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O ESTUDO DAS CEFALEIAS PRIMÁRIAS NA DOENÇA DE PARKINSON E NA EPILEPSIA DO LOBO TEMPORAL MESIAL ASSOCIADA À ESCLEROSE DO HIPOCAMPO

Jean Costa Nunes

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DEDICATÓRIA

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“Se atravessarmos a vida convencidos que a nossa é a única maneira de pensar que existe, vamos acabar perdendo todas as oportunidades que surgem a cada dia”.

(AKIO MORITA)

RESUMO

Justificativa: As cefaleias primárias apresentam uma alta prevalência na população geral. Embora o avanço no entendimento das cefaleias tenha sido significativo nas últimas décadas, vários aspectos da sua fisiopatologia permanecem obscuros. Isto se deve em grande parte à complexidade dos mecanismos subjacentes e às limitações metodológicas para abordagem de alterações morfológicas e funcionais em humanos. O estudo das cefaleias em pacientes com doenças neurológicas cuja fisiopatologia é parcialmente conhecida pode auxiliar na elucidação de alguns destes mecanismos. **Objetivos**: i) Investigar a prevalência de migrânea e cefaleia do tipo tensional (CTT) em pacientes com doença de Parkinson (DP) e com Epilepsia do Lobo Temporal Mesial associada à esclerose do hipocampo refratária ao tratamento farmacológico (ELTM-EH), comparando com indivíduos da população geral; ii) Investigar a concordância entre o lado de predomínio da cefaleia e o lado da EH em pacientes com ELTM-EH; iii) investigar a concordância entre o lado de predomínio da cefaleia e o lado de início dos sintomas motores em pacientes com DP. **Desenho dos estudos:** Foram realizados três estudos observacionais analíticos, sendo dois casos-controle e um transversal. **Métodos:** Foram incluídos 100 pacientes consecutivos com ELTM-EH acompanhados no Centro de Epilepsia de Santa Catarina entre 2009 e 2010 e 98 pacientes com DP acompanhados no centro de referência para distúrbios de movimento no Hospital Governador Celso Ramos entre 2010 e 2012. O grupo controle foi composto por 100 indivíduos pareados para idade residentes em Santa Catarina e randomicamente selecionados a partir de um estudo prévio de base populacional para investigação de cefaleia no Brasil. Foi aplicado um questionário padronizado de acordo com os critérios da *International Headache Society*. O diagnóstico de cefaleia foi baseado na segunda edição da Classificação Internacional das Cefaleias. **Resultados:** Observou-se uma prevalência significativamente maior ($p = 0,001$) de cefaleia no último ano nos pacientes com ELTM-EH (92%) quando comparados aos controles (73%). Pacientes com DP apresentaram uma prevalência significativamente menor (40,8%) de cefaleia no último ano do que os controles (69,4%; $p = 0,03$). Os pacientes com ELTM-EH unilateral ($n = 42$) apresentaram uma significativa concordância entre o lado de predomínio da cefaleia e o

lado da EH (OR 8,5; IC 95% 2,1 – 35,1; p = 0,003). A cefaleia foi ipsilateral ao lado de início dos sintomas motores da DP em 84% dos pacientes com sintomas unilaterais (p = 0,001). ELTM-EH esteve significativamente associada ao diagnóstico de cefaleia crônica diária (OR 6,1; IC 95% 1,7 – 22; p = 0,005). **Conclusão:** Este trabalho demonstrou uma elevada prevalência de cefaleia em pacientes com ELTM-EH quando comparado aos controles, e quando unilateral, é frequentemente ipsilateral ao lado da EH, além de apresentar uma elevada chance de cronificação. A prevalência de cefaleia foi menor em pacientes com PD que nos controles e congruente com o lado de início dos sintomas motores unilaterais. Embora o delineamento do presente estudo não permita afirmar relações de causa e efeito, as associações descritas sugerem a participação da hiperexcitabilidade cortical e da modulação talâmica na fisiopatologia das cefaleias primárias.

Palavras-chave: Cefaleia. Migrânea. Cefaleia tipo tensional. Epilepsia de Lobo Temporal Mesial. Doença de Parkinson.

ABSTRACT

Justification: Primary headache disorders have a high prevalence in the general population. Although many critical points remain unclear, the understanding of the pathophysiology of headache has advanced greatly during the past years. The reasons for this incomplete knowledge are the complexity of the underlying mechanisms of this condition associated with difficulties in assessing the functional and structural abnormalities of the human brain. The study of headache in patients with other neurological diseases with known pathological abnormalities might help to understand these mechanisms. **Objectives:** Investigate the prevalence of migraine and tension-type headache (TTH) in patients with Parkinson's disease (PD) and mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS), compared with individuals from general population. Moreover, we investigate the lateralizing value of headache in MTLE-HS and the concordance between the predominant laterality of the headache and the side of the initial symptoms of PD. **Study design:** We performed three observational analytical studies, two case-controls and one cross-sectional. **Methods:** One hundred consecutive MTLE-HS patients under comprehensive presurgical evaluation were evaluated from 2009 to 2010. We also interviewed 98 consecutive patients with an established diagnosis of PD assisted at Hospital Governador Celso Ramos between 2010 and 2012. The control group consisted of 100 age-matched individuals who were randomized from a nationwide Brazilian headache database. A standardized questionnaire was applied according to the criteria of the International Headache Society (IHS). Headache diagnosis was based on the second edition of the International Classification of Headache Disorders (ICHD-II). **Results:** There was a significantly higher prevalence of headache (92%) among the MTLE-HS patients when compared with the controls (73%; $p = 0.001$). PD patients showed a significantly lower prevalence (40.8%) of headache in the previous year than controls (69.4%) ($p = 0.03$). MTLE-HS patients with unilateral HS and predominantly unilateral headache (irrespective of the type), presented pain ipsilateral to the HS (OR 8.5; CI 95% = 2.1-35.1; p=0.003). The headache side was ipsilateral to the side of PD onset in 21 patients (84%), with a concordance of 85.7% on the left side and 81.8% on the right side ($p < 0.01$). Chronic daily headache (CDH) was significantly

associated with MTLE-HS (OR 6.1, CI 95% 1.7 - 22, $p = 0.005$) but we did not find any association between the diagnosis of migraine or tension-type headache and MTLE-HS. **Conclusion:** This study demonstrated a high prevalence of headache in MTLE-HS patients, often ipsilateral to the HS side and with an increased likelihood to a chronic course. The prevalence of primary headache was significantly lower in patients with PD than controls and the predominant side of headache was ipsilateral to the side of initial motor signs of PD. Although the design of this study did not allow inferences about causes and effects, the associations described in the both diseases favor the role of the hyperexcitability and the abnormal modulation of thalamus in the pathophysiology of primary headaches.

Key words: Headache. Migraine. Tension-type headache. Epilepsy. Hippocampal sclerosis. Parkinson's disease.

LISTA DE TABELAS

LISTA DE ABREVIATURAS E SIGLAS

CTT	Cefaleia do Tipo Tensional
DP	Doença de Parkinson
EH	Esclerose Hipocampal
ELTM	Epilepsia do Lobo Temporal Mesial
ILAE	International League Against Epilepsy
PD	Parkinson's Disease

SUMÁRIO

1. INTRODUÇÃO

1.1. CEFALEIAS

1.1.1. Aspectos Gerais

A cefaleia é o sintoma neurológico mais prevalente e consiste em uma experiência vivenciada por praticamente todas as pessoas [1]. As cefaleias podem indicar a presença de uma doença grave, entretanto, na maioria dos casos, consistem em desordens benignas categorizadas como cefaleias primárias, tais como a migrânea e a cefaleia do tipo tensional (CTT) [2]. Entretanto, apesar de benignas, ocasionam um sofrimento substancial para os pacientes e seus familiares, além de acarretarem um ônus social significativo devido à alta taxa de prevalência na população geral [3].

As cefaleias representaram o sétimo sintoma mais frequentemente referido por pacientes que consultaram nas unidades de cuidados primários nos Estados Unidos [4]. Em uma revisão sistemática realizada em colaboração por inúmeros países europeus que incluiu 49 estudos diferentes e um total de 205.000 participantes adultos, identificou-se uma prevalência de 53% de cefaleia no último ano entre adultos, sendo 61% entre as mulheres e 45% entre os homens [5]. Este mesmo estudo identificou uma prevalência de cefaleia no último ano de 53% entre crianças e adolescentes, em uma população de 37.000 participantes provenientes de 12 estudos restritos a esta faixa etária [5].

Um estudo transversal realizado entre os anos de 2008 e 2009 entre oito países da União Europeia investigou os custos diretos (medicações, hospitalizações, investigações complementares) e indiretos (absenteísmo e redução da produtividade laboral) relacionados à cefaleia [6]. Este estudo encontrou um gasto pessoa/ano de aproximadamente €1.222 entre os pacientes migranosos e €303 entre os pacientes com CTT. Os gastos anuais totais relacionados à cefaleia foram estimados em, aproximadamente, €173 bilhões entre os países participantes do estudo [6]. Estes dados enfatizam a necessidade de intensos

esforços da área médica, científica e de gestão em saúde pública para ampliação da assistência a estes pacientes, oferecendo um amplo sistema de atendimento que permita fazer o diagnóstico precoce e tratamento apropriado. O incentivo à área científica se torna prioritário, visto que o conhecimento parcial da fisiopatologia das cefaleias primárias restringe o surgimento de novas terapêuticas mais efetivas.

1.1.2. Classificação das Cefaleias

Devido ao amplo espectro de doenças que podem se manifestar através de cefaleia, utiliza-se atualmente uma abordagem sistemática para classificação e diagnóstico. A Classificação Internacional das Cefaleias 2ª. edição [7], é mundialmente reconhecida e amplamente utilizada por clínicos e pesquisadores. De acordo com esta classificação as cefaleias podem ser categorizadas como primárias e secundárias. As cefaleias classificadas como secundárias apresentam causas identificáveis, tais como lesões neoplásicas, infecciosas ou vasculares, e apresentam-se divididas em oito categorias distintas.

As cefaleias primárias estão subdivididas em quatro grandes categorias: a) migrânea; b) CTT; c) cefaleia em salvas e outras cefaleias trigêmino-autonômicas; e d) outras cefaleias primárias. Dentre as cefaleias primárias, as duas categorias que abrangem todas as subclassificações de migrânea e de CTT, tornam-se substancialmente mais relevantes em relação às demais, em virtude de suas altas prevalências.

1.1.3. Migrânea

A migrânea é uma doença neurológica episódica e com fisiopatologia complexa, que se manifesta através de episódios recorrentes de cefaleia latejante e unilateral, com intensidade moderada a severa e, frequentemente, associada a náuseas, fotofobia, fonofobia e exacerbação pela atividade física rotineira [8]. Em um terço dos pacientes a cefaleia é precedida por sintomas neurológicos transitórios que frequentemente são

visuais, mas que podem envolver outras funções, tais como a linguagem, motricidade e outras modalidades sensitivas [9].

A migrânea pode ser subdivida em dois tipos principais: a) migrânea sem aura e b) migrânea com aura. A migrânea sem aura é o subtipo mais comum, tendo uma frequência de crises maior e geralmente sendo mais incapacitante. A migrânea com aura se manifesta através de crises acompanhadas ou antecedidas por sintomas neurológicos focais reversíveis que geralmente se desenvolvem gradualmente em cinco a dez minutos e que duram menos de 60 minutos [7].

A migrânea consiste em uma doença com hereditariedade complexa com taxas de penetrância altas, tais como 50%, e com herança multifatorial poligênica [10-12]. A complexidade da doença depende predominantemente da interação de múltiplos genes e de fatores ambientais [10-12]. Atualmente, a maior parte do conhecimento sobre a biologia molecular associada à migrânea originou-se da investigação de migrânea hemiplégica familiar, uma forma rara de cefaleia com herança autossômica dominante [11,12]. Entretanto, os genes que contribuem para outros subtipos mais comuns de migrânea ainda precisam ser estudados [10].

O fator predominante que distingue os pacientes com migrânea dos demais doentes é a susceptibilidade às ativações recorrentes dos sistemas trigeminovascular e cervical superior [13]. A recorrência da cefaleia pode ser devida a uma susceptibilidade à ativação das vias álgicas pela presença de um limiar relativamente baixo à dor ou devido à perda da modulação inibitória [13]. Um número elevado de evidências indiretas indicam que o desenvolvimento da migrânea depende da ativação e da sensitização de vias aferentes sensoriais trigeminais que inervam os tecidos cranianos, especialmente as meninges e os vasos de maior calibre [14,15]. Contudo, se os estímulos nociceptivos se originam na pia-máter, na dura-máter, ou nas fibras aferentes periarteriais extra-cranianas, permanece incerto [15]. Aventa-se a possibilidade de que os três setores possam estar envolvidos em diferentes subtipos de migrânea [15].

Os fatores químicos que desencadeiam as crises migranosas permanecem parcialmente desconhecidos, sendo

provavelmente múltiplos [16]. O peptídio relacionado ao gene da calcitonina (CGRP) e a substância P aumentam os fatores pró-inflamatórios, vasoativos e substâncias algiogênicas: citocinas, 5-HT, histamina e óxido nítrico. Estes mediadores ativam as células endoteliais, mastócitos e plaquetas [16]. Estas células aumentam os níveis de aminas extracelulares, derivados do ácido araquidônico, peptídios e íons. Além disso, estes mediadores aumentam a síntese e a liberação de CGRP, gerando um ciclo vicioso [17]. A inflamação neurogênica estimula as fibras sensitivas, que transmitem impulsos para o sistema nervoso central através dos axônios trigeminais até o tronco encefálico. Estes estímulos são processados no núcleo trigeminal caudal e posteriormente estas informações seguem através do tronco cerebral até o tálamo e, por conseguinte, o córtex [16].

A cefaleia dos pacientes migranosos parece estar associada a uma facilitação dos impulsos nociceptivos. Este fenômeno conhecido como sensitização ocorre tanto no nível periférico quanto central, conforme demonstrado em modelos experimentais de migrânea [18]. A sensitização periférica está relacionada ao desencadeamento da inflamação neurogênica nos vasos sanguíneos meníngeos. Os neurônios liberam fatores vasoativos e peptídios neuroinflamatórios que ativam os nociceptores periféricos, traduzindo estes estímulos nocivos em impulsos nervosos [16].

Sequencialmente ao processo de sensitização periférica, um mecanismo paralelo de sensitização central tem sido postulado durante a evolução das crises migranosas. Este mecanismo tem sido fundamentado em resultados de pesquisas com modelos experimentais. Estudos em animais demonstraram que os neurônios de segunda ordem localizados no complexo trigêmino-cervical (raízes dorsais de C1 e C2; porção caudal do núcleo do nervo trigêmio) apresentaram uma hiperresponsividade prolongada a estímulos mecânicos inócuos ou a estimulação térmica facial, após a estimulação meníngea sequencial por agentes inflamatórios [8]. Os neurônios trigêmino-vasculares de terceira ordem localizados na região posterior do tálamo mostraram respostas anômalas persistentes tanto a estímulos cefálicos quanto extra-cefálicos [8]. Este mecanismo

independente é favorecido pelo fato de que um bloqueio anestésico dos nervos aferentes durais em animais, não inibe a hipersensibilidade prolongada aos estímulos cutâneos [8].

A relevância da ativação dos núcleos do tronco encefálico e do diencéfalo é enfatizada por inúmeros autores, os quais argumentam que em pacientes com migrânea estes estímulos periféricos poderiam ser anormalmente interpretados, fazendo com que estímulos normais oriundos das meninges sejam percebidos como sensações álgicas. O tálamo consiste na estrutura fundamental para o processamento e integração dos estímulos nociceptivos. O núcleo ventral póstero-medial (VPM) é o principal núcleo talâmico para onde convergem estímulos nociceptivos e de onde são retransmitidos estímulos para as regiões específicas do córtex cerebral [19]. A transmissão de estímulos do complexo trigêmino-cervical para o VPM é conhecida, sendo indiretamente possível a recepção de estímulos crânio-vasculares. Estes dados sugerem que tanto o tálamo quanto o córtex cerebral estão envolvidos no processamento de experiências dolorosas e na recepção de sinais consequentes da cefaleia [19].

Embora a patogenia da Depressão Alastrante Cortical (DAC) seja complexa e apenas parcialmente entendida, aumentam as evidências de que as auras típicas da migrânea são oriundas deste fenômeno. Este fenômeno ictal compartilha mecanismos patogênicos com a epilepsia, envolvendo canais iônicos e neurotransmissores, proporcionando também uma hiperexcitabilidade anormal do córtex cerebral [16].

1.1.4. Cefaleia do Tipo Tensional (CTT)

A CTT é a cefaleia primária mais frequente, com uma prevalência durante toda a vida de aproximadamente 78% [20]. Entretanto, esta prevalência apresenta variações de acordo com a idade, sexo e localização geográfica [20]. Em ambos os sexos, o pico de prevalência encontra-se na faixa etária entre 30 e 39 anos, sendo que esta taxa é influenciada negativamente com o aumento da idade [21]. A CTT tem uma distribuição geográfica heterogênea, sendo que estudos realizados no continente europeu

reportam prevalências anuais acima de 80%, e nos continentes asiático e americano entre 20 e 30% [22]. No Brasil, a prevalência anual de CTT foi de 13% (15,4% para os homens e 9,5% para as mulheres) e a prevalência de provável CTT foi de 22,6% [23].

A CTT apresenta três subtipos distintos: a) CTT episódica infrequente, na qual a cefaleia ocorre, em média, um dia ou menos por mês; b) CTT episódica frequente, na qual a cefaleia ocorre entre um e 14 dias por mês, durante os últimos três meses; e c) CTT crônica, na qual ocorre mais de 15 dias por mês [7].

A etiologia da CTT permanece incerta. Os mecanismos periféricos miofasciais e a regulação central anômala das estruturas que processam os estímulos nociceptivos estão implicados na patogênese da CTT. Entretanto, a relevância de cada um destes mecanismos apresenta uma variação interpessoal e é influenciada pela frequência da cefaleia [24].

A sensação dolorosa pericraniana é o achado extra-cefálico mais bem documentado e reprodutível em pacientes com CTT [25]. Jensen *et al*. encontraram uma correlação positiva entre a frequência de CTT crônica e o dolorimento muscular a palpação [26]. Contudo, esta relação não foi encontrada em todos os pacientes com CTT, tampouco está limitada aos dias de cefaleia, sugerindo que a sensação dolorosa pericraniana não é, simplesmente, uma consequência linear da cefaleia. Postula-se que a inflamação local poderia desencadear a dor e o dolorimento pericraniano [25]. Contudo, os estudos falharam em demonstrar esta associação através de resultados consistentes. A sugestão de que pacientes com CTT teriam um aumento da isquemia também foi investigada, porém não foram observadas concentrações anormais de lactato nos músculos investigados [27].

Os mecanismos centrais envolvidos na CTT são pouco investigados. Um aumento da frequência da CTT está correlacionado com um significativo decréscimo no limiar sensitivo, manifestando-se através de um aumento na sensibilidade nociceptiva e, também, para outros estímulos inicialmente inócuos. O surgimento de dores em outros locais do corpo e o envolvimento de outras modalidades sensoriais sugerem que a sensitização central possa se expandir para

neurônios de terceira ordem localizados possivelmente no tálamo [25].

1.2. EPILEPSIAS

As epilepsias são síndromes neurológicas crônicas caracterizadas pela ocorrência de crises epilépticas recorrentes [28-30]. Acredita-se que mais de 65 milhões de pessoas em todo o mundo sofram de alguma forma de epilepsia, fazendo com que esta seja a desordem neurológica mais comum após os acidentes vasculares cerebrais, gerando grandes custos para os sistemas de saúde pública [31]. As estimativas sobre a ocorrência de epilepsia variam substancialmente entre as populações estudadas, sendo aproximadamente 50 doentes por 100.000 habitantes em países desenvolvidos [32].

Há poucos estudos epidemiológicos sobre as epilepsias no Brasil. Contudo, levando-se em consideração que a população brasileira (Censo Demográfico, IBGE 2010) era de 190.732.694 pessoas, e supondo-se que a prevalência de epilepsia no Brasil fosse igual à descrita em Porto Alegre [33] (16.5/1.000 de epilepsia ativa), estima-se atualmente em torno de 3.147.000 pacientes com epilepsia no país. Estes dados colocam a epilepsia como um problema de saúde relevante no país e no mundo, justificando claramente a necessidade de investimentos na capacitação de recursos tanto na área de assistência como também em pesquisa de alta qualidade.

Em 2010, a *International League Against Epilepsy* (ILAE) publicou uma revisão sobre as terminologias e classificações utilizadas em epilepsia [34]. Considerou-se que crises epiléticas generalizadas seriam as crises epiléticas originadas em algum ponto, contudo com rápida abrangência de conexões distribuídas bilateralmente. Estas conexões bilaterais poderiam incluir estruturas corticais e subcorticais, sendo que não necessariamente incluem todo o córtex. Embora neste tipo de crise epilética o início da crise possa parecer localizado, a localização e a lateralização não são consistentes de uma crise para outra [34]. As crises epiléticas focais foram conceituadas como crises que se originam em regiões limitadas a um hemisfério. Estas crises

podem ser bem localizadas ou mais amplamente distribuídas, e nota-se uma consistência no início ictal de uma crise para outra, com uma propagação preferencial que pode envolver o hemisfério contralateral [34].

A epilepsia do lobo temporal (ELT) é a forma mais comum de epilepsia parcial, representando em torno de 30-40% entre todos os casos de epilepsia. A ELT inclui um grupo heterogêneo de epilepsias cuja zona epileptogênica localiza-se no lobo temporal, entretanto com diferentes etiologias, prognósticos, respostas terapêuticas e variações nas manifestações clínicas [35]. A ELT é dividida em dois grupos principais, mesial ou lateral, de acordo com a localização da zona epileptogênica no lobo temporal. A epilepsia do lobo temporal mesial (ELTM) é responsável pela imensa maioria dos casos, em detrimento da epilepsia do lobo temporal lateral cujo foco está localizado no neocórtex do lobo temporal e seria responsável por apenas 10% dos casos [35].

Em torno de 20 a 30% dos pacientes com epilepsia não obtém controle satisfatório das crises mesmo com uso adequado de fármacos sendo candidatos à avaliação pré-cirúrgica [36]. A cirurgia tornou-se o tratamento padrão para pacientes com epilepsia focal refratária aos tratamentos medicamentosos, especialmente àqueles com achados positivos de neuroimagem [37]. Resultados de meta-análises realizadas entre os anos de 1985 e 2003 indicaram que cerca de dois terços dos pacientes permanecem livres de crises nos primeiros 2 a 3 anos após a cirurgia [37].

Estima-se que 70-80% das séries cirúrgicas de casos intratáveis farmacologicamente sejam de ELTM associada à esclerose do hipocampo (ELTM-EH) [36]. Esta síndrome é frequentemente associada à história de um "insulto precipitante inicial" (IPI) na infância, podendo este ser uma crise epiléptica prolongada associada ou não a febre, ou outro insulto neurológico (ex. traumatismo crânio-encefálico, meningite). Depois do insulto inicial ocorre um período de latência variável (em geral entre cinco e dez anos) que se caracteriza por um período livre de sintomas ou complicações. Após este período começam as crises espontâneas. Inicialmente, as crises epilépticas espontâneas

podem ser controladas com uso de fármacos, mas para alguns pacientes as crises tornam-se refratárias ao tratamento ou até mesmo ao procedimento cirúrgico [38]. O período latente entre o insulto inicial e o início das crises recorrentes parece estar associado à epileptogênese e envolve alterações estruturais e bioquímicas que levam às crises espontâneas. Histopatologicamente destacam-se os processos reativos astrogliais e as perdas neuronais, além da formação de brotamentos aberrantes nas fibras musgosas, vistos tanto em modelos animais quanto em tecidos humanos oriundos de ressecções neurocirúrgicas [39]. Paralelamente às alterações estruturais, inúmeras modificações bioquímicas e de transdução de sinal têm sido reportadas. Interessantemente uma proporção significativa de pacientes não relatam a ocorrência de nenhum evento sugestivo de IPI, sendo que outros iniciam as crises recorrentes imediatamente após o IPI ou a primeira crise na infância, não apresentando nenhum período latente.

A perda neuronal foi a primeira alteração morfológica observada na ELTM-EH. Alguns estudos referem que a perda neuronal seja decorrente do evento precipitante [40], porém outros estudos referem que a perda neuronal poderia ser progressiva como resultado das crises repetidas [41]. A EH é histologicamente caracterizada por uma perda segmentar de neurônios piramidais nos setores CA1, CA3 e CA4 da formação hipocampal em diferentes proporções. De acordo com a classificação de Blümcke *et al* [42], a EH pode ser dividida nos seguintes padrões: EH clássica, EH predominantemente em CA1, esclerose do endofólio e EH severa. Esta classificação é baseada em dados morfológicos e semi-quantitativos de acordo com as perdas neuronais em diferentes setores, tendo valor prognóstico independente no seguimento pós-cirúrgico. As modificações oriundas das crises epiléticas que ocasionam a formação de brotamentos aberrantes também são desconhecidas. Como estas alterações nas células granulosas do giro denteado estariam relacionadas à epileptogênese também são questionáveis. Alguns pesquisadores postulam que as células da granulosa se tornariam hiperexcitáveis com os brotamentos recorrentes [43]. Esta hipótese é favorecida pelo fato de as fibras musgosas serem

glutamatérgicas e pela formação de circuitos excitatórios dentro da camada molecular interna [43]. O papel da astrogliose na epilepsia também permanece incerto. A contribuição da astrogliose na epileptogênese pode se originar do fato que astrócitos reativos liberam neurotrofinas que levam ao brotamento de projeções axonais e formação de novas sinapses levando a hiperexcitabilidade [44]. Os astrócitos também desempenham um papel chave na recaptação de glutamato na fenda sináptica e sua participação no processo de epileptogênese vem ganhando atenção na literatura científica [45].

Embora a ELTM seja reconhecidamente uma doença predominantemente cortical, tornou-se relevante o estudo sobre os mecanismos subcorticais que podem também estar envolvidos nas crises espontâneas. Uma fenomenologia clínica frequentemente observada em pacientes com ELTM-EH são as crises parciais complexas. Neste tipo de crise observa-se uma perturbação parcial ou completa da consciência, sem que necessariamente ocorra uma expansão da atividade epilética a extensas áreas corticais dos lobos frontal e temporal bilateralmente. Estas manifestações podem dever-se ao comprometimento das funções de formação da memória declarativa e linguagem durante o estado hipersincrônico do lobo temporal, bem como a uma modulação ou propagação da crise para núcleos localizados no tronco encefálico e/ou no diencéfalo. Desta forma, sugere-se que a atividade cortical anormal de pacientes com epilepsia possa modular e ser modulada direta ou indiretamente através de conexões subcorticais [46]

Os pacientes com epilepsia, em especial os com ELTM, podem apresentar além dos sintomas ocasionados pelas crises epilépticas, outras comorbidades que acarretam dificuldades sociais e físicas, tanto quanto distúrbios psiquiátricos e neuropsicológicos que reduzem significativamente a qualidade de vida dos pacientes. Um estudo demonstrou que mais de 58% dos pacientes com epilepsia refratária à terapêutica clínica apresentam ou apresentaram alguma desordem psiquiátrica durante toda a vida [47]. Dalmagro *et al.* relataram uma prevalência de 35,4% de desordens do eixo I e 7% de desordens do eixo II em pacientes com ELTM [48]. Os pacientes com ELTM queixam-se também

com frequência de distúrbios do sono, dificuldades de aprendizagem, perda de atenção, entre outros sintomas.

Um sintoma que aparentemente não estaria diretamente relacionado às crises epiléticas e frequentemente observado na prática clínica é a cefaleia. Embora esta associação seja muito discutida nas últimas décadas, pouco se sabe sobre o substrato fisiopatológico comum às duas condições. Ambas apresentam características que se sobrepõem tais como a recorrência das crises, associação a desordens psíquicas e emocionais, alguns fatores desencadeantes, sintomas associados e relacionados às modalidades sensitivas, alterações visuais, associação com sintomas gastrointestinais e relação com alterações hormonais. Também é relevante o papel de algumas drogas antiepiléticas no tratamento das cefaleias, reforçando o fato de que as similaridades observadas na clínica possam se estender, ao menos em parte, às bases fisiopatológicas. A presença da hiperexcitabilidade cortical e das estruturas subcorticais poderia ser o fator comum às duas condições.

1.3. DOENÇA DE PARKINSON

A doença de Parkinson foi descrita originalmente por James Parkinson em 1817, no clássico "Ensaio sobre a paralisia agitante". É a segunda doença neurodegenerativa mais frequente, sendo superada somente pela doença de Alzheimer [49]. Os sintomas cardinais relacionados à doença de Parkinson incluem tremor de repouso, bradicinesia, rigidez e instabilidade postural. Também são frequentes as manifestações não-motoras, tais como sintomas psiquiátricos, desordens do sono, constipação, parestesias, dentre outras.

A prevalência da doença de Parkinson em países industrializados foi estimada em 0,3% da população geral e de, aproximadamente, 0,5 a 1% em pessoas na faixa etária entre 65 e 69 anos [50]. A prevalência aumenta com a idade, chegando a 1-3% em pacientes com mais de 80 anos. Em geral, as taxas de incidência em estudos que incluíram todas as faixas etárias variam entre 1,5 e 22 casos por 100,000 pessoas/ano. Em estudos restritos apenas a indivíduos acima de 65 anos, a taxa de

incidência foi consideravelmente maior, em torno de 160 casos por 100,000 pessoas/ano, pressupondo o surgimento de 59,000 novos casos por ano nos Estados Unidos [51].

O diagnóstico da doença de Parkinson em vida é baseado em achados exclusivamente clínicos, em virtude da ausência de achados laboratoriais e radiológicos específicos. Os critérios da *UK Parkinson's Disease Society Brain Bank* [52] incluem a presença de: 1) bradicinesia e 2) tremor de repouso, ou rigidez muscular ou instabilidade postural. Os critérios de exclusão são [52]: 1) história de acidentes vasculares encefálicos repetidos; 2) história de traumas cranianos repetidos; 3) história definida de encefalite; 4) início dos sintomas após uso de neurolépticos; 5) mais de um familiar afetado; 6) remissão sustentada; 7) sintomas estritamente unilaterais após um período de três anos; 8) paralisia da mirada supranuclear, sinais cerebelares ou sinal de Babinski; 9) envolvimento autonômico precoce e severo; 10) demência severa precoce; 11) presença de tumor cerebral ou hidrocefalia comunicante em exame de imagem; 12) ausência de resposta ao tratamento com levodopa ou 13) exposição a MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine).

Os fatores genéticos envolvidos na doença de Parkinson foram por muito tempo considerados incomuns, pois a maioria dos pacientes apresenta doença esporádica e estudos iniciais em gêmeos monozigóticos e dizigóticos mostraram taxas de concordância igualmente baixas [53]. Os conhecimentos relacionados aos fatores genéticos da doença de Parkinson ampliaram-se de forma substancial com a descoberta de inúmeros locus e genes. O gene LRRK2 tem emergido como o gene mais envolvido tanto com as formas familiares e esporádicas [54]. Inúmeras variantes do gene LRRK2 e SNCA têm sido associadas com o aumento do risco de doença de Parkinson idiopática [54].

A doença de Parkinson é caracterizada pela perda progressiva e seletiva de neurônios, incluindo-se neurônios dopaminérgicos na pars compacta da substância negra, neurônios serotoninérgicos e catecolaminérgicos em núcleos do tronco encefálico, neurônios colinérgicos no núcleo basal de Meynert, neurônios hipotalâmicos, pequenos neurônios corticais no giro do cíngulo e no córtex entorrinal, além de perdas neuronais no bulbo

olfatório, gânglios simpáticos e parassimpáticos [55]. Os mecanismos responsáveis pelas perdas neuronais na doença de Parkinson permanecem obscuros. Evidências crescentes sugerem que a morte neuronal na pars compacta da substância negra se deva a apoptose [55]. Todavia, inúmeros fatores podem estar implicados na degeneração neuronal relacionada à doença de Parkinson, incluem-se dentre estes disfunções mitocondriais, estresse oxidativo, ação de excitotoxinas e mecanismos imunológicos [55].

Os achados histopatológicos da doença de Parkinson são caracterizados pela perda neuronal e pela presença de corpos de Lewy e neuritos de Lewy. Os corpos de Lewy são inclusões hialinas eosinófilas, esféricas, com centro denso e hialino, circundado por um halo claro de aparência, frequentemente, "targetoide". Tanto os mecanismos que levam a formação, quanto a relevância dos corpos de Lewy na patogênese da doença de Parkinson, permanecem incertos. Os neuritos de Lewy são processos neuronais que contém agregados proteicos positivos para alfa-sinucleína, comumente visualizados nos setores CA2/CA3 da formação hipocampal e na substância negra [56]. Embora tanto os corpos de Lewy quanto os neuritos sejam constituídos por alfa-sinucleína, os neuritos apresentam em termos absolutos, uma quantidade superior em relação aos corpos de Lewy [57].

O conhecimento a respeito das modificações que ocorrem na atividade cerebral com a perda de neurônios dopaminérgicos tem aumentado substancialmente nas últimas décadas [58]. As conexões intrínsecas dos gânglios da base foram descritas há aproximadamente três décadas com a formulação dos conceitos de vias "direta" e "indireta" [59]. Estas duas vias originam-se de diferentes populações de neurônios estriatais, os quais são modulados de diferentes formas pela dopamina [58]. A via "direta" é uma projeção inibitória monossináptica entre os neurônios estriatais que expressam receptores D1 de dopamina além de substância P e neurônios do globo pálido interno e da pars reticulata da substância negra. A via "indireta" é uma conexão polissináptica que envolve uma projeção inibitória oriunda dos neurônios estriatais que expressam receptores D2 de

dopamina e encefalina para neurônios do globo pálido externo, e subsequentemente para projeções inibitórias diretas entre o globo pálido externo e o globo pálido interno, ou através de projeções indiretas através do núcleo subtalâmico [58].

Assim a ativação de neurônios estriatais que estimulam a via "direta" poderia resultar na inibição do globo pálido interno e da pars reticulata da substância negra, que poderiam levar a uma redução da inibição das projeções dos neurônios tálamo-corticais, levando a uma facilitação do movimento. Entretanto a ativação da via "indireta" ocasionaria um efeito oposto tendo como resultado final a supressão do movimento [59]. Postula-se que a depleção da dopamina estriatal resulte em um incremento da atividade inibitória na via "indireta" e uma atividade reduzida da via "direta", levando a um aumento do "*output"* inibitório do globo pálido interno para o tálamo. Assim alguns sintomas relacionados com a doença de Parkinson, tal como a bradicinesia podem ser interpretados com um desequilíbrio entre os dois sistemas estriato-palidais ocasionados pela depleção de dopamina, no qual uma restrição da via "indireta" leva a uma redução de movimentos intencionais (atividade cortical) [60].

1.4. TÁLAMO E CÓRTEX CEREBRAL

Todas as áreas do córtex cerebral conectam-se através de projeções aferentes e eferentes a diversas estruturas subcorticais, entretanto, enfatiza-se a relevância da relação entre o córtex cerebral e o tálamo. Esta estreita relação pode ser exemplificada pelas distinções entre as doenças que ocasionam lesões exclusivamente corticais e doenças que ocasionam lesões conjuntas entre o tálamo e o córtex. Nestas os danos geralmente são proporcionalmente potencializados, visto que a excitação talâmica é necessária para quase todas as atividades corticais. Estas conexões são acionadas no sentido tálamo-córtex e regressam no sentido córtex-tálamo. Assim, quando algumas conexões talâmicas são interrompidas, as funções executadas pela área cortical correspondente são quase totalmente perdidas. O córtex cerebral opera em estreita relação com o tálamo sendo

considerado por muitos autores como uma unidade funcional, chamada de sistema tálamo-cortical [61].

Esta relação tornou-se ainda mais estudada após a invenção do eletroencefalograma (EEG) por Hans Berger em 1924. O EEG passou a ser um instrumento fundamental para o estudo da atividade elétrica cerebral cortical refletindo os padrões de descarga do sistema tálamo-cortical, um componente necessário para a manutenção do estado de vigília [62].

O tálamo é o maior componente do diencéfalo e está subdividido em núcleos que possuem conexões aferentes e eferentes com inúmeras outras regiões cerebrais. Quase todas as modalidades sensoriais passam pelo tálamo para chegar ao córtex, com exceção da olfação. Alguns dos núcleos talâmicos recebem informações sensoriais oriundas dos receptores e vias sensoriais gerais e especiais. Alguns destes núcleos projetam-se para as respectivas áreas corticais somatossensoriais. Os demais núcleos apresentam distintas funções e apresentam estreitas relações com as áreas motoras e de associação corticais, além de participarem do sistema límbico e do mecanismo de sono-vigília.

O núcleo ventral posterior é responsável pela percepção consciente da sensibilidade somática oriunda dos receptores de superfície e conduzidos pelas via coluna dorsal-lemnisco medial e pelos tratos espinotalâmicos e trigeminotalâmicos. A partir deste núcleo, alguns neurônios se projetam para o córtex cerebral homolateral através da cápsula interna e terminam na área somestésica primária do lobo parietal.

A condução nervosa dolorosa rápida através do trato neo-espinotalâmico tem origem nos receptores de superfície e após sinapse na lâmina I do corno dorsal da medula, também termina no complexo ventrobasal talâmico, sendo que algumas destas fibras também seguem para as áreas somatossensorias primárias do lobo parietal. Já a condução nervosa dolorosa lenta através do trato paleo-espinotalâmico projeta-se para os núcleos da formação reticular, para a área tectal mesencefálica e para a substância cinzenta periaquedutal, sendo que apenas uma pequena parcela dos neurônios se projeta até o complexo ventrobasal talâmico. Esta via estimula os neurônios da formação reticular e os núcleos

intralaminares talâmicos, que por sua vez ativarão o córtex cerebral.

O núcleo ventral lateral (VL) possui as divisões anterior (VLa) e posterior (VLp), sendo estas duas subdivisões essenciais para o aprimoramento da atividade voluntária. O VLp está conectado à área motora primária no giro pré-central, enquanto o VLa apresenta projeções para as áreas pré-motoras e motoras suplementares. A atividade destes núcleos é realizada através do circuito córtico-estriato-tálamo-córtex.

Entretanto, a homeostase do sistema tálamo-cortical pode ser perturbada por inúmeras doenças sistêmicas e por doenças primariamente neurológicas. Dentre as doenças sistêmicas tornam-se exemplos frequentes os distúrbios metabólicos ocasionados pela insuficiência renal, pela insuficiência hepática, pela liberação de mediadores inflamatórios na sepse e pelas intoxicações exógenas, dentre inúmeras outras causas. Dentre as doenças primariamente neurológicas encontram-se exemplos nas doenças degenerativas, doenças vasculares, doenças metabólicas, doenças infecciosas e inflamatórias.

Entre os distúrbios neurológicos primários, duas doenças apresentam mecanismos fisiopatológicos distintos em relação à excitação e à inibição relativas do sistema tálamo-cortical sendo estas, respectivamente, ELTM-EH e a doença de Parkinson. Apesar de estas duas doenças apresentarem características morfológicas e fisiológicas incomparáveis, com inúmeras particularidades que as tornam entidades únicas, em relação à ativação do sistema tálamo-cortical especulamos que elas teriam papéis opostos. Além disso, as duas doenças apresentam, em sua maioria, manifestações clínicas e alterações estruturais assimétricas, uma característica peculiar que possibilita além da comparação entre si, a comparação entre o hemisfério doente (ou com doença mais avançada) e o hemisfério não-doente (ou com doença mais leve).

A doença de Parkinson, conforme discutido anteriormente, é ocasionada inicialmente por uma perda de neurônios dopaminérgicos na substância negra. Esta perda começa a ser clinicamente notada a partir do terceiro estágio da doença e se amplia com o avanço do processo patológico. Com a perda das

projeções estriatais dopaminérgicas, os neurônios estriatais da via "direta" tornam-se insuficientemente ativados e os neurônios da via "indireta" insuficientemente inibidos. Este desequilíbrio resulta em uma excessiva ativação do núcleo subtalâmico. Consequentemente, isto resulta em uma hiperativação do globo pálido interno e uma inibição da atividade tálamo-cortical [63]. A partir do quarto estágio da doença, também surgem alterações patológicas relevantes nos núcleos intralaminares talâmicos que exacerbam de forma substancial a inibição da atividade tálamo-cortical [63]. Já nos estágios 5 e 6, alterações estruturais tornam-se relevantes nas áreas pré-motoras e nas áreas associativas sensoriais [63]. Por motivos ainda não elucidados, as perdas neuronais não são equânimes e as manifestações clínicas, tais como as alterações histopatológicas são assimétricas. Os sintomas motores têm uma predileção por um dos lados do corpo, mantendo-se mais evidentes neste lado até as fases avançadas da doença. Em relativa correspondência, as alterações patológicas estruturais e funcionais tornam-se mais difusas e acentuadas no hemisfério cerebral oposto ao início da sintomatologia clínica até as fases mais avançadas do processo neurodegenerativo.

A ELTM-EH está associada à fenômenos comportamentais complexos, perturbação da consciência, posturas distônicas e alterações neuroendócrinas que sugerem uma propagação da atividade elétrica para a uma rede neural envolvendo estruturas situadas fora do lobo temporal. Neste contexto, uma estrutura que desperta um interesse especial é o tálamo, visto que recebe inúmeras projeções neurais oriundas do lobo temporal mesial, possuindo amplas conexões recíprocas com outras regiões corticais e outras estruturas subcorticais [64]. A propagação da atividade epiléptica através do tálamo poderia ocasionar perdas neuronais ou menos intensamente modificações plásticas decorrentes da atividade excitatória contribuindo para anormalidades estruturais ou funcionais extra-temporais [64]. Estudos prévios sugerem que os núcleos mediais talâmicos estão envolvidos no circuito das crises límbicas. Além disso, algumas subdivisões mediais talâmicas, tais como o núcleo médio-dorsal, tem conexões densas e recíprocas com o córtex mesial temporal e com o neocórtex [65]. Estudos em animais relataram que

associações entre perdas neuronais e alterações sinápticas nas subdivisões mediais talâmicas podem ocasionar um incremento da excitabilidade dos circuitos talâmicos [66]. Este fato possivelmente se deve ao desenvolvimento de conexões aberrantes no sistema límbico que podem resultar na reorganização funcional deste sistema [67]. Ademais, o grau e a distribuição das alterações talâmicas estão relacionadas com a topografia e extensão das alterações neocorticais, favorecendo o conceito de que o tálamo tem um papel significativo nas conexões patológicas da ELTM-EH [65]. Estas alterações morfológicas e funcionais talâmicas são mais pronunciadas no lado que apresenta esclerose hipocampal.

1.5. JUSTIFICATIVA

O espectro das doenças que acometem o sistema nervoso é amplo e inclui inúmeras entidades nosológicas prevalentes que ocasionam limitações de curta e longa duração, acarretando um ônus emocional, financeiro e social para os pacientes, familiares e gestores em saúde pública. De acordo com um estudo do *European Brain Council*, as doenças cerebrais ocasionaram custos de aproximadamente 800 bilhões de euros em 2010. Dentre as doenças mais relevantes que acometem o sistema nervoso central destacam-se as cefaleias primárias, tanto pela alta taxa de prevalência na população geral, como pelo sofrimento físico e psíquico que impõem a estes pacientes. A migrânea e a CTT acometem especialmente pessoas em uma faixa etária produtiva originando encargos sociais significativos, sendo estes diretamente relacionados aos custos com medicações e cuidados médicos e, indiretamente, às altas taxas de absenteísmo e redução da atividade laboral.

Embora sejam indiscutíveis os avanços relacionados à fisiopatologia das cefaleias primárias nas últimas décadas, ainda permanecem muitos pontos obscuros a serem elucidados. Estas dificuldades podem ser atribuídas, em parte, à complexidade dos mecanismos envolvidos na patogênese destas doenças, mas, sobretudo às dificuldades para acessar as modificações morfológicas e fisiológicas encefálicas ocasionadas pela

migrânea e pela CTT. A ausência de modelos animais que representem de forma equânime as manifestações que ocorrem em seres humanos acrescenta uma barreira substancial à evolução científica nesta área. Os modelos animais existentes, frequentemente, estão relacionados a tipos específicos de cefaleia, em geral ligados a síndromes genéticas, e esbarram nas dificuldades para generalização dos achados. Deve-se ainda levar em consideração que a sintomatologia álgica relacionada às cefaleias é subjetiva, tornando ainda mais difícil a interpretação dos achados em animais.

A ELTM-EH consiste em uma doença conhecida pela hiperexcitabilidade cortical com possibilidade de modulação diencefálica que acarreta crises epiléticas espontâneas, frequentemente precedidas, acompanhadas ou seguidas por cefaleias e descrita no passado por muitos autores como fazendo parte de um "continuum". A investigação das cefaleias primárias nesta população também possibilitaria a investigação indireta de características morfológicas radiológicas, histopatológicas e funcionais que possam estar envolvidas nos mecanismos das cefaleias primárias.

A doença de Parkinson constitui um modelo de deficiência dopaminérgica ocasionada pela perda de neurônios na pars compacta da substância negra. Esta perda das projeções dopaminérgicas ocasiona um desequilíbrio entre as vias "direta" e "indireta" que resulta em uma inibição relativa da atividade tálamo-cortical, conforme discutido anteriormente.

Diante de tantas dificuldades metodológicas para os estudos experimentais, a investigação das cefaleias primárias em doenças neurológicas com mecanismos fisiopatológicos parcialmente elucidados, distintos e assimétricos surge como uma alternativa plausível para elaboração de novas hipóteses.

1.6. HIPÓTESES

Pacientes com ELTM-EH apresentam uma prevalência de cefaleia maior do que indivíduos da população geral.

Os pacientes com ELTM-EH unilateral apresentam cefaleia predominantemente ipsilateral ao lado da esclerose do hipocampo.

Pacientes com doença de Parkinson apresentam uma prevalência de cefaleia menor do que indivíduos da população geral.

Dentre os pacientes com doença de Parkinson que apresentam cefaleia unilateral, a cefaleia está mais frequentemente localizada no mesmo lado de início dos sintomas motores da doença.

2. OBJETIVOS

2.1. OBJETIVO GERAL

Investigar as características clínicas das cefaleias primárias (migrânea e cefaleia do tipo tensional) em pacientes com doença de Parkinson e em pacientes com Epilepsia do Lobo Temporal Mesial associada à Esclerose do Hipocampo.

2.2. OBJETIVOS ESPECÍFICOS

- Investigar a prevalência de migrânea e CTT em pacientes com ELTM-EH e comparar com indivíduos da população geral;
- Avaliar a concordância entre o lado de predomínio da cefaleia e o lado da EH em pacientes com ELTM-EH unilateral;
- Investigar a prevalência de migrânea e CTT em pacientes com doença de Parkinson e comparar com indivíduos da população geral;
- Avaliar a associação entre o lado de predomínio da cefaleia e o lado de início dos sintomas motores na doença de Parkinson.

3. CAPÍTULO I

HIPPOCAMPAL SCLEROSIS AND IPSILATERAL HEADACHE AMONG MESIAL TEMPORAL LOBE EPILEPSY PATIENTS

Nunes JC, Zakon DB, Claudino LS, Guarnieri R, Bastos A, Queiroz LP, Walz R, Lin K. (Published in: ***Seizure 2011;20(6):480-4***).

Abstract

Purpose: To investigate the frequency and patterns of headache in a well-defined and homogeneous group of mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) patients.

Methods: One hundred consecutive MTLE-HS patients under comprehensive presurgical evaluation were evaluated from May 2009 to April 2010. A standardized questionnaire was applied according to the criteria of the International Headache Society (IHS). Headache diagnosis was based on the second edition of the International Classification of Headache Disorders (ICHD-II).

Results: Ninety-two patients (92%) had at least one headache episode during the previous 12 months. Migraine occurred in 51.9% of patients and tension-type headache (TTH) in 39.1%. Patients with migraine presented higher frequency (p=0.002) and severity of episodes (p<0.001), as well as lateralized pain (p=0.001) than individuals with TTH. MTLE-HS patients with unilateral HS and predominantly unilateral headache (irrespective of the type), presented pain ipsilateral to the HS (OR 8.5; CI 95% = 2.1-35.1; p=0.003).

Conclusions: Headache is a frequent clinical symptom of lateralizing value, which may share common pathophysiology with epileptogenesis among MTLE-HS patients.

INTRODUCTION

Epilepsy is a chronic condition that causes great impact in patient's quality of life and on the health care budget. Its prevalence is approximately 0.5 to 1% in general population [1]. In developing countries, the incidence and prevalence rates are higher due to the high proportion of young individuals and their

hygiene and public health conditions [2]. Twenty percent of the epilepsies are medically intractable and mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) has been recognized as a well-defined surgically remediable epileptic syndrome [3-5]. The adequate selection of these patients for surgery depends on the concordance of clinical, neuroimaging and electroencephalographic (EEG) data [4].

Few abnormalities may be found on general neurologic interview and examination other than the seizures among MTLE-HS patients, as facial asymmetry with lower facial weakness contralateral to HS [6]. These symptoms or signs may be a clinically useful clue that may assist in lateralizing the site of seizure onset, aiding in the presurgical selection of these patients.

The association between epilepsy and headache is still poorly understood although it has been recognized for a long time [7]. Both migraine and epilepsy are chronic neurological disorders manifested as paroxysmal episodes of transient brain dysfunction with clinical characteristic symptoms often including gastrointestinal and autonomic manifestations, postictal lethargy, altered level of consciousness, visual disturbances, hormonal involvement, dizziness, numbness, hemiparesis and aphasia [7-9]. Welch et al.[10] proposed that an altered excitability status of occipital cortex may be an important pathogenic factor for migraine, probably lowering the threshold for the development of cortical spreading depression (CSD). Moreover, experimentally induced CSD in human neocortical slices was able to induce sharp potentials [11], representing a possible link between migraine and epilepsy.

We investigated the prevalence, clinical patterns and lateralizing value of headache in a well-defined and homogeneous group of MTLE-HS patients.

METHODS

This was an observational, cross-sectional and analytic study. From May 2009 to April 2010, we interviewed all MTLE-HS patients undergoing presurgical evaluation in Centro de Epilepsia de Santa Catarina (CEPESC), Florianópolis, SC, Brazil, due to refractory epilepsy.

The comprehensive presurgical evaluation consisted of a detailed clinical history, neurologic examination, cerebral 1.5 T magnetic resonance imaging (MRI), neuropsychological and psychiatric studies, and psychosocial assessments. Patients also underwent 2–6 days of continuous video-EEG monitoring with 32-channel EEG recording, with electrodes placed according to 10-10 system on the temporal lobes. All patients had clear MRI findings consistent with HS and concordant interictal and ictal EEG data. Hippocampal sclerosis was defined if atrophy, an increased T2-weighted signal, a decreased T1-weighted signal, and disrupted internal structure of the hippocampus were present on visual inspection of MRI pictures [12-14]. The epileptogenic zone was determined by predominantly ipsilateral interictal epileptic abnormalities (70% cutoff) and unequivocal unilateral seizure onset recorded during prolonged video-EEG monitoring.

Clinical features were recorded prospectively according to a specific protocol developed for this study. Patients' previous medical charts were also reviewed. The exclusion criteria [15-17] were: 1) focal neurological abnormalities on physical examination suggesting a constellation other than MTLE-HS; 2) generalized or extra-temporal EEG spikes; 3) marked cognitive impairment on neuropsychological testing suggesting a more widespread disease other than MTLE-HS and subject to compromising the interview.

A standardized questionnaire was applied according to the criteria of the International Headache Society (IHS) by one researcher (DBZ) blinded for all the clinical, radiological and EEG data of patients. Ten percent of these interviews were also applied in the same patient by the first author (JCN) to assure the reproducibility of the questionnaire. Headache diagnosis was made by a board certified neurologist (JCN) based on the second edition of the International Classification of Headache Disorders (ICHD-II) [18], according to the headache episodes presented in the previous year. Patients were divided into two groups: 1) Migraine patients and 2) Tension-type headache (TTH) patients. The headache diagnosis was blinded for all the clinical, radiological and EEG data related to the epileptic syndrome including the MRI findings.

Clinical and demographic characteristics included age, gender and schooling. The use of sodium valproate was also controlled due to its effect on headache prophylaxis. Regarding headaches, the following features were analyzed: presence of headache episodes in lifetime and in the previous year; frequency; age of onset; pattern; predominant side; severity (assessed using an analogical scale: 0-10; 0, no pain and 10, worst possible pain); duration; associated symptoms and symptomatic medicines used during the events. For those patients presenting more than one type of headache, the most severe and troublesome type was taken into consideration for this study. According to the temporal relation between headaches and seizures, headache was classified as interictal (non-temporal relation) and peri-ictal (well-established temporal association). Some patients referred both, but the peri-ictal type was the only one considered for the analysis of its lateralizing value in relation to HS.

This study was approved by the Ethics Committee on Human's Research of our hospital and informed consent was obtained from all patients.

Statistical analysis:

Statistical analysis was performed using the SPSS for Windows 17.0 (SPSS Inc., Chicago, IL, USA).

Categorical variables were analyzed by Fisher's exact test. Continuous variables were analyzed by Student's t-test (parametric distribution) or Mann-Whitney U test (non-parametric distribution) accordingly. Posteriorly, continuous variables were categorized in order to allow analysis of the association between the headache type and clinical, demographic and neuroimaging variables by binary logistic regression. Also, the association between the side of HS and unilateral headache was analyzed by binary multiple logistic regression.

The association between the age of epilepsy onset (age of recurrent seizures) and the age of headache onset was analyzed by simple linear regression.

The "p" levels lower than 0.01 were considered significant. This more stringent criterion for the "p" level of

significance was based on the Bonferroni adjustment for multiple tests [19].

RESULTS

A hundred consecutive patients were interviewed. Their median age was 38 (29-45) years and 55 (55%) were female.

Clinical and demographic variables according to the presence of headache are demonstrated in Table 3.1. Headache episodes were referred by 92 (92%) of all patients and they were classified according to ICHD-II [18]. There were no statistical differences concerning gender, age of first epileptic seizure, frequency of seizures and MRI findings between patients with and without headache ($p > 0.32$). There was a non-significant trend for lower age of epilepsy onset ($p = 0.12$) and longer duration of epilepsy ($p = 0.19$) among patients presenting headache.

The most frequent diagnosis was migraine without aura in 24 patients (24%) followed by probable migraine in 19 (19%). Furthermore, infrequent episodic TTH was diagnosed in 15 (15%) and migrainous-type chronic daily headache (CDH) in 8 (8%) patients.

Table 3.1. Clinical variables of MTLE-HS patients with and without headache

Variables	All Patients *n* = 100 (%)	Presence of headache		*p*
		Positive *n* = 92 (%)	Negative *n* = 8 (%)	
Gender[a]				
Man	45 (45%)	42 (45.7%)	3 (37.5%)	0.73
Woman	55 (55%)	50 (54.3%)	5 (62.5%)	
Age (years)[b]				
Median (IQ range 25-75)	38 (29-45)	38 (29-45.7)	36 (23.7-43)	0.40
Education (years)[b]				
Median (IQ range 25-75)	7 (4-10)	7(4-10)	5.5 (3.2-10.5)	0.39
Age at first epileptic seizure (yo)[b]				
Median (IQ range 25-75)	4 (1.1-12)	4 (1-12)	10 (5.3-18.9)	0.32
Age at epilepsy onset (yo)[b]				
Median (IQ range 25-75)	12 (7-18)	12 (6-18)	16.5 (15.2-19.5)	0.12
Duration of epilepsy (years)[b]				
Median (IQ range 25-75)	24 (15-31)	24 (15-32)	19 (13-24.7)	0.19
Frequency of seizures (month)[b]				
Median (IQ range 25-75)	3.5 (2-12)	3 (1.2-11.5)	5 (2.2-11.5)	0.53
Hippocampal sclerosis[a]				
Left	46 (46%)	43 (46.7%)	3 (37.5%)	0.51
Right	46 (46%)	41 (44.6%)	5 (62.5%)	
Bilateral	8 (8%)	8 (8.7%)	0 (0%)	

IQ 25-75 = Interquartile Range 25% and 75%; MTLE-HS = mesial temporal epilepsy with hippocampal sclerosis; yo = years-old.
a Fisher's exact test
b Mann-Whitney U test

The association among the type of headache, clinical, demographic and neuroimaging data as well as headache severity and frequency are presented in Table 3.2. The Crude Odds Ratio indicates the level of association between the analyzed variables and migrainous headache. Migraine occurred in 51.9% while TTH in 39.1% patients. As expected, patients with migraine had higher frequency ($p < 0.006$), duration ($p < 0.02$), severity ($p < 0.001$) and lateralized pain ($p < 0.002$) than TTH ones. In comparison to interictal headache, peri-ictal headache was 3.9 times more associated to migraine than TTH (OR 3.9; CI 95% 1.4

– 11.2; p = 0.01). There were no statistical differences concerning the age of epilepsy onset (p = 0.95), HS side (p > 0.65) and treatment with sodium valproate (p = 0.45) between migranous and TTH patients. Patients with annual-monthly headache episodes presented 2 seizures/month [IQ(25-75)= 2-3], while patients with 2-14 or more than 14 headache episodes/month, presented 4 [IQ(25-75)= 2-12] and 8 [IQ(25-75)= 2-16] seizures/month respectively (p < 0.01), suggesting a positive association between the frequency of seizures and headache episodes.

Table 3.2. Clinical, demographic and neuroimaging patterns according to headache type of MTLE-HS patients

Variables	Headache n = 92 (%)	Migraine n = 56 (51.9%)	TTH n = 36 (39.1%)	Crude Odds Ratio (CI 95%)	p value
Age of onset[b]					
Median (± SD)	16.4 (5.6-27.2)	16.4 (5.6-27.2)	16.3 (5.4-27.2)	N.A.	0.95
Headache frequency[a]					
Annual or monthly	23 (25)	7 (12.5)	16 (44.4)	1.0	
2-14 days per month	47 (51)	33 (58.9)	14 (38.9)	5.4 (1.8-16)	0.002*
≥15 days per month	22 (23)	16 (28.6)	6 (16.7)	6.1 (1.7-22.2)	0.006*
Duration of headache[a]					
<1 hour	9 (9.8)	3 (5.4)	3 (10)	1.0	
1-3 hours	27 (29.3)	11 (19.6)	14 (46.7)	1.4 (0.3-6.7)	0.69
4-12 hours	14 (15.2)	8 (14.3)	6 (20.0)	2.7 (0.5-15.3)	0.27
13-24 hours	25 (27.2)	20 (35.7)	4 (13.3)	8 (1.5-43.7)	0.01*
>24 hours	17 (18.5)	14 (25)	3 (10.0)	9.3 (1.4-60.2)	0.02*
Headache severity[b]					
Median (± SD)	7.6 (5.4-9.8)	8.4 (6.8-10)	6.2 (3.9-8.5)	N.A.	< 0.001*
Side of headache[a]					
Bilateral	46 (50.0)	18 (32.1)	28 (77.8)	1.0	
Left	24 (26.1)	20 (35.7)	4 (11.1)	7.8 (2.3-26.5)	0.001*
Right	22 (23.9)	18 (32.1)	4 (11.1)	7 (2.0-24.1)	0.002*
Side of HS[a]					
Bilateral	8 (8.7)	5 (8.9)	3 (8.3)	1.0	
Left	43 (46.7)	29 (51.8)	14 (38.9)	1.2 (0.2-5.9)	0.79
Right	41 (44.6)	22 (39.3)	19 (52.8)	0.7 (0.1-3.3)	0.65
Headache and seizures[a]					
Interictal headache	20 (21.7)	7 (12.5)	13 (36.1)	1.0	
Peri-ictal headache	72 (78.3)	49 (87.5)	23 (63.9)	3.9 (1.4-11.2)	0.01*
Sodium valproate treatment[a]					
No	73 (79.3)	46 (82.1)	27 (25)	1.0	
Yes	19 (20.7)	10 (17.9)	9 (75)	0.6 (0.2-2.1)	0.45

CI = confidence interval; HS = Hippocampal Sclerosis; MTLE-HS = Mesial Temporal Lobe Epilepsy with Hippocampal Sclerosis; NA = Not applied; TTH = Tension-type Headache;
a Binary Logistic regression
b Student's t-test.
* Statistically significant at p < 0.01

Among the 42 patients with predominantly unilateral headache and unilateral HS, the headache was ipsilateral to HS in 31 patients (17 left and 14 right). Patients with headache occurring predominantly on the left side was 8 times more associated with left HS in comparison to the right HS (OR 8.5; CI 95% 2.1-35.1; p = 0.003) irrespectively to the headache type (Table 3.3).

Table 3.3. Association between the predominant side of headache and the side of the HS.

Variables	Patients	Side of Hippocampal sclerosis		CrudeOdds Ratio (CI 95%)	
	Headache *n* = 42 (%)	Left *n* = 24 (51%)	Right *n* = 18 (49%)		*P*
Predominant side of headache[a]					
Right	21 (25)	7 (16.3)	14 (34.1)	1.0	
Left	21 (25)	17 (39.5)	4 (9.8)	8.5 (2.1-35.1)	0.003*
Classification of headache[a]					
Tensional	33 (39)	14 (32.6)	19 (46.3)	1.0	
Migraine	51 (61)	29 (67.4)	22 (53.7)	1.6 (0.3-9.5)	0.61

CI = confidence interval

[a] Binary Logistic Regression.

* Statistically significant at $p < 0.01$

DISCUSSION

This study showed a higher prevalence of headache among MTLE-HS patients (92%) in comparison to the 80.8% in the general population of our city previously reported in an epidemiological study [20].

Other studies have attempted to demonstrate an association between epilepsy and headaches. Headache episodes were associated with the occurrence of seizures in 15-62% of patients with epilepsy, in which 55% were of migrainous-type and 37% tension-type, being 34-60% exclusively peri-ictal [21-24]. Our prevalence was higher than previously reported, probably related to higher frequency of seizures and duration/severity of epilepsy of our patient population, selected from a tertiary health care center.

Among patients with unilateral HS, we evidenced a significant association between the predominant side of headache

and the side of HS. Our findings are in agreement with other studies, which demonstrated association between the headache lateralization and seizure onset zone in patients with temporal lobe epilepsy [25]. Our study also provided evidence for the possible relation between headache and epilepsy by demonstrating the temporal association between the seizure frequency and headache episodes.

Our findings may have implications in the current knowledge of the headache pathophysiology. Despite the fact that the association between epilepsy and headache has already been discussed for many years, its pathophysiology remains obscure. There seems to be an agreement regarding the side of headache and HS, which would suggest a common underlying brain dysfunction. In fact, the most frequently accepted mechanism for the relation between vascular and neuronal function in migraine aura is the CSD described by Leão (1944) [26]. CSD consists of a wave of cortical hyperarousal followed by an inhibitory wave, which is evidenced by the reduction of 15-53% of cerebral blood flow during visual auras in occipital cortex contralateral to the affected visual field. Interestingly, only one of our patients presented migraine with aura. After the binary multiple logistic regression analysis we demonstrated an association between the HS and predominant headache side which remained significant, independently of the type of headache (migraine x TTH). The epilepsy surgery enables the direct visualization of cortical vessel vasodilation during an epileptic attack. It has also been extensively documented by ictal Single Photon Emission Computed Tomography (SPECT) [27]. Nitric oxide (NO) is involved in the regulation of basal cerebral circulation during hypercapnia, neuronal activation and ictal brain vasodilation [28]. The NO is an important neurotransmitter in the glutamatergic excitatory synapses [29] which may be the common link related with the neuronal hyperactivity and brain hyperperfusion during epileptic seizures and headache episodes [30].

There are some limitations that need to be acknowledged regarding the present study. The first one concerns the cross-sectional design and the second one concerns the frequency of headache episodes, which was based on retrospective recall by

the patient. We tried to avoid this recall bias by taking into account only the headache episodes occurred within the last year. Furthermore, the findings in our study may not be applied to all epilepsy patients due to the fact that it included only refractory patients from a tertiary health care center.

In conclusion, physicians should be familiar with the principles of the diagnosis and treatment of both epilepsy and headache. Specific strategies must be applied to both comorbidities once they are often seen in association. Further prospective, placebo-controlled, double-blind and randomized studies are required to determine the best therapeutic strategy to treat headache in patients with epilepsy.

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4. CAPÍTULO II

HEADACHE AMONG MESIAL TEMPORAL LOBE EPILEPSY PATIENTS: A CASE-CONTROL STUDY

Nunes JC, Zakon DB, Claudino LS, Guarnieri R, Nunes FC, Queiroz LP, Lin K, Walz R . (Published in: ***J Neurol Sci 2011;306:20-3***).

Abstract

Purpose: Epilepsy and headache are two chronic disorders that are characterized by recurrent attacks, but the relationship between them is not completely understood. **Methods:** Using a structured questionnaire, we investigated the prevalence of headache during the previous year in a homogeneous group of 100 patients with mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS). The control group consisted of 100 age-matched individuals who were randomized from a nationwide Brazilian headache database.

Results: There was a significantly higher prevalence of headache (92%) among the MTLE-HS patients when compared with the controls (73%; $p = 0.001$). Chronic daily headache (CDH) was significantly associated with MTLE-HS (OR 6.1, CI 95% 1.7 - 22, $p = 0.005$). We did not find any association between the diagnosis of migraine or tension-type headache and MTLE-HS.

Conclusions: This study showed that MTLE-HS increases the likelihood of a headache diagnosis. In addition, CDH was more prevalent among the MTLE-HS patients, which supports a common pathophysiological mechanism for epilepsy and headache.

INTRODUCTION

Although a possible association between epilepsy and headache has long been reported, this relationship is poorly understood [1]. Migraine and epilepsy are both chronic disorders that are characterized by recurrent neurologic attacks accompanied by gastrointestinal, autonomic and psychological features [2]. Other symptoms, including post-event lethargy, impaired or loss of consciousness, visual disturbances, visual and

hormonal triggering factors, vertigo, paresthesias, hemiparesis and aphasia, are commonly observed in both conditions [3].

Ottman and Lipton reported that individuals with epilepsy were 2.4 times more likely to have migraine compared to their relatives without epilepsy [4]. Yankovsky *et al.* found that 59% of patients with medically intractable partial epilepsy had recurrent headaches [5]. In addition, among migraineurs, there is a higher prevalence of epilepsy compared to that expected in the general population. Baulac *et al.* found a 5.9% prevalence of epilepsy in a population of migraineurs, which is substantially higher than the 0.5 – 1% that is reported in the general population [6].

Considering both a genetic [7-9] and clinical point of view, the concept of a "*continuum*", or perhaps an "overlap", between headache and epilepsy is gaining increasingly strong evidence-based support [10-12]. Headache attacks can originate at either the cortical or subcortical level, whereas an epileptic focus arises cortically and can be modulated at the subcortical level. However, the mechanisms that underlie this association remain uncertain. A shared neuronal hyperexcitability may be the pathophysiological link that accounts for the bidirectional comorbidity of these two disorders and for the efficacy shown by antiepileptic drugs for both conditions.

Because epileptic patients and physicians are usually more concerned about seizures than headache episodes, headache symptoms are often neglected [13]. Comprehensive study and a multidisciplinary approach may contribute to a reduction in the morbidity of these diseases. Physicians should consider this association when dealing with epileptic and headache patients so that they can accurately diagnose and appropriately treat them.

We investigated the prevalence of headache during the previous year among refractory mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) patients compared to a non-epileptic control group. We also compared the demographic and clinical variables that are related to headache to evaluate some of the possible associations with refractory MTLE-HS.

METHODS

This was a cross-sectional case-control study. We interviewed one hundred consecutive patients with an established diagnosis of MTLE-HS according to the Commission on Classification and Terminology of ILAE [14]; these patients were possible candidates for epilepsy surgery and were undergoing presurgical evaluation between May 2009 and April 2010 at the Centro de Epilepsia de Santa Catarina (CEPESC), which is a regional referral center for refractory epilepsy in the state of Santa Catarina in southern Brazil.

The comprehensive presurgical evaluation consisted of a detailed clinical history, a neurologic examination, a cerebral 1.5 T MRI, neuropsychological and psychiatric studies and psychosocial assessments. Patients also underwent 2 – 6 days of continuous video-EEG monitoring and 32-channel EEG recording with placement of the electrodes over the temporal regions according to the 10-10 system. All patients had clear MRI findings that were consistent with unilateral HS and concordant interictal and ictal EEG data. Hippocampal sclerosis (HS), which was defined as the combination of atrophy, an increased T2-weighted signal, a decreased T1-weighted signal, and disrupted internal structure of the hippocampus, was observed on visual inspection of the MRI images [15-17]. The epileptogenic zone was determined by predominantly ipsilateral interictal epileptic abnormalities (70% cutoff) and unequivocal unilateral seizure onset that were recorded during prolonged video-EEG monitoring.

Clinical features were prospectively recorded according to a specific protocol developed for this study. Patients' previous medical charts were also reviewed. The exclusion criteria [18-21] were as follows: 1) focal neurological abnormalities on physical examination that suggested a disorder other than MTLE-HS; 2) generalized or extra-temporal EEG spikes; and 3) marked cognitive impairment on neuropsychological testing that suggested a disease that was more widespread than MTLE-HS that could compromise the success of the interview.

A standardized questionnaire was administered according to the criteria of the International Headache Society (IHS) by one

researcher (DBZ) who was blinded to the clinical, radiological and electrophysiological patient data. To ensure the reproducibility of the questionnaire, 10% of the interviews were also administered to the same patients by the first author (JCN) of this study. Headache diagnosis was determined by a board-certified neurologist (JCN) and was based on the second edition of the International Classification of Headache Disorders (ICHD-II) [22]; the diagnosis included only the headache episodes that presented within the previous year. The headache diagnosis was determined without access to the clinical, radiological and electrophysiological data related to the epileptic syndrome. Patients were divided into three groups: 1) migraine, 2) tension-type headaches (TTH) and 3) chronic daily headache (CDH).

Demographic variables included age and gender. Clinical variables included the presence or absence of headache during the year prior to the interview and the diagnosis of migraine, TTH or CDH. For patients who presented with more than one type of headache, the most severe, frequent and incapacitating type was considered for this study. CDH was diagnosed if headaches occurred at least 15 days per month for a minimum of three months.

One hundred control subjects were obtained from a nationwide population-based study database that contained 3,848 randomized subjects from all 27 Brazilian states who were interviewed between September 2006 and January 2007 [23]. All subjects who were living in Santa Catarina state (n = 122) according to this database were considered for our study, but to allow pairing of patients and controls according to age, 22 were excluded because they were older than 65 years. All control subjects completed the same interview as the MTLE-HS patients, excluding the epilepsy-related questions.

This study was approved by the Ethics Committee of our hospital and informed consent was obtained from all patients.

Statistical Analysis:

Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were analyzed using the independent Student's *t*-test, and

categorical variables were analyzed using the non-parametric Chi-Square test.

The association between refractory MTLE-HS and the presence or absence of headaches as well as the different types of headaches was determined by binary logistic regression. Statistical significance was determined by "*p*" values less than 0.01. This more stringent significance criterion for the "*p*" values was based on the Bonferroni adjustment for multiple tests [24]. The strength of the association between factors and outcome was expressed by odds ratios (OR). All results are described with 95% confidence intervals (CI 95%).

RESULTS

Clinical and demographic variables are shown in Table 4.1. The mean age of the MTLE-HS patients was 37 (SD=1.1) and that of the control subjects was 39.4 (SD=1.0). Moreover, 45 (45%) of the MTLE-HS patients were men compared to 39 (39%) in the control group. Ninety-two (92%) of the patients with refractory MTLE-HS recalled having at least one type of headache during the last year compared to 73 (73%) from the control group (OR 4.3, CI 95% 1.8 – 9.9, $p = 0.001$).

Table 4.1. Clinical variables of patients with mesial temporal lobe epilepsy associated to hippocampal sclerosis (MTLE-HS) and non-epileptic control group.

Variables	MTLE-HS n = 100	Controls n = 100	Crude Odds Ratio (CI 95%)	*p*
Age in years				
Mean (SD)	37 (1.1)	39.4 (1.0)	N.A.	0.14a
> 25 years	19 (19)	8 (8)	1	
≤ 25 years	81 (81)	92 (92)	2.7 (1.1 – 6.5)	0.02b
Gender				
Male	45	39	1	
Female	55	61	1.3 (0.7 – 2.2)	0.39b
Headache during the previous year				
No	8 (8%)	27 (27%)	1	
Yes	92 (92%)	73 (73%)	4.3 (1.8 – 9.9)	0.001b*

N.A. = Not applicable; SD = Standard deviation.
[a] Student's *t*-test.
[b] Binary Logistic Regression.
* Statistically significant at $p < 0.01$.

The differences in the diagnosis of migraine, TTH and CDH between the MTLE-HS patients and the controls are shown in Table 4.2. There were no statistical differences in the prevalence of migraine between the MTLE-HS patients and the controls (OR 1.5, CI 95% 0.8 – 2.9, $p = 0.18$); TTH was reported by 36 (36%) of the refractory MTLE-HS patients compared to 30 (30%) of the control group (OR 0.9, CI 95% 0.5 – 1.7, $p = 0.74$) and CDH was reported six times more frequently by the refractory MTLE-HS patients compared to the controls (OR 6.1, CI 95% 1.7 – 22, $p = 0.005$).

Table 4.2. Characteristics of headache in mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) patients compared with non-epileptic control group.

Variables	MTLE-HS (n = 92)	Controls (n = 73)	Crude Odds Ratio[a] (CI 95%)	*p*	Adjusted Odds Ratio[b] (CI 95%)	*p*
Migraine						
No	36	36	1		1	
Yes	56	37	1.5 (0.8-2.8)	0.19	1.5 (0.8-2.9)	0.18
Tension-type headache						
No	56	43	1		1	
Yes	36	30	0.9 (0.5-1.7)	0.80	0.9 (0.5-1.7)	0.74
Chronic daily headache						
No	75	70	1		1	
Yes	17	3	5.3 (1.5-18.8)	0.01	6.1 (1.7-22)	0.005*

[a] Crude odds ratio determined by Binary Logistic Regression.
[b] Adjusted odds ratio for age, determined by Binary Logistic Regression.
* Statistically significant at $p < 0.01$.

DISCUSSION

This study showed a significantly higher prevalence of headache (92%) in the refractory MTLE-HS patients during the previous year compared to the control group (73%). However, we did not observe an association between migraine or TTH and the refractory MTLE-HS patients compared with control subjects. CDH was six times more frequently associated with refractory MTLE-HS patients (OR 6.1; CI 95% 1.7 – 22; $p = 0.005$).

Syvertsen *et al.* reported a 65% prevalence of headache in a general epileptic population [25]. Yankovsky *et al.* investigated one hundred patients who were undergoing presurgical evaluation for pharmacologically intractable partial epilepsy, and recurrent headache was reported by 59% of the patients [5]. Our patients presented a higher prevalence (92%) of headache when compared with other studies. This difference could be related to the fact that our sample was obtained from a tertiary healthcare center that specializes in treating refractory epilepsy, and all referred patients experience uncontrolled seizures despite the use of high-dose antiepileptic drugs.

A nationwide cross-sectional epidemiological study of headache in Brazil showed a prevalence of 68.5% in the general population [23]. In this study, the prevalence of migraine and probable migraine was 16.3% and 26.9%, respectively [23]. Queiroz *et al.* reported an 80.8% prevalence of headache in our city [26]. We confirmed the strong association between headache and epilepsy by demonstrating that refractory MTLE-HS patients experienced headaches four times more frequently than the control subjects ($p = 0.001$).

The association between headache and epilepsy is well known although the mechanisms that underlie this association remain uncertain [27]. There may be several etiopathogenetic mechanisms that converge unto a common pathway that is associated with neuronal membrane hyperexcitability [28]. For instance, the pathophysiology of migraine is associated with Cortical Spreading Depression (CSD), which is characterized by a slow propagating wave of strong sustained neuronal depolarization that generates intense spike activity as it progresses through the tissue and is followed by neural

suppression, which may last for minutes [29]. Cortical brain depolarization has also been implicated in the underlying pathophysiology of different types of epilepsy. The Na^+ -K^+ ATPase pump plays a critical role in the regulation of seizure onset by participating in the membrane depolarization and the CSD by modifying the local K^+ concentration [30]. The onset and propagation of the depolarizations are triggered when these neurophysiological events reach a certain threshold ("all or nothing events"), which is lower for the onset of CSD than that for seizures [30]. These events might represent a range or a spectrum of possibilities where symptoms and signs of one merge into the other without any clear boundary [28].

However, the previously described mechanisms only partially explain the link between headache and epilepsy. The proposed common pathophysiology includes CSD, which is an intrinsic phenomenon observed only in migraine. We demonstrated that despite the high prevalence of headache in the refractory MTLE-HS patients, there was a proportional increase in migraine and TTH. This finding should encourage future investigations of other mechanisms and pathways that are common to migraine and TTH.

Another intriguing finding was the significantly higher prevalence of CDH (17%) among refractory MTLE-HS patients. CDH was six times more frequent among epileptic patients compared to controls (OR 6.1; CI 95% 1.7 – 22; $p = 0.005$). A nationwide population-based CDH study in Brazil reported a prevalence of 9.5% in women and 4% in men with a 2.4:1 female / male ratio [31]. In fact, these data suggest an association between the severity of the epilepsy and the increasing number of headache episodes. An altered brain state with neuronal hyperexcitability might also contribute to a higher frequency of headaches.

There are some limitations that need to be acknowledged and addressed regarding the present study. The cross-sectional design and the frequency of headache were based on retrospective recall of the patient's pain episodes, which may be subject to memory bias. Moreover, the findings of our study cannot be applied to all epileptic patients because this study was

conducted at a tertiary healthcare center with refractory patients. Furthermore, the control group was obtained from a randomized sample of the Santa Catarina's state population, which may have included people with epilepsy. However, considering the approximately 0.5 - 1% prevalence of epilepsy, this may not have significantly changed the results of the statistical analysis.

This study confirmed an association of headache and CDH with refractory MTLE-HS. In contrast to the previous studies, we did not observe an association with migraine. In our previous article, we also demonstrated a lateralizing value of headache according to the epileptogenic zone [32]. These data favor a possible link between epilepsy and headache and suggest a common TTH and migraine pathway that is probably in the same side of the brain. Finally, headache is a common comorbidity associated with refractory MTLE-HS that contributes to a reduced quality of life. Physicians should be familiar with the principles of the diagnosis and treatment of both epilepsy and headache. Moreover, new studies are necessary to elucidate the intrinsic mechanisms that link these frequent neurologic entities.

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5. CAPÍTULO III

CLINICAL FEATURES OF HEADACHE IN PATIENTS WITH PARKINSON'S DISEASE

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Abstract

Objectives: We compared the lifetime prevalence and the prevalence of headache during the previous year in patients with Parkinson's disease (PD) and control subjects. We also investigated the association between the side of PD symptoms onset and the side of the headache.

Methods: We interviewed 98 consecutive patients with an established diagnosis of PD between December 2010 and January 2012. The control group consisted of the 98 oldest sex-matched individuals from the nationwide Brazilian headache database. **Results:** PD patients showed a significantly lower prevalence (40.8%) of headache in the previous year than controls (69.4%) (Adjusted OR 0.5, CI 95% 0.2 – 0.9, p = 0.03). PD patients also showed a lower prevalence of headache throughout life (74.5%) than controls (93.9%) (Adjusted OR 0.2, CI 95% 0.1 – 0.6, p = 0.01). Considering only patients that presented headache during the previous year, PD patients showed a higher association with occurrence of migraine than tension-type headache compared with controls (Adjusted OR 3.3, CI 95% 1.2 – 8.9, p = 0.02). The headache side was ipsilateral to the side of PD onset in 21 patients (84%), with a concordance of 85.7% on the left side and 81.8% on the right side (p < 0.01). **Conclusions:** The prevalence of primary headache was significantly lower in patients with PD than controls. The predominant side of headache was ipsilateral to the side of initial motor signs of PD.

INTRODUCTION

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, and affects more than 1% of the elderly population worldwide [1]. PD is

characterized by the presence of severe nigral pars-compacta cell loss and the accumulation of aggregated alfa-synuclein in specific brainstem, spinal cord and cortical regions [2].

Although PD is predominantly defined as a movement disorder, patients also experience a wide range of non-motor symptoms [3]. These symptoms comprise a variety of cognitive, neuropsychiatric, sleep, autonomic and sensorial disorders that reflect a wide array of neuropathological changes associated with this condition [4]. PD also affects other domains such as social, communication, economic and occupational functioning [5,6,7].

Headache is a symptom that is often associated with neurological disorders. However, the clinical practice confirmed by previous researches demonstrated that this comorbidity is less associated with PD than with other disorders. Barbanti et al. showed a lifetime migraine prevalence of 27.8% and a current migraine prevalence of 13.1% in PD patients [8]. These data differ substantially from the 92% prevalence of headache reported by patients with mesial temporal lobe epilepsy related to hippocampal sclerosis [9].

Although many critical points remain unclear, the understanding of the pathophysiology of headache has advanced greatly during the past twenty years [10]. The reason for this incomplete knowledge is the complexity of the underlying mechanisms of this condition associated with difficulties in assessing the functional and structural abnormalities of the human brain. In this context, the study of headache in patients with other neurological diseases with known pathological abnormalities might help us to understand these mechanisms.

PD is the paradigm of human brainstem dopaminergic disorder and represents a model of dopaminergic impairment [8]. This abnormality influences the modulation of the basal ganglia motor circuit and thalamocortical output involved in normal movement. Increasing evidence indicates that migraine pathophysiology may partly include the dysfunction of subcortical structures [10,11]. They include diencephalic and brainstem nuclei that can modulate the activation of the trigeminovascular system, which carries sensory information from the cranial vasculature to the brain [10]. Since PD is

accompanied by cortical and subcortical hypoexcitability influenced by lower thalamocortical output, we suppose that the prevalence of headache may be lower in these patients. We also suspect that the more affected side of the brain, which is the origin of the motor symptoms and where there is more intense damage of dopaminergic cells, may lead to a lower prevalence of headache than the contralateral side.

The aim of this study was to investigate the lifetime prevalence of headache and the prevalence of headache during the previous year in patients with PD compared to non-parkinsonian control subjects. We also investigated the concordance between the predominant laterality of the headache and the side of the initial symptoms of PD.

METHODS

This was an observational, analytical and case-control study. We interviewed one hundred consecutive patients with an established diagnosis of PD between December 2010 and January 2012, assisted at Hospital Governador Celso Ramos (HGCR), which is the most important regional referral center for PD treatment in the state of Santa Catarina in southern Brazil.

All patients with PD were diagnosed according to UK Parkinson's Disease Society Brain Bank criteria, including presence of [12]: 1) bradykinesia and 2) rest tremor, or muscular rigidity or postural instability. Patients with the following conditions were excluded, according to these same criteria [12]: 1) history of repeated strokes; 2) history of repeated head injury; 3) history of definite encephalitis; 3) oculogyric crises; 4) neuroleptic treatment at onset of symptoms; 5) more than one affected relative; 6) sustained remission; 7) strictly unilateral features after three years; 8) supranuclear gaze palsy, cerebellar signs or Babinski sign; 9) early severe autonomic involvement; 10) early severe dementia; 11) presence of cerebral tumor or communicating hydrocephalus on CT scan; 12) negative response to therapeutic dosage of levodopa or 13) MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine) exposure.

All patients with PD were followed up in a movement disorders center where they were comprehensively submitted to

standardized evaluations by a neurologist specialized in movement disorders, a psychiatrist and a neuropsychologist.

Clinical features were recorded from patients and caregivers interviews using a protocol specifically developed for this study and an analysis of the medical charts to investigate data related to PD characteristics, such as the side and age of initial symptoms, age at diagnosis and UPDRS (Unified Parkinson's disease rating scale) motor part (part 3) [13] performed by a physician specialized in movement disorders (FCF). A standardized questionnaire for headache was applied according to the criteria of the International Headache Society (IHS) by one researcher (ENCB) blinded to all patients' clinical data. How PD has motor symptoms that can be easily observed in a clinical evaluation, all interviews considering headache variables were made by telephone to avoid an interviewer bias. Ten percent of these interviews were also administered to the same patients by the first author (JCN) to assure the reproducibility of the questionnaire.

The diagnosis of headache was determined by a board-certified neurologist (JCN) and was based on the second edition of the International Classification of Headache Disorders (ICHD-II) [14]. We collected data about the characteristics of headache throughout the patients' life and during the previous year to minimize recall bias. Migraine and tension type headache (TTH) were diagnosed when all ICHD-II were fulfilled. The difference between migraine with and without aura was not investigated because the presence of another neurological disease could hamper the analysis of this information. The diagnosis of probable migraine was made by the presence of all migraine criteria, except one. The diagnosis of probable TTH was given when all criteria were fulfilled, except one. When patients had more than one type of headache, they were encouraged to describe the most frequent type that they experienced, and each patient was diagnosed according to the pattern of the predominant type of headache.

We excluded PD patients with evident signs of dementia in the neuropsychological evaluation as this condition would compromise their ability to understand our questionnaire or the

purpose of this study and which would be associated with Parkinson-plus syndromes. We also excluded patients with any other neurologic comorbidities (other than PD and headache) that would add confounding variables to our sample.

The control subjects were obtained from a nationwide population-based study database that contained 3,848 randomized subjects from all 27 Brazilian states who were interviewed by telephone between September 2006 and January 2007 [15]. For this study, we only considered patients living in Santa Catarina state (n = 122) according to this database. The patients and controls were paired according to age and gender. The 24 youngest controls from the database were excluded. All control subjects were submitted to a complete interview with the same headache questionnaire, except for PD related investigation.

This study was approved by the Ethics Committee of HGCR and Universidade Federal de Santa Catarina (UFSC). Informed consent was obtained from all patients before the interview was initiated.

Statistical Analysis

We initially investigated the association between the clinical and demographic variables of PD patients and the occurrence of headache during the last year. We grouped the patients with headache in two categories to statistical analysis: 1) headache type migraine and 2) TTH. Continuous variables were analyzed using the Student's *t*-test for independent samples, and categorical variables were analyzed using the Chi-Square test.

The associations between PD and the presence or absence of headache throughout life and headache during the previous year as compared to control patients were accessed by an univariate analysis using binary logistic regression. The magnitude of the association between the dependent variable and independent variables was measured by crude odds ratio (OR) and 95% confidence intervals (CI 95%). Afterward, a multiple logistic regression was performed to determine the independent association between clinical variables and PD. This analysis only included variables with a "*p*" level of significance < 0.20 as demonstrated by a univariate analysis. The final model shows the

OR derived after an adjustment for age and gender and the respective 95% confidence intervals (CI 95%). The statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Clinical variables according to the presence or absence of headache during the previous year in PD patients are shown in Table 5.1. Forty patients (40.8%) with PD had experienced headache during the previous year. The occurrence of headache was associated with female gender ($p = 0.03$) and younger age ($p = 0.01$). There was a trend ($p = 0.09$) for an association between the occurrence of headache in PD patients and earlier disease onset. Disease duration, UPDRS-III score and the side of initial symptoms were not associated with the occurrence of headache ($p \geq 0.33$). Among the 40 PD patients that had headache during the previous year, 11 (27.5%) had migraine, 15 (37.5%) had probable migraine, seven (17.5%) had TTH, 5 (12.5%) had probable TTH and two (5%) had other types of headache. Among the 68 controls that suffered headache during the previous year, 16 (23.5%) had migraine, 15 (22%) had probable migraine, 20 (29.4%) had TTH, 13 (19.1%) had probable TTH and 4 (5.8%) had other types of headache.

The association between the predominant side of headache during the previous year and the side of initial PD symptoms in 25 patients with unilateral PD onset was also investigated. The remaining 15 patients with PD were not included in this analysis because in three of them we could not determine the side of the initial symptoms, two referred bilateral PD onset and other 10 patients suffered from bilateral headache. The predominant side of headache was ipsilateral to the side of initial symptoms of PD in 21 patients (84%), with a concordance of 85.7% on the left side and 81.8% on the right side ($p < 0.01$) (data not shown). Among these 21 patients, one patient had migraine without aura, seven had probable migraine without aura, seven had probable migraine with aura, two had chronic migraine, one had probable chronic migraine and three had tensional headache.

Table 5.1. Clinical variables of patients with Parkinson's disease (PD) with and without headache during the previous year.

Variables	All	Presence of headache during the previous year		
	Patients	Positive	Negative	
	n = 98	*n* = 40	*n* = 58	*p*
Gender				
Man	57 (58.2%)	18 (45%)	39 (67.2%)	
Woman	41 (41.8%)	22 (55%)	19 (32.8%)	0.03 [a]
Age (years)				
Mean (SD)	60.8 (10.4)	57.4 (10.2)	62.8 (9.7)	0.01 [b]
Age at initial symptoms of PD (years)				
Mean (SD)	52.1 (11.2)	49.9 (12.2)	53.8 (10.1)	0.09 [b]
Duration of PD (years)				
Mean (SD)	9.7 (6.4)	9 (5.3)	10.3 (7.1)	0.33 [b]
UPDRS				
Mean (SD)	26.3 (15.3)	24.5 (16.1)	27.3 (14.9)	0.47 [b]
Corporal side of initial symptoms [c]				
Left	47 (48%)	21 (52.5%)	26 (46.4%)	
Right	46 (46.9%)	17 (42.5%)	29 (51.8%)	0.5 [a]

UPDRS: Unified Parkinson's disease rating scale (part3); [a] Pearson Chi-Square test; [b] Student's *t* test; [c] The side of initial symptoms could not be determined in three patients.

In comparison, patients with PD showed a significantly ($p < 0.01$) higher age (60 ± 10 years) than controls (46 ± 12 years). There was also a trend ($p = 0.12$) for a higher prevalence of males (58.2%) among patients with PD compared to the control group (49%) (data not shown). The association between the headache prevalence and PD is shown in Table 5.2. In order to avoid confounding bias related to gender and age imbalances between PD patients and controls, these two variables were included in the multiple logistic regression models. Compared to controls, there was a lower association between PD and the occurrence of headache during the previous year (Adjusted OR 0.05, CI 95% 0.2 - 0.9, $p = 0.03$) and during the whole lifetime of the patients (Adjusted OR 0.2, CI 95% 0.1 – 0.6, $p = 0.01$). The prevalence of migraine during the previous year among PD patients was 26.5% compared to 31.6% in controls. The prevalence of TTH during the previous year among PD patients was 12.2% compared to 33.7% in control subjects. Considering only patients that presented headache during the previous year, PD patients showed

a higher association with occurrence of migraine than tension-type headache compared with controls (Adjusted OR 3.3, CI 95% 1.2 – 8.9, p = 0.02).

Two patients were excluded from this study because they also had epilepsy. Cognitive impairments or psychiatric disturbances that could interfere in evaluations were not detected.

DISCUSSION

This study demonstrated that PD patients had a lower prevalence of headache during the previous year as well as during their entire lifetime compared to controls. Ayzenberg et al. reported a headache prevalence of 62.9% among a countrywide population-based random sample of 2,725 individuals [16]. These data resemble the results obtained by Queiroz et al. in a nationwide cross-sectional epidemiological study of headache in Brazil, which showed a headache prevalence of 68.5% in the general population [15]. Lorentz et al. found no significant differences in the total prevalence of headache among patients with PD and controls [17]. Our study showed a lower prevalence of lifetime headache and headache during the previous year (40.8%) in patients with PD and confirmed these results by comparing them with a non-parkinsonian control group. Our results showing an association of a lower prevalence of headache and PD cannot be attributed to a confounding bias related to the age imbalances between PD patients and controls because the variable age was included in the multiple logistic regression analysis.

The high correlation between the side of headache and the side of PD onset in patients with unilateral PD onset is a very interesting finding and confirmed our pre-test hypothesis. To the best of our knowledge, this is the first study that investigated this association. In fact, this important clinical feature may also contribute to our understanding of the pathophysiology of headaches in the non-PD population. Although the protective effect carried out by the brain hemisphere with the initial parkinsonian disturbances for the presence of headache (contralateral to corporal side of motor initial signs) remains unclear, we speculate that hypoexcitability in thalamocortical

output might have a relevant role in these mechanisms. The exact role of dopamine in headache, especially in migraine, is still somewhat unclear, with evidence indicating that dopamine acts in either pathogenic and therapeutic mechanisms [11,18]. A substantial number of studies have pointed toward the involvement of monoamine serotonin 5-HT receptors and agonists [19]; however, dopamine receptors are known to exist in the trigeminal ganglion and spinal trigeminal nuclei in mouse and rat [11]. There is also an increased frequency of dopamine D2 receptor gene alleles in patients diagnosed with migraine with aura [20]. Moreover, many dopamine antagonists, particularly D2 antagonists, may contribute to the treatment of headache [21], indicating that this neurotransmitter may have a role in pathogenesis of primary headaches.

PD represents a model of dopaminergic impairment that allows us to understand the effects of this neurotransmitter in the human brain. We recently demonstrated a possible opposite effect of thalamocortical hyperexcitability in a previous study with patients with temporal lobe epilepsy related to unilateral hippocampal sclerosis and unilateral headache. In this study, we found that the association between the side of headache and the side of epileptogenic lesion (hippocampus sclerosis) was 8 times greater than the association between the side of headache and the non-lesioned side, suggesting that an association exists between the hyperexcitable region and the occurrence of headache [9,22].

We cannot exclude a role of other molecules, as known a progressive loss of orexin/hypocretin cells with PD progression [23]. The spinal cord and several brain regions involved in the regulation of pain receive orexinergic projections, including the hypothalamus, lamina I, II and X of the spinal and trigeminal dorsal horns [24].

Barbanti et al. reported the presence of migraine in PD patients in a cross-sectional study and found a lifetime migraine prevalence of 27.8% and a current migraine prevalence of 13.1% [8]. Our study showed a prevalence of migraine (26.5%) in the previous year that was lower than controls (31.6%) but higher than the results of Barbanti et al. These higher rates of migraine in our sample may be related to other factors that could contribute

to trigger migraine, such as depression, anxiety and sleep disorders, which are common comorbidities in patients with chronic diseases treated in tertiary centers and were not considered in this study.

There are some limitations in the present study that need to be acknowledged. The control group comprised subjects from another study that investigated headache, and since this previous study did not investigate symptoms related to PD we cannot exclude the presence of individuals with PD among the controls. We assumed that the prevalence of PD in the control group is similar to the prevalence in the general population (0.1 – 0.2%) [25] which would not be sufficient to change the results of this study. Moreover, considering that this was a cross-sectional study based on retrospective recall of pain episodes, we cannot exclude any memory bias or tolerance to pain, which could be higher in PD patients due to non-motor difficulties related to cognitive function or psychiatric disturbances. Furthermore some drugs that have been used in treatment of PD could interfere in the prevalence of headache.

In conclusion, patients with PD report significantly lower headache events during the previous year as well as during their lifetime. The predominant side of unilateral headache was ipsilateral to the side of initial motor signs of PD. Although a cause and effect relationship cannot be proven by the present experimental design, our findings may add evidence towards the knowledge about the dopaminergic modulation of headache [18,26].

Furthermore, new studies controlling for non-motor dysfunction in PD including the cognitive performance and psychiatric symptoms are necessary to elucidate the intrinsic mechanisms linking the lower headache reported in patients with PD.

Table 5.2. Comparison between headache prevalence in PD patients and controls.

Variables	PD patients n = 98 (%)	Controls n = 98 (%)	Crude [a] OR (CI 95%)	*"p" level*	Adjusted [b] OR (CI 95%)	*"p" level*
Headache during the previous year						
No	58 (59.2)	30 (30.6)	1		1	
Yes	40 (40.8)	68 (69.4)	0.3 (0.2 – 0.5)	< 0.01	0.5 (0.2 – 0.9)	0.03
Headache during the life						
No	25 (25.5)	6 (6.1)	1		1	
Yes	73 (74.5)	92 (93.9)	0.2 (0.1 – 0.5)	< 0.01	0.2 (0.1 – 0.6)	0.01
Type of headache during the previous year [c]						
No	54 (58.7)	30 (31.9)	1		1	
Tension-type headache	12 (13)	33 (35.1)	0.2 (0.1 – 0.4)	< 0.01	0.2 (0.1 – 0.6)	< 0.01
Migraine	26 (28.3)	31 (33)	0.5 (0.2 – 0.9)	0.03	0.8 (0.3 – 1.8)	0.6
Type of headache [d]						
Tension-type headache	12 (31.6)	33 (51.6)	1		1	
Migraine	26 (68.4)	31 (48.4)	2.3 (1 – 5.4)	0.05	3.3 (1.2 – 8.9)	0.02

[a] Crude OR = Crude Odds Ratio determined by binary Logistic Regression; [b] Adjusted OR = Adjusted Odds Ratio for age and gender determined by Binary Multiple Logistic Regression; [c] Analysis excluded patients with other types of headache; [d] Analysis including patients showing isolated migraine or tensional headache (n = 38).

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6. COMENTÁRIOS FINAIS E IMPLICAÇÕES

Neste estudo demonstramos uma prevalência de cefaleia em pacientes com ELTM-EH significativamente maior que em indivíduos da população geral, sendo que estes pacientes apresentam também altas taxas de cefaleia crônica diária. Dentre os pacientes com ELTM-EH que referiram cefaleia predominante unilateral, demonstramos uma associação significativa entre o lado da cefaleia e o lado da EH. A extensão desta investigação a outras formas de epilepsia incluindo as focais e generalizadas primárias é um ponto a ser considerado nesta linha de pesquisa.

A prevalência das cefaleias primárias foi significativamente mais baixa em pacientes com doença de Parkinson comparados com indivíduos da população geral. Quando unilateral, a cefaleia foi predominantemente ipsilateral ao lado de início dos sintomas motores da doença de Parkinson.

Embora o delineamento do presente estudo não permita afirmar relações de causa e efeito, a alta frequência de cefaleias primárias em pacientes com ELTM-EH, a maior chance de cronificação e a predileção da cefaleia pelo hemisfério cerebral onde se localiza a zona epileptogênica favorecem a hipótese de participação da hiperexcitabilidade cortical e da modulação talâmica na fisiopatologia das cefaleias primárias. Da mesma forma, a baixa prevalência de cefaleia em pacientes com doença de Parkinson associada à menor frequência de cefaleia no hemisférico onde a patologia está mais avançada, e por conseguinte, com menor excitação neocortical e talâmica, corroboram com a proposta inicial deste estudo.

As implicações do presente estudo estendem-se tanto para as áreas clínicas quanto experimentais. A alta taxa de prevalência de cefaleias primárias nos pacientes com ELTM-EH justifica a introdução de abordagens sistemáticas e pormenorizadas dos pacientes com este tipo de epilepsia, possibilitando a formulação de um diagnóstico precoce e a instituição de um tratamento apropriado que evite a cronificação e reduza o sofrimento ocasionado por esta frequente comorbidade. Este estudo também fornece elementos que favorecem o papel da hiperexcitabilidade cortical e talâmica na fisiopatologia tanto da migrânea quanto da

CTT. Embora a participação dos mecanismos periféricos envolvidos nas cefaleias primárias sejam discutidos e extensivamente estudados durante os últimos anos, os dados apresentados neste estudo enfatizam a relevância dos mecanismos centrais e da ativação do sistema tálamo-cortical. Estes fatores têm sido subvalorizados principalmente no estudo dos mecanismos envolvidos na CTT, e podem ser determinantes para o surgimento de novas abordagens terapêuticas mais eficazes.

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APÊNDICE A – PRODUÇÃO CIENTÍFICA DURANTE O PERÍODO DO DOUTORAMENTO

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ANEXO A – AMERICAN JOURNAL EXPERTS CERTIFICATION
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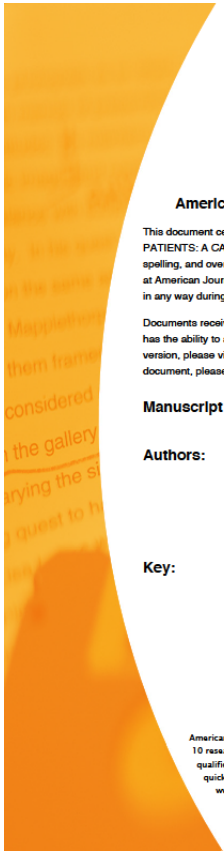
EADACHE AMONG TEMPORAL LOBE EPILEPSY PATIENTS: A CASE-CONTROL STUDY



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ANEXO B – AMERICAN JOURNAL EXPERTS CERTIFICATION
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