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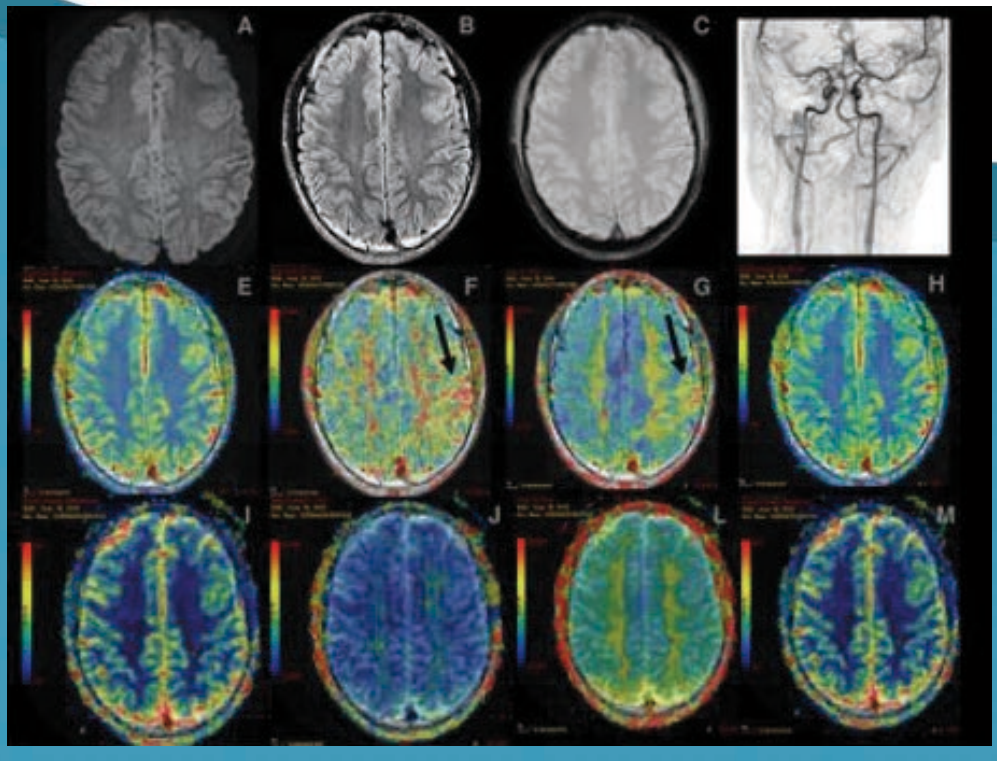
SOCIEDADE BRASILEIRA DE CEFALEIA

Brazilian Headache Society



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CONTENTS

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CONSELHO EDITORIAL

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Cláudio Manoel Brito
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Migraine, Dizziness and Motion Sickness: Are we going in straight lines?

In these edition, Headache Medicine brings two articles about the relation of migraine with common symptoms reported by patients, dizziness and motion sickness, leading to important management dilemmas. A nice report from Argentina (1), researchers from Fleni Hospital in Buenos Aires showed motion sickness not only occurring unrelated to migraine but also as a trigger of headache attacks.

Another study done by Turbino et al (2) in 143 patients diagnosed with vestibular migraine in a tertiary headache center observed associated symptoms such as nausea, vomiting, osmophobia, tinnitus, motion sickness higher in migraine with aura patients.

What are the lines between those symptoms? Do we have same genetic backgrounds, same underlying mechanisms? Which brain structures are involved? Is the cerebellum, the vestibular system, thalamus, hypothalamus, or cerebral cortex affected? Can we classify those patients in a different way? How are we going to treat headaches with dizziness and or motion sickness?

We still have more questions than answers in this topic, hopefully more studies will come so we better understand it.

Marcelo M Valença
Mario F P Peres

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Full Head Block for headache treatment: technical description, indications and mechanisms

Bloqueio completo da cabeça no tratamento das cefaleias: Descrição técnica, indicações e mecanismos

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ABSTRACT

Headache is a most prevalent neurological condition in the world and has a major impact on quality of life. The causes are usually multifactorial and may have a chronic character. Headache management involves pharmacological and non-pharmacological approach; invasive and noninvasive. Peripheral nerve block is already a viable, safe, and effective treatment option, such as major occipital nerve block. Full head block is a minimally invasive proposal of peripheral pain neuromodulation for the treatment of refractory or severe headache, mainly. The aim of this paper is to describe a technique and discuss the role of full head block in the headache management. The proposal is bilaterally anesthetizing the following nerves: major and minor occipital, supraorbital, supratrochlear, zygomatic-temporal and auriculo-temporal with local anesthetic and a corticosteroid. Many aspects should be studied: efficacy and safety of the technique, clinical indications, professional training, need for USG guidance, adequate dose of anesthetic and corticosteroids. In order to further evaluate the role of peripheral blocks in headaches randomized controlled trials are required.

Keywords: Nerve blocks; Occipital nerve; Auriculotemporal nerve; Supraorbital nerve; Supratrochlear nerve; Zygomatic nerve; Primary headache

RESUMO

Cefaleias primárias são condições neurológicas prevalentes no mundo com grande impacto na qualidade de vida. As causas são geralmente multifatoriais e podem ter caráter crônico. O gerenciamento da dor de cabeça envolve abordagem farmacológica e não farmacológica; invasivo e não invasivo. O bloqueio do nervo periférico já é uma opção viável, segura e eficaz de tratamento, como o bloqueio do nervo occipital maior. O bloqueio cefálico completo é uma proposta minimamente invasiva da neuromodulação da dor periférica, principalmente para o tratamento de cefaleias refratárias ou intensas. O objetivo deste artigo é descrever uma técnica e discutir o papel do bloqueio cefálico completo no manejo das cefaleias. A proposta é uma anestesia local bilateraldos seguintes nervos: occipital maior e menor, supraorbital, supratroclear, zigomático-temporal e aurículo-temporal com anestésico local associado a corticoide. Muitos aspectos devem ser estudados: eficácia e segurança da técnica, indicações clínicas, treinamento profissional, necessidade de orientação por ultrassonografia, dose adequada de anestésico e corticosteróide. Para melhor avaliação do papel dos procedimentos periféricos nas cefaleias, ensaios clínicos randomizados e robustos são necessários.

Descritores: Bloqueios nervosos; Nervo occipital; Nervo auriculotemporal; Nervo supraorbital; Nervo supratroclear; Nervo zigomático; Cefaleias

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INTRODUCTION

Headache is the most prevalent neurologic condition in the world[1]. It most affects patient in productive age and is associated with a substantial personal and societal burden. Migraine represents the first highest cause of disability under 50 years of age and the second worldwide[2]. Migraine, the most common primary headache, has been found in 15,2% in Brazil[3], followed by tension-type headache (13%)[4] and chronic headaches (6,9%)[5]. They are frequently multifactorial and have a chronic character. Its treatment can be challenging and involves pharmacological and non-pharmacological, invasive and non-invasive approaches, as well as acute and prophylactic therapy[6].

There are now several non-invasive and invasive options to manage headache. Peripheral nerve block is a minimally invasive therapy and represents an excellent alternative to conventional drugs (responsible for a wide range of side effects due to its action on several neurotransmitters) and to non-pharmalogical neuromodulation, like Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS)[7]. The nerve block can be used in primary (migraine, cluster headache, and nummular headache) and secondary headaches (cervicogenic headache and headache attributed to craniotomy), as well in cranial neuralgias (trigeminal neuropathies, glossopharyngeal and occipital neuralgias)[8]. Nerve block provides rapid pain relief to patients and its analgesic effect often long-lasting (sometimes for weeks to months). The mechanism includes an interruption of neural conduction in peripheral nerves and nerve trunks by the injection of a local anesthetic agent (e.g., lidocaine, bupivacaine). However, it is still incomplete understood, but is likely secondary to effects on central pain modulation via second order neurons in the trigeminocervical complex[9].

Several peripheral cranial nerve targets have been aimed in this approach. Greater occipital nerve is the most studied peripheral nerve block, but there are some others sites already tested, such as lesser occipital nerve, supratrochlear nerve, supraorbital nerve and auriculotemporal[10]. The procedure is fast, easy, generally safe and well tolerated, becoming attractive for clinicians and patients, especially for resistant headaches.

A similar procedure has been done in neurosurgical anesthesia where all peripheral nerves are blocked to anesthetize the scalp, the so-called scalp block[11]. Scalp block involves regional anesthesia to the nerves that innervate the scalp, providing analgesia for tumor excision, epilepsy surgery and deep brain stimulation surgery[12]. Full head block is different from scalp block because of its therapeutic target and technique.

Our study aimed to describe the technique and discuss the role of a full head block in headache management treatment.

METHODS

The proposal of full head nerve block is to anesthetize bilaterally greater lesser and third occipital, supraorbital, supratrochlear, zygomatic-temporal and auriculotemporal nerves. The techniques of each nerve block are detailed below.

Greater occipital nerve (GON) block.

GON is located approximately two thirds of the distance on a line drawn from the center of the mastoid to the external occipital protuberance. GON can also be located palpating occipital artery; because of that, care needs to be taken to avoid intra-arterial injection. Another option is to inject approximately 2 cm lateral to the external occipital protuberance[13].

Lesser occipital nerve (LON) block.

LON is located approximately one third of the way on a line drawn from the center of the mastoid to the greater occipital protuberance[14].

Third occipital nerve (TON) block.

TON is located deep to the semispinalis capitis muscle and two anatomic landmarks are used: the tip of the mastoid process and the C3 spinous process[14]. The

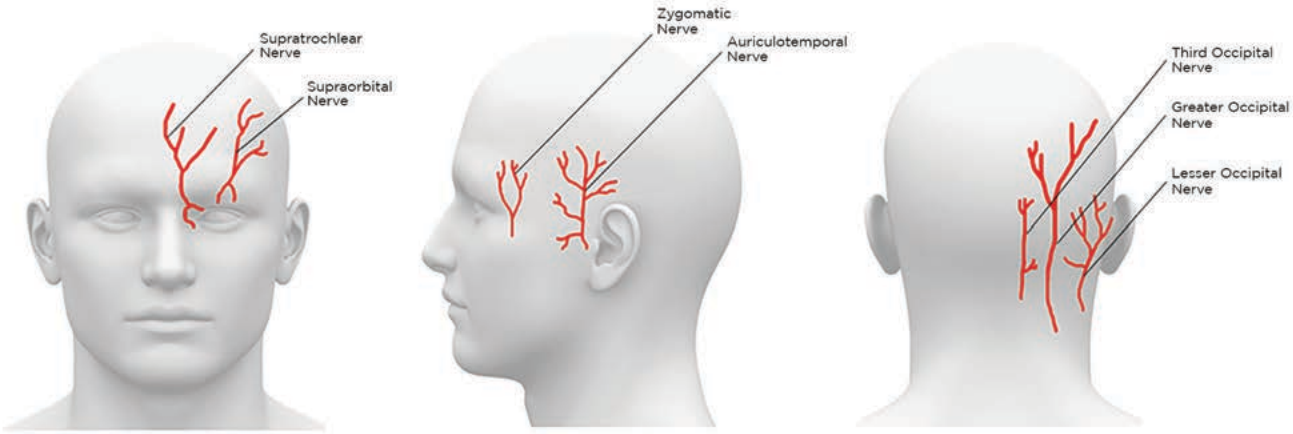

Figure 1. Topography of the nerve's blockage in full head block propose

third occipital nerve lies medial to great occipital nerve and have fibers communication between both, and is blocked in the same injection of GON by the intimacy proximity.

Auriculotemporal nerve (ATN) block

ATN is located at superior to the posterior portion of the zygomatic bone just anterior to the ear. It follows superficial temporal artery that can be palpated and used as a reference for the block[14].

Supraorbital nerve (SON) block

SON, which runs approximately 2 cm lateral to the supratrochlear nerve, the injection can be done in this point, or the needle can be advanced laterally through the same puncture that was used for the STN[13,14].

Supratrochlear nerve (STN) block

STN is blocked by inserting the needle just above the eyebrow over its medial border[13,14].

Zygomatic nerve (ZN) block

ZN is blocked by placing the index finger on ventral rim of the orbit at the lateral canthus of the eye, and firmly press against the supraorbital portion of the zygomatic arch[12,14].

POSSIBLE INDICATIONS

Full head block can be performed together with botulinum toxin, as a bridge therapy, while waiting to the toxin starting to work[15-17]. Refractory headache, primary headache in pregnancy and the presence of contraindications for other treatment's options.

Peripheral nerve block has already been tested for primary headache disorders like migraine prevention, migraine acute treatment, cluster, neuralgia and tension-type, as well as to secondary headache disorders such posttraumatic headache, post-surgical headache and scar related pain. It can also be considered as a transitional treatment in chronic headaches.

LIMITATIONS

The major side effects occur due to local injection. There are related cases of local infection, nerve damage with later neuroma formation, hematoma, local injury to adjacent structures and, rarely, systemic manifestations due to absorption of local anesthetics (seizure, alteration in consciousness and cardiac conduction effects when high doses are used). Using small needles and aiming for perineural sites are helpful in avoiding these side effects. When patient has anatomic abnormalities, such as skull defects, local infection or previous surgical scars, the procedure is not indicated.

Assistant's training about the location of structures, technique and aseptic environment is necessary for a great performance of the procedure. Studies must be designed to identify the efficient amount of local anesthetic, necessity of ultrasound guided[18] and addition of corticosteroid (methylprednisolone or betamethasone).

FUTURE DIRECTIONS

Thereby, clinical trials are important to assess the role of the full head block for headache treatment. It represents the combination of several well tolerated and effective therapy, with a lack of side effects.

DISCUSSION

There are many examples of peripheral targeted treatments, such as low-level laser therapy, topical lidocaine, dry needling, electrical stimulation and massaging[19]. There are other forms of inducing anesthesia with nerve blocks, e.g., lidocaine transdermal patch[20].

It has already been discussed through literature about the role of peripheral nerve block on headache management[21,22]. Peripheral nerve block can result in rapid relief of pain and allodynia, reduce the number of headache days and medication consumption[23] and its effects may last for several weeks. Thereby, nerve block is a viable and safe treatment option for selected groups of headache patients, particularly those with intractable headache.

Although there are many studies about effectiveness of a specific nerve block[24-26], especially greater occipital nerve block[27], there is no case report that apply full head block for treatment of primary headache. Why should we do a full head block? Due to: (1) distribution nerve pain - headaches are not limited to one nerve; (2) necessity of a complete peripheral detachment to arouse neuromodulation; (3) acute response in headache attack; and (4) refractory headaches to others procedures.

CONCLUSION

Considering this rational, structured scientific evidence with blinded and sham-controlled studies is needed to understand the action mechanism, validate doses of the anesthetics, train professionals and establish the efficacy of full nerve block in headache disorders.

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Alice in Wonderland Syndrome

Síndrome de Alice no País das Maravilhas

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At the end of my office hours, I saw to a distressed mother. Her 9-year-old daughter presented that day during recess a condition characterized by strange perceptions. She reported seeing huge and deformed people (big noses, crooked mouths, exceedingly long arms...). The manifestation lasted approximately 15 minutes and was followed by facial paleness and an episode of mental confusion, with verbalization of disconnected words and incoherent phrases. Some minutes later, the child became drowsy and fell asleep. When her mother arrived at the school, she was still sleeping. When she woke up, two hours later, she was lucid and reported only feeling a heaviness in her head.

During questioning, the mother informed that since the age of 8 years, her daughter presented headache episodes preceded sometimes by blurry vision. The mother is a migraineur and her own mother, already deceased, was also one. Nothing abnormal was found when examining the minor and I stated to the mother that the episode was probably a migraine, which during childhood can present this kind of manifestation. In face of the unbelief of the mother, I requested a computed tomography of the head and an EEG – both of which did not show abnormalities.

I had the opportunity to follow-up on this patient over the course of three years. During this time, she presented headache episodes, not all of which were preceded by visual manifestations. In this case, the diagnosis was settled as migraine with aura, consisting of a variant called Alice in Wonderland Syndrome.

Visual auras are the most common and originate from the posterior portion of the brain (occipital lobe). The description of a visual aura is not always easy for the patient. The most detailed and precise descriptions are done through own experience, by either doctors or other healthcare professionals that suffer from this sort of migraine. Data are frequently collected from patients through the anamnesis, in complaints during the crises at emergency services, using questionnaires during interviews, and by analyzing drawings made during the postcritical period. All methods present limitations. Loss of vision in half the visual field (hemianopsia) or in certain points of the visual field (negative scotoma) are common complaints. Scotoma can also be positive and manifest in several ways: focused flashes, colorful circles, the illusion of blinking lights, eye floaters, zigzagging lines, mosaic vision (like a kaleidoscope)... Scotoma can have various colors (gray, red, golden, blue or purple), though the color may not be specific and be more like a very bright white. There is also a form of negative scotoma in which the migraineur sees objects split in half. This condition can either increase in size as the crises evolve or become fragmented into smaller parts.

Auras can be more elaborate and present themselves as distortions of visual figures. These phenomena are more frequent in children and are externalized as perception disorders, which can include various types of body image distortions (macropsias, micropsias, metamorphopsias), feelings of derealization and depersonalization, and changes to their perception of time. This is the Alice in Wonderland syndrome. In this curious syndrome, the patient has the feeling that

people are either exceedingly large (macropsias) or disproportionally small (micropsias). This inadequacy in size can also be perceived regarding one's own body, such that an individual may feel for example that one of their limbs is gigantic. Other manifestations may occur: distortion of their own body segments (as if looking into a distorting mirror) or of others, feeling of levitation or of a double personality, loss of spatial recognition, etc. Transitory alterations in certain areas of the brain (particularly in parietal lobe areas) seem to be responsible for these described psychosensory abnormalities. Auras are believed to be determined through spreading depression, though it is not clear why extremely elaborate auras – with important perception disorders – are more frequent during childhood. Perhaps the immature brain (not entirely myelinated) can be more vulnerable to a spreading depression event. This type of migraine is more common in children and usually begins around the age of 8 years. The associated manifestations, translated into elaborate auras, usually give way during adolescence.

The Alice in Wonderland syndrome was reported for the first time in 1955 by the English psychiatrist John Todd, who believed the syndrome was related to defects in parts that form the eyes. However, it is known now that the condition occurs due to a neural change in perception that affects vision, feelings, touch and even body image. The condition was initially described as Todd's syndrome, but as a reader and admirer of Lewis Carroll, the psychiatrist proposed the name that established Carroll as an author.

Though this is a polemic discussion, it seems like migraines influenced Lewis Carroll's description of some characters in the book Alice in Wonderland. The Englishman Charles Lutwitge Dodgson (1832-1898) adopted the name Lewis Carroll as a pseudonym to sign his works of fiction (4). This is the explanation. Lewis Carroll was a professor, mathematician, poet, painter, amateur photographer and deacon of the Anglican Church. He would sign his academic publications (math and logic) with his real name. Carroll was a curious person that did not get along with adults and adored young girls. He dedicated his most successful books to a girl named Alice, daughter of dean Liddell. It seems that Carroll loved Alice deeply, a 10-year-old girl, while he was 32 years old. The author was also an excellent photographer (photography was considered at the time avant-garde art) and enjoyed photographing girls in either revealing clothes or naked (2,3).

Regardless of Carroll's "bilious headaches", detailed records from his diary (collected 20 years after they were reported) demonstrated that he suffered from migraines with aura. However, the book Alice in Wonderland appeared in 1865, which according to scholars researching his biography was before the beginning of his migraines. Nevertheless, the subject is still under discussion, with some believing the author had already experienced previous migraine events.

In conclusion, I must emphasize that the Alice in Wonderland syndrome is not a prerogative to migraine and should be considered as a differential diagnosis for epilepsy, use of hallucinogenic drugs (such as LSD), consumption of hallucinogenic mushrooms, schizophrenia, and brain tumors. The syndrome can also occur during the initial phases of infection by the Epstein-Barr virus in children (1).

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"No Pain, More Gain"? Affect and Adherence to Exercise in Migraine Patients: A Prospective Cohort Study

"No Pain, More Gain"? Resposta Afetiva e Aderência ao Exercício em Pacientes com Migrânea: Um Estudo Prospectivo

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ABSTRACT

Objectives: To compare the affective and perceptual responses to a standardized exercise session between episodic migraine patients and non-headache persons, and its influence on adherence to an 12-week exercise training program. **Methods:** In a secondary analyses of a prospective cohort enrolled in a clinical trial, we assessed the affective response at rest, at 15th min of exercise, and immediately after an acute 40-min exercise session previously the training program. All measurements were undertaken in headache-free days. Participants were subsequently randomly assigned to a 12-week aerobic exercise-training program, or to a waitlist. In a multiple linear regression model, variables tested as possible predictors of adherence were body mass index, cardiorespiratory fitness, and the perceived exertion and affect scores elicited in the previous exercise session. **Results:** Fifty-four participants were analyzed for acute exercise session data (mean3SD age: 37.37311.5; mean3SD BMI: 26.734.5). Patients (N=28) and controls (N=26) showed no differences in anthropometric characteristics and cardiorespiratory fitness. Compared to controls, migraine patients showed reduced affective response during and after exercise, but showed no differences in perceived exertion. Twenty-five participants (patients: N=13; controls: N=13) concluded the 12-week exercise-training program. Adherence was lower in migraine group (p = 0.1, d = 0.641). Multiple linear regression analysis showed post-exercise affect score as the only predictor variable of adherence to the exercise-training program (β =0.405, p = 0.040). **Conclusions:** This study indicates that migraine patients have lower affective response to exercise, which was associated with adherence to the training program.

Keywords: Psychology; Headache Disorders; Healthy Lifestyle; Sedentary Behavior; Exercise.

RESUMO

Objetivos: Comparar as respostas de valência afetiva e percepção do esforço entre pessoas com migrânea e sem cefaleias durante uma sessão de exercício padronizada e sua influência na aderência a um programa de 12 semanas de treinamento aeróbio. **Métodos:** Em análise secundária de uma coorte prospectiva de um estudo clínico, controlado e randomizado, avaliamos a resposta afetiva basal, no 15º minuto de exercício e imediatamente após uma sessão aguda de exercício aeróbio previamente ao programa de treinamento aeróbio. Todas as mensurações foram conduzidas interictalmente. Um modelo de regressão linear múltipla testou as variáveis basais de IMC, aptidão cardiorrespiratória e percepção do esforço e escores afetivos da sessão aguda de exercício como preditoras de aderência ao programa. **Resultados:** Cinquenta e quatro participantes foram avaliados (média3DP idade: 37,37311,5; média3DP IMC: 26,734,5). Pacientes (N=28) e controles (N=26) não apresentaram diferenças nas características antropométricas e aptidão cardiorrespiratória. Comparado aos controles, pacientes com migrânea exibiram uma resposta afetiva reduzida durante e após a sessão de exercício aguda, mas sem diferenças significativa na percepção do esforço. Vinte e cinco participantes (pacientes: N=13; controles: N=12) concluíram o protocolo de treinamento aeróbio. Aderência foi menor no grupo de pacientes (p = 0,1, d = 0,641). A análise de regressão mostrou a resposta afetiva após a sessão aguda de exercício como única variável preditora de aderência (β = 0,405, p = 0,040). **Conclusão:** Esse estudo sugere que pacientes com migrânea apresentam uma resposta afetiva reduzida ao exercício, a qual está associada a menor aderências ao programa de treinamento aeróbio.

Descritores: Psicologia; Distúrbios da dor de cabeça; Estilo de vida saudável; Comportamento Sedentário; Exercício.

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INTRODUCTION

Even though regular aerobic exercise has been shown effective for migraine prevention (1–4), as a chronic pain condition, migraine may represent an obstacle to physical activity participation. Epidemiological data have shown increased risk for having migraine among individuals in the lowest quintile of cardiorespiratory fitness level (5) and a negative association between migraine prevalence and physical activity levels (6–10). Migraine attacks per se can hinder physical activity participation, and physical activity is considered a trigger factor for around 50-60 % of patients, while 75.6 % and 84.2 % of patients believe that moderate and vigorous exercise can worsen attacks, respectively (11,12). Thus, the prevailing argument to explain this negative relationship between physical activity and migraine has been ascribed to fear-avoidance behavior or kinesiophobia (6–12).

Alternatively, another explanation for this negative association between physical activity and migraine might lie in the affective response to exercise. Affective response to exercise refers to a basic affect domain, or the pleasure/displeasure one may feel when exercising, and it has been established as a determinant factor of future adherence to physical activity participation (13,14). Its theoretical framework encompasses the rewarding, self-reinforcing (hedonic) component of the physical activity behavior (15–17). Exercise performed in the positive valence is associated with higher adherence, whereas exercise eliciting negative responses are more likely to be discontinued (15–17). The affective response to exercise is believed to be operationalized under the so-called dual-mode theory (16-18). This theory proposes a dimensional, rather than categorical, measure of affect, which in its turn depends on whether the exercise is performed below, at, or above the ventilatory threshold (16-18). The ventilatory threshold represents a ventilatory parameter that indicates the cardiometabolic turning point marking the transition from aerobic to anaerobic energy metabolism, above which by-products from anaerobic metabolism (e.g., CO_2, protons, etc.) build-up in the working skeletal muscles, contributing to metabolic acidosis, hyperventilation, limb pain, and early fatigue (16-18). Overall, the affective response is stable and kept on positive valence when the exercise is performed slightly below the ventilatory threshold (or mild to moderate exercise), it largely varies among individuals at the ventilatory threshold (moderate exercise), and decreases to negative valence as exercise intensity surpasses the ventilatory threshold (e.g., vigorous exercise) (18).

Affective response to exercise has never been assessed in migraine patients. Understanding psychological factors related to physical activity behavior in people with migraine has become particularly relevant, since accumulating evidence points to increased risk for mental and cardiovascular diseases in this population (19–22), which in turn can be reduced by regular physical activity (23). Thus, we wondered whether migraine patients would exhibit altered affective response to a single bout of exercise (i.e., acute session) performed at the ventilatory threshold (moderate intensity) compared to non-headache individuals, and whether this previous measure of affect would predict adherence to a subsequent aerobic exercise-training program performed at the same exercise intensity. We hypothesized that individuals with migraine would rate lower affective scores in the exercise session compared to non-headache individuals, and the affective response to exercise would be positively associated with future adherence to the exercise-training program.

METHODS

This is a prospective cohort study using secondary, post hoc analyses of affect and perceptual measures during an exercise session, and their influence in adherence to future exercise participation in a supervised exercise training program. Data were retrieved from patients enrolled in a clinical trial registered in the National Institute of Health (www.ClinicalTrials.gov) under #NCT01972607, and part of the clinical trial results has been published elsewhere (2). The study protocol complied with the Good Clinical Practice Principles and the Helsinki Declaration, and was approved by the Research Ethics Committee of the Federal University of São Paulo/Brazil, registered under #08152011.

Participants

Participants were recruited from São Paulo Hospital´s Headache Unit and a tertiary clinic, The inclusion criteria were: individuals aged 20 to 60 years, of both sexes, physically inactive (defined as ≤ 1 day/week of leisure-time physical activity the previous 12 months), non-headache individuals and patients with episodic migraine (having 1-14 attacks per month), including migraine without aura, migraine with aura, or presenting both migraine subtypes, according to the 2nd edition of the International Classification of Headache Disorders (24). Exclusion criteria were: taking any prescribed preventive medication, except abortive medication during migraine attacks, taking dietary supplements, pregnancy, clinical history of cardiovascular, pulmonary, metabolic, rheumatic, musculoskeletal, and others neurological diseases, including other headaches. All participants had a neurological and cardiac (electrocardiographic) examination before inclusion in study and gave signed informed consent.

After being screened for inclusion in the study by two headache-trained neurologists (authors RTR and MFPP), all participants were given a headache diary and were examined every 4 weeks (clinical visits) until the end of the study for checking headache status (paper-based headache diaries). Participants who self-reported never having migraine, without any headache in the past 3 months, and did not present any headache in their diaries, were considered as controls.

Procedures and Measures

The cardiopulmonary exercise tests, affect measures, and the aerobic exercise-training program were

conducted at the Center for Studies in Psychobiology and Exercise, a University-based center, on two separated experimental visits. About 1-2 weeks after the screening visit, participants were scheduled for the cardiorespiratory fitness assessment. Around a week later, participants performed an acute, 40-min aerobic exercise session for assessment of the affective response. Figure 1 summarizes the study's design. All measurements were undertaken between 8:00AM and 11:00AM, interictally. All women were assessed within the follicular period of the menstrual cycle for the affective response.

After the acute exercise session, researcher ABO randomly assigned participants (simple randomization, 1:1 assignment rate) to receive a 12-week aerobic exercise-training program or enter a waitlist. An online software generated random numbers, previously attributed as follows: odd numbers = exercise-training program, even numbers = waitlist.

Cardiorespiratory Fitness Assessment

Participants underwent a maximal cardiopulmonary exercise test on a treadmill (Centurion 300, MICROMED, Brasília, DF, Brazil) with ramp protocol for determination of peak oxygen uptake (VO_{2Peak}), a gold-standard measure of cardiorespiratory fitness, and the ventilatory threshold, an amply used cardiometabolic parameter of submaximal exercise intensity. The ventilatory threshold consist of a ventilatory indicator reflecting the skeletal muscle energy metabolism, which set the turning point of exercise intensity above which the metabolic acidosis from anaerobic metabolism supplementation cannot be buffered (25). Determination criteria for VO_{2Peak} consisted of meeting at least two of the following criteria: 1) to reach the maximal age-predicted heart rate (220-age); 2) respiratory exchange ratio > 1.1; 3) rate of perceived exertion (RPE) ≥ 18. The ventilatory threshold was determined adopting the ventilatory equivalents method, defined as the stage where the first rise in the ventilatory equivalent of O2 (VE/VO2) occurs without concurrent rise in the ventilatory equivalent of CO2 (VE/VCO2) (25). Tests were conducted by a cardiologist and exercise physiologist, not informed about participants assignment and independent of the study.

Affective Response and Perceived Exertion Assessment

Participants were informed that they would perform a moderate aerobic exercise session according to the current guidelines for exercise prescription. They were also aware that the main goal at this visit was to assess psychological aspects of exercise.

The exercise session consisted of 40 minutes of moderate walking/jogging on treadmill (depending on participant's initial fitness level), composed by 5 minutes of warm-up, 30 minutes inside the aimed intensity, and 5 minutes of cool down period. Intensity was set at the work rate ($m.min^{-1}$), rate of perceived exertion (RPE), and heart rate (HR) corresponding to the ventilatory threshold. The HR was monitored by a heart rate monitor(Polar® Electro, model F5, Finland) and the RPE was assessed by the 20-point Borg's scale (26) . The RPE score measured at the last minute of the exercise session was used in the analyses.

Feeling Scale (FS) was used as a measure of affect. FS is a bipolar, Likert-type scale amply used as a broad dimension of pleasure/displeasure (basic affect) during exercise (27). It is composed by 11 points ranging from +5 to -5, with anchors at zero ("Neutral") and at each odd integer, from "Very Good" (+5) to "Very Bad" (-5). The affective response was assessed by two experienced exercise physiologists (ABO, DLG), randomly assigned (coin flipping) to conduct each experiment. FS was employed at three time points: at rest, just before the exercise initiates (FSREST), at the 15th minute of exercise (FSEXE), and immediately after the exercise cessation (FSPOST). Conversation was limited to answering participants' questions regarding the protocol, and participants were not allowed to listen to music, or to use any portable electronics. Participants experiencing migraine attacks during the exercise sessions were excluded from the analysis.

Aerobic Exercise-Training Protocol

Exercise sessions reproduced the acute exercise session protocol with regard duration and intensity, and were delivered 3 times per week. All exercise sessions were supervised by exercise physiologists (ABO, DLG, and MTM).

Statistical Analyses

Differences between migraine and control groups for anthropometric variables, cardiopulmonary fitness, and adherence for the exercise-training groups were analyzed by independent t-test. Comparisons between groups for affective response were analyzed by repeated-measures ANOVA,with 2 groups x 3 time points (FSREST, FSEXE, and FSPOST); Bonferroni's adjustments were computed for the confidence intervals of multiple pairwise comparisons. If

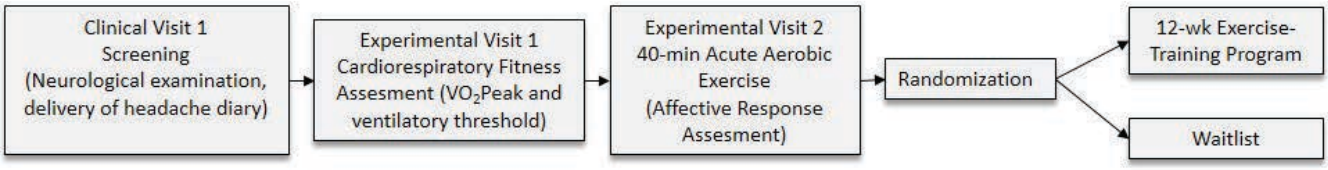

Figure 1. Study´s design.

the assumption of sphericity was violated in the repeated-measures ANOVAs, the degrees of freedom were adjusted by Greeenhouse-Geisser´s correction.

A multiple linear regression model was applied to test the predictors of adherence to exercise (dependent variable). Adherence was defined as the percentage of attendance to the exercise protocol sessions. Predictors variables were, body mass index (BMI), VO_{2Peak}, RPE, FSREST, FSEXE, and FSPOST. A stepwise method for variables selection was employed in the regression model. Analyses were computed by the SPSS software (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY), and graphs were designed by GraphPad Prism® software (GraphPad Software Inc., Version 5.0, San Diego, CA). A $p < 0.05$ was considered statistically significant.

RESULTS

Participants' flow in the study is shown in Figure 2. Fifty-four participants (Male: N = 10, Female: N = 44; mean3SD age: 37.37311.5 and BMI: 26.734.5) were included in the analyses. Migraine (n = 28) and control (n = 26) groups were homogenous regarding sex, age, BMI, cardiorespiratory fitness, as well as there were no difference between groups for the cardiorespiratory data and work rate elicited at the ventilatory threshold (both ~ 55 % of maximal cardiorespiratory fitness, and ~70 % of maximal heart rate) (Table 1).

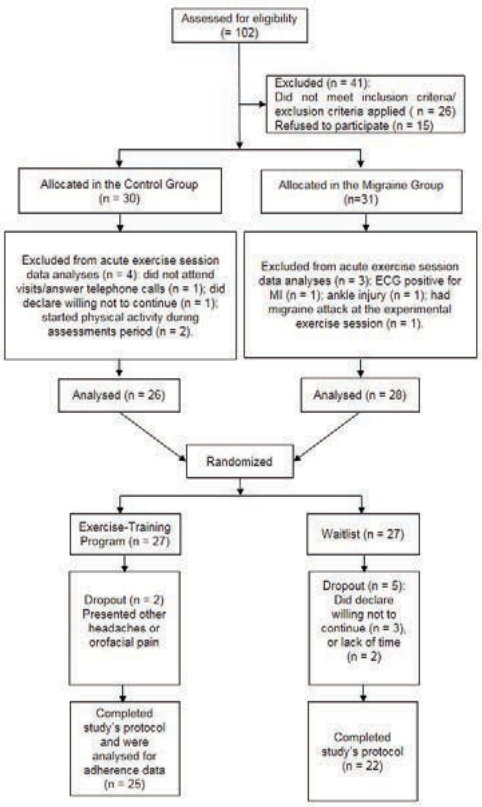

Figure 2. Participants' flow in the study.

Table 1. Participants` anthropometrical, clinical, and cardiorespiratory data.

Variables	Migraine (N=28)	Control (n=26)
Anthropometric Data		
Sex (%)		
Male	5(17.9)	5(19.2)
Female	23(82.1)	21(80.8)
Age (years)	38.6±12.4	35.9±10.5
Body Weight (kg)	72.1±16.0	69.7±11.7
Height (m)	1.62±0.08	1.63±0.08
BMI (kg/m²)	26.9±5.0	26.4±3.9
Clinical Data		
Living w/ Disease (yrs)	17.6±11.1	0
Days with Headaches (/month)	9.5±6.0	0
Migraine Frequency (/month)	8.6±6.0	0
Pain Intensity (0-3)	1.58±0.3	0
Cardiopulmonary Data		
At Peak		
VO_{2Peak} ($mL.kg.min^{-2}$)	31.8±6.7	32.5±7.5
HR (b.p.m)	181.7±15.1	182.8±9.5
HR (% age predicted)	100.3±6.6	99.5±4.8
WR (watts)	110.0±32.5	116.2±34.5
RPE	19.4±0.9	19.3±0.9
At the Ventilatory Threshold		
VO_2 (% VO_{2Peak})	55.2±9.4	55.4±7.3
HR (b.p.m)	127.7±17.7	125.1±15.6
WR (watts)	66.1±20.2	64.2±16.6
RPE	10.3±2.5	10.1±2.3

VO_{2Peak}: Peak oxygen uptake. HR: Heart rate. WR: Work rate. RPE: Rate of perceived effort.

For the affective response to acute exercise, repeated-measures ANOVA of FS showed a main effect of time [$F(1, 52) = 37.5$; $p < 0.001$; $\eta^2 = 0.64$], a main effect of group [$F(1, 52) = 10.6$; $p < 0.002$; $\eta^2 = 0.41$], and interaction [$F(2, 104) = 5.9$; $p < 0.048$; $\eta^2 = 0.2$] (Fig. 3a). Multiple pairwise comparisons showed no differences between migraine and control groups for FSREST (mean3SD = 3.531.9 vs 431.1, respectively, $p = 0.262$), while there was a significant progressive decline from FSREST to FSPOST for both groups (Fig. 3a). The migraine group had a steeper decline, which was significantly lower than control group for FSEXE (mean3SD = 2.031.3 vs 2.931.3, $p < 0.031$, respectively) and FSPOST (mean3SD = 1.431.4 vs 2.731.3, $p = 0.001$, respectively) (Fig. 2a). The RPE at the end of the exercise session was not different between control and migraine groups (mean3SD = 11.631.4 *vs* 12.431.4, $p > 0.05$, $d = 0.1$, respectively) (Fig. 3b).

For the adherence data, twenty-five (migraine: n = 13; control: n = 12) completed the exercise-training program and were analyzed in the regression model. There was no difference between groups for adherence

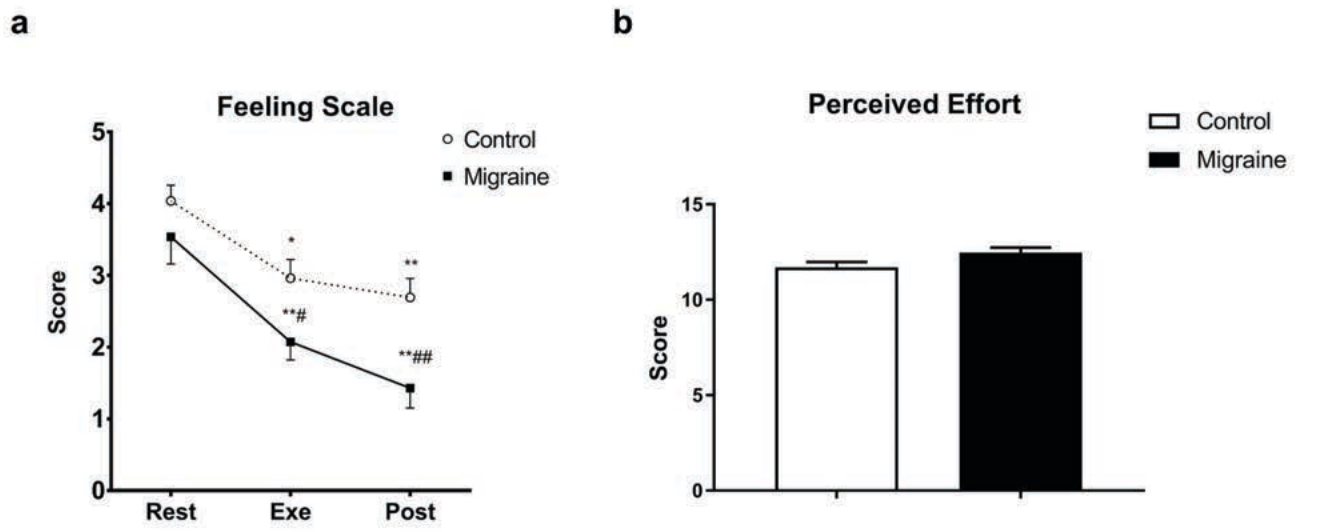

Figure 3. Affective response (a) and perceived effort (b) of a 40-min. aerobic exercise session; Data are expressed as mean±SE. *: $p < 0.05$ *vs* REST; **: $p < 0.01$ *vs* REST; #: $p < 0.05$ *vs* Control; ##: $p < 0.01$ *vs* Control; Multiple pairwise comparisons of repeated-measure ANOVA.

to the exercise program [55.9318.4 % *vs* 66.4313.0 %, respectively; $t(23) = 1.6$, $p = 0.1$, d = 0.64], although a large effect size was observed.

In the whole exercise-training cohort, multiple linear regression analysis showed FSPOST the only predictor variable of adherence to subsequent exercise-training program ($\beta = 0.405$, $p = 0.04$). Based on the adjusted R^2 data of our model, 12.9 % of variance in adherence was explained by FSPOST. Also, the coefficients of this model showed that, if all the other variables were kept constant, every 1-point drop in the FS score resulted in 4.2 % drop in adherence.

In order to further explore whether adherence could be affected by migraine attacks frequency, we used Pearson's correlations test (as these variables presented normal distribution) for analyses between clinical variables and adherence in the exercise-training migraine cohort. There were no significant correlations between adherence and changes in pre-post values (Δ values) for days with migraine ($r = -0.01$, $p = 0.981$), or migraine frequency ($r = -0.18$, $p = 0.544$) (Table 2). Neither there were correlations between clinical and affective variables.

DISCUSSION

Our study shows for the first time a reduced affective response to aerobic exercise, both during and after an acute exercise session, in individuals with migraine compared to non-headache individuals. Also, we provided further evidence to the idea considering the affective response to exercise captured by the feeling scale as a potential determinant factor of physical activity behavior (14-17), by showing a predictive value of post-exercise affect on future adherence to an exercise program.

Although physical activity behavior is determined by a myriad of social, cultural, and affective-cognitive factors, the affective response to exercise is a relevant and well-established topic in behavioral research, since it is associated with physical activity participation, and its public health implications in terms of management and prevention of mental and cardiovascular diseases (14-17). Indeed, in recognition of the relevance of affective response on future exercise participation, current exercise prescription guidelines have included the feeling scale as a complementary parameter of exercise intensity (28).

We recognize that physical activity behavior is complex, and in migraine patients, attack-related pain *per se* can hinder physical activity participation and contribute to fear-avoidance behavior/kinesiophobia (11-13). In fact, anxiety-related processes seem to play a relevant role in physical activity behavior in this population. For example, in a cohort of 100 patients, Farris et al (2019) showed that intentional avoidance of physical activity is prevalent in up to 78 % of patients, and it positively correlates with migraine frequency (11). Still in this study, over 70 % of patients reported avoiding both moderate and vigorous exercise on average 3 times *per* week in the previous month, indicating that intentional avoidance constitutes a relevant factor contributing to lower physical activity in this population (11). In another analysis, the same group found that physical activity avoidance is influenced by anxiety sensitivity, and higher anxiety score were associated with a significant increase in the odds of PA avoidance at both moderate and vigorous intensities, with stronger associations between the domains physical concerns and vigorous exercise avoidance (up to 7.5-fold increase) (12). Although we did not inquire our patients about their believes/perceptions of exercise as a trigger, or anxiety sensitivity scores, migraine frequency or days with migraine had no correlation with adherence

Table 2. Correlations between adherence and migraine clinical data.

		Adherence to Exercise	Migraine Days	Migraine Frequency	Δ Migraine Days	Δ Migraine Frequency
Adherence	-	-				
	-					
Migraine Days	*r*	-.35	-			
	p	.23				
Migraine Frequency	*r*	-.37	.86	-		
	p	.20	<.001			
Δ Migraine Days	*r*	-.00	.36	.30	-	
	p	.98	.22	.31		
Δ Migraine Frequency	*r*	-.18	.17	.20	.88	-
	p	.54	.57	.49	<.001	

to the training program or affective response, and our sample was composed by patients voluntarily interested in exercise who did not report any attack attributed to physical exercise (based on headache diaries data). As such, the results found here add a new perspective in understanding the negative relationship between migraine and physical activity levels, which to date has been unanimously ascribed to fear-avoidance/anxiety mechanisms. The affect-based process contemplates the hedonic, self-reinforcing properties of physical activity (14-18), which are thought to be mediated by common neurophysiological mechanisms disrupted in migraine pathophysiology, such as monoaminergic, opioidergic, and endocannabinoidergic signaling (2,4). Therefore, it is likely that altered affective processes occurring during the physical exercise session could also influence this negative relationship between migraine and physical activity. This merits further investigation.

Lastly, but not least, anxiety-related processes may eventually underlie the negative affect-exercise adherence relationship, as anxiety sensitivity has shown to moderate the affective response to exercise in other clinical populations (29). Farris's group showed that in low-active smokers seeking treatment for smoking cessation, anxiety sensitivity negatively associated with physical activity enjoyment scale (PACES) and correlated with anxiety and mood in the 1-mile walk test (29). The authors ponder that anxiety sensitivity may attenuate positive physical feelings (enjoyable feelings) elicited by physical activity, exacerbate the forcasting of negative affective and physical outcomes, resulting in affective states that contribute to avoidance behavior (29).

With regard the exercise intensity and its implication on the affect-adherence relationship, a consistent line of evidence suggests a negative association between vigorous exercise and long-term adherence to physical activity (14-18). These authors criticize the "no pain, no gain" pop culture, arguing that in terms of public health, pursuing higher exercise intensity may be detrimental for assuring long-term adherence to physical activity participation. Exercise performed at the ventilatory threshold, as used here, prevents the build-up of by-products and metabolites from anaerobic metabolism, and hence hyperventilation, limb pain, and early fatigue (19). It also promotes cardiorespiratory fitness and is a standardized cardiometabolic parameter of exercise intensity. Nonetheless, affective response at this intensity largely varies in the population (19). On the other hand, as vigorous exercise may also promote specific therapeutic effects, recent work has aimed at manipulating exercise prescription in order to conceive vigorous exercise with positive affect, and hence, promote long-term adherence to high intensity exercise (30). These authors have employed repeated, short high-intensity bouts of exercise (also known as high intensity interval training, or "HIIT") (30). In the context of migraine, data from clinical trials have shown preventive effects with either moderate (i.e., at the ventilatory threshold) (2-4), or vigorous exercise performed as HIIT (≥ 90% of maximal HR) (31). In the later study, vigorous exercise performed with the HIIT approach promoted superior clinical effects on migraine frequency, cardiorespiratory fitness, and retinal blood vessels dilation, suggesting greater clinical and cardiovascular effects compared to moderate exercise (31). Because to date there is no study comparing long-term adherence between vigorous *vs* moderate exercise in migraine patients, these data underscore the need for further studies aiming at investigating psychological and physiological outcomes from different exercise prescriptions in migraine trials, and developing new strategies to increase the affective component of physical activity.

The affective response and adherence to exercise should be further investigated in people with migraine. As outlined by Farris et al (2019), clinicians should aim at managing the subjective appraisal of bodily sensations by incorporating psychoeducation strategies to reinforce the clinical benefits of regular physical activity (2-3), adjusting current exercise prescriptions frames to fit gradual exposure approaches (i.e., desensitization), and by comparing beliefs of migraine trigger effects of physical activity with objective data (12). We propose for the newbie patient that is physically inactive or low-active (i.e., those not meeting the minimum amount of physical activity recommended by health and exercise guidelines), practitioners should preconize a reduced session time for aerobic exercise (e.g., up to

20 minutes), with gradual, progressive load increment until targeted perceptual (e.g., keep between 11 and 13 on 20-point Borg´s scale, the verbal anchors "Light" and "Somewhat hard", respectively), affective (e.g., no lower than +1 on feeling scale, the verbal anchor "Good"), and cardiovascular parameters (e.g., not above ventilatory threshold, or ~70 % of maximal age-predicted HR). Other exercise prescription approaches (e.g., HIIT) should be also tested in this population to establish safe, enjoyable, and realistic exercise routines that assure adherence.

One should be aware of several limitations in this study while interpreting these findings. This study found a large effect size for the affect variables outcome, but the small sample size yielded underpowered data (β = 0.73), and limit extrapolation from the regression model. From clinical practice, we perceive that migraine patients interested in participating in studies with physical exercise represent a minority of this population, and this may constitute selection bias. Additionally, based on headache diaries checking, physical activity was not a trigger among the patients of this study, most participants were women, and there were some restrictive inclusion criteria. All these factors limit the generalizability of our results. Importantly, the expectation towards improvement in headaches through exercise training might have rendered patients more motivated than control individuals. Yet, if this was true, our results would be underestimated. Another limitation concerns to performance bias, as the experimenters that conducted the exercise sessions were not blinded to participants' conditions. This could have resulted in unequal attention delivered by the experimenters to the participants, influencing the affect scores. Lastly, although the exercise protocol tried to reproduce a regular aerobic exercise session, it is not possible to exclude the influence of factors related to the laboratory/experimental settings.

The strengths of this study are the prospective design, the use of gold-standard measure of cardiorespiratory fitness, and standardized exercise testing and prescription based on ventilatory threshold, which allowed us to compare subjective psychological parameters in response to an objective, physiologic stimulus.

CONCLUSIONS

In conclusion, the affective response to an aerobic exercise of equivalent physiological intensity is reduced in migraine patients compared to non-headache individuals, and predicted adherence to future participation in an exercise-training program. Interventions with physical activity/exercise should adopt the feeling scale as a complementary parameter of exercise intensity and exploit activities that elicit higher affective responses.

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Accompanying Symptoms in Vestibular Migraine

Sintomas Acompanhantes na Enxaqueca Vestibular

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ABSTRACT

Objective: The aim of this study was to classify the patients with vestibular migraine into the subgroups with and without aura, and to evaluate the occurrence of the accompanying symptoms of migraine in each subgroup. **Methods:** A prospective study performed at a tertiary center of vestibular migraine, with patients fulfilling definitive diagnostic criteria for vestibular migraine through International Classification of Headache Disorders ICHD-3 β. Patients were stratified in the subtypes with and without aura, and the accompanying symptoms were verified in each subgroup. **Results:** A total of 143 patients were included, 124 women and 19 men (86% and 13%, respectively). The mean age of onset of migraine in the patients ranged from 4 to 71 years (SD: 16.0) with a mean of 23 years, and an average headache frequency of 17 days per month (SD: 19.6), with a visual analog scale mean of 7.45 (SD: 1.88). Of the 143 patients evaluated, 101 (70%) had ICHD-3 β criteria for the diagnosis of migraine with aura. In patients with the migraine subgroup with aura, we found a higher relative risk for nausea 2,78 (CI: 0.15-1.0; p0.04), vomiting, 2.65 (CI: 1.26-5.55; p0.009), phonophobia 3,546 (1,647-7,637, p0,001), osmophobia 3,016 (1,219-7,462, p0,014), kinesiophobia, 2,391 (1,128-5,071, p, 021), tinnitus 2,275 (1,062-4,873, 032), aural fullness 3,934 (1,519 - 10,192, p0,003), motion sickness associated with dizziness 3,924 (1,415 - 10,881, p0,006). **Conclusion:** In our center, migraine with aura was the most frequent subtype of migraine in patients with vestibular migraine. During the head attacks, some associated symptoms were more likely to occur in the aura subgroup, among them: nausea, vomiting, phonophobia, osmophobia, kinesiophobia, tinnitus, aural fullness and motion sickness accompanied by dizziness. In our sample, vestibular migraine associated with migraine with aura showed a higher risk of associated symptoms, suggesting that this subgroup is more severe, and with a more disabling disease.

Keywords: Migraine with aura; Migraine without aura; Vertigo; Vestibular disorders; Dizziness.

RESUMO

Objetivo: O objetivo deste estudo foi classificar os pacientes com enxaqueca vestibular nos subgrupos com e sem aura e avaliar a ocorrência dos sintomas associados à enxaqueca em cada subgrupo. **Métodos:** Estudo prospectivo realizado em um centro terciário de enxaqueca vestibular, com pacientes preenchendo critérios diagnósticos definitivos para enxaqueca vestibular por meio da Classificação Internacional de Distúrbios da Dor de Cabeça ICHD-3 β. Os pacientes foram estratificados nos subtipos com e sem aura, e os sintomas associados foram verificados em cada subgrupo. **Resultados:** Foram incluídos 143 pacientes, 124 mulheres e 19 homens (86% e 13%, respectivamente). A idade média de início da enxaqueca nos pacientes variou de 4 a 71 anos (DP: 16,0), com média de 23 anos e frequência média de cefaleia de 17 dias por mês (DP: 19,6), com média da escala visual analógica de 7,45 (DP: 1,88). Dos 143 pacientes avaliados, 101 (70%) apresentavam critérios ICHD-3 β para o diagnóstico de enxaqueca com aura. Nos pacientes com subgrupo de enxaqueca com aura, encontramos maior risco relativo de náusea 2,78 (IC: 0,15-1,0; p0,04), vômitos 2,65 (IC: 1,26-5,55; p0,009), fonofobia 3.546 (1.647-7.637, p0.001), osmofobia 3.016 (1.219-7.462, p0.014), cinesiofobia, 2.391 (1.128-5.071, p, 021), zumbido 2.275 (1.062-4.873, 032), plenitude auricular 3.934 (1.519 - 10.192, p0.003), enjoo de movimento associado a tontura 3.924 (1.415 - 10.881, p0.006). **Conclusão:** Em nosso centro, a enxaqueca com aura foi o subtipo mais frequente de enxaqueca em pacientes com enxaqueca vestibular. Durante os ataques na cabeça, alguns sintomas associados apresentaram maior probabilidade de ocorrer no subgrupo aura, entre eles: náusea, vômito, fonofobia, osmofobia, cinesiofobia, zumbido, plenitude aural e enjoo acompanhados de tontura. Em nossa amostra, a enxaqueca vestibular associada à enxaqueca com aura apresentou maior risco de sintomas associados, sugerindo que esse subgrupo é mais grave e com uma doença mais incapacitante.

Descritores: Enxaqueca com aura; Enxaqueca sem aura; Vertigem; Distúrbios vestibulares; Tontura.

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INTRODUCTION

Vestibular migraine (VM) is one of the variants of migraine, with vestibular symptoms (VS) beyond the typical disease model, with a lifetime prevalence of 1%.[1] It is the most common cause of episodic vertigo and the second most frequent cause of vertigo in general.[2]

Studies on vertigo and dizziness showed a prevalence of 4% to 51.7% among patients with migraine.[3] A tertiary neuro-otology center studied the epidemiology of vestibular disorders and their clinical form and found 28.2% of patients with VM. [4]

Many authors have already demonstrated the association between migraine and vestibular symptoms, which are three times more common in the migraine population.[2]

The International Headache Society (IHS) has included in an appendix, in 2013, the third edition of the International Classification of Headache Disorders a first step towards the identification of new entities.[5,6] (Table 1)

The accompanying symptoms are part of the diagnostic criteria for both migraine and vestibular migraine and may be responsible together with vestibular symptoms for the significant impact on patients' quality of life.[7]

Table 1. VM diagnostic criteria - ICHD-B β diagnosis

Definite V	
1.	At least five episodes with vestibular symptoms of a moderate or severe intensity, lasting 5 minutes to 72 hours.
2.	Current or previous history of migraine with or without aura according to the International Classification of Headache Disorders (ICHD).
3.	One or more migraine features with at least 50% of the vestibular episodes: - Headache with at least two of the following characteristics: one-sided location, pulsating quality, moderate or severe pain intensity, aggravation by routine physical activity; - Photophobia and phonophobia; - Visual aura.
4.	Not better accounted for by another vestibular or ICHD diagnosis.

Photophobia, phonophobia, nausea, and vomiting are present in the diagnostic criteria of VM and should accompany at least 50% of the episodes of dizziness.[5-6]

The association of VM with subtypes of migraine, migraine with and without aura, and its association with accompanying symptoms has not been consistently analyzed in the literature.

OBJECTIVE

To classify the patients with definitive diagnosis of VM in the subtypes of migraine with and without aura and to evaluate the accompanying symptoms of each subgroup.

METHODS

A prospective study carried out in a tertiary VM outpatient clinic at the Federal University of São Paulo, from Jan 2014 to July 2016, by a neurologist specialized in headache, where demographic data was collected, as diagnosis of the migraine subtypes and accompanying symptoms.

We evaluated 198 patients with vestibular symptoms and headache, and 55 patients were excluded. All patients included had diagnostic criteria for definitive VM by ICHD-3β, and the neurological and otoneurological examination of these patients was normal.

We excluded 55 patients, where dizziness could be attributed to systemic causes, or to patients with neurological diseases (epilepsy, stroke) and vestibular, as well as those who used ototoxic medications, chronic alcoholics, patients with a history of drug addiction, previous history of otologic diseases (antecedent of repeated ear infections, ear trauma) and cranial injuries.

Audiometric examination and computerized cranial tomography were performed, before inclusion of the patients. Patients with low-frequency sensorineural hearing loss were excluded, as well as patients with ischemic lesions in neuroimaging

Regarding statistics, we first characterized the sample collected by calculating frequencies and percentages or means and standard deviations. Patients were then divided into migraine without aura and migraine with aura and the rates and the percentages were obtained for each group.

The groups were compared with respect to the follow-up symptoms, using the chi-square test [7] and, if necessary, the Fisher's exact test.[8]. Odds ratios (OR) and respective 95% confidence intervals (95% CI) were also calculated.[8]

The statistical package used was Minitab, version 18.

This research was approved by the Ethics Committee of the University and the patients completed the Informed Consent Term.

RESULTS

Of the 198 patients evaluated, 55 were excluded with a definitive diagnosis of VM. Thus, the group consisted of 124 women and 19 men (86% and 13%, respectively). The mean age of onset of migraine in patients ranged from 4 to 71 years, with a mean of 23 years (SD16), with a mean frequency of 17 days of headache per month (SD10.8). Of the 143 patients with VM, 101 (70%) had ICHD-3 β criteria for migraine with aura (MA) and 29% (42) for migraine without aura (MWO) (Table 2).

As for the type of aura, 87 (86%) patients presented visual aura, 31 (30%), sensory aura and 3 (2.9%), motor aura (Table 3).

Concerning pain intensity assessed by visual analog scale (VAS), a mean of 7.45 (SD1.88) was obtained.

During VM crises, we evaluated some accompanying symptoms in the subgroups of migraine with and without aura. The symptoms were more frequent in VM with aura.

Table 2. Demographic and clinical characteristics of patients with migraine

Variable	N	Mean	SD
Age (years)	143	37.83	17.66
Age at headache onset (years)	143	23.13	16.08
Pain duration (hours)	143	15.43	9.92
Pain frequency (days/ month)	143	17.52	10.82
Daily headache (months)	143	13.53	19.68
Pain intensity (VAS)	143	7.45	1.88
Sex		Female 86.71%	Male 13.29%
Aura		with aura 70.63%	without aura 29.37%

SD: standard deviation, VAS: visual analog scale.

Table 3. Frequency distribution of the variable Type of aura

Type of aura	Yes		No	
	n	%	n	%
Visual aura	87	86,14	14	13,86
Sensory Aura	31	30,69	70	69,31
Motor aura	3	2,97	98	97,03
Others	2	1,98	99	98,02

n: number of patients.

In the MA subgroup we found a higher relative risk for: nausea 2,788 (1,020 - 7,623, p0,040); vomiting 2,655 (1,269-5,557, p0.009); phonophobia 3,546 (1,647 - 7,637, p = 0.001), osmophobia 3,016 (1,219 - 7,462, p = 0,014), kinesiophobia 2,391 (1,128 - 5,071, p = 0,021), tinnitus 4,273 (1,215 - 15,049, p = 3,934 (1,519-10,192, p = 0.003), motion sickness associated with dizziness 3,924 (1,415-10,881, p = 0.006) (Table 4).

DISCUSSION

The migraine association with aura and MV remains controversial. In the study by Calhoun et al.[9], which aimed to determine and characterize the prevalence of dizziness in migraine, 425 patients were evaluated, of which 28% had MA. The prevalence of dizziness was twice as high (24.5% vs 12.1%) in migraine with aura compared to migraine without aura (P <0.01). Prevalence also increased with age (P <0.05).

Another study[10] evaluated the prevalence of vertigo, dizziness, and VM over the years in patients diagnosed with migraine, comparing them with a control group. Both groups were assessed for symptoms of dizziness and vertigo.

The study included 327 patients diagnosed with migraine with and without aura and 324 controls with no history of a frequent headache. 199 (60.9%) patients had migraine with aura (MA), 128 (39.1%) migraine without aura (MWA).

Patients of the MA subgroup had, more frequently, vertigo symptoms/dizziness than those with MWA. Of the 199 patients in the MA subgroup, 19 (14.84%) always reported vertigo symptoms/dizziness associated with headache, than those of the MWA 19 subgroup (9.55%) reported. Patients in the MA subgroup had a higher association with dizziness and vertigo (P <0001).

In Neuhauser's study[11], 4869 patients were evaluated on the epidemiology of MV in the general population. In this sample 33 patients had VM, being 36% MA and 64% MWA, and after regression analysis of migraine with aura, it was not a risk factor for VM.

In the study by Cohen et al,(12), they identified predictive factors of the VM of the 147 individuals, 100 (68%) were women and 47 (32%) men aged 15 to 92 years (mean age 45 years). Of the 147 evaluated, 57 (39%) had migraine with aura and 90 (61%) had no aura;

Table 4. Joint frequency distribution between patient characteristics and VM and migraine groups with aura and without aura, p-value of the chi-square test, odds ratio and respective 95% confidence interval.

Variables	Without aura		With aura		P Value	Odds ratio	Confidenc interval	
	n	%	n	%				
Nausea	33	78,57	92	91,02	0,040	2,788	1,020	7,623
Vomiting	17	40,48	65	64,36	0,009	2,655	1,269	5,557
Phonophobia	13	30,95	101	61,39	0,001	3,546	1,647	7,637
Photophobia	14	33,33	51	50,50	0,060	2,040	0,963	4,322
Osmophobia	7	16,67	38	37,62	0,014	3,016	1,219	7,462
Kinesiophobia	14	33,33	55	54,46	0,021	2,391	1,128	5,071
Tinnitus	3	7,14	25	24,75	0,016	4,273	1,215	15,049
Headache	25	59,52	75	74,26	0,080	1,962	0,917	4,197
Aural fullness	6	14,29	40	39,60	0,003	3,934	1,519	10,192
Hearing loss	5	11,90	18	17,82	0,380	1,605	0,554	4,650
Motion sickness + headache	6	14,29	30	29,70	0,053	2,535	0,967	6,647
Motion sickness + dizziness	5	11,90	35	34,65	0,006	3,924	1,415	10,881
Motion sickness	6	14,29	29	28,71	0,068	2,417	0,920	6,348

Source: the author

of the subgroup with aura 21 (37%) were male and 36 (63%) female. A significant difference was observed in the subgroups of migraine patients with vestibular symptoms: sensitivity to bright lights occurred in 74% of the subgroup with aura and 43% in the subgroup without aura (p <0001), motion sickness (51% with aura and 39% without aura) and climate changes (54% with aura and 31% without aura), the differences approached but did not reach significance (P = 0.08 and .07, respectively).

To investigate the clinical features of multiple diseases that involved vertigo/dizziness, Esch et al.[13] investigated 122 patients, and only 16 were diagnosed with VM, where the accompanying symptoms were evaluated. Of the patients, 7 (44%) had aura, 16 (100%) reported nausea, 7 (44%) vomiting, 11 (69%) photophobia and 11 (69%) phonophobia, as well as asymmetric hearing loss in 12 (75%) and tinnitus in 2 (13%).

A study published in the Neurology Journal [14] on VM, its clinical evolution and cochlear dysfunctions in a 9-year follow-up, followed 61 patients with the diagnosis. The accompanying symptoms were assessed at baseline and followed-up after nine years.

The most frequent accompanying symptoms at the initial evaluation were photophobia in 59% of the patients and phonophobia in 54%, during the 9-year follow-up, these symptoms were 80% and 77%, respectively.

During VM crises, cochlear symptoms appeared in 49% of the patients, tinnitus in 33%, auditory symptoms (tinnitus symmetrical, aural fullness) in 26% and hearing difficulty in 26%. Initially, 18% of the patients reported aura and, during follow-up, 44% of the patients reported symptoms.

This study followed patients with a definitive diagnosis of VM for nine years, their accompanying and cochlear symptoms both at admission and during follow-up, showed worsening of symptoms also in the interictal period. It was possible to observe the appearance of aura during the patients' follow-up of the patients. The author of the publication suggests that the worsening of the evolution of symptoms, including in the interictal period, may be associated with a progressive deterioration of the vestibular system caused by the disease.

In our sample, patients with VM diagnosis of the aura subgroup had a higher chance of presenting nausea, vomiting, phonophobia, osmophobia, kinesiophobia, tinnitus, auricular fullness and motion sickness associated with dizziness. Photophobia, headache, hearing loss, headache-associated kinesis, and isolated kinesis were not associated with the MA subgroup.

There are, to date, no other studies correlating the odds ratio of the accompanying symptoms between the VM and the subgroups of migraine.

We must emphasize the significant size of this sample, and that this is a tertiary research center of VM. All patients were diagnosed by a neurologist specialized in headache and vestibular symptoms and met the criteria of VM according to ICHD-3 β.

Although there was no statistical difference between the groups (migraine with or without aura regarding vestibular symptoms), they appeared three times more in the subgroup with aura. However, because of the size of our sample, it may not be possible to state that having aura is a risk factor for developing vestibular symptoms. Thus, studies with larger populations should be carried out.

It is still relevant to note that, in the aura subgroup, the accompanying symptoms had a higher relative risk ratio for several accompanying symptoms, which demonstrates the greater severity and a more debilitating condition for this association of diagnoses.

Leão's cortical spreading depression[15] in migraine with aura and neuronal hyperexcitability exacerbate the trigeminal activation process, thus causing neurogenic inflammation. This could contribute to the activation and sustained sensitization of this process, as well as cause reversible vasospasm of the internal auditory artery, responsible for vestibular symptoms, both during VM crises, and could also be responsible for damages in this pathway, which could justify vestibular symptoms, even during the interictal period.[16,17]

CONCLUSION

Patients with vestibular migraine and migraine with aura, when compared to patients with VM and migraine without aura, present a higher relative risk of having accompanying symptoms such as nausea, vomiting, phonophobia, osmophobia, kinesiophobia, tinnitus, auricular fullness, and motion sickness associated with dizziness.

Detailed anamnesis and the active search for the presence of aura, during the initial assessment and also during the evolution of the patient with VM, are necessary, in order to diagnose vestibular symptoms. Diagnosing this subgroup with aura, where the accompanying symptoms are more frequent, makes them a group of patients with a more severe disease and with a worse prognosis.

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Motion Sickness in Headache Patients

Cinetose em pacientes com cefaleias

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ABSTRACT

Introduction: Headache is one of the most frequent consultations in neurology. Some patients with headache report intolerance to passive mobilization, associated with dizziness, nausea, vomiting, known as motion sickness. These symptoms are caused by a conflict between the systems: visual, vestibular and somatosensitive. **Objective:** To determine the prevalence of motion sickness in patients who consult due to headache. **Method:** Cross-sectional, retrospective and descriptive study. It included patients over 18 years of age, who consulted for headache at the Headache Clinic, during the period from January 2 to June 30, 2017, through a structured interview. **Results:** Of a total of 266 patients: 62 (23.30%) presented motion sickness (mean age 41.5 years; 80.6% were women). 14 described motion sickness only in childhood and 48 persisted with symptoms until the time of consultation. Among the patients with headache and motion sickness 52 (83.87%) presented migraine; 7 patients presented tension headaches; 2 in salvos; 1 undetermined The prevalence of migraine was higher in those who reported motion sickness only in childhood compared to those who continued with motion sickness (85.7 vs. 56.25%, p = 0.045), 12.5% of patients with current motion sickness reported it as a migraine trigger, 204 patients did not have motion sickness (76.7%). **Conclusion:** We consider that in patients with headache it is important to identify motion sickness as it can be limiting and also be a migraine trigger. Its diagnosis and treatment would improve the quality of life of our patients.

Keywords: Individual susceptibility, Motion sensitivity, Motion sickness, Migraine.

RESUMO

Introdução: Dor de cabeça é uma das razões mais frequentes de consultas em neurologia. Alguns pacientes com dor de cabeça relatam intolerância à mobilização passiva, associada a tontura, náusea, vômito, conhecida como cinetose. Esses sintomas são causados por um conflito entre os sistemas: visual, vestibular e somatossensitivo. **Objetivo:** Determinar a prevalência de cinetose em pacientes consultados por dor de cabeça. **Método:** Estudo transversal, retrospectivo e descritivo. Foram incluídos pacientes com idade superior a 18 anos, consultados para dor de cabeça na Clínica de Dor de Cabeça, do Hospital Fleni, Buenos Aires, Argentina, no período de 2 de janeiro a 30 de junho de 2017, por meio de entrevista estruturada. **Resultados:** Do total de 266 pacientes: 62 (23,3%) apresentaram cinetose (idade média de 41,5 anos; 80,6% eram mulheres), 14 descreveram-na apenas na infância e 48 persistiram com sintomas até o momento da consulta. Entre os pacientes com dor de cabeça e cinetose 52 (83,9%) apresentaram enxaqueca, 7 pacientes apresentaram cefaléia tensional, 2 cefaleia em salvas. A prevalência de enxaqueca foi maior naqueles que relataram cinetose apenas na infância em comparação aos que continuaram com ela (85,7 vs. 56,2%, p = 0,045), 12,5% dos pacientes com cinetose atual relataram isso como um gatilho para enxaqueca. 204 pacientes não apresentaram cinetose (76,7%). **Conclusão:** Consideramos que em pacientes com dor de cabeça é importante identificar a cinetose, pois pode ser limitante e também desencadear uma enxaqueca. Seu diagnóstico e tratamento melhorariam a qualidade de vida de nossos pacientes.

Descritores: Susceptibilidade individual, Sensibilidade a movimentos, Cinetose, Enxaqueca.

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INTRODUCTION

Headache is one of the most frequent causes for consultations in neurology. Headache represents a broad and heterogeneous group of clinical entities; being tension-type headache the most prevalent in the general population; followed by migraine.

Migraine prevalence varies between 10-16%, with female predominance of 3/1; representing a significant socio-economic and personal impact (1). It is among the ten most prevalent disorders and is classified as the second cause of disability of all diseases worldwide (2). Migraine is characterized by recurrent attacks of moderate to severe pain, of pulsatile characteristic, associated with photophobia or, phonophobia, nausea and / or vomiting, which sometimes becomes incapacitating for the individual's daily life, in both social and labor aspects.

Some patients who consult for headache also report intolerance to passive mobilization; known as motion sickness. More than two thousand years ago Hippocrates observed that "…. Sailing in the sea caused movement disorder … (Reason and Brand, 1975), The term "nausea" derives from the Greek root "Naus" which means a ship (3). Motion sickness is a syndrome present in healthy subjects, triggered by passive movement (car trips, trains, airplanes, ships) or by the illusion of movement (environmental movement surrounding it; exposure to 3D movies, virtual reality). Active movement of the head during a trip in a means of transport (passive movement) can cause or worsen it (3).

This syndrome is characterized by a group of signs and symptoms, among which are mentioned, dizziness, nausea, vomiting, drowsiness, yawns, irritability, paleness, bradycardia, palpitations, ataxic gait, arterial hypotension, apathy, headache. (4). The severity of symptoms varies according to individual susceptibility and the intensity of the stimulus to which the subject is exposed. Increased susceptibility has been suggested in women, the menstrual cycle being implicated as a trigger; In addition to some evidence of genetic contribution, variables such as anxiety or fear and sleep deprivation may contribute; reason why the prevalence described in the literature is very variable (1-90%) (5). Susceptibility begins around 6 or 7 years of age; with a peak between 9 and 10 years; which implies that hormonal changes per se would not have a direct effect. These symptoms are caused by incongruous sensory interactions; a conflict between the visual, vestibular and somatosensitive systems. Before an acute trigger the symptoms last for hours to a day after the stimulus is suspended; If the stimulus continues, such as a boat trip, relief occurs by central adaptation (habituation) in approximately 3 days.

OBJECTIVES

The primary objectives of this study were to determine the prevalence of motion sickness in patients who consulted a neurology service due to headache; and identify what type of headache is most frequently associated with motion sickness. Secondary objectives, to determine the severity of motion sickness and identify motion sickness as a possible migraine trigger.

METHODS

A cross-sectional, retrospective and descriptive study was carried out; which included patients over 18 years of age, who consulted for headache as the primary complaint in the Headache Section of Pain Clinic, Hospital Fleni, Buenos Aires, Argentina, during the period from January 2 to June 30, 2017. A structured questionnaire was used for the interview and the data were analyzed.

Headache diagnoses were made applying the criteria of the International Classification of Headache Disorders, 2013. Motion sickness was classified using the Motion sickness susceptibility questionnaire short-form (MSSQ-Short) (6) according to the stimulus that triggers the symptom in Mild: terrestrial trigger , Moderate: acquatic trigger; Severe: aerial and visual trigger.

The STATA v13 program was used. Quantitative data were expressed in means +/- SD or numbers and their percentages. Normality was evaluated according to asymmetry, kurtosis and Z test. For the comparison of proportions, a non-parametric Wilcoxon rank-sum test was used.

Study approved by the Research and Ethics Committee, given the exception of taking informed consent.

RESULTS

Of a total of 266 patients who consulted Fleni Hospital due to headache, 62 (23.3%) presented motion sickness, mean age was 41.5 years; 80.6% were women. Of which 14 patients described motion sickness exclusively during childhood and 48 patients reported persisting with the symptoms until the time of consultation (Graph 1). The latter were classified according to the intensity of motion sickness in: mild 64.5%; moderate 16.7% and severe 18.8%.

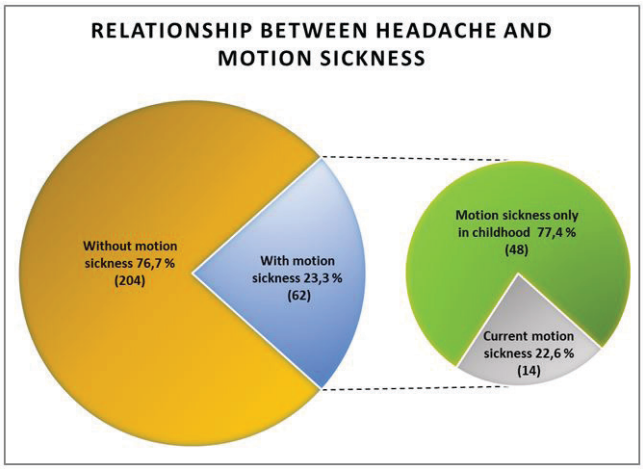
From the group of patients with headache and motion sickness; 52 (83.9%) met diagnostic criteria for migraine (62.9% episodic, 9.7% with aura and 11.3% chronic); 11.3% of patients had tension headache; 3.2% cluster headache and 1.6% headache of undetermined characteristic (Graph 2).

The prevalence of migraine was higher in those patients who reported motion sickness only in childhood compared to those who continued with motion sickness (85.7 vs. 56.2%, p = 0.045). 12.5% of patients with current motion sickness reported it as a migraine trigger.

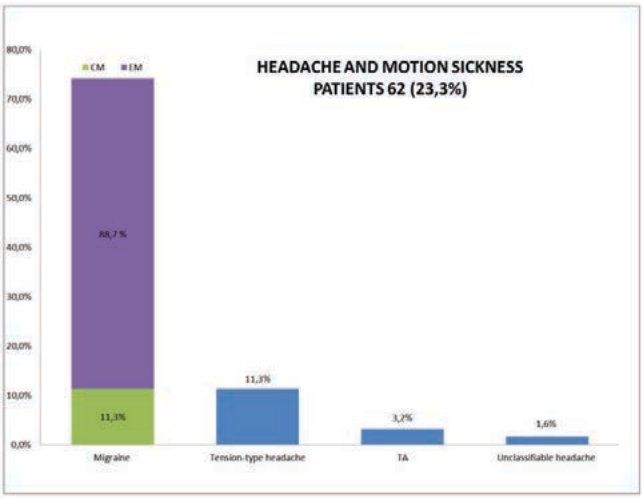
204 patients did not have motion sickness (76.7%); the average age was 43.5 years; and 81.8% were women. 83.33% presented migraine (67.6% episodic; 17.6% chronic; 14.7% with aura), 9.3% had tension headache, 2.9% cluster headache, 1.5% had undetermined headaches and 2% cranial neuralgia (Graph 3).

DISCUSSION

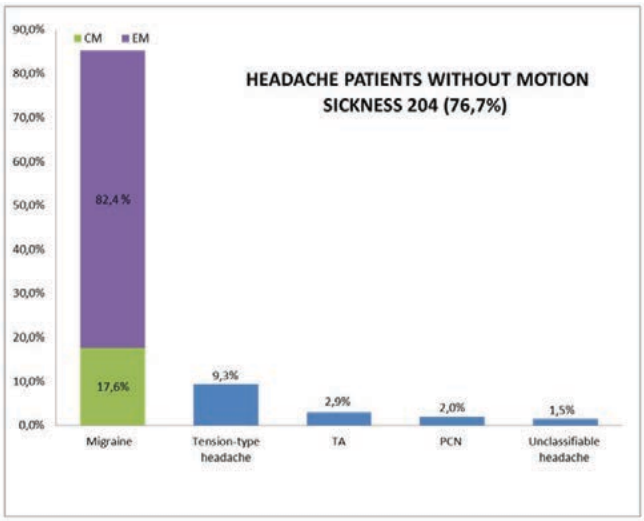
Reports in the literature describes the association between migraine and motion sickness may reache up to 50%; also 20% of patients with tensión-type headache



Graph 1. Headache patients with Motion Sickness.



Graph 2. MA: migraine with aura, MC: chronic migraine, ME: episodic migraine; TA: trigemeno-autonomic cephalgias, Indet: undetermined.



Graph 3. MA: migraine with aura, MC: chronic migraine, ME: episodic migraine; TA: trigemeno-autonomic cephalgias, Indet: undetermined, AC: cranial neuralgias.

also experience motion sickness (7). Our study revealed a prevalence of motion sickness in patients with headache of 23.3%; of these, 84% suffered some type of migraine; and 11% had tension headache; 12.5% reported motion sickness as a trigger for a migraine attacks.

Motion sickness not only interferes with long-distance trips such as pleasure trips; but also in those of short distance, such as daily transfers to work, activities such as going to a shopping, supermarket or cinema. It affects both adults and children. At present, the use of mobile devices during the trips, possibly facilitates the increase of this symptom; since performing active movements during a passive movement favors its presentation.

Given that it is a frequent condition, which can become disabling and even trigger a migraine attack, it must be taken into account in the medical consultation, in order to indicate the appropriate treatment, both non-pharmacological and pharmacological (scopolamine, promethazine, anti-histamines). Rizatriptan was studied as a preventive treatment (prior to the exposure of stimuli) of motion sickness (8) showing clinical improvement.

A group of patients identified motion sickness as a trigger for a migraine attacks. This information could be useful to evaluate the clinical behavior of the migraine attacks, so recognizing it may be helpful in its managament.

CONCLUSION

Motion sickness is an important issue in migraine management, causing limitations in daily life activities. In first consultations, headache patients should be asked about it, since proper diagnosis and timely treatment would make it possible to improve patients' quality of life. Future research should be done to better clarify motion sickness as a migraine trigger.

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Histomorphometric analysis of mast cells in different regions of human intracranial dura mater

Análise histomorfométrica de mastócitos em diferentes regiões da dura-máter intracraniana humana

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ABSTRACT

Objective: To analyze mast cell histomorphometry in three different regions of the human intracranial dura mater. **Method:** Three specimens of dura mater were collected after approval by the Ethics Committee (CAAE No. 57692216.5.0000.5208). Each dura mater was obtained from human cadavers between 7 and 24 hours after death. After collection, the samples were fixed, cut into two fragments and longitudinally placed in the following way: external (periosteum) and internal (meningeal) sides. The fragments (1.5 cm^2) were taken from three different regions: proximity of the right middle meningeal artery, the proximity of the left middle meningeal artery and superior sagittal sinus. These fragments were submitted to microtomy (10 Qm), stained with 0.1% toluidine blue and analyzed by optical microscopy. The histomorphometric parameters adopted were: the distance from the mast cells to the vessels, the number and if the mast cells were degranulated. Five fields from each case were analyzed. For this analysis, the Image J 1.52a 2019 software was used. **Results:** A higher number of mast cells was observed in the periosteal layer when compared with the meningeal layer (p=0.026). When the distribution of the mast cells was evaluated, we observed that the cells were localized in the proximity of the middle meningeal artery (p<0.05). **Conclusion:** In human dura mater, the mast cells are localized in the proximity of dural arteries.

Keywords: Mast cell; Dura mater; Human; Meningeal artery; Migraine.

RESUMO

Objetivo: Analisar a histomorfometria dos mastócitos em três regiões diferentes da dura-máter intracraniana humana. **Método:** Três amostras de dura-máter foram coletadas após aprovação pelo Comitê de Ética (CAAE nº 57692216.5.0000.5208). Cada dura-máter foi obtida de cadáveres humanos entre 7 e 24 horas após a morte. Após a coleta, as amostras foram fixadas, cortadas em dois fragmentos e dispostas longitudinalmente da seguinte maneira: face externa (periósteo) e interna (meníngeo). Os fragmentos (1,5 cm^2) foram retirados de três regiões diferentes: proximidade da artéria meníngea média direita, proximidade da artéria meníngea média esquerda e seio sagital superior. Esses fragmentos foram submetidos à microtomia (10 Qm), corados com azul de toluidina a 0,1% e analisados por microscopia óptica. Os parâmetros histomorfométricos adotados foram: distância dos mastócitos aos vasos, número e se os mastócitos estavam desgranulados. Foram analisados cinco campos de cada espécime. Para esta análise, foi utilizado o software Image J 1.52a 2019. **Resultados**: Observou-se maior número de mastócitos na camada periosteal quando comparada à camada meníngea (p = 0,026). Quando avaliada a distribuição dos mastócitos, observamos que as células estavam localizadas nas proximidades da artéria meníngea média (p <0,05). Conclusão: Na dura-máter humana, os mastócitos estão localizados nas proximidades das artérias durais.

Descritores: Mastócito; Dura-máter; Humano; Artéria meningeal; Enxaqueca.

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INTRODUCTION

Recent evidence strongly suggests a vital role of dura mater mast cell in the genesis of migraine.[1-5]

Gupta and Harvima described the mast cells as a "*powerhouse*" since they release "algogenic and pruritogenic mediators, which initiate a reciprocal communication with specific nociceptors on sensory nerve fibers."[6]

Mast cells are cells found in abundance in the dura mater and by local mechanism regulates vascular and neural functions, releasing substances such as histamine. Scientific evidence suggests that mast cells participate in the pathophysiology of triggering a migraine attack by inducing local sterile inflammation near the dura mater nociceptors.

Curiously, the mast cells are located in the proximity of the arteries in the dura mater, in close association with neurons. These cells appear to be activated through the trigeminal nerve. It is postulated that many neuropeptides, namely calcitonin gene-related peptide (CGRP), hemokinin A, neurotensin (NT), pituitary adenylate cyclase-activating peptide (PACAP), and substance P may activate mast cells, resulting in the release of vasoactive and pro-inflammatory mediators, involved in the pathophysiology of migraine.[4] Mast cells can also release substances with pro-inflammatory and vasoactive actions (e.g., interleukin-6 and vascular endothelial growth factor (VEGF).[4]

The objective of the present study was to analyze mast cell histomorphometry in three different regions of the human intracranial dura mater.

METHOD

Three specimens of dura mater were collected after approval by the Ethics Committee (CAAE No. 57692216.5.0000.5208).

Each dura mater was obtained from human cadavers between 7 and 24 hours after death.

After collection, the samples were fixed, cut into two fragments and longitudinally placed in the following way: external (periosteum) and internal (meningeal) sides.

The fragments (1.5 cm^2) were taken from three different regions: proximity of the right middle meningeal artery, the proximity of the left middle meningeal artery and superior sagittal sinus.

These fragments were submitted to microtomy (10 Qm), stained with 0.1% toluidine blue and analyzed by optical microscopy. The histomorphometric parameters adopted were: the distance from the mast cells to the vessels, the number and if the mast cells were degranulated. Five fields from each case were analyzed. For this analysis, the Image J 1.52a 2019 software was used.

RESULTS AND DISCUSSION

A higher number of mast cells was observed in the periosteal layer when compared with the meningeal layer (p=0.026).

When the distribution of the mast cells was evaluated, we observed that the cells were localized in the proximity of the middle meningeal artery (Figure 1), suggesting that there is a significant role played by the mast cells in dura mater to regulate vascular function. Probably the relationship between mast cells and meningeal arteries is an essential component in the migraine pathogenesis.

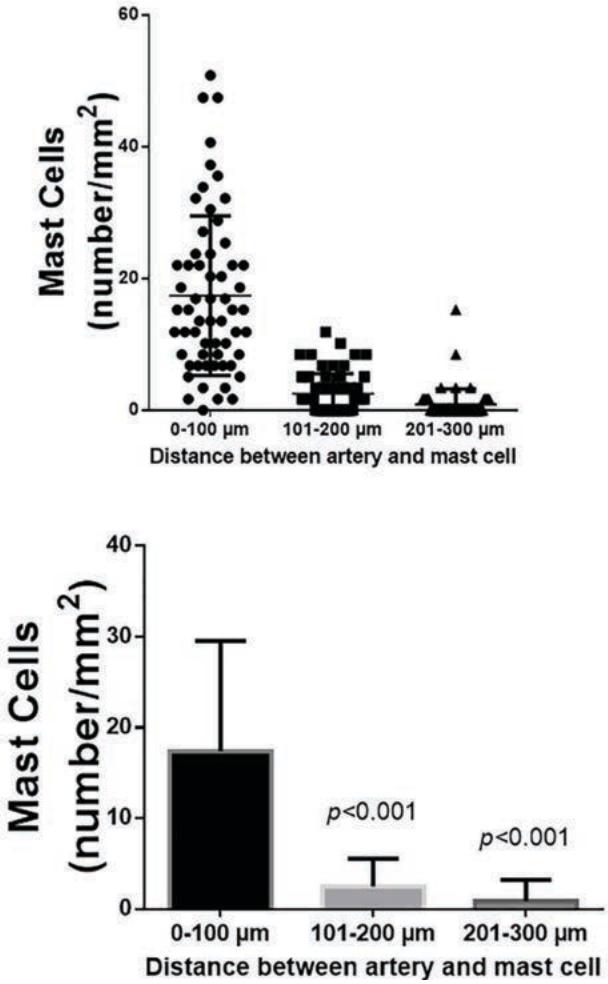

Figure 1. Mast cell density per mm2 in relation to the distance to the vessel. P versus 0-100 Qm group, Kruskal-Wallis test and Dunn´s multiple compatisons test.

The distance between the artery and the mast cell was measured in 153 cells (57 65 m, min 0 - max 247; median 33, 95%IC 46-67). No differences were observed in the concentration of mast cells in convexity of the dura mater versus the superior sagittal sinus.

In his study, with human dura mater postmortem, 60-70% of the mast cells were degranulated. Migraine is a disorder with significant autonomic dysfunction. Clinically, long-lasting flushing suggests degranulation of mast cells.[5]

In conclusion, in human dura mater, the mast cells are localized in the proximity of dural arteries.

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Migraine with aura: MRI with perfusion aspects in the ictal and interictal phases

Enxaqueca com aura: aspectos da ressonância magnética com perfusão nas fases ictal e interictal

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We describe the case of a 16-year-old adolescent with diagnostic previous of migraine without and with aura (only sensory), who presented with aphasia of speech, associated with severe retroorbital pain and frontal headache on the left, associated with nausea, photo and phonophobia. He was admitted to the emergency room with suspected stroke and was submitted to magnetic resonance perfusion imaging of the brain (Figure 1). After ruling out suspected cerebral ischemia, treatment with symptomatic medications was performed, progressing to improvement of symptoms after about 2 hours.

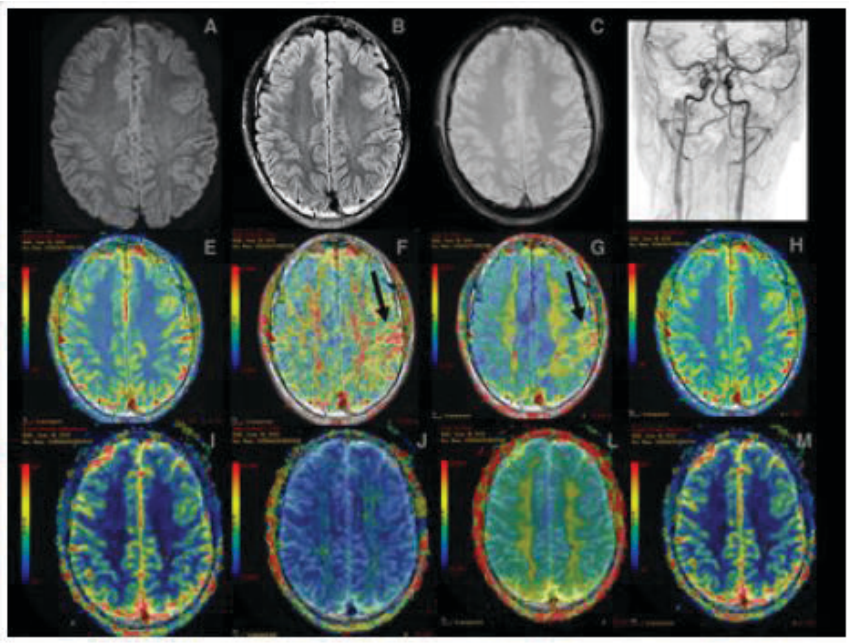

Figure 1. A-D demonstrated fast protocol to exclude recent ischemia or bleeding, with patency of large intracranial vessels and without significant changes in structural images (Diffusion, Gradient-Echo and FLAIR). E-H with the reconstructions of the perfusion study and highlighting the important increase in time to the plateau (TTP - figure G) and mean transit time (MTT - figure F), with no changes of the other parameters. I-M with the perfusion control study and characterizing the regression of the previously evidenced changes.

Approximately 1 month later, a new perfusion MRI was performed for comparison, which revealed complete disappearance of the alterations of the first exam. In this interval, the patient presented only episodes of migraine without aura.

Migraine with aura (MwA) accounts for about 30% of all cases of migraine and predominates in females [1]. Its diagnosis was recently updated by the third edition of the International Classification of Headache Disorders [2]. Visual aura accounts for 99% of auras, followed by sensory (54%) and speech / language (32%) [1].

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Usually at the first manifestation or at the change in the aura pattern, neuroimaging is necessary, considering secondary headache, because one of the main differential diagnoses is the stroke. The gradual onset of neurological deficits, the association with headache that is typically migrainous, and the absence of ischemia on neuroimaging exams are suggestive of MwA [2,3]. Perfusion MRI in the ictal phase reveals decreased cerebral blood flow, with no abnormalities in the DWI sequence, that is, at sub-ischemic levels. Vascular alteration that is reversed in the interictal period [3].

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