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Aquecendo os motores para o XXVI Congresso Brasileiro de Cefaleia

Nesta segunda edição de 2012 da Headache Medicine, o leitor encontrará um conjunto de artigos que certamente proporcionará uma leitura agradável e proveitosa. Além do relato original descrevendo um levantamento sobre cefaleia e alodinia em um grande grupo de indivíduos, realizado pela equipe da Universidade Federal de Pernambuco, temos um artigo de pesquisa histórica cujo tema é a fundação da nossa Sociedade Brasileira de Cefaleia, escrito pelo colega Silva-Néto - que vem tornando-se a referência para quem busca conhecer a história da cefaliatria brasileira e seus fundadores. A sessão Neuroarte traz a visão de um artista de rua sobre a migrânea, sendo muito interessante a concordância da imagem desenhada por ele com o quadro clínico habitual da migrânea, em contraponto com a sua compreensão enviesada - ao nosso ver - sobre a natureza do sintoma cefaleia. Os artigos de revisão nos permitem "absorver" o estado-da-arte em três assuntos de grande importância: cefaleia e gravidez, cefaleia e melatonina e neuralgia do trigêmeo & dor facial persistente idiopática. Os dois primeiros, escritos, respectivamente, por André Gonçalves, Reinaldo Ribeiro e Mário Peres e por Eliana Melhado e Andressa Galego, mostram os frutos do estudo aprofundado de alguns temas específicos por colegas da SBCe, compartilhados com a comunidade cefaliátrica nesta publicação. O último é a benvinda contribuição de um dos grupos de maior destaque da cefaliatria mundial, o grupo da Universidade de Duisburg-Essen, que nos oferece uma revisão aprofundada, e ao mesmo tempo voltada para a prática clínica, destes dois temas.

Não podemos deixar de citar a proximidade do XXVI Congresso Brasileiro de Cefaleia, que terá lugar na fantástica cidade do Rio de Janeiro, em setembro próximo - acreditamos que esta edição da Headache Medicine será um bom aperitivo para os tradicionais três dias de intensa aquisição de conhecimento e troca de experiências que caracterizam os encontros anuais da nossa SBCe.

Warming-up for the XXVI Brazilian Headache Congress

In this Headache Medicine 2012 second number, the reader will find a set of papers that will certainly ensure a pleasant and fruitful reading. Besides an original work that describes headache and allodynia association in a large group, made by Universidade Federal de Pernambuco team, we have a historic research article, written by Silva-Néto - who is becoming the reference for those who want to know the history of the Brazilian Headache Society and its founders. The Neuroart section brings the point of view of a street artist on headache and the intriguing harmony between his drawing and migraine usual clinical presentation, in opposition to his biased understanding - in our view - about the nature of head pain. The review articles allow us to "absorb" the state-of-art of three extremely important subjects: headache and pregnancy, headache and melatonin and trigeminal neuralgia & persistent idiopathic facial pain. The two first, written respectively by André Gonçalves, Reinaldo Ribeiro, Mário Peres and by Eliana Melhado and Andressa Galego, are representative of the profound dedication to specific headache fields by some Brazilian Headache Society members. The last one is a welcome contribution from the Duisburg-Essen University group, one of the most prominent of world headache, which offers a review at the same time profound and oriented to the clinical practice.

It is imperative to mention how close we are from the XXVI Brazilian Headache Congress, which will take place in the wonderful city of Rio de Janeiro in September - we think that this edition of Headache Medicine will be a good appetizer to the traditional three days of intense acquisition of knowledge and experiences exchange that characterize SBCe annual meetings.

Fernando Kowacs & Marcelo Moraes Valença

"Next time you have a headache, remember – pain is an illusion..."

"Na próxima vez que tiver uma dor de cabeça, lembre-se – a dor é uma ilusão..."

Marcelo Moraes Valença[1], Luciana Patrízia A. Andrade-Valença[1], Maria Helena Costa[2]

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Valença MM, Andrade-Valença LP, Costa MH. "Next time you have a headache, remember – pain is an illusion...". Headache Medicine. 2012;3(2):53-4

INTRODUÇÃO

During the 54th Annual Meeting of the American Headache Society in Los Angeles we visited Santa Monica, California on Sunday June 24, 2012. It was a beautiful sunny day, with a happy crowd walking along the Third Street Promenade. There were many musicians, dancers, jugglers, among other artists entertaining the crowd. On the sidewalk we met Sterling Simons, a young American who was in the company of two friends offering his drawing artistic expertise to the public. He could draw a picture of anything of somebody's choice. Our request was for him to draw whatever he could think of (or interpret as) a "headache". He asked us to return in 30 minutes. Half an hour later he showed us the drawing of a woman with migraine, which he entitled "The migraine" (Figure 1). On the reverse side of the drawing Simons wrote: "Next time you have a headache, remember - pain is an illusion..." (Figure 2). Simons reported that he had frequent headache attacks. We paid U$15.00 for this precious work of art.

Trying to interpret the drawing, we think the artist, whether consciously or not, represented the right part of the woman's face somewhat blurred, as if a visual aura were present. In addition, the hair covering the right eye suggests the woman was suffering from some degree of photophobia. The photophobia is also suggested by the fact that both eyes are closed. It seems to represent a severe attack, since she appears to express the facial

Figure 1. Drawing: "The migraine".

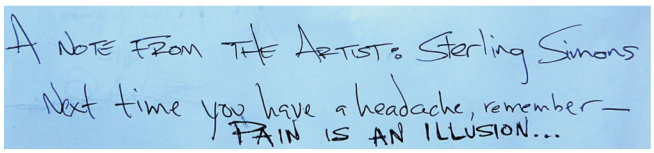

Figure 2. The reverse side of the drawing.

mimicry of pain, reinforced by a clenched positioning of the teeth, characteristic of a person suffering from pain. Her hair is also uncombed, indicating an intense feeling of sickness, common in migraineurs, and the characteristic restful undisturbed behavior and less concern for personal appearance during the period of suffering.

Thus, this is another example of neuroart, in which neurological disorders depicted in a drawing may transmit feelings of pain. Furthermore, the representation itself tells us more about someone's (in this case, the artist's) particular view on a specific subject which must be interpreted within the context of a general (cultural?) understanding (in some cases, misunderstanding) of a particular subject. In the end, artistic representations influence the way the subject itself is regarded, viewed, understood and interpreted.

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HISTORICAL PAPER

Sociedade Brasileira de Cefaleia: como tudo começou

Brazilian Headache Society: how it all began

Raimundo Pereira da Silva-Néto

Centro de Neurologia e Cefaleia do Piauí, Teresina, PI, Brasil

Silva-Néto RP. [Brazilian Headache Society: how it all began]. Headache Medicine. 2012;3(2):55-60. Portuguese

RESUMO

A Sociedade Brasileira de Cefaleia (SBCe) foi fundada no dia 19 de maio de 1978 graças ao empenho de Edgard Raffaelli Júnior (1930-2006). Ele foi o pioneiro no estudo da cefaleia na América Latina e dedicou toda a sua vida a essa causa. Tudo começou com 14 médicos e, hoje, a SBCe tem quase 400 membros associados, distribuídos por todas as regiões do País. A partir de 1979, a SBCe passou a organizar uma reunião científica anual (simpósio, curso ou congresso).

Palavras-chave: Cefaleia; Sociedade Brasileira de Cefaleia

ABSTRACT

The Brazilian Headache Society (BHS) was founded on May 19, 1978 thanks to the efforts of Edgard Raffaelli Jr. (1930-2006). He pioneered the study of headache in Latin America and he dedicated his life to this cause. It began with 14 doctors and today, BHS has approximately 400 associate members spread across all regions of the country. Since 1979, the BHS organized an annual scientific meeting (symposium, conference or course).

Keywords: Headache; Brazilian Headache Society

A IDEALIZAÇÃO

A Sociedade Brasileira de Cefaleia (SBCe) foi fundada no dia 19 de maio de 1978. No entanto, a sua história é bem mais antiga e se confunde com a história de Edgard Raffaelli Júnior (1930-2006), o pioneiro no estudo da cefaleia na América Latina.[1]

No ano de 1956, Raffaelli, aos 26 anos, ex-funcionário do Citibank, era estudante do terceiro ano de medicina. Naquele ano, procurou um neurologista, que lhe disseram ser um dos melhores do país, para tratar uma cefaleia diária que apresentava há mais de sete anos. Após a consulta, saiu sem diagnóstico e sem tratamento, apenas orientado a procurar um psiquiatra. Decepcionado, ele disse a si mesmo que, se os melhores neurologistas do Brasil não conheciam cefaleia, ele iria estudá-la.[1,2]

Concluiu o curso de medicina em 1959 e, após três anos, a residência médica em neurocirurgia. Em 1973, ocorreu o seu doutoramento pela Faculdade de Medicina da Universidade de São Paulo. Por conta própria, dedicou-se ao estudo da cefaleia. Contudo, a partir de 1973, já não conseguia mais progredir nos estudos aqui no Brasil. Desde então, começou a participar de todos os congressos de cefaleia, na Europa e nos Estados Unidos (em média, quatro ao ano), sem jamais encontrar outro brasileiro (e isso continuou assim até 1983), e só duas ou três vezes encontrando outro latino-americano, o professor Gustavo Poch, catedrático de Neurologia na Universidade Ramos Mejia, de Buenos Aires.[1,2]

Em 1975, fechou seu consultório na Avenida Paulista para fundar, na Avenida Eusébio Matoso, a primeira clínica de cefaleia da America Latina e que mantinha ligações internacionais com o Migraine Trust of London (Dra. Marcia Wilkinson), em Londres; Centro Cefalee di Firenze (Prof. Federigo Sicuteri), em Florença; Centro Cefalee di Torino (Prof. Giovani Nattero), em Turim; Headache Clinic of the Faulkner Hospital (Dr. John Graham), em Boston; Headache Clinic of Chicago (Dr. Seymour Diamond), em Chicago; Headache Clinic of Hospital Mount Sinai (Dr. David Coddon), em Nova Iorque; Headache Clinic of Surrey County Hospital (Dr. Desmond Carroll), na Inglaterra; Headache Clinic of California (Dr. Lee Kudrow), na Califórnia; Grupo Australiano, liderado pelo Dr. James Lance e o Grupo Escandinavo (Noruega), liderado pelo Prof. Ottar Sjaastad.[1,3]

Há alguns anos, Raffaelli procurava outro brasileiro que se interessasse por cefaleia. Então, pediu a um amigo, o ortopedista Júlio Casoy, médico do Laboratório Sandoz, que o ajudasse. Com muita dificuldade, Casoy encontrou dois neurologistas no Brasil que eram estudiosos em cefaleia: Wilson Farias da Silva (1933-2008), em Recife, e Gilberto Rebello de Mattos (1932-2011), em Salvador. Em 1976, num encontro histórico, Edgard Raffaelli, Wilson Farias, Gilberto Rebello de Mattos e Júlio Casoy decidiram fundar uma sociedade.[1,2]

OS FUNDADORES

Não foi uma tarefa fácil; somente no dia 19 de maio de 1978, numa noite de sexta-feira, Raffaelli conseguiu reunir, na sua clínica de cefaleia, situada à Avenida Eusébio Matoso, 366, bairro Pinheiros, em São Paulo, um grupo de 14 médicos (alguns pouco interessados em cefaleia) para a fundação da Sociedade Brasileira de Cefaleia e Enxaqueca (SBCe). O seu endereço tornou-se a sede oficial da SBCe, conforme consta nos estatutos da Sociedade. O Ce foi criado, por Raffaelli, para diferenciar da SBC (Sociedade Brasileira de Cardiologia) e o adendo "e Enxaqueca" foi para evitar que algum outro grupo inventasse criar uma Sociedade Brasileira de Enxaqueca, omitindo a cefaleia. Somente em 1992, não mais temendo que se fundasse outra Sociedade no Brasil, mudou-se o nome para Sociedade Brasileira de Cefaleia.[1,2]

Foram esses os médicos que fundaram a SBCe (Tabela 1): Edgard Raffaelli Júnior (Neurologista, São Paulo), Wilson Farias da Silva (Neurologista, Recife), Wilson Luiz Sanvito (Neurologista, São Paulo), Orlando J. Martins (Neurologista, São Paulo), Roberto Melaragno Filho (Neurologista, São Paulo), Nelson Augusto Pedral Sampaio (Ginecologista, São Paulo), Reinaldo de Souza Correa (Psiquiatra, São Paulo), Gilberto Rebello de Mattos (Neurologista, Salvador), Luiz Márcio Itkis Hummel (Otorrinolaringologista, São Paulo), Osmar Trojan (Ginecologista, São Paulo), Julio Casoy (Ortopedista, São Paulo), Ozir Scarante (Neurologista, São Paulo), José Ivan Cipoli Ribeiro (Neurologista, Londrinas), Antônio Douglas Menon (Otorrinolaringologista, São Paulo). Naquela assembleia, além dos 14 médicos, havia uma mulher, Paula Nohara, funcionária da clínica e que exerceu a função de secretária da Sociedade até 1996. Portanto, é importante reconhecer o seu silencioso trabalho de apoio, companheirismo e luta incansável por uma causa de valor imensurável em prol da cefaliatria brasileira.[1-3]

Tabela 1. Relação dos 14 fundadores da Sociedade Brasileira de Cefaleia com suas respectivas especialidades

Membro	Cidade	Especialidade
Edgard Raffaelli Júnior (1930-2006)	São Paulo - SP	Neurologista
Wilson Farias da Silva (1933-2008)	Recife - PE	Neurologista
Gilberto Rebello de Mattos (1932-2011)	Salvador - BA	Neurologista
Roberto Melaragno Filho (1919-1998)	São Paulo - SP	Neurologista
Wilson Luiz Sanvito	São Paulo - SP	Neurologista
Orlando J. Martins	São Paulo - SP	Neurologista
Ozir Scarante	São Paulo - SP	Neurologista
José Ivan Cipoli Ribeiro	Londrina - PR	Neurologista
Antonio Douglas Menon	São Paulo - SP	Otorrinolaringologista
Luiz Márcio Itkis Hummel	São Paulo - SP	Otorrinolaringologista
Osmar Trojan	São Paulo - SP	Ginecologista
Nelson Augusto Pedral Sampaio	São Paulo - SP	Ginecologista
Reinaldo de Souza Correa	São Paulo - SP	Psiquiatra
Júlio Casoy	São Paulo - SP	Ortopedista

Dos 14 fundadores, a maioria era conhecida por Raffaelli de longa data. Por exemplo, em 1973, ele encaminhava os exames otoneurológicos ao Dr. Antônio Douglas Menon, e os pacientes que necessitavam de avaliação psiquiátrica, ao Dr. Reinaldo de Souza Correa. Por outro lado, atendia as pacientes migranosas encaminhadas pelo Dr. Osmar Trojan. Quando inaugurou a sua Clínica de Cefaleia, criou o serviço de otoneurologia e, por indicação do Dr. Antônio Menon, convidou para trabalhar o Dr. Luiz Márcio Itkis Hummel. No período de 1970 a 1976, Raffaelli foi o chefe do serviço de Neurologia e Neurocirurgia do Hospital e Maternidade Brasil,

em Santo André, São Paulo. Lá, ele conheceu o Dr. Orlando J. Martins, que sempre fez parte da clínica de cefaleia, desde a sua fundação.[3]

Era amigo do Dr. Nelson Augusto Pedral Sampaio e, graças a essa amizade, conseguiu criar, em 1979, um ambulatório de cefaleia na Clínica Ginecológica do Hospital das Clínicas da Universidade de São Paulo (HC-USP). Quanto aos doutores Wilson Luiz Sanvito e Roberto Melaragno Filho, amigos de Raffaelli, foram convidados, obviamente, por serem renomados neurologistas e também demonstrarem interesse pela cefaleia. No ano de 1976, no encontro de Salvador, conheceu Wilson Farias da Silva e Gilberto Rebello de Mattos.[3]

Roberto Melaragno Filho (1919-1998) formou-se na Faculdade de Medicina, da Universidade de São Paulo (USP), em 1942. Nos anos de 1947 e 1948, realizou seus estudos em Neurologia como Assistente-Estrangeiro, na Faculdade de Medicina de Paris, no serviço do Professor Raymond Garcin. Foi professor livre-docente da Faculdade de Medicina da USP.[4]

Foi autor de vários livros, entre eles, destacam-se: Afecções vasculares cerebrais (1959); Neuroimunologia (1982); Esclerose Múltipla – manual para pacientes e suas famílias (1992). Além disso, escreveu capítulos de diversos livros didáticos de clínica médica e de neurologia, assim como dezenas de trabalhos publicados em revistas científicas. Faleceu no dia oito de fevereiro de 1998, aos 79 anos.[4]

Wilson Farias da Silva (1933-2008) formou-se pela Faculdade de Medicina da Universidade do Recife (hoje, Universidade Federal de Pernambuco), em 1957. Foi professor titular de Neurologia e chefe do Departamento de Neuropsiquiatria, da Universidade Federal de Pernambuco. Em 2006, recebeu o título de Professor Emérito daquela instituição. Contribuiu na formação de inúmeras gerações de neurologistas, tanto na graduação como na pós-graduação. Faleceu, em Recife, no dia 24 de outubro de 2008, aos 75 anos.[5,6]

Na década de 1960, iniciou seus estudos em cefaleia e realizou as primeiras publicações sobre esse tema, na América Latina. No entanto, o seu encantamento pelas cefaleias veio, definitivamente, a partir de 1974.[5] Em 1976, conheceu Edgard Raffaelli Júnior naquele encontro histórico com Gilberto Rebello de Mattos e Júlio Casoy, quando decidiram fundar a SBCe.[5-7]

Ele, juntamente com Edgard Raffaelli Júnior, foi uma das maiores autoridades brasileiras nos estudos e pesquisas em cefaleias, com inúmeros artigos e livros publicados. Finalmente, em 2000, a SBCe reconheceu o seu mérito e criou o "Prêmio Wilson Farias da Silva", um incentivo aos pesquisadores brasileiros no campo da cefaleia.[5,6]

Gilberto Rebello de Mattos (1932-2011) formou-se pela Faculdade de Medicina da Universidade Federal da Bahia (UFBA), em 1956. Fez residência médica em Neurologia, na Santa Casa da Misericórdia, Rio de Janeiro, de 1957 a 1959. Fez curso de Neuropediatria, no HC-USP, em 1962. Foi professor adjunto de Clínica Neurológica da Universidade Federal da Bahia e chefe dos serviços de Neurologia e Eletroencefalografia do Hospital Universitário Dr. Edgard Santos, em Salvador. Em 1981, publicou o primeiro livro em língua portuguesa sobre migrânea, intitulado *Enxaqueca – o controle das crise*, com a colaboração de Wilson Farias da Silva.[8] Após a aposentadoria, como professor da UFBA, em 1988, foi morar em Sergipe, onde faleceu no dia dois de abril de 2011, aos 79 anos.[9]

Dos 14 membros fundadores, ainda vivos, apenas dois participam, regularmente, das reuniões anuais da SBCe: Wilson Luiz Sanvito e Orlando J. Martins. Segundo Raffaelli, desses 14, sete compareceram apenas à reunião de fundação da Sociedade, assinaram a ata, mas não persistiram.[1]

Wilson Luiz Sanvito formou-se pela Faculdade de Medicina da Universidade Federal do Paraná, em 1958. Iniciou o seu treinamento em Clínica Neurológica no Serviço de Neurologia do Hospital das Clínicas de São Paulo e complementou a sua formação de especialista no Hospital da Salpétrière, na França. Lá, obteve o título de Assistant Étranger da Faculdade de Mecidina de Paris. Atualmente, é médico da Irmandade da Santa Casa de Misericórdia de São Paulo e professor titular de Neurologia da Faculdade de Ciências Médicas da Santa Casa de São Paulo.

Publicou mais de uma centena de trabalhos científicos em revistas nacionais e estrangeiras. É autor de sete livros em neurociências e vários volumes de crônicas. São livros de sua autoria: *O mau gênio do cérebro: o impacto da doença neurológica* (A girafa, 2006); *Esclerose Múltipla no Brasil: aspectos clínicos e terapêuticos* (Atheneu, 2005); *Doença de Parkinson: prática clinica e terapêutica* (Atheneu, 2005); *O mundo das minhas reflexões* (Atheneu, 2005); *O Homen* (Im) Perfeito (Atheneu, 2002); *O Livro das Cefaleias* (Atheneu, 2001); *O colecionador de idéias* (Atheneu, 1998); *A arte de pensar & Outras artes* (Lemos Editorial, 1998).

Orlando J. Martins formou-se pela Escola Paulista de Medicina da Universidade Federal de São Paulo

(Unifesp), em 1969. Fez residência médica em Neurologia no Hospital do Servidor Público do Estado de São Paulo, de 1970 a 1972. Recebeu os títulos de especialista em Neurologia, concedido pela Associação Médica Brasileira, em convênio com a Academia Brasileira de Neurologia, em 1978, e de especialista em Eletroencefalografia, concedido pela Associação Médica Brasileira e pela Sociedade Brasileira de Eletrofisiologia Clínica, em 1978.[10]

Ele participou de todos os congressos, simpósios, encontros e cursos de atualização em cefaleia, organizados pela SBCe, desde a sua fundação até 1998.

Dentre os grandes vultos da cefaliatria nacional, deve-se lembrar o nome de Eliova Zurkerman que, mesmo não tendo participado da fundação da SBCe, tinha interesse em cefaleia há muito tempo. No ano da fundação da SBCe, em 1978, ele inaugurou o Setor de Investigação e Tratamento da Cefaleia, na Escola Paulista de Medicina.[2]

OS CONGRESSOS

Em 1979, a SBCe organizou o seu primeiro simpósio, no Hospital do Servidor Público Estadual, em São Paulo, com a presença de 126 participantes. Foram convidados três professores estrangeiros: John Graham (EUA), Federigo Sicuteri (Itália) e Gustavo Poch (Argentina). A partir desse ano (Tabela 2), a SBCe passou a organizar uma reunião anual (simpósio, curso ou congresso).[1,2]

Naquela época, não era fácil conseguir patrocínio e, nos primeiros anos, Raffaelli pagava, às suas próprias custas, todas as despesas. Teve que comprar um mimeógrafo usado para reproduzir os boletins da SBCe.

Fotos do Primeiro Simpósio Brasileiro de Cefaleia e Enxaqueca (1979).

Tabela 2 - Relação dos simpósios, cursos de atualização e congressos da SBCe, no período de 1979 a 2011

Evento	Data	Local
I Simpósio	09 e 10/03/79	Hospital Servidor Público Estadual
I Curso	11 a 13/10/79	Hospital Albert Einstein
II Curso	17 e 18/10/80	Foz do Iguaçu
II Simpósio	20 e 21/11/81	Recife - PE
III Curso	25 e 26/11/82	Laboratório Ache
III Simpósio	25 e 26/11/83	Laboratório Ache
IV Curso	30/11 e 01/12/84	Laboratório Ache
IV Simpósio	29 e 30/11/85	Laboratório Ache
V Curso	28 e 29/11/86	Centro de Convenções Rebouças
V Simpósio	13 e 14/11/87	Centro de Convenções Rebouças
VI Curso	11 e 12/11/88	Centro de Convenções Rebouças
VI Simpósio	24 e 25/11/89	Centro de Convenções Rebouças
VII Curso	16/03/91	Ribeiro Preto - SP
VII Simpósio	08 e 09/11/91	Associação Paulista de Medicina
VIII Curso	23 e 24/03/93	Associação Paulista de Medicina
VIII Simpósio	15 e 16/04/94	Associação Paulista de Medicina
IX Congresso	31/03 e 01/04/95	Associação Paulista de Medicina
X Congresso	29 e 30/03/96	Associação Paulista de Medicina
XI Congresso	05/97	Ribeirão Preto - SP
XII Congresso	28 a 30/05/98	Ribeirão Preto - SP
XIII Congresso	13 a 15/05/99	Salvador - BA
XIV Congresso	01 a 03/06/00	São Paulo - SP
XV Congresso	27 a 29/09/01	Rio de Janeiro - RJ
XVI Congresso	25 a 27/07/02	Rio de Janeiro - RJ
XVII Congresso	21 a 23/08/03	Recife - PE
XVIII Congresso	05 a 07/08/04	Curitiba - PR
XIX Congresso	15 a 17/09/05	Fortaleza - CE
XX Congresso	19 a 21/10/06	Belo Horizonte - MG
XXI Congresso	20 a 22/09/07	Florianópolis - SC
XXII Congresso	09 a 11/10/08	Natal - RN
XXIII Congresso	08 a 10/10/09	Vitória - ES
XXIV Congresso	07 a 09/10/10	Gramado - RS
XXV Congresso	15 a 17/09/11	São Paulo - SP

1. Não houve nenhuma reunião da SBCe nos anos de 1990 e 1992
2. O XXVI Congresso será no Rio de Janeiro-RJ, em 2012; o XXVII Congresso será em Goiânia-GO, em 2013; e o XXVIII Congresso será em Aracaju-SE, em 2014

Somente em 1994 veio a ser publicada a revista *Migrâneas & Cefaleias* (criada e batizada com esse nome, por Raffaelli) e que, no ano de 2010, passou a ser chamada de Headache Medicine.[2,3,11]

Em 1979, durante a realização do I Simpósio de Cefaleia, em São Paulo, o artista plástico Francisco Raffaelli, falecido em julho de 1997, criou a logomarca[12] da SBCe. Ele era irmão de Edgard Raffaelli Júnior.

OS MEMBROS

Atualmente, a SBCe tem 383 membros associados e distribuídos em 25 estados do Brasil e no Distrito Federal. No estado de Alagoas tem apenas um membro. Ainda não está presente nos estados do Amapá e Roraima.

A maioria de seus membros se encontra na região sudeste, principalmente no estado de São Paulo. Isto se deve ao fato da SBCe ter sido fundada naquele estado. No entanto, é bom lembrar que a primeira reunião feita pelos neurologistas Edgard Raffaelli Júnior, Gilberto Rebello de Mattos e Wilson Farias da Silva ocorreu no Nordeste, na cidade de Salvador e, curiosamente, essa região desponta em segundo lugar em número de associados (Tabela 3).

Tabela 3 - Distribuição dos associados da SBCe nas regiões do Brasil

Região	N	%
Sudeste	227	59,3
Nordeste	57	14,9
Sul	53	13,8
Centro-Oeste	33	8,6
Norte	13	3,4
Total	383	100,0

A SBCe tem participação ativa, através de seus membros, no Departamento Científico (DC) de Cefaleia da Academia Brasileira de Cefaleia. Em 2007, esse departamento criou o dia nacional da cefaleia, a exemplo da Europa, que comemora o *migraine day*, no dia 12 de setembro, e dos EUA, o *headache day*, no dia 10 de novembro. No Brasil, foi escolhido o dia 19 de maio, uma homenagem ao dia da fundação da SBCe.

AS DIRETORIAS

Raffaelli foi o comandante que determinou o plano de voo da SBCe e, no período de 1978 a 1996, ele esteve à frente da Sociedade, ora como presidente, ora como secretário (quando o presidente era Sanvito ou Wilson Farias). A partir de 1996, os presidentes da SBCe (Tabela 4) foram, Carlos Alberto Bordini (1996 a 2000), Pedro Moreira Ferreira Filho (2000 a 2004), Jano Alves de Sousa (2004 a 2008), Carlos Alberto Bordini (2008 a 2010) e Marcelo Cedrinho Ciciarelli (a partir de 2010),[1,2]

Tabela 4 - Relação das diretorias executivas da SBCe, de 1978 até 2011

Biênio	Presidente	Secretário	Tesoureiro
1978-1980	Edgard Raffaelli Júnior	Reinaldo de Souza Correa	Nelson Augusto Pedral Sampaio
1980-1982	Edgard Raffaelli Júnior	Wilson Luiz Sanvito	Ozir Scarante
1982-1984	Wilson Farias da Silva	Edgard Raffaelli Júnior Marco Otávio Saraiva Valença	Américo dos S. Poça D'água Filho Ana Maria Van Der Linden
1984-1986	Wilson Luiz Sanvito	Paulo Hélio Monzilo	Américo dos S. Poça D'água Filho
1986-1988	Wilson Luiz Sanvito	Edgard Raffaelli Júnior	Américo dos S. Poça D'água Filho
1988-1990	Wilson Luiz Sanvito	Reinaldo de Souza Correa	Américo dos S. Poça D'água Filho
1990-1992	Edgard Raffaelli Júnior	Célia Aparecida de Paula Roesler	Reinaldo de Souza Correa
1992-1994	Edgard Raffaelli Júnior	Célia Aparecida de Paula Roesler	Reinaldo de Souza Correa
1994-1996	Edgard Raffaelli Júnior	Célia Aparecida de Paula Roesler	Reinaldo de Souza Correa
1996-1998	Carlos Alberto Bordini	Marco Antônio Arruda	Marcelo Cedrinho Ciciarelli
1998-2000	Carlos Alberto Bordini	Marco Antônio Arruda	Marcelo Cedrinho Ciciarelli
2000-2002	Pedro Ferreira Moreira Filho	Jano Alves de Souza	Carla da Cunha Jevoux
2002-2004	Pedro Ferreira Moreira Filho	Jano Alves de Souza	Carla da Cunha Jevoux
2004-2006	Jano Alves de Sousa	Carla da Cunha Jevoux	Cláudio Manoel de Brito
2006-2008	Jano Alves de Sousa	Carla da Cunha Jevoux	Cláudio Manoel de Brito
2008-2010	Carlos Alberto Bordini	Marco Antônio Arruda	Marcelo Cedrinho Ciciarell
2010-2012	Marcelo Cedrinho Ciciarelli	Luiz Paulo Queiroz	Carlos Alberto Bordini

CONCLUSÃO

Seguramente, não existiria uma SBCe sem Edgard Raffaelli Júnior, um homem que se aventurou a ser mal falado numa época em que cefaleia não era bem vista pela classe médica. Graças à sua seriedade e honestidade, emprestando o seu nome à SBCe, a cefaliatria brasileira tem, hoje, renome internacional.

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COMENTÁRIOS

Nosso colega e amigo de Teresina, Silva-Néto é um historiador da Sociedade Brasileira de Cefaleia. Conviveu com o Dr. Rafaelli alguns anos, tendo sido um dos seus últimos estagiários. Contou-nos que durante esse contato com nosso saudoso professor, este lhe confidenciou inúmeros dados relativos à sociedade. Dr. Raffaelli ainda relatou varias passagens importantes de sua vida. Em algum dos nossos congressos conversei longamente com Silva-Neto sobre sua missão de tornar públicas todas as conversas que teve com nosso grande mestre, e vejo com alegria e interesse os seus artigos publicados na revista abordando a história da SBCe. Considero este artigo, ora publicado, um marco, pois Silva-Néto descreve o perfil de cada um dos precursores de nossa sociedade, que se desenvolveu com o esforço e determinação dos colegas citados nesse artigo, sob a batuta firme e imparcial do Dr. Raffaelli. Todos nós podemos avaliar como foi difícil esse começo, com a cefaleia desacreditada como problema maior de saúde. Silva-Néto nos dá uma ideia, na medida certa, do quanto devemos para esses pioneiros e apaixonadas pelo ensino das cefaleias. Os congressos no exterior eram pagos do próprio bolso e os congressos e simpósios brasileiros eram subsidiados pelos seus organizadores. As listagens dos congressos e das diretorias aqui colocadas foram possíveis por causa da obstinação de Silva-Néto. Meu incentivo agora é que Silva-Néto organize o Museu da Cefaleia e conclamo todos os que possuem algo interessante e que retrate uma parte importante da vida da SBCe e dos seus membros natos que entreguem esse material ao Silva-Néto a fim de que ele os organize e os reúna em um local público aberto à visitação dos interessados.

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Melatonin in headache disorders

A melatonina nas cefaleias

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ABSTRACT

Melatonin have diverse physiological functions, including the control of circadian rhythms, sleep regulation, enhancement of immunological functioning, free radical scavenging and antioxidant effects, inhibition of oncogenesis, mood regulation, vasoregulation, regulation of seasonal reproductive activity and analgesia. Melatonin also have several actions within the central nervous system and in the pathophysiology of headaches, which include an anti-inflammatory effect, toxic free radical scavenging, reduction of proinflammatory cytokine up-regulation, nitric oxide synthase activity and dopamine release inhibition, membrane stabilization, GABA and opioid analgesia potentiation, glutamate neurotoxicity protection, neurovascular regulation, serotonin modulation, and the similarity of chemical structure to that of indomethacin. A relation with seasonal and circadian pattern has been observed in cluster an hypnic headache. The literature of headache is convergent in pointing to low levels of melatonin in patients with migraine and cluster headache. Treatment of headache disorders with melatonin and other chronobiotic agents is promising. Some trials showed that melatonin was effective in cluster headache and migraine prevention but future studies are necessary for the better understanding of the role of melatonin in headache disorders treatment.

Keywords: Melatonin; Pineal gland; Migraine; Pathophysiology; Treatment

RESUMO

A melatonina tem diversas funções fisiológicas, incluindo o controle de ritmos circadianos, regulação do sono, melhoria do funcionamento imunológico, varredura de radicais livres e efeitos antioxidantes, inibição da oncogênese, regulação do humor, vasoregulação, regulamentação da atividade reprodutiva sazonal e analgesia. A melatonina também tem várias ações dentro do sistema nervoso central e na fisiopatologia das cefaleias, as quais incluem um efeito anti-inflamatório e de limpeza de radicais livres tóxicos, a redução de citocinas pró-inflamatórias, da inibição da atividade da óxido nítrico sintase e da produção de dopamina, a estabilização das membranas, potencialização da analgesia GABA e de opioides, proteção contra a neurotoxicidade do glutamato, regulação neurovascular, modulação da serotonina, além de possuir estrutura química similar à da indometacina. Uma relação com padrão sazonal e circadiano tem sido observada na cefaleia em salvas e hipnica. A literatura de dor de cabeça e melatonina é convergente em apontar a presença de baixos níveis deste hormônio em pacientes com enxaqueca e cefaleia em salvas. O tratamento das cefaleias com melatonina e outros agentes cronobióticos é promissor. Alguns estudos mostraram que a melatonina foi eficaz na cefaleia em salvas e na prevenção da enxaqueca, porém futuros estudos são necessários para comprovar seu beneficio no tratamento das cefaleias.

Palavras-chave: Melatonina; Glândula Pineal; Enxaqueca; Fisiopatologia; Tratamento

INTRODUÇÃO

Melatonin (5-methoxy-N-acetyltryptamine) was discovered by Aaron Lerner in 1958. Melatonin synthesis has been described in numerous peripheral organs, such as the retina,[1] bone marrow,[2] skin,[3] platelets,[4] lymphocytes,[5] testis,[6] and in the gastrointestinal tract.[7,8] In these tissues melatonin seems to plays either an autocrine or a paracrine role. Data on messenger RNA expression

of two key enzymes responsible for melatonin synthesis, arylalkyamine-N-acetyltransferase and hydoxyindole-O-methyltransferase, suggest that even more peripheral organs may be able to produce this hormone.[9]

Physiology of melatonin

The pineal gland is highly vascular and consists of two types of cells: neuroglial cell and pinealocytes, which predominate and produce indolamines (melatonin) and peptides (such as arginine vasotocin). In the biosynthesis of melatonin, tryptophan is converted by tryptophan hydroxylase to 5-hydroxytryptophan, which is decarboxylated to serotonin. Melatonin is produced after serotonin is catalyzed by two enzymes (arylalkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase).[10,11] The production and secretion of melatonin are mediated largely by postganglionic retinal nerve fibers that pass through the retinohypothalamic tract to the suprachiasmatic nucleus, then to the superior cervical ganglion, and finally to the pineal gland. This neuronal system is activated by darkness and suppressed by light. The activation of alpha-1 and beta-1-adrenergic receptors in the pineal gland raises cyclic AMP and calcium concentrations and activates arylalkylamine N-acetyltransferase, initiating the synthesis and release of melatonin. The daily rhythm of melatonin secretion is also controlled by an endogenous, free-running pacemaker located in the suprachiasmatic nucleus. Melatonin is able to enter every cell of the body and readily crosses the blood-brain barrier and the placenta. Melatonin is enzymatically degraded in the liver by hydroxylation (to 6-hydroxymelatonin) and, after conjugation with sulfuric or glucuronic acid and is finally excreted in the urine as 6-sulphatoxymelatonin (aMT6s). Analysis of urine by the ELISA method is used as a measure of melatonin secretion, since it closely parallels with the profile of plasma nocturnal melatonin concentrations.[12] There is some evidence suggesting that a seasonal variation exists in the synthesis of melatonin in humans, the levels possibly being higher in winter than in summer.[13]

Melatonin is a potent antioxidant, which can exert its action in directly or indirectly. In addition to its direct free radical scavenging action, melatonin has been reported to increase the activity of some important antioxidant enzymes at molecular level, including superoxide dismutase and glutathione peroxidase.[14] Also melatonin decreases the activity of nitric oxide synthase, a pro-oxidative enzime.[15] In fact melatonin can also scavenge hydroxy radical, peroxil radical, peroxinitrite anion, and singlet oxigen protecting cell membrane, proteins in the cytosol and DNA in the nucleus.

Pharmacology

The half-life of melatonin in the serum is between 30 and 57 minutes.[16] Intravenously administered melatonin is rapidly distributed and eliminated.[17] In normal subjects, 80 mg of melatonin orally administered promote serum melatonin concentrations that were 350 to 10,000 times higher than the usual nighttime peak, 60 to 150 minutes later, and these values remained stable for 90 minutes.[18] Lower oral doses (1 to 5 mg), result in serum melatonin concentrations that are 10 to 100 times higher than the usual nighttime peak, within one hour after ingestion, followed by a decline to base-line values in four to eight hours. Very low oral doses (0.1 to 0.3 mg) given in the daytime result in peak serum concentrations that are within the normal nighttime range.[19]

Potential use of melatonin in analgesia: mechanisms of action

Melatonin has been shown to exert antinociceptive and antiallodynic actions in a variety of experimental models in animals.[20] Induction of pain involves the release of several pro-inflammatory mediators like cytokines and the activation of a number of neurotransmitter receptor sites present in both the spinal cord and brain. The mechanisms that melatonin may act in pain are control the release of pro-inflammatory mediators; inhibit the activation of receptors involved in pain perception present at spinal cord; inhibit receptor activation in brain regions involved in pain perception and promote sleep that can be extremely effective for controlling/inhibiting pain perception.

The available evidence demonstrates that melatonin seems to have a action in the opioid system and a modulatory effect on the circadian rhythm of nociception. Yousaf, in a review[21] of the use of melatonin in peri-operative setting, reports anxiolytic and analgesic properties. Melatonin premedication is effective in ameliorating perioperative anxiety in adults. Compared with midazolam, melatonin has similar anxiolytic efficacy but less psychomotor impairment and fewer side effects. The elderly population has been shown to be refractory to the hypnotic and anxiolytic effects of melatonin.[22] The clinical impact of melatonin on pain need to more studied and the evidence regarding its potential analgesic effects in the perioperative setting is inconsistent and limited. Melatonin premedication was associated with an analgesic

effect in the studies with pain as a primary outcome, whereas the lack of analgesic effect was observed in studies with pain as a secondary outcome.[23-25] It seems that high doses of melatonin are required to produce major analgesic effects.[20] The antinociceptive and antiallodynic properties of melatonin have a perspective in future studies in patients that suffer from pain due to inflammation, occurring during headache, cancer patients, neuropathic pain and fibromyalgia. It may be useful in patients with comorbidities like anxiety that is frequently associated with headache disorders.

Table 1- The pathophysiological and therapeutic role of melatonin

Disease	Melatonin Response	Melatonin Pathophysiology
Cluster headache	RCT shows efficacy	Decreased levels
Paroxysmal hemicrania	Potential	Unknown
Hypnic headche	Case report	Unknown
Hemicrania continua	Case report	Unknown
Episodic migraine	Open study shows good results	Decreased levels
Chronic migraine	Potential	Decreased levels and peak shift
Tension-type headache	Open-label trial shows good results	Unknown

RCT = Randomized, placebo- controlled clinical trial

MELATONIN AND HEADACHES

Melatonin indeed demonstrates several actions within the central nervous system (SNC), which may account for its putative analgesic role in headache.[26] (Table 1).

First, melatonin potentiates the inhibitory action of GABA on SNC and several GABAergic drugs have been used successfully in the prophylaxis of migraine, such as topiramate, divalproex and gabapentin.Thus, reduced concentrations of melatonin might lower the activation threshold of pain circuits normally inhibited by GABAergic transmission. Second, because melatonin modulates the entry of calcium into cells, a reduction in melatonin might alter the tone or vasoreactivity of cerebral blood vessels. Furthermore, melatonin receptors have been identified on cerebral arteries and melatonin has also been shown to modulate 5-HT2 receptors on cerebral arteries. Antagonism at this 5-HT receptor is exploited by drugs used to prevent migraine and CH. Additionally, a melatonin-driven modulation of 5HT2 receptors was suggested, similar to drugs used for migraine prophylaxis, such as flunarizine, methysergide and beta-blockers.[27] Melatonin modulates different serotonin receptors which is known to be important in the pathophysiology of migraine. Finally, melatonin inhibits the synthesis of prostaglandin E_2, which has been identified as one of many substances that can lead to sterile perivascular inflammation (neurogenic inflammation) that activates the trigeminovascular nociceptive afferents.

Potential therapeutic use of melatonin in headache disorders

Melatonin has been implicated in the treatment of different types of headaches (Table 2).

Table 2 - Mechanism of action of melatonin in the central nervous system

Mechanisms of action of melatonin in CNS
GABA and opioid analgesia potentiation
Calcium entry into the cells modulation and promotion of neurovascular regulation
Modulation of 5HT2 receptors on cerebral arteries
Serotonin modulation
Anti-inflammatory effect
Toxic free radical scavenging
Reduction of proinflammatory cytokine up-regulation
Nitric oxide synthase activity and dopamine release inhibition
Glutamate neurotoxicity protection
Membrane stabilization

MIGRAINE

The literature of headache and melatonin is convergent point to low levels of this hormone in patients with migraine,[28-29] menstrual migraine,[30-31] chronic migraine[32] and cluster headache.[33-38]

Claustrat et al.[28] were the first to demonstrate lower plasma melatonin levels in samples from migraine patients compared with controls. Migraine patients without depression had lower levels than controls, but migraineurs with superimposed depression exhibited the greatest melatonin deficiency. Murialdo et al.[31] also found nocturnal urinary melatonin to be significantly decreased throughout the ovarian cycle of migraine patients without aura compared with controls. Melatonin excretion was further decreased when patients suffered a migraine attack.

Brun et al.[30] studied urinary melatonin in women with migraine without aura attacks associated with menses and controls. Melatonin levels throughout the cycle were significantly lower in the migraine patients than in controls. In the control group, melatonin excretion increased significantly from the follicular to the luteal phase, whereas no difference was observed in the migraine group.

Peres et al.[32] studied plasma melatonin nocturnal profile in chronic migraine patients and controls. Lowered melatonin levels in patients with insomnia were observed compared with those without insomnia, and a phase delay in the melatonin peak in patients versus controls.

Masruha et al.[39] were the first to demonstrate reduction in melatonin levels during attacks in episodic and chronic migraine. The study assessed 6-sulphatoxymelatonin (aMT6s) levels in a large consecutive series of patients with migraine, comparing with controls. A total of 220 subjects were evaluated (146 had migraine and 74 were control subjects). aMT6s urinary samples were measured with quantitative ELISA technique. Among patients with migraine, 53% presented pain on the day of the urine samples collection. Their urinary aMT6s concentration was significantly lower than in the urine of patients without pain. There was no significant difference in the aMT6s concentration of patients with migraine without pain on the day of their urine samples collection. AMT6s levels were even lower in patients with chronic migraine and in the presence of a migraine attack. It was also observed that the higher is the frequency of migraine attacks, lower levels of aMT6s. These are also strongly correlated, inversely, with levels of depression, anxiety, fatigue, diagnosis of excessive daytime sleepiness and the number of points of fibromyalgia.[40]

CHRONIC MIGRAINE

The role of the hypothalamus in the pathophysiology of chronic migraine (CM) was first studied by Peres el al.[32] in a experiment to explore the hypothalamic-tuberoinfundibular system (prolactin, growth hormone), the hypothalamic hypophyseal-adrenal axis (cortisol), and pineal gland function (melatonin) in CM. A total of 338 blood samples (13/patient) from 17 patients with CM and nine (age and sex matched) healthy volunteers were taken. Melatonin, prolactin, growth hormone, and cortisol concentrations were determined every hour for 12 hours. The study showed an abnormal pattern of hypothalamic hormonal secretion in CM. Forty-seven per cent of patients with CM had a significant phase delay in the melatonin peak, and half had insomnia. Melatonin concentrations, peak secretion, and AUCs were significantly lower in patients with CM who had insomnia than in controls and patients with CM without insomnia. In conclusion, they found a decreased nocturnal prolactin peak, a increased cortisol concentrations, a delayed nocturnal melatonin peak in patients with CM, and lower melatonin concentrations in patients with CM with insomnia. It supports the report of Nagtegaal et al.[41] that showed a phase delay in the nocturnal melatonin peak in patients with delayed sleep phase syndrome and associated headaches. They had a great improvement of both symptoms after treatment with 5 mg melatonin.

Treatment of migraine

Claustrat et al.[29] reported six patients with status migranous which were treated with infusion of 20 mg of melatonin. Four patients have a headache relief in the morning after night melatonin infusion and the other two patients reported an improvement after the third night of infusion, and three patients reported a decrease in intensity during the migraine attacks.

Nagtegaal et al.[41] reported the case of a 54-year-old man who suffered from disabling migraine attacks without aura, twice a week. After starting melatonin treatment, only three migraine attacks were reported in 12 months.

In an open study carried out by Peres et al.[42] the use of 3 mg of melatonin was effective in the preventive treatment of migraine. Of the 34 patients who were evaluated, 78.1% showed clinical response, defined as a reduction greater than 50% of the frequency of attacks. The complete response, i.e. a reduction of 100% of seizures, was observed in 25% of patients. The frequency of headache, duration, intensity and analgesic consumption decreased significantly ($p < 0.001$) in the first month of treatment in relation to the baseline period.

Miano et al.[43] designed a 3-month open label trial of melatonin prophylaxis in children with primary headache. After a one month baseline period patients received preventive therapy with melatonin (3 mg) administered orally at bedtime for three months without receiving preventive drugs. A total of 22 children were enrolled and 13 subjects had migraine without aura, one male had migraine with aura. On assessment at the completion of the trial, 14 of the 21 subjects reported that the headache attacks had decreased by more than 50% with respect to baseline, and 4 reported having no headache attacks. In 7 of the 21 children the frequency of headache attacks remained unchanged from baseline (three with migraine without aura and four with chronic tension-type headache). None of the patients reported an increased number of attacks during the trial. One subject dropped out because of excessive daytime sleepiness.

Side effects have been reported in association with the ingestion of melatonin but are not serious. Physiologic

effects of the hormone (hypothermia, increased sleepiness, decreased alertness, and possibly reproductive effects), that are dose-dependent, have not yet been properly evaluated in individuals that use large doses of melatonin for prolonged periods of time.

TENSION-TYPE HEADACHE

In 1998, Nagtegaal et al.[41] reported three women (aged 14, 14, and 23) suffering from chronic tension-type headache (CTTH) in a total of 30 patients with delayed sleep phase syndrome which were treat with 5 mg melatonin. After treatment with melatonin their headache disappeared within two weeks.

In a trial of melatonin prophylaxis in children, Miano et al.[43] treated eight patients with CTTH in total of 22 children with primary headache. After a one month baseline period without receiving preventive drugs, all children received a 3-month course of melatonin (3 mg) administered orally, at bedtime. The study lasted four months: during the first month (baseline period) patients received no preventive therapy for recurrent headache and for the next three months received therapy with pure melatonin (3 mg) administered orally at bedtime. From the total of eight patients four are males. Headache attacks had decreased, by more than 50%, in four patients, and none reported a complete remission of headache.

CLUSTER HEADACHE

The circadian rhythmicity of CH has oriented the studies toward the hypothalamus. The suprachiasmatic nucleus (SCN) is the main control center of the biological clock, which receives retinal information on luminosity and projects it to the pineal gland where melatonin needs to be produced in a circadian rhythm to act satisfactorily.[44] During the symptomatic phase of CH, the melatonin production is reduced until its nocturnal peak disappears,[35] thus altering biological rhythms and decreasing its additional analgesic effect related to gabaergic reinforcement,[33] calcium modulation[26] and prostaglandin synthesis inhibition.[45]

In 1984, Chazot et al.[35] detected a decrease in nocturnal melatonin secretion and abolished melatonin rhythm in CH patients. Waldenlind et al.[37] also showed lowered nocturnal melatonin levels during cluster periods than remissions and found that women had higher melatonin levels than men throughout the year.[36] Smokers had lower levels than non-smoking cluster headache patients. Leone et al.[34] observed melatonin and cortisol peaks significantly correlated in controls but not in cluster headache patients, indicating a chronobiological disorder in these patients. Blau and Engel[46] observed that 75 of 200 CH patients have a increase in body temperature from exercise, and hot bath or elevated environmental temperature may trigger cluster headache attacks. This finding can be explained by a decrease in melatonin secretion caused by temperature increase.[47]

Melatonin has been implicated in the treatment of cluster headache. There is one study Class II RCT on melatonin for cluster prevention.[33] This is a double-blind, placebo-controlled, parallel-group trial. The RCT (20 people; 18 with episodic cluster headache; two with chronic cluster headache) compared oral melatonin 10 mg daily versus placebo for two weeks. In comparison to the run-in period, there was a reduction in daily headache frequency in the melatonin group ($p < 0.03$), but not the placebo group. Two patients with chronic cluster headache did not respond to melatonin therapy. Adverse events were not reported.

Peres and Rozen[48] described two chronic CH patients who responded to melatonin (9 mg at bedtime). Melatonin prevented nocturnal cluster attacks and also daytime attacks. Nagtegaal et al.[41] reported one patient with delayed sleep phase syndrome in association with episodic CH in whom both disorders improved after melatonin treatment. There are a few trials to evaluate melatonin in prevention of CH and it was considered Level C for the prevention of CH.[49]

INDOMETHACIN-RESPONSIVE HEADACHE SYNDROMES

Melatonin has a chemical structure similar to that of indomethacin and thi fact has led researchers to use melatonin in the treatment of indomethacin-responsive headache.

Primary stabbing headache

Rozen[50] reported three patients with primary stabbing headache (PSH) with a positive response to indomethacin that were administered melatonin to assess its effectiveness. The three patients were given different dosages of melatonin (3, 9 and 12 mg, respectively). All the patients became asymptomatic and remained so throughout a 2- to 4-month follow-up. Melatonin appears to be an effective alternative treatment for PSH. Melatonin has a clearly more favorable side-effect profile than indomethacin. Rozen recommended to start with a bedtime

dose of 3 mg and then to increase the dose by 3 mg every four nights until pain relief is obtained, setting 24 mg as the upper dose limit. However, in most cases, no treatment is necessary given that PSH has a natural course of spontaneous fluctuations, with only 14% of patients experiencing persistent symptoms.[51]

Hypnic headache

Hypnic headache (HH) or primary sleep-related headache is a rare primary headache disorder that mainly affects elderly people. It was first described by Raskin, in 1988,[52] and 174 cases have been reported in the literature so far.[27] The exact pathophysiological mechanisms of HH have not yet been elucidated. It has been postulated that HH may be the result of a chronobiological disorder, serotonin, and melatonin dysregulation or a disturbance of rapid eye movement (REM) sleep. In most of the patients with HH who had polysomnographic studies, attacks were associated with REM sleep,[53-57] however, non-REM related HHs have also been reported.

Many patients reported a good response to indomethacin, but some could not tolerate it. Caffeine and melatonin treatments did not yield robust evidence to recommend their use as single preventive agents. Nevertheless, their association with lithium or indomethacin seems to produce an additional therapeutic efficacy. Lithium indirectly increases the level of melatonin[58-60] and may thus affect the pathophysiology of HH.

Domitrz describes a case of HH, which were effectively treated with flunarizine and melatonin (3 mg) in a 45-year-old woman.[61]

Dodick[54] describe a 68-year-old woman presented with a 6-year history of nocturnal headaches that awaken her from sleep. Treatment with melatonin (3 mg) at bedtime was begun, and headache severity decreased from moderate to mild and duration decreased to 15 to 20 minutes. The dose was increased to 6 mg, which rendered her headache-free over a 4-month period.

Ghiotto et al.[62] report two cases of HH that improve after treatment with melatonin.

Melatonin seems to be effective in a daily dose 3-5 mg and in association with caffeine or another drug for prophylaxis of HH. Melatonin was effective in four of 174 cases, in a recent review; thus, more studies are necessary to evaluate your efficacy in HH.[27,63]

Hemicrania continua

In a few reports melatonin was shown to be effective for HC. Spears[64] reported a case of hemicrania continua in which attacks were successfully eliminated while taking melatonin (7 mg) at bedtime after the patient was no longer able to tolerate indomethacin due to gastrointestinal side effects. Rozen[65] also reported an improvement in the hemicrania continua after treatment with melatonin.

HEADACHES AND PINEAL CYSTS

Pineal cysts are benign lesions found in up to 2.6% of adults. Asymptomatic pineal cysts are usually an incidental neuroimaging finding.

Peres et al. described five cases of primary headaches associated with pineal cysts and suggested that pineal cysts could be related to headache disorders not because of compression but abnormal secretion of the pineal hormone melatonin.[66] Seifert et al. studied 51 pineal cysts patients compared with 51 controls. Pineal cyst patients had 2-fold more headaches than controls (51% vs 25%).The most common diagnosis in pineal cysts patients was migraine in 26%, including 14% with migraine with aura. One patient had hemicrania continua. The authors suggest pineal cysts may be related to headaches, particularly migraine. Interestingly, cyst diameter was not different in patients with headache as compared with those without headache. This finding supports the idea of Peres et al.[66] that melatonin dysfunction may be the main mechanism related to the headache. Melatonin has been linked extensively to headache disorders with experimental and clinical evidence.[33,39,42,67,68] Unfortunately, to date, no measures of melatonin secretion have been performed in pineal cysts patients. Small, asymptomatic pineal cysts require no therapy. If they become symptomatic from hydrocephalus, surgical options can be considered. The patient with a headache disorder and a pineal cyst may be treated preventively with melatonin starting with 3 mg at bedtime and increasing to 15 mg.[67]

MELATONIN, HEADACHE AND MEDICINAL PLANTS

Melatonin have been found in several plants of medicinal value in species like feverfew (*Tanacetum parthenium*), St John's wort (*Hypericum perforatum*) and huang-qin (*Scutellaria baicalensis*).[69-71] Feverfew has been used in migraine treatment but sufficient scientific evidence of efficacy has not been established to date.[72,73] *Angelicae Dahurica* combined with *Scutellaria baicalensis* has been widely used as herb-pairs in traditional Chinese medicine to treat migraine headache. The interplay between

melatonin and these other reportedly potent compounds may be a promising field of future research.

Melatonin agonists

Melatonin and melatoninergic agonists may also be important in migraine comorbidity.[67] Insomnia in headache patients is the most likely associated condition in migraine to respond to melatonin therapy. Ramelteon (Rozeren®), a selective melatonin 1 or 2 receptor agonist can also be used for treatment of insomnia in migraine patients and have a profile with few side effects comparing with hypnotics drugs.

Agomelatine is a novel antidepressant and a melatonin agonist, a MT1 and MT2 receptor-site. It has been approved for major depression in Brazil.

Although no controlled studies with large samples have been published, two randomized clinical trials controlled with placebo for migraine prevention are registered in clinicaltrials.org, one with melatonin and other with ramelteon.

In Brazil there is no approval of Brazilian Health Survillance Agency (ANVISA) for the use of melatonin as a vitamin, as is in the United States and most of developed countries, we totally agree with that. Brazilian law enables public advertisement when a compound is registered as a vitamin and this is not desirable for melatonin with the current health assistance access for the general population. In contrast, melatonin as a natural substance found in the human body cannot be applied for a patent, it is cheap, therefore no pharmaceutical company has financial interest in the application of melatonin as a medication. Important to notice that melatonin is not a banned drug, and not prohibited in Brazil, it is only not registered as a vitamin or a medication, as many other compounds, including vitamins and not yet approved medication for oncology treatments, the patient has the right to take it and receive the best treatment option, and the physician has the right to prescribe the best treatment option for his or her patient. We hope in the near future melatonin could be better delivered to patients with the regulatory issues resolved.

CONCLUSION

Melatonin plays a significant role in the patho-physiology of headaches. Melatonin can also be a good option in the treatment of primary headaches, not only those with nocturnal occurrence but also migraine and other headaches. In the presence of insomnia or circadian rhythm disturbance melatonin may also be helpful. However more randomized clinical trials should be done in order to give more evidence for melatonin prescription in our current practice (see take home messages).

Table 3. Take home messages

Melatonin should be considered in association with another drugs in the preventive treatment of headaches
Use melatonin in comorbidities with sleep disorders
Further studies are necessary for evaluating the effectiveness of melatonin in primary headache

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Headache and pregnancy

Cefaleia e gravidez

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ABSTRACT

Headache in pregnancy is a peculiarity of woman life phase. Correct diagnosis in pregnancy is the best thing for a management gold standard. Some secondary headaches that mimic migraine may begin during pregnancy, and can be caused by vasculitis, brain tumor, pituitary tumor, arteriovenous malformation, sinus disease, idiopathic intracranial hypertension, subarachnoid hemorrhage, stroke, cerebral venous thrombosis, pre-eclampsia and eclampsia. These headaches must be correctly diagnosed. At the conclusion, if a pregnant patient presents primary headache, it will be necessary to treat her. The classic teratogenic risk occurs from the 29th day to the 70th day of gestation. Women with severe headache during this period should be treated because nausea and vomiting in association with pain can be teratogenic to the fetus. Non-pharmacological techniques are effective for acute and preventive treatment and should be applied. If drugs are necessary, will be choose minimal doses and medications that causes fewer problems in pregnancy. Management of pregnant women with migraine should be done with caution, keeping in mind the low level of scientific evidences.

Key words: Pregnancy; Headache; Migraine; Treatment.

RESUMO

Cefaleia na gestação é uma peculiaridade de uma fase da vida da mulher. O diagnóstico correto da cefaleia na gravidez é a chave para um tratamento de excelência. Algumas cefaleias secundárias que mimetizam migrânea podem se iniciar durante a gestação, e podem ser causadas por vasculites, tumor cerebral, tumor hipofisário, malformação arteriovenosa, sinusopatias, hipertensão intracraniana idiopática, hemorragia subaracnóidea, acidente vascular encefálico, trombose venosa cerebral, pré-eclâmpsia e eclâmpsia. Tais cefaleias devem ser diagnosticadas corretamente. Ao se concluir que a paciente grávida apresenta cefaleia primária, é necessário tratá-la. O risco teratogênico clássico das drogas ocorre a partir do 29° até o 70° dia a partir do 1° dia da última menstruação da mulher. Mulheres com cefaleia intensa nesse período devem ser tratadas, pois náuseas e vômitos em associação com dor podem ser teratogênicos ao feto. Técnicas não farmacólogicas são efetivas para tratamento agudo e preventivo e devem ser empregadas. Se drogas forem necessárias, escolher as menores doses e que causem menos problemas na gravidez. O tratamento da gestante com enxaqueca deve ser realizado com muita cautela, tendo-se em mente que o nível de evidência é baixo.

Palavras-chave: Cefaleia; Gravidez; Enxaqueca; Tratamento

INTRODUCTION

Pregnancy is a peculiar woman life phase, considered optional. It usually occurs during woman´s professional highest peak. Headache in pregnancy is a woman's particularity, and like other disturbances in this phase, must be seen with caution. Its progress must be followed and its treatment must be carefully addressed.[1]

Correct diagnosis

The diagnosis of a headache disorder must be correct for a suitable management. In pregnant and lactating woman this is done through the Classification of the International Headache Society (2004).[2]

On the anamnesis of a pregnant woman with headache, it´s important to always ask her if she had headaches before pregnancy, or if the headaches started during pregnancy, or if she had a prior headache and there were changes in the headache characteristics during the pregnancy.

It is always necessary to distinguish between pre-existing headaches and those initiated during pregnancy because there may be three possibilities: (1) monitoring the behavior of an existing headache prior to pregnancy, during pregnancy; (2) appearance of a new headache during pregnancy; and (3) the woman had presented a headache before getting pregnant and then develops a new one during pregnancy.

SECONDARY HEADACHES

Migraine-like headache that began during pregnancy may be secondary to vasculitis, brain tumor, chorio-carcinoma, pituitary tumor, arteriovenous malformation (AVM), sinus disease, idiopathic intracranial hypertension, subarachnoid hemorrhage, stroke, cerebral venous thrombosis, pre-eclampsia and eclampsia.[3,4]

Some comments about specific secondary headaches:

1. The diagnosis of sinusitis is often overstated, chronic sinus does not cause headache;[3,4]

2. Only 48% of brain tumor patients develop headache during pregnancy. Pregnancy does not increase the risk of brain tumor;

3. Pregnant women have 13 times the risk of having a stroke. One of the most common stroke during pregnancy is cerebral venous thrombosis. Most cases present neurological deficits, but the superior sagittal sinus thrombosis may present with progressive headache, without neurological signs or symptoms;

4. Subarachnoid hemorrhage explains 50% of intracranial bleeding during pregnancy. Subarachnoid hemorrhage may mimic eclampsia. Most cases of intracranial hemorrhage, especially in the eclampsia group, result from hypertension. Illicit substances (alcohol and cocaine) is a cause of subarachnoid and intracerebral hemorrhage during pregnancy;[3]

5. Differential diagnosis of thunderclap headaches of sudden onset includes reversible cerebral vaso-constriction syndrome, subarachnoid hemorrhage by aneurysm, cerebral venous thrombosis, dissection of the carotid or vertebral artery, intraparenchymal hemorrhage and pituitary apoplexy. Neuroimaging is required in such cases. Reversible cerebral vasoconstriction syndrome encompasses a diverse group of conditions, including hypertensive encephalopathy and vasculopathy associated with pregnancy and the postpartum period (postpartum angiopathy). Reversible cerebral vaso-constriction syndrome is characterized by sudden onset of a severe headache that subsides within a few days to weeks and resolves in most patients, approximately 12 weeks after the presentation. A similar syndrome can be seen with pre-eclampsia and eclampsia occurring before birth or postpartum. A diagnosis of reversible cerebral vaso-constriction syndrome requires the exclusion of other causes of headache accompanied by tomography or magnetic resonance imaging and magnetic angiography resonance to evaluate arterial and venous vasoconstriction or cerebral edema, and exclude cerebral venous thrombosis. Cerebrospinal fluid obtained via lumbar puncture can eliminate vasculitis or infection.[5]

Symptomatic headaches require neuroimaging or lumbar puncture to diagnose. The guidelines for neuro-imaging in patients who are or may be pregnant are:

1. Determinate the necessity and the potential risks of the procedure.

2. If possible, perform the examination during the first 10 days postmenses, or if the patient is pregnant, delay the examination until the third trimester or preferably postpartum.

3. Pick the procedure with the highest accuracy balanced by the lowest radiation.

4. Use MRI if possible.

5. Avoid direct exposure to the abdomen and pelvis;

6. Avoid contrast agents.

7. Do not avoid radiologic testing purely for the sake of the pregnancy.

8. If significant exposure in incurred by a pregnant patient, consult a radiation biologist.

9. Consent forms are neither required nor recommended.[4]

Head CT is relatively safe during pregnancy and is the study of choice for head trauma and possible non-traumatic subarachnoid, subdural or intraparenchymal haemorrhage.

MRI is preferable for all other non-traumatic or non-haemorrhagic craniospinal pathologies. The potential risks of MRI in pregnancy are still controversial. First use angiography to evaluate suspected vascular pathology, but, when necessary, angiography is reasonably safe in pregnant patient.[4]

A CT scan exposes the mother to a radiation of <0.01 Gray (Gy), while the threshold of fetal damage with ionizing radiation directly into the maternal pelvis is >0.1 to 0.2 Gy. To maintain the safety margin, the National Council for Radiation Protection and Measurements grouped the acceptable limits of radiation in all scan sat 0.05 Gy. MRI does not show the same level of risk associated with ionizing radiation.

Gadolinium-based contrast agents have been associated with the development of nephrogenic systemic sclerosis . This condition is rare and has been reported to occur in patients with compromised renal function. Gadolinium can cross the placenta into the fetal circulation and, subsequently, is excreted into the amniotic fluid, where the agent can remain for an extended period of time. No prospective studies with large numbers of patients have evaluated the risk of teratogenic or mutagenic effects.

The American College of Radiology Guidelines Document for Safe MR Practices recommends that pregnant patient should only receive gadolinium-contrast agents after careful consideration of the risk-benefit ratio. Iodinated CT contrast agent has been associated with contrast-induced nephropathy in as many as 21% of patients who had a baseline glomerular filtration rate of <50 ml/min/1.73 m^2. Nephropathy induced by iodinated CT contrast agent is usually reversible, but the condition can be associated with nonrenal complications that can prolong hospital stays and increase in-hospital mortality. Free iodide in the contrast medium given to the mother has the potential to depress fetal and neo natal thyroid function. Neonatal thyroid function should, therefore, be checked after delivery in such patients. The risk associated with absorption of contrast medium during lactation is small and can be considered insufficient to warrant stopping of breastfeeding. The neonatal thyroid should be checked after labor in such patients.[5-10]

Potential indications for computed tomography or MRI in headache investigation during pregnancy are the same as an average patient with suspected secondary headache (Table 1).

Table 1 - When suspect of a secondary headache

First episode of sudden onset of headache, or worst headache of life
Followed by disturbance of consciousness, fever, neck stiffness
Changes in frequency, intensity, or the clinical characteristics of headache attacks
Abnormal neurological examination (followed by signs/irritative or deficitary neurological symptom)
Progressive headache or new daily persistent
Neurological symptoms that do not fulfill the criteria for migraine with typical aura
Persistent neurological deficit
Evidence of a defined focal lesion in the electroencephalogram (EEG)
Changes in skin or orbit suggestive of AVM
Comorbidity of partial seizures
Followed by endocrine disorders or high blood pressure;
Related to coughing or physical effort
Triggered by sexual activity, and vomiting lasting hours
Changing pattern; new headache superimposed on the old one
Start after 50 years of age

MEDICATIONS ON PREGNANCY AND FETUS

If the conclusion is that the pregnant patient presents primary headache, it will be necessary to treat headaches during pregnancy. Then, there will be a concern with regarding the treatment.

Management

Treatment of pregnant women is a part of medicine based in low scientific quality of evidence. The experience in treating these women comes from case-control studies and and populational retrospectives.

Tables with drugs risks in pregnancy risk of learning disabilities are deficient, and 40% of the drugs do not have a listed category. The decision about what to use during pregnancy should be made case by case, using incomplete information.

It must always be applied in migraineurs pregnant women non-pharmacological treatment which is free from risk to fetus and mother.[1,11]

The classic teratogenic risk occurs from the 29th day to the 70th day of gestation (after the first day of the woman's last menstruation). Women with severe headache during this period should be treated because nausea and vomiting resulting due to pain may be teratogenic to the fetus.[12]

The evaluation of the first trimester is therefore a serious methodological error, only the second and third months represent the critical period of most major congenital abnormalities (CAs). On the other hand, we know that the critical period of some CAs exceeds the end of third month, e.g., the critical period of posterior cleft palate and hypospadias covers the 12th-14th and 14th-16th weeks of gestation, while the critical period of undescended testis and patent *ductus arteriosus* is 7 to 9 months and 9 to 10 months, respectively. Thus, the optimal approach is to consider the specific critical period of each CA separately.[12]

The FDA (Food and Drug Administration) lists five categories of labeling for drug use in pregnancy. These categories provide therapeutic guidance, weighting the risks as well as the benefits of the drug. An alternate rating system is TERIS (an automated teratogen information resource wherein ratings for each drug or agent are based on a consensus of expert opinion and

the literature) which was designed to measure the teratogenic risk to the fetus from drug exposure (Tables 2 and, 3).

Table 4 presents some drugs and their risk categories (FDA and TERIS)[3-5,12-16]

Table 2 - FDA drugs risk categories, and the corresponding TERIS at the first column

Category A (TERIS - none None-minimal)	Controlled humans studies show no risk
Category B (TERIS - Minimal)	No evidence of risk in humans, but there are no controlled humans studies
Category C (TERIS - Undetermined)	Risk in humans has not been ruled out
Category D (TERIS - Minimal-small)	Positive evidence of risk to humans from human and/or animal studies
Category X (TERIS - High)	Contraindicated in pregnancy

Table 3 - Teratogenic information service (TERIS) risk rating

Risk proportion	Definition
N	None (A)
N-Min	None-minimal (A)
Min	Minimal (B)
Min-S	Minimal-small (D)
S	Small
S-Mod	Small-Moderate
Mod	Moderate
H	High (X)
U	Undetermined (C)

Preventive or prophylactic treatment

Classes of drugs that can be used like prophylactic on pregnant woman migraine:

Beta-blockers

– Propranolol – adverse events: delay uterine growth, hypoglycemia, bradycardia and breathless;

– Atenolol – adverse events: lower weight at birth;

– Metoprolol -adverse effects: growth delay;

– Labetalol[11]

Corticosteroids – helpful for occasional use in a regimen of short prophylaxis helps in the maturation of fetal lungs.[15]

Prednisone and prednisolone – no risk, they must have preference over dexamethasone, as the latter crosses the placental barrier.

Serotonin reuptake inhibitors (SSRIs) – fluoxetine and sertraline are useful in migraine and comorbid conditions such as anxiety or depression.

Magnesium, riboflavin, pyridoxine hydrochloride – there is no evidence of risk of multiple congenital anomalies associated with periconceptional use of vitamin supplementation.[17]

Symptomatic treatment of migraineur pregnant women

Measures that can be used taken symptomatic therapy in migraine of pregnant women are:

– Hydration.

– NSAIDs (ibuprofen, naproxen, can close the fetal *ductus arteriosus*), corticosteroids (useful, occasional).

– Aspirin (low dose).

– Common analgesics (acetaminophen).

– Narcotic analgesics.

– Chlorpromazine, promethazine, metoclopramide;

– Triptans (naratriptan and sumatriptan) (no evidence of abnormality, can be used if other drugs do not solve, to avoid during the 2nd and 3rd months).

– Pyridoxine (for nausea – not teratogenic).

What not to use in pregnant women with headache

Natural or herbal therapy (because they are less studied); feverfew (by presenting possible teratogenicity); ergotamine, dihydroergotamine (are contraindicated for showing an association with increased risk of neural tube defects and a higher proportion of premature births, neonatal lower weight birth and low gestational age;[18] benzodiazepines and barbiturates (for cleft palate occurrence and heart and urogenital defects), valproate and divalproex[1] (for neural tube defects such as bifid spina and myelomeningocele, cardiac abnormalities, such as levocardia, aortic stenosis, patent *ductus arteriosus*, tetralogy of Fallot, partial right bundle branch block, ventricular septal defect, and various facial defects); Receptor inhibitors of the angiotensin converting enzyme (ACE) (association with fetal kidney problems).[1]

CONCLUSIONS

It is recommend that women at childbearing age take vitamin supplement with 0.4 g of folic acid to reduce risk of neural tube defect. If pregnancy is desired by the migraineurs, discontinuation of medications must be made before conception. If the woman becomes pregnant during treatment, the conduct will depend of the used medication.

Non-pharmacological techniques are effective for acute and preventive treatment.

Table 4 - Risk factors for some drugs (FDA e TERIS)

Analgesic	FDA	TERIS
Aspirin	C (D - if 3rd trimester)	Minimal
Acetaminophen	B	None
Caffeine	B	None
Dipyrone	C	
AINH		
Ibuprofen	B (D - if 3rd trimester)	Minimal
Indomethacin	B (D)	None
Naproxen	B (D - if 3rd trimester)	Undetermined
Narcotics		
Butorphanol	C (D)	
Codeine	C (D - prolonged or term pregnancy)	Unlikely
Meperidine	B (D - prolonged or term pregnancy)	None-minimal
Methadone	B (D)	None-minimal
Morphine	B (D - prolonged or term pregnancy)	None-minimal
5HT Antagonists		
Pizotifen	Does not apply (C)	Security no stablished
Methisergide	X	Security no stablished
Methylergonovine	C	Undetermined
Serotonergic agonists and ergot		
Ergotamine	X	Undetermined/ Minimal
Ergotamine	X	Undetermined/ Minimal
Sumatriptan	C	Undetermined
Corticosteroids		
Dexamethasone	C	None-minimal
Prednisone	B	None-minimal
Prednisolone	C (D- if 3rd trimester)	None-minimal
Barbiturates		
Butalbital	C (D)	None-minimal
Phenobarbital	D	None-minimal
Benzodiazepines		
Chlordiazepoxide	D	None-minimal
Diazepam	D	None-minimal
Clonazepan	C	Undetermined
Antihistamines		
Cyclizine	B	Undetermined
Cyproheptadine	B	Undetermined
Dimenhydrinate (dramamine)	B	None-minimal
Meclizine	B	None-minimal
Oxcarbazepina	D	
Ethosuximida	C	
Neuroleptics		
Phenothiazines		
Chlorpromazine	C	None-minimal
Prochlorperazine	C	None
Butyrophenones		
Haloperidol	C	None-minimal

Table 4 - Risk factors for some drugs (FDA e TERIS) (Cont.)

Analgesic	FDA	TERIS
Antiemetics		
Metoclopramide	B	Minimal
Dimenhydrinate	B/D	
Ondansetron	B	
Domperidone	C	Undetermined
Others		
Emetrol	B	
Doxylamina		None
Pyridoxine	B	None
Lithium	D	
Beta-blockers	Dosage	
Atenolol	50-120 mg/d D	Undetermined
Propranolol	40-320 mg/d C (D- prolonged or term pregnancy)	Undetermined
Nadolol	40-240 mg/d C (D- prolonged or term pregnancy)	Undetermined
Metoprolol	50-100 mg/d C (D- prolonged or term pregnancy)	Undetermined
Timolol	C (D - prolonged or term pregnancy)	Undetermined
Antidepressives		
Tricyclics		
Amitriptyline	10-250 mg/d C	Unlikely
Nortriptyline	10-100 mg/d C	Undetermined
Imipramine	C	Unlikely
IRSS		
Fluoxetine	10-80 mg/d B	None
Paroxetine	10-50 mg/d C	Undetermined
Sertraline	B	Unknown
Calcium Channel Blockers		
Verapamil	240-720 mg/d C	Undetermined
Diltiazem	120-360 mg/d C	Undetermined
Flunarizine	5-10 mg/d (Does not apply (C)	Segurity no established
Anticonvulsants		
Valproic acid	D	Moderate
Divalproex	500-3000 mg/d (D)	Moderate
Topiramate	D	
Carbamazepine	B	
Gabapentin	C	Undetermined
Lamotrigine	C	Undetermined
Phenytoin	D	
Oxcarbazepina	D	
Ethosuximida	C	

If drugs are necessary, you will choose small doses and drugs that cause fewer problems in pregnancy.

Experts (Hungarian, American and European) after several reviews, ask if we can improve our uncertain ties about the treatment of the pregnant migraineurs and answer that little can be expected about changing the situation in the future. Forbidding to use drugs during pregnancy is mostly due to ignorance of its action over the fetus than the opposite.

The treatment of pregnant women with migraine should be done with caution, bearing in mind that the evidence is low, and this fact will not change in the future. Headache in pregnancy is a vast theme and should be studied in a more complex way because it involves two beings: the pregnant woman and the fetus. The message here is that there is still much to be done in order to clarify this so great universe of headache in pregnant women.

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Trigeminal neuralgia and persistent idiopathic facial pain

A neuralgia do trigêmeo e a dor facial persistente idiopática

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ABSTRACT

Trigeminal neuralgia (TN) and persistent idiopathic facial pain (PIFP) are two of the most puzzling orofacial pain conditions and affected patients often are very difficult to treat. TN is characterized by paroxysms of brief but crucial pain, followed by asymptomatic periods without pain. In some patients a constant dull background pain may persist. This constant dull pain sometimes makes the distinction from PIFP difficult. PIFP is defined as continuous facial pain, typically localized in a circumscribed area of the face, which is not accompanied by any neurological or other lesion identified by clinical examination or clinical investigations. The pain usually does not stay within the usual anatomic boundaries of the trigeminal nerve distribution and is a diagnosis of exclusion. Epidemiologic evidence on TN and even more so on PIFP is quite scarce, but generally both conditions are considered to be rare diseases. The aetiology and underlying pathophysiology of TN and more so PIFP remain unknown. Treatment is based on only few randomized controlled clinical trials and insufficiently evaluated surgical procedures.

Keywords: Trigeminal neuralgia; Persistent idiopathic facial pain; Atypical facial pain; Pathophysiology; Treatment; Differential diagnosis

RESUMO

A neuralgia do trigêmeo (NT) e a dor facial persistente idiopática (DFPI) são duas das mais intrigantes condições dolorosas orofaciais, e os pacientes afetados são, frequentemente, muito difíceis de tratar. A NT é caracterizada por paroxismos de dor breve mas excruciante, seguidos por períodos assintomáticos sem dor. Em alguns pacientes, uma dor de fundo maçante e constante pode persistir. Esta torna difícil, às vezes, distinguir a NT da DFPI. A DPFI é definida como uma dor facial contínua, localizada tipicamente em uma região circunscrita da face e que não é acompanhada por qualquer lesão – neurológica ou de outra natureza – identificada através do exame clínico ou de investigação complementar. A dor geralmente não permanece restrita aos limites anatômicos da distribuição do nervo trigêmeo e é um diagnóstico de exclusão. Evidências epidemiológicas sobre a NT, e ainda mais sobre a DFPI, são bastante escassas, mas usualmente ambas condições são consideradas doenças raras. A etiologia e a fisiopatologia da NT e, mais ainda, da DFPI, permanecem desconhecidas. O tratamento é baseado em apenas uns poucos ensaios clínicos randomizados e controlados e em procedimentos cirúrgicos insuficientemente avaliados.

Descritores: Neuralgia do trigêmeo; Dor facial persistente idiopática; Dor facial atípica; Fisiopatologia; Tratamento; Diagnóstico diferencial

INTRODUCTION

The prevalence of orofacial pain in the general population was estimated between 17%-26% with 7%-11% of those patients having been considered as presenting a chronic condition.[1] The disorders that are often summarized as orofacial pain are quite heterogeneous and include acute and chronic pain syndromes that often show a considerable overlap in

clinical presentation or present with atypical features. This makes the differential diagnosis very difficult sometimes. Trigeminal neuralgia (TN) and persistent idiopathic facial pain (PIFP) are two of the most common forms of orofacial pain assessed and treated by neurologists and pain specialists.[2]

DEFINITION AND CLINICAL PRESENTATION OF TRIGEMINAL NEURALGIA

Trigeminal neuralgia (TN) is defined by the International Headache Society (IHS) as "unilateral disorder characterized by brief electric shock-like pains, abrupt in onset and termination, and limited to the distribution of one or more divisions of the trigeminal nerve".[3] The IHS recommends the classification of TN in classical (essential or idiopathic) TN and symptomatic TN ("pain indistinguishable from that of classical TN, but caused by a demonstrable structural lesion other than vascular compression").[3] The absence of clinically evident neurological deficit is required for the diagnosis of classical TN. It generally starts in the second or third divisions of the trigeminal nerve, affecting the cheek or the chin.[3] The ophthalmic division alone is involved in less than 5% of cases.[4] A typical TN attack lasts between less than a second and a few seconds, but it may present in clusters of variable intensity with up to two minutes duration. In many cases it is followed by a brief refractory period during which a new stimulation is not able to evoke another attack. Between paroxysms the patient is usually pain free, but a dull background pain may persist in some cases.[3] The mechanisms associated with the development of this persistent pain are not well understood but concomitant background pain is associated with poor medical and surgical outcome.[5-7]

DEFINITION AND CLINICAL PRESENTATION OF PERSISTENT IDIOPATHIC FACIAL PAIN

Persistent idiopathic facial pain (PIFP) was previously termed atypical facial pain and was first introduced by neurosurgeons in the 1920s as a distinct clinical entity.[8] The IHS defined it, as "a persistent facial pain that does not have the characteristics of cranial neuralgias, presents daily and persists for all or most of the day. The pain is confined at onset to a limited area on one side of the face and is deep and poorly localized".[3] Common sites of onset are the nasolabial fold or the side of the chin. It may spread to the upper or lower jaw or a wider area of the face and neck, not following specific peripheral neuroanatomic distributions. It is most often felt unilaterally, but over time, in about one-third of patients the pain becomes bilateral. The pain is often initiated by minor surgery or injury to the face, teeth or gums, but persists without any demonstrable cause.[3] Sensory loss or other physical signs are not present and clinical investigations are usually unremarkable. The diagnosis of PIFP is one of exclusion and should be made only after local orofacial disease, neurologic disorders, and related systemic diseases are ruled out.[9] The IHS added a comment on their classification that a facial pain located in the area of the ear or temple may be associated with undiagnosed lung cancer causing referred pain as a result of vagal nerve involvement.[3]

EPIDEMIOLOGY OF TRIGEMINAL NEURALGIA

TN is the most common form of cranial neuralgias with an incidence of 4.3 per 100,000 persons per year, with a slightly higher incidence for women (5.9/100,000) compared to men (3.4/100,000).[10] The gender ratio women to men is approximately 2:1.[11] The prevalence of this relatively rare disorder has been reported to be 15.5 cases per 100,000 in the United Kingdom.[12] In Germany the prevalence of TN is prevalence of 0.3% of the general population.[13] Sjaastad et al. (2007) found only two patients out of 1838 to fit the diagnostic criteria for TN (0.1%) in a large Norwegian epidemiological study (Vågå-Study).[14] TN can first appear at any age, but disease onset is after the age of 40 years in over 90% of cases. The peak age is between the ages of 50 to 60 years.[12] The right side of the face is more often involved that the left .[15] About 2% of the patients with MS complain about symptoms identical to those of TN.[14] TN seldomly affects more than one member of the family, but increased risk was reported in patients living in the same household, suggesting disease associated environmental factors.[16,17]

EPIDEMIOLOGY OF PERSISTENT IDIOPATHIC FACIAL PAIN

PIFP prevalence remains largely unclear. In general, orofacial pain is considered to be a common problem affecting between 17%-26% of the adult population with increasing prevalence corresponding to increasing age.[18] Approximately 7%-11% of patients have chronic facial pain in this regard.[19] Atypical odontalgia, often

considered a subtype of PIFP and defined as a continuous pain in the teeth or in a tooth socket after extraction in the absence of any identifiable dental cause, occurs in 3%-6% of patients that undergo endodontic treatment.[20] A large population based sample reported the prevalence of PIFP in the general population in Germany at 0.03% [95% CI < 0.08%].[13] The incidence was estimated at one patient out of 100,000 in PIFP but the authors proposed that there might be a huge underestimation of PIFP in their large patient population due to the lack of diagnostic reconfirmation tests.[21] A gender ratio of women compared to men of 2:1 was reported and female hormones were suggested as a risk factor for the development of PIFP.[22]

AETIOLOGY AND PATHOPHYSIOLOGY OF TRIGEMINAL NEURALGIA

Current opinion is that TN is caused by a proximal compression of the trigeminal nerve root close to the brainstem (root entry zone) by a tortuous or ectasic blood vessel (artery or vein) leading to mechanical twist of nerve fibers and secondary demyelination, probably mediated by microvascular ischemic damages.[23] These changes lower the excitability threshold of affected fibers and promote inappropriate ephaptic propagation towards adjacent fibers.[24] Thus, tactile signals coming from the fast myelinated (A-beta) fibers can directly activate the slow nociceptive (A-delta) fibers resulting in the high-frequency discharges characteristic for TN. After a few seconds these repetitive discharges spontaneously run out and are followed by a brief period of inactivity that resembles the refractory period observed clinically.[2] Demyelination and remyelination processes within the root entry zone (i.e., 6 mm of central myelin from the brainstem; Obersteiner-Redlich line = transition of central to peripheral myelin of the trigeminal nerve) observed in electronic microscopy studies might provide one explanation for the periodicity of the syndrome.[25,26] Spontaneous remission of at least 6 months were described in 50% of the cases and remissions of over one year in 25%.[27] Marinkovic et al. (2007) described trigeminal vascular pathology with immunoreactivity in TN patients suggesting a more local concentrated pathological origin of disease.[23] A recent diffusion tensor imaging (DTI) study showed a reduced fractional anisotropy (FA) of the trigeminal nerve in six patients with TN on the affected side confirming tissue damage associated with demyelination likely due to compression.[28]

While Jannetta et al. (1967) described 88% of their investigated patients to have a nerve vessel conflict, 6% had MS and 6% showed a cerebellar-pontine angle tumour,[29] more recent investigations demonstrated that not all patients that were considered classical TN did have a nerve vessel conflict (usually the superior cerebellar artery) and that at least 25% of people without any clinical signs of TN did show a nerve artery contact on magnetic-resonance imaging (angio-3D-TOF).[30] A different study showed that out of 220 investigated trigeminal nerves 110 (49%; 51 women, 57 men) came into contact with some vasculature on routine MRI performed for different reasons.[31] The quick pain relief following microvascular decompression surgery in 90% of patients is a strong indicator for the relevance of this mechanism, but lacks explanation as to why a large percentage of patients experience recurrence of their complaints.[32] It was suggested that hyperexcitability of the compressed nerve is necessary but alone insufficient to cause the disease, so that a nerve-vessel conflict may represent a risk factor for the development of TN.[33] Possible involvement of central factors come more and more into focus of current research, suggesting a central facilitation and resulting hyperexcitability of the trigeminal system sustained by peripheral as well as central mechanisms.[34] Sensitisation of second order wide dynamic range (WDR) neurons in lamina V of the dorsal horns and the trigeminal nerve nuclei due to hypersensitivity of tactile A-beta fibers were discussed as additional pathophysiological mechanism. Since these WDR neurons receive convergent information from tactile (A-beta) and nociceptive (A-delta and C) fibers, their sensitization could facilitate nociceptive input while promoting the perception of pain in response to tactile stimuli (i.e., allodynia, trigger factors). Central facilitation was recently demonstrated in TN patients with additional constant dull background pain besides their typical TN attacks using pain-related evoked potentials (PREP) and nociceptive blink reflex (nBR).[6] This provides strong evidence for the involvement of supraspinal structures in TN. Borsook et al. (2007) reported increased fMRI activation of a single TN patient in the primary somatosensory cortex, insula, anterior cingulate, and thalamus to further support supraspinal involvement.[35] Whether supraspinal facilitation is part of the underlying cause of TN or merely a consequence of the disease will need further research. While concomitant constant pain is a predictor for poor surgical and medical outcome it is probably not due to progressing disease or illness duration as it is frequently observed in patients with

average disease duration.[6,34] It might be regarded as disease variant.

AETIOLOGY AND PATHOPHYSIOLOGY OF PERSISTENT IDIOPATHIC FACIAL PAIN

The aetiology and pathophysiology of PIFP is not as well understood. Surgery or injury in the distribution of the trigeminal nerve was suggested as the initiating event as many patients attribute their pain to an antecedent event such as dental procedure/ extraction or other minor trauma to the face.[36] PIFP could represent a neuropathic pain condition. It was suggested, that the pain may be a consequence of deafferentation and long term neuroplastic changes initiated by the frequently occuring minor injuries of afferent trigeminal nerve fibers explaining the suggested peripheral as well as central component of this complex disease.[2]

For many years, a psychogenic origin of PIFP was assumed mainly based on the often observed psychiatric comorbidities presented by patients such as depression and anxiety disorders.[37] The prevalence of psychiatric disorders in fact was shown to be increased with up to 30% of PIFP patients suffering from anxiety disorders, 16% from affective disorders, 15% from somatoform disorders, and 6% with psychosis.[38] This pure psychological concept is disputed more and more recently with emerging evidence of measurable neurobiological correlates for the patients' complains that are similar to other chronic pain conditions. A recent imaging study showed structural brain changes in regions well known to be associated with central pain processing.[39] A decrease in gray matter volume in the anterior cingulate cortex (ACC), the temporo-insular region, as well as the sensory-motor area projecting to the representational area of the face were demonstrated in patients with PIFP similar to previously described brain alterations in primary headache disorders (i.e., tension-type headache) and other chronic pain conditions (i.e., chronic back pain).[39] Whether these changes are due to the PIFP pathophysiology or merely represent changes due to chronic pain remain uncertain, but these results support the opinion of a neurobiological origin of PIFP. A functional imaging study with positron emmission tomography (PET) on six patients with PIFP showed an increased blood flow in the ACC and a decreased blood flow in the prefrontal cortex compared to healthy controls after application of heat pain stimuli applied to the hand.[40] A similar PET study showed an increased D2 receptor density in the putamen stressing the relevance of dopaminergic neurotransmission in the modulation of pain perception in PIFP.[41] Neurophysiological testing using blink reflex (BR) recordings and quantitative sensory testing (QST) showed neuropathic changes and central hyperexcitability similar to alterations described in TN and other neuropathic causes of chronic orofacial pain.[2] These test results, however, were quite heterogeneous across the investigated patients and did not show reliable abnormalities in all investigated PIFP patients. Therefore, authors underlined a multifactorial and heterogeneous origin of disease in PIFP with a peripheral (i.e., nerve injury, small-fiber neuropathy) and central component (i.e., disturbed or disregulated pain regulation of ascending or descending nociceptive and antinociceptive brain centers).[42] Besides the neuropathy part of suspected peripheral pathology in PIFP, a neuromuscular component of PIFP pathology was described only recently in a study that found an increased muscular activity of the masseter muscles and the anterior temporal muscles in PIFP using electromyography (EMG). This increased activity decreased after rehabilitation with a neuromuscular orthosis in parallel to the reduction of individual pain perception on a visual analogue scale (VAS) from 9.5 to 3.1.[43]

Further research is needed to identify responsible mechanisms and subdivide the different patho-physiological aspects and contributing factors possibly leading to PIFP.

DIAGNOSTICS AND DIFFERENTIAL DIAGNOSIS

The correct clinical diagnosis is the most important factor for sufficient treatment in both orofacial pain conditions alike. History remains the essential tool for diagnosis. The following six questions were proposed to determine the correct diagnosis in orofacial pain:[44]

1) Does the pain occur in attacks or is it constant?

2) How long are the attacks (seconds to minutes)?

3) Are the attacks electric shock like or dull, pressing or pulsating?

4) Is the pain unilateral?

5) Is the pain confined to the distribution of a particular branch or branches of the trigeminal nerve (ophthalmic = V1, maxillary = V2, mandibular = V3)?

6) Are trigeminal autonomic symptoms present (e.g., lacrimation, rhinorrea, conjunctival injection, nasal congestion, ptosis)?

Table 1 - Differential diagnoses of trigeminal neuralgia and persistent idiopathic facial pain

Acute glaucoma, refraction anomalies, strabismus
Ear disorders
Sinusitis
Disorders of the jaw, teeth, and related structures
Disorders of the temporomandibular joint (TMD)
Disorders of cranial nerves such as: - trigeminal compression - optic neuritis, diabetic ocular neuritis - herpes zoster, postherpetic neuralgia - Tolosa-Hunt syndrome - neck-tongue syndrome
Other cranial neuralgias: - glossopharyngeal neuralgia - intermediate nerve neuralgia - superior laryngeal neuralgia - nasocilliary neuralgia - supraorbital neuralgia
Trigeminal autonomic cephalalgias (TAC): - cluster headache - hemicrania continua - SUNCT/SUNA = short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing/ short-lasting, unilateral neuralgiform headache attacks with autonomic symptoms)
Pain due to bone disorders of the skull
Cervicogenic headache
External compression headache and cold stimulus headache
Ophthalmic migraine
Anaesthesia dolorosa
Central post-stroke pain

Trigeminal autonomic cephalalgias (e.g., cluster headache, SUNCT, paroxysmal hemicrania) are important to differentiate, especially in patients with first division pain only.[45]

Other important differential diagnoses are nasopharyngeal tumors and hidden dental problems such as infections of the maxillary cavities or jaws after previous tooth extraction as well as disorders of the temporomandibular joint (Table 1). For correct differentiation a thorough examination by an oral/ maxillofacial surgeon or facial pain experienced dentist is required. The finding of septal deviation is irrelevant and does not rule out the diagnosis.[46] Cranial magnetic resonance imaging (MRI) should be performed in patients with atypical presentation of TN and PIFP even though data on clinical specificity or sensitivity are unavailable. Thorough diagnostic workup is especially important in PIFP as it is a diagnosis of exclusion. It should include a radiologic examination of the chest, since in rare occasions PIFP may be the presenting symptom of a lung cancer.[47]

In TN the main objective of special diagnostic procedures is the differentiation of classical TN (CTN) from symptomatic TN (STN). Clinical presentation with bilateral TN as well as trigeminal sensory deficits are indicative of STN, but due to low sensibility, their absence does not rule out STN.[32,48] Magnetic resonance imaging detects symptomatic causes other than nerve vessel conflict in approximately 15% (95% CI, 11-20) of patients. Multiple sclerosis (MS) plaques and cerebello-pontine angle tumours are the most common findings. Blink reflex studies and other trigeminal reflex testing has a considerably high diagnostic value with sensitivity of 94% (95% CI, 91-97), and specificity of 87% (95% CI, 77-93). Evoked potentials are insufficient to separate STN from CTN.[32,48]

The sensitivity and specificity of imaging techniques such as MRI to detect a microvascular conflict were reported with wide range (sensitivity 52% to 100%; specificity 29% to 93%).[32,48] The usefulness of MRI in the assessment of TN remains subject to debate. Newer imaging techniques and MR-sequences try to fill this gab. The combination of 3D reconstructed high-resolution balanced fast-field echo (BFFE) images, 3D time-of-flight (TOF) magnetic resonance (MR) angiography, and Gd-enhanced 3D spoiled gradient recalled sequence were able to identify 15 out of 18 CTN patients. This clearly shows that more sophisticated techniques as well as higher resolution of ultra-high field MRI scanners at 7 tesla may be able to revolutionize the diagnostic possibilities for TN in the future.[49,50] One patient diagnosed as PIFP with concomitant nerve vessel conflict did not improve after decompression surgery.[51]

MEDICAL TREATMENT

Treatment options for TN are numerous including both medical and surgical treatment options, but mostly restricted by low clinical evidence. The treatment options of PIFP generally consist of medical treatment with newer and conventional antidepressants (tricyclics and selective-serotonin reuptake inhibitors) as well as antiepileptic drugs. No class I or II evidence exists.[44] Psychological support in terms of behavioural therapy is strongly recommended by many authors in PIFP. In general psychological support should be considered in all chronic pain conditions. Active participation in support groups may help many patients dealing better with their disease and with suggested therapy.[52]

TRIGEMINAL NEURALGIA MEDICAL TREATMENT

General recommendation is to start with medical therapy and consider surgical procedures in patients that are refractory to medical treatment.

First-line treatment options

First-line therapy should be carbamazepine (CBZ; 200-1200 mg/day) and oxcarbazepine (OXC; 600-1800 mg/day) according to current evidence based treatment guidelines.[32,48] Although the evidence for CBZ is stronger,[53-56] OXC has a better safety profile.[57] Approximately 6% to 10% of patients cannot tolerate CBZ.[58] Multiple pharmacologic interactions and a narrow therapeutic window of tolerability further limit the use of CBZ. As the incidence of TN increases with age,[59] age related physiologic changes that alter pharmacokinetics such as reduced hepatic and renal function, blood flow decline, less predictable drug protein-binding and interactions with multiple other medications required due to concomitant illness will come more and more into focus. Hyponatraemia is an issue with both medications and can become a serious problem in elderly patients.

Second line treatment options

Second line treatment is based on very little evidence and includes add-on therapy with lamotrigine (400 mg/day),[60] or a switch to lamotrigine, baclofen (40-80 mg/day)[61] or pimozide (4-12 mg/day). Other antiepileptic drugs have been investigated in small open-label studies. Benefit was suggested from phenytoin, clonazepam, gabapentin, pregabalin, topiramate and valproate, as well as tocainide (12 mg/day).[62] Especially the newer antiepileptic drugs (AED) with less interaction to other medication and lesser side effects will be worth further investigation. The newer AED that were tested within the past two years were topiramate and pregabalin. Pregabalin was tested in an open-label study including 53 patients (14 with concomitant constant facial pain) with one year follow-up. Pregabalin (150-600 mg/day) proved to be effective in reducing TN pain in 74% of patients with minor efficacy reduction over the one-year observational period. Patients without concomitant facial pain showed better response rates (32 of 39, 82%) compared to patients with concomitant chronic facial pain (7 of 14, 50%, $p = 0.020$).[6] Topiramate (100-400 mg/day) was effective in 75% of patients in a very small sample of only eight patients.[63] Two small open label trials investigated the efficacy of levetiracetam (Keppra) in the treatment of TN and showed moderate efficacy. Both studies concluded that randomized controlled trials of levetiracetam will be needed to reconfirm these findings.[64,65]

Alternative treatment options

Alternative treatment options are subcutaneous sumatriptan and botulinum neurotoxin type A (BoNT-A) injections. Sumatriptan and zolmitriptan showed efficacy in controlling allodynic pain following nerve injury in an animal model for trigeminal neuropathic pain.[66] A single-blind study of subcutaneous sumatriptan compared to placebo showed efficacy of sumatriptan on pain symptoms in patients with TN after 15 and 30 minutes compared to placebo. This effect lasted only 7 h on average and limits the clinical usefulness substantially.[67] Several descriptions postulated an analgesic effect of BoNT-A through local release of anti-nociceptive neuropeptides such as substance P, glutamate and calcitonin-gene related peptide (CGRP) inhibiting central and possibly peripheral sensitization.[68] Reports of isolated TN patients treated with BoNT-A and a small, uncontrolled clinical trial (N = 13) showed significant relief from symptoms after treatment with BoNT-A.[69]

MEDICAL TREATMENT FOR PERSISTENT IDIOPATHIC FACIAL PAIN

Treatment of PIFP can be difficult and unsatisfactory due to the modest knowledge of the underlying pathophysiological mechanisms. Sufficient evidence from randomized controlled clinical trials is scarce. Tricyclic antidepressants (TCA) have a moderate efficacy at doses between 25-100 mg/day.[70] Positive results were also reported with selective serotonin- and serotonin-noradrenalin reuptake inhibitors (SSNRI) fluoxetine[71] and venlafaxine[72](Table 2).In the fluoxetine study 178 patients with chronic facial pain but without depression improved in pain severity.[71] Venlafaxine was efficient in 30 patients with PIFP in a randomized, double-blind, crossover comparison study, but only twenty patients completed the trial due to adverse events and/ or non-compliance.[72] A single case report suggested efficacy of topiramate in PIFP treatment.[73] Calcitonin did not show sufficient pain relief in a randomized controlled trial on PIFP.[74] Sumatriptan showed only a transient effect on pain score reduction but this effect was very small so that sumatriptan was not

Table 2 - Treatment options in persistent idiopathic facial pain

Drug/Treatment	Dose
Amitriptyline	25-100 mg/day
Venlafaxine	50-75 mg/day
Fluoxetine	10-20 mg/day
Topiramate	25-100 mg/day
Transcutaneous nerve stimulation (TNS)	Conventional and acupuncture-like
Pulsed radiofrequency treatment (PRF)	Sphenopalatinum ganglion 45 V with max. temp. of 42° for 120 seconds once or several times
Spinal cord stimulation (SCS)	Upper thoracic dorsal column stimulation
Cognitive behavioural therapy	

considered an appropriate therapeutic option for the treatment of PIFP in two randomized placebo-controlled clinical trials.[75,76] Hydrocodone was used successfully in one patient and further supports a central origin of PIFP.[46] Kanpolat et al. showed pain relief after percutaneous trigeminal tract and nucleus ablation, also suggesting that central, rather than peripheral mechanisms may be the dominant factor in this disorder.[77]

Cognitive behavioural therapy is recommended for the treatment of PIFP, but objective assessment of efficacy remains unavailable.[44]

Invasive treatment of persistent idiopathic facial pain

Transcutaneous nerve stimulation (TNS) demonstrated satisfactory analgesia in 45% (N = 20) of patients from conventional and acupuncture-like TNS in a two-year follow-up evaluation.[78] Pulsed radiofrequency (PRF) treatment of the ganglion sphenopalatinum in patients with different orofacial pain conditions including PIFP was evaluated retrospectively. Out of the treated patients 21% reported complete pain relief, and 65% experienced a good to moderate improvement in this observational trial.[79] One patient showed almost complete pain relief from his PIFP following upper thoracic spinal cord stimulation (SCS) for refractory angina.[80]

SURGICAL TREATMENT

Before surgical intervention is being considered in the treatment of TN most experts suggest at least three adequate conventional treatments attempts with different drugs at sufficient dosage. One of the drugs should be carbamazepine. However, there are patients that specifically request surgery despite sufficient pain relief by medication, because they are concerned of disease progression or relapse over time. Medical treatment was patients' least favourite choice when asked what treatment they would choose for themselves[81] mostly because they were afraid of side effects. Surgery in the treatment of TN is generally considered safe and has good efficacy.[82] Zakrzewska and Lopez (2003) suggested a checklist that should be done before surgery in order to improve the evaluation quality of surgical treatment.[83]

Surgical treatment of PIFP is currently not recommended. Trigeminal vascular decompression and deep-brain stimulation of the hypothalamus were not effective. Patients should be preserved from unnecessary dental or surgical procedures as long as a causal understanding of any procedure to alleviate pain is reached.

Surgical treatment of trigeminal neuralgia

A lot of literature on possible interventional treatment for medical refractory TN was presented in the past without sufficient scientific evidence for general treatment recommendation. Currently considered efficient are percutaneous procedures on the Gasserian ganglion, gamma knife surgery, and microvascular decompression. These methods are either destructive (ablative) with intentionally destroying the trigeminal nerve sensory function, or non-destructive decompressive where the normal nerve function is preserved. Gasserian ganglion percutaneous techniques include radiofrequency thermocoagulation (RFT), balloon compression (BC) and percutaneous glycerol rhizolysis (PGR). Pain relief is reported by 90% of patients following these procedures. However, the persistence of this pain relief in many patients does not persist with a recurrence rate of 15-32% within the first year, after three years recurrence rate is between 36%-46%, and half of the patients have a return of symptoms after five years post radiofrequency thermocoagulation. Most common side effects are sensory loss (50%), dysesthesias (6%), anesthesia dolorosa (4%), corneal numbness with risk of keratitis (4%). Gasserian ganglion therapies require short acting anaesthetics, are primarily overnight minor procedures with extremely low mortality.[32,48]

Gamma knife surgery severs the trigeminal nerve at the root in the posterior fossa with a focused beam of radiation. Sixty nine percent of patients were pain free without additional medication after gamma knife surgery with 52% remain pain free at three years follow-up. Pain

relief may be delayed by one month and longer (mean one month). Side effects were sensory complications in 6%, facial numbness 9%-37% which improves over time and paresthesias 6%-13% (no anaesthesia dolorosa).[32,48] Quality of life improves by 88%.[84]

The most sustained pain relief is achieved by microvascular decompression with 90% of patients reporting initial pain relief and over 80% remain pain free at one year follow-up. 75% after three years and 73% after five years. However, to reach the trigeminal nerve in the posterior fossa major surgery craniotomy is required with corresponding complications. The average mortality rate ranges from 0.2%-0.5%, and up to 4% of patients suffer from major problems such as CSF leakage, infarcts, or hematomas. Most common complication is aseptic meningitis (11%), sensory loss (7%), and hearing loss (10%) as long-term complication.[32,48]

More recent investigations have focused mainly on treatment evaluation in long-term follow-up studies.[85,86] and improvement of existing surgical techniques.[87-89] Even thought this has been the most active field of TN research over the past years the vast majority of studies remain on a descriptive level making evidence based comparison and recommendation difficult. The right timing for surgical intervention is yet to be determined.[81] Some TN experts suggest early surgical referral in patients that fail to respond to first-line medical therapy, while others request to have tried at least two different medical regimens including combination therapy before considering surgery including carbamazepine at a sufficient dose. There is no supporting evidence for either of the two opinions. Referral for surgical intervention seems reasonable in TN patients refractory to medical therapy.

EXPERT COMMENTARY

For the correct diagnosis and accurate management of TN a stepwise diagnostic and treatment approach is mandatory. The diagnosis of TN and the distinction between symptomatic TN and classical TN is generally made clinically. Suspicious of STN are bilateral involvement or sensory deficits. In STN MRI should be considered. Blink reflex studies may also be helpful in the distinction of STN and CTN. Carbamazepine (600-1200 mg/day) or oxcarbazepine (600-1800 mg/day) should be the first line therapy. It may be supplemented with or switched to lamotrigine (200-400 mg/day), pregabalin (150-600 mg/day), gabapentin (1800-4200 mg/day) or topiramate (100-400 mg/day). In case the the combination therapy is insufficient baclofen (40-80 mg/day) can be tried. The option of surgical intervention should be discussed early on with the patient and reluctance in referral to surgery may be disadvantageous to the patient after three different medications and at least one combination therapy turned out to provide insufficient pain relieve. The patient should be involved in the decision on what kind of intervention (Gasserian ganglion procedures, gamma knife surgery, microvascular decompression) deems appropriate regarding his own individual wishes and overall medical condition. As a general rule of thumb the consenting physician should remember that older patients with serious co-morbidities should receive less invasive treatment depending on their biological age and current medical status.

The diagnosis of persistent idiopathic facial pain is generally made by elimination of other causes and often requiring multidisciplinary examination and consultation. The underlying pathophysiological mechanisms remain unclear and probably are a combination of peripheral nervous and muscular as well as central and psychological mechanisms. It may represent one end of the spectrum of neuropathic pain when understood in broader terms to also include subclinical neuropathies, pure small-fiber neuropathies, or neurogenic dysfunction in the form of deficient central top-down inhibitory control. Pharmacological treatment with tricyclic antidepressants and selective serotonin-noradrenalin reuptake inhibitors may be tried. Amitriptyline (25-100 mg/day) is commonly considered first line therapy along with venlafaxine (50-75 mg/day) and fluoxetine (10-20 mg/day). When pharmacological therapy fails, PRF treatment of the ganglion sphenopalatinum may be considered. Cognitive behavioural therapy should accompany medical therapy if possible.

Five-year view

Continuous scientific research has worked towards a better understanding of orofacial pain over the past decades and provided an increased awareness of these diverse and very disabling painful conditions in neurologists, neurosurgeons, dentists, and primary care physicians. More recent clinical, electrophysiological, and imaging studies provided greater insight into the underlying pathophysiological mechanisms and will continue to do so in the coming years. The focus of future research should be mainly on the central component and the associated nociceptive and antinociceptive modulatory

networks that influence chronic orofacial pain conditions like TN or PIFP. Better imaging techniques will be necessary to untangle these networks. Controlled studies with long term follow-up will be needed that compare surgical and medical therapy directly with one another and determine the optimal timing for surgical intervention. This also includes studies that investigate second-line medical therapy after the first-line has failed in stepwise, standardized regimen. The development of newer, antinociceptive drugs for the treatment of orofacial pain needs thorough investigation toward treatment efficacy in TN as well as PIFP.

KEY ISSUES

– Trigeminal neuralgia (TN) and persistent idiopathic facial pain (PIFP) are rare, but excruciatingly painful disorders mainly affecting the second and third division of the trigeminal nerve.

– TN with concomitant, dull, less intense, but constant facial pain is a variant of classical TN and has poor response to medical and surgical treatment. This is sometimes hard to distinguish from PIFP.

– Magnetic resonance imaging (MRI) and trigeminal reflex testing are reliable to differentiate symptomatic TN from classical TN, but no reliable test exists to confirm PIFP.

– First-line therapy for TN is carbamazepine (CBZ; 600-1200 mg) or oxcarbazepine (OXC; 600-1800 mg). First-line therapy for PIFP is amitriptyline (25-100 mg) as well as fluoxetine (10-20 mg) and venlafaxine (50-75 mg).

– Lamotrigine (400 mg/day), Baclofen (40-80 mg/day), Pimozide (4-12 mg/day) are second line treatment options for TN.

– TN patients refractory to medical treatment should receive early surgical therapy (percutaneous procedures on the Gasserian ganglion, gamma knife, or microvascular decompression). PIFP patients not responding to medical treatment may be considered for pulsed radiofrequency treatment (PRF) of the sphenopalatine ganglion.

– Cognitive behavioural therapy is generally recommended as supportive treatment in PIFP patients and may be helpful in all other chronic orofacial pain patients as well.

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ORIGINAL ARTICLE

Alodinia é mais frequente nos indivíduos com crises mais intensas de cefaleia e nas mulheres

Allodynia is more frequent in the individuals with more intense attacks of headache and in women

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RESUMO

Objetivo: Identificar a presença de alodinia em alunos com cefaleia primária de uma Instituição de Ensino Superior. **Método:** Foram avaliados 378 alunos (273 mulheres) com idade entre 18 e 45 anos (22 ± 5 anos). Foi utilizado um questionário sobre as características clínicas da cefaleia, baseado nos critérios da ICHD-II (2004), e um questionário para identificação e diferenciação da alodinia cefálica e extracefálica. **Resultados:** Na amostra estudada, 374/378 (98,9%) dos alunos apresentaram cefaleia ao longo da vida [271/273 (99,3%) mulheres e 103/105 (98,1%) homens, p = 0,309; χ^2] e 334/378 (88,4%) queixaram-se de cefaleia nos últimos três meses [248/273 (90,8%) mulheres e 86/105 (81,9%) homens, p = 0,020; χ^2]. Dos alunos com cefaleia nos últimos três meses 331/378 (87,6%) apresentaram alodinia [250/273 (91,6%) mulheres e 81/105 (77,1%) homens, p<0,001; χ^2]. Houve associação entre a intensidade da cefaleia nos últimos três meses e a presença de alodinia [5/12 (41,7%) dos indivíduos com dor leve, 211/236 (89,4%) dor moderada e 83/86 (96,5%) dor intensa; p<0,001; χ^2]. A alodinia cefálica foi mais frequente nas seguintes condições: pentear o cabelo (43,5%), rabo de cavalo (57,3%) nas mulheres; uso de óculos (33,7%), nos homens; uso de chapéu ou boné (53,6% mulheres e 59,3% homens), exposição ao frio (45,6% mulheres e 41,9% homens) e ao calor (56,9% mulheres e 50% homens). A alodinia extracefálica foi mais frequentemente desencadeada na exposição ao calor (60,9% mulheres e 59,3% homens) e ao frio (42,7 mulheres e 38,4% homens). **Conclusão:** Alodinia é mais frequente nas mulheres e em indivíduos durante crises mais intensas de cefaleia.

Palavras-chave: Cefaleia; Migrânea; Alodinia sensitiva

ABSTRACT

Objective: Identifying the presence of allodynia in students with primary headache in a college. **Method:** It was evaluated 378 students (273 women) aged between 18 and 45 years (22 ± 5 years). A questionnaire was used on the clinical characteristics of headache based on ICHD II-2004 criteria, and another one for the identification and differentiation of cephalic and extra-cephalic allodynia. **Results:** In this sample 374/378 (98.9%) students had headaches throughout life [271/273 (99.3%) females and 103/105 (98.1%) men, p= 0.309; χ^2] and 334/378 (88.4%) complained of headache in the last three months [248/273 (90.8%) women and 86/105 (81.9%) men, p=0.020; χ^2]. Of the students with headache in the last three months 331/378 (87.6%) had allodynia [250/273 (91.6%) women and 81/105 (77.1%) men, p<0.001; χ^2]. There was an association between the intensity of the headache in the last three months and the presence of allodynia [5/12 (41.7%) of the individuals with mild pain, 211/236 (89.4%) moderate pain and 83/86 (96.5%) severe pain; p<0.001; χ^2]. Cephalic allodynia was more frequent in conditions such as combing the hair (43.5) the use of ponytail (57.3%), use of glasses (33.7%), use of hat or cap (53.6% women and 59.3% man), exposure to coldness (45.6% women and 41.9% man) and heat exposure (56.9% woman and 50% men). The extra-cephalic allodynia was more frequently triggered in heat exposure (60.9% women and 59.3% men) and coldness (42.7% women and 38.4% men). **Conclusion:** Allodynia is more frequent in women and in individuals with more intense attacks of headache.

Keywords: Headache; Migraine; Sensory allodynia

INTRODUÇÃO

A migrânea é um distúrbio comum e complexo do sistema nervoso central que apresenta como sinais e sintomas dor de cabeça, náuseas e sensibilidade a luz, ao som, ao cheiro ou a movimentação da cabeça.[1] Em indivíduos com cefaleia, em especial migranosos crônicos, a alodinia é frequentemente associada, sendo esta definida como uma percepção de dor ou incômodo ao receber estímulos não dolorosos táteis ou térmicos na pele normal, durante atividades cotidianas.[2,3]

A alodinia, em migranosos, resulta de uma alteração na regulação da via nociceptiva central.[2] O gênero feminino e a frequência das crises de cefaleia também possuem uma forte associação com presença de alodinia nesses pacientes.[2,4]

A alodinia pode se apresentar durante ou após os episódios de migrânea e os indivíduos que a apresentam tornam-se incapazes de executar qualquer ação que envolva o toque na região do rosto, do couro cabeludo ou em algumas regiões corporais. Estudos demonstram que se pode interpretar a alodinia como um marcador da frequência da migrânea e está presente em 80% dos casos, nas fases posteriores de um ataque agudo.[5,6]

A alodinia, durante uma crise de migrânea, geralmente se distribui na região álgica, mas também pode estar presente em outras áreas cefálicas ou extracefálicas.[2] A alodinia cefálica acomete a região da cabeça e tem como principais sintomas referidos pelos indivíduos: dor ao pentear o cabelo, barbear o rosto, uso de óculos, uso de brincos, colares, chapéus, toucas ou atacas de cabelos. Já a extracefálica é caracterizada com dor ou sensação desagradável em uma região corpórea durante uma crise de cefaleia, isso ocorre ao usar roupas apertadas, relógio, pulseira, ao tomar banho, exposição ao calor ou frio.[7]

Desta maneira, tanto a alodinia quanto a cefaleia (migrânea) podem influenciar negativamente o bem-estar e cotidiano do indivíduo, o que acarreta um grande impacto socioeconômico, uma vez que há uma redução da sua produtividade, aumento nos custos referentes aos serviços de saúde, absenteísmo trabalhista, comprometimento do estado psicoafetivo, dentre outras, determinando assim prejuízos diretos na sua qualidade de vida.[8-10]

O objetivo desse estudo é avaliar a presença de alodinia sensitiva em estudantes com cefaleia de uma instituição de ensino superior.

MÉTODO

Este estudo foi realizado na Faculdade ASCES – Associação Caruaruense de Ensino Superior, Caruaru, PE, Brasil. Trata-se de um estudo corte transversal realizado no período de agosto de 2010 a fevereiro de 2011. Foram entrevistados 378 alunos (273 mulheres), regularmente matriculados, com idade entre 18 e 45 anos (22 ± 5 anos). Foram excluídos indivíduos com doença neurológica conhecida e aqueles com algum tipo de cefaleia secundária. Todos os participantes responderam a um formulário contendo informações sociodemográficas.

Para diagnóstico do tipo de cefaleia foi utilizado os critérios da International Headache Society – IHS (ICHD-II, 2004).[11] Alunos que apresentavam tanto cefaleia do tipo tensional (CTT) quanto migrânea foram incluídos no grupo de migranosos. Para avaliar a alodinia foi utilizado um questionário adaptado que identifica e diferencia a alodinia em cefálica e extracefálica.[12] A intensidade da dor foi quantificada pela escala numérica de dor (0-10).

O questionário de alodinia é dividido em duas partes: para avaliar a alodinia cefálica o questionário é composto por 13 questões relativas ao indivíduo apresentar dor ou alguma sensação desagradável quando realiza atividades cotidianas como pentear o cabelo, usar rabo de cavalo, se expor ao calor e/ou ao frio, dentre outras; e para a extracefálica, sete questões, que identificam se o indivíduo possui sensação desagradável ou dor ao usar roupas apertadas ou objetos no punho, tomar banho, dentre outras. As respostas foram estruturadas de forma dicotômica, lidas e respondidas pelo próprio voluntário.

Os dados obtidos na pesquisa são mostrados como média ± erro padrão. Utilizamos o teste Kolmogorov-Smirnov para verificar o tipo de distribuição das variáveis a serem estudadas. Para as variáveis que não apresentaram uma distribuição normal utilizamos o teste não paramétrico de Mann-Whitney. Na análise das variáveis categóricas aplicamos o qui-quadrado (χ^2) ou o teste exato de Fisher, conforme a frequência esperada nas células. O nível de significância considerado como diferente estatisticamente foi $p < 0,05$. Para o processamento e análise dos dados foi o utilizado o programa GraphPad Prism versão 5.0.

RESULTADOS

Na amostra estudada 374/378 (98,9%) dos alunos referiram cefaleia ao longo da vida [271/273 (99,3%) mulheres e 103/105 (98,1%) homens, $p = 0,309$; χ^2] e

334/378 (88,4%) queixaram-se de cefaleia nos últimos três meses [248/273 (90,8%) mulheres e 86/105 (81,9%) homens, p=0,020; χ^2]. Dos alunos com cefaleia nos últimos três meses 331/378 (87,6%) apresentaram alodinia [250/273(91,6%) mulheres e 81/105 (77,1%) homens], p<0,001; χ^2. Houve associação entre a intensidade da cefaleia nos últimos três meses e a presença de alodinia [5/12 (41,7%) dos indivíduos com dor leve e 83/86 (96,5%) dor intensa; OR 38,7 (IC 95% 7,6 - 197), p<0,001] (Figura 1).

As Tabelas 1 e 2 mostram a distribuição percentual das condições que desencadeiam cada uma das formas de alodinia, cefálica e extracefálica, respectivamente.

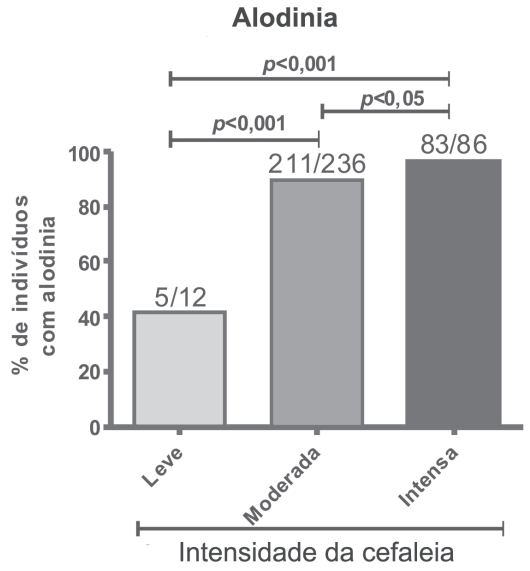

Figura 1. Presença de alodinia nos indivíduos com cefaleia de acordo com a intensidade das crises de cefaleia. Comparações estatísticas utilizando o teste exato de Fisher.

Tabela 1. Distribuição percentual das condições que desencadearam alodinia cefálica entre os gêneros nos 331 alunos com cefaleia

Condições que desencadearam alodinia cefálica	Mulheres %	Homens %
Pentear o cabelo	43,5	11,6
Uso de rabo de cavalo	53,7	-
Barbear-se	-	14,0
Usar óculos	35,5	3,7
Usar lentes de contato	14,5	12,8
Usar brincos	16,1	10,5
Usar cordão no pescoço	24,6	15,1
Usar chapéu ou boné	53,6	59,3
Usar anel no dedo	14,1	9,3
Lavar o rosto	17,3	14,0
Colocar a cabeça no travesseiro	28,6	29,1
Expor-se ao calor	56,9	50,0
Expor-se ao frio	45,6	41,9

A alodinia cefálica foi mais frequente nas condições: pentear o cabelo (43,5%), rabo de cavalo (57,3%), nas mulheres; uso de óculos (33,7%), nos homens; uso de chapéu ou boné (53,6% mulheres e 59,3% homens), exposição ao frio (45,6% mulheres e 41,9% homens) e ao calor (56,9% mulheres e 50% homens). A alodinia extracefálica foi mais frequentemente desencadeada na exposição ao calor (60,9% mulheres e 59,3% homens) e ao frio (42,7 mulheres e 38,4% homens).

Tabela 2 - Distribuição percentual das condições que desencadearam alodinia extracefálica entre os gêneros nos 331 alunos com cefaleia

Condições que desencadearam alodinia extracefálica	Mulheres %	Homens %
Usar roupas apertadas	35,0	30,2
Usar algum objeto no punho (relógio, pulseiras)	15,3	16,3
Cobrir-se com um cobertor mais pesado	12,5	15,1
Tomar banho	14,5	15,1
Expor-se ao calor	60,9	59,3
Expor-se ao frio	42,7	38,4

DISCUSSÃO

No presente estudo, nos 378 voluntários a porcentagem de mulheres afetadas com cefaleia primária e alodinia foi mais elevada quando comparado ao sexo oposto (91,6% e 77,1%, respectivamente), havendo consenso com outros autores,[2,13-15] que também acharam em seus estudos altos índices para tais variáveis. Estudos demonstram que as mulheres apresentam até quatro vezes mais risco de ter cefaleia do que os homens, sendo esse achado unânime na literatura e é possível que a sua explicação seja decorrente das variações hormonais que as mulheres sofrem no decorrer do ciclo menstrual.[13,16]

Estudos mostram que a ação de hormônios no sistema reprodutor feminino, na dor, pode em parte explicar a maior prevalência de sintomas de alodinia sensorial e outras síndromes dolorosas nas mulheres, havendo assim uma associação da mesma com o efeito hormonal.[12] Tal opinião é corroborada por outros estudos que mostram que os níveis de dor na cefaleia e outros distúrbios álgicos, aparecem por todo ciclo menstrual.[12,17-19]

O estudo de Stewart et al. (1995),[20] realizado através de meta-análise, mostrou que o sexo e a idade são fatores responsáveis pela variação nos achados de prevalência da cefaleia. Nesse estudo, os autores apontaram que o gênero é responsável por 15% dessa variabilidade e somado à idade corresponde por 30% de tais diferenças.[8,20]

A alodinia associada a cefaleia vem atraindo interesse por parte dos pesquisadores, visto que é reconhecida como um sinal da sensibilização central durante episódios de cefaleia e fator de risco para a progressão da cefaleia crônica.[7] Com relação à intensidade dolorosa, neste estudo, observou-se que indivíduos que têm cefaleia e alodinia possuem uma maior tendência a dor de moderada a intensa. Estudos com testes sensorias e/ou dados extraídos de questionários sugerem que até 80% dos pacientes com cefaleia possuem crises de alodinia associadas.[17,19,21,22] Tais estudos coincidem com o resultado obtido neste trabalho.

O presente estudo encontrou um grande percentual de indivíduos com cefaleia e da mesma associada com alodinia em indivíduos do sexo feminino estando de acordo com a literatura. Indivíduos com cefaleia além do sofrimento individual apresentam um prejuízo econômico de custos diretos (atenção médica e medicamentosa) e indiretos (redução da sua produtividade, absenteísmo e até mesmo incapacidade durante as crises) o que favorece o comprometimento global da sua qualidade de vida. Diante do exposto, é imprescindível à conscientização e educação a respeito do tema, alertando para a grande importância de uma profilaxia, tratamento e acompanhamento médico, multi e interprofissional adequado, corroborando assim na efetiva redução da frequência e intensidade da cefaleia o que reflete positivamente no bem-estar, na relação custo-benefício, na produtividade e melhora da qualidade de vida do indivíduo.

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