes.

Huge amounts of money have been spent by pharmaceutical companies to develop new drugs, and the companies' efforts in this regard should be recognized. As a result, we have acquired a very high level of understanding of the mechanisms of action of triptans and their possible clinical applications.

Regarding the clinical use of triptans for migraine attacks, a long-action triptan is the ideal treatment for patients with crises of headache lasting over six hours. Among the triptans naratriptan (5-6 hours) and frovatriptan (26 hours) present a relatively long half-life, and should therefore be remembered when prescribing for such patients.[2] If a short-action triptan is to be used, the physician may recommend an abortive dose of the triptan in addition to a complementary "prophylactic" dose a few hours later, and before the expected recurrence of the headache, in order to maintain the patient free of headache, bearing in mind the maximum safety dose of the drug that one may use daily. This form of treating (abortive/preventive) is not usual in clinical practice. Some authors use the combination of a triptan and NSAIDs to treat such migraine attacks.

The efficacy of a specific triptan does not always correlate with the patient's preferred treatment. The choice of a triptan by the physician will depend upon his or her previous experience, the brand name, marketing pressure, the usual features of the migraine attacks, drug availability, cost, possible adverse side effects, the patient's risk of concomitant atheromatosis, vasospasm susceptibility, or a previous failure or side effect with a particular triptan reported by the patient.

The consensus is that triptan treatment in migraineurs does not increase the risk of stroke, cardiovascular death, or ischemic heart disease.[5] The contraindications for the use of triptans are still poorly defined. There is general agreement that triptans should not be used by patients with a previous stroke or cardiovascular events. However, we should be concerned when dealing with patients with more than two of the following risk factors for atheromatous disease: age >55 years, smoking, arterial hypertension, dyslipidemia, diabetes mellitus or a familial history of myocardial infarction at a young age. Migraine with aura by itself seems to be a risk factor for ischemic cardiovascular disease in women, and the widespread use of hormonal contraception further enhances this risk.

Considering the potential vasoconstriction of the coronary artery elicited by triptans as *in vitro* studies have shown, the number of cardiovascular adverse events reported is surprisingly low.[5] I wonder whether this is a consequence of the characteristic behavior of the migraineurs in avoiding intense physical activities or to the attempt to remain at rest during a migraine attack.

Considering the abovementioned risk factors, we still do not know if there is a significant risk of symptomatic vasoconstriction if we treat an athlete performing a sporting activity with triptan. This scenario must be relatively frequent since the current recommendation is an early treatment of a migraine attack when the pain is still mild.[6, 7] In this line of thinking, should one be afraid of an ischemic event if during an exercise a person presents "triptan sensations" (*i.e.* chest, jaw or arm discomfort)?[8] This question remains to be answered.

As future research priorities we should address the following questions: Why do some patients not respond to triptan? What are the clinical and demographic characteristics of patients who respond, compared to nonresponders[9]? By answering this, we can, therefore, identify those less likely to respond to triptan before prescribing this particular pharmacological agent. Could rest or sleep in a dark room potentiate the action of a triptan compared to subjects that continue their daily activities? Do some environmental conditions (light/

darkness, noise, weather), physiological events or mental states (sleep, anxiety, stress, fear, hunger) influence the action of the drug on the specific migraine attack treated with triptan? It seems that this may be so, which would account for the absence of consistency observed with the use of triptans used at the same dose at different times and by the same individual.

Could variables such as age and gender influence the response to triptans? Why do some patients respond to a specific triptan after reporting a failure of response to a different triptan? Pharmacogenetics may explain this at some future date.

One topic to be discussed is the use of triptans by sexually active women during their fertile period. Although triptans should be avoided during pregnancy, women may use this drug in the first month before realizing that they are pregnant. Does this increase the chance of a possible teratogenic effect of the drug compared to other classes of analgesics? Evidence has suggested that the use of triptans during pregnancy is associated with atonic uterus and blood loss during labor, but the risk of major birth defects is comparable to that of the general population.[10]

Another important issue is whether the physician should explain the contraindications of triptans to the patient. Some may argue that this is not necessary for young patients with no cardiovascular risks. However, it is not uncommon for patients to recommend a painkiller to colleagues and family members, so they need to be made aware that triptans may have serious adverse effects when taken inappropriately. Furthermore, a patient may use triptans for decades without returning to the prescribing physician and his or her safety profile may change with age. This is another point to be borne in mind, considering the importance of patient education.

Thus, despite the fact that an enormous amount of information has accumulated over the last few decades on triptans, several questions still remain to be answered and research priorities need to be addressed.

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Cardiac cephalalgia: A deadly case report

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ABSTRACT

Cardiac cephalalgia is a nosologic entity that has only been acknowledged by the turn of the century, and is, consequently, often underdiagnosed, even by experienced neurologists. Unlike most headaches, however, failing to provide a proper and timely diagnosis can have deadly consequences. Report of a case of cardiac headache attended at the emergency department and literature review. This entity was first described in 1997; no studies have yet determined its prevalence, with the literature relying on case reports. The pathophysiology remains a mystery, with three main hypothesis: spinal convergence of cardiac visceral afferent nerves with somatic afferent nerves from the head, increase of intracranial pressure from decrease in cerebral venous return originated from the reduced cardiac output, and release of inflammatory markers during cardiac ischaemia, such as bradykinin, serotonin and histamin, causing vascular changes. Distinguishing this pathology from others, especially migraine, with which it shares many traits, is of paramount importance: vasoconstrictor drugs such as triptans are absolutely contraindicated, and the outcome can be dramatic. This case illustrates the need to promptly recognize this rare entity since failure to diagnose it can have devastating consequences.

Keywords: Cardiac Cephalalgia; Myocardial Ischemia; Cardiac Arrest.

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INTRODUCTION

Cardiac cephalalgia is a nosologic entity that has only been acknowledged by the turn of the century, and is, consequently, often underdiagnosed, even by experienced neurologists. Unlike most headaches, however, failing to provide a proper and timely diagnosis can have deadly consequences[1].

CASE REPORT

We aim to report he case of ES, a 62 years old Caucasian male with no previous history of headache who went to the ER due to a aching, holocranial, and intense headache lasting over two weeks, with few moments of respite in the meantime, with nausea and emesis but no photo/phonophobia. He developed angina pectoris at the exact same time, and was subjected to a series of cardiac exams in the weeks before the pain, which appeared normal. His comorbities included having been subjected to a kidney transplantation in 2004, being still in dialysis, cardiac pacemaker in 2012, as well as diabetes, heart failure and hypertension. His admission laboratory workup showed creatinine of 9.16, troponine of 1,95 and CK-MB of 24.24; six hours later, the exams showed an increase to 1.85 and 26.83, respectively. His EKG showed no ST-segment elevation.

The hypothesis of cardiac cephalalgia was raised and his care was transferred to the cardiology department. He was admitted to the Coronary Unit, received ASA and clopidogrel and the patient underwent a percutaneous intervention, which subsequently demonstrated critical lesions in anterior descending and right coronaries as well as thrombus in circumflex artery. After an emergency coronary artery bypass, he developed hyperkalemia and went into cardiac arrest, with unsuccessful reanimation attempts. He fulfilled criteria for cardiac cephalalgia, as the headache developed in close temporal relation to the ischaemia and had both moderate to severe intensity, nausea and absence of photophobia (Table 1).

DISCUSSION

This entity was first described in 1997[2]; no studies have yet determined its prevalence, with the literature relying on case reports[3]. The pathophysiology remains a mystery, with three main hypothesis: spinal convergence of cardiac visceral afferent nerves with somatic afferent nerves from the head, increase of intracranial pressure from decrease in cerebral venous return originated from the reduced cardiac output, and release of inflammatory markers during cardiac ischaemia, such as bradykinin, serotonin and histamin, causing vascular changes[4]. Distinguishing this pathology from others, especially migraine, with which it shares many traits, is of paramount importance: vasoconstrictor drugs such as triptans are absolutely contraindicated, and the outcome can be dramatic. In a review of seven cases, three had triple arterial lesion as well, but in all cases the patient survived[4].

CONCLUSION

This case illustrates the need to promptly recognize this rare entity since failure to diagnose it can have devastating consequences.

Table 1. Diagnostic criteria for Cardiac Cephalalgia.

International Headache Classification - 3rd edition	Part two - secondary headaches
A. Any headache fulfilling criterion C.	
B. Acute myocardial ischaemia has been demonstrated.	
C. Evidence of causation demonstrated by at least two of the following:	
1. headache has developed in temporal relation to onset of acute myocardial ischaemia.	
2. either or both of the following:	
a) headache has significantly worsened in parallel with worsening of the myocardial ischaemia.	
b) headache has significantly improved or resolved in parallel with improvement in or resolution of the myocardial ischaemia.	
3. headache has at least two of the following four characteristics:	
a) moderate to severe intensity.	
b) accompanied by nausea.	
c) not accompanied by phototophia or phonophobia.	
d) aggravated by exertion.	
4. headache is relieved by nitroglycerine or derivatives of it.	
D. Not better accounted for by another ICHD-3 diagnosis.	

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Coexistence of Sunct Syndrome and pituitary tumor: A possible association to be recognized

Coexistência entre Cefaleia do tipo SUNCT e tumor pituitário: Uma associação que deve ser reconhecida

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A 46-year-old woman reported headache with migraine without aura and SUNCT symptoms. A previous diagnosis of pituitary macroadenoma was confirmed with MR and an increased prolactin. Cabergoline was started with improvement of symptoms. An imaging follow-up showed a reduction of the macroadenoma (Figure 1). Pituitary adenoma is a intracranial tumor that has been reported in about 8% of patients with SUNCT. Dural stretch and hormonal dysfunction are possible mechanisms for this association. The fact that tumor and SUNCT were ipsilateral and that headache improved after cabergoline may suggest an association between these entities, supporting MR investigation when this type of headache is diagnosed.

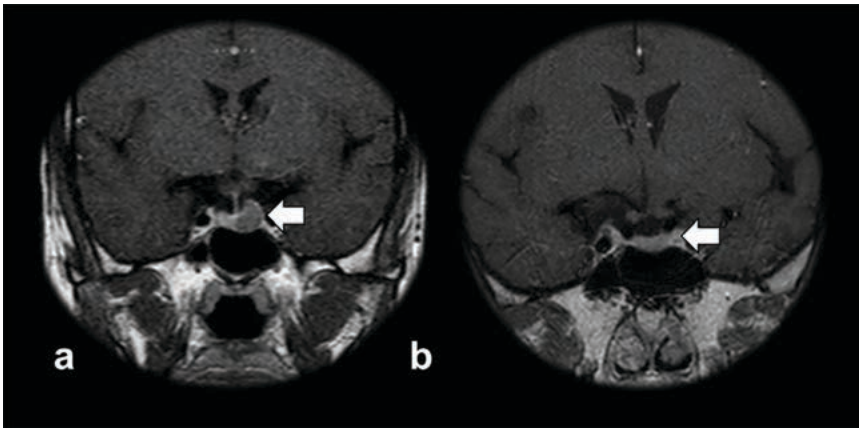

Figure 1. Pituitary MRI, coronal post-gadolinium T1-weighted sequence (a) demonstrate a rounded region of delayed enhancement in the left pituitary compared to the rest of the gland, compatible with adenoma. (b) Imaging follow-up showed a significant reduction of the lesion.

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