Universidade de São Paulo

Faculdade de Medicina de Ribeirão Preto

2018

Light-induced discomfort, posture control and vestibular symptoms in women with migraine – a controlled study

Carina Ferreira Pinheiro

Tese

CARINA FERREIRA PINHEIRO

Light-induced discomfort, posture control and vestibular symptoms in women with migraine – a controlled study

Thesis presented to Ribeirão Preto Medical School of University of São Paulo to obtain a Doctoral degree (PhD) in Sciences

Area: Physical Therapy

Advisor: Débora Bevilaqua Grossi, PhD

Co-advisor: Renato de Moraes, PhD

Ribeirão Preto

2018

CARINA FERREIRA PINHEIRO

Desconforto induzido pela luz, controle postural e sintomas vestibulares em mulheres com migrânea – um estudo controlado

Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do título de Doutor em Ciências

Área de concentração: Fisioterapia

Orientadora: Profa. Dra. Débora Bevilaqua Grossi

Co-orientador: Prof. Dr. Renato de Moraes

Ribeirão Preto

2018

Versão corrigida. A versão original encontra-se disponível tanto na Biblioteca da Unidade que aloja o Programa, quanto na Biblioteca Digital de Teses e Dissertações da USP (BDTD)

Publication listing

Ribeirão Preto Medical School of University of São Paulo

Pinheiro, Carina Ferreira

Light-induced discomfort, posture control and vestibular symptoms in women with migraine – a controlled study. Ribeirão Preto, 2018.

p.74 : il.5; 30cm

Doctoral Thesis presented to the Ribeirão Preto Medical School/USP – Post-Graduation Program of Rehabilitation and Functional Performance. Area: Physical Therapy

Advisor: Bevilaqua-Grossi, Débora

KEY-WORDS: 1. Migraine Disorders, 2. Photophobia, 3. Postural Balance, 4.Dizziness, 5. Pain

Catalogação da Publicação

Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo

Pinheiro, Carina Ferreira

Desconforto induzido pela luz, controle postural e sintomas vestibulares em mulheres com migrânea – um estudo controlado. Ribeirão Preto, 2018.

p.74: il.5; 30cm

Tese de doutorado apresentada à Faculdade de Medicina de Ribeirão Preto/USP – Programa de Pós-Graduação em Reabilitação e Desempenho Funcional. Área de concentração: Fisioterapia.

Orientadora: Bevilaqua-Grossi, Débora.

PALAVRAS – CHAVE: 1. Transtornos Migranosos, 2. Fotofobia, 3. Equilíbrio Postural, 4. Tontura, 5. Dor

APPROVED PAGE

Carina Ferreira Pinheiro

Light-induced discomfort, posture control and vestibular symptoms in women with migraine – a controlled study.

Thesis presented to Ribeirão Preto Medical School of University of São Paulo in the Department of Health Sciences to obtain a doctoral degree (PhD) in Sciences by the Post-Graduation Program Rehabilitation and Functional Performance

Area: Physical Therapy

Approved in: November 1st, 2018

Examination Board

Professor Ana Cláudia Mirândola Barbosa Reis. PhD
Institution: University of São Paulo
Signature:_____

Professor Fernando Henrique Magalhães, PhD
Institution: University of São Paulo
Signature:_____

Professor Fernando Augusto Vasilceac, PhD
Institution: University of São Carlos
Signature:_____

FOLHA DE APROVAÇÃO

Carina Ferreira Pinheiro

Desconforto induzido pela luz, controle postural e sintomas vestibulares em mulheres com migrânea – um estudo controlado.

Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo junto ao Departamento de Ciências da Saúde para obtenção do título de Doutor em Ciências pelo Programa de Pós-Graduação em Reabilitação e Desempenho Funcional.

Área de concentração: Fisioterapia

Aprovado em: 01 de Novembro de 2018

Banca Examinadora

Profa. Dra. Ana Cláudia Mirândola Barbosa Reis
Instituição: Universidade de São Paulo
Assinatura:_____

Prof. Dr. Fernando Henrique Magalhães
Instituição: Universidade de São Paulo
Assinatura:_____

Prof. Dr. Fernando Augusto Vasilceac
Instituição: Universidade de São Carlos
Assinatura:_____

Aos meus pais, Marcones e Cleusa, com todo o meu amor e gratidão,

pois eles são a minha base e fonte de amor e incentivo incondicional

Acknowledgments / Agradecimentos

Agradeço inicialmente a Deus pela permissão para que eu pudesse caminhar sob a Tua guia, me levando por caminhos designados por Ele para que eu alcançasse meus objetivos. Obrigada Senhor, por todo o cuidado que tens comigo, por abrir meus olhos para enxergar os sinais do Teu amor e por abençoar os meus planos.

À minha família, por todo o apoio e amor. Vocês são a minha base, minha fonte contínua de aprendizado, amor e força e meus exemplos de fé, disciplina, persistência, dedicação e humildade. Obrigada por compreenderem as minhas ausências, por vibrarem com as minhas conquistas e me apoiarem em todos os momentos.

À minha orientadora, Profa. Débora Bevilaqua Grossi, inicialmente pela oportunidade de mais uma vez trabalhar em sua equipe. Em seguida, pela orientação neste trabalho, pela convivência diária rica em ensinamentos científicos, profissionais, pessoais e cristãos, por toda a motivação e inspiração. Sou muito grata por ter a chance de assistir de perto a sua forma de trabalhar e ainda poder adquirir conhecimento além do campo acadêmico-científico.

Ao Prof. Renato de Moraes, meu co-orientador, pela oportunidade e confiança depositados. Obrigada pela sua enorme contribuição no meu aprimoramento teórico e científico, pelos momentos descontraídos, pela paciência que tem comigo e pelas portas que me abriu durante o doutorado para uma nova área de pesquisa, e subsequentemente para o desafio de estudar no exterior.

Ao Prof. Richard van Emmerik da Universidade de Massachusetts, que me recebeu e acolheu com muita paciência e gentileza. Que me deu suporte teórico, despertou minha curiosidade e me impôs desafios de trabalho que muito contribuíram para o meu desenvolvimento científico. Ainda sobre meu período na UMass, agradeço aos colegas do Departamento de Cinesiologia (Kin-Family) pela acolhida e convivência, em especial à Gabriela Borin, que teve um papel inestimável na minha empreitada de viver em outro país.

Ao especialista de laboratório, Dr. Tenysson Will de Lemos, por todas as horas de trabalho (braçal e intelectual) às quais em muito depende essa tese. Obrigada por todo o suporte metodológico e científico que você me deu, além das discussões sobre física, computação, programação e até filosofia, sempre com um misto de seriedade e descontração que deixa o trabalho mais leve e fluido.

Aos meus colegas do LAPOMH, dos quais não citarei nomes para não cometer a injustiça de esquecer alguém. Obrigada pela convivência em grupo, nesse caso marcada pelo apoio nos momentos bons e ruins, pelas discussões científicas, comemorações, churrascos e cafezinhos. Em especial Lidiane Florencio, Gabriela Carvalho, Jaqueline Martins e Profa. Anamaria Siriani, com quem pude trabalhar desde a Iniciação Científica e além de profissionais e amigas, também são exemplos de mulher para mim.

Ao grupo da ATM e Cefaleia pela convivência mais intensa, e todo o aprendizado proporcionado. Aos alunos de iniciação científica com quem trabalhei nesse período, obrigada pela oportunidade de me deixarem praticar o exercício de não somente ensinar, mas também aprender com vocês.

Aos colegas do LaBioCom, que também me acolheram com muito carinho e com os quais tive oportunidade de trabalhar e partilhar conhecimento e conquistas.

Aos meus amigos, Mariana, Elaine, Mirela, Raquel e Charles, pessoas com as quais eu sempre posso contar, reclamar e brindar, independente da distância. Obrigada por todo ouvido e apoio de sempre.

À CAPES e FAPESP e pelo apoio financeiro destinado à minha formação, realização e divulgação dos projetos envolvidos nesta tese.

A todas as participantes dos estudos contidos nesta tese, que voluntariamente cederam seu tempo em favor da pesquisa científica. À equipe de neurologistas do ambulatório de Cefaleia do Hospital das Clínicas da FMRP-USP, em especial Profa. Fabiola Dach e Dr. Roberto Cetlin, com os quais é um privilégio trabalhar e aprender.

“Ninguém é tão grande que não possa aprender, nem tão pequeno que não possa ensinar”

Esopo

Abstract

Pinheiro CF. Light-induced discomfort, posture control and vestibular symptoms in women with migraine – a controlled study. [thesis]. São Paulo. University of São Paulo. Ribeirão Preto Medical School, 2018. 74p.

Objective: To verify if there was any relationship between the handicap related to vestibular symptoms and the presence of aura and the chronicity of migraine attacks. Subsequently, to investigate the visual sensitivity in migraineurs and non-headache subjects, as well as the response of balance control to light stimulation. **Methods:** Women with migraine and non-headache women were assessed in the studies presented in the current thesis. Initially, the migraineurs were stratified as migraine with aura, migraine without aura and chronic migraine. Information regarding vestibular symptoms was collected, and the self-perceived handicap related to vestibular symptoms was assessed through the Dizziness Handicap Inventory questionnaire. On the second moment, both migraine group and control group were evaluated in bipodal and unipodal postures under three light conditions: (1) ambient, (2) visual discomfort threshold and (3) intense visual discomfort, in order to analyze variables of the center of pressure. Both visual discomfort conditions were determined based on the report of discomfort of the migraine individuals. Finally, data about the intensity of visual discomfort during daily activities were collected. **Results:** Patients with migraine exhibited greater Dizziness Handicap Inventory scores than controls, and the presence of migraine is associated with a greater risk of vestibular symptoms and with a greater risk of moderate-to-severe handicap. Considering the subtypes of migraine, patients with migraine with aura and chronic migraine reached greater scores than those migraineurs without aura. Also, migraine aura, intensity and frequency can predict the dizziness handicap. In the analysis of visual discomfort, the migraine group reported a visual discomfort threshold of 450 lx and intense visual discomfort at 2000 lx, while controls did not report visual discomfort. Migraineurs also presented higher discomfort intensity to perform daily activities, especially to driving and to walking in a sunny day. On the stabilometric analysis, subjects with migraine presented greater center of pressure (CoP) area under the three conditions, and greater CoP velocity and RMS under the visual discomfort light conditions, compared to controls. Only the migraine group showed greater CoP area, velocity and RMS for both visual discomfort light conditions compared to the ambient condition. **Conclusions:** The prevalence of vestibular symptoms is increased in migraine, particularly in migraine with aura and chronic migraine along with an increased handicap due to those symptoms. Furthermore, we can also assume that patients with migraine present visual

sensitivity during the interictal period, and the light-induced discomfort might be a disturbing factor that worsens balance even during quiet standing posture.

Resumo

Pinheiro CF. Desconforto induzido pela luz, controle postural e sintomas vestibulares em mulheres com migrânea – um estudo controlado. [tese]. São Paulo: Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, 2018. 74p.

Objetivos: Verificar a relação entre a incapacidade relacionada aos sintomas vestibulares e a presença de aura e cronicidade da migrânea. Além disso, investigar a sensibilidade visual em indivíduos com migrânea e sem cefaleia, bem como o controle de equilíbrio postural perante estimulação luminosa. **Métodos:** mulheres com migrânea e mulheres sem cefaleia foram avaliadas nos estudos apresentados nesta tese. Inicialmente, as mulheres com migrânea foram estratificadas em migrânea com aura, migrânea sem aura e migrânea crônica. Informações sobre sintomas vestibulares foram coletadas e a autopercepção de incapacidade relacionada aos sintomas vestibulares foi avaliada por meio do questionário Dizziness Handicap Inventory. Posteriormente, os grupos migrânea e controle foram avaliados nas posturas bipodal e unipodal sob três condições de luz: (1) ambiente, (2) limiar de desconforto visual e (3) desconforto visual intenso, para analisar variáveis do centro de pressão (CoP). Ambas as condições de desconforto visual foram determinadas com base no relato de desconforto dos participantes do grupo migrânea. Por fim, foram coletados dados sobre a intensidade de desconforto visual durante as atividades diárias. **Resultados:** Os pacientes com migrânea apresentaram maiores escores do Dizziness Handicap Inventory do que os controles, e a presença de enxaqueca está associada a um maior risco de sintomas vestibulares, bem como a um maior risco de incapacidade moderada a grave. Considerando os subtipos de migrânea, os grupos com aura e migrânea crônica apresentaram pontuações mais elevadas no questionário do que o grupo migrânea sem aura. Ainda, a aura, a intensidade e a frequência da migrânea podem predizer a incapacidade da tontura. Na análise do desconforto visual, o grupo com enxaqueca relatou limiar de desconforto visual de 450 lux e desconforto visual intenso a 2000 lux, enquanto os controles não relataram desconforto visual. O grupo migrânea também apresentou maior intensidade de desconforto para realizar as atividades diárias, principalmente para dirigir e caminhar em dias ensolarados. Na análise estabilométrica, os indivíduos com migrânea apresentaram maior área do centro de pressão (CoP) nas três condições, e maior velocidade e RMS do CoP sob as duas condições de desconforto visual, quando comparados aos controles. Apenas o grupo migrânea apresentou maior área, velocidade e RMS do CoP para ambas as condições de desconforto visual em comparação com a condição ambiente. **Conclusões:** A prevalência de sintomas vestibulares é maior na migrânea, particularmente nos subtipos com aura e crônica, juntamente com uma

maior incapacidade relacionada a esses sintomas. Ademais, também podemos assumir que os pacientes com migrânea apresentam sensibilidade visual durante o período interictal, e o desconforto induzido pela luz pode ser um fator perturbador que piora o equilíbrio, mesmo durante a postura em pé.

Abbreviation List

ANOVA – Analysis of variance

AP – Antero-posterior

BMI – Body Index Mass

CG – Control group

CGRP – Calcitonin gene-related peptide

CM – Chronic migraine

CoM – Center of mass

CoP – Center of pressure

CSD – Cortical spreading depression

DHI – Dizziness Handicap Inventory

ICHD – International Classification of Headache Disorders

IHS – International Headache Society

MA – Migraine with aura

MG – Migraine group

MIDAS – Migraine Disability Assessment

ML – Medio-lateral

MoA – Migraine without aura

NPRS – Numeric Pain Rating Scale

RMS – Root Mean Square

SD – Standard deviation

TCC – Trigeminocervical complex

VAS – Visual Analogic Scale

WHODAS – World Health Organization Disability Assessment Schedule

Summary

1 THEORETICAL CONTEXTUALIZATION

Migraine is a disabling brain condition characterized by attacks of unilateral, throbbing head pain lasting 4–72 hours, and moderate to severe intensity. Usually, it is accompanied by nausea and/or photophobia and phonophobia, and worsened by routine physical exertion [1,2]. Migraine is a common disorder, considered the sixth condition most prevalent in the world [3]. Its prevalence range between 15% to 18% of the worldwide population, in many cases during peak years of productivity [1,4]. In Brazil, the 1-year prevalence is around 9% for men and 22% for women [5]. Also, can be considered an incapacitating chronic disease, reported as the first world disabling neurological disease and the second global cause of years with disability [3].

As migraine is a primary headache, it is not dependent on another condition. It may be considered as a brain state of altered excitability, associated to dysfunction in areas of the brain stem and diencephalon that alter the perception of sensory inputs, and cause other neurological deficits [1]. Regarding all clinical manifestations of a migraine attack, the attack has divided into four phases:

1. Premonitory symptoms: The earliest clinical signs of a migraine attack are so-called premonitory symptoms, which occur before head pain but already tell the patient that a headache is on its way. Based on their manifestation, they are likely related to the hypothalamus and include concentration problems, tiredness, irritability, or depression [1].
2. Aura Phase: Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms but can also occur at the same time or even independently from any headaches [1,6]. The symptoms presented depends on cortex area affected, may presenting as scintillating lights and scotomas - visual cortex; paresthesia and numbness - somatosensory cortex; tremor and unilateral muscle weakness - motor cortex or basal ganglia; and aphasia - speech area [7].
3. Headache Phase: A headache begins, and as it progress, it may be accompanied by a variety of autonomic symptoms (nausea, vomiting, rhinorrhea, lacrimation, ptosis, yawning), affective symptoms (depression and irritability), cognitive symptoms (attention deficit, difficulty finding words), and sensory symptoms (photophobia, phonophobia, osmophobia, muscle tenderness, and cutaneous allodynia) [1,7].

4. Postdrome: This phase follows the end of head pain for hours or days when the patient is pain-free but still does not feel back to normal due to the following symptoms: fatigue, depression, irritability, yawning, muscle tenderness, neck stiffness, abnormal sensitivity to light, sound, and smell, depression, and anhedonia [1,7].

In some cases, the headache begins with no warning signs and ends with sleep. Indeed, much is still unclear about how we understand migraine. It is most likely that many of the ideas surrounding its pathophysiology are relevant, from a genetic predisposition to brain hyperexcitability, to peripheral and central sensitization, and brainstem and hypothalamic dysfunction [1,2].

A migraine attack is thought to originate in the activation of nociceptors innervating meningeal blood vessels, as well as large cerebral arteries [1,8]. Activation of these structures by mechanical, electrical or chemical stimulation, give rise to headaches that are remarkably similar to the pain of migraine and its associated symptoms above-mentioned [7,9]. Vasoactive neuropeptides such as substance P and calcitonin gene-related peptide (CGRP) reach the dura mainly through the trigeminal nerve and by neurons in the upper cervical dorsal root ganglia, causing vasodilation of dural and pial vessels [1,2,7]

Central processes of meningeal sensory afferents enter the brainstem via the trigeminal tract and terminate in the spinal trigeminal nucleus and upper cervical spinal cord, together known as the trigeminocervical complex (TCC), that also receive additional input from the adjacent skin and muscles [7,10]. This convergence of neuronal inputs into the TCC and the convergence of inputs from intracranial and extracranial structures likely contributes to the referred pain perception in the periorbital, occipital, and higher cervical regions[1,2,7]. Moreover, all nociceptive information from craniovascular structures is relayed to other areas of the brainstem and diencephalon, involved in the processing of pain and other sensory information[1].

Preceding the headache phase, it would occur the cortical spreading depression (CSD), a phenomenon considered generator of the aura. CSD is a slowly propagating wave of depolarization/excitation followed by hyperpolarization/inhibition in cortical neurons and glia [1,2,7,10]. Despite the process that initiates the CSD is not clear, it is known a host of changes in cortical perfusion and enzymatic activity [7]. Secondary to this decreased metabolic demand, the CSD also promotes a decrease in regional cerebral blood flow in the posterior parietal and occipital lobes [2,11]. It has been speculated that, for individuals with migraine without aura, the CSD occurs in silent areas, or the activation of trigeminovascular system is provoked by glial cells [2,6].

One of the main diagnostic criteria for migraine, photophobia is defined by ICHD-III as ‘‘hypersensitivity to light, usually causing avoidance’’ [6]. The light-induced aggravation of headache during a migraine attack is reported by 60–90 % of migraineurs [12], and even during the period between attacks, 75% of patients with migraine report light sensitivity [10,13]. Despite the neural mechanism to explain the photophobia is not completely understood, it suggested that exacerbation of migraine headache by light is driven by photic signals transmitted from the retina via the optic nerve to thalamic trigeminovascular neurons that process nociceptive signals from the meninges and project its axons to multiple cortical areas including somatosensory and visual cortices [9,10,14–16].

Due to the known sensitization process of migraine, the light-sensitivity also persists during the interictal period [16,17]. Compared to migraineurs without interictal photosensitivity, migraineurs with this symptom presenting greater cortical thickness in the right parietal-occipital and left fronto-parietal regions [18]. It’s have been suggested that the presence of photosensitivity could be mediated by somatomotor and visual processing regions while the severity of visual discomfort might be mediated by affective regions [18]. Also, studies using functional magnetic resonance image data suggest that oculomotor proprioception and photophobic pain are related to primary somatosensory and primary motor activation [19,20].

Previous studies evaluated photophobia in patients with migraine using questionnaires [18,21], striped patterns [21] and light stimulation [12,13,22]. Using this last-mentioned method, the authors observed that visual discomfort threshold ranged between 300–680 lx for patients with migraine and 1700–2000 lx for non-headache individuals [13,22], while the maximum tolerance to lighting stimulus was 1600 and 15900 lx for migraineurs and controls, respectively [22]. In general, the light level is more common in the range 500 - 1000 lx - depending on activity (i.e. offices, classes room, supermarkets). For precision and detailed works, the light level may even approach 1500 - 2000 lx, and for some special visual tasks of small size (i.e. surgeries), may achieve 20000 lx [23].

Besides photophobia, vestibular symptoms are commonly associated with migraine [24–26]. The Bárány Society’s Classification of Vestibular Symptoms [27] describes four primary vestibular symptoms:

- Dizziness: Sensation of disturbed or impaired spatial orientation without a false or distorted sense of motion.

- Vertigo (internal): Sensation of self-motion (of head/body) when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement.
- Vestibulovisual symptoms (external vertigo): Visual symptoms that usually result from vestibular pathology or the interplay between visual and vestibular systems. These include false sensations of motion or tilting of the visual surround and visual distortion linked to vestibular failure.
- Postural symptoms: Balance symptoms related to maintenance of postural stability, occurring only while upright (seated, standing, or walking).

The prevalence of some of these symptoms ranging between 30–50% in general population [28,29] and between 51% to 91% in migraineurs [28,30]. Studies have shown the presence of vestibular dysfunction to be concomitant with abnormalities of both peripheral and central vestibular pathways [31,32] and with permanent brainstem and cerebellar deficits [33,34].

The mechanisms underlying vestibular abnormalities in patients with migraine are still unclear. Some authors have suggested that vertigo symptoms may be a "brainstem aura," which is a spreading wave of depression of neural activity possibly accompanied by changes in blood flow affects indirectly the blood-brain barrier permeability, leading to exacerbation of neuronal damage caused by microvascular ischemia [33–36]. Other mechanisms of the migraine attack, such as local excessive neuronal activation, neurogenic inflammation, neuropeptide and cytokine release or excitotoxity also are suggested as hypothesis to explain the ischemic-like lesions in migraineurs and may lead to a central and peripheral irreversible disorder [33,37].

Furthermore, it's also suggested that reciprocal connections between vestibular nuclei and trigeminal nucleus caudalis may provide a tight linkage between vestibular and vascular-trigeminal processing during migraine attacks [33]. Thus, the vestibular abnormalities in migraine might be caused due to a functional vestibular tone imbalance caused by an asymmetric activation or deactivation of bilateral vestibular neuronal activity during the attack [34].

In consequence of these vestibular abnormalities, balance aspects have been investigated in migraineurs. There is evidence of increased postural sway [32,38–42], decreased stability limits [43], and poor performance during functional activities, such as gait, sit-to-stand transitions, and up/down stepping [41,42]. Moreover, migraine is associated with the risk of falling and present a higher prevalence of imbalance and falls [44]. These impairments are worsened in migraine with an aura and chronic migraine, and this observation could be related to the higher

severity of brain ischemic-like lesions on migraineurs with aura and in those with more frequent migraine attacks [42,44–46].

Postural control encompasses two main aspects: postural orientation and postural equilibrium. Postural orientation involves the active control of body alignment and tone concerning gravity, support surface, visual environment and internal references, using the interpretation of convergent sensory information from somatosensory, vestibular and visual systems. Postural equilibrium involves the coordination of sensorimotor strategies to stabilize the body's center of mass (CoM) during any disturbances in postural stability [47].

As the upright standing is naturally an unstable posture, requires continuous sensory feedback to remain upright. Therefore, the information carried by individual sensory channels is combined, and a 'weight' is assigned to the various input sources depending upon the postural task itself, and the context in which function is being performed. However, any change in environmental conditions or musculoskeletal and/or neurological injury leads the central nervous system to reweight the sensorial inputs [48,49].

Despite the number of studies exploring the relationship between migraine and vestibular abnormalities, there is a lack on the literature about the functional impact of vestibular symptoms on migraineurs' life. In addition, regarding the influence of sensory systems on posture control, the contribution of vestibular system is well-established [50,51], but the influence of visual system, in terms of environment illumination, has been investigated in conditions with opened/closed eyes [41,52], and in dim lighting condition [53–56]. Thus, to the best of our knowledge, there is no information about the postural behavior in conditions with brighter lighting levels, especially in individuals with light sensitivity, such as migraineurs.

The current thesis will present two articles developed during the doctoral period about the investigation of vestibular symptoms and postural impairments relative to migraine and its comorbidities, especially photophobia. First (Study 1), we assessed 240 individuals divided into three groups of patients with migraine and a control group to investigate the presence and handicap due to vestibular symptoms. Secondly (Study 2), we analyzed the visual discomfort and balance of 14 women with migraine and 14 non-headache under different light conditions.

Our first objective was to verify if there was any relationship between the handicap related to vestibular symptoms and the presence of aura and the chronicity of migraine attacks. Subsequently, the second aim was to investigate the visual sensitivity in migraineurs and non-headache subjects, as well as the response of balance control to light stimulation. We hypothesized that migraine overall, as well as aura and migraine frequency, would correlate

with the presence of and impact due to vestibular symptoms, and the photophobia could alter the visual sensitivity and cause systematic decrements in postural control as a function of increased light intensity.

The investigation of vestibular symptoms and their impact on patients with migraine is very important to the understanding and management of this condition, considering the singularity of each migraine subtype. At the same time, the knowledge about the light stimulus` influence on upright standing posture can contribute to understanding mechanisms underlying balance deficits in subjects with migraine.

2 MATERIAL AND METHODS

2.1 Study 1 (Article 1)

Ethical Aspects

The study was performed in accordance with the Helsinki Declaration and with the approval of the Local Ethics Committee (protocol number: no 16693/2012). Written informed consent was obtained from all participants.

Sample

Consecutive patients diagnosed with migraine were screened from a tertiary headache clinic between February 2014 to March 2015 for this cross-sectional study. The diagnoses were made by headache specialists according to the International Classification of Headache Disorders ICHD - 3rd edition and they were classified as: migraine with aura group (MA), migraine without aura group (MoA) and chronic migraine group (CM).[6] Patients were diagnosed with chronic migraine if they had at least 15 days with headache within a month in the last three months (and at least 8 of them fulfilled the migraine criteria). Patients with less than 15 days with headache in the last three months were diagnosed with migraine with or without aura. Vestibular migraine criteria was not considered to characterize the patients. Non-headache subjects were identified among patients' family members and hospital employees in order to compose the control group (CG).

Female subjects were included in the sample when they were between the ages of 18 to 55 years old. Specific for migraine patients, inclusion criteria comprised migraine diagnosis in the previous 1 year and presence of at least three attacks within a month during the last three months. The exclusion criteria adopted for all subjects were: diagnosis of any concomitant headache (1), use of any medication prescribed for vertigo or dizziness treatment such as meclizine, flunarizine, cinnarizine, betahistine, and/or benzodiazepinics (2), self-report or history of vestibular disease (3), abnormal neurological exam (4), any musculoskeletal impairment that could affect balance (5), presence of a migraine attack during the interview (6), pregnancy (7) and any systemic disease with rheumatic, cardiovascular, neurologic or metabolic etiology (8).

Procedures

A structured questionnaire was used to interview the participants regarding the following aspects: demographics, migraine onset, pain intensity (numeric pain rating scale, NPRS), attack frequency (number of days in the prior month) and duration (hours), presence and description of vestibular symptoms, during and between migraine attacks. Patients with the report of vestibular symptoms prior to the migraine onset, with the presence of them just between the migraine attacks or with chronic dizziness were also excluded. Primary vestibular symptoms including vertigo (sensation of self-motion), dizziness (disturbing spatial orientation), vestibulovisual (false sensation of motion or tilting) or postural symptoms (symptoms related to balance to the postural stability) were classified according to the Bárány Society's Classification of Vestibular Symptoms[12] and patients who referred multiple symptoms were included in more than one classification.

Furthermore, a senior headache specialist administered the questionnaire Dizziness Handicap Inventory (DHI) in order to assess the self-perceived impairment related to the vestibular symptoms. This questionnaire was applied just for the subjects with any report of vestibular symptoms. The DHI has 25 questions encompassing physical (7 questions, 0 – 28 points), functional (9 questions, 0 – 36 points) and emotional aspects (9 questions, 0 – 36 points), with total score ranging from 0 to 100 points (0 = no, 2 = sometimes, 4 = yes). Total scores are classified as a mild handicap (0 – 30 points), moderate handicap (31 – 60 points) and severe handicap (61 – 100 points).[13] This tool provides a useful, reliable and valid measure of self-perceived handicap associated with dizziness[14, 15] considering the total score as well as the physical, functional and emotional domains.[16, 17] This questionnaire is correlated with functional measures of gait and balance.[18-20]

2.2 Study 2 (Article 2)

Ethical Aspects

The study was performed in accordance with the Helsinki Declaration and with the approval of the Ethics Committee of Ribeirão Preto Clinical Hospital (protocol number: no 15269/2016). Written informed consent was obtained from all participants before data collection.

Sample

Participants in the migraine group were screened from a tertiary clinic and from the local community and diagnosed by specialized neurologists according to the International Classification of Headache Disorders – ICHD-III [6]. The control group was composed by non-headache participants identified in the community.

Women aged between 18 and 55 years-old were included in the sample. Patients with migraine were considered eligible to participate if they had reported at least three migraine episodes per month within the last three months. The exclusion criteria were body mass index (BMI) higher than 30, pregnancy, report of any vestibular disease, musculoskeletal dysfunction or any systemic conditions such as fibromyalgia, non-controlled hypertension, rheumatoid arthritis, and diabetes mellitus. Migraineurs with a diagnosis of other concomitant headache or with headache at the evaluation appointment were also excluded.

Questionnaires

A screening questionnaire was used to identify sample descriptive characteristics such as frequency, intensity, onset of migraine, presence of ictal and interictal dizziness, and height and body mass to compute the BMI. We also evaluated the level of visual discomfort during the following situations: driving a car, watching TV/cinema, social activities and walking on a sunny day. The participants were requested to classify the level of discomfort induced by lighting using the Visual Analogic Scale (VAS), ranging from 0 to 10.

Procedures

Participants were instructed to stand between the set of reflectors (Fig. 1) and to report the level of visual discomfort perceived in the room using a visual analogic scale (VAS), ranging from 0 to 10. The initial luminance was 270 lx, and from 300 lx it was increased gradually every 30 seconds by 100 lx, reaching a maximum of 2000 lx. The luminance was measured with a digital lux meter (Plux 1000, Instrutherm®) at the participants' eye level.

A force plate (Bertec, Columbus, OH, EUA) was used to measure the ground reaction forces and moments to compute the center of pressure (CoP) displacement with a sample rate of 100 Hz in three different conditions: 1) ambient condition, where the participant reported absence of visual discomfort (270 lx); 2) visual sensitivity threshold condition, where the participant reported the beginning of visual discomfort; and 3) intense visual discomfort condition, where the participant reported maximum visual discomfort or when the test reached 2000 lx (the maximum luminance possible in our setup). In order to compare to the migraine

group, the luminance level used in the balance assessment of the control group was based on the migraine group median for the visual sensitivity threshold and the high visual discomfort condition. Postural sway was assessed in the orthostatic position (arms along the body, open eyes, looking at a fixed point at 2 m distance) in bipodal and unipodal stance. The order of conditions was randomized for each participant and repeated three times for a duration of 30-s each.

As there were no previous studies that used this method to assess visual sensitivity threshold in migraine population, intra-subject reliability was tested in the migraine group with a retest within a seven to twenty-one days interval. Retests were performed under the same conditions as the first evaluation, and it was found a moderate reliability of 0.56 [22].

3 RESULTS

3.1 Article 1 – Published at Cephalalgia 2018 Jan

doi: 10.1177/0333102418769948. [Epub ahead of print]

Presence of vestibular symptoms and related disability in migraine with and without aura and chronic migraine

Gabriela F Carvalho[1], PT, Ph.D; Flávia Heck Vianna-Bell[1], PT; Lidiane L Florencio[1], PT, Ph.D; Carina F Pinheiro[1], PT, Ms; Fabiola Dach[2], MD, Ph.D; Marcelo E Bigal[3], MD, Ph.D; Debora Bevilaqua-Grossi[1], PT, Ph.D.

[1]Department of Biomechanics, Medicine and Locomotor Apparatus Rehabilitation – Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto – SP, Brazil.

[2] Department of Neurosciences and Behavioral Sciences – Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto – SP, Brazil.

[3] Research and Development Department, Teva Pharmaceuticals, Frazer, PA, USA

Corresponding Author:

Ph.D G. F. Carvalho

Department of Biomechanics, Medicine and Locomotor Apparatus Rehabilitation – Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto-SP, Brazil. Madre Rita St. 850, Franca/SP – Brazil. Zip code: 14400-270. Email: gabriela.fisioterapia@gmail.com

Date received: 19 December 2017; revised: 8 February 2018; accepted: 26 February 2018

Abstract

Objective: To assess the presence and handicap due to vestibular symptoms in three subgroups of patients with migraine and controls.

Methods: Women between 18 to 55 years old were diagnosed by headache specialists and stratified as migraine with aura (MA, n=60), migraine without aura (MoA, n=60), chronic migraine (CM, n=60) and controls (n=60). Information regarding demographics, headache and vestibular symptoms aspects were collected in this cross-sectional study. The self-perceived handicap related to vestibular symptoms were assessed through the questionnaire Dizziness Handicap Inventory (DHI).

Results: A total of 85% of women with MA and CM had vestibular symptoms contrasted to 70% of the MoA group ($p<0.05$) and 12% of the CG reported symptoms ($p<0.0001$). Patients with migraine exhibited greater DHI scores than controls ($p<0.001$); and MA and CM groups reached greater scores than MoA ($p<0.01$). Presence of migraine is associated with a greater risk of vestibular symptoms (MoA: 5.20, MA: 6.60, CM:6.20, $p<0.0003$) and with a greater risk of moderate-to-severe handicap (MoA: 20.0, MA: 40.0, CM: 40.0, $p<0.0003$). The presence of aura and greater migraine frequency adds to the risk of any handicap (MA: 1.9, CM: 1.7, $p<0.04$) and to the risk of moderate-to-severe handicap (MA: 2.0, CM: 2.0, $p<0.0003$). Migraine aura, intensity and frequency predict 36% of the dizziness handicap.

Conclusion: The prevalence of vestibular symptoms is increased in migraine during and between headache attacks, particularly in migraine with aura and chronic migraine along with an increased handicap due to those symptoms. Vestibular symptoms among subgroups of migraine should be considered when evaluating the functional impact of migraine.

Keywords: Dizziness, migraine with aura, chronic migraine, headache, disability evaluation.

Introduction

Headache and the presence of vestibular symptoms are commonly associated in the clinical practice and may coexist in different ways.[1, 2] The understanding of the relationship between migraine and vestibular symptoms is considered a challenging issue, since vestibular symptoms can manifest as an inherent migraine feature[3] or a vestibular diasease can coexists with migraine.[1, 3-5] The vestibular migraine criteria have been included in the appendix of the International Classification of Headache Disorders (ICHD 3rd edition beta), indicating that further investigation should be done in order to consolidate it as a valid diagnosis.[6]

Besides the variety of clinical presentations of vestibular symptoms in patients with migraine, including its occurrence in patients with brainstem aura, there is no confirmatory test for the diagnosis of vestibular migraine.[5] Up to 58% of patients with migraine present some evidence of vestibular dysfunction during otoneurological tests, regardless the complaint of clinical symptoms.[2, 7-9] For that reason, the diagnosis of vestibular migraine is made on the basis of the patients' clinical history, and not by vestibular examination.[2]

Moreover, the spectrum of symptoms in vestibular migraine is broad[10] and studies assessing the influence of migraine chronicity on vestibular symptoms are scarce.[6] However, it is established that patients with chronic migraine present a greater number of comorbidities, including vertigo.[11] Therefore, the investigation of vestibular symptoms and their impact on patients with migraine is very important to the understanding and management of this condition, considering the singularity of each migraine subtype.

The aim of this study was to investigate the association between migraine and vestibular symptoms in patients with aura, without aura and chronic migraine; including the self-perceived handicap due to dizziness among those patients. We hypothesized that migraine overall, as well as aura and migraine frequency would correlate with presence of and impact due to vestibular symptoms

Methods

Consecutive patients diagnosed with migraine were screened from a tertiary headache clinic between February 2014 to March 2015 for this cross-sectional study. The diagnoses were made by headache specialists according to the International Classification of Headache Disorders ICHD - 3rd edition and they were classified as: migraine with aura group (MA), migraine without aura group (MoA) and chronic migraine group (CM).[6] Patients were

diagnosed with chronic migraine if they had at least 15 days with headache within a month in the last three months (and at least 8 of them fulfilled the migraine criteria). Patients with less than 15 days with headache in the last three months were diagnosed with migraine with or without aura. Vestibular migraine criteria was not considered to characterize the patients. Non-headache subjects were identified among patients' family members and hospital employees in order to compose the control group (CG).

Female subjects were included in the sample when they were between the ages of 18 to 55 years old. Specific for migraine patients, inclusion criteria comprised migraine diagnosis in the previous 1 year and presence of at least three attacks within a month during the last three months. The exclusion criteria adopted for all subjects were: diagnosis of any concomitant headache (1), use of any medication prescribed for vertigo or dizziness treatment such as meclizine, flunarizine, cinnarizine, betahistine, and/or benzodiazepinics (2), self-report or history of vestibular disease (3), abnormal neurological exam (4), any musculoskeletal impairment that could affect balance (5), presence of a migraine attack during the interview (6), pregnancy (7) and any systemic disease with rheumatic, cardiovascular, neurologic or metabolic etiology (8).

A structured questionnaire was used to interview the participants regarding the following aspects: demographics, migraine onset, pain intensity (numeric pain rating scale, NPRS), attack frequency (number of days in the prior month) and duration (hours), presence and description of vestibular symptoms, during and between migraine attacks. Patients with the report of vestibular symptoms prior to the migraine onset, with the presence of them just between the migraine attacks or with chronic dizziness were also excluded. Primary vestibular symptoms including vertigo (sensation of self-motion), dizziness (disturbing spatial orientation), vestibulovisual (false sensation of motion or tilting) or postural symptoms (symptoms related to balance to the postural stability) were classified according to the Bárány Society's Classification of Vestibular Symptoms[12] and patients who referred multiple symptoms were included in more than one classification.

Furthermore, a senior headache specialist administered the questionnaire Dizziness Handicap Inventory (DHI) in order to assess the self-perceived impairment related to the vestibular symptoms. This questionnaire was applied just for the subjects with any report of vestibular symptoms. The DHI has 25 questions encompassing physical (7 questions, 0 – 28 points), functional (9 questions, 0 – 36 points) and emotional aspects (9 questions, 0 – 36

points), with total score ranging from 0 to 100 points (0 = no, 2 = sometimes, 4 = yes). Total scores are classified as a mild handicap (0 – 30 points), moderate handicap (31 – 60 points) and severe handicap (61 – 100 points).[13] This tool provides a useful, reliable and valid measure of self-perceived handicap associated with dizziness[14, 15] considering the total score as well as the physical, functional and emotional domains.[16, 17] This questionnaire is correlated with functional measures of gait and balance.[18-20]

The study was performed in accordance with the Helsinki Declaration and with the approval of the Local Ethics Committee (protocol number: no 16693/2012). Written informed consent was obtained from all participants.

Based on a pilot study, the sample size was calculated to provide a power of 95% to the selected α level of 5% to detect 13 DHI points of difference between any migraine group and controls with a standard deviation (SD) of 10.6. The sample was calculated as being 55 subjects for each group, therefore 60 were included to account for imprecision on the pilot study.

Demographic data of the four groups were normally distributed (Kolmogorov-Smirnov test NS) and then they were compared using an ANOVA two-way with Bonferroni's *post-hoc* test. A Qui-square test was used to analyze the frequency of presence of vestibular symptoms in the sample during and between migraine attacks. DHI total scores and subscale scores were contrasted among groups through the Kruskal Wallis test with a Dunn's *post-hoc* test. Since the DHI questionnaire has a different number of questions for each domain, a Fisher's exact test was used to contrast frequency of physical, functional and emotional subscales as well as the level of handicap severity among groups. A backwise multiple linear regression model was used to correlate DHI scores (dependent variable) with demographic data and migraine frequency, onset and intensity (independent variables). Prevalence ratio of any DHI handicap and of moderate/severe handicap were calculated considering CG and MoA as a reference. Data analysis was performed in the SPSS software version 21.0 and a significance level of 5% was set.

Results

Among 320 potential patients, 28 were excluded due to the presence of systemic diseases such as fibromyalgia, diabetes, non-controlled hypertension, stroke and idiopathic intracranial hypertension. Up to 17 subjects were excluded due to concomitant headaches such

as post-traumatic headache, tension-type headache or medication-overuse headache. Up to 15 subjects presented musculoskeletal impairments such as knee osteoarthritis, injury of knee or ankle ligaments and prior knee surgery. Up to 11 subjects had less than three migraine attacks per month and 9 reported histories of vestibular diseases including labitinthitis and BPPV. Therefore, 240 subjects were included in the study, equally distributed among the four groups (MoA, n=60; MA, n=60; CM, n=60; CG, n=60).

No difference was found among groups regarding age, migraine onset and pain intensity (*p*: NS). Patients with MA presented greater BMI compared to CG and MoA groups ($p<0.05$). CM patients presented greater frequency of headache than MoA and MA groups ($p<0.05$) as expected (Table 1).

Table 1. Average and standard deviation (SD) of demographic data among subjects with migraine with aura (MA) and without aura (MoA), chronic migraine (CM) and controls (CG).

	CG (n=60)	MoA (n=60)	MA (n=60)	CM (n=60)
Age (years)	35.3 (9.8)	34.6 (10.1)	36.3 (9.8)	37.1 (9.9)
BMI (Kg/cm^2)	24.1 (3.8)	24.4 (4.3)	26.4 (4)*	25.9 (3.8)
Migraine onset (years)	-	15.6 (11)	18.4 (11.8)	17.8 (10.7)
Days of headache (monthly)	-	6.6 (3.3)	5.8 (3.3)	21.2 (8.4)**
Duration of headache (hours)	-	20 (25.5)	25.1 (28.1)	23.0 (32.1)
Intensity (VAS)	-	8.0 (1.7)	8.5 (1.3)	8.1 (1.6)

*$p<0.05$ MA *versus* CG and MoA; **$p<0.002$ CM *versus* MoA and MA.

Relative to 12% in the control group, 85% of patients with MA ($p<0.0001$) and CM ($p<0.0001$) and 70% of MoA ($p<0.0001$) noted vestibular symptoms. Patients with MA and CM also reported vestibular symptoms more often compared to MoA ($p<0.05$). This prevalence distribution was also observed regarding the vestibular symptoms that occurs during the migraine attack (MA and CM *versus* MoA: $p<0.05$). On the other hand, 25% of MoA, 40% of MA and CM groups reported vestibular symptoms also interictally. The prevalence of interictal vestibular symptoms was greater in all migraine groups compared to controls ($p<0.05$), without differences between migraine subgroups ($p=0.11$). Patients with MA and CM reported

symptoms of vertigo predominantly (*versus* CG: $p<0.0001$ and *versus* MoA: $p<0.05$). MoA and MA groups reported postural symptoms more often compared to GC ($p<0.05$) (Table 2).

Table 2. Presence and classification of vestibular symptoms among subjects migraine with aura (MA) and without aura (MoA), chronic migraine (CM) and controls (CG).

	CG (n=60)	MoA (n=60)	MA (n=60)	CM (n=60)
Self-report of vestibular symptoms	12%	70%*	85%*†	85%*†
Interictal	12%	25%‡	40%‡	40%‡
Ictal	-	70%	85%†	85%†
Dizziness classification				
Vertigo	6%	26%*	54%*†	54%*†
Postural symptoms	9%	43%*	37%*	23%
Dizziness	0%	6%	3%	11%

For cells with n<5, the Fisher's exact test was performed.

*$p<0.0001$ *versus* CG; †$p<0.05$ *versus* MoA; ‡$p<0.05$ *versus* CG.

Considering only the subjects with the presence of vestibular symptoms in each group, average DHI scores of MoA, MA and CM were higher compared to CG ($p<0.001$). Patients with MA and CM also reached higher DHI scores compared to MoA patients ($p<0.01$). The distribution among the different levels of severity demonstrated that patients with MA and CM presented greater frequency of moderate and severe handicap while MoA and CG presented greater frequency of no or mild handicap ($p<0.05$) (Table 3).

Regarding the DHI domains, patients with MA and CM reached higher scores than MoA and CG considering the physical, functional and emotional scores ($p<0.01$ and $p<0.001$, respectively). Moreover, the MoA group exhibited higher scores for all domains compared to CG ($p<0.001$) (Table 3). However, since the DHI domains have a distinct number of questions/maximal score, the frequency of impairment among domains demonstrated that the most impaired was the physical aspect followed by the functional aspect for all groups ($p<0.05$)(Figure 1).

Table 3. Average (95% CI) of Dizziness Handicap Inventory (DHI) scores and handicap frequency among subjects with migraine with (MA) and without aura (MoA), chronic migraine (CM) and controls (CG).

	CG (n=60)	MoA (n=60)	MA (n=60)	CM (n=60)
DHI total score	20.0 (11.6 to 28.4)	34.1* (26.2 to 42.0)	47.5*† (40.3 to 54.7)	51.1*† (43.6 to 58.5)
*Distribution according to the handicap severity***				
No Handicap	87%	30%	13%	18%
Mild Handicap	12%	37%	20%	15%
Moderate Handicap	0%	25%	45%	42%
Severe Handicap	2%	8%	22%	25%
Scores according to the DHI domains				
Physical Aspects	9.5 (8.0 to 10.9)	13.0* (11.1 to 14.8)	17.3*† (15.9 to 18.6)	16.4*† (14.9 to 17.9)
Functional Aspects	6.5 (3.6 to 9.3)	12.8* (10.6 to 14.9)	18.8*† (16.5 to 21.0)	19.5*† (17.2 to 21.7)
Emotional Aspects	4.0 (2.1 to 5.9)	8.3* (5.9 to 10.4)	11.4*† (9.1 to 13.6)	15.4*† (13.1 to 17.5)

*p<0.001 *versus* CG; †p<0.01 *versus* MoA. **p<0.05 Fisher's exact test.

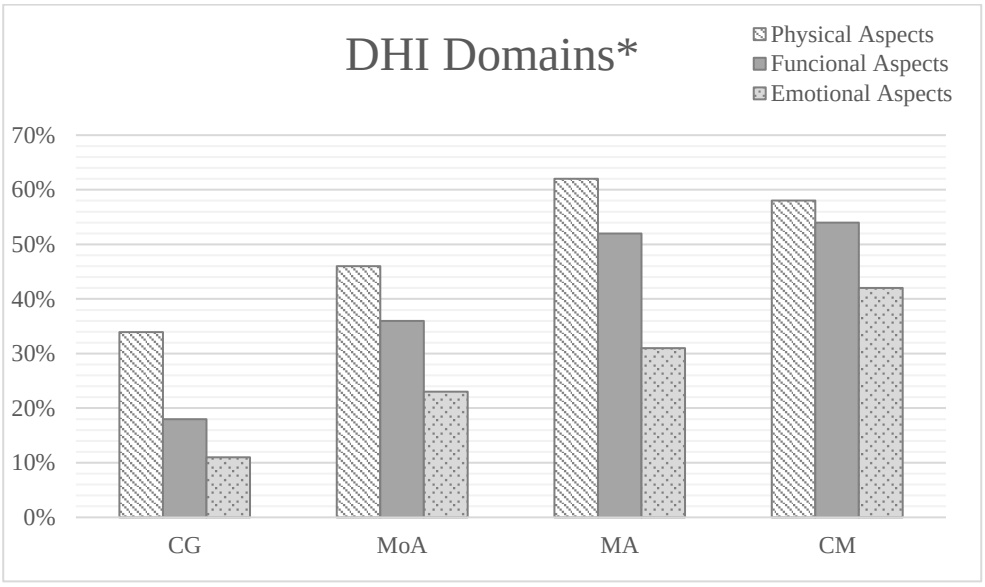


Figure 1. Physical, functional and emotional domains of the Dizziness Handicap Inventory (DHI) among patients with migraine without aura (MoA), with aura (MA), chronic migraine (CM) and controls (CG). *p<0.05 Fisher's exact test.

Prevalence ratio analysis demonstrated that migraine is associated to the risk of presence of vestibular symptoms compared to controls in the range of 5.20 to 6.60-fold (p<0.0003) and presence of aura adds to the risk 1.27-fold, compared to MoA (p<0.04). Presence of vertigo is associated to MA and CM in 9.50-fold (p<0.0003) and MoA in 4.50-fold (p<0.04) compared to controls. While contrasted to the MoA group, the presence of vertigo is associated to MA and CM 2.11-fold (p<0.04). Postural symptoms are associated to MoA in 5.00-fold and in 4.33-fold to MA, compared to controls (p<0.04). The risk of dizziness is not incresed according to the presence of migraine (p<0.05) (Table 4).

The presence of migraine is associated with a greater risk of any handicap due to dizziness (MoA: 5.25, MA: 6.50 and CM: 6.12, p<0.0003) and also to a greater risk of presence of moderate-to-severe handicap (MoA: 20.0, p<0.04; MA: 40.0 and CM: 40.0, p<0.0003) compared to controls. Furthermore, the presence of aura and greater frequency of headache is also associated with a greater risk of any handicap due to dizziness (MA: 1.9 and CM: 1.7, p<0.04) and to a greater risk of moderate-to-severe handicap (MA: 2.0 and CM: 2.0, p<0.0003), compared to MoA group (Table 4).

Table 4. Prevalence Ratios of the presence of any kind of vestibular symptoms and Dizziness Handicap (DHI) among subjects with migraine using controls and migraine without aura groups as references (ref.).

Vestibular Symptoms	CG	MoA	MA	CM
Presence of vestibular symptoms	Ref.	5.20* (2.26 to 11.98)	6.60* (2.91 to 14.91)	6.20* (2.73 to 14.07)
	-	Ref.	1.27† (1.02 to 1.56)	1.19 (0.94 to 1.49)
Presence of Vertigo	Ref.	4.50† (1.04 to 19.35)	9.50* (2.39 to 37.74)	9.50* (2.39 to 37.74)
	-	Ref.	2.11† (1.11 to 4.00)	2.11† (1.11 to 4.00)
Presence of Postural Symptoms	Ref.	5.00* (1.58 to 15.75)	4.33† (1.35 to 13.88)	2.67 (0.77 to 9.22)
	-	Ref.	0.86 (0.48 to 1.54)	0.53 (0.25 to 1.09)
Presence of Dizziness	Ref.	5.00 (0.25 to 100.00)	3.00 (0.12 to 71.21)	9.00 (0.50 to 161.13)
	-	Ref.	0.50 (0.04 to 5.26)	2.00 (0.39 to 10.22)
Dizziness Handicap Inventory				
Presence of any handicap	Ref.	5.25* (2.69 to 10.21)	6.50* (3.38 to 12.48)	6.12* (3.17 to 11.80)
	-	Ref.	1.90† (1.30 to 2.60)	1.70† (1.20 to 2.30)
Moderate/severe handicap	Ref.	20.00† (2.77 to 144.31)	40.00* (5.68 to 281.70)	40.00* (5.68 to 281.70)
	-	Ref.	2.00* (1.34 to 2.98)	2.00* (1.34 to 2.98)

Ref.: Prevalence ratio reference. *$p<0.0003$; †$p<0.04$.

GC: Control group, MoA: Migraine without aura group, MA: Migraine with aura group, CM: Chronic migraine group.

Table 5 describes the relation between the variability of DHI scores in contrast to demographic and migraine features. The final model (model 3) indicated that migraine aura, frequency and intensity are able to explain 36% of the DHI variability. If the migraine frequency and migraine aura are stable, the migraine intensity can predict 34% of the DHI scores ($p<0.000$). On the other hand, when migraine intensity and migraine aura are stable, the migraine frequency can predict 27% of the DHI scores ($p<0.0001$). Finally, if migraine intensity and frequency are stable, migraine aura can predict 21% of the DHI scores ($p<0.001$).

Table 5. Linear regression models explaining the variability of the DHI scores by migraine and demographic variables.*

	B	SE B	β	*p*	R^2	Adjusted R^2
Model 1					.364	.351
Constant	3.535	6.356		.579		
Age	-.057	.168	-.020	.735		
Migraine aura	13.240	3.968	.207	.001		
Migraine frequency	.805	.203	.265	.000		
Migraine intensity	2.321	.564	.321	.000		
Migraine onset	.120	.169	.053	.480		
Model 2					.364	.353
Constant	1.591	2.749		.563		
Migraine aura	13.229	3.961	.207	.001		
Migraine frequency	.801	.202	.264	.000		
Migraine intensity	2.368	.546	.327	.000		
Migraine onset	.092	.149	.041	.535		
Model 3					.363	.355
Constant	1.694	2.740		.537		
Migraine aura	13.555	3.921	.212	.001		
Migraine frequency	.823	.199	.271	.000		
Migraine intensity	2.502	.501	.346	.000		

*Dependent variable: Dizziness Handicap Inventory scores (DHI).
Independent variables: age, migraine aura, frequency, intensity and onset.

Discussion

Our findings support the possibility of a link between migraine and vestibular symptoms, with a greater frequency when patients exhibit aura or chronic migraine. The handicap severity is higher in both chronic and aura groups, despite the presence of some level of handicap in all migraineurs compared to controls. The presence of migraine, especially with aura and chronic, is associated with the risk of vestibular symptoms, mainly vertigo; and of any handicap or moderate-to-severe handicap related to vestibular symptoms. The dizziness handicap level is influenced by the presence of aura, by migraine frequency and intensity.

Previous studies have found a prevalence of dizziness or vertigo ranging from 12% to 52% among patients with migraine,[2, 21, 22] reaching up to 62% in women.[21] Lower prevalence rates are usually related to the diagnosis of migraine without aura, while higher prevalence is verified when migraine aura is present.[2, 22] Furthermore, the prevalence of headache among patients reporting dizziness and vertigo is around 35%.[23]

The prevalence found in the present study of 70 to 85% refers to all categories of vestibular symptoms described by the Bárány Society's Classification of Vestibular Symptoms, including the postural symptoms,[12] which was not accounted for in the above-mentioned studies. Since the patients may refer to more than one category of vestibular symptom, we verified a point-prevalence of dizziness ranging from 3% to 11% and of vertigo from 26% to 54% among patients with migraine without aura, with aura and chronic migraine. These results are according to the previous studies and also highlight the greater prevalence in patients with aura.

Considering the broad variability of the found confidence intervals, we can highlight that the presence of migraine is associated to the risk of presenting vestibular symptoms in 5.20 to 6.60-fold; and patients with aura and greater migraine frequency are more likely to present vertigo than controls. On the other hand, patients with migraine without aura are more likely to report postural symptoms.

An interesting aspect verified in our sample was the similar prevalence of vestibular symptoms among patients with aura and chronic migraine. The chronicity of migraine frequency is not accounted in the proposed vestibular migraine criteria[6] and it is poorly explored by the studies in the topic.[5, 10, 21, 22, 24-28] This fact could be due to the challenge of establishing a temporal relationship between migraine and other conditions, such as vestibular symptoms;[21]

or to the modification of migraine features along with the increment of attacks (>15 within a month).[29] However, Calhoun *et al*[2] reported additional presence of dizziness and vertigo with increasing age, suggesting an association with a greater lifetime burden of illness or with migraine chronicity.

Cho *et al*[30] reported a concomitant diagnosis of chronic migraine of 29% among patients who fulfilled the vestibular migraine criteria. We can speculate that a part of our sample would meet the vestibular migraine criteria since 26% of MoA, 54% of MA and of CM reported vertigo during the migraine attacks. However, according to the proposed criteria for vestibular migraine, at least 50% of the vestibular symptoms should be associated with migrainous features.[6] If patients with chronic migraine exhibit vestibular symptoms just along the headache days that do not fulfill the migraine features, they would not meet the proposed criteria.

The etiology of vestibular symptoms in patients with migraine could be related to the overlap between the trigeminal and vestibular pathways,[26] suggesting a concomitant activation of vestibular and cranial nociceptive afferents.[25] The vascular, neurogenic inflammation and neural mechanisms involved in the migraine pathophysiology are also verified in the inner ear and vestibular pathways.[26] Moreover, several migraine neurotransmitters play a role in the modulation of vestibular neurons activity.[3] Furthermore, other theories involving the cortical spreading depression can also trigger vestibular symptoms due the activation of multisensory cortical areas,[3, 26] and genetic defects of ion channels may also be involved in the MV pathogenesis.[3]

The presence of abnormalities in the vestibular function[7, 9, 28, 31, 32] and balance changes[31-37] are commonly verified among patients with migraine. Interestingly, some authors demonstrated those alterations regardless of the presence of vestibular symptoms or diagnosis of vestibular migraine.[7, 9, 26, 33, 34] It highlights the plausible hypothesis of a continuum between migraine and vestibular migraine, suggesting that both conditions should not be considered separate entities with distinct pathophysiologies.[7, 9]

Furthermore, despite the greater report of vestibular symptoms during a migraine attack, we observed that 25% of the MoA group and 40% of the MA and CM groups presented symptoms in the headache-free interval. It was already verified in previous studies[3, 9, 26] and suggests that those symptoms can be considered inherent of the migraine condition, such as other interictal manifestations including cutaneous allodynia,[38] photo and phonophobia.[39]

It is known that the overall migraine disability increases with the presence of vestibular symptoms.[21, 27] Patients diagnosed with vestibular migraine had lower quality of life scores compared to dizziness-free controls.[27] Also, the presence of dizziness is independently associated with migraine-related disability (MIDAS), depression, and disability (WHODAS).[21]

Data regarding the DHI questionnaire in patients with migraine is scarce, but a baseline of a clinical trial with patients with vestibular migraine demonstrated an overall score of around 50 points.[40] Another study found similar scores among patients with vestibular migraine and Menière's disease (38 and 36.6, respectively).[41] The lack of information regarding the presence of aura and chronicity in those studies may interfere with the comparison to our results; but in general, all scores were classified as mild-to-moderate handicap due to dizziness.

The verified handicap mainly in the physical and functional aspects of the DHI, along with its correlation to functional measures of gait and balance,[18-20] and the verified balance changes[31-37] demonstrate the impact of migraine and vestibular symptoms on patients' daily living. Those scores are influenced in 36% by migraine aura, attacks frequency and intensity. Moreover, the presence of migraine and the presence of aura or greater frequency are associated to the risk of presenting moderate-to-severe levels of dizziness handicap in at least 2.8 times, according to the lower bound of the prevalence ratio's CI95%. Its clinical significance can not be neglected during the migraine treatment. Along with pain management, physical therapy strategies including vestibular rehabilitation and balance retraining should be encouraged.[42-44]

We can list the following limitations of the present study. The data collection in a tertiary clinical setting and inclusion of a sample of women may restrict the generalizability and overestimate our results. Moreover, due to the cross-sectional design, no statement regarding causality can be done. This study had no intention to establish populational prevalence values since methodological strategies for this kind of research was not performed. We concluded the data collection when the pre-established number of individuals in each group was reached, in a random and consecutive sampling. Despite the similarities of our results compared to population-based samples, the data cannot be extrapolated as prevalence for the disease.

Another important limitation is the lack of individual application of the vestibular migraine criteria or the assessment of specific physicological conditions such as anxiety in our sample. The diagnosis of vestibular migraine would provide the possibility of association between the different categories described by the IHS and the Bárány Society's Classification of Vestibular Symptoms, even though it is not a validated diagnosis. However, the description

of the vestibular symptoms and its relation to the migraine attack in different subgroups of migraine adds to the current knowledge of this emerging area.

This is the first study that included the investigation of vestibular symptoms and measured their specific handicap in patients with chronic migraine. Along with exclusion of any case with the history of a vestibular disease and a robust sample size, conclusions regarding the association and risk between migraine and vestibular symptoms can be done. The present results are of clinical importance and may contribute to the understanding of the vestibular migraine entity.

Conclusion

Vestibular symptoms are prevalent in patients with migraine, especially vertigo in individuals with aura and chronic migraine. These symptoms are related to a greater perceived handicap due to dizziness especially both migraine subgroups, impacting mainly the physical and functional domains. The presence of migraine, especially with aura and chronic, is associated with the risk of vestibular symptoms, of any handicap and of moderate-to-severe handicap related to vestibular symptoms. Migraine aura, intensity and frequency can be considered predictors of the handicap related dizziness.

Article Highlights

- Prevalence of vestibular symptoms and handicap due dizziness are greater in patients with migraine than controls.
- Vertigo is the main presentation among the vestibular symptoms in patients with aura and chronic migraine.
- Patients with aura and chronic migrane have an additional impairment due vestibular symptoms, especially in the physical and funtional domains.
- The presence of migraine is associated to the risk of vestibular symptoms in 5.2 to 6.6-fold, and to moderate-to-severe handicap due dizziness in 20.0 to 40.0-fold.
- Migraine aura, intensity and frequency can predict 36% of the handicap due dizziness.

Acknowledgements

We would like to thank the Ambulatory of Craniofacial Pain of the Ribeirão Preto Clinics Hospital.

Conflicts of Interest Statement

The authors declare that there is no conflict of interest.

Founding

This work was supported by the FAPESP Foundation (grant number: 2012/20046-2).

References

1. Cohen JM, Escasena CA. Headache and Dizziness: How to Differentiate Vestibular Migraine from Other Conditions. Curr Pain Headache Rep 2015;19:31.

2. Calhoun AH, Ford S, Pruitt AP, Fisher KG. The point prevalence of dizziness or vertigo in migraine and factors that influence presentation. Headache 2011;51:1388-1392.

3. Lempert T, Neuhauser H. Migrainous vertigo. Neurol Clin 2005;23:715-730, vi.

4. Cass SP, Furman JM, Ankerstjerne K, Balaban C, Yetiser S, Aydogan B. Migraine-related vestibulopathy. Ann Otol Rhinol Laryngol 1997;106:182-189.

5. O'Connell Ferster AP, Priesol AJ, Isildak H. The clinical manifestations of vestibular migraine: A review. Auris Nasus Larynx 2017;44:249-252.

6. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.

7. Baker BJ, Curtis A, Trueblood P, Vangsnes E. Vestibular functioning and migraine: comparing those with and without vertigo to a normal population. J Laryngol Otol 2013;127:1169-1176.

8. Bir LS, Ardic FN, Kara CO, Akalin O, Pinar HS, Celiker A. Migraine patients with or without vertigo: comparison of clinical and electronystagmographic findings. J Otolaryngol 2003;32:234-238.

9. Boldingh MI, Ljostad U, Mygland A, Monstad P. Comparison of Interictal Vestibular Function in Vestibular Migraine vs Migraine Without Vertigo. Headache 2013;53:1123-1133.

10. Pereira CB, Nader SN, Kanashiro AK, de Carvalho WL. Vestibular Migraine: Vestibular Symptom May Identify Different Subgroups. Otol Neurotol 2016;37:281-283.

11. Chen YC, Tang CH, Ng K, Wang SJ. Comorbidity profiles of chronic migraine sufferers in a national database in Taiwan. J Headache Pain 2012;13:311-319.

12. Bisdorff AR, Staab JP, Newman-Toker DE. Overview of the International Classification of Vestibular Disorders. Neurol Clin 2015;33:541-550, vii.

13. Whitney SL, Wrisley DM, Brown KE, Furman JM. Is perception of handicap related to functional performance in persons with vestibular dysfunction? Otol Neurotol 2004;25:139-143.

14. Castro AS, Gazzola JM, Natour J, Gananca FF. Brazilian version of the dizziness handicap inventory. Pro Fono 2007;19:97-104.

15. Enloe LJ, Shields RK. Evaluation of health-related quality of life in individuals with vestibular disease using disease-specific and general outcome measures. Phys Ther 1997;77:890-903.

16. Georgieva-Zhostova S, Kolev OI, Stambolieva K. Translation, cross-cultural adaptation and validation of the Bulgarian version of the Dizziness Handicap Inventory. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation 2014;23:2103-2107.

17. Jacobson GP, Newman CW. The development of the Dizziness Handicap Inventory. Arch Otolaryngol Head Neck Surg 1990;116:424-427.

18. Jacobson GP, Newman CW, Hunter L, Balzer GK. Balance function test correlates of the Dizziness Handicap Inventory. J Am Acad Audiol 1991;2:253-260.

19. Robertson DD, Ireland DJ. Dizziness Handicap Inventory correlates of computerized dynamic posturography. J Otolaryngol 1995;24:118-124.

20. Vereeck L, Truijen S, Wuyts FL, Van de Heyning PH. The dizziness handicap inventory and its relationship with functional balance performance. Otol Neurotol 2007;28:87-93.

21. Bisdorff A, Andree C, Vaillant M, Sandor PS. Headache-associated dizziness in a headache population: prevalence and impact. Cephalalgia 2010;30:815-820.

22. Vukovic V, Plavec D, Galinovic I, Lovrencic-Huzjan A, Budisic M, Demarin V. Prevalence of vertigo, dizziness, and migrainous vertigo in patients with migraine. Headache 2007;47:1427-1435.

23. Teggi R, Manfrin M, Balzanelli C, et al. Point prevalence of vertigo and dizziness in a sample of 2672 subjects and correlation with headaches. Acta Otorhinolaryngol Ital 2016;36:215-219.

24. Bisdorff A. Migraine and dizziness. Curr Opin Neurol 2014;27:105-110.

25. Dieterich M, Obermann M, Celebisoy N. Vestibular migraine: the most frequent entity of episodic vertigo. J Neurol 2016;263 Suppl 1:S82-89.

26. Furman JM, Marcus DA, Balaban CD. Vestibular migraine: clinical aspects and pathophysiology. Lancet Neurol 2013;12:706-715.

27. Neuhauser HK, Radtke A, von Brevern M, et al. Migrainous vertigo: prevalence and impact on quality of life. Neurology 2006;67:1028-1033.

28. Yollu U, Uluduz DU, Yilmaz M, et al. Vestibular migraine screening in a migraine-diagnosed patient population, and assessment of vestibulocochlear function. Clin Otolaryngol 2016.

29. Yalin OO, Uluduz D, Ozge A, Sungur MA, Selekler M, Siva A. Phenotypic features of chronic migraine. J Headache Pain 2016;17:26.

30. Cho SJ, Kim BK, Kim BS, et al. Vestibular migraine in multicenter neurology clinics according to the appendix criteria in the third beta edition of the International Classification of Headache Disorders. Cephalalgia 2016;36:454-462.

31. Celebisoy N, Gokcay F, Sirin H, Bicak N. Migrainous vertigo: clinical, oculographic and posturographic findings. Cephalalgia 2008;28:72-77.

32. Teggi R, Colombo B, Bernasconi L, Bellini C, Comi G, Bussi M. Migrainous vertigo: results of caloric testing and stabilometric findings. Headache 2009;49:435-444.

33. Ongun N, Atalay NS, Degirmenci E, Sahin F, Bir LS. Tetra-ataxiometric Posturography in Patients with Migrainous Vertigo. Pain physician 2016;19:E87-96.

34. Panichi R, Cipriani L, Sarchielli P, et al. Balance control impairment induced after OKS in patients with vestibular migraine: an intercritical marker. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies 2015;272:2275-2282.

35. Carvalho GF, Florencio LL, Pinheiro CF, Dach F, Bigal ME, Bevilaqua-Grossi D. Functional Balance Deterioration on Daily Activities in Patients With Migraine: A Controlled Study. Am J Phys Med Rehabil 2017.

36. Carvalho GF, Bonato P, Florencio LL, et al. Balance Impairments in Different Subgroups of Patients With Migraine. Headache 2017;57:363-374.

37. Carvalho GF, Chaves TC, Dach F, et al. Influence of Migraine and of Migraine Aura on Balance and Mobility - A Controlled Study. Headache 2013;53:1116-1122.

38. Lovati C, D'Amico D, Bertora P, et al. Acute and interictal allodynia in patients with different headache forms: an Italian pilot study. Headache 2008;48:272-277.

39. Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. Headache 1997;37:492-495.

40. Sugaya N, Arai M, Goto F. Is the Headache in Patients with Vestibular Migraine Attenuated by Vestibular Rehabilitation? Frontiers in neurology 2017;8:124.

41. Bremova T, Caushaj A, Ertl M, et al. Comparison of linear motion perception thresholds in vestibular migraine and Meniere's disease. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies 2016.

42. Vitkovic J, Winoto A, Rance G, Dowell R, Paine M. Vestibular rehabilitation outcomes in patients with and without vestibular migraine. J Neurol 2013;260:3039-3048.

43. Wrisley DM, Whitney SL, Furman JM. Vestibular rehabilitation outcomes in patients with a history of migraine. Otol Neurotol 2002;23:483-487.

44. Whitney SL, Wrisley DM, Brown KE, Furman JM. Physical therapy for migraine-related vestibulopathy and vestibular dysfunction with history of migraine. Laryngoscope 2000;110:1528-1534.

3.2 Article 2 – Submitted at Plos One

PLOS ONE

Light intensity and postural control in patients with migraine - A controlled study

–Manuscript Draft–

Manuscript Number:	
Article Type:	Research Article
Full Title:	Light intensity and postural control in patients with migraine - A controlled study
Short Title:	Light and posture control in migraine
Corresponding Author:	Carina F Pinheiro, Ms, PT Ribeirão Preto Medical School, University of São Paulo Ribeirão Preto, São Paulo BRAZIL
Keywords:	Photosensitivity, headache, posture, visual discomfort.
Abstract:	Postural control changes as well as photophobia are known to occur in people with migraine. The influence of light intensity on balance is reported for older adults only for dark ambient light conditions. It is unknown if higher lighting levels also affect balance, especially for individuals with visual hypersensitivity as in those migraineurs. We analyzed the visual discomfort and balance of women with migraine and non-headache under different light conditions. The sample consisted of 14 women with migraine (30.6 ± 8.1 years) and 14 women non-headache controls (27.2 ± 2.8 years). Participants were evaluated in bipodal and unipodal postures under three light conditions: (1) ambient, (2) visual discomfort threshold and (3) intense visual discomfort. Center of pressure (CoP) velocity, root mean square (RMS), and frequency for anterior-posterior (AP) and medial-lateral (ML) directions and CoP area were analyzed and compared between groups across the 3 light conditions using ANOVA ($p<.05$). The migraine group reported a visual discomfort threshold of 450 lx and intense visual discomfort at 2000 lx. Controls did not report visual discomfort. The migraine group presented greater CoP area under the three conditions, greater CoP velocity and RMS under the visual discomfort light conditions, compared to controls ($p<.05$). Intra-group analysis showed greater CoP area, velocity and RMS for both visual discomfort light conditions compared to the ambient condition, but only for the migraine group ($p<.05$). Patients with migraine present visual sensitivity during the interictal period, and the light-induced discomfort might be a disturbing factor that worsens balance even during quiet standing posture.
Order of Authors:	Carina F Pinheiro, Ms, PT
	Renato Moraes
	Gabriela Ferreira Carvalho
	Lais Sestari
	Nicoly Machado Maciel
	Fabiola Dach
	Richard van Emmerik
	Debora Bevilaqua-Grossi

Light intensity and postural control in patients with migraine – a controlled study

Carina F. Pinheiro[1¶*], Renato de Moraes[2¶], Gabriela F. Carvalho[1&], Lais Sestari[1&], Nicoly M. Maciel[1&], Fabiola Dach[3&], Richard van Emmerik[4&], Debora Bevilaqua-Grossi[1¶]

[1]Department of Health Sciences, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto – SP, Brazil

[2]Biomechanics and Motor Control Lab, School of Physical Education and Sports of Ribeirão Preto, University of São Paulo, Ribeirão Preto – SP, Brazil

[3]Department of Neurosciences and Behavioral Sciences, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto – SP, Brazil

[4]Department of Kinesiology, School of Public Health and Health Sciences, University of Massachusetts, Amherst – MA, United States

*Corresponding author

E-mail: carinafp@hotmail.com (CFP)

¶These authors contributed equally to this work

&These authors contributed equally to this work

Abstract

Postural control changes as well as photophobia are known to occur in people with migraine. The influence of light intensity on balance is reported for older adults only for dark ambient light conditions. It is unknown if higher lighting levels also affect balance, especially for individuals with visual hypersensitivity as in those migraineurs. We analyzed the visual discomfort and balance of women with migraine and non-headache under different light conditions. The sample consisted of 14 women with migraine (30.6 ± 8.1 years) and 14 women non-headache controls (27.2 ± 2.8 years). Participants were evaluated in bipodal and unipodal postures under three light conditions: (1) ambient, (2) visual discomfort threshold and (3) intense visual discomfort. Center of pressure (CoP) velocity, root mean square (RMS), and frequency for antero-posterior (AP) and medio-lateral (ML) directions and CoP area were analyzed and compared between groups across the 3 light conditions using ANOVA ($p<.05$). The migraine group reported a visual discomfort threshold of 450 lx and intense visual discomfort at 2000 lx. Controls did not report visual discomfort. The migraine group presented greater CoP area under the three conditions, greater CoP velocity and RMS under the visual discomfort light conditions, compared to controls ($p<.05$). Intra-group analysis showed greater CoP area, velocity and RMS for both visual discomfort light conditions compared to the ambient condition, but only for the migraine group ($p<.05$). Patients with migraine present visual sensitivity during the interictal period, and the light-induced discomfort might be a disturbing factor that worsens balance even during quiet standing posture.

Key-words: Photosensitivity, headache, posture, visual discomfort.

Introduction

Migraine is a severe and disabling neurological condition that affects approximately 15-18% of the worldwide population, predominantly females aged between 20 to 45 years-old [1]. Photophobia, the perception of pain and discomfort caused by lighting brightness, is a symptom frequently reported by migraineurs [1]. Its occurs during the headache attacks in 60% to 90% of patients and also persists at a lower intensity in the interictal period [1–3].

Visual discomfort thresholds for luminous stimuli in migraineurs are between 300 and 680 lx while for controls it is between 1700 and 2000 lx [4,5]. Furthermore, the maximum tolerance to the luminous stimulus of these same groups are on average 1600 lx and 15900 lx, respectively [5]. However, those studies did not evaluate this discomfort in ambient conditions with indirect light-stimulation, as we found in daily situations such as rooms and under the sunlight.

Although light is often a perturbing factor for individuals with migraine [6], photosensitivity mechanisms are not yet clearly identified. Previous investigations suggest that hyperexcited trigeminovascular thalamic neurons project into multiple cortical areas when receiving information from the retina [7]. These areas include motor and somatosensory and may play a role in the impaired motor function and difficulty on concentrating [6]. It is known that in addition to the neuronal changes involved in the process of photophobia, migraine is directly related to decreased cerebral blood flow, affecting the white matter of the cerebellum, brain stem and inner ear [1,8]. These factors might contribute to the occurrence of vertigo and balance impairments such as increased postural oscillations [9].

Modifications in the balance of migraineurs have been demonstrated by increased postural sway [9–13] and decreased stability limits, expressed by slower reaction time and movement velocity, and smaller excursion endpoint [14] during the limits of stability test. These individuals also exhibit a greater time to perform functional activities, such as gait, sit-to-stand transitions, and up/down stepping [15].

It is well-established that postural sway increases during standing when the patients' eyes are closed [16]. However, the efficiency of the visual system for the maintenance of posture may depend on levels of illumination [17]. In dim light conditions, postural sway of older adults is increased [18,19] compared to younger adults and compared to bright ambient light conditions [20]. To the best of our knowledge, there is no information about the postural behavior in conditions with brighter lighting levels, especially in individuals with light

sensitivity, such as migraineurs. Since visual hypersensitivity remains during interictal period [2,3], it is important to verify whether photophobia, both at the sensitivity threshold or under visual discomfort conditions, influences postural control of patients with migraine in addition to that observed under ambient light levels.

Therefore, this study aims to analyze the visual discomfort and postural control of women with migraine and non-headache participants in upright standing posture under different light conditions. Our hypothesis is that individuals with migraine would demonstrate visual sensitivity and systematic decrements in postural control as a function of increased light intensity, ranging from ambient to intense visual discomfort, differently from the controls.

Materials and Methods

Sample

Participants in the migraine group were screened from a tertiary clinic and from the local community and diagnosed by specialized neurologists according to the International Classification of Headache Disorders – ICHD-III [21]. The control group was composed by non-headache participants identified in the community.

Women aged between 18 and 55 years-old were included in the sample. Patients with migraine were considered eligible to participate if they had reported at least three migraine episodes per month within the last three months. The exclusion criteria were body mass index (BMI) higher than 30, pregnancy, report of any vestibular disease, musculoskeletal dysfunction or any systemic conditions such as fibromyalgia, non-controlled hypertension, rheumatoid arthritis, and diabetes mellitus. Migraineurs with a diagnosis of other concomitant headache or with headache at the evaluation appointment were also excluded.

A screening questionnaire was used to identify sample descriptive characteristics such as frequency, intensity, onset of migraine, presence of ictal and interictal dizziness, and height and body mass to compute the BMI. We also evaluated the level of visual discomfort during the following situations: driving a car, watching TV/cinema, social activities and walking on a sunny day. The participants were requested to classify the level of discomfort induced by lighting using the Visual Analogic Scale (VAS), ranging from 0 to 10.

The study was performed in accordance with the Helsinki Declaration and with the approval of the Ethics Committee of Ribeirão Preto Clinical Hospital (protocol number: no 15269/2016). Written informed consent was obtained from all participants before data collection.

Procedure description

Participants were instructed to stand between the set of reflectors (Fig. 1) and to report the level of visual discomfort perceived in the room using a visual analogic scale (VAS), ranging from 0 to 10. The initial luminance was 270 lx, and from 300 lx it was increased gradually every 30 seconds by 100 lx, reaching a maximum of 2000 lx. The luminance was measured with a digital lux meter (Plux 1000, Instrutherm®) at the participants' eye level.

A force plate (Bertec, Columbus, OH, EUA) was used to measure the ground reaction forces and moments to compute the center of pressure (CoP) displacement with a sample rate of 100 Hz in three different conditions: 1) ambient condition, where the participant reported absence of visual discomfort (270 lx); 2) visual sensitivity threshold condition, where the participant reported the beginning of visual discomfort; and 3) intense visual discomfort condition, where the participant reported maximum visual discomfort or when the test reached 2000 lx (the maximum luminance possible in our setup). In order to compare to the migraine group, the luminance level used in the balance assessment of the control group was based on the migraine group median for the visual sensitivity threshold and the high visual discomfort condition. Postural sway was assessed in the orthostatic position (arms along the body, open eyes, looking at a fixed point at 2 m distance) in bipodal and unipodal stance. The order of conditions was randomized for each participant and repeated three times for a duration of 30-s each.

As there were no previous studies that used this method to assess visual sensitivity threshold in migraine population, intra-subject reliability was tested in the migraine group with a retest within a seven to twenty-one days interval. Retests were performed under the same conditions as the first evaluation, and it was found a moderate reliability of 0.56 [22].

Data processing

Force plate data were collected using the Nexus software (Vicon, Oxford, UK) and processed by a custom-made Matlab function (R2014a version, Mathworks, Natick, MA USA). Matlab *detrend.m* function was used to remove any drift in the raw CoP data. Subsequently, the raw data were filtered with a fourth-order low-pass Butterworth digital filter with cutoff frequency of 10 Hz. The following variables were computed from the CoP displacement for each trial: (1) sway area - area of the ellipse adjusted to the CoP displacement encompassing 95% of its displacement; (2) sway velocity - the total displacement of the CoP divided by the

total duration of the trial; (3) Root Mean Square (RMS); and (4) frequency at 80% of the CoP power - the Welch's method was used to obtain the Power Spectrum Density. Except for the sway area, all variables were calculated in anteroposterior (a-p) and mediolateral (m-l) directions. These variables were calculated according to the Duarte and Freitas [23].

Statistical analysis

The sample size for the study was calculated to detect 1 cm^2 of difference in the displacement area parameter (standard deviation =1.5) during bipodal posture between groups and conditions. The sample size estimation was based on data collected during a pilot study from 5 subjects in each group. Power was set at 80% and the significance level was set at 5%. This process led to an estimate of 9 participants in each group.

Demographic data (age and body mass index) of the two groups were normally distributed as indicated by the Kolmogorov-Smirnov test, and compared between groups using Student's t-test for independent samples.

Due to non-normality of CoP data, it was transformed using $\log_e$. A mixed two-factor ANOVA (2 groups [control and migraine] x 3 lighting conditions [ambient, visual discomfort threshold and intense visual discomfort]), with repeated measures in the second factor, was performed for each CoP dependent variable during bipodal and unipodal stances. Mean values between right and left sides were used for the unipodal analysis as no significant differences were observed between sides for all variables. Post-hoc test using Bonferroni adjustment were performed when necessary. The statistical analysis was performed with SPSS (version 20.0), and the significance level was set at 5%.

Results

Among 38 participants compatible with inclusion and exclusion criteria, 28 were included in this sample. Ten volunteers were excluded from the migraine group due the following reasons: three subjects could not finish the assessment tasks due to visual discomfort, five did not report any visual discomfort during the evaluation, and two reported discomfort in the minimal luminance condition tested.

There was no significant difference between groups regarding age and BMI (Table 1).

Table 1. Sample characteristics

		Control (n=14)	Migraine (n=14)	p-value
Age (years)		27.2 (2.8)	30.6 (8.1)	.86
BMI (kg/cm²)		23.6 (3.8)	23.7 (2.7)	.15
Migraine onset (years)		-	13.8 (7.9)	-
Migraine frequency (monthly)		-	12.2 (6.6)	-
Migraine intensity (VAS)		-	6.9 (1.6)	-
Ictal dizziness		-	86%	-
Interictal dizziness		0%	57%	-
Visual discomfort (VAS)	Driving	3.6 (2.2)	6.1 (2.6)	.01*
	Watching TV	0.4 (1.0)	3.2 (2.3)	.00*
	Social Activity	0.2 (0.8)	3.0 (3.3)	.00*
	Walking on a sunny day	1.1 (1.4)	5.2 (2.0)	.00*

*Student t-test ($p < .05$). BMI: body mass index, VAS: visual analogic scale

Visual sensitivity

The migraine group (MG, n=14) presented greater visual discomfort during all daily activities than controls (CG, n=14) (Table 1), with the highest discomforts reported for the driving and walking on a sunny day. For migraineurs, the median visual sensitivity threshold was 400 lx (interquartile range from 400 to 500), and the median intense visual discomfort was 2000 lx (interquartile range from 1900 to 2000). The mean discomfort intensity measured using the VAS for those two conditions were 0.8 ±1.6 and 6.8 ±1.9 points, respectively. Both the median threshold and intense discomfort values were used to assess the control group and none of the control participants reported any visual discomfort during all lighting conditions (VAS=0).

CoP area

For CoP area in *bipodal stance,* an interaction between group and lighting conditions was observed ($F_{2,52} = 6.89$, $p = .002$). The MG showed greater CoP area than controls in all three lighting conditions (p's < .05). Within the MG, the CoP area increased with luminance level with differences among all conditions (p's < .05). The CG did not present significant differences among lighting conditions (p's > .05, Fig 2).

During *unipodal stance* there was also an interaction between group and lighting conditions ($F_{2,52} = 7.37$, $p = .005$). The CoP area was greater in the MG compared to the controls for all conditions (p's < .05). The migraine intra-group analysis showed greater CoP area in

both increased lighting conditions compared to the ambient light condition (p's < .01). The CG did not present significant differences among lighting conditions (p's > .05, Fig 2).

CoP velocity

During *bipodal stance* there was an interaction between group and lighting conditions for a-p CoP velocity ($F_{2,52}$ = 5.13, p = .019). The MG exhibited greater CoP a-p velocity than controls only in the intense visual discomfort condition (p < .05). Intra-groups analysis revealed that all conditions were different for a-p CoP velocity within the MG (p's < .05), but not for the CG (p's > .05). There was no interaction between group and illumination for m-l direction ($F_{(2,52)}$=3.37, p=.067, Fig 3).

During *unipodal stance* there was an interaction between group and lighting condition in both a-p and m-l CoP velocity ($F_{2,52}$ = 6.62, p = .008 and $F_{2,52}$ = 5.40, p = .016, respectively). The MG exhibited greater a-p CoP velocity than the CG for the visual threshold and intense visual discomfort conditions (p's < .05). Intra-group analysis did not reveal differences among conditions for both groups in a-p direction (p's > .05). In the m-l direction, CoP velocity was greater in the MG than CG just in the intense visual discomfort condition (p < .05). The migraine intra-group analysis demonstrated no significant differences (p's > .05), but intra-group analysis for the CG showed smaller m-l CoP velocity for both increased lighting conditions compared to the ambient light condition (p's < .05, Fig 3).

CoP RMS

During *bipodal stance* there was an interaction between group and lighting conditions for both a-p and m-l CoP RMS ($F_{2,52}$ = 3.88, p = .027 and $F_{2,52}$ = 4.04, p = .035, respectively). In the a-p direction, RMS was significantly greater for the visual threshold and intense visual discomfort conditions in the MG compared to the CG (p's < .01). Intra-group analysis showed that the MG had greater a-p CoP RMS in both increased lighting conditions than in the ambient light condition (p's < .05). The MG had greater m-l CoP RMS for the intense visual discomfort condition than the CG (p < .05). Intra-group analysis showed that the MG exhibited greater m-l CoP RMS in the intense visual discomfort condition than in the other conditions (p's < .05, Fig 4).

For *unipodal stance*, interactions between group and lighting conditions were observed for a-p and m-l CoP RMS ($F_{2,52}$ = 5.13, p = .018 and $F_{2,52}$ = 7.86, p = .003, respectively). The RMS was significantly greater in the MG compared to the CG for the visual threshold and

discomfort conditions, in both a-p and m-l directions (p's < .05). Intra-group analysis showed that the MG had greater a-p CoP RMS in both increased lighting conditions than in the ambient light condition (p's < .05, Figure 4). The CG did not present differences among light conditions for the RMS in any of the postures (i.e., bipodal and unipodal) assessed (p's > .05, Fig 4).

CoP frequency

No interactions were observed between group and lighting conditions for a-p and m-l CoP frequency for both postures, bipodal ($F_{2,52}$ = 1.96, p = .151 and $F_{2,52}$ = 0.13, p = ,876, respectively) and unipodal ($F_{2,52}$ = 0.14, p = .869 and $F_{2,52}$ = 0.62, p = .485, respectively).

Discussion

Our study aimed analyze the visual discomfort and postural control of women with migraine and non-headache participants in upright standing posture under different light conditions. The hypothesis was that individuals with migraine would demonstrate visual sensitivity and increments in postural sway as a function of increased light intensity, differently from the controls. We found visual discomfort in the migraine individuals, but not on the controls, and the results of the comparison of CoP area, velocity and RMS indicated that both visual light-discomfort conditions significantly increased the postural sway of migraineurs compared to the ambient lighting condition. In addition, such changes were not observed for the control group for all variables, except for only one difference in the unipodal posture CoP m-l velocity

As expected according to previous studies [10–12], the CoP area increased for the migraineurs compared to the control group during the ambient lighting condition. However, we did not find differences between groups in a-p and m-l CoP velocity in both standing postures. Akdal et al. [12] found greater center of mass (CoM) velocity during bipodal standing posture for patients with migraine than for controls. Although the overall pattern of the CoP and CoM trajectories show similarities, it has been suggested that CoP velocity is a more representative measure of CoM acceleration than CoM velocity [24]. Therefore, we can attribute the different results to a different method of analysis.

This study adds novel insights into the effects of increased light intensity levels on postural control in migraineurs. For the migraine group, both increased lighting conditions (visual threshold and discomfort) showed increased CoP area compared to the ambient light

condition in both bipodal and unipodal conditions. The same pattern was verified for CoP RMS for two orthogonal directions. Kinsella-Shaw et al. [18] found lower bipodal a-p CoP RMS on dim light than ambient lighting condition, and discuss that a-p direction would be less stable than m-l direction during bipodal posture. Therefore, our results show evidence of how substantial postural disturbances are caused by the increased bright light in migraineurs, as both a-p and m-l directions were impacted.

The lack of previous data about the effect of increased bright light on postural control makes comparisons of our results difficult. Taken together, our data suggest poor postural control in people with migraine under conditions of light-induced discomfort. Postural stability deficits usually are related to risk to falls, and it is known that individuals with migraine have a high risk of falls [25]. The current results may suggest that visual discomfort conditions increase the risk of falls in these individuals. However, we must be careful on this statement since we did not directly verify the CoP position relative to the boundaries of the base of support.

Supporting previous studies [3,4], our results showed that migraine subjects, even during the pain-free period, present visual sensitivity. Also, during this period between episodes of headache attacks, the migraine group reported moderate visual discomfort to perform daily activities, especially driving and walking during the sunny day. The intensity of light level found in the visual threshold condition (450lx) is the average light level used in workplaces. Then, as these individuals are frequently exposed to indoor or outdoor discomfort light conditions, the light-induced discomfort seems to be a frequent symptom, although not emphasized, that also can play a role on functional activities, contribute to trigger or to perpetuate a migraine attack [26] besides possible worsening balance.

Our results showed that up to 80% of the migraine group report ictal dizziness, and almost 60% report dizziness during interictal period. Dizziness is a symptom reported frequently by migraineurs [10,27–29]. The prevalence found in our sample is in agreement with presented by previous studies [10,27]. Despite some authors consider that the role of dizziness in migraine posture control be related with vestibular migraine [30,31], other studies did not find differences in the postural control between patients with migraine and vestibular migraine [32,33]. The International Classification of Headache Disorder do not consider migraine vestibular as a diagnostic criterion, but vestibular symptoms are very common in patients with migraine. Carvalho et al [34] demonstrated that 70% - 85% of patients with migraine with aura, without aura and chronic migraine presented vestibular symptoms. Despite the suggestions that

the balance disorders seen in migraineurs are related to subclinical cerebellar or brainstem dysfunction [35,36] and alterations of the central vestibular pathways [9,12,34], our results showed a possible impairment on visual system as well.

It is still unclear what mechanisms are involved in linking visual sensitivity and balance. In general, postural changes observed in dim light condition are described in function of visual input reduction [16,18,19]. We suggest that due to the visual hypersensitivity, light can be recognized as disturbing stimuli and cause a decreased efficiency of the visual system, as occurs on some chronic visual conditions [16]. The visual impairment due to hypersensitivity may be compensated with stronger activation of the other postural subsystems, as somatosensory and vestibular [16,37,38] but in migraineurs, such subsystems also present impairments [1,8].

This study is not without limitations. Our sample included just women and part of the migraine group was composed of patients from a tertiary clinic; then, these factors may restrict the generalizability and may overestimate our results. Since sample size was calculated on basis of CoP displacement area, we cannot ensure the absence of major differences on the remaining variables. Future studies with bigger sample size would confirm the results regarding CoP velocity and RMS.

Based on the results of balance impairments in individuals with migraine and the disturbing effect of light intensity on postural control of migraineurs, we recommend the need for therapy to minimize the impact of these factors in the quality of life of these patients. The physical therapy already have been considered as an effective approach to improve balance abilities in patients with migraine-related to vestibulopathies [25]. Therefore, the proprioceptive training should be implemented as part of the migraine rehabilitation process, and the light sensitivity influence on balance also should be considerate to delineate therapeutic approaches for patients with migraine.

Conclusion

People with migraine present a visual sensitivity during the interictal period, and this is a discomfort factor to perform daily activities. The exposure to bright light that triggers a visual discomfort alters the postural balance of these patients, boosting some pre-existing deficits, while the same lighting levels does not affect individuals without migraine.

Acknowledgements

The authors would like to thank Mr. Tenysson Will de Lemos for his methodological support. and the clinical team of the Ambulatory of Headache and Craniofacial Pain from Ribeirão Preto Clinics Hospital.

Financial Disclosures

This work was supported by both São Paulo Research Foundation – FAPESP (www.fapesp.br) [grant number 2015/18031-5] and Foundation for the Coordination and Improvement of Higher Level or Education Personnel – CAPES (www.capes.gov.br). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

References

[1] Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine – A disorder of sensory processing 2017:553–622. doi:10.1152/physrev.00034.2015.

[2] Chong CD, Starling AJ, Schwedt TJ. Interictal photosensitivity associates with altered brain structure in patients with episodic migraine. Cephalalgia 2016;36:526–33. doi:10.1177/0333102415606080.

[3] Harriott AM, Schwedt TJ. Migraine is Associated With Altered Processing of Sensory Stimuli. Curr Pain Headache Rep 2014;18. doi:10.1007/s11916-014-0458-8.

[4] Kowacs PA, Piovesan EJ, Werneck LC, Tatsui CE, Lange MC, Ribas LC, et al. Influence of intense light stimulation on trigeminal and cervical pain perception thresholds. Cephalalgia 2001;21:184–8. doi:10.1046/j.1468-2982.2001.00178.x.

[5] Vanagaite J, Pareja J, Storen O, White L, Sand T, Stovner L. Light-induced discomfort and pain in migraine. Cephalagia 1997;17:733–41.

[6] Noseda R, Burstein R. Migraine Pathophysiology- Anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. Pain 2014;154 Suppl:44–53. doi:10.1016/j.pain.2013.07.021.Migraine.

[7] Noseda R, Kainz V, Jakubowski M, Gooley JJ, Clifford B, Digre K, et al. A neural mechanism for exacerbation of headache by light. Nat Neurosci 2010;13:1–17. doi:10.1038/nn.2475.A.

[8] Swartz R, Kern R. Migraine Is Associated With Magnetic Resonance Imaging White Matter Abnormalities: a meta-analysis. Arch Neurol 2004;61:1366. doi:10.1001/archneur.61.9.1366.

[9] Ishizaki K, Mori N, Takeshima T, Fukuhara Y, Ijiri T, Kusumi M, et al. Static stabilometry in patients with migraine and tension-type headache during a headache-free period. Psychiatry Clin Neurosci 2002;56:85–90. doi:10.1046/j.1440-1819.2002.00933.x.

[10] Carvalho GF, Chaves TC, Dach F, Pinheiro CF, Gonçalves MC, Florencio LL, et al. Influence of migraine and of migraine aura on balance and mobility - A controlled study. Headache 2013;53:1116–22. doi:10.1111/head.12135.

[11] Rossi C, Alberti A, Sarchielli P, Mazzotta G, Capocchi G, Faralli M, et al. Balance disorders in headache patients: Evaluation by computerized static stabilometry. Acta Neurol Scand 2005;111:407–13. doi:10.1111/j.1600-0404.2005.00422.x.

[12] Akdal G, Dönmez B, Öztürk V, Angin S. Is balance normal in migraineurs without history of vertigo? Headache 2009;49:419–25. doi:10.1111/j.1526-4610.2008.01256.x.

[13] So CWL, Bent LR. Increased vestibular contribution to posture control in individuals with chronic headache. J Vestib Res Equilib Orientat 2009;19:49–58. doi:10.3233/VES-2009-0340.

[14] Carvalho GF, Bonato P, Florencio LL, Pinheiro CF, Dach F, Bigal ME, et al. Balance Impairments in Different Subgroups of Patients With Migraine. Headache J Head Face Pain 2016. doi:10.1111/head.13009.

[15] Carvalho GF, Florencio LL, Pinheiro CF, Dach F, Bigal ME, Bevilaqua-Grossi D. Functional Balance Deterioration on Daily Activities in Patients With Migraine. Am J Phys Med Rehabil 2017;00:1. doi:10.1097/PHM.0000000000000793.

[16] Palm HG, Strobel J, Achatz G, von Luebken F, Friemert B. The role and interaction of visual and auditory afferents in postural stability. Gait Posture 2009;30:328–33. doi:10.1016/j.gaitpost.2009.05.023.

[17] Blanchard Y, McVeigh R, Graham M, Cadet M, Mwilambwe K, Scott C. The influence of ambient lighting levels on postural sway in healthy children. Gait Posture 2007;26:442–5. doi:10.1016/j.gaitpost.2006.10.009.

[18] Kinsella-Shaw JM, Harrison SJ, Colon-Semenza C, Turvey MT. Effects of visual environment on quiet standing by young and old adults. J Mot Behav 2006;38:251–64. doi:10.3200/JMBR.38.4.251-264.

[19] Brooke-Wavell K, Perrett LK, Howarth PA, Haslam RA. Influence of the Visual Environment on the Postural Stability in Healthy Older Women. Gerontology 2002;48:293–7.

[20] Hamel KA, Okita N, Higginson JS, Cavanagh PR. Foot clearance during stair descent: effects of age and illumination. Gait Posture 2005;21:135–40. doi:10.1016/j.gaitpost.2004.01.006.

[21] Olesen J. The International Classification of Headache Disorders, 3rd edition.

Cephalagia 2013;33:629–808. doi:10.1177/0333102413485658.

[22] Toutenburg H. Fleiss, J. L.: Statistical Methods for Rates and Proportions. John Wiley & Sons, New Jersey: Wiley; 2003. Biom Z 2003. doi:10.1002/bimj.19740160814.

[23] Duarte M, Freitas SM. Revision of posturography based on force plate for balance evaluation. Rev Bras Fisioter 2010;14:183–92. doi:S1413-35552010000300003 [pii].

[24] Masani K, Vette AH, Abe MO, Nakazawa K. Center of pressure velocity reflects body acceleration rather than body velocity during quiet standing. Gait Posture 2014;39:946–52. doi:10.1016/j.gaitpost.2013.12.008.

[25] Whitney SL, Wrisley DM, Brown KE, Furman JM. Physical therapy for migraine-related vestibulopathy and vestibular dysfunction with history of migraine. Laryngoscope 2000;110:1528–34. doi:10.1097/00005537-200009000-00022.

[26] Becker WJ. The premonitory phase of migraine and migraine management. Cephalalgia 2013;33:1117–21. doi:10.1177/0333102412437390.

[27] Bisdorff A, André E C, Vaillant M, Sándor PS. Headache-associated dizziness in a headache population: Prevalence and impact. Cephalagia 2010;30:815–20. doi:10.1177/0333102409353617.

[28] Teggi R, Manfrin M, Balzanelli C, Gatti O, Mura F, Quaglieri S, et al. Point prevalence of vertigo and dizziness in a sample of 2672 subjects and correlation with headaches. Acta Otorhinolaryngol Ital 2016;36:215–9. doi:10.14639/0392-100X-847.

[29] Cha Y-H, Baloh RW. Migraine Associated Vertigo. J Clin Neurol J Clin Neurol 2007;3:121–6.

[30] Teggi R, Colombo B, Bernasconi L, Bellini C, Comi G, Bussi M. Migrainous vertigo: Results of caloric testing and stabilometric findings. Headache 2009;49:435–44. doi:10.1111/j.1526-4610.2009.01338.x.

[31] N Çelebisoy, F Gökçay, H Şirin and NB. Migrainous vertigo: clinical, oculographic and posturographic findings. Cephalalgia 2007;28:72–7. doi:10.1111/j.1468-2982.2007.01474.x.

[32] Ongun N, Atalay N, Degirmenci E, Sahin F, Bir L. Tetra-ataxiometric Posturography in Patients with Migrainous Vertigo. Pain Physician 2016;19:87–95.

[33] Panichi R, Cipriani BL, Sarchielli BP, Di Mauro BM, E Pettorossi B V, Ricci BG, et al. Balance control impairment induced after OKS in patients with vestibular migraine: an intercritical marker. Eur Arch Otorhinolaryngol 2014;272. doi:10.1007/s00405-014-3179-z.

[34] Carvalho GF, Heck Vianna-Bell F, Florencio LL, Pinheiro CF, Dach F, Bigal ME, et al. Presence of vestibular symptoms and related disability in migraine with and without aura and chronic migraine n.d. doi:10.1177/0333102418769948.

[35] Harno H, Hirvonen T, Kaunisto MA, Aalto H, Levo H, Isotalo E, et al. Subclinical vestibulocerebellar dysfunction in migraine with and without aura. Neurology 2003;61:1748–52. doi:10.1212/01.WNL.0000098882.82690.65.

[36] Akdal G, Balci BD, Angin S, Öztürk V, Halmagyi GM. Acta Oto-Laryngologica A longitudinal study of balance in migraineurs A longitudinal study of balance in migraineurs. Acta Otolaryngol 2012;132:27–32. doi:10.3109/00016489.2011.616532doi.org/10.3109/00016489.2011.616532.

[37] Friedrich M, Grein HJ, Wicher C, Schuetze J, Mueller A, Lauenroth A, et al. Influence of pathologic and simulated visual dysfunctions on the postural system. Exp Brain Res 2008;186:305–14. doi:10.1007/s00221-007-1233-4.

[38] Hafstrom A, Fransson PA, Karlberg M, Ledin T MM. Visual influence on postural control, with and without visual motion feedback. Acta Otolaryngol 2002;122:392–7.

Figures legends

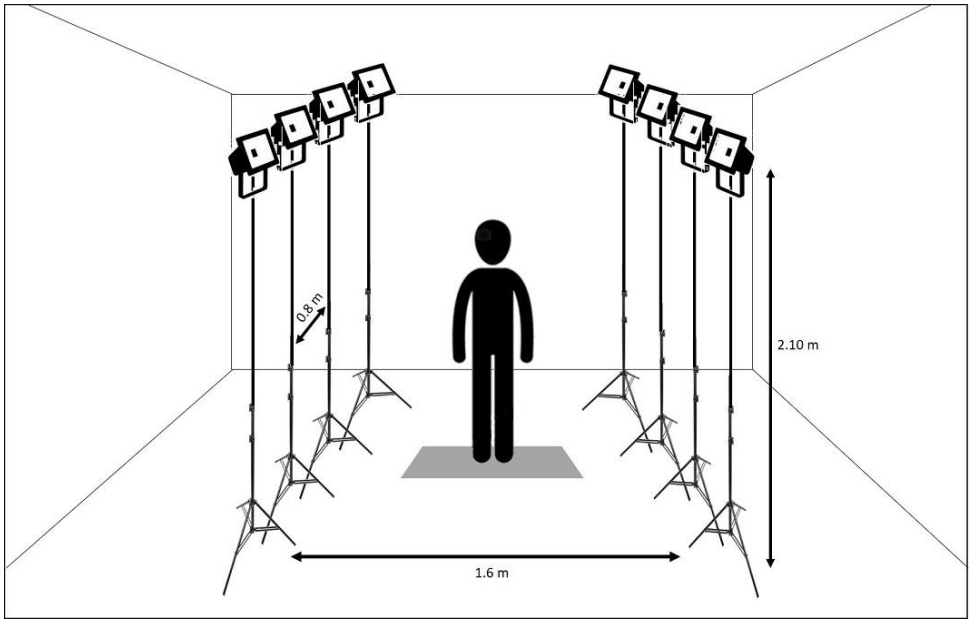
Figure 1. Data collection set and patient's position.

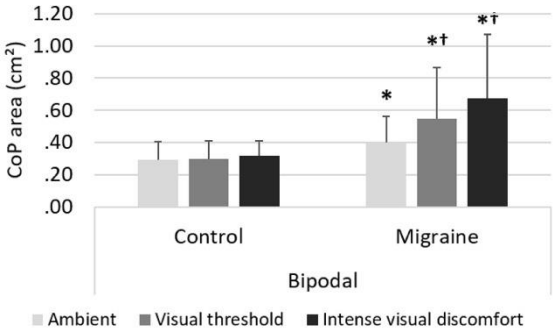
Figure 2. Mean and standard deviation of the center of pressure (CoP) area for control and migraine groups in all three visual conditions for both bipodal (left) and unipodal (right) postures.
*difference between groups in the same lighting condition; †intra-group difference to other two lighting conditions. Mixed ANOVA ($p < .05$). Log_e-transformed variable.

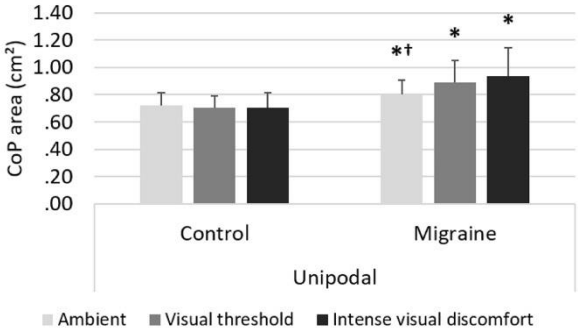
Figure 3. Mean and standard deviation of the center of pressure (CoP) velocity for control and migraine groups in all three visual conditions for both bipodal (left) and unipodal (right) postures (a-p direction on top and m-l direction on bottom).
*difference between groups in the same lighting condition; †intra-group difference to other two lighting conditions. Mixed ANOVA ($p < .05$). Log_e-transformed variable.

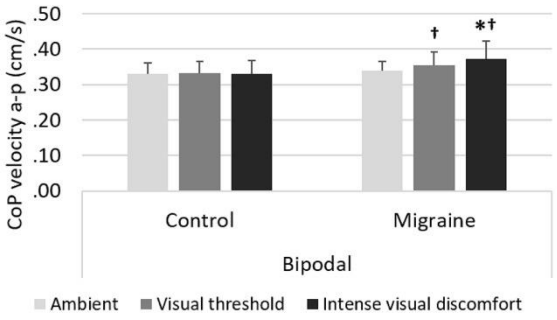
Figure 4. Mean and standard deviation of the center of pressure (CoP) Root Mean Square (RMS) for control and migraine groups in all three visual conditions for both bipodal (left) and unipodal (right) postures (a-p direction on top and m-l direction on bottom).
*difference between groups in the same lighting condition; †intra-group difference to other two lighting conditions. Mixed ANOVA ($p < .05$). Log_e-transformed variable.

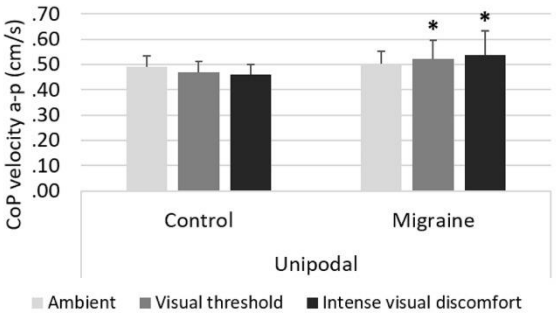
Figures

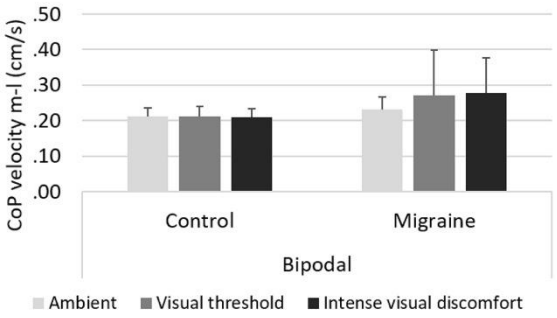


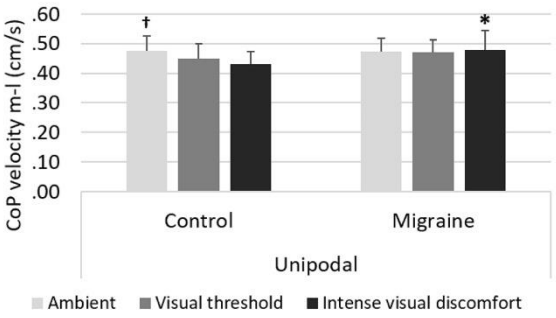

1.20
1.00
.80
.60
.40
.20
.00
CoP area (cm²)
*
*†
*†
Control
Migraine
Bipodal
Ambient
Visual threshold
Intense visual discomfort

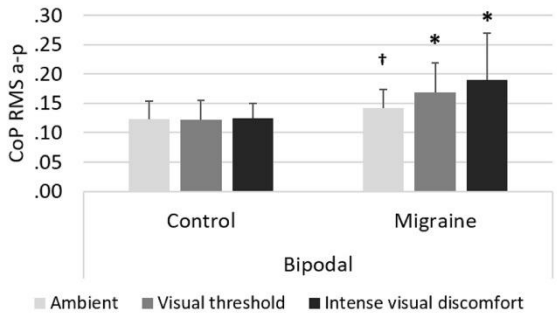

1.40
1.20
1.00
.80
.60
.40
.20
.00
CoP area (cm²)
*†
*
*
Control
Migraine
Unipodal
Ambient
Visual threshold
Intense visual discomfort

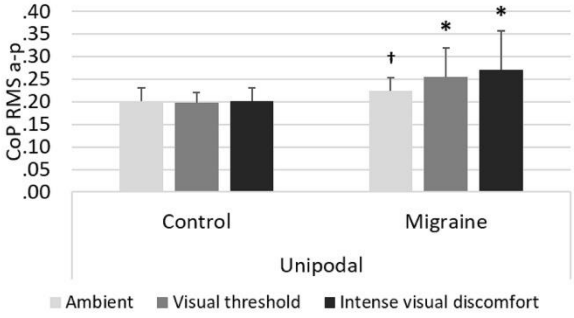

CoP velocity a-p (cm/s)
.50
.40
.30
.20
.10
.00
†
*†
Control
Migraine
Bipodal
Ambient
Visual threshold
Intense visual discomfort

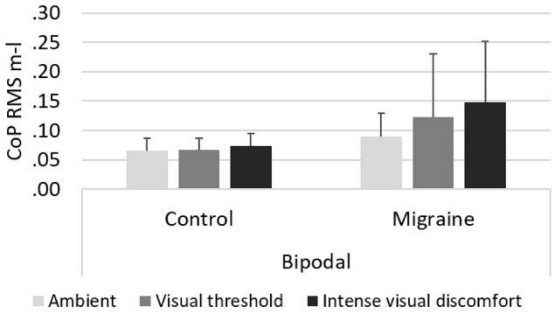

CoP velocity a-p (cm/s)
.70
.60
.50
.40
.30
.20
.10
.00
*
*
Control
Migraine
Unipodal
Ambient
Visual threshold
Intense visual discomfort

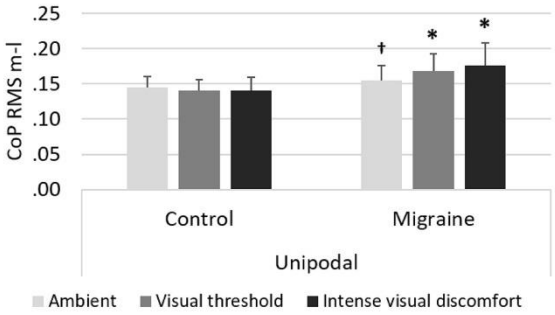

CoP velocity m-l (cm/s)
.50
.40
.30
.20
.10
.00
Control
Migraine
Bipodal
Ambient
Visual threshold
Intense visual discomfort


CoP velocity m-l (cm/s)
.60
.50
.40
.30
.20
.10
.00
†
*
Control
Migraine
Unipodal
Ambient
Visual threshold
Intense visual discomfort


CoP RMS a-p
.30
.25
.20
.15
.10
.05
.00
†
*
*
Control
Migraine
Bipodal
Ambient
Visual threshold
Intense visual discomfort


CoP RMS a-p
.40
.35
.30
.25
.20
.15
.10
.05
.00
†
*
*
Control
Migraine
Unipodal
Ambient
Visual threshold
Intense visual discomfort


CoP RMS m-l
.30
.25
.20
.15
.10
.05
.00
Control
Migraine
Bipodal
Ambient
Visual threshold
Intense visual discomfort


CoP RMS m-l
.25
.20
.15
.10
.05
.00
†
*
*
Control
Migraine
Unipodal
Ambient
Visual threshold
Intense visual discomfort

4 CONCLUDING REMARKS

Our data, taken together, allowed us to conclude that migraine is associated with the presence of vestibular symptoms. These symptoms are more incapacitating in those with aura and with higher attacks frequency, and even so, despite the vestibular abnormalities be suggested as the cause of balance problems, the posture control still can be affected by light stimulus.

Thus far, the vestibular system has been investigated and theories to justify the relationship between migraine and vestibular problems have been elucidated. As our study confirmed, we can not reject the role of the vestibular system on migraine comorbidities. However, our results open the window to the investigation of the role of others sensory systems in migraine, as the visual and the somatosensory. Regarding the visual system, it seems the illumination, since the visual sensitivity threshold, can modify the strategies to maintain the standing upright posture in migraineurs.

Indeed, much still need to be investigated to explain the influence of light brightness on posture control, once today we don’t have a consistent neurophysiologic base to justify our findings. Taking account that photophobia is not a symptom exclusive of migraine, other neurological and ophthalmological conditions can exhibit balance deficits triggered by light stimulation.

Finally, we have to assume that just the variables analyzed in this study cannot be extrapolated to functional posture deficits. So, futures studies are necessary to investigate the functional repercussion of the light stimulus, including the evaluation of possible increased risk of falls in brightness conditions

5 REFERENCES

1. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of Migraine – A disorder of sensory processing. 2017;(386):553–622.
2. Cutrer F. Pathophysiology of migraine. Semin Neurol. 2010;30:120–30.
3. Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, Abdulkader RS, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211–59.
4. Lipton RB, Bigal ME, Diamond M, Freitag F, Reed ML, Stewart WF. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343–9.
5. Queiroz LP, Silva Junior AA. The prevalence and impact of headache in Brazil. Headache. 2015;55(S1):32–8.
6. Olesen J. The International Classification of Headache Disorders, 3rd edition. Cephalagia. 2013;33(9):629–808.
7. Burstein R, Noseda R, Borsook D. Migraine: Multiple Processes, Complex Pathophysiology. J Neurosci. 2015;35(17):6619–29.
8. Bigal ME, Ashina S, Burstein R, Reed ML, Buse D, Serrano D, et al. Prevalence and characteristics of allodynia in headache sufferers: A population study. Neurology. 2008;70(17):1525–33.
9. Noseda R, Kainz V, Jakubowski M, Gooley JJ, Clifford B, Digre K, et al. A neural mechanism for exacerbation of headache by light. Nat Neurosci. 2010;13(2):1–17.
10. Noseda R, Burstein R. Migraine Pathophysiology- Anatomy of the trigeminovascular pathway and associated neurological symptoms, CSD, sensitization and modulation of pain. Pain. 2014;154 Suppl:44–53.
11. Olesen J, Friberg L, Olsen TS, Iversen HK, Lassen NA, Andersen AR, et al. Timing and topography of cerebral blood flow, aura, and headache during migraine attacks. Ann Neurol. 1990;28(6):791–8.
12. Main A, Dowson A, Gross M. Photophobia and phonophobia in migraineurs between attacks. Headache. 1997;37(8):492–5.
13. Vanagaite J, Pareja J, Storen O, White L, Sand T, Stovner L. Light-induced discomfort and pain in migraine. Cephalagia. 1997;17:733–41.
14. Noseda R, Bernstein CA, Nir RR, Lee AJ, Fulton AB, Bertisch SM, et al. Migraine photophobia originating in cone-driven retinal pathways. Brain. 2016;139(7):1971–86.
15. Noseda R, Copenhagen D, Burstein R. Current understanding of photophobia, visual networks and headaches. Cephalalgia. 2018;
16. Harriott AM, Schwedt TJ. Migraine is Associated With Altered Processing of Sensory Stimuli. Curr Pain Headache Rep. 2014;18(11).
17. Coppola G, Di Lorenzo C, Schoenen J, Pierelli F. Habituation and sensitization in primary headaches. J Headache Pain. 2013;14(1):65.

18. Chong CD, Starling AJ, Schwedt TJ. Interictal photosensitivity associates with altered brain structure in patients with episodic migraine. Cephalalgia. 2016;36(6):526–33.

19. Moulton EA, Becerra L, Rosenthal P, Borsook D. An approach to localizing corneal pain representation in human primary somatosensory cortex. PLoS One. 2012;7(9):e44643.

20. Balslev D, Albert NB, Miall C. Eye muscle proprioception is represented bilaterally in the sensorimotor cortex. Hum Brain Mapp. 2011 Apr;32(4):624–31.

21. Chu MK, Im HJ, Chung CS, Oh K. Interictal pattern-induced visual discomfort and Ictal photophobia in episodic migraineurs: An association of interictal and Ictal photophobia. Headache. 2011;51(10):1461–7.

22. Kowacs PA, Piovesan EJ, Werneck LC, Tatsui CE, Lange MC, Ribas LC, et al. Influence of intense light stimulation on trigeminal and cervical pain perception thresholds. Cephalalgia. 2001;21(3):184–8.

23. Engineering ToolBox. Illuminance - Recommended Light Level. 2004. Available at: https://www.engineeringtoolbox.com/light-level-rooms-d_708.html. [Acessed 20 Jul 2018]

24. Calhoun AH, Ford S, Pruitt AP, Fisher KG. The Point Prevalence of Dizziness or Vertigo in Migraine - and Factors That Influence Presentation. Headache J Head Face Pain. 2011 Oct;51(9):1388–92.

25. Cohen JM, Escasena CA. Headache and Dizziness: How to Differentiate Vestibular Migraine from Other Conditions. Curr Pain Headache Rep. 2015;19:31.

26. Teggi R, Colombo B, Albera R, Asprella Libonati G, Balzanelli C, Batuecas Caletrio A, et al. Clinical Features, Familial History, and Migraine Precursors in Patients With Definite Vestibular Migraine: The VM-Phenotypes Projects. Headache J Head Face Pain. 2018 Apr;58(4):534–44.

27. Bisdorff AR, Staab JP, Newman-Toker DE. Overview of the International Classification of Vestibular Disorders. Neurol Clin. 2015;33(3):541–50.

28. Vuković V, Plavec D, Galinović I, Lovrenčić-Huzjan A, Budišić M, Demarin V. Prevalence of Vertigo, Dizziness, and Migrainous Vertigo in Patients With Migraine. Headache J Head Face Pain. 2007 Dec 3;47(10):1427–35.

29. Cha Y-H, Lee H, Santell LS, Baloh RW. Association of benign recurrent vertigo and migraine in 208 patients. Cephalalgia. 2009 May;29(5):550–5.

30. Cohen JM, Bigal ME, Newman LC. Migraine and Vestibular Symptoms-Identifying Clinical Features That Predict “Vestibular Migraine.” Headache J Head Face Pain. 2011 Oct;51(9):1393–7.

31. Harno H, Hirvonen T, Kaunisto MA, Aalto H, Levo H, Isotalo E, et al. Subclinical vestibulocerebellar dysfunction in migraine with and without aura. Neurology. 2003;61(12):1748–52.

32. Rossi C, Alberti A, Sarchielli P, Mazzotta G, Capocchi G, Faralli M, et al. Balance disorders in headache patients: Evaluation by computerized static stabilometry. Acta Neurol Scand. 2005;111(6):407–13.

33. Teggi R, Colombo B, Bernasconi L, Bellini C, Comi G, Bussi M. Migrainous vertigo: Results of caloric testing and stabilometric findings. Headache. 2009;49(3):435–44.

34. Dieterich M, Brandt T. Episodic vertigo related to migraine (90 cases): vestibular migraine? J Neurol. 1999;246:883–92.

35. Kruit MC, van Buchem M a, Hofman P a M, Bakkers JTN, Terwindt GM, Ferrari MD, et al. Migraine as a risk factor for subclinical brain lesions. JAMA. 2004;291(4):427–34.

36. Kruit MC, Launer LJ, Ferrari MD, Van Buchem MA. Infarcts in the posterior circulation territory in migraine. The population-based MRI CAMERA study. Brain. 2005;128(9):2068–77.

37. Kruit MC, Van Buchem MA, Launer LJ, Terwindt GM, Ferrari MD. Migraine is associated with an increased risk of deep white matter lesions, subclinical posterior circulation infarcts and brain iron accumulation: The population-based MRI CAMERA study. Cephalalgia. 2010;30(2):129–36.

38. Ishizaki K, Mori N, Takeshima T, Fukuhara Y, Ijiri T, Kusumi M, et al. Static stabilometry in patients with migraine and tension-type headache during a headache-free period. Psychiatry Clin Neurosci. 2002;56(1):85–90.

39. Akdal G, Dönmez B, Öztürk V, Angin S. Is balance normal in migraineurs without history of vertigo? Headache. 2009;49(3):419–25.

40. So CWL, Bent LR. Increased vestibular contribution to posture control in individuals with chronic headache. J Vestib Res Equilib Orientat. 2009;19(1–2):49–58.

41. Carvalho GF, Chaves TC, Dach F, Pinheiro CF, Gonçalves MC, Florencio LL, et al. Influence of migraine and of migraine aura on balance and mobility - A controlled study. Headache. 2013;53(7):1116–22.

42. Carvalho GF, Florencio LL, Pinheiro CF, Dach F, Bigal ME, Bevilaqua-Grossi D. Functional Balance Deterioration on Daily Activities in Patients With Migraine. Am J Phys Med Rehabil. 2018;97(2):90–5.

43. Carvalho GF, Bonato P, Florencio LL, Pinheiro CF, Dach F, Bigal ME, et al. Balance Impairments in Different Subgroups of Patients With Migraine. Headache J Head Face Pain. 2016;

44. Carvalho G, Almeida C, Florencio L, Pinheiro C, Dach F, Bigal M, et al. Do patients with migraine have increased prevalence of falls and fear of falling? Physiotherapy. 2017;

45. Kurth T, Mohamed S, Maillard P, Zhu Y-C, Chabriat H, Mazoyer B, et al. Headache, migraine, and structural brain lesions and function: population based Epidemiology of Vascular Ageing-MRI study. BMJ. 2011 Jan 18;342:c7357.

46. Schmitz N, Admiraal-Behloul F, Arkink EB, Kruit MC, Schoonman GG, Ferrari MD, et al. Attack Frequency and Disease Duration as Indicators for Brain Damage in Migraine. Headache J Head Face Pain. 2008 Jul 1;48(7):1044–55.

47. Horak FB. Postural orientation and equilibrium: What do we need to know about neural control of balance to prevent falls? Age Ageing. 2006;35(SUPPL.2):7–11.

48. Hwang S, Agada P, Kiemel T, Jeka JJ. Identification of the unstable human postural control system. Front Syst Neurosci. 2016;10(March):1–12.

49. Kabbaligere R, Lee B-C, Layne CS. Balancing sensory inputs: Sensory reweighting of ankle proprioception and vision during a bipedal posture task. Gait Posture. 2017;52:244–50.

50. Lopez C, Falconer CJ, Deroualle D, Mast FW. In the presence of others: Self-location, balance control and vestibular processing. Neurophysiol Clin Neurophysiol. 2015 Nov 1;45(4–5):241–54.

51. Takakusaki K. Functional Neuroanatomy for Posture and Gait Control. J Mov Disord. 2017;10(1):1–17.

52. Palm HG, Strobel J, Achatz G, von Luebken F, Friemert B. The role and interaction of visual and auditory afferents in postural stability. Gait Posture. 2009;30(3):328–33.

53. Blanchard Y, McVeigh R, Graham M, Cadet M, Mwilambwe K, Scott C. The influence of ambient lighting levels on postural sway in healthy children. Gait Posture. 2007;26(3):442–5.

54. Kinsella-Shaw JM, Harrison SJ, Colon-Semenza C, Turvey MT. Effects of visual environment on quiet standing by young and old adults. J Mot Behav. 2006;38(4):251–64.

55. Hamel KA, Okita N, Higginson JS, Cavanagh PR. Foot clearance during stair descent: effects of age and illumination. Gait Posture. 2005;21:135–40.

56. Brooke-Wavell K, Perrett LK, Howarth PA, Haslam RA. Influence of the Visual Environment on the Postural Stability in Healthy Older Women. Gerontology. 2002;48:293–7.

6 ATTACHMENTS

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
DE RIBEIRÃO PRETO DA UNIVERSIDADE DE SÃO PAULO

Desde 1956 60 ANOS
COMPROMISSO E DEDICAÇÃO À VIDA

HC FMRP-USP RIBEIRÃO PRETO

Ribeirão Preto, 09 de fevereiro de 2017

Ofício nº 392/2017
CEP/MGV

Prezada Senhora,

O trabalho intitulado **"FOTOFOBIA E FONOFOBIA EM PACIENTES COM MIGRÂNEA: IDENTIFICAÇÃO E CONFIABILIDADE DO LIMIAR DE DESCONFORTO E REPERCUSSÃO NO CONTROLE MOTOR" – versão 2, de 25/01/2017,** foi analisado pelo Comitê de Ética em Pesquisa em sua 443ª Reunião Ordinária, realizada em 06/02/2017 e enquadrado na categoria: **APROVADO,** bem como o Termo de Consentimento Livre e Esclarecido – versão 2, de 25/01/2017, de acordo com o Processo HCRP nº 15269/2016.

De acordo com Carta Circular nº 003/2011/CONEP/CNS, datada de 21/03/2011, o sujeito de pesquisa ou seu representante, quando for o caso, deverá rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última do referido Termo; o pesquisador responsável deverá da mesma forma, rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última página do referido Termo.

Este Comitê segue integralmente a Conferência Internacional de Harmonização de Boas Práticas Clínicas (IGH-GCP), bem como a Resolução nº 466/12 CNS/MS.

Lembramos que devem ser apresentados a este CEP, o Relatório Parcial e o Relatório Final da pesquisa.

Atenciosamente.

DRª. MARCIA GUIMARÃES VILLANOVA
Coordenadora do Comitê de Ética em
Pesquisa do HCRP e da FMRP-USP

Ilustríssima Senhora
CARINA PINHEIRO
Depto. de Biomecânica, Medicina e Reabilitação do Aparelho Locomotor

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA
DE RIBEIRÃO PRETO DA UNIVERSIDADE DE SÃO PAULO

FMRP-USP
RIBEIRÃO PRETO

Ribeirão Preto, 08 de março de 2013

Ofício nº 719/2013
CEP/MGV

Prezadas Senhoras,

O trabalho intitulado **"ALTERAÇÕES NO EQUILÍBRIO FUNCIONAL EM PACIENTES COM MIGRÂNEA CRÔNICA E EPISÓDICA",** foi analisado pelo Comitê de Ética em Pesquisa, em sua 361ª Reunião Ordinária realizada em 04/03/2013, e enquadrado na categoria: **APROVADO,** bem como o **Termo de Consentimento Livre e Esclarecido**, 2ª versão, datada de 05/02/2013, de acordo com o Processo HCRP nº 16693/2012.

De acordo com Carta Circular nº 003/2011/CONEP/CNS, datada de 21/03/2011, o sujeito de pesquisa ou seu representante, quando for o caso, deverá rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última do referido Termo; o pesquisador responsável deverá da mesma forma, rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última página do referido Termo.

Este Comitê segue integralmente a Conferência Internacional de Harmonização de Boas Práticas Clínicas (IGH-GCP), bem como a Resolução nº 196/96 CNS/MS.

Lembramos que devem ser apresentados a este CEP, o Relatório Parcial e o Relatório Final da pesquisa.

Atenciosamente.

DRª. MARCIA GUIMARÃES VILLANOVA
Coordenadora do Comitê de Ética em Pesquisa do HCRP e da FMRP-USP

Ilustríssimas Senhoras
GABRIELA FERREIRA CARVALHO
PROFª. DRª. DÉBORA BEVILAQUA GROSSI (Orientadora)
Depto. de Biomecânica, Medicina e Reabilitação do Aparelho Locomotor