Faculdade de Medicina
Universidade Federal de Minas Gerais

TATIANA ROCHA SILVA

POTENCIAL EVOCADO MIOGÊNICO VESTIBULAR PARA AVALIAR A EXTENSÃO DO COMPROMETIMENTO NEUROLÓGICO NA INFECÇÃO PELO HTLV-1

Belo Horizonte
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Tese apresentada como requisito parcial para a obtenção do título de Doutor em Ciências da Saúde: Infectologia e Medicina Tropical do Programa de Pós-Graduação da Universidade Federal de Minas Gerais.

Orientadora: Profª. Denise Utsch Gonçalves
Coorientador: Prof. Dr. Marco Aurélio Rocha Santos
Coorientadora: Prof.ª Luciana Macedo de Resende

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"POTENCIAL EVOCADO MIOGÊNICO VESTIBULAR PARA AVALIAR A EXTENSÃO DO COMPROMETIMENTO NEUROLÓGICO NA INFECÇÃO PELO HTLV-1"

TATIANA ROCHA SILVA

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Profa. Denise Utsch Gonçalves - Orientadora
UFMG

Prof. Marco Aurelio Rocha Santos - Coorientador
UFMG

Profa. Luciana Macedo de Resende - Coorientadora
UFMG

Profa. Eliane Maria Dias Von Sohsten Lins
FASM

Profa. Aline Tenório Lins Carnaúba
UNCISAL

Profa. Sarah Teixeira Camargos
UFMG

Profa. Sirley Alves da Silva Carvalho
UFMG

Belo Horizonte, 1 de outubro de 2020.

RESUMO

Introdução: O potencial miogênico evocado vestibular (VEMP) pode ser usado para testar as vias vestibulares centrais do mesencéfalo à coluna lombar, de acordo com o músculo de registro. **Objetivo:** Comparar a lesão medular na mielopatia associada ao HTLV-1 (HAM) e na infecção assintomática usando o VEMP com diferentes músculos de registro. **Métodos:** O VEMP foi registrado em 90 indivíduos (30 HAM, 30 portadores assintomáticos e 30 controles negativos) no músculo oculomotor (oVEMP), testando o reflexo vestíbulo-ocular; no músculo cervical (cVEMP) e no músculo sóleo (sVEMP), testando os reflexos vestibulares espinhais, respectivamente, nos níveis da coluna cervical e da coluna lombar. O tipo de estimulação foi auditivo para oVEMP e cVEMP e galvânico para sVEMP. As variáveis comparadas foram as latências das ondas eletrofisiológicas. **Resultados:** O grupo assintomático foi semelhante ao grupo controle em relação ao oVEMP (p=0,461), mas foi diferente em relação ao cVEMP (p ≤0,001) e sVEMP (p ≤0,001). O grupo HAM apresentou as piores latências e foi diferente do grupo assintomático para todas as modalidades de VEMP (p ≤0,001). A alteração concomitante nos três VEMPs no mesmo indivíduo ocorreu em 2 (6,7%) portadores assintomáticos e em 20 (66,7%) pacientes com HAM (p=0,001). A alteração em cada VEMP separadamente foi identificada no grupo assintomático em 3 (10,0%) indivíduos para oVEMP, 10 (33,3%) para cVEMP e 13 (43,3%) para sVEMP. No grupo HAM, o oVEMP foi alterado em 23 (76,6%) indivíduos, o cVEMP em 27 (90%) e o sVEMP em 30 (100%). **Conclusão:** O dano neurológico na infecção pelo HTLV-1 segue uma progressão ascendente que se inicia na fase assintomática, aparentemente clínica, e a HAM afeta não apenas a coluna vertebral, mas também o mesencéfalo.

Descritores: Testes de função vestibular, Potencial evocado motor, Vírus linfotrópico T tipo 1 humano, Equilíbrio postural, Nervo vestibular, Sáculo e utrículo

ABSTRACT

Introduction: Vestibular Evoked Myogenic Potential (VEMP) can be used to test central vestibular pathways from the midbrain to the lumbar spine, according to the muscle tested. **Purpose:** To compare the spinal cord alteration in individuals with HTLV-1-associated myelopathy (HAM) and with HTLV-1-asymptomatic infection using the VEMP recorded from different muscles. **Methods:** VEMP was recorded in 90 individuals of whom 30 had HAM, 30 were HTLV-1 asymptomatic carriers, and 30 negative controls. VEMP was recorded in the oculomotor muscle (oVEMP), testing the vestibulo-ocular reflex, and in the cervical muscle (cVEMP) and soleus muscle (sVEMP), testing the vestibulospinal reflex, respectively, in the cervical and in the lumbar spinal level. The type of stimulation was auditory for oVEMP and cVEMP, and galvanic for sVEMP. The compared variables were the latencies of the electrophysiological waves. **Results:** HTLV-1-asymptomatic group was similar to the controls regarding oVEMP ($p = 0.461$), but different regarding cVEMP ($p < 0.001$) and sVEMP ($p < 0.001$). HAM group has presented the worst latencies and was different from the HTLV-1-asymptomatic group in the VEMP of all the tested muscles ($p < 0.001$). The concomitant occurrence of VEMP alterations in the three recorded muscles of the same individual was found in 2 (6.7%) asymptomatic carriers and in 20 (66.7%) patients with HAM ($p = 0.001$). The analysis of VEMP alteration per group and per muscle has showed that, in HTLV-1-asymptomatic group, oVEMP was altered in 3 (10.0%) individuals, cVEMP in 10 (33.3%) and sVEMP in 13 (43.3%). In HAM group, oVEMP was altered in 23 (76.6%) individuals, cVEMP in 27 (90%), and sVEMP in 30 (100%). **Conclusion:** HTLV-1-neurological damage has followed an ascendant progression beginning at the lumbar spine in the stage of a clinically asymptomatic infection, whereas HAM has affected not only the spine, but also the midbrain.

Keywords: Vestibular function tests, Motor evoked potentials, Human T lymphotropic virus 1, Postural balance, Vestibular nerve, Saccule and utricle

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LISTA DE ABREVIATURAS E SIGLAS

AIDS	Síndrome da Imunodeficiência Adquirida
ATL	Leucemia / linfoma de células T do adulto
cVEMP	Potencial evocado miogênico vestibular cervical
DNA	*Deoxyribonucleic acid*
ELISA	Ensaio imunoenzimático
GIPH	Grupo Interdisciplinar de Pesquisas em HTLV
HAM	Mielopatia associada ao HTLV-1
HIV	Vírus da imunodeficiência humana
HTLV-1	Vírus linfotrófico humano de células T tipo 1
LCR	Líquido cefalorraquidiano
oVEMP	Potencial evocado miogênico vestibular ocular
PCR	Reação em cadeia de polimerase
RNM	Ressonância nuclear magnética
SNC	Sistema nervoso central
sVEMP	Potencial evocado miogênico vestibular do músculo sóleo
UFMG	Universidade Federal de Minas Gerais
USP	Universidade de São Paulo
VEMP	Potencial evocado miogênico vestibular
WB	*Western Blot*

SUMÁRIO

CONSIDERAÇÕES INICIAIS

A proposta deste estudo surgiu a partir de pesquisas com o potencial evocado miogênico vestibular (VEMP), desenvolvidas no Grupo Interdisciplinar de Pesquisas em HTLV (GIPH), do qual faço parte desde 2016. Até então, todos os estudos utilizaram o VEMP para avaliar a medula (FELIPE *et al*., 2008; FELIPE *et al*., 2013; LABANCA *et al*., 2015). O uso do VEMP para a avaliação de indivíduos com mielopatias motoras tem se mostrado válido para o diagnóstico precoce da mielopatia associada ao HTLV-1 (HAM), seja com estímulo auditivo, seja com estímulo elétrico (FELIPE *et al*., 2008; FELIPE *et al*., 2013; LABANCA *et al*., 2015; CAPORALI *et al*., 2018).

Na evolução do conhecimento sobre a fisiopatologia da HAM, pesquisadores consideraram que a HAM comprometia a região lombo-sacral (CERVILLA; CARTIER; GARCÍA, 2006; IWASAKI, 1993). Posteriormente, demostrou-se que a HAM é uma mielopatia que compromete toda a medula, podendo acometer a medula cervical ainda na fase assintomática da doença (FELIPE *et al*., 2008; FELIPE *et al*., 2013; LABANCA *et al*., 2015). Mais recentemente, consideraram que o córtex é comprometido nas fases mais avançadas da HAM (CHAMPS *et al.*, 2019). A proposta do presente estudo foi dar seguimento para a avaliação eletrofisiológica do sistema nervoso central (SNC) de indivíduos infectados pelo vírus linfotrópico humano de células T tipo 1 (HTLV-1) assintomáticos e com mielopatia, de modo a melhor esclarecer alterações subcorticais, com base nas respostas eletrofisiológicas de vias neuronais ascendentes associadas ao equilíbrio corporal.

Eu tenho estudado o VEMP há alguns anos. Na minha dissertação de mestrado, avaliei o uso do VEMP na doença de Meniére, uma labirintopatia periférica de diagnóstico clínico. Eu utilizei, para captação da resposta, os músculos extraoculares e o músculo esternocleidomastóideo com o objetivo de avaliar as respostas do utrículo e do sáculo, respectivamente. A novidade do meu estudo foi a captação simultânea das duas respostas musculares, de modo a reduzir o tempo de realização do exame. Esse estudo foi publicado no *Brazilian Journal of Otorhinolaryngology*, tornando-se referência para a técnica de VEMP simultâneo. Três profissionais em Otoneurologia da Universidade de São Paulo (USP) estiveram em treinamento no serviço de Otorrinolaringologia do Hospital das Clínicas da Universidade Federal de Minas Gerais (UFMG) (22 e 23/01/2020) e um dos objetivos ressaltados pelos profissionais foi o interesse pela técnica do VEMP simultâneo (ANEXO A).

No VEMP, a resposta evocada demonstra a integridade da via anatômica testada e essa via varia de acordo com o músculo de captação da resposta. Assim, o VEMP captado na musculatura ocular (oVEMP) relaciona-se a avaliação da integridade da região subcortical, possivelmente mesencéfalo. A resposta em músculos cervicais (cVEMP) avalia a medula cervical (C1-C2) e a resposta em músculos da panturrilha, sendo mais utilizado o músculo sóleo (sVEMP), avalia a medula lombar (L5-S1). Com base nisso, a nossa hipótese foi que o oVEMP poderia ser um exame valioso para avaliação de um comprometimento subcortical associado ao HTLV-1, visto que estudos recentes tem mostrado que o HTLV-1 causaria comprometimento não apenas na medula, mas também em todo o SNC, o que já foi estabelecido nas fases mais avançadas da HAM. Porém, nada é sabido sobre o portador assintomático. Haveria um comprometimento no SNC mais difuso ocorrendo de modo subclínico em indivíduos considerados portadores assintomáticos do HTLV-1? Essa foi a nossa principal pergunta. Em acréscimo, avaliamos não só o oVEMP desses indivíduos, mas também o cVEMP e o sVEMP a fim de esclarecer o valor do VEMP para avaliar a extensão do comprometimento neurológico na infecção pelo HTLV-1.

O presente trabalho está inserido na linha de pesquisa Infecções virais - HIV/AIDS, HTLV-I/II e outros vírus do Programa de Pós-graduação em Infectologia e Medicina Tropical. O volume consta de introdução, revisão de literatura, objetivos, materiais e métodos, resultados e discussão, considerações gerais, conclusões e referências bibliográficas. Na seção revisão de literatura, apresento o meu primeiro artigo feito durante o doutorado, uma revisão de literatura sobre o VEMP, publicado na revista *Audiology - Communication Research* em maio de 2019. Na seção materiais e métodos apresento um fluxograma das etapas do estudo. Na seção resultados e discussão, o segundo e o terceiro artigos são apresentados. O segundo artigo, publicado na revista *PLoS One* em dezembro de 2019, aborda o uso do oVEMP e do cVEMP na infecção pelo HTLV-1. O terceiro artigo, publicado na revista *Frontiers in Neurology* em maio de 2020, aborda o uso do oVEMP, do cVEMP e do sVEMP na infecção pelo HTLV-1. Em apêndices e anexos, foram apresentadas as informações relacionadas à pesquisa na forma de documentos que não foram apresentados nos artigos.

A tese segue a Resolução nº 02/2013, de 18 de setembro de 2013, que regulamenta o formato dos trabalhos finais, estabelecendo condições para a marcação da defesa de teses e dissertações do Programa de Pós-Graduação em Ciências da Saúde: Infectologia e Medicina Tropical da Faculdade de Medicina da UFMG.

1 INTRODUÇÃO

O HTLV-1 tem ampla distribuição mundial e estima-se que 15 a 20 milhões de pessoas estejam contaminadas (YOSHIDA; JEANG, 2005). No Brasil, a infecção pelo HTLV-1 é considerada endêmica e, aproximadamente, 2,5 milhões de pessoas estão infectadas pelo vírus, o que torna o Brasil o país com maior número absoluto de casos. (DOURADO *et al*., 2003; JACOB *et al*., 2007; SILVA *et al*., 2009).

O modo como a interação entre o vírus e o hospedeiro se desenvolve é determinante para o estado de portador assintomático ou de doente. As doenças mais frequentemente associadas ao HTLV-1 são a leucemia/linfoma de células T do adulto (ATL) e a HAM e estima-se que 5% dos portadores possam desenvolver alguma doença relacionada ao HTLV-1 (CARNEIRO-PROIETTI *et al*., 2006).

A HAM é doença grave por causa das limitações motoras que acometem os membros inferiores somadas à disfunção autonômica (BHIGJEE *et al*., 1991). Os sinais e sintomas mais frequentes na HAM são espasticidade, hiperreflexia, parestesia em membros inferiores, clônus e/ou sinal de Babinski, queixas urinárias, dor lombar, constipação e sensibilidade vibratória diminuída. (GOTUZZO *et al*., 2000). O diagnóstico é baseado nos sinais e sintomas associados à sorologia positiva para o HTLV-1 (CASTRO-COSTA *et al*., 2006). Logo, o diagnóstico clínico é tardio.

O diagnóstico se baseia na alteração do exame neurológico, alterações em exames de imagem e no líquor, associado à sorologia positiva para o HTLV-1. Um estudo demonstrou que alterações imunológicas da cascata inflamatória precedem as manifestações clínicas na HAM (STARLING *et al*., 2015). Com esse enfoque, marcadores subclínicos de prognóstico para a evolução de portador assintomático para HAM são de grande valor científico.

O tratamento é, ainda, apenas sintomático e estudos têm avançado na busca por um tratamento que de fato controle a evolução da doença (ARAYA *et al*., 2016; BUELL *et al*., 2016). O consenso é que qualquer medida terapêutica efetiva somente terá valor se iniciada na fase inicial da doença, ainda sem lesão neuronal estabelecida (BUELL *et al*., 2016). Por isso, o diagnóstico precoce é muito importante.

A queixa de instabilidade postural pode ser uma das primeiras manifestações clínicas que indicam evolução de portador assintomático para HAM (LABANCA *et al*., 2015). De fato, naqueles considerados como “portador assintomático”, alterações eletrofisiológicas associadas ao trato vestíbulo-espinal, vistas através do cVEMP,

parecem indicar aqueles que evoluirão para HAM (FELIPE *et al*., 2008; FELIPE *et al*., 2013). Por isso, a queixa de tontura é um relato comum na fase inicial da HAM e precede alterações objetivas no exame neurológico (LABANCA *et al*., 2015).

O VEMP é uma técnica complementar para a avaliação da função vestibular. O VEMP é um potencial evocado de curta latência gerado por um reflexo muscular vestíbulo-espinal ou vestíbulo ocular, que depende da integridade funcional da mácula sacular e utricular, do nervo vestibular inferior, do nervo vestibular superior, dos núcleos vestibulares, das vias vestibulares e da placa neuromuscular (KANTNER; GÜRKOV, 2012).

Para o diagnóstico eletrofisiológico da lesão subclínica medular relacionada à HAM, publicações anteriores utilizaram o VEMP com captação de resposta na musculatura cervical e de membros inferiores com o propósito de testar o trato vestíbulo-espinal descendente (FELIPE *et al*., 2008; FELIPE *et al*., 2013; LABANCA *et al*., 2015).

O VEMP com estimulação galvânica e captação da resposta eletromiográfica em membros inferiores (sVEMP) oferece informações sobre o trato vestibuloespinhal, o qual se estende até a medula lombar (ILES *et al*., 2004; LIECHTI *et al*., 2008; WATSON & COLEBATCH, 1998). O estímulo galvânico apresenta aplicabilidade clínica bem definida para esse fim e o teste pode auxiliar na identificação de possível alteração medular associada ao HTLV-1 (FELIPE *et al*., 2013; CUNHA *et al*., 2013). Estudo piloto realizado em pacientes assintomáticos e com HAM demonstrou alterações em pacientes com HAM e em 30% daqueles assintomáticos, indicando possível acometimento medular (CUNHA *et al*., 2013).

O conceito mais aceito é que a HAM é uma mielopatia motora com comprometimento cortical tardio (CERVILLA; CARTIER; GARCÍA, 2006). Porém, estudos têm demonstrado que o comprometimento cortical pode estar associado à HAM ainda em sua fase inicial (CERVILLA; CARTIER; GARCÍA, 2006). O presente estudo permitirá esclarecer essas questões, principalmente por avaliar por meio de exames eletrofisiológicos indivíduos infectados pelo HTLV-1 na fase assintomática comparando-os aos pacientes com HAM.

2 REVISÃO DA LITERATURA

2.1 Vírus linfotrópico humano de células T-tipo 1 (HTLV-1)

No ano de 1979 foi descrito o primeiro retrovírus humano, o HTLV-1 (GALLO, 2005). Estudos posteriores comprovaram a participação do vírus como agente etiológico da leucemia de células T do adulto (ATL) (POIESZ *et al*., 1980; GALLO, 2005) e na etiologia da HAM (TAYLOR; MATSUOKA, 2005). Estudos preconizam que a África é o reservatório primário desse retrovírus, sendo o mesmo endêmico em diversas partes do mundo (SANTOS; LIMA, 2005).

No Brasil, estudos de prevalência confirmam a presença do HTLV-1 em todo o país. Entre doadores de sangue provenientes das diferentes regiões do país, a prevalência é variável, sendo de 0,08% no Norte e no Sul do país (Manaus e Florianópolis); 0,33% no Nordeste e no Sudeste (Recife e Rio de Janeiro) e 1,35% em Salvador (CATALAN-SOARES; PROIETTI; CARNEIRO-PROIETTI, 2001; SANTOS; LIMA, 2005). A soroprevalência média encontrada entre doadores brasileiros aptos à doação é cerca de 20 a 100 vezes mais alta do que a relatada para os Estados Unidos e Europa. Esse fato, aliado à extensão territorial e ao tamanho da população, indica que o Brasil abriga o maior número absoluto de indivíduos soropositivos para HTLV-1 entre todos os países endêmicos (CARNEIRO-PROIETTI *et al*., 2006).

A transmissão do HTLV-1 se dá por via transplacentária, durante o parto, amamentação, relação sexual, transfusão de sangue, hemoderivados contaminados e uso de drogas injetáveis (SANTOS; LIMA, 2005).

O diagnóstico sorológico da infecção pelo HTLV-1 baseia-se na detecção de anticorpos específicos contra o vírus. O teste de triagem mais utilizado é o ensaio imunoenzimático (ELISA) (RUDOLPH *et al.,* 1993) e os testes confirmatórios são o Western Blot (WB) (LAL *et al*., 1992) e a detecção do DNA proviral, através da reação em cadeia de polimerase (PCR) (HENEINE *et al*., 1992).

A história natural da infecção pelo HTLV-1 não está completamente elucidada, principalmente porque o tempo decorrido entre a exposição/infecção e o início de sintomatologia é muito longo (BORDUCCHI; KERBAUY; OLIVEIRA, 1999). Aproximadamente 95% dos indivíduos infectados permanecem assintomáticos ao longo da vida (SANTOS; LIMA, 2005). Estudos demonstram que 0,25 a 4% dos indivíduos

desenvolverão HAM e outros 2 a 6% desenvolverão ATL (YAMANO *et al*., 2002; ORLAND *et al*., 2003).

2.1.1 Mielopatia associada ao HTLV-1 (HAM)

A HAM é uma doença neurológica de progressão lenta e irreversível e a alteração na marcha, caracterizada por uma paraparesia espástica, surge gradualmente com sinais de envolvimento do trato piramidal (GOTUZZO *et al*., 2000). Uma minoria pode apresentar uma progressão rápida dos sintomas neurológicos (MILAGRES *et al*., 2002). Acomete mais mulheres do que os homens numa proporção de 8:3, com início dos sintomas na quarta década de vida (GOTUZZO *et al*., 2000).

Fortes evidências sugerem que o tecido nervoso seja lesado de forma indireta pelo HTLV-1. Linfócitos infectados, que apresentam maior capacidade de migração para o interior do SNC, possuem a capacidade de liberar citocinas e outros fatores neurotóxicos que seriam lesivos às células do parênquima (JOHNSON, 2003).

Por outro lado, as lesões de parênquima podem não estar limitadas à medula espinhal, mas também ser observadas na substância branca subcortical, o que foi demonstrado em estudo histopatológico e em exames de imagem como a ressonância nuclear magnética (RNM) (SILVA *et al.*, 2003; PUCCIONI-SOHLER *et al*., 2012; UMEHARA *et al*., 2007).

Outros estudos sugerem a ocorrência de alterações inflamatórias simultaneamente em todo o SNC, podendo ser observadas no córtex, cerebelo e tronco cerebral (GASCÓN *et al.*, 2017; TANAJURA *et al.*, 2015; SCHÜTZE *et al.*, 2017*;* IWASAKI, 1993). Há relatos de comprometimento cognitivo, sendo encontradas alterações na inteligência fluida, na memória visual imediata e no processamento da informação (GASCÓN *et al.*, 2017). Lesões temporais com distúrbios na memória e atenção também foram observadas (MENDES *et al.*, 2014).

Um estudo descreveu alterações no SNC relacionadas ao HTLV-1, observando, no encéfalo, áreas de inflamação perivascular na substância branca cerebral (CERVILLA; CARTIER; GARCÍA, 2006). Achados histopatológicos mostram que uma inflamação crônica acomete o SNC e a medula, sendo caracterizado por um infiltrado linfocitário perivascular composto principalmente por linfócitos T-CD4+ na doença inicial e linfócitos T-CD8+ na doença avançada, seguida por uma fase atrófica com menos celularidade (TAYLOR; MATSUOKA, 2005).

A HAM é uma doença de elevada morbidade e ainda com tratamento apenas sintomático. Após 10 anos de início da mielopatia, o paciente estará limitado a uma cadeira de rodas (GOTUZZO *et al*., 2000). Estudos têm avançado na busca por um tratamento que controle a evolução da doença (ARAYA *et al*., 2016; BUELL *et al*., 2016). O consenso é que qualquer medida terapêutica efetiva somente tem valor se iniciada na fase inicial da doença, ainda sem lesão neuronal estabelecida (LABANCA *et al.*, 2018). Por isso, o diagnóstico precoce é muito importante.

Castro-Costa e outros (2006) elaboraram proposta de um modelo modificado para o diagnóstico e classificação da HAM baseado em uma revisão da literatura sobre o assunto e nos critérios propostos pela Organização Mundial de Saúde. Os resultados deste estudo encontram-se resumidos no quadro 1.

Quadro 1. Critérios para os níveis de definição diagnóstica da Mielopatia associada ao HTLV-1 (HAM)

Definido:
Paraparesia espástica progressiva, não remissiva associada à marcha suficientemente comprometida para ser percebida pelo próprio paciente. Sintomas ou sinais sensitivos podem ou não estar presentes. Quando presentes permanecem sutis e sem nível sensitivo. Sinais ou sintomas esfincterianos anais e urinários podem ou não estar presentes;
Presença de anticorpos anti-HTLV-1 no soro e líquido cefalorraquidiano (LCR), confirmados por *Western Blot* (WB) e/ou detecção do *Deoxyribonucleic acid* (DNA) proviral no sangue e/ou LCR;
Exclusão de outras condições que se assemelham à HAM.
Provável:
Apresentação monossintomática: espasticidade ou hiperreflexia dos membros inferiores ou sinal de Babinski com ou sem sinais sensitivos sutis ou bexiga neurogênica isolada confirmada por testes urodinâmicos;
Presença de anticorpos anti-HTLV-1 no soro e LCR, confirmados por WB e/ou detecção do DNA proviral no sangue e/ou LCR;
Exclusão de outras condições que se assemelham à HAM.
Possível:
Apresentação clínica completa ou incompleta;
Presença de anticorpos anti-HTLV-1 no soro e LCR, confirmados por WB e/ou detecção do DNA proviral no sangue e/ou LCR;
Não exclusão de outras condições que se assemelham à HAM.

Fonte: CASTRO-COSTA *et al.* 2006

2.2 Equilíbrio corporal

O equilíbrio é consequência da interação contínua entre os sistemas vestibulares, proprioceptivos e visuais, os quais são integrados e modulados por todos os níveis do SNC.

As informações captadas pelos receptores periféricos chegam ao SNC por meio da porção vestibular do nervo vestíbulo coclear. O nervo vestibular possui dois ramos, o superior e o inferior. O primeiro recebe fibras provenientes do utrículo e canais semicirculares anterior e lateral e o segundo, recebe fibras do sáculo e do canal posterior. Além disso, o nervo auditivo recebe fibras do sáculo e o nervo vestibular inferior recebe fibras provenientes do órgão de Corti, demonstrando as conexões entre o aparelho auditivo e vestibular (GUERRAZ; DAY, 2005; HAIN; RAMASWAMY; HILLMAN, 2002).

O sistema sensorial periférico possui receptores vestibulares que enviam informações ao SNC sobre os movimentos e a posição da cabeça no espaço. Esses órgãos receptores são os canais semicirculares, que fornecem informações dos movimentos de rotação da cabeça, o utrículo, sensível a informação de movimento no plano horizontal e inclinação da cabeça e o sáculo, sensível a aceleração vertical. O sáculo e utrículo são denominados órgãos otolíticos. Os reflexos otolíticos respondem a variações de aceleração linear, principalmente por meio do trato vestíbulo-espinhal lateral, que produz uma excitação dos neurônios para musculatura extensora ipsilateral com inibição recíproca dos flexores (BONALDI, 2004; MUROFUSHI; CURTHOYS; GILCHRIST, 1996; DIDIER; CAZALS; AUROUSSOU, 1987).

A porção vestibular do VIII par projeta-se aos núcleos vestibulares lateral, inferior, medial e superior no tronco cerebral. Os núcleos vestibulares medial e superior recebem aferências principalmente dos canais semicirculares, projetando-se, por intermédio do fascículo longitudinal medial, aos núcleos oculomotores, cujos motoneurônios inervam os músculos extrínsecos oculares. Dentre os reflexos que se destinam a manter essa estabilidade destaca-se o reflexo vestíbulo-ocular. Este é desencadeado por movimentos da cabeça que tenderiam a deslocar a imagem projetada na retina. Movimentos oculares compensatórios são assim deflagrados a partir da informação vestibular, sendo que os olhos tendem a se mover de tal forma a anular o deslocamento da imagem que seria provocado pelo movimento da cabeça (BARMACK, 2003; BONALDI, 2004).

O núcleo medial envia também projeções bilaterais ao nível cervical da medula espinhal por intermédio do trato vestíbulo-espinhal medial. Essas projeções influenciam os motoneurônios medulares que inervam músculos cervicais, participando de reflexos que controlam movimentos do pescoço de maneira correlacionada e sinérgica aos movimentos oculares (BONALDI, 2004).

A porção ventral do núcleo vestibular lateral recebe aferências do utrículo e dos canais semicirculares, contribuindo também para os circuitos vestíbulo-oculares. A porção dorsal desse núcleo, recebendo aferências do cerebelo e da medula espinhal, envia projeções ipsilaterais ao corno anterior da medula espinhal, por intermédio do trato vestíbulo-espinhal lateral. Essas projeções sobre motoneurônios que inervam os músculos dos membros exercem excitação tônica sobre músculos extensores dos membros inferiores contribuindo na manutenção da postura (GUERRAZ; DAY, 2005; BONALDI, 2004).

O núcleo vestibular inferior recebe aferências tanto dos canais semicirculares quanto do sáculo e utrículo, além de projeções cerebelares. Suas projeções incluem circuitos vestíbulo-espinhais, integrando aferências vestibulares e cerebelares (BONALDI, 2004; MUROFUSHI; CURTHOYS; GILCHRIST, 1996).

Os reflexos vestíbulo-espinhais têm a função de estabilizar a cabeça no espaço e em relação ao tronco, assim como manter a postura ereta. Estímulos labirínticos levam a diferentes padrões de ativação na musculatura cervical e dos membros. Reflexos fásicos de curta latência são mediados pelos canais semicirculares por meio do trato vestíbulo-espinhal medial (vestíbulo-cólico). Estes têm a função de ativar músculos cervicais específicos, com consequente estabilização da cabeça no espaço, a partir de estímulos dos canais semicirculares (BONALDI, 2004; COLLARD, 1994).

O trato retículo-espinhal tem sua origem na formação reticular bulbar, sendo que a maioria dos neurônios retículo-espinhais ponto bulbares recebe aferências dos órgãos otolíticos e canais semicirculares e se projetam principalmente para neurônios medulares lombares e em menor número para neurônios cervicais (BONALDI, 2004).

Nas lesões do sistema vestibular, a vertigem decorre de informações sensoriais labirínticas conflitantes com as informações visuais e somatossensoriais. Muitas vezes, é acompanhada de sintomas neurovegetativos, como náuseas, vômitos, sudorese, palidez e taquicardia (STRUPP *et al.*, 2017).

2.3 Potencial Evocado Miogênico Vestibular (VEMP)

2.3.1 Artigo 1

Literature Review

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Applications of vestibular-evoked myogenic potentials: a systematic literature review

Aplicações dos potenciais evocados miogênicos vestibulares: revisão sistemática de literatura

Tatiana Rocha Silva[1], Marco Aurélio Rocha Santos[2], Luciana Macedo de Resende[3], Ludimila Labanca[1], Júlia Fonseca de Morais Caporali[4], Marjore Rhaissa de Sousa[5], Denise Utsch Gonçalves[6]

ABSTRACT

Purpose: To review the scientific literature on the main techniques used to generate vestibular-evoked myogenic potential (VEMP) and its clinical applications. **Research strategy:** A search for articles describing VEMP recording methods and applications was conducted in the PubMed, Web of Science, MEDLINE, Scopus, LILACS and SciELO databases. The search was limited to articles published in English, Portuguese, and Spanish between January 2012 and May 2018. **Selection criteria:** Articles addressing the technical aspects for performing ocular, cervical or soleus VEMP with auditory or galvanic stimulation and articles on the clinical applications of VEMP were included in this review, whereas articles repeated in the databases, literature reviews, case reports, letters, and editorials were excluded. **Results:** The search strategy resulted in the selection of 28 articles. The studies evidenced three methods of VEMP recording: responses from the cervical, ocular and soleus muscle. Clinical applications of VEMP included Meniere's disease, vestibular neuritis, superior semicircular canal dehiscence syndrome, Parkinson's disease, central ischemic lesions, and motor myelopathies. **Conclusion:** Regardless of the recording technique, VEMP has proved to be useful as a complementary tool for the diagnosis of peripheral and central vestibular diseases.

Keywords: Vestibular Nuclei; Vestibular-evoked Myogenic Potential; Postural balance; Vestibular function tests; Vestibular nerve

RESUMO

Objetivos: Revisar a literatura científica sobre as principais técnicas usadas para gerar o potencial evocado miogênico vestibular (VEMP) e suas aplicações clínicas. **Estratégia de pesquisa:** Os artigos que descrevem os métodos de registro e as aplicações do VEMP foram localizados nas bases de dados PubMed, Web of Science, MEDLINE, Scopus, LILACS e SciELO. O levantamento realizado limitou-se aos artigos publicados nos idiomas Inglês, Português e Espanhol, entre janeiro de 2012 e maio de 2018. **Critérios de seleção:** Artigos sobre os aspectos técnicos para a realização do VEMP ocular, cervical ou do músculo sóleo, com estimulação auditiva ou galvânica e artigos sobre as aplicações clínicas do VEMP foram incluídos; artigos repetidos nas bases de dados, artigos de revisão de literatura, relato de casos, cartas e editoriais foram excluídos. **Resultados:** A estratégia de busca resultou na seleção de 28 artigos. Os estudos evidenciaram três métodos de registro do VEMP: cervical, ocular e no músculo sóleo. As aplicações clínicas do VEMP incluíram doença de Ménière, neurite vestibular, síndrome da deiscência do canal semicircular superior, doença de Parkinson, lesões centrais isquêmicas e mielopatias motoras. **Conclusão:** Independentemente da técnica de registro, o VEMP mostrou-se útil como ferramenta complementar para o diagnóstico de doenças vestibulares periféricas e centrais.

Palavras-chave: Núcleos vestibulares; Potencial evocado miogênico vestibular; Equilíbrio postural; Testes de função vestibular; Nervo vestibular

Study carried out at Universidade Federal de Minas Gerais – UFMG, Belo Horizonte (MG), Brasil.

[1]Programa de Pós-graduação em Ciências da Saúde, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG), Brasil.
[2]Programa de Pós-graduação em Ciências Fonoaudiológicas, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG), Brasil.
[3]Departamento de Fonoaudiologia, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG), Brasil.
[4]Departamento de Clínica Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG), Brasil.
[5]Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG), Brasil.
[6]Departamento de Otorrinolaringologia, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG), Brasil.

Conflict of interest: No.

Author contributions: TRS was the main researcher, responsible for the study design and scheduling, literature search, collection and analysis of data, and writing and submission of the manuscript; MARS was one of the research co-advisers, in charge of the study design and scheduling, data analysis, and revision and approval of the manuscript; LMR was one of the research co-advisers, responsible for the study design and revision and approval of the manuscript; LL and JFMC were collaborating researchers, in charge of data analysis and revision of the manuscript; MRS was a collaborating researcher, participated in the collection and analysis of data; DUG was the research adviser, responsible for the study design and writing and approval of the manuscript.

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Corresponding author: Denise Utsch Gonçalves. e-mail: deniseg@medicina.ufmg.br

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INTRODUCTION

Vestibular-evoked myogenic potential (VEMP) is an electrophysiological method used to assess integration of the otolith organs and vestibular nerves with the brainstem and the muscular system. Therefore, it is a complementary exam that presents the differential of evaluating the central vestibular function, and it is related to a disynaptic reflex that has been considered to investigate brainstem function[1,2].

The VEMP is generated from the muscle reflex responses resulted of the vestibulo-ocular, the vestibulomasseteric and the vestibulospinal reflexes. These reflexes depend on the functional integrity of the utricular and saccular maculae, the inferior and superior vestibular nerves, the vestibular nuclei, the central vestibular pathways, and the neuromuscular plaques[3,4]. Changes in The VEMP are observed if any of the listed structures present injury.

The VEMP has been utilized to study a variety of vestibular diseases. Among peripheral diseases, Meniere's disease[5,6], vestibular neuritis[7], superior semicircular canal dehiscence[8-10], large vestibular aqueduct syndrome[11], and vestibular schwannoma[12,13] are highlighted, whereas among central vestibular diseases, vestibular migraine[14], Parkinson's disease[15], central ischemic lesions[16-18], and motor myelopathies[19-25] stand out.

The VEMP can be generated through auditory or galvanic stimulation and evoked responses can be obtained from several muscles such as extraocular, cervical, masseter, intercostal, brachialis, soleus, or gastrocnemius. The basic principle is the action of the muscular response in the postural control, either through vestibulo-ocular, vestibulocollic, or vestibulospinal reflex[2,3]. With this approach, VEMP application varies according to the type of stimulation and the electromyographic muscular response[2,5]. In its several modalities, this test presents characteristics favorable to its use in clinical practice: objectivity, non-invasiveness, easy execution, low cost, rapidity, and minimal discomfort for the patient. As any other electrophysiological examination, the examiner's experience is a determining factor for the test reliability[2].

PURPOSE

This study aimed at revising the scientific literature addressing the main techniques used to generate vestibular-evoked myogenic potentials (VEMP) and their clinical applications.

RESEARCH STRATEGY

A systematic review of the literature was conducted, without meta-analysis, based on the following question: What are the different methods used to generate VEMP and their clinical applications? A search was conducted in the PubMed, Web of Science, MEDLINE, Scopus, LILACS, and SciELO electronic databases for articles published between January 2012 and May 2018. The following descriptors were used in the search: *Vestibular-evoked myogenic potential*, *auditory stimulation*, *electric stimulation*, *postural balance*, and *vestibular nuclei*. Keywords were selected based on consultation with the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH), and were combined using the Boolean operator *AND*. The following combinations were used: *Vestibular-evoked myogenic potential* AND *auditory stimulation*; *Vestibular-evoked myogenic potential* AND *electric stimulation*; *Vestibular-evoked myogenic potential* AND *postural balance; Vestibular-evoked myogenic potential* AND *vestibular nuclei*.

Through these search strategies, 396 publications were found (205 in PubMed, 96 in Web of Science, 35 in MEDLINE, 52 in Scopus, and eight in SciELO). No publications were found on the LILACS database. First, the article titles were analyzed, and those associated with the theme proposed for the review were selected. Titles should make reference to VEMP. A second selection was conducted by analyzing the abstracts, which should include the clinical application of VEMP.

SELECTION CRITERIA

The articles met the following criteria to be included in this revision: 1) be published in Portuguese, English, or Spanish between January 2012 and May 2018; 2) titles should contain the word VEMP and a clinical application should be described in the title or abstract.

Articles that did not address VEMP and their clinical application in the title or abstract, did not mention the characteristics of the VEMP used, and did not describe the results of the evaluation were excluded. Articles repeated in the databases, literature reviews, case reports, letters, and editorials were also excluded from the review.

After analysis, 28 articles that met the inclusion criteria were selected for review. The article selection process was based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA Statement[26] (Figure 1).

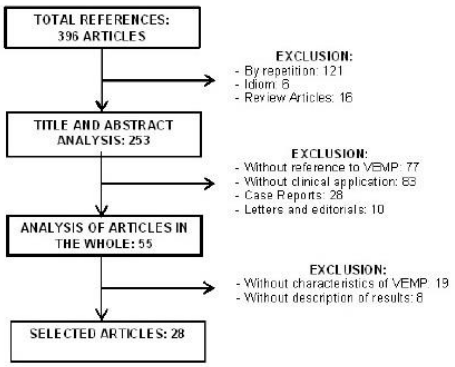

Figure 1. Summary of the study selection criteria
Subtitle: VEMP = Vestibular-evoked myogenic potential

DATA ANALYSIS

Initially, the studies were analyzed through the reading of their titles and abstracts. Subsequently, the studies included in the review were read in full. The recommendations included in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE statement)[27] were followed to analyze the selected studies. The following data were extracted from the articles after analysis: authors, year of publication, country where the research was conducted, VEMP recording method, method characterization, recording parameters, sample size, clinical application, and results.

A descriptive analysis of the results was performed and, due to the heterogeneity of the data, it was not possible to perform a meta-analysis.

RESULTS

The Chart 1 presents a summary of the 28 studies included in this review. The variables country of origin and design were described to assist with characterization of the studies included in the review, but are not part of the main outcomes. All articles selected were published in English. The countries with the largest number of publications were the USA (5; 18%)[8,10,16,18,28] and

Chart 1. Characterization of the 28 studies included in the review

Authors	Year / Country	Design	Sample	VEMP recording method	Method characterization	Application
Chang et al.[5]	2017 / Taipei (Taiwan)	Cross-sectional descriptive	70 individuals with unilateral Meniere's disease	VEMP cervical and ocular	Galvanic stimulation on the sternocleidomastoid muscle at 5 mA intensity, air-conducted sound stimulation (at 105 dB nHL intensity), and bone-conducted vibration (at 142 dB intensity), click at 600 Hz frequency	Use of cervical and ocular VEMP to investigate vestibular function in patients with Meniere's disease
Lin et al.[6]	2013 / Taipei (Taiwan)	Cross-sectional descriptive	50 individuals with unilateral Meniere's disease	VEMP cervical and ocular	Bone-conducted tone burst auditory stimulation at 500 Hz frequency and 144 dB intensity	Use of cervical and ocular VEMP to investigate the relationship with body balance in individuals with Meniere's disease
Walther and Blödow[7]	2013 / Mannheim (Germany)	Cross-sectional comparative	20 individuals with acute unilateral vestibular neuritis and a control group	VEMP cervical and ocular	Air-conducted tone burst sound stimulation at 500 Hz frequency and 100 dB nHL intensity	Assessment of cervical and ocular VEMP in patients with vestibular neuritis to verify the involvement of the semicircular canals and the otolith organs
Janky et al.[8]	2014 / Baltimore (USA)	Cross-sectional comparative	16 individuals with SSCD and a control group	VEMP cervical and ocular	Air-conducted sound stimulation, click (at 105 dB nHL intensity) and tone burst (at 125 dB SPL intensity), at 500 Hz frequency	Use of cervical and ocular VEMP in patients with SSCD to evaluate intralabyrinthine pressure
Manzari et al.[9]	2013 / Cassino (Italy)	Cross-sectional comparative	22 individuals with SSCD and a control group	VEMP cervical and ocular	Air-conducted sound stimulation (at 120 dB SPL intensity) and bone-conducted auditory stimulation (at 130 dB FL intensity), tone burst, at 125-8000 Hz frequency	Use of cervical and ocular VEMP to assist with diagnosis of SSCD
Zuniga et al.[10]	2013 / Baltimore (USA)	Cross-sectional comparative	29 individuals with SSCD and a control group	VEMP cervical and ocular	Air-conducted sound stimulation, click, at 500 Hz frequency and 105 dB nHL intensity	Use of cervical and ocular VEMP to evaluate sensitivity and specificity in the diagnosis of SSCD
Mahdi et al.[12]	2013 / Tehran (Iran)	Cross-sectional comparative	10 subjects with vestibular schwannoma and a control group	VEMP cervical	Air-conducted sound stimulation (at 95 dBnHL intensity) and bone-conducted auditory stimulation (at 70 dBnHL intensity), tone burst, at 500 Hz frequency	Use of cervical VEMP to evaluate vestibular function in patients with vestibular schwannoma

Subtitle: VEMP = Vestibular-evoked myogenic potential; BPPV = Benign paroxysmal positional vertigo; SSCD = Superior semicircular canal dehiscence

Chart 1. Continued...

Authors	Year / Country	Design	Sample	VEMP recording method	Method characterization	Application
Chiarovano et al.[13]	2014 / Paris (France)	Cross-sectional comparative	83 subjects with vestibular schwannoma and a control group	VEMP cervical and ocular	Air-conducted sound stimulation, click (at 105 dB nHL intensity) and tone burst (at 128 dB SPL intensity) and bone-conducted auditory stimulation, tone burst (at 135 dB intensity), at 500 Hz frequency	Use of cervical and ocular VEMP to assess the vestibular nerve function in patients with vestibular schwannoma
Kim et al.[14]	2015 / Gangwon-do (South Korea)	Cross-sectional comparative	38 individuals with migraine without aura, 30 individuals with tension headache, and a control group	VEMP cervical and ocular	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 125-130 dB nHL intensity	Use of cervical and ocular VEMP to investigate vestibular function in patients with migraine and tension headache
Shalash et al.[15]	2017 / Cairo (Egypt)	Cross-sectional comparative	15 individuals with Parkinson's disease and a control group	VEMP cervical and ocular	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 90 dBnHL intensity	Use of cervical and ocular VEMP to evaluate motor and non-motor symptoms in individuals with Parkinson's disease
Miller et al.[16]	2014 / Chicago (USA)	Cross-sectional descriptive	17 individuals with post-stroke spastic hypertonia	VEMP cervical	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 95 dB nHL intensity	Use of cervical VEMP to evaluate the level of spasticity in patients with post-stroke spasticity
Oh et al.[17]	2013 / Jeonju (South Korea)	Cross-sectional descriptive	52 individuals with acute brain injury	VEMP ocular	Air-conducted sound stimulation, tone burst, at 1000 Hz frequency and 100 dB nHL intensity	Use of ocular VEMP to evaluate the otolith ocular function involved in acute brain lesions
Miller et al.[18]	2016 / Pittsburgh (USA)	Cross-sectional descriptive	19 post-stroke individuals	VEMP ocular	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 95 dB nHL intensity	Assessment of ocular VEMP to analyze the ascending vestibulo-ocular pathways in post-stroke patients
Squair et al.[19]	2016 / Vancouver (Canada)	Cross-sectional comparative	16 individuals with spinal cord injury and a control group	VEMP cervical and soleus	Galvanic stimulation on the sternocleidomastoid muscle at 2 mA intensity and air-conducted sound stimulation, tone burst, at 500 Hz frequency and 125 dB intensity.	Use of cervical and soleus VEMP to evaluate muscle activity in individuals with spinal cord injury
Caporali et al.[20]	2016 / Belo Horizonte (Brazil)	Cross-sectional comparative	22 individuals with schistosomal myeloradiculopathy and control group	VEMP soleus	Galvanic stimulation on the sternocleidomastoid muscle at 2 mA intensity	Use of soleus VEMP to assess spinal cord function in individuals with schistosomal myeloradiculopathy
Felipe et al.[21]	2013 / Belo Horizonte (Brazil)	Cross-sectional comparative	60 individuals infected with Human T-lymphotropic virus type 1 (HTLV-1) and a control group	VEMP cervical	Air-conducted sound stimulation, tone burst, at 1000 Hz frequency and 118 dB HL intensity	Use of cervical VEMP to investigate subclinical neurological changes associated with HTLV-1 infection
Pelosi et al.[28]	2013 / Nashville (USA)	Cross-sectional descriptive	31 individuals with isolated unilateral utricular dysfunction	VEMP ocular	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 95 dB HL intensity	Use of ocular VEMP to define the characteristics of isolated unilateral utricular dysfunction

Subtitle: VEMP = Vestibular-evoked myogenic potential; BPPV = Benign paroxysmal positional vertigo; SSCD = Superior semicircular canal dehiscence

Chart 1. Continued...

Authors	Year / Country	Design	Sample	VEMP recording method	Method characterization	Application
Silva et al.[29]	2017 / Belo Horizonte (Brazil)	Cross-sectional comparative	30 individuals with unilateral Meniere's disease, 30 individuals with vestibular hyporeflexia, and a control group	VEMP cervical and ocular	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 120 dBnHL intensity	Use of cervical and ocular VEMP to assess vestibular function in patients with Meniere's disease and vestibular hyporeflexia
Saka et al.[30]	2012 / Nishinomiya (Japan)	Cross-sectional descriptive	25 individuals with otosclerosis	VEMP cervical	Bone-conducted auditory stimulation, tone burst, at de 250 Hz frequency and 60 dB nHL intensity	Use of cervical VEMP to evaluate balance in individuals with otosclerosis
Tal et al.[31]	2016 / Haifa (Israel)	Cross-sectional descriptive	30 sailors on medication for motion sickness	VEMP cervical	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 90 dB nHL intensity	Use of cervical VEMP to assess absorption and efficacy of motion sickness medication
Brantberg and Verrecchia[32]	2012 / Stockholm (Sweden)	Cross-sectional comparative	38 individuals with SSCD and a control group	VEMP cervical	Air-conducted sound stimulation, click (at 80-90 dB nHL intensity) and tone burst (at 130 dB SPL intensity), at 500 Hz frequency	Use of cervical VEMP as a screening test in patients with SSCD
Demirhan et al.[33]	2016 / Istanbul (Turkey)	Cross-sectional comparative	30 individuals with cochlear implant and a control group	VEMP cervical	Air-conducted sound stimulation, tone burst, at 500 and 1000 Hz frequencies and 100 dB nHL intensity	Use of cervical VEMP in individuals with cochlear implant to assess vestibular function
Tax et al.[34]	2013 / Sidney (Australia)	Cross-sectional comparative	Eight individuals with bilateral vestibular dysfunction and a control group	VEMP cervical, ocular, and soleus	Galvanic stimulation at 1 mA intensity	Evaluation of VEMP with galvanic stimulation to analyze the vestibulospinal reflex in individuals with bilateral vestibular dysfunction
Sreenivasan et al.[35]	2015 / Puducherry (India)	Cross-sectional comparative	15 individuals with BPPV and a control group	VEMP cervical	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 105 dB nHL intensity	Assessment of cervical VEMP to define the characteristics of BPPV
Güven et al.[36]	2014/ Cankaya (Turkey)	Cross-sectional comparative	50 individuals with multiple sclerosis and a control group	VEMP cervical	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 120 dB intensity	Use of cervical VEMP to evaluate the contribution of this myogenic potential to the diagnosis of multiple sclerosis
Harirchian et al.[37]	2013 / Tehran (Iran)	Cross-sectional comparative	20 individuals with multiple sclerosis and a control group	VEMP cervical	Air-conducted sound stimulation, click, at 500 Hz frequency and 95 dB NHL intensity	Use of cervical VEMP to assess sensitivity in the diagnosis of multiple sclerosis
Iwasaki et al.[38]	2013 / Tokyo (Japan)	Cross-sectional comparative	14 individuals with unilateral peripheral vestibular dysfunction and a control group	VEMP ocular	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 135 dBSPL intensity	Use of ocular VEMP to investigate vestibular function in individuals with vestibular dysfunction
Parkes et al.[39]	2017 / Toronto (Canada)	Longitudinal cohort	33 individuals with cochlear implant assessed by VEMP and a non-exposed group	VEMP cervical and ocular	Air-conducted sound stimulation, tone burst, at 500 Hz frequency and 124 dB SPL intensity	Use of cervical and ocular VEMP in individuals with cochlear implant

Subtitle: VEMP = Vestibular-evoked myogenic potential; BPPV = Benign paroxysmal positional vertigo; SSCD = Superior semicircular canal dehiscence

Brazil (3; 11%)[20,21,29]. Sample size of the studies ranged from eight to 83 individuals with peripheral and central vestibular disorders.

Regarding the design, eight (29%) studies were descriptive[5-6,16-18,28,30-31], 19 (68%) were comparative cross-sectional[7-10,12-15,19-21,29,32-38], and one (3%) was longitudinal cohort[39].

With respect to the diseases, the most commonly investigated clinical applications in patients with vestibular disorders referred to Meniere's disease[5-6,29], superior semicircular canal dehiscence syndrome[8-10,32], vestibular schwannoma[12-13], and central ischemic lesions[15-21,36-37].

Three methods of vestibular-evoked myogenic potential (VEMP) recording were identified in the 28 articles assessed, with the cervical and the ocular as the most commonly used methods (Figure 2).

Concerning the type of applied stimulation, the number (%) of studies using the sound or the electric stimulation were: 19 (68%), auditory - rarefaction tone burst[6-7,9,12,14-18,21,28-31,33,35-36,38-39]; three (11%), auditory - rarefaction tone burst and click[8,13,32]; two (7%), auditory - click[10,37]; two (7%), galvanic[20,34]; one (3.5%), auditory - click and galvanic[5]; one (3.5%), auditory - rarefaction tone burst and galvanic[19]. The electric current intensity of galvanic stimulation ranged from 1 to 5 mA[5,19,20,34].

Regarding the frequency of auditory stimulation, 500 Hz was predominant - used in 21 (81%) studies[6-8,10,12-16,18-19,28-29,31-33,35-39], followed by 1000 Hz - applied in two (7%) investigations[17,21], 600 Hz - used in one (4%) survey[5], 250 Hz - utilized in one (4%) study[30], and one research used various frequencies[9].

Regarding the type of stimulus conduction, 21 (81%) studies used air-conducted sound[7-10,14-19,21,28-29,31-33,35-39], two (7%) researches applied bone-conducted vibration[6,30], and three (12%) surveys utilized both air- and bone-conducted stimulation[5,12,13].

All the studies that used VEMP to evaluate Meniere's disease[5-6,29] adopted either cervical or ocular recording. About the type of stimulus, two of these surveys[6,29] used rarefaction tone burst auditory stimulation at a frequency of 500 Hz and one[5] applied click auditory stimulation at 600 Hz. Air-conducted sound[29], bone-conducted vibration[6], and both air- and bone-conducted stimulation[5] were also observed.

With respect to application of VEMP to superior semicircular canal dehiscence[8-10,32], this review verified that three studies[8-10] used cervical and ocular VEMP recording and one used only cervical recording. Of these studies, one[9] applied rarefaction tone burst auditory stimulation at variable frequency, one[10] used click auditory stimulation at 500 Hz, and two[8,32] utilized both rarefaction tone burst and click auditory stimulation at a frequency of 500 Hz. The air-conducted sound stimulation was the only chosen in all the studies[8-10,32].

As for application to vestibular schwannoma[12,13], one study[13] used cervical and ocular VEMP recording and the other[12] used only cervical recording. One[12] utilized air-conducted rarefaction tone burst sound stimulation at a frequency of 500 Hz and the other[13] applied both air-conducted sound and bone-conducted vibration stimulation using rarefaction tone burst and click at 500 Hz.

About VEMP for testing central ischemic lesions[15-21,36,37], this review found that one study[15] used both cervical and ocular VEMP, four[16,21,36,37] used only cervical VEMP, two[17,18] only ocular VEMP, one[20] only soleus VEMP, and one[19] applied both cervical and soleus VEMP. Of these studies, four[15-16,18,36] used air-conducted rarefaction tone burst sound stimulation at a frequency of 500 Hz, two[17,21] applied air-conducted rarefaction tone burst sound stimulation at 1000 Hz, one[37] utilized air-conducted click sound stimulation at 500 Hz, one[19] used air-conducted rarefaction tone burst sound stimulation at 500 Hz and galvanic stimulation at an electric current of 2 mA, and one[20] applied only galvanic stimulation at 2 mA.

The Chart 2 shows a summary of the main characteristics of the VEMP recording methods. Figures 3, 4, and 5 show VEMP recording methods according to the type of stimulation and neural pathway, positioning of the electrodes for muscle response, and electrophysiological waveform generated.

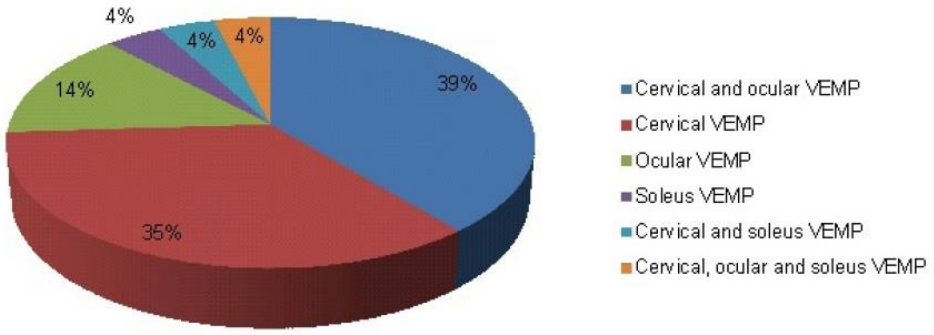

Figure 2. Distribution of the studies according to the methods of vestibular myogenic evoked potential (VEMP) recording
Subtitle: VEMP = Vestibular-evoked myogenic potential

Chart 2. Summary of the main characteristics of the vestibular-evoked myogenic potential (VEMP) recording methods

Types of VEMP	Ocular VEMP	Cervical VEMP	Soleus VEMP
Record of the response muscle	Extraocular, mainly inferior oblique	Sternocleidomastoid	Soleus or Gastrocnemius
Stimulation more used	Auditory (sound)	Auditory (sound)	Galvanic (electric)
Neural pathway assessed	Contralateral vestibulo-ocular tract	Medial vestibulospinal tract (ipsilateral via)	Lateral vestibulospinal tract (ipsilateral via)
Biphasic electrophysiological waveform	N10 - P15	P13 - N23	SL – ML

Subtitle: VEMP = Vestibular-evoked myogenic potential; N10 = Negative peak N with mean latency of 10 ms; P15 = Positive peak P with mean latency of 15 ms; P13 = Positive peak P with mean latency of 13 ms; N23 = Negative peak N with mean latency of 23 ms; SL = Short-latency component (approximately 60 ms); ML = Medium-latency component (approximately 110 ms)

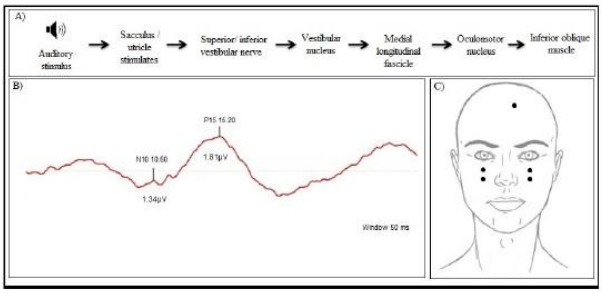

Figure 3. Ocular vestibular-evoked myogenic potential (ocular VEMP). (A) Type of stimulation and neural pathway; (B) Electrophysiological waveform; (C) Positioning of the electrodes for recording

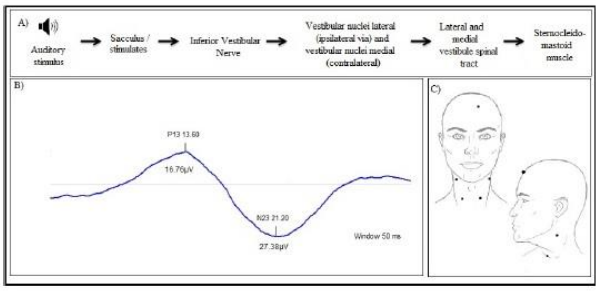

Figure 4. Cervical vestibular-evoked myogenic potential (cervical VEMP). (A) Type of stimulation and neural pathway; (B) Electrophysiological waveform; (C) Positioning of the electrodes for recording

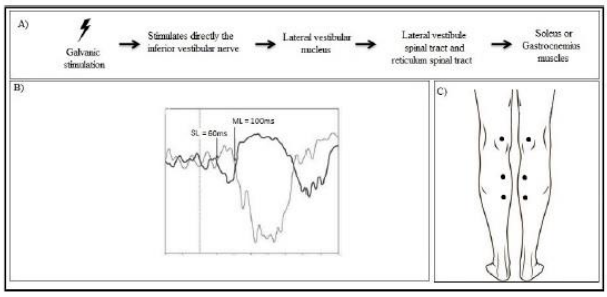

Figure 5. Soleus muscle vestibular-evoked myogenic potential (soleus VEMP). (A) Type of stimulation and neural pathway; (B) Electrophysiological waveform; (C) Positioning of the electrodes for recording

DISCUSSION

The studies about VEMP with auditory stimulation have evidenced this test as an assisting tool for the diagnosis of several types of peripheral vestibular disorders, predominantly Meniere's disease[5,6,29,40] and superior semicircular canal dehiscence (SSCD)[8-11,32], as well as diseases related to central vestibular disorders, such as motor myelopathies[19-25] and Parkinson's disease[15,41-43].

In Meniere's disease, some authors have reported that cervical VEMP changes occur in consequence of the cochleosaccular hydrops[5,6], while other authors have understood that the changes depend on the stage of this disease[29,40]. In the early stages of the disease, increased amplitudes are observed in cervical VEMP owing to hypersensitivity of the saccule, which would be caused by saccular dilatation, whereas in late stages, the amplitudes may be attenuated as a result of atrophy of the sensory epithelium of the saccular membrane[29]. Concomitant changes in cervical and ocular VEMP would be associated with involvement of the saccule and the utricle, respectively[5,40]. Therefore, simultaneous alteration of cervical and ocular VEMP occurs more commonly in the advanced stage of Meniere's disease[29,40].

The literature reports that, in SSCD, the cervical and the ocular VEMP recording presents a pattern of response that is different from those observed in other vestibular diseases[8-10]. Electrophysiological response with auditory stimulation at lower sound intensity (approximately 70 dB nHL) is observed, as well as waveforms with increased amplitude on the compromised side, keeping the normal morphology[11,32]. This finding has been associated with a change in the bone layer that covers the superior semicircular canal[8-10] that when thinner, can cause a decrease in impedance and, consequently, an increased sound transmission to the labyrinth, with greater sensitivity of the saccule to sound stimulation. VEMP response at low sound stimulation associated with higher wave amplitude that increases according to the level of sound intensity for both the cervical and the ocular potentials, suggest the diagnosis of SSCD and indicate that the central vestibular system is not affected in this syndrome[8-11,32].

Regarding central lesions, studies addressing infectious myelopathies showed that cervical VEMP responses were altered in over half of the individuals with myelopathy[22-23]. Cervical VEMP enabled to diagnose a spinal disfunction that was subclinical, in addition to assessing the disease evolution[21].

In Parkinson's disease, cervical VEMP and ocular VEMP were used to evaluate the postural control. A study that assessed the vestibulocollic reflex in individuals with Parkinson's disease reported that cervical VEMP responses showed reduced amplitudes. According to the authors, these findings suggest reduction in the reflexes that correlate with the vestibular activity[15]. Another study showed changes in cervical and ocular VEMP responses in patients with Parkinson's disease and postural instability[43].

About the type of sound stimulus used to generate VEMP, the tone burst auditory stimulation was identified in several studies and it is justified by the fact that the threshold of saccular excitability is lower for this type of stimulus when compared to click stimulation, and it is more comfortable for the individual[4]. The frequency of 500 Hz is the most common choice because it generates a more homogeneous and constant response[4,44].

With respect to the comparison of air-conducted sound and bone-conducted vibration auditory stimulation, some authors believe that the advantage of the latter lies in the possibility of testing individuals with conductive hearing loss[7,12,17,30]. However, bone-conducted stimulation is seldom used, considering that galvanic stimulation, which is independent of the middle ear, offers more robust electrophysiological response[42,45,46].

Studies have observed that VEMP obtained through galvanic stimulation presents the advantage of acting on the postsynaptic membrane, next to the vestibular nuclei and, when associated with other vestibular battery tests, enables distinction between peripheral and central vestibular disorders[45,46]. As galvanic stimulation reaches the terminal axons of the vestibular nerve in the junction with the vestibular nucleus, when comparing the response to VEMP using auditory stimulation with that of VEMP using galvanic stimulation in the same patient, it is possible to differentiate whether the lesion is vestibular or retrovestibular[42,45-47]. For example, in the presence of peripheral vestibular neuropathy, VEMP with auditory stimulation will show altered results, whereas VEMP with galvanic stimulation will present normal result[25].

VEMP with galvanic stimulation has been proved to be an important tool for the subclinical diagnosis of motor myelopathies[20,21,25] and for the definition of the level of spinal cord involvement[19-21]. For instance, when assessing patients with motor or traumatic myelopathy and submitting them to VEMP with galvanic stimulation with the response recorded in different postural muscles (e.g. cervical, intercostal, and soleus), it is possible to infer about the topodiagnosis of the medullar lesion based on which muscle presented VEMP response. In clinical practice, recording of soleus VEMP triggered by auditory stimulation is difficult to obtain due to lower accumulation of energy, compared with that of the galvanic method, which is much more robust[46]. Thus, for the VEMP of the soleus muscle, the best stimulus is the galvanic one. For ocular and cervical VEMP, the response can be generated with both auditory and galvanic stimuli.

The different methods related to the parameters used to perform VEMP and the presentation of the results limited the comparison among studies. On the other hand, the importance of using different VEMP recording methods to assess otolith function and vestibular pathway is the diversity of vestibular diseases that can be evaluated through VEMP. Therefore, in vestibular electrophysiology research, VEMP has emerged as an outstanding complementary examination to assess vestibular function. The use of VEMP, coupled with other vestibular tests, enables a more comprehensive evaluation and, consequently, a better knowledge about the structures contained in the labyrinth and their neural pathways.

CONCLUSION

In this article, we reviewed the clinical aspects of VEMP, the stimulus modalities and the muscles most used to register the evoked response. Cervical VEMP, ocular VEMP and soleus VEMP are the most used. The auditory stimulus is the most used to generate the cervical and ocular VEMP, while the galvanic (electric) stimulus is the most used to generate the VEMP of the soleus muscle. These tests are very important for the evaluation of peripheral and central vestibular system function.

REFERENCES

1. Silva TR, Resende LM, Santos MAR. Potencial evocado miogênico vestibular ocular e cervical simultâneo em indivíduos normais. CoDAS. 2016;28(1):34-40. http://dx.doi.org/10.1590/2317-1782/20162015040. PMid:27074187.
2. Kantner C, Gürkov R. Characteristics and clinical applications of ocular vestibular evoked myogenic potentials. Hear Res. 2012;294(1-2):55-63. http://dx.doi.org/10.1016/j.heares.2012.10.008. PMid:23123220.
3. Cunha LCM, Labanca L, Tavares MC, Gonçalves DU. Vestibular evoked myogenic potential (VEMP) with galvanic stimulation in normal subjects. Braz J Otorhinolaryngol. 2014;80(1):48-53. http://dx.doi.org/10.5935/1808-8694.20140011. PMid:24626892.
4. Park HJ, Lee IS, Shin JE, Lee YJ, Park MS. Frequency-tuning characteristics of cervical and ocular vestibular evoked myogenic potentials induced by air-conducted tone bursts. Clin Neurophysiol. 2010;121(1):85-9. http://dx.doi.org/10.1016/j.clinph.2009.10.003. PMid:19892592.
5. Chang CM, Young YH, Jaw FS, Wang CT, Cheng PW. Degeneration of the vestibular nerve in unilateral Meniere's disease evaluated by galvanic vestibular-evoked myogenic potentials. Clin Neurophysiol. 2017;128(9):1617-24. http://dx.doi.org/10.1016/j.clinph.2017.06.004. PMid:28719825.
6. Lin CY, Wang SJ, Young YH. Correlations between foam posturography and vestibular-evoked myogenic potential tests in Ménière's disease. Ear Hear. 2013;34(5):673-9. http://dx.doi.org/10.1097/AUD.0b013e31828d267f. PMid:23985977.
7. Walther LE, Blödow A. Ocular vestibular evoked myogenic potential to air conducted sound stimulation and video head impulse test in acute vestibular neuritis. Otol Neurotol. 2013;34(6):1084-9. http://dx.doi.org/10.1097/MAO.0b013e318280da47. PMid:23370570.
8. Janky KL, Zuniga MG, Schubert MC, Carey JP. The effect of increased intracranial pressure on vestibular evoked myogenic potentials in superior canal dehiscence syndrome. Clin Neurophysiol. 2015;126(4):780-6. http://dx.doi.org/10.1016/j.clinph.2014.06.049. PMid:25103787.
9. Manzari L, Burgess AM, McGarvie LA, Curthoys IS. An indicator of probable semicircular canal dehiscence: ocular vestibular evoked myogenic potentials to high frequencies. Otolaryngol Head Neck Surg. 2013;149(1):142-5. http://dx.doi.org/10.1177/0194599813489494. PMid:23674567.
10. Zuniga MG, Janky KL, Nguyen KD, Welgampola MS, Carey JP. Ocular versus cervical VEMPs in the diagnosis of superior semicircular canal dehiscence syndrome. Otol Neurotol. 2013;34(1):121-6. http://dx.doi.org/10.1097/MAO.0b013e31827136b0. PMid:23183641.
11. Janky KL, Nguyen KD, Welgampola M, Zuniga MG, Carey JP. Air-conducted oVEMPs provide the best separation between intact and superior canal dehiscent labyrinths. Otol Neurotol. 2013;34(1):127-34. http://dx.doi.org/10.1097/MAO.0b013e318271c32a. PMid:23151775.
12. Mahdi P, Amali A, Pourbakht A, Yazdi AK, Bassam A. Vestibular evoked myogenic potential produced by bone-conducted stimuli: a study on its basics and clinical applications in patients with conductive and sensorineural hearing loss and a group with vestibular Schawannoma. Iran J Otorhinolaryngol. 2013;25(72):141-6. PMid:24303434.
13. Chiarovano E, Darlington C, Vidal PP, Lamas G, de Waele C. The role of cervical and ocular vestibular evoked myogenic potentials in the assessment of patients with vestibular schwannomas. PLoS One. 2014;9(8):1-10. http://dx.doi.org/10.1371/journal.pone.0105026. PMid:25137289.
14. Kim CH, Jang MU, Choi HC, Sohn JH. Subclinical vestibular dysfunction in migraine patients: a preliminary study of ocular and rectified cervical vestibular evoked myogenic potentials. J Headache Pain. 2015;16(1):1-9. http://dx.doi.org/10.1186/s10194-015-0578-5. PMid:26527349.
15. Shalash AS, Hassan DM, Elrassas HH, Salama MM, Méndez-Hernández E, Salas-Pacheco JM, et al. Auditory – and vestibular – evoked potentials correlate with motor and non-motor features of Parkinson's disease. Front Neurol. 2017;8:1-8. http://dx.doi.org/10.3389/fneur.2017.00055. PMid:28289399.
16. Miller DM, Klein CS, Suresh NL, Rymer WZ. Asymmetries in vestibular evoked myogenic potentials in chronic stroke survivors with spastic hypertonia: evidence for a vestibulospinal role. Clin Neurophysiol. 2014;125(10):2070-8. http://dx.doi.org/10.1016/j.clinph.2014.01.035. PMid:24680197.
17. Oh SY, Kim JS, Lee JM, Shin BS, Hwang SB, Kwak KC, Kim C, Jeong SK, Kim TW. Ocular vestibular evoked myogenic potentials induced by air-conducted sound in patients with acute brainstem lesions. Clin Neurophysiol. 2013;124(4):770-8. http://dx.doi.org/10.1016/j.clinph.2012.09.026. PMid:23121898.
18. Miller DM, Baker JF, Rymer WZ. Ascending vestibular drive is asymmetrically distributed to the inferior oblique motoneuron pools in a subset of hemispheric stroke survivors. Clin Neurophysiol. 2016;127(4):2022-30. http://dx.doi.org/10.1016/j.clinph.2016.01.019. PMid:26971485.
19. Squair JW, Bjerkefors A, Inglis JT, Lam T, Carpenter MG. Cortical and vestibular stimulation reveal preserved descending motor pathways in individuals with motor-complete spinal cord injury. J Rehabil Med. 2016;48(7):589-96. http://dx.doi.org/10.2340/16501977-2101. PMid:27292455.
20. Caporali JFM, Gonçalves DU, Labanca L, Oliveira LD, Trindade GVM, Pereira TA, et al. Vestibular evoked myogenic potential (VEMP) triggered by galvanic vestibular stimulation (GVS): a promising tool to assess spinal cord function in Schistosomal Myeloradiculopathy. PLoS Negl Trop Dis. 2016;10:1-11.
21. Felipe L, Kingma H, Lambertucci JR, Carneiro-Proietti AB, Gonçalves DU. Testing the vestibular evoked myogenic potential (VEMP) to identify subclinical neurological alterations in different phases of human T-lymphotropic virus type 1 infection. Spine J. 2013;13(4):397-401. http://dx.doi.org/10.1016/j.spinee.2012.11.015. PMid:23267739.
22. Felipe L, Gonçalves DU, Santos MA, Proietti FA, Ribas JG, Carneiro-Proietti AB, Lambertucci JR. Vestibular-Evoked Myogenic Potential (VEMP) to Evaluate Cervical Myelopathy in Human T-Cell Lymphotropic Virus Type I Infection. Spine. 2008;33(11):1180-4. http://dx.doi.org/10.1097/BRS.0b013e31817152ed. PMid:18469690.
23. Labanca L, Starling AL, Sousa-Pereira SR, Romanelli LC, Carneiro-Proietti ABF, Carvalho LN, et al. Electrophysiological analysis shows dizziness as the first symptom in Human T Cell Lymphotropic Virus Type-Associated Myelopathy/Tropical Spastic Paraparesis. AIDS Res Hum Retroviruses. 2015;31(6):649-54. http://dx.doi.org/10.1089/aid.2014.0153. PMid:25760424.
24. Iles JF, Baderin R, Tanner R, Simon A. Human standing and walking: comparison of the efects of stimulation of the vestibular system. Exp Brain Res. 2007;178(2):151-66. http://dx.doi.org/10.1007/s00221-006-0721-2. PMid:17031681.
25. Cunha LCM, Tavares MC, Criollo CJT, Labanca L, Paz CCSC, Martins HR, et al. Contribution of galvanic vestibular stimulation in the diagnosis of HTLV-1-associated myelopathy/tropical spastic paraparesis. J Clin Neurol. 2013;9(4):252-8. http://dx.doi.org/10.3988/jcn.2013.9.4.252. PMid:24285967.

26. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. PLoS Med. 2009;6(7):e1000097. http://dx.doi.org/10.1371/journal.pmed.1000097. PMid:19621072.

27. Malta M, Cardoso LO, Bastos FI, Magnanini MM, Silva CM. Iniciativa STROBE: subsídios para a comunicação de estudos observacionais. Rev Saude Publica. 2010;44(3):559-65. http://dx.doi.org/10.1590/S0034-89102010000300021. PMid:20549022.

28. Pelosi S, Schuster D, Jacobson GP, Carlson ML, Haynes DS, Bennett ML, et al. Clinical characteristics associated with isolated unilateral utricular dysfunction. Am J Otolaryngol. 2013;34(5):490-5. http://dx.doi.org/10.1016/j.amjoto.2013.04.008. PMid:23759133.

29. Silva TR, Resende LM, Santos MAR. Combined ocular and cervical vestibular evoked myogenic potential in individuals with vestibular hyporeflexia and in patients with Ménière's disease. Rev Bras Otorrinolaringol (Engl Ed). 2017;83(3):330-40. http://dx.doi.org/10.1016/j.bjorl.2016.04.017. PMid:27320652.

30. Saka N, Seo T, Fujimori K, Mishiro Y, Sakagami M. Vestibular-evoked myogenic potential in response to bone-conducted sound in patients with otosclerosis. Acta Otolaryngol. 2012;132(11):1155-9. http://dx.doi.org/10.3109/00016489.2012.694473. PMid:22830649.

31. Tal D, Shemy S, Kaminski-Graif G, Wiener G, Hershkovitz D. Vestibular evoked myogenic potentials and motion sickness medications. Clin Neurophysiol. 2016;127(6):2350-4. http://dx.doi.org/10.1016/j.clinph.2016.03.010. PMid:27178852.

32. Brantberg K, Verrecchia L. Effectiveness of different click stimuli in diagnosing superior canal dehiscence using cervical vestibular evoked myogenic potentials. Acta Otolaryngol. 2012;132(10):1077-83. http://dx.doi.org/10.3109/00016489.2012.689858. PMid:22779948.

33. Demirhan H, Yıldız M, Yiğit Ö. Do Vestibular-evoked myogenic potential abnormalities in patients with cochlear implant only reflect saccular dysfunction? J Int Adv Otol. 2016;12(2):166-9. http://dx.doi.org/10.5152/iao.2016.2522. PMid:27716603.

34. Tax CMW, Bom AP, Taylor RL, Todd N, Cho K-KJ, Fitzpatrick RC, Welgampola MS, et al. The galvanic whole-body sway response in health and disease. Clin Neurophysiol. 2013;124(10):2036-45. http://dx.doi.org/10.1016/j.clinph.2012.12.041. PMid:23849702.

35. Sreenivasan A, Sivaraman G, Parida PK, Alexander A, Saxena SK, Suria G. The clinical utility of vestibular evoked myogenic potentials in patients of benign paroxysmal positional vertigo. J Clin Diagn Res. 2015;9(6):1-3. PMid:26266140.

36. Güven H, Bayır O, Aytaç E, Ozdek A, Comoğlu SS, Korkmaz H. Vestibular-evoked myogenic potentials, clinical evaluation, and imaging findings in multiple sclerosis. Neurol Sci. 2014;35(2):221-6. http://dx.doi.org/10.1007/s10072-013-1483-9. PMid:23807120.

37. Harirchian MH, Karimi N, Nafisi S, Akrami S, Ghanbarian D, Gharibzadeh S. Vestibular evoked myogenic potential for diagnoses of multiple sclerosis: is it beneficial? Med Glas (Zenica). 2013;10(2):321-6. PMid:23892852.

38. Iwasaki S, Egami N, Inoue A, Kinoshita M, Fujimoto C, Murofushi T, et al. Ocular vestibular evoked myogenic potential elicited from binaural air-conducted stimulations: clinical feasibility in patients with peripheral vestibular dysfunction. Acta Otolaryngol. 2013;133(7):708-13. http://dx.doi.org/10.3109/00016489.2013.767476. PMid:23768055.

39. Parkes WJ, Gnanasegaram JJ, Cushing SL, McKnight CL, Papsin BC, Gordon KA. Vestibular evoked myogenic potential testing as an objective measure of vestibular stimulation with cochlear implants. Laryngoscope. 2017;127(2):E75-81. http://dx.doi.org/10.1002/lary.26037. PMid:27291637.

40. Wen MH, Cheng PW, Young YH. Augmentation of ocular vestibular evoked myogenic potentials via bone-conducted vibration stimuli in Meniere's disease. Otolaryngol Head Neck Surg. 2012;146(5):797-803. http://dx.doi.org/10.1177/0194599811433982. PMid:22237297.

41. Kataoka H, Okada Y, Kiriyama T, Kita Y, Nakamura J, Morioka S, et al. Can postural instability respond to galvanic vestibular stimulation in patients with Parkinson's Disease? J Mov Disord. 2015;9(1):40-3. http://dx.doi.org/10.14802/jmd.15030. PMid:26648182.

42. Samoudi G, Jivegard M, Mulavara AP, Bergquist F. Effects of stochastic vestibular galvanic stimulation and LDOPA on balance and motor symptoms in patients with Parkinson's disease. Brain Stimul. 2015;8(3):474-80. http://dx.doi.org/10.1016/j.brs.2014.11.019. PMid:25573070.

43. Natale ER, Ginatempo F, Paulus KS, Pes GM, Manca A, Tolu E, et al. Abnormalities of vestibular-evoked myogenic potentials in idiopathic Parkinson's disease are associated with clinical evidence of brainstem involvement. Neurol Sci. 2015;36(6):995-1001. http://dx.doi.org/10.1007/s10072-014-2054-4. PMid:25567081.

44. Cheng PW, Huang TW, Young YH. The influence of clicks versus short tone bursts on the vestibular evoked myogenic potentials. Ear Hear. 2003;24(3):195-7. http://dx.doi.org/10.1097/01.AUD.0000069225.80220.CB. PMid:12799540.

45. Carmona S, Ferrero A, Pianetti G, Escolá N, Arteaga MV, Frankel L. Galvanic vestibular stimulation improves the results of vestibular rehabilitation. Ann N Y Acad Sci. 2011;1233(1):1-7. http://dx.doi.org/10.1111/j.1749-6632.2011.06269.x. PMid:22360772.

46. Watson SRD, Colebatch JG. Vestibular-evoked electromyographic responses in soleus: a comparison between click and galvanic stimulation. Exp Brain Res. 1998;119(4):504-10. http://dx.doi.org/10.1007/s002210050366. PMid:9588785.

47. Collard M. The vestibular system: from structure to function. Rev Prat. 1994;44(3):295-8. PMid:8178092.

3 OBJETIVOS

3.1 Objetivo geral

- Avaliar, por eletrofisiologia, a extensão do comprometimento neurológico na infecção pelo HTLV-1

3.2 Objetivos específicos

- Caracterizar as respostas do VEMP ocular, cervical e do músculo sóleo em indivíduos com infecção assintomática pelo HTLV-1 e com mielopatia;

- Comparar as respostas do VEMP ocular, cervical e do músculo sóleo em indivíduos infectados pelo HTLV-1 assintomáticos e com mielopatia.

4 METODOLOGIA

Para evitar redundância, as informações referentes aos materiais e métodos que estão nos artigos foram suprimidas desta secção. Abaixo, um fluxograma do estudo.

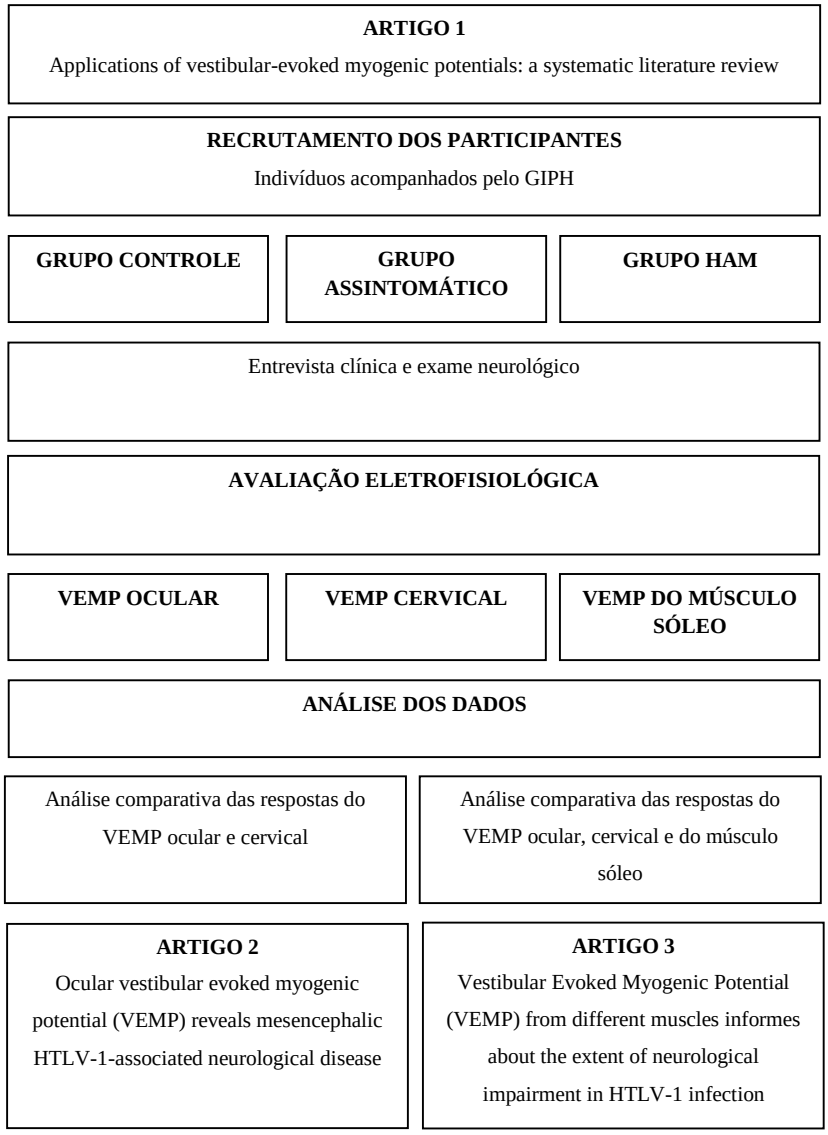

Figura 1: **Fluxograma do estudo**

5 RESULTADOS E DISCUSSÃO

5.1 Artigo 2

PLOS ONE

RESEARCH ARTICLE

Ocular vestibular evoked myogenic potential (VEMP) reveals mesencephalic HTLV-1-associated neurological disease

Tatiana Rocha Silva[1], Ludimila Labanca[1], Júlia Fonseca de Morais Caporali[1], Marco Aurélio Rocha Santos[2], Luciana Macedo de Resende[2], Rafael Teixeira Scoralick Dias[1], Denise Utsch Gonçalves[1]*

1 Programa de Pós-Graduação em Infectologia e Medicina Tropical, Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil, 2 Programa de Pós-Graduação em Ciências Fonoaudiológicas, Faculdade de Medicina da Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

* deniseg@medicina.ufmg.br

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Abstract

Purpose

Vestibular Myogenic Evoked Potential (VEMP) evaluates vestibulo-ocular and vestibulo-collic reflexes involved in the function of the otolithic organs and their afferent pathways. We compared the results of cervical and ocular VEMP in HTLV-1 associated myelopathy (HAM) and HTLV-1-asymptomatic infection.

Participants and methods

This cross-sectional study included 52 HTLV-1-infected individuals (26 HAM and 26 asymptomatic carriers) and 26 seronegative controls. The groups were similar regarding age and gender. Participants underwent simultaneous ocular and cervical VEMP. The stimulus to generate VEMP was a low-frequency tone burst sound tone burst, with an intensity of 120 decibels normalized hearing level, bandpass filter from 10 to 1,500 Hertz (Hz), with 100 stimuli at 500 Hz and 50 milliseconds recording time. The latencies of the electrophysiological waves P13 and N23 for cervical VEMP and N10 and P15 waves for ocular VEMP were compared among the groups. The absence or delay of the electrophysiological waves were considered abnormal results.

Results

Ocular VEMP was similar among the groups for N10 ($p = 0.375$) and different for P15 ($p \leq 0.001$). Cervical VEMP was different for P13 ($p = 0.001$) and N23 ($p = 0.003$). About ocular VEMP, in the HTLV-1-asymptomatic group, normal waves were found in 23(88.5%) individuals; in HAM group, normal waves were found in 7(26.9%). About cervical VEMP, 18 (69.2%) asymptomatic carriers presented normal waves and only 3(11.5%) patients with HAM presented normal waves. Abnormalities in both VEMPs were found in 1(3.8%) asymptomatic carrier and in 16(61.5%) patients with HAM.

(CAPES/COFECUB) - http://www.capes.gov.br/. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

Conclusion

Neurological impairment in HAM was not restricted to the spinal cord. The mesencephalic connections, tested by ocular VEMP, have been also altered. Damage of the oculomotor system, responsible for eye stabilization during head and body movements, may explain why dizziness is such a frequent complaint in HAM.

Introduction

The Human T-cell lymphotropic virus type 1 (HTLV-1) infection affects approximately 5–10 million people worldwide [1]. The majority of the infected individuals remain asymptomatic throughout their lives [2]. The host genetic and immunological factors seem to be related to the development of HTLV-1-associated diseases [1,2].

The range of neurological manifestations of HTLV-1-associated myelopathy (HAM) includes not only the spine, with the classical motor limitations affecting the lower limbs, but also the autonomic dysfunction [3]. In fact, inflammatory alterations due to HAM can be detected in the cortex, subcortical white matter, cerebellum, and brainstem, mainly in the advanced phases of this disease [4–7].

The complaint of dizziness has proven to be frequent in patients with HAM and can be one of the first symptoms of HTLV-1-neurological impairment [8,9]. Therefore, individuals infected with HTLV-1 may present vague complaints, with no motor, sensitive, or autonomic abnormalities [4–6]. HAM diagnosis is based on clinical criteria that reveals established neurological damage [10].

Vestibular Evoked Myogenic Potential (VEMP) has been established as a reliable and practical physiological test of the otolithic organs saccule and utricle and their pathways [11]. A normal VEMP depends on the functional integrity of the saccular and utricular maculae, the inferior vestibular nerve, the superior vestibular nerve, the vestibular nuclei, the central vestibular pathways, and the neuromuscular plaques involved in these reflexes [12–15]. Thus, VEMP tests the peripheral and central vestibular pathway, including the brainstem [11,12] and the vestibular reflexes such as the vestibulo-ocular, the vestibulo-collic and the vestibulospinal [11–14].

The subclinical spinal cord injury related to HAM has been already shown through VEMP of cervical and of lower limbs muscles, exams that are used to test the vestibulo-collic reflex [8,9,13,16,17]. The present study proposes the use of VEMP of the oculomotor system (ocular VEMP) to test the brainstem pathways associated with body balance to verify the extension of the HTLV-1-neurological damage.

Methods

Study design

The study was a comparative cross-sectional analysis. Cervical VEMP and ocular VEMP were compared between individuals with definite HAM, HTLV-1-asymptomatic carriers and healthy controls.

Ethical aspects

This research was conducted in accordance with the principles expressed in the Declaration of Helsinki and was approved by the Research Ethics Committee from Universidade Federal de

Minas Gerais (COEP UFMG), logged under protocol number CAAE 92928518.3.0000.5149. All participants provided voluntary written consent and declared that they were aware of the study procedures and their choice to participate. The written informed consent (as described in the PLOS consent form) was obtained for image publication.

Sample size

The sample size was calculated using G* Power software 3.1.9.2 (Heinrich-Heine Universitat Düsseldorf, Düsseldorf, Germany, 2007) to achieve a power of 80% and a significance level of 5% based on the mean and standard deviation of the P13-N23 response of patients with HAM and healthy controls [8]. The final calculation included 26 participants per group.

Participants

The groups of study were recruited from a cohort of former blood donors infected with HTLV-1 who have received follow-up from the Interdisciplinary HTLV Research Group (GIPH) since 1997, in Belo Horizonte, Brazil [18]. The GIPH evaluates the natural history, clinical manifestations and epidemiological aspects of HTLV infection.

Seventy-eight individuals, 32 to 60 years of age, were invited to participate in this study. The participants consisted of 26 individuals with definite HAM, 26 with HTLV-1-asymptomatic infection, and a control group of 26 individuals not infected by HTLV-1. The control group consisted of the active blood donors followed by GIPH as the negative controls.

The classification of the participants infected by HTLV-1 regarding neurological impairment followed the Expanded Disability Status Scale (EDSS) [19] and the Osame´s Motor Disability Score (OMDS) [20]: asymptomatic individual, (EDSS and OMDS—0 on both scales) and definite diagnosis of HAM (EDSS and OMDS greater than 1 on both scales).

Individuals with positive serology for the Human Immunodeficiency Virus (HIV), HTLV-2, or any other blood-tested disease were excluded, as well as an undetermined serology for HTLV-1 and a positive *Venereal Disease Research Laboratory* (VDRL) test.

Concerning all the participants, we excluded the individuals with neurological diseases, otitis, tympanic membrane perforation, history of otologic surgery or peripheral vestibular disease, as well as individuals with any alteration in the clinical neurological examination of the cranial nerves or unable to perform cervical rotation.

Vestibular evoked myogenic potential (VEMP)

VEMP was performed with Labat® equipment, using two channels. The stimuli were presented through ER 3A insertion phones, with disposable foam eartips. Tone burst stimuli at an intensity of 120 decibels normalized hearing level (dB nHL) were used. In this study, a band-pass filter of 10 to 1,500 Hertz (Hz) was used. To obtain each record, 100 stimuli were presented at a frequency of 500 Hz at a rate of four stimuli per second. The total duration of the 100 stimuli was 25 seconds. The scan window was 50 milliseconds (ms). Each subject underwent at least two stimulations per side, to verify the replication of the potential, and each stimulation was composed of 200 stimuli repeated in two consecutive cycles, no plateau (ramp = 2 and plateau = 0). The impedance values, which had to be below 5 kiloohm (KΩ), were checked before each record [11].

The recording of cervical VEMP and ocular VEMP was performed simultaneously. Channel 1 electrodes were used to record ocular VEMP and channel 2 electrodes to record cervical VEMP [11].

The active electrode related to cervical VEMP was placed on the same side of the auditory stimulus at the anterior border of the sternocleidomastoid muscle in its upper third, and the

reference electrode was placed in the sternal notch region. For ocular VEMP recording, the active electrode (negative electrode) in channel 1 was placed approximately 1 centimeter (cm) below the lower eyelid of the opposite side of the auditory stimulus, and the reference electrode (positive electrode) was placed at a distance of approximately 1 cm from the active electrode. The ground electrode was placed on the forehead (Fpz) (Fig 1).

Participants were instructed to sit on the chair and keep their heads rotated to the opposite side of the stimulated ear, causing contraction of the sternocleidomastoid muscle. At the same time, the participant was instructed to look at a stationary target located on the wall in front of him and then immediately at a fixed point located above the target, which formed a vertical viewing angle of approximately 30˚ above the horizontal plane. The protocol of simultaneous ocular and cervical VEMP is available at doi.org/10.17504/protocols.io.zmzf476.

The ocular VEMP is composed of two sets of biphasic waveforms. The first biphasic potential has a negative peak (N) with an average latency of 10 ms, followed by a positive peak (P) with an average latency of 15 ms, which is known as N10–P15. The cervical VEMP consists of two sets of biphasic waveforms. The first biphasic potential has a positive peak (P) with an average latency of 13 milliseconds (ms), followed by a negative peak (N) with an average latency of 23 ms, which it known as P13–N23 (Fig 2).

The American Society of Encephalography and Evoked Potentials' criteria for evoked potentials were considered for the analysis of the latency values of the cervical VEMP and ocular VEMP waves. The definition of altered latency values includes those that exceed 2.5 standard deviations (SD) [21]. Thus, for ocular VEMP, we considered normal latency values within the range of 7.5 to 12.5 ms for N10 and within the range of 12.5 to 17.5 ms for P15. For cervical VEMP, we considered normal latency values within the range of 10.5 to 15.5 ms for P13 and within the range of 20.5 to 25.5 ms for N23 [22,23]. The validation of the analyzed reference values was guaranteed by comparing these with parameters already established in other national and international peer reviews [11,24,25].

The parameters considered in the VEMP analysis are the latency and amplitude of the waves. However, the amplitude may vary according to age, muscular strength [24,26], and Meniere's disease [27,28]. Therefore, amplitude was not considered in the analysis since this variable is not consistent to define neural conduction abnormalities.

VEMP results were classified as normal and altered. Latency prolongation and no response were considered as the altered results. Ocular and cervical VEMP were compared between the groups infected and not infected by HTLV-1.

Statistical analysis of data

Statistical analysis was performed using the *Statistical Package for Social Sciences* (SPSS), version 20.0. Regarding the continuous variables (latencies in milliseconds) the normality of the samples was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. Since the distribution of the variables was not normal, the comparison between groups was performed using the Kruskal-Wallis test. Chi-square or Fisher's Exact test were used to compare nominal variables between groups. The adopted level of significance was 5% ($p \leq 0.05$). The magnitude of the difference of normal or altered VEMP between groups was calculated using the odds ratio (OR). The confidence interval (95%) was calculated in order to evaluate the sample variability.

Results

The characteristics of the studied population and the classification in the neurological scales are described in Table 1. The groups were similar regarding gender and age.

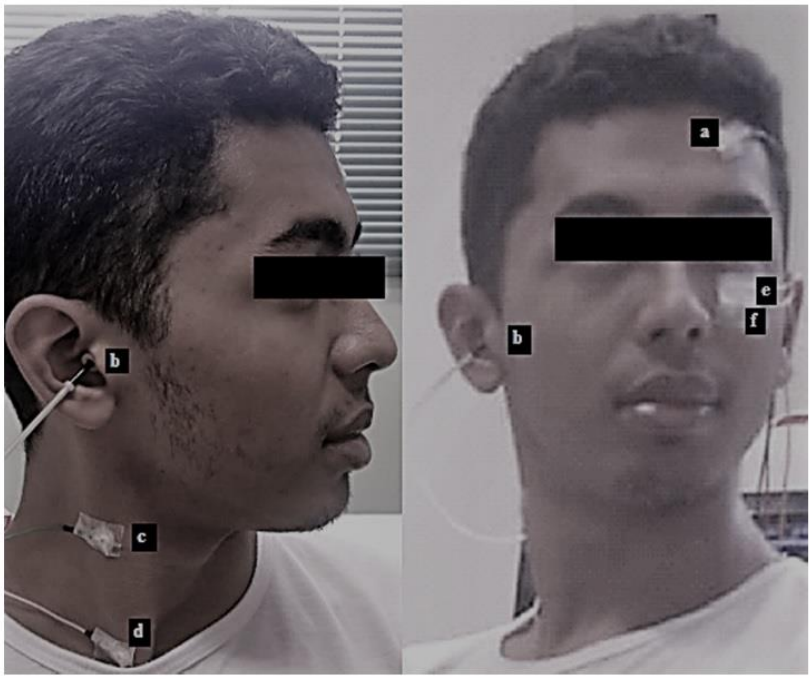

Fig 1. Simultaneous cervical and ocular VEMP. (a) ground electrode. (b) auditory stimulus. (c) active electrode on channel 2 at the anterior border of the sternocleidomastoid muscle in its upper third. (d) reference electrode on channel 2 at the sternal notch region. (e) active electrode on channel 1 below the lower eyelid. (f) reference electrode on channel 1 below the active electrode. The written informed consent was given by the person.

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The VEMP latencies were different among the groups. Table 2 indicates the comparative analysis and identifies the groups with a relevant difference. The data points behind means, medians and variance measures was included in S2 Table.

Table 3 describes the frequency of normal and altered results for cervical and ocular VEMP in each group. The seronegative group of healthy controls was not included in the table because of normality in all the exams (cervical and ocular VEMP). The comparison of the controls with the group of asymptomatic carriers showed no difference between groups for ocular VEMP ($p = 0.118$) and difference for cervical VEMP ($p = 0.002$).

The VEMP result was categorized as 1) latency delay of N10-P15 waves (ocular) or of P13-N23 waves (cervical); 2) absence of wave; 3) normal wave. Fig 3 shows the comparative analysis for ocular VEMP and Fig 4 for cervical VEMP.

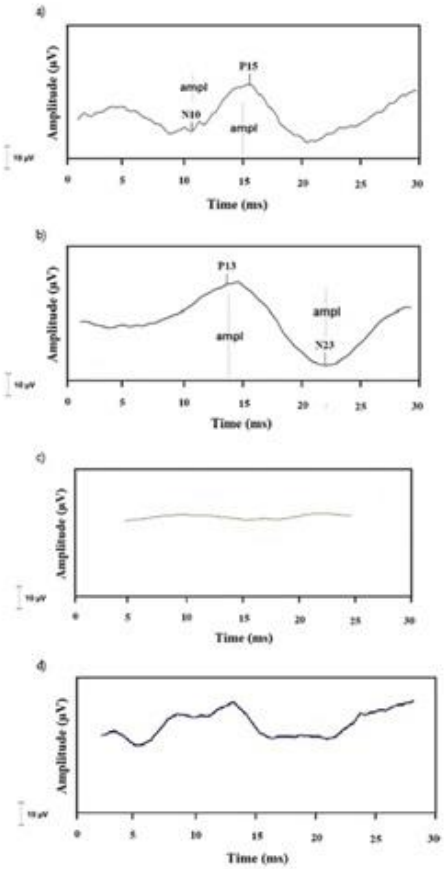

Fig 2. Examples of tracings obtained by the VEMP records. a) normal ocular VEMP. b) normal cervical VEMP. c) altered ocular VEMP (no response). d) altered cervical VEMP (no response).

https://doi.org/10.1371/journal.pone.0217327.g002

Discussion

The auditory stimulus that evokes VEMP goes through the vestibular regions of the brain, especially the pre-motor cortex, the inferior and medial temporal gyrus, the Brodmann area, as well as the typically auditory areas, such as the primary auditory cortex [29].

Table 1. Comparison of the groups with HTLV-1-associated myelopathy (HAM), asymptomatic infection and healthy controls according to general characteristics and the disability scales (EDSS and OMDS).

Variables	Control (n = 26)	Asymptomatic (n = 26)	HAM (n = 26)	p-value
Age	53.27 (3.39)	53.73 (7.65)	55.69 (4.44)	0.073[a]
Female Male	18 [69.2] 8 [30.8]	16 [61.5] 10 [38.5]	19 [73.1] 7 [26.9]	0.662[b]
EDSS	0 (0)	0 (0)	3 (2.08)	≤0.001[a]
OMDS	0 (0)	0 (0)	2.30 (1.85)	≤0.001[a]

EDSS, expanded disability status scale; OMDS, Osame motor disability score; n, number of participants. Data are expressed as mean (standard deviation); absolute number [percentage].

[a] Kruskal-Wallis Test ($p \leq 0.05$)

[b] Chi-square Test ($p \leq 0.05$)

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The latency delay of cervical VEMP has been related to the demyelination of the primary afferent axon of the vestibulo-collic tract and/or involvement of the vestibular nucleus [30–32]. The absence of electrophysiological response may be explained by a severe impairment of the vestibular-spinal pathway [33].

When the evoked potential changes from a prolonged latency to no response, it is understood that there is a worsening in the neuronal damage [11,24,25]. This pattern of response was previously observed in a cohort study of individuals infected by HTLV-1 with myelopathy and asymptomatic carriers that were tested by cervical VEMP [8,13]. Axonal degeneration along the spinal cord may play a more prominent role in disease progression in HAM/TSP and may explain the significant correlation of VEMP alteration in early stage HAM and even in the HTLV-1-asymptomatic carrier who has more chance of evolving to HAM [13].

Regarding cervical VEMP in the present study, we found that the great majority of the patients with definite HAM presented alteration in cervical VEMP response (88,5%). This data confirms previous studies that disclosed a cervical spinal cord damage in HAM, emphasizing

Table 2. Comparison of the groups with HTLV-1-associated myelopathy, asymptomatic infection and healthy controls according to the latency (ms) of cervical VEMP (P13 and N23 waves) and ocular VEMP (N10 and P15 waves).

Variables		G1 (n = 26)	G2 (n = 26[a])	G3 (n = 26[b])	p - value *	Comparison groups	p - value **
Ocular VEMP	Lat N10	10.49 (0.65)	10.38 (0.92)	11.51 (2.80)	0.375	-	-
	Lat P15	15.40 (0.66)	15.74 (1.35)	18.17 (3.30)	≤0.001	G1 X G2 G1 X G3 G2 X G3	1.000 ≤0.001 0.002
Cervical VEMP	Lat P13	12.80 (0.91)	13.73 (1.03)	14.83 (3.22)	0.001	G1 X G2 G1 X G3 G2 X G3	0.007 0.002 1.000
	Lat N23	22.30 (1.36)	23.04 (2.44)	25.75 (4.43)	0.003	G1 X G2 G1 X G3 G2 X G3	0.919 0.003 0.060

G1, group control; G2, group of asymptomatic individuals; G3, group of individuals with HAM; SD, standard deviation; Lat, latency; n, number of participants. Data are expressed as mean (standard deviation).

[a]For Lat N23 data analysis, one case in which the response was absent was excluded.

[b]For Lat P13 and Lat N23 data analysis, 3 and 6 cases, respectively, in which the response was absent were excluded. For Lat N10 and Lat P15 data analysis, 2 and 3 cases, respectively, in which the response was absent were excluded.

* Kruskal-wallis Test ($p \leq 0.05$).

** Bonferroni Test.

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Table 3. Comparison of the groups with HTLV-1-associated myelopathy (HAM), asymptomatic infection and healthy controls according to the result (normal/altered) of ocular and cervical VEMP.

VEMP type	VEMP result						
	Comparison between groups	Normal - n (%)	Altered - n (%)		p-value	OR	CI (inferior-superior)
			Delayed wave	Absent wave			
Ocular n (%)	Asymptomatic	23 (88.5)	3 (11.5)		< 0.001	3.28	1.71–6.28
			3 (11.5)	0 (0.0)			
	HAM	7 (26.9)	19 (73.1)				
			8(30.8)	11(42.3)			
Cervical n (%)	Asymptomatic	18 (69.2)	8 (30.8)		< 0.001	6.00	2.00–17.93
			1(3.8)	7(26.9)			
	HAM	3 (11.5)	23 (88.5)				
			2(76.9)	21(80.8)			
Cervical and Ocular n (%)	Asymptomatic	25 (96.1)*	1 (3.8)**		< 0.001	2.5	1.52–4.090
	HAM	10 (38.5)*	16 (61.5)**				

n, number of participants; OR, odds ratio; CI, confidence interval; Data are expressed as absolute number (percentage).

*Normal cervical and ocular VEMP or just one altered.

**Cervical and Ocular VEMP altered.

Chi-square test or Fisher's Exact ($p \leq 0.05$)

https://doi.org/10.1371/journal.pone.0217327.t003

that the medullary abnormalities in HAM are not restricted to the thoracolumbar level [13,34,35].

Regarding ocular VEMP, 61.5% of the patients with definite HAM and alteration in cervical VEMP, presented also alteration in ocular VEMP (Table 3). The neural connections involved in the generation of ocular VEMP are mainly mesencephalic [19,36–38]. The presumed pathway includes the vestibular primary afferent, the vestibular nuclear complex, the medial longitudinal fasciculus, the oculomotor nucleus and the oculomotor nerves [36]. Thus, a latency delay or an absence of response depends on the disorganization of the primary afferents

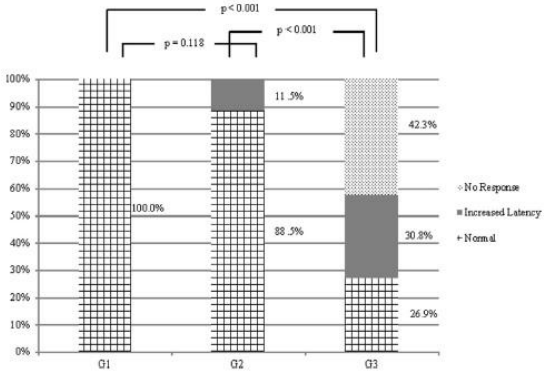

Fig 3. Comparison of ocular VEMP responses in individuals with HTLV-1-associated myelopathy, with asymptomatic infection and seronegative controls (n = 78). G1, group control; G2, group of asymptomatic individuals; G3, group of individuals with HAM. Chi-square or Fisher's Exact test ($p \leq 0.05$).

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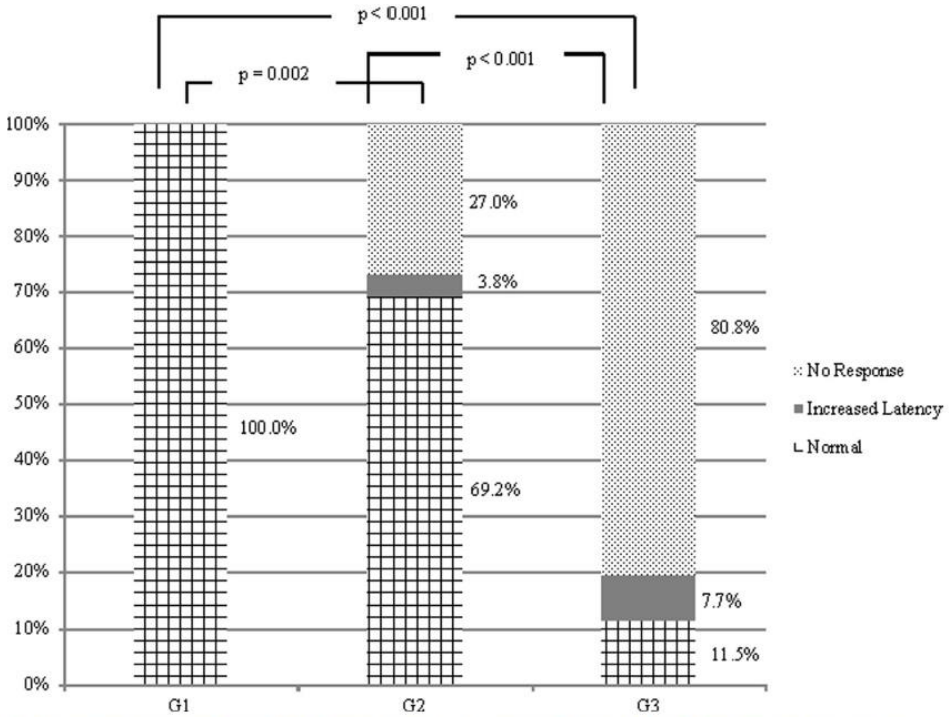

Fig 4. Comparison of cervical VEMP responses in individuals with HTLV-1-associated myelopathy, with asymptomatic infection and seronegative controls (n = 78). G1, group control; G2, group of asymptomatic individuals; G3, group of individuals with HAM. Chi-square or Fisher's Exact test ($p \leq 0.05$).

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involved in the vestibulo-ocular reflex [36,37]. Currently, the major pathophysiological mechanism considered to explain CNS involvement in the HTLV-1 neurological disease is an immuno-mediated chronic inflammatory process in response to HTLV-1 infection, which damages nearby CNS components [39]. The higher frequency of simultaneous alteration in ocular and cervical VEMP in HAM group confirms a spread of neurological impairment in these individuals when compared to the group with asymptomatic infection.

VEMP can detect subclinical neurological changes in HTLV-1 infection [13,16,29]. We showed that many of those labeled as asymptomatic carriers, presented altered cervical VEMP and normal ocular VEMP, indicating alteration in cervical spine but not in the upper CNS. When effective therapeutic options for HTLV-1 neurological disease are available, the subclinical diagnosis of neuronal injury will have implications in decision-making regarding the beginning of the treatment in the stage of incipient damage. For example, recent studies have shown that low doses of corticosteroid can be beneficial in slowing HAM progression if treatment is implemented at the onset of the HTLV-1-neurological manifestation [40].

Limitations

We do not include image and immunological data, such as proviral load and inflammatory markers in the serum. In the GIPH cohort, neither the image nor the proviral load have a good positive predictive value for the classification of the patients in the spectrum of HTLV-1 neurological disease [41,42].

The spinal cord atrophy seen in magnetic resonance imaging (MRI) and clinical disability have been correlated in advanced HAM [43], but not in early stage HAM [44]. The serum inflammatory profile that is typical of HAM does not present a good validity to be used in the clinical practice to differentiate the real HTLV-1-aymptomatic carrier from those who are developing HAM [45,46]. Therefore, although image and immunological data could add information to the present work, the lack of these results does not influence the valuable information that in HTLV-1 infection classified as asymptomatic, the cervical spine can present subclinical alterations, but not the upper CNS. On the contrary, in HAM, abnormal cervical VEMP and ocular VEMP have showed alterations in the spine as well as in the upper CNS, which is in line with the findings of cognitive alterations in HAM [47].

In HTLV-1-asymptomatic infection, subclinical alterations can be disclosed by electrophysiological tests but not by MRI [44].

Conclusion

The mesencephalic impairment in HAM, showed by ocular VEMP changes, confirmed that HTLV-1 neurological disease in HAM is not restricted to the spinal cord. The alteration of the oculomotor system responsible for the eye stabilization during head and body movements can explain the high frequency of dizziness in patients with HAM. The impairment in cervical spine, showed by cervical VEMP changes, was found in HAM as well as in asymptomatic carriers. This fact shows that cervical spinal cord damage is indeed frequent and may represent an earlier stage in in relation to upper CNS involvement.

Supporting information

S1 Appendix. Questionnaire.
(PDF)

S1 Data List. Dataset of absolute values of the latencies according to sex, age, group of study and neurological scales.
(XLSX)

S1 Table. Diagnostic criteria of human T-cell lymphotropic virus type 1 (HTLV-1)- associated myelopathy (HAM)[a]. [a]Castro-costa CMDE, Araújo AQC, Barreto MM, Takayanagui OM, Sohler MP, Silva ELMDA, et al. Proposal for diagnostic criteria of tropical spastic paraparesis/HTLV-1-associated myelopathy (HAM/TSP). AIDS Res Hum Retroviruses. 2006;22:931–935. Doi: 10.1089/aid.2006.22.931.
(PDF)

S2 Table. Descriptive variables of healthy controls, asymptomatic infection group, and HTLV-1-associated myelopathy group: Age, disability scales (EDSS and OMDS), the latency (ms) of cervical VEMP (P13 and N23 waves) and ocular VEMP (N10 and P15 waves).
(PDF)

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Author Contributions

Conceptualization: Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

Data curation: Tatiana Rocha Silva, Denise Utsch Gonçalves.

Formal analysis: Tatiana Rocha Silva, Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

Funding acquisition: Tatiana Rocha Silva, Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

Investigation: Rafael Teixeira Scoralick Dias.

Methodology: Tatiana Rocha Silva, Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

Project administration: Tatiana Rocha Silva, Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

Resources: Tatiana Rocha Silva, Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

Supervision: Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

Validation: Tatiana Rocha Silva, Ludimila Labanca, Júlia Fonseca de Morais Caporali, Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Rafael Teixeira Scoralick Dias, Denise Utsch Gonçalves.

Visualization: Tatiana Rocha Silva, Ludimila Labanca, Júlia Fonseca de Morais Caporali, Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

Writing – original draft: Tatiana Rocha Silva, Denise Utsch Gonçalves.

Writing – review & editing: Tatiana Rocha Silva, Ludimila Labanca, Júlia Fonseca de Morais Caporali, Marco Aurélio Rocha Santos, Luciana Macedo de Resende, Denise Utsch Gonçalves.

References

1. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. Front Microbiol. 2012; 3:1–23. https://doi.org/10.3389/fmicb.2012.00001
2. Orland JR, Engstrom J, Fridey J, Sacher RA, Smith JW, Nass C, et al. Prevalence and clinical features of HTLV neurologic disease in HTLV outcomes study. Neurology. 2003; 61:1588–1594. https://doi.org/10.1212/01.wnl.0000096011.92542.da PMID: 14663047
3. Bhigjee AI, Wiley CA, Wachsman W, Amenomori T, Pirie D, Bill PL, et al. HTLV-I-associated myelopathy: clinicopathologic correlation with localization of provirus to spinal cord. Neurology. 1991; 41 (12):1990–1992. https://doi.org/10.1212/wnl.41.12.1990 PMID: 1745362
4. Gascón MRP, Cassebd J, Smid J, Vidal JE, Fonseca LAM, Paiva A, et al. Cognitive impairment is frequent among symptomatic carriers of human T-cell lymphotropic virus type 1 (HTLV-1), regardless of their clinical status. J Neurol Sci. 2017; 377:185–189. https://doi.org/10.1016/j.jns.2017.04.019 PMID: 28477692

5. Mendes GB, Kalil RS, Rosadas C, de Freitas MRG, Puccioni-Sohler M. Neurological manifestations in human T-cell lymphotropic virus type 1 (HTLV-1)–infected individuals without HTLV-1–associated myelopathy/tropical spastic paraparesis: a longitudinal cohort study. CID. 2015; 61:49–56.
6. Schütze M, Romanelli LC, Rosa DV, Carneiro-Proietti AB, Nicolato R, Romano-Silva MA, et al. Brain metabolism changes in patients infected with HTLV-1. Front Mol Neurosci. 2017; 10:1–8. https://doi.org/10.3389/fnmol.2017.00001
7. Ferraz AC, Gabbai AA, Abdala N, Nogueira RG. Ressonância magnética na mielopatia associada ao HTLV-I: Leucoencefalopatia e atrofia medular. Arq. Neuro-Psiquiatr. [online]. 1997; 55(4):728–736.
8. Felipe L, Gonçalves DU, Santos MA, Proietti FA, Ribas JG, Carneiro-Proietti AB, et al. Vestibular evoked myogenic potential (VEMP) to evaluate cervical myelopathy in human T-cell lymphotropic virus type i infection. Spine (Phila Pa 1976). 2008; 33:1180–1184.
9. Labanca L, Starling AL, de Sousa-Pereira SR, Romanelli LC, de Freitas Carneiro-Proietti AB, Carvalho LN, et al. Electrophysiological analysis shows dizziness as the first symptom in human T cell lymphotropic Virus type-associated myelopathy/tropical spastic paraparesis. AIDS Res Hum Retroviruses. 2015; 31(6):649–654. https://doi.org/10.1089/AID.2014.0153 PMID: 25760424
10. De Castro-Costa CM, Araújo AQ, Barreto MM, Takayanagui OM, Sohler MP, da Silva EL, et al. Proposal for diagnostic criteria of tropical spastic paraparesis/HTLV1-associated myelopathy (TSP/HAM). AIDS Res Hum Retroviruses. 2006; 22(10):931–935. https://doi.org/10.1089/aid.2006.22.931 PMID: 17067261
11. Oh SY, Kim JS, Lee JM, Shin BS, Hwang SB, Kwak KC et al. Ocular vestibular evoked myogenic potentials induced by air-conducted sound in patients with acute brainstem lesions. Clin Neuro-physiol. 2013; 124:770–778.
12. Kantner C, Gürkov R. Characteristics and clinical applications of ocular vestibular evoked myogenic potentials. Hearing Research. 2012; 294(1–2):55–63. https://doi.org/10.1016/j.heares.2012.10.008 PMID: 23123220
13. Felipe L, Kingma H, Lambertucci JR, Carneiro-Proietti AB, Gonçalves DU. Testing the vestibular evoked myogenic potential (VEMP) to identify subclinical neurological alterations in different phases of human T-lymphotropic virus type 1 infection. Spine J. 2013; 13(4):397–401. https://doi.org/10.1016/j.spinee.2012.11.015 PMID: 23267739
14. Cunha LC, Labanca L, Tavares MC, Gonçalves DU. Vestibular evoked myogenic potential (VEMP) with galvanic stimulation in normal subjects. Braz J Otorhinolaryngol. 2014; 80(1):48–53. https://doi.org/10.5935/1808-8694.20140011 PMID: 24626892
15. Park HJ, Lee IS, Shin JE, Lee YJ, Park MS. Frequency-tuning characteristics of cervical and ocular vestibular evoked myogenic potentials induced by air-conducted tone bursts. Clin Neurophysiol. 2010; 121(1):85–89. https://doi.org/10.1016/j.clinph.2009.10.003 PMID: 19892592
16. Labanca L, de Morais Caporali JF, da Silva Carvalho SA, Lambertucci JR, Carneiro Proietti ABF, Romanelli LCF, et al. Vestibular-evoked myogenic potential triggered by galvanic vestibular stimulation may reveal subclinical alterations in human T-cell lymphotropic virus type 1-associated myelopathy. PLoS One. 2018; 13(7):1–17.
17. Caporali JFM, Labanca L, Florentino KR, Souza BO, Utsch Gonçalves D. Intrarater and interrater agreement and reliability of vestibular evoked myogenic potential triggered by galvanic vestibular stimulation (galvanic-VEMP) for HTLV-1 associated myelopathy testing. PLoS One. 2018; 13(9):1–13.
18. Allain JP, Stramer SL, Carneiro-Proietti AB, Martins ML, Lopes da Silva SN, Ribeiro M. Transfusion-transmitted infectious diseases. Biologicals. 2009; 37(2):71–77. https://doi.org/10.1016/j.biologicals.2009.01.002 PMID: 19231236
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983; 33(11):1444–1452. https://doi.org/10.1212/wnl.33.11.1444 PMID: 6685237
20. Osame M. Review of WHO Kagoshima meeting and diagnostic guidelines for HAM/TSP. In: Blattner W. (ed) Human retrovirology: HTLV. Raven. 1990:191–197.
21. American Eeg Society. Clinical evoked potentials guidelines. Recommended standards for normative studies of evoked potentials, statistical analysis of results and criteria for clinically significant abnormality. Journal of Clinical Neurophysiology. 1994; 11:45–47.
22. Wang SJ, Yeh TH, Chang CH, Young YH. Consistent latencies of vestibular evoked myogenic potentials. Ear Hear. 2008; 29(6):923–929. https://doi.org/10.1097/AUD.0b013e3181853019 PMID: 18685495
23. Li C, Zuniga MG, Nguyen KD, Carey JP, Agrawal Y. How to interpret latencies of cervical and ocular vestibular-evoked myogenic potentials: Our experience in fifty-three participants. Clin Otolaryngol. 2014; 39(5):297–301. https://doi.org/10.1111/coa.12277 PMID: 24962335

24. Lim CL, Clouston P, Sheean G, Yiannikas C. The influence of voluntary EMG activity and click intensity on the vestibular click evoked myogenic potential. Muscle Nerve. 1995; 18(10):1210–1213. https://doi.org/10.1002/mus.880181021 PMID: 7659119

25. Murofushi T, Matsuzaki M, Wu CH. Short tone burst-evoked myogenic potentials on the sternocleidomastoid muscle: are these potentials also of vestibular origin? Arch. Otolaryngol. Head Neck Surg. 1999; 125(6):660–664. https://doi.org/10.1001/archotol.125.6.660 PMID: 10367923

26. Akin FW, Murnane OD, Panus PC, Caruthers SK, Wilkinson AE, Proffitt TM. The influence of voluntary tonic EMG level on the vestibular-evoked myogenic potential. J Rehabil Res Dev. 2004; 41:473–480. https://doi.org/10.1682/jrrd.2003.04.0060 PMID: 15543465

27. De Waele C, Tran Ba Huy P, Diart JP, Freyss G, Vidal PP. Saccular dysfunction in Meniere's disease. Am J Otol. 1999; 20:223–232. PMID: 10100527

28. Young YH, Huang TW, Cheng PW. Assessing the stage of Meniere's disease using vestibular evoked myogenic potentials. Arch Otolaryngol Head Neck Surg. 2003; 129:815–818. https://doi.org/10.1001/archotol.129.8.815 PMID: 12925337

29. Mcnerney K. S. The use of 64-channel electroencephalography and positron emission tomography to study vestibular evoked myogenic potentials. (Thesis). New York: Department of Communicative Disorders and Sciences; 2007.

30. Bangham CRM, Osame M. Cellular immune response to HTLV-1. Oncogene. 2005; 24:6035–6046. https://doi.org/10.1038/sj.onc.1208970 PMID: 16155610

31. Shimizu K, Murofushi T, Sakurai M, Halmagyi M. Vestibular evoked myogenic potentials in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2000; 69:276–277. https://doi.org/10.1136/jnnp.69.2.276 PMID: 10960289

32. Murofushi T, Shimizu K, Takegoshi H, Cheng PW. Diagnostic value of prolonged latencies in the vestibular evoked myogenic potential. Arch Otolaryngol Head Neck Surg. 2001; 27(9):1069–1072.

33. Colebatch JG, Rothwell JC, Bronstein A, Ludman H. Click-evoked vestibular activation in the Tullio phenomenon. J Neurol Neurosurg Psychiatry. 1994; 57(12):1538–1540. https://doi.org/10.1136/jnnp.57.12.1538 PMID: 7798988

34. Akizuki S, Nakazato O, Higuchi Y, Tanabe K, Setoguchi M, Yoshida S, et al. Necropsy findings in HTLV-I associated myelopathy. Lancet. 1987; 17(1):156–157.

35. Ribas JGR, Melo GCN. Mielopatia associada ao vírus linfotrópicos humano de células T do tipo 1 (HTLV-1). Rev Soc Bras Med Trop. 2002; 35(4):377–384. https://doi.org/10.1590/s0037-86822002000400015 PMID: 12170334

36. Rosengren SM, Welgampola MS, Colebatch JG. Vestibular evoked myogenic potentials: past, present and future. Clin Neurophysiol. 2010; 121(5):636–651. https://doi.org/10.1016/j.clinph.2009.10.016 PMID: 20080441

37. Chihara Y, Iwasaki S, Ushio M, Murofushi T. Vestibular evoked extraocular potentials by air-conducted sound: another clinical test for vestibular function. Clin Neurophysiol. 2007; 118(12):2745–2751. https://doi.org/10.1016/j.clinph.2007.08.005 PMID: 17905655

38. De Natale ER, Ginatempo F, Paulus KS, Pes GM, Manca A, Tolu E, et al. Abnormalities of vestibular-evoked myogenic potentials in idiopathic Parkinson's disease are associated with clinical evidence of brainstem involvement. Neurol Sci. 2015; 36(6):995–1001. https://doi.org/10.1007/s10072-014-2054-4 PMID: 25567081

39. Fuzii HT, da Silva Dias GA, de Barros RJ, Falcão LF, Quaresma JA. Immunopathogenesis of HTLV-1-assoaciated myelopathy/tropical spastic paraparesis (HAM/TSP). Life Sci. 2014; 104(1–2):9–14. https://doi.org/10.1016/j.lfs.2014.03.025 PMID: 24704970

40. Coler-Reilly ALG, Sato T, Matsuzaki T, Nakagawa M, Niino M, Nagai M, Nakamura T, Takenouchi N, Araya N, Yagishita N, Inoue E, Yamano Y. Effectiveness of Daily Prednisolone to Slow Progression of Human T-Lymphotropic Virus Type 1-Associated Myelopathy/Tropical Spastic Paraparesis: A Multicenter Retrospective Cohort Study. Neurotherapeutics. 2017; 14(4):1084–1094. https://doi.org/10.1007/s13311-017-0533-z PMID: 28536850

41. Martins ML, de Freitas Carneiro-Proietti AB, Nicolato R, de Miranda DM, Romanelli LCF. HTLV-1 proviral load in cerebrospinal fluid may not be a good marker to differentiate asymptomatic carriers with high proviral load in blood from HAM/TSP patients. J Neurovirol. 2018; 24(4):432–438. https://doi.org/10.1007/s13365-018-0632-6 PMID: 29589290

42. Romanelli LCF, Miranda DM, Carneiro-Proietti ABF, Mamede M, Vasconcelos HMM, Martins ML, et al. Spinal cord hypometabolism associated with infection by human T-cell lymphotropic virus type 1(HTLV-1). PLoS Negl Trop Dis. 2018; 12(8):e0006720. https://doi.org/10.1371/journal.pntd.0006720 PMID: 30148843

43. Liu W, Bakshi A, Massoud R, Brunetto GS, Reich DS, Nair G, et al. Quantifying spinal cord cross-sectional area in HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP). Retrovirology. 2014; 11(Suppl 1): 22.

44. Taniguchi A, Mochizuki H, Yamashita A, Shiomi K, Asada Y, Nakazato M. Spinal cord anteroposterior atrophy in HAM/TSP: Magnetic resonance imaging and neuropathological analyses. J Neurol Sci. 2017; 381:135–140. https://doi.org/10.1016/j.jns.2017.08.3243 PMID: 28991665

45. Starling AL, Coelho-Dos-Reis JG, Peruhype-Magalhães V, Pascoal-Xavier MA, Gonçalves DU, Béla SR, et al. Immunological signature of the different clinical stages of the HTLV-1 infection: establishing serum biomarkers for HTLV-1-associated disease morbidity. Biomarkers. 2015; 20(6–7):502–512. https://doi.org/10.3109/1354750X.2015.1094141 PMID: 26474234

46. Rosa DV, Magno LA, Pereira NC, Romanelli LC, Albuquerque MR, Martins ML, et al. Plasma and cerebrospinal fluid levels of cytokines as disease markers of neurologic manifestation in long-term HTLV-1 infected individuals. Biomark Med. 2018; 12(5):447–454. https://doi.org/10.2217/bmm-2017-0313 PMID: 29737866

47. Champs APS, de Azeredo Passos VM, Carvalho G, Barreto SM, Meirelles C, Caramelli P. Cognitive impairment in HTLV-1-associated myelopathy, proviral load and inflammatory markers. Int J Infect Dis. 2019; 84:121–126. https://doi.org/10.1016/j.ijid.2019.05.010 PMID: 31085316

5.2 Artigo 3

frontiers in Neurology

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Vestibular Evoked Myogenic Potential on Ocular, Cervical, and Soleus Muscles to Assess the Extent of Neurological Impairment in HTLV-1 Infection

*Tatiana Rocha Silva[1], Marco Aurélio Rocha Santos[2], Luciana Macedo de Resende[2], Ludimila Labanca[1,2], Júlia Fonseca de Morais Caporali[1], Rafael Teixeira Scoralick Dias[1] and Denise Utsch Gonçalves[1]**

[1] Graduate Program in Infectious Diseases and Tropical Medicine, School of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil, [2] Graduate Program in Phonoaudiological Sciences, School of Medicine, Universidade Federal de Minas Gerais, Belo Horizonte, Brazil

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Edited by:
Avindra Nath, National Institute of Neurological Disorders and Stroke (NINDS), United States

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Sally M. Rosengren, Royal Prince Alfred Hospital, Australia
Jiawei Wang, Capital Medical University, China

***Correspondence:**
Denise Utsch Gonçalves
deniseg@medicina.ufmg.br

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Introduction: Vestibular Evoked Myogenic Potential (VEMP) can be used to test central vestibular pathways from the midbrain to the lumbar spine, according to the muscle tested.

Purpose: to compare the spinal cord alteration in individuals with HTLV-1-associated myelopathy (HAM) and with HTLV-1-asymptomatic infection using the VEMP recorded from different muscles.

Methods: VEMP was recorded in 90 individuals of whom 30 had HAM, 30 were HTLV-1 asymptomatic carriers, and 30 negative controls. VEMP was recorded in the oculomotor muscle (oVEMP), testing the vestibulo-ocular reflex, and in the cervical muscle (cVEMP) and soleus muscle (sVEMP), testing the vestibulospinal reflex, respectively, in the cervical and in the lumbar spinal level. The type of stimulation was auditory for oVEMP and cVEMP, and galvanic for sVEMP. The compared variables were the latencies of the electrophysiological waves.

Results: HTLV-1-asymptomatic group was similar to the controls regarding oVEMP ($p = 0.461$), but different regarding cVEMP ($p < 0.001$) and sVEMP ($p < 0.001$). HAM group has presented the worst latencies and was different from the HTLV-1-asymptomatic group in the VEMP of all the tested muscles ($p < 0.001$). The concomitant occurrence of VEMP alterations in the three recorded muscles of the same individual was found in 2 (6.7%) asymptomatic carriers and in 20 (66.7%) patients with HAM ($p = 0.001$). The analysis of VEMP alteration per group and per muscle has showed that, in HTLV-1-asymptomatic group, oVEMP was altered in 3 (10.0%) individuals, cVEMP in 10 (33.3%) and sVEMP in 13 (43.3%). In HAM group, oVEMP was altered in 23 (76.6%) individuals, cVEMP in 27 (90%), and sVEMP in 30 (100%).

Conclusion: HTLV-1-neurological damage has followed an ascendant progression beginning at the lumbar spine in the stage of a clinically asymptomatic infection, whereas HAM has affected not only the spine, but also the midbrain.

Keywords: vestibular function tests, motor evoked potentials, human T-lymphotropic virus 1, postural balance, vestibular nerve, saccule and utricle

INTRODUCTION

Human lymphotropic T-cell virus type 1 (HTLV-1) is widely disseminated worldwide, and it is estimated that 15 to 20 million people have been infected (1). The means through which the interaction between the virus and the host develops is a determining factor in the state of the asymptomatic carrier or disease (2, 3).

Numerous diseases are correlated with HTLV-1 infection: uveitis, Sjogren's syndrome, infectious dermatitis, polymyositis, arthropathies, thyroiditis, polyneuropathies, lymphocytic alveolitis, cutaneous T-cell lymphoma, strongyloidiasis, scabies, leprosy, tuberculosis, and HTLV-1 associated myelopathy (HAM) (4–6).

In HAM, the site of major involvement is the lower thoracic spine, although the entire neuro-axis can also be involved (7). Alterations in the cervical spine have been identified even in the asymptomatic phase (8). Moreover, the parenchymal lesions may not be limited to the spinal cord (9–11). In fact, there is evidence of diffuse involvement of the central nervous system (CNS) caused by HTLV-1 infection (7, 12). Reports of cognitive impairment have been associated with this infection, including changes in fluid intelligence, semantic memory, attention, and information processing (13, 14).

Postural instability is a frequent clinical manifestation in HAM (15). The complaint of dizziness can be one of the first clinical manifestations of neurological alteration, indicating a possible evolution from asymptomatic carrier to HAM (15). Some patients considered to be "asymptomatic carriers" present electrophysiological changes in the vestibulospinal tract, which participates in the postural control (15).

Vestibular Evoked Myogenic Potential (VEMP) is an electrophysiological test of a tri-synaptic reflex that evaluates the peripheral vestibular system and the central function related to the labyrinth connections. It is considered a test that evaluates the brainstem response (16, 17). The muscles that are the most commonly used to record VEMP are the oculomotor, also called ocular VEMP (oVEMP); the sternocleidomastoid, also called cervical VEMP (cVEMP); and the soleus muscle, also called soleus VEMP (sVEMP) (18–20).

In oVEMP, the activation of the vestibulo-ocular reflex is presumed to follow the vestibular primary afferent, possibly medial longitudinal fasciculus, nucleus, and oculomotor nerves, including the mesencephalic connections (18). In cVEMP, the vestibulocollic reflex goes through the primary vestibular afferent, medial vestibulospinal tract and spinal accessory nerve (18). In sVEMP, the vestibulospinal reflex is conducted through the inferior vestibular nerve, lateral vestibular nucleus, lateral vestibulospinal tract, and reticulospinal tract (21–23). Thus, VEMP varies according to the type of stimulation and to the muscle used to record the electromyographic (EMG) response.

To better characterize the neurological disease associated with HTLV-1 infection, this study aims at comparing VEMP recorded from different muscles in patients with HAM and in HTLV-1 asymptomatic carriers, assessing the CNS at different levels.

METHODS

Ethical Aspects

This research was conducted in accordance with the principles expressed in the Declaration of Helsinki and was approved by the Research Ethics Committee from Universidade Federal de Minas Gerais (COEP UFMG), logged under protocol number CAAE 92928518.3.0000.5149. This protocol number refers to a main project that includes subprojects of which the present study is one of them. All participants provided voluntary written consent and declared that they were aware of the study procedures and their choice to participate.

Study Design

This study was a comparative cross-sectional analysis. The oVEMP, the cVEMP, and the sVEMP were compared among individuals classified as definite HAM, HTLV-1-asymptomatic carriers, and healthy seronegative controls (24).

Sample Size

The sample size was calculated using G* Power software 3.1.9.2 (Heinrich-Heine Universitat Düsseldorf, Düsseldorf, Germany, 2007) to achieve a power of 80% and a significance level of 5% based on the mean and standard deviation of the P13-N23 waves in the cVEMP response of patients with HAM and healthy controls (15). The final calculation estimated an inclusion of 30 participants per group.

Participants

The studied groups were recruited from a cohort of former blood donors infected with HTLV-1 who have been followed by the Interdisciplinary HTLV Research Group (GIPH) since 1997, in Belo Horizonte, Brazil. The GIPH evaluates the natural history, clinical manifestations, and epidemiological aspects of HTLV infection (25).

Ninety participants of the GIPH cohort were invited to participate in this study. They consisted of 30 individuals with definite HAM, 30 with HTLV-1-asymptomatic infection, and a control group of 30 individuals not infected by HTLV-1 (24). The control group consisted of active and healthy blood donors. They were submitted to clinical interviews and neurological examinations before being submitted to VEMP.

The classification of the participants infected by HTLV-1 regarding neurological impairment followed the Expanded Disability Status Scale (EDSS) (24, 26) and the OMDS scale (24, 27): asymptomatic individual (EDSS and OMDS - 0 on both scales) and definite diagnosis of HAM (EDSS and OMDS greater than 1 on both scales).

Individuals with a positive serology for the Human Immunodeficiency Virus (HIV), HTLV-2, or any other blood-tested disease were excluded, as well as an undetermined serology for HTLV-1 and a positive Venereal Disease Research Laboratory test. To avoid confusion factors related to the exam, we excluded individuals using metal prosthesis; with neurological diseases, neoplasms, otitis, and tympanic membrane perforation; with a history of cranio-encephalic trauma or otologic surgery, and peripheral vestibular disease; as well as individuals unable to perform cervical rotation and that were unable to remain in an orthostatic position.

Vestibular Evoked Myogenic Potential (VEMP)

VEMP can be evoked by either auditory or electrical stimulus (galvanic) (20, 21). The technique to perform the test using auditory stimulus is simpler when compared to the galvanic test. However, the recording of VEMP in lower limbs (soleus or gastrocnemius muscle) triggered by auditory stimulus is more difficult because of the lower accumulated energy up to the final neurological path when compared to the galvanic stimulus, which is a more robust one. Thus, the galvanic stimulus is more appropriate to record VEMP in the lower limbs (21). However, it is more uncomfortable for the patient when compared to the auditory stimulus. Because of this, in the present study, we have used the auditory stimulus to obtain oVEMP and cVEMP, and the galvanic stimulus to obtain sVEMP. The parameters considered in the comparison of VEMP analyses were the latency and the reproducibility of the EMG wave.

Ocular VEMP (oVEMP) and Cervical VEMP (cVEMP)

The oVEMP and cVEMP were performed simultaneously (model Labat/Epic Plus, Labat Asia Pvt Ltd., Mohali, India), using two channels. The stimuli were presented through ER 3A insertion phones (of brand Etymotic Research Inc.), with disposable foam ear tips. Tone burst stimuli at an intensity of 120 decibels, a normalized hearing level (dB nHL), were used. In this study, a bandpass filter of 10 to 1,500 Hertz (Hz) was used. To obtain each record, 100 stimuli were presented at a frequency of 500 Hz at a rate of four stimuli per second. The scan window was 50 milliseconds (ms). Each subject underwent at least two stimulations per side in order to verify the replication of the potential. The impedance values, which had to be below 5 kiloohms, were checked before each recording (16).

For oVEMP recordings, the active electrode (model Grass Gold Electrodes Silicone, Natus) on channel 1 was placed ~1 centimeter (cm) below the lower eyelid, and the reference electrode was placed distant approximately 1 cm from the active electrode. The ground electrode was placed on the forehead (Fpz). For cVEMP recording, the active electrode on channel 2 was placed on the opposite side of channel 1, on the anterior border of the sternocleidomastoid muscle in its upper third, while the reference electrode was placed in the sternal notch region (**Figure 1**).

The participants were instructed to sit on the chair and keep their heads rotated to the opposite side of the stimulated ear in order to contract the sternocleidomastoid muscle. We compared reflexes of approximately similar size, where the cVEMP asymmetry between sides was <34%. At the same time, the participant was instructed to look at a stationary target located on the wall in front of him/her and then immediately at a fixed point located above the target, which formed a vertical viewing angle of approximately 30° above the horizontal plane. The oVEMP and cVEMP protocols are available at dx.doi.org/10.17504/protocols.io.zmzf476.

The oVEMP trace is a biphasic wave. The two phases are characterized by a negative peak with an average latency of 10 milliseconds (ms) (N10), followed by a positive peak with an average latency of 15 ms (P15), which is known as N10–P15. The cVEMP trace consists also of a wave with two phases. The first peak is positive with an average latency of 13 ms (P13), followed by a negative peak with an average latency of 23 ms (N23), which it known as P13–N23 (**Figure 2**).

Soleus VEMP (sVEMP)

Galvanic stimulation has been considered a tool to activate the vestibular system inducing both ocular and postural movements (21). The stimulus usually varies from 2 to 4 mA and the duration goes from 20 to 400 ms. The higher the current, the shorter the time of the stimulus (21, 22, 28). The EMG response, that is the VEMP, can be recorded in a muscle involved in either the ocular or the postural movements. The EMG response in the soleus muscle is characterized by a short latency (SL) wave, beginning at around 60 ms, followed by a response in the opposite direction at medium latency (ML), beginning at around 100 ms (21, 22, 29); Both SL and ML responses can only be detected if the muscle is actively contracting (21). In the soleus, SL and ML responses to the transmastoid stimulation are clearest when the subjects head is turned to one side. Both SL and ML responses invert when the head is turned to the opposite side or when the cathode and anode are reversed (21, 22). Cathodal stimulation has been shown to excite, and anodal stimulation to inhibit the vestibular nerve afferent discharge (30). The responses that invert in response to stimulation of opposite polarities and have latencies similar to those previously described, are taken to be of vestibular origin (21, 22).

In the present study, the galvanic vestibular stimulation (GVS) was characterized as a direct, monophasic, and rectangular current with an intensity of 2 mA and duration of 400 ms (model EvP4/ATCPlus, Contronic, Ltd., Pelotas, Brazil). The galvanic stimulus was offered at randomized intervals of 4–5 s and responses to 120 stimulations were measured. The bipolar current was applied on the mastoid processes using self-adhesive, circular surface electrodes (3 cm diameter; model CF3200, Valutrode, Axelgaard, Fallbrook, CA).

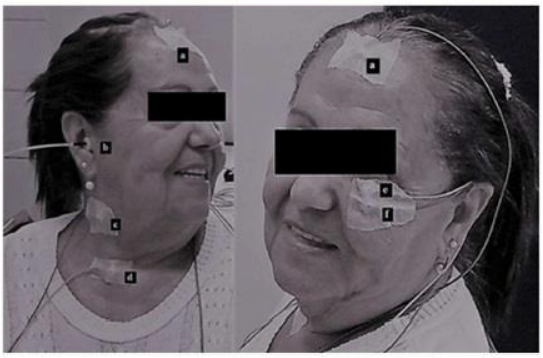

FIGURE 1 | Simultaneous cervical and ocular VEMP: **(a)** ground electrode, **(b)** auditory stimulus, **(c)** active electrode on channel 2 at the anterior border of the sternocleidomastoid muscle in its upper third, **(d)** reference electrode on channel 2 at the sternal notch region, **(e)** active electrode on channel 1 below the lower eyelid, and **(f)** reference electrode on channel 1 below the active electrode.

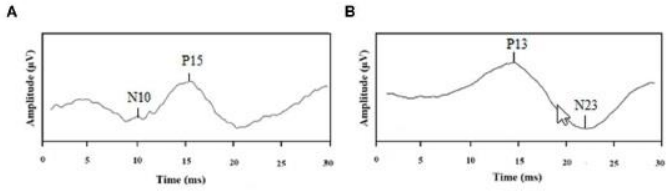

FIGURE 2 | Examples of tracings: **(A)** normal ocular VEMP and **(B)** normal cervical VEMP.

For transmastoid stimulation, the two current polarity settings were cathode left and anode right (CLAR) and cathode right and anode left (CRAL). The stimulation polarity was controlled by a computer. For each test, four sets of 30 stimuli were applied and distributed, resulting in 30 responses recorded from the left lower limb (15 CLAR and 15 CRAL stimuli) and 30 responses recorded from the right lower limb (15 CLAR and 15 CRAL stimuli). This procedure was repeated for each leg to ensure data replication.

During the acquisitions, the subjects stood barefoot on a flat surface with their eyes closed, feet close together, and bodies leaning forward to contract the soleus muscle. To induce a stronger response, subjects were instructed to turn their heads approximately 90° to the side contralateral to the leg undergoing EMG response recording.

The EMG response triggered by GVS was measured using self-adhesive electrodes (model 2223BRQ, 3M, Saint Paul, MN). A pair of recording electrodes were placed bilaterally 5 cm below the popliteal fossa, which coincides with the position over the soleus muscles. Each pair was placed vertically distant 5 cm from each other. This distance can vary from 3 to 10 cm, according to the best recorded wave (21, 22). A reference electrode was placed on the back of the thigh at approximately 10 cm above the upper most recording electrode. The sVEMP was first measured in the left leg and then in the right leg. The tests were performed with a 2-min resting interval to avoid muscle fatigue (**Figure 3**).

The EMG signals were measured, corrected, with a bandpass filter of 10 to 1,000 Hz, and digitized at a sampling frequency of 5,000 Hz. Data were recorded during 500 ms, starting 100 ms before GVS. The EMG responses to 15 consecutive stimuli associated with each polarity configuration (i.e., CLAR and CRAL) were averaged to produce the final traces. The sVEMP protocol is available at dx.doi.org/10.17504/protocols.io.nxbdfin.

The EMG tracings were analyzed for the time of onset, in milliseconds, of the short latency response (SL), and the mean latency response (ML). Following the superimposition of traces with inverted polarity (i.e., CRAL and CLAR), the point where the traces diverged from the EMG baseline, which marked the onsets of SL and ML, could be visualized and measured by a cursor. The first trace divergence, which occurred at approximately 50 ms, marked the onset of the SL response. Following this, the traces returned to baseline and then diverged again. The second trace divergence, which occurred at

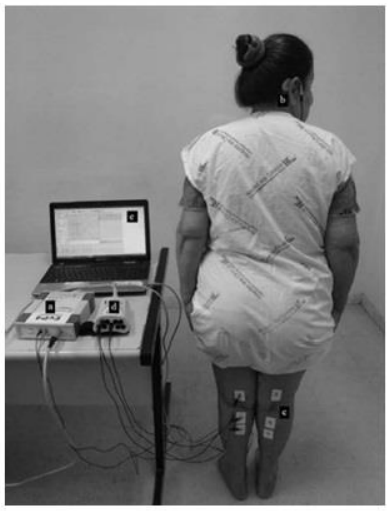

FIGURE 3 | Vestibular-evoked myogenic potential triggered by galvanic vestibular stimulation. The figure shows: the standing position of the patient (barefoot on a hard flat surface with eyes closed, feet close together, and body leaning forward in order to cause the soleus muscle contraction); the equipment used for stimulus generation **(a)**; the electrode positions for GVS **(b)**; the electrode position for electromyography on the soleus muscle **(c)**; the equipment for signal processing **(d)**; and the laptop **(e)** connected to **(a)** and **(d)**.

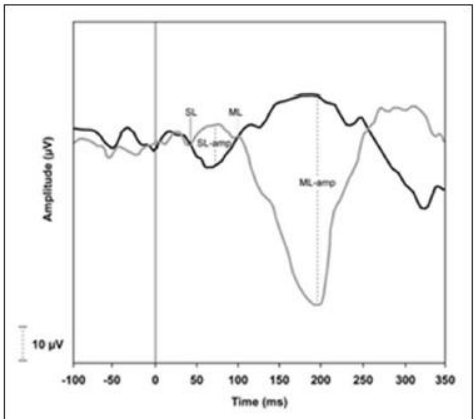

FIGURE 4 | Example of traces obtained by VEMP recording from soleus muscle.

approximately 100 ms, marked the onset of the ML response. The end of this response was defined as the point at which traces return to the baseline. To obtain a single value of the components of SL and ML, it was considered the worst response between the right and left sides (**Figure 4**).

Statistical Analysis of Data

The parameters considered in the VEMP analysis are the latency and amplitude of the waves. However, the amplitude can vary according to age, muscular strength (31), and cochlear diseases (32, 33). Although these variables were controlled in the present study, muscular atrophy in the lower limbs is characteristic of HAM and could therefore act as a possible bias, inducing false positive results. Therefore, the amplitude was not a variable in the analysis.

VEMP results were classified as normal and altered. The results with latency prolongation or no response were considered as altered. The VEMP latency prolongation was defined as a delay of 2.5 standard deviation (SD) when compared to the values of a normal control population, according to the American Society of Encephalography and Evoked Potentials' criteria for evoked potentials (34). The latency values used in this study for the purpose of comparison were the VEMP latencies of the HTLV-1-seronegative group. The validation of the analyzed reference values was guaranteed by comparing these latencies with parameters already established in other national and international peer reviews (16, 35). Among the tested participants, in order to obtain only one value for the peaks N10-P15 (oVEMP), P13-N23 (cVEMP), and SL-ML (sVEMP), the worst response between the right and left sides was considered. Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS), version 20.0. The normality of the samples was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The results of oVEMP, cVEMP, and sVEMP were compared between the groups infected and not infected by HTLV-1. The comparison between groups was performed using the Kruskal-Wallis test, ANOVA test, Chi-square or Fisher's Exact test, Kruskal-wallis with Bonferroni correction, and ANOVA with Bonferroni correction. The adopted level of significance was 5% ($p \leq 0.05$).

The receiver operating characteristic curve (ROC) was performed with the objective of identifying the sensitivity and specificity for each latency cutoff of oVEMP, cVEMP, and sVEMP, considering the neurological examination as the gold standard.

RESULTS

The general characteristics of the studied sample can be seen in **Table 1**. The groups were similar in relation to gender ($p = 0.549$) and age ($p = 0.069$).

The comparison of oVEMP, cVEMP, and sVEMP among the groups regarding the delay of latencies of each peak of the biphasic waves is shown in **Table 2**. The statistical analysis has showed that, in cVEMP and sVEMP, the change has started in the first component of the wave, followed by a delay in the second component. This can be seen by comparing the latencies

between HTLV-1-asymptomatic group and the controls. The latency of the first components were different (P13, $p = 0.039$; SL, $p < 0.001$), while the latency of the second components have remained similar between groups (N23, $p = 0.575$; ML, $p = 0.187$). The comparison between HTLV-1-asymptomatics and HAM has showed a delay in the first components for both groups (P13, $p = 1{,}000$; SL, $p = 0.199$), and the second components have not changed comparing to the controls. With regard to oVEMP, the prolonged latency was observed only in the HAM group.

Figure 5 shows the comparative analysis of oVEMP, cVEMP, and sVEMP, considering the latencies categorized as normal, latency prolongation, and no response. It shows the progressive VEMP alteration from the asymptomatic stage to HAM and from the lumbar spinal damage, detected by sVEMP, to cervical damage, detected by cVEMP, and a more frequent mesencephalic alteration, detected by oVEMP, in patients with HAM as compared to HTLV-1-asymptomatic carriers.

In **Table 3**, oVEMP, cVEMP, and sVEMP were categorized as normal and altered and the results are presented as an analysis between-groups, according to VEMP stratification of the altered results per group. When a concomitant alteration in VEMP recorded from the three muscles was considered, HTLV-1-asymptomatic group did not differ from the normal controls ($p = 0.983$), but it was different from the HAM group ($p = 0.001$).

To evaluate the use of VEMP tests in clinical practice, VEMP latencies were then compared to the neurological examination as the gold standard. We have constructed ROC curves to evaluate latency prolongation of N10-P15 for oVEMP, P13-N23 for cVEMP, and SL-ML for sVEMP (**Figure 6**). The better cut-off points regarding the HTLV-1 infected population were 11 ms for

TABLE 1 | General characteristics of the patients with HTLV-1 associated myelopathy (HAM), HTLV-1-asymptomatic carriers and seronegative controls, EDSS and OMDS disability scales ($n = 90$).

Variable	G1 ($n = 30$)	G2 ($n = 30$)	G3 ($n = 30$)	*p* value
Age	53 [50/55]	56.5 [49/60]	57 [52/59]	0.069[a]
EDSS	0 [0/0]	0 [0/0]	1.75 [1.5/4.5]	<0.001[a]
OMDS	0 [0/0]	0 [0/0]	1.0 [1.0/3.0]	<0.001[a]
Gender				
Female	20 (66.7)	18 (60.0)	22 (73.3)	
Male	10 (33.3)	12 (40.0)	8 (26.7)	

G1, HTLV-1 seronegative; G2, HTLV-1-asymptomatic carriers; G3, HAM; n, number of participants; median [1° quartile / 3° quartile] for continuous variables with asymmetric distribution; absolute number (percentage) for categorical variables; EDSS, extended functional disability scale; OMDS, Osame motor disability scale.
[a] Kruskal-Wallis Test ($p \leq 0.05$).
[b] Chi-square Test ($p \leq 0.05$).

TABLE 2 | Comparison among the groups HTLV-1 associated myelopathy (HAM), HTLV-1-asymptomatic carriers, and seronegative controls regarding the VEMP latency recorded in ocular, cervical, and soleus muscles ($n = 90$).

EMG waves latencies*	G1 ($n = 30$)	G2 ($n = 30$)	G3 ($n = 30$)	*p* value	Comparison groups	*p* value**
Ocular VEMP[a]						
N10	10.63 [9.96/11.00]	10.38 [9.91/10.93]	10.40 [9.95/13.60]	0.675[d]	–	–
P15	15.39 (0.63)	16.11 (2.08)	18.47 (3.03)	<0.001[e]	G1 X G2	0.461
					G1 X G3	<0.001
					G2 X G3	0.001
Cervical VEMP[b]						
P13	12.93 (0.92)	13.71 (0.97)	13.99 (1.73)	0.006[e]	G1 X G2	0.039
					G1 X G3	0.013
					G2 X G3	1.000
N23	22.28 (1.32)	23.27 (2.77)	26.59 (6.41)	0.005[e]	G1 X G2	0.575
					G1 X G3	0.004
					G2 X G3	0.043
Soleus VEMP[c]						
SL	55.81 (3.47)	59.62 (4.25)	62.25 (3.10)	<0.001[e]	G1 X G2	<0.001
					G1 X G3	<0.001
					G2 X G3	0.199
ML	111.88 (7.36)	115.87 (9.13)	128.90 (3.48)	<0.001[e]	G1 X G2	0.187
					G1 X G3	<0.001
					G2 X G3	<0.001

G1, HTLV-1 seronegative; G2, HTLV-1-asymptomatic carriers; G3, HAM.
** Components of the electromyographic (EMG) wave: N10 and P15 for ocular VEMP; P13 and N23 for cervical VEMP; SL (short latency); ML (medium latency) for soleus VEMP; n = number of participants; median [1° quartile / 3° quartile] for continuous variables with asymmetric distribution; mean (standard deviation) for continuous variables with symmetric distributions. The cases of lack of latency were excluded from this analysis: 15 HAM in ocular VEMP[a]; 25 HAM and 9 HTLV-1-asymptomatic carriers in cervical VEMP[b], and 20 HAM and 6 HTLV-1-asymptomatic carriers in soleus VEMP[c].*
[d] Kruskal-Wallis Test ($p \leq 0.05$).
***[e] Anova ($p \leq 0.05$).*

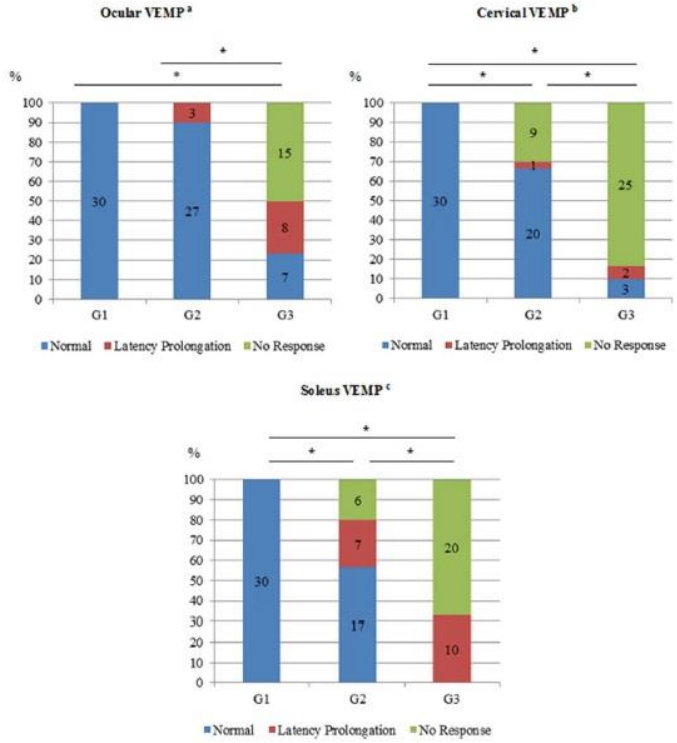

FIGURE 5 | Comparison of VEMP recorded from ocular, cervical, and soleus muscles in the groups HTLV-1 seronegative ($n = 30$), HTLV-1-asymptomatic carriers ($n = 30$) and HAM patients ($n = 30$). G1, HTLV-1 seronegative; G2, HTLV-1-asymptomatic carriers; G3, HAM; The altered responses were categorized as the latency prolongation and the lack of latency of N10-P15 for ocular VEMP[a]; P13-N23 for cervical VEMP[b]; SL-ML for soleus VEMP[c]. *$p \leq 0.001$, Fisher's Chi-Square or Exact Test.

N10, with a sensitivity of 70.0% and a specificity of 91.7%; 16 ms for P15, with a sensitivity of 83.3% and a specificity of 93.3%; 15 ms for P13, with a sensitivity of 60.0% and a specificity of 93.3%; 25 ms for N23, with a sensitivity of 90.0% and a specificity of 83.3%; 65 ms for SL, with a sensitivity of 76.7% and specificity of 86.7%; and 123 ms for ML, with a sensitivity of 100.0% and a specificity of 80.0%. The criterium of using the worst EMG response between the sides contributed to increase the sensitivity of the test, since only one altered side was enough to categorized the patient as altered whereas the normal result was categorized like that only when the waves were truly normal in both sides.

Figure 6 shows that the area under the ROC curve was greater for the second component of the biphasic waves in VEMP of the three tested muscles. Therefore, this component was shown to be the most reliable to define early EMG changes.

DISCUSSION

The HAM diagnosis is based on a set of clinical criteria established by an international consortium in 2006 (24). However, the clinical manifestations related to HAM seem to precede the diagnosis of definite HAM in years, in such a way that they are more frequent in the considered asymptomatic HTLV-1-carriers than in the non-infected individuals (36–38).

More recently, a longitudinal study based on eight years of follow-up has confirmed that the asymptomatic carrier has presented elevated morbidity related to HTLV-1, such as, autonomic changes, including alteration in bowel habits, urinary incontinence or urgency, erectile dysfunction, as well as motor disabilities (39). Thus, the diagnosis of HAM based on clinical criteria establishes the final event of neurological sequelae as the initial mark to define the diagnosis of a disease of chronic

TABLE 3 | Stratified between-groups comparison of VEMP recorded in ocular, cervical, and soleus muscles of HAM ($n = 30$), HTLV-1-asymptomatic carriers ($n = 30$), and HTLV-1-seronegative ($n = 30$) groups.

Electrophysiological Evaluation (VEMP)	G1 ($n = 30$)	G2 ($n = 30$)	G3 ($n = 30$)	*p* value*	Comparison groups	*p* value**
	N (%)	*N* (%)	*N* (%)			
Normal	30 (100.0)	12 (40.0)	0 (0.0)	<0.001	G1 X G2	0.002
					G1 X G3	<0.001
					G2 X G3	0.003
Only oVEMP altered	0 (0.0)	0 (0.0)	0 (0.0)	–	–	–
Only cVEMP altered	0 (0)	5 (16.7)	0 (0.0)	0.925	–	–
Only sVEMP altered	0 (0)	7 (23.3)	0 (0.0)	0.876	–	–
oVEMP + cVEMP altered	0 (0)	0 (0.0)	0 (0.0)	–	–	–
oVEMP + sVEMP altered	0(0)	1 (3.3)	3 (10.0)	0.741	–	–
cVEMP + sVEMP altered	0(0)	3 (10.0)	7 (23.3)	0.689	–	–
oVEMP + cVEMP + sVEMP altered	0(0)	2 (6.7)	20 (66.7)	0.001	G1 X G2	0.983
					G1 X G3	0.004
					G2 X G3	0.001

G1, HTLV-1 seronegative; G2, HTLV-1-asymptomatic carriers; G3, HAM; oVEMP, ocular VEMP; cVEMP, cervical VEMP; sVEMP, soleus VEMP.
Fisher's Chi-Square or Exact Test ($p \leq 0.05$)/ Bonferroni Test.*

evolution. In this context of a late diagnosis for HAM, VEMP is a very useful electrophysiological tool, as it contributes to the detection of alterations related to HTLV-1 before a visible alteration in the neurological examination. VEMP tests the vestibulo-ocular reflex that is related to the stabilization of the image in the retina with the movement of the head and tests the vestibulospinal and reticulospinal tracts related to the postural control (40).

Regarding oVEMP, it is assumed that the neural connections involved in EMG response are mesencephalic (18, 19, 26, 41). The altered responses, such as the latency prolongation or the absence of EMG waves, depend on the disorganization of the primary afferents involved in the vestibulo-ocular reflex (18, 19). In this study, we have found that oVEMP was more frequently altered in the HAM group when compared to the HTLV-1-asymptomatic group (**Figure 5**). In addition, the worst changes were seen in the HAM group. While in this last group the lack of EMG response was the most common change, in the asymptomatic group, this alteration was not found. The oVEMP response in the asymptomatic group did not differ from the controls. These results reinforce the hypothesis that midbrain is compromised in HAM but not in HTLV-1-asymptomatic carriers (7, 12–14).

Regarding cVEMP, as expected, EMG responses were worse in the HAM group when compared to the HTLV-1-asymptomatic group. These data confirm that HAM compromises the cervical spine, although the alterations have been worse in the thoracolumbar region (42, 43). The change from a latency prolongation to a lack of EMG waves suggests that an increase in the neuronal damage occurred (16, 22, 32). This premise can be confirmed by the analysis of the frequency of absent EMG response in the HAM group comparing to the asymptomatic group.

The analysis of sVEMP shows that, in HAM group, all the participants have had altered responses, with a higher frequency of absence of EMG waves (**Figure 5**). In the HTLV-1-asymptomatic group, the comparison of cVEMP and sVEMP results (**Table 2** and **Figure 5**) shows that the electrophysiological alterations were already present in a significant proportion of participants in both cervical and lumbar levels, although the frequency of changes was much higher in HAM group. In fact, VEMP recorded from different muscles may be used to clarify the range of the neurological injury (45).

In sVEMP, the first component of the wave (SL) is assumed to result from a synchronous discharge of a common supraspinal structure, which means, the reticulospinal and the vestibulospinal tract, while the second component (ML) represents the polysynaptic synchrony (21, 22). In accordance with the present study, previous studies have already shown that ML is the best component to discriminate changes since this peak is easier to define with the best intrarater and interrater agreement and presents the best area under the ROC curve comparing to SL (47–49). Conversely, SL can be often indistinguishable from the baseline and its measurement has presented the worst interrater correlation comparing to ML (45, 47–49).

The **Table 3** shows a higher frequency of simultaneous changes in oVEMP, cVEMP, and sVEMP in HAM group. This fact has confirmed the greater spinal impairment in HAM when compared to the group with asymptomatic infection. The changes in oVEMP have occurred only in HAM group, which indicates a midbrain involvement. This finding is precisely in accordance with the best knowledge about HAM physiopathology and reinforces the validity and accuracy of VEMP for clinical use (44–49). In this study, the best contribution of VEMP in the evaluation of the HTLV-1 population was to the asymptomatic infection. A subclinical diagnosis of neurological impairment seems to be possible using VEMP, and it will make difference when the scientific

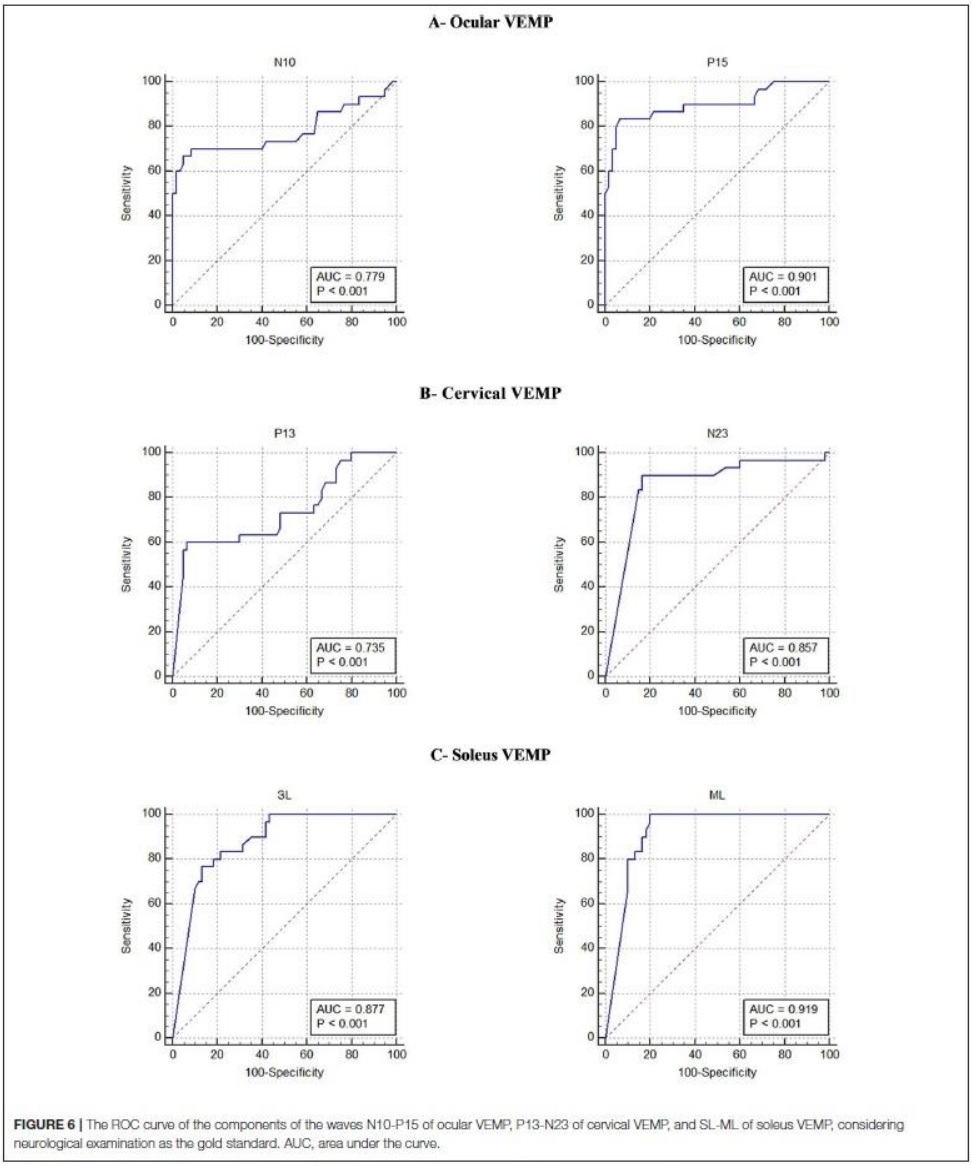

FIGURE 6 | The ROC curve of the components of the waves N10-P15 of ocular VEMP, P13-N23 of cervical VEMP, and SL-ML of soleus VEMP, considering neurological examination as the gold standard. AUC, area under the curve.

progress comes to a more effective treatment of HAM. Our results allow to infer about a pattern of VEMP changes that has occurred. The deficit has started with subtle latency delay and has progressed through degradation of the response and has ended with an absent response. Considering cVEMP and sVEMP, the EMG alteration has started at the first component

(P13, and SL), followed by a latency prolongation at the second component (N23, and ML) until the EMG response has become absent.

In short, we have found that the neurological damage related to HTLV-1 follows an ascending progression since the subclinical stage. The image of the spinal atrophy in the advanced HAM confirms the ascendant damage as it shows that the spinal cord is thinner at the thoracolumbar region than at the cervical one (44). Considering the length of the central pathway, sVEMP has represented a better tool for the early diagnosis of HAM than oVEMP and cVEMP, since these lasts show functional degradation in structures that are anatomically higher in CNS and sVEMP shows degradation that is located in a lower level. On the other hand, oVEMP was useful for the early detection of midbrain changes found in HAM (13, 14).

Vestibular-evoked muscle responses have been used to evaluate the spinal cord in trauma and other neuroinfectious diseases (45, 48). The Schistosomal myeloradiculopathy (SMR) is the most severe and disabling ectopic form of *Schistosoma mansoni* infection and represents 6% of non-traumatic transverse myelopathies in endemic areas (50). The sVEMP triggered by galvanic stimulation was shown to be a promising tool to add electrophysiological information about the spine of patients with chronic SMR. The sVEMP was a reliable and reproducible method to define the integrity of the vestibulospinal tract, with an excellent intrarater and interrater agreement and reliability. Both in HAM and SMR, the component ML was shown to be the most reliable to define alteration (47, 48).

One limitation of the present study was the lack of control of the height and the gender as potential confounding variables. Women have predominated in this study and the ML is more prolonged in women than in men (19). Moreover, VEMP latency has been found to correlate with height (33). Therefore, the cutoff values for the latencies considered in the present study deserve caution regarding the use of these values for the validation of VEMP in different groups of people under different conditions. To avoid this problem, in case of using VEMP in clinical practice, it is desirable to conduct studies that assess VEMP latencies in local healthy people under local conditions for the definition of reliable cutoffs (29).

Another limitation was its transversal design. Although the GIPH cohort includes incident cases of HAM, the participants of the present sectional analysis were not submitted to the entire battery of VEMP tests when they were asymptomatic carriers and afterwards evolved to HAM. Therefore, we cannot make any supposition, based on the present data, about the prognostic value of VEMP alterations within HAM development. The absence of a battery of neurocognitive tests, in addition to the clinical examination, was also a limitation. We have constructed the ROC curve based on the neurological examination, but it would be interesting to analyze the correlation of HTLV-1 cognitive alterations and oVEMP. We do not know if the HTLV-1 infected population with a midbrain alteration would also present a greater risk for cortical alterations. This question deserves a properly designed study to remedy this matter.

CONCLUSION

VEMP analysis of different muscles showed that in HAM the neurological damage has occurred in the spine as well as at the midbrain level. In the asymptomatic carriers, a sub-clinical damage has followed an ascending progression, since changes in VEMP were more frequent in the lumbar as compared to the cervical spine. Thus, VEMP recorded from the soleus muscle, compared to the cervical and ocular muscles, was a better clinical tool for the early diagnosis of neurological changes in a HTLV-1-infected population.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/**Supplementary Material**.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by This research was conducted in accordance with the principles expressed in the Declaration of Helsinki and was approved by the Research Ethics Committee from Universidade Federal de Minas Gerais (COEP UFMG), logged under protocol number CAAE 92928518.3.0000.5149. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TS: conceptualization, data curation, formal analysis, funding acquisition, methodology, project administration, resources, validation, visualization, writing-original draft, writing-review and editing. MR and LM: conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, supervision, validation, visualization, writing-review and editing. LL and JC: validation, visualization, writing-review and editing. RS: investigation and validation. DU: data curation, formal analysis, funding acquisition, methodology, project administration, resources, supervision, validation, visualization, writing-original draft, writing-review and editing.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00433/full#supplementary-material

REFERENCES

1. Gessain A, Cassar O. Epidemiological aspects and world distribution of HTLV-1 infection. *Front Microbiol.* (2012) 3:388. doi: 10.3389/fmicb.2012.00388
2. Santos FLN, Lima FWM. Epidemiologia, fisiopatogenia e diagnóstico laboratorial da infecção pelo HTLV-1. *J Bras Patol Med Lab.* (2005) 41:105–16. doi: 10.1590/S1676-24442005000200008
3. Carneiro-Proietti AB, Catalan-Soares BC, Castro-Costa CM, Murphy EL, Sabino EC, Hisada M, et al. HTLV in the Americas: challenges and perspectives. *Rev Panam Salud Publica.* (2006) 19:44–53. doi: 10.1590/S1020-49892006000100007
4. Mori S, Mizoguchi A, Kawabata M, Fukunaga H, Usuku K, Maruyama I, et al. Bronchoalveolar lymphocytosis correlates with human T lymphotropic virus type I (HTLV-I) proviral DNA load in HTLV-I carriers. *Thorax.* (2005) 60:138–43. doi: 10.1136/thx.2004.021667
5. Seguchi T, Kyoraku Y, Kazuko Saita K, Toshihiko Ihi T, Nagai M, Akiyama Y, et al. Human T-cell lymphotropic virus type I (HTLV-1) associated myelopathy and Sjögren's syndrome representing pulmonary nodular amyloidosis and multiple bullae: report of an autopsy case. *Virchows Arch.* (2006) 448:874–6. doi: 10.1007/s00428-005-0028-x
6. Cooper SA, Loeff MS, Taylor GP. The neurology of HTLV-1infection. *Pract Neurol.* (2009) 9:16–26. doi: 10.1136/jnnp.2008.167155
7. Cervilla JO, Cartier LR, García LF. Brain and spinal cord magnetic resonance imaging in spastic paraparesis associated to human T-lymphotropic virus. *Rev Med Chil.* (2006) 134:1010–8. doi: 10.4067/s0034-98872006000800010
8. Felipe L, Gonçalves DU, Santos MA, Proietti FA, Ribas JG, Carneiro-Proietti AB, et al. Vestibular evoked myogenic potential (VEMP) to evaluate cervical myelopathy in human T-cell lymphotropic virus type I infection. *Spine (Phila Pa 1976).* (2008) 33:1180–4. doi: 10.1097/BRS.0b013e31817152ed
9. Silva MTT, Mattos P, Araújo AQC. Neuropsychological assessment in HTLV-1 infection: a comparative study among TSP/HAM, asymptomatic carriers, healthy controls. *Neurosurg. Psychiatry.* (2003) 74:1085–9. doi: 10.1136/jnnp.74.8.1085
10. Puccioni-Sohler M, Gasparetto E, Cabral-Castro MJ, Slatter C, Vidal CM, Cortes RD, et al. HAM/TSP: association between white matter lesions on magnetic resonance imaging, clinical and cerebrospinal fluid finding, Arq. *Neuropsiquiatr.* (2012) 70:246–52. doi: 10.1590/S0004-282X2012000400004
11. Umehara F, Nose H, Saito M, Fukuda M, Ogino M, Toyota T, et al. Abnormalities of spinal magnetic resonance images implicate clinical variability in human T-cell lymphotropic virus type 1-associated myelopathy. *J Neurovirol.* (2007) 13:260–7. doi: 10.1080/13550280701258431
12. Iwasaki, Y. Human T cell leukemia virus type 1 infection and chronic myelopathy. *Brain Pathol.* (1993) 3:1–10. doi: 10.1111/j.1750-3639.1993.tb00719.x
13. Gascón MRP, Cassebd J, Smid J, Vidal JE, Fonseca LAM, Paiva A, et al. Cognitive impairment is frequent among symptomatic carriers of human T-cell lymphotropic virus type 1 (HTLV-1), regardless of their clinical status. *J Neurol Sci.* (2017) 377:185–9. doi: 10.1016/j.jns.2017.04.019
14. Mendes GB, Kalil RS, Rosadas C, Freitas MRG, Puccioni-Sohler M. Temporal lesions and widespread involvement of white matter associated with multi-organ inflammatory disease in human T-lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). *Int J Infect Dis.* (2014) 25:1–3. doi: 10.1016/j.ijid.2014.03.1374
15. Labanca L, Starling AL, de Sousa-Pereira SR, Romanelli LC, de Freitas Carneiro-Proietti AB, Carvalho LN, et al. Electrophysiological analysis shows dizziness as the first symptom in human T cell lymphotropic Virus type-associated myelopathy/tropical spastic paraparesis. *AIDS Res Hum Retroviruses.* (2015) 31:649–54. doi: 10.1089/aid.2014.0153
16. Silva TR, Resende LM, Santos MAR. Potencial evocado miogênico vestibular ocular e cervical simultâneo em indivíduos normais. *CoDAS.* (2016) 28:34–40. doi: 10.1590/2317-1782/20162015040
17. Kantner C, Gürkov R. Characteristics and clinical applications of ocular vestibular evoked myogenic potentials. *Hearing Res.* (2012) 294:55–63. doi: 10.1016/j.heares.2012.10.008
18. Rosengren SM, Welgampola MS, Colebatch JG. Vestibular evoked myogenic potentials: past, present and future. *Clin Neurophysiol.* (2010) 121:636–51. doi: 10.1016/j.clinph.2009.10.016
19. Chihara Y, Iwasaki S, Ushio M, Murofushi T. Vestibular evoked extraocular potentials by air-conducted sound: another clinical test for vestibular function. *Clin Neurophysiol.* (2007) 118:2745–51. doi: 10.1016/j.clinph.2007.08.005
20. Silva TR, Santos MAR, Resende LM, Labanca L, Caporali JFM, Sousa MR et al. Aplicações dos potenciais evocados miogênicos vestibulares: revisão sistemática de literatura. *Audiol Commun Res.* (2019) 24:1–10. doi: 10.1590/2317-6431-2018-2037
21. Fitzpatrick RC, Burke D, Gandevia SC. Task-dependent reflex responses and movement illusions evoked by galvanic vestibular stimulation in standing humans. *J Physiol.* (1994) 478:363–72. doi: 10.1113/jphysiol.1994.sp020257
22. Britton TC, Day BL, Brown P, Rothwell JC, Thompson PD, Marsden CD. Postural electromyographic responses in the arm and leg following galvanic vestibular stimulation in man. *Exp Brain Res.* (1993) 94:143–51. doi: 10.1007/BF00230477
23. Cathers I, Day BL, Fitzpatrick RC. Otolith and canal reflexes in human standing. *J Physiol.* (2005) 563:229–34. doi: 10.1113/jphysiol.2004.079525
24. De Castro-Costa CM, Araújo AQ, Barreto MM, Takayanagui OM, Sohler MP, da Silva EL, et al. Proposal for diagnostic criteria of tropical spastic paraparesis/HTLV1-associated myelopathy (TSP/HAM). *AIDS Res Hum Retroviruses.* (2006) 22:931–5. doi: 10.1089/aid.2006.22.931
25. Allain JP, Stramer SL, Carneiro-Proietti AB, Martins ML, Lopes da Silva SN, Ribeiro M. Transfusion-transmitted infectious diseases. *Biologicals.* (2009) 37:71–7. doi: 10.1016/j.biologicals.2009.01.002
26. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology.* (1983) 33:1444–52. doi: 10.1212/WNL.33.11.1444
27. Osame M. Review of WHO Kagoshima meeting and diagnostic guidelines for HAM/TSP. In: Blattner W, editor. *Human Retrovirology: HTLV Raven.* (1990). p. 191–7.
28. Fitzpatrick RC, Day BL. Probing the human vestibular system with galvanic stimulation. *J Appl Physiol.* (2004) 96:2301–16. doi: 10.1152/japplphysiol.00008.2004
29. Cunha LC, Labanca L, Tavares MC, Gonçalves DU. Vestibular evoked myogenic potential (VEMP) with galvanic stimulation in normal subjects. *Braz J Otorhinolaryngol.* (2014) 80:48–53. doi: 10.5935/1808-8694.20140011
30. Goldberg JM, Smith CE, Fernández C. Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *J Neurophysiol.* (1984) 51:1236–56. doi: 10.1152/jn.1984.51.6.1236
31. Akin FW, Murnane OD, Panus PC, Caruthers SK, Wilkinson AE, Proffitt TM. The influence of voluntary tonic EMG level on the vestibular-evoked myogenic potential. *J Rehabil Res Dev.* (2004) 41:473–80. doi: 10.1682/JRRD.2003.04.0060
32. De Waele C, Tran Ba Huy P, Diart JP, Freyss G, Vidal PP. Saccular dysfunction in Meniere's disease. *Am J Otol.* (1999) 20:223–32.
33. Young YH, Huang TW, Cheng PW. Assessing the stage of Meniere's disease using vestibular evoked myogenic potentials. *Arch Otolaryngol Head Neck Surg.* (2003) 129:815–8. doi: 10.1001/archotol.129.8.815

34. American Eeg Society. Clinical evoked potentials guidelines. Recommended standards for normative studies of evoked potentials, statistical analysis of results and criteria for clinically significant abnormality. *J Clin Neurophysiol.* (1994) 11:45-7.
35. Murofushi T, Matsuzaki M, Wu CH. Short tone burst-evoked myogenic potentials on the sternocleidomastoid muscle: are these potentials also of vestibular origin? *Arch. Otolaryngol Head Neck Surg.* (1999) 125:660–4. doi: 10.1001/archotol.125.6.660
36. Wang SJ, Yeh TH, Chang CH, Young YH. Consistent latencies of vestibular evoked myogenic potentials. *Ear Hear.* (2008) 29:923–9. doi: 10.1097/AUD.0b013e3181853019
37. Li C, Zuniga MG, Nguyen KD, Carey JP, Agrawal Y. How to interpret latencies of cervical and ocular vestibular-evoked myogenic potentials: Our experience in fifty-three participants. *Clin Otolaryngol.* (2014) 39:297–301. doi: 10.1111/coa.12277
38. Guiltinan AM, Kaidarova Z, Behan D, Marosi C, Hutching S, Kaiser M et al. Major depression and generalized anxiety disorder among human T-lymphotropic virus types I- and II-infected former blood donors. *Transfusion.* (2013) 53:60–8. doi: 10.1111/j.1537-2995.2012.03677.x
39. Tanajura D, Castro N, Oliveira P, Neto A, Muniz A, Carvalho NB et al. Neurological manifestations in human t-cell lymphotropic virus type 1 (HTLV-1)-infected individuals without HTLV-1-associated myelopathy/tropical spastic paraparesis: a longitudinal cohort study. *Clin Infect Dis.* (2015) 61:49–56. doi: 10.1093/cid/civ229
40. Collard M. The vestibular system: from structure to function. *Rev Prat.* (1994) 44:295–58.
41. De Natale ER, Ginatempo F, Paulus KS, Pes GM, Manca A, Tolu E, et al. Abnormalities of vestibular-evoked myogenic potentials in idiopathic Parkinson's disease are associated with clinical evidence of brainstem involvement. *Neurol Sci.* (2015) 36:995–1001. doi: 10.1007/s10072-014-2054-4
42. Akizuki S, Nakazato O, Higuchi Y, Tanabe K, Setoguchi M, Yoshida S, et al. Necropsy findings in HTLV-I associated myelopathy. *Lancet.* (1987) 17:156–7. doi: 10.1016/S0140-6736(87)91984-2
43. Ribas JGR, Melo GCN. Mielopatia associada ao vírus linfotrópicos humano de células T do tipo 1 (HTLV-1). *Rev Soc Bras Med Trop.* (2002) 35:377–84. doi: 10.1590/S0037-86822002000400015
44. Romanelli LCF, Bastos RHC, Silva LC, Martins T, Reiss DB, Freitas GS, et al. Sensitivity and specificity of spinal cord magnetic resonance imaging in the diagnosis of HTLV-1 associated myelopathy. *Retrovirology.* (2014) 11:12. doi: 10.1186/1742-4690-11-S1-P12
45. Iles JF, Ali AS, Savic G. Vestibular-evoked muscle responses in patients with spinal cord injury. *Brain.* (2004) 127:1584–92. doi: 10.1093/brain/awh173
46. Cunha LCM, Tavares MC, Criollo CJT, Labanca L, Paz CCSC, Martins HR, et al. Contribution of galvanic vestibular stimulation in the diagnosis of HTLV-1-associated myelopathy/tropical spastic paraparesis. *J Clin Neurol.* (2013) 9:252–8. doi: 10.3988/jcn.2013.9.4.252
47. Caporali JFM, Labanca L, Florentino KR, Souza BO, Utsch Gonçalves D. Intrarater and interrater agreement and reliability of vestibular evoked myogenic potential triggered by galvanic vestibular stimulation (galvanic-VEMP) for HTLV-1 associated myelopathy testing. *PLoS ONE.* (2018) 13:e0204449. doi: 10.1371/journal.pone.0204449
48. Caporali JF de M, Utsch Gonçalves D, Labanca L, Dornas de Oliveira L, Vaz de Melo Trindade G, de Almeida Pereira T, et al. Vestibular evoked myogenic potential (VEMP) triggered by galvanic vestibular stimulation (GVS): A promising tool to assess spinal cord function in schistosomal myeloradiculopathy. *PLoS Negl Trop Dis.* (2016) 10:e0004672. doi: 10.1371/journal.pntd.0004672
49. Labanca L, Caporali JFM, Carvalho SAS, Lambertucci JR, Carneiro Proietti ABF, Romanelli LCF et al. Vestibular-evoked myogenic potential triggered by galvanic vestibular stimulation may reveal subclinical alterations in human T-cell lymphotropic virus type 1-associated myelopathy. *PLoS ONE.* (2018) 13:e0200536. doi: 10.1371/journal.pone.0200536
50. Ferrari TC, Moreira PR. Neuroschistosomiasis: clinical symptoms and pathogenesis. *Lancet Neurol.* (2011) 10:853–64. doi: 10.1016/S1474-4422(11)70170-3

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6 CONSIDERAÇÕES GERAIS

As alterações encontradas no sVEMP, no cVEMP e no oVEMP em pacientes com HAM indicaram acometimento de toda a medula até o mesencéfalo. Dessa maneira, o acometimento mesencefálico demonstra que a doença não fica restrita à medula, mas avança para o encéfalo, o que está em linha com resultados recentes que mostram acometimento encefálico relacionado ao HTLV-1. Observamos também um comprometimento ascendente, o que já está bem estabelecido na literatura. O fato do cVEMP e do sVEMP estarem mais alterados tanto nos pacientes com HAM quanto nos portadores assintomáticos permite concluir que o acometimento medular é, de fato, mais frequente que o encefálico. Chamou a atenção um paciente com HAM com resultado do cVEMP normal e do oVEMP alterado, sugerindo que a doença pode não respeitar contiguidade de localização. Porém, sendo apenas um paciente, nenhuma conclusão pode ser estabelecida, permanecendo apenas como uma hipótese a ser testada.

Os achados do presente estudo foram apresentados no 19th International Conference on Human Retrovirology: HTLV and Related Viruses realizado em Lima no Peru em abril de 2019. O trabalho foi apreciado pela comunidade científica e, juntamente com outros trabalhos do mesmo grupo de pesquisa, foi premiado. A premiação foi utilizada para custear a taxa de publicação do artigo *Ocular vestibular evoked myogenic potential (VEMP) reveals mesencephalic HTLV-1 associated neurological disease (*Artigo 2, *PLoS One)*

Acredito que o presente estudo contribuiu para o avanço do conhecimento sobre a fisiopatologia da HAM. Por enquanto, não existe tratamento curativo para a HAM, de modo que o arsenal terapêutico disponível visa apenas o controle dos sintomas. Contudo, muitas pesquisas vêm sendo desenvolvidas sobre o HTLV-1 com enfoque em terapia. No momento em que algum tratamento se mostre eficaz para evitar que o paciente desenvolva a mielopatia, o diagnóstico de dano medular na fase pré-clínica será essencial para a seleção dos candidatos ao tratamento. Nesse momento, o VEMP se mostrará como uma ferramenta muito útil.

Para pesquisas futuras, sugere-se estudos com delineamento prospectivo na avaliação do SNC, ou seja, acompanhar os indivíduos infectados pelo HTLV-1 com a finalidade de se definir o valor prognóstico da alteração do VEMP ocular na evolução para uma alteração cognitiva relacionada ao HTLV-1.

7 CONCLUSÃO

O VEMP mostrou-se útil para a identificação de alteração mesencefálica em indivíduos infectados pelo HTLV-1 e para a melhor compreensão sobre o comprometimento neurológico na infecção pelo HTLV-1. Seguindo um padrão progressivo de alteração eletrofisiológica, a piora na resposta do VEMP evoluiu de aumento de latência para ausência de resposta, de acordo com a piora no quadro neurológico. Além disso, as alterações seguiram um padrão ascendente, com alterações eletrofisiológicas subcorticais frequentes nos pacientes com HAM e que também foram observadas, embora de modo menos frequente, na fase de infecção assintomática. O dano neurológico subclínico parece preceder por anos as manifestações clínicas da HAM.

REFERÊNCIAS

ARAYA, N. *et al*. Developing novel treatments for HTLV-1-associated myelopathy (HAM) by investigating molecular pathomechanisms. **Nihon Rinshō Men'eki Gakkai kaishi**, v. 39, n. 3, p. 207-212. Apr. 2016.

BARMACK, N. H. Central vestibular system: vestibular nuclei and posterior cerebellum. **Brain Research Bulletin**, v.15, n.5, p. 511-541. Jun. 2003.

BHIGJEE, A. I. *et al*. HTLV-I-associated myelopathy: clinicopathologic correlation with localization of provirus to spinal cord. **Neurology**, v. 41, n.12, p. 1990-1992. Dec. 1991.

BONALDI, L. V. **Bases Anatômicas da audição e do equilíbrio**. São Paulo: Santos Livraria, 2004.

BORDUCCHI, D. M. M.; KERBAUY, J.; OLIVEIRA, J. S. R. Linfoma/leucemia de células T do adulto. **Revista da Associação Médica Brasileira**, v. 45, n. 1, p. 63-70. Jul-Aug. 1999.

BUELL, K. G. *et al*. Effect of Pulsed Methylprednisolone on Pain, in Patients with HTLV-1-Associated Myelopathy. **PLoS One**, v.11, n.4, p. 1-14. Apr. 2016.

CAPORALI, J. F. M. *et al*. Intrarater and interrater agreement and reliability of vestibular evoked myogenic potential triggered by galvanic vestibular stimulation (galvanic-VEMP) for HTLV-1 associated myelopathy testing. **PLoS One**, v.13, n. 9, p.1-13. Sep. 2018.

CASTRO-COSTA, C. M. *et al*. Proposal for diagnostic criteria of tropical spastic paraparesis/HTLV1-associated myelopathy (TSP/HAM). **AIDS Research and Human Retroviruses**, v. 22, n. 10, p. 931-935. Oct. 2006.

CATALAN-SOARES, B. C.; PROIETTI, F. A.; CARNEIRO-PROIETTI, A. B. F. O vírus linfotrópicos de células T-humanos (HTLV) na última década (1990-2000): aspectos epidemiológicos. **Revista Brasileira de Epidemiologia**, v. 4, n. 2, p. 81-95. 2001.

CERVILLA, J. O.; CARTIER, L. R.; GARCÍA, L. F. Brain and spinal cord magnetic resonance imaging in spastic paraparesis associated to human T-lymphotropic virus. **Revista Médica de Chile**, v. 134, p. 1010-1018. Aug. 2006.

CHAMPS, A.P.S. *et al*. Cognitive impairment in HTLV-1-associated myelopathy, proviral load and inflammatory markers. **International Journal of Infectious Diseases**, v.84, p. 121–126. 2019.

COLLARD, M. The vestibular system: from structure to function. **La Revue du Praticien**, v. 44, n. 3, p. 295-298. Feb. 1994.

CUNHA, L. C. M. *et al*. Contribution of galvanic vestibular stimulation in the diagnosis of HTLV-1-associated myelopathy/tropical spastic paraparesis. **Journal of Clinical Neurology**, v. 9, n. 4, p. 252-258. Oct. 2013.

DIDIER, A.; CAZALS, Y.; AUROUSSOU, C. Brainstem connections of the anterior and posterior parts of the saccule of the guinea pig. **Acta Oto-laryngologica**, v. 104, n. 5- 6, p. 385-391. Nov-Dec. 1987.

DOURADO, I. *et al*. HTLV-I in the general population of Salvador, Brazil: a city with African ethnic and sociodemographic characteristics. **Journal of Acquired Immune Deficiency Syndromes**, v. 34, n. 5, p. 527-531. Dec. 2003.

FELIPE, L. *et al*. Vestibular-evoked myogenic potential (VEMP) to evaluate cervical myelopathy in human T-cell lymphotropic virus type I infection. **Spine**, v. 33, n.11, p. 1180-1184. May. 2008.

FELIPE, L. *et al*. Testing the vestibular evoked myogenic potential (VEMP) to identify subclinical neurological alterations in different phases of human T-lymphotropic virus type 1 infection. **The Spine Journal**, v. 13, n. 4, p. 397-401. Apr. 2013.

GALLO, R. C. History of the discoveries of the first human retroviruses: HTLV-1 and HTLV-2. **Oncogene**, v.24, n. 39, p. 5926-5930. Sep. 2005.

GANANÇA, M. M. *et al*. O acompanhamento da evolução do paciente vertiginoso. *In*: Caovilla, H. H. *et al*. **Equilibriometria clínica**. São Paulo: Atheneu, 1999.

GASCÓN, M. R. P. *et al*. Cognitive impairment is frequent among symptomatic carriers of human T-cell lymphotropic virus type 1 (HTLV-1), regardless of their clinical status. **Journal of the Neurological Sciences**, v. 377, p.185-189. Jun. 2017.

GOTUZZO, E. *et al*. Human T-cell lymphotropic virus-1 in Latin America. **Infectious Disease Clinics of North America**, v. 14, n. 1, p. 211-239. Mar. 2000.

GUERRAZ, M.; DAY, B. L. Expectation and the vestibular control of balance. **Journal of Cognitive Neuroscience**, v. 17, n. 3, p. 463-469. Mar. 2005.

HAIN, T. C.; RAMASWAMY, T. S.; HILLMAN, M. A. Anatomia e fisiologia do sistema vestibular normal. *In*: HERDMAN, S. J. **Reabilitação Vestibular**. 2 ed. Manole, 2002.

HENEINE, W.; *et al*. Sensitive and Specific Polymerase Chain Reaction Assays for Diagnosis of Human T-Cell Lymphotropic Virus Type I (HTLV-I) and HTLV-II Infections in HTLV-I/II-Seropositive Individuals. **Journal of Clinical Microbiology**, v.30, p. 1605-1607. Aug. 1992.

ILES, J. F.; ALI, A. S.; SAVIC, G. Vestibular-evoked muscle responses in patients with spinal cord injury. **Brain: a journal of neurology**, v. 127, n. 7, p. 1584-1592. May. 2004.

IWASAKI, Y. Human T cell leukemia virus type 1 infection and chronic myelopathy. **Brain Pathology**, v. 3, n. 1, p. 1-10. Jan. 1993.

JACOB, F. *et al*. Performances of HTLV serological tests in diagnosing HTLV infection in high-risk population of São Paulo, Brazil. **Revista do Instituto de Medicina Tropical de São Paulo**, v. 49, n. 6, p. 361-364. Nov-Dec. 2007.

JOHNSON, R. T. Emerging viral infections of the nervous system. **Journal of NeuroVirology**, v. 9, p. 140-147. Mar. 2003.

KANTNER, C.; GÜRKOV, R. Characteristics and clinical applications of ocular vestibular evoked myogenic potentials. **Hearing Research**, v. 294, n. 1-2, p. 55-63. Dec. 2012.

LABANCA, L. *et al*. Electrophysiological analysis shows dizziness as the first symptom in human T cell lymphotropic Virus type-associated myelopathy/tropical spastic paraparesis. **AIDS Research and Human Retroviruses**, v. 31, n. 6, p. 649-654. Jun. 2015.

LABANCA, L. *et al.* Vestibular-evoked myogenic potential triggered by galvanic vestibular stimulation may reveal subclinical alterations in human T-cell lymphotropic virus type 1-associated myelopathy. **PLoS One**, v.13, n. 7, p.1-17. 2018.

LAL, R. B. *et al*. Sensitivity and specificity of a recombinant transmembrane glycoprotein (rgp21)-spiked Western immunoblot for serological confirmation of human T-cell lymphotropic virus type I and type II infections. **Journal of Clinical Microbiology**, v. 30, n. 2, p. 296-299. Feb. 1992.

LIECHTI, M. *et al*. Vestibulospinal responses in motor incomplete spinal cord injury. **Clinical Neurophysiol**, v. 119, n. 12, p. 2804-12, 2008.

MENDES, G. B. *et al*. Temporal lesions and widespread involvement of white matter associated with multi-organ inflammatory disease in human T-lymphotropic virus type 1-associated myelopathy/tropical spastic paraparesis (HAM/TSP). **International Journal of Infectious Diseases**, v. 25, p. 1-3. Aug. 2014.

MILAGRES, A. *et al*. Human T cell lymphotropic virus type 1- associated myelopathy in São Paulo, Brazil: Epidemiologic and clinical features of a university hospital cohort. **Neuroepidemiology**, v. 21, n.3, p.153-158. May-Jun. 2002.

MUROFUSHI, T.; CURTHOYS, I. S.; GILCHRIST, D. P. Response of guinea pig vestibular nucleus neurons to clicks. **Experimental Brain Research**, v. 111, n.1, p. 149-152. Sep. 1996.

ORLAND, J. R. *et al*. Prevalence and clinical features of HTLV neurologic disease in the HTLV Outcomes Study. **Neurology**, v. 61, n. 11, p. 1588-1594. Dec. 2003.

OSAME, M. Review of WHO Kagoshima meeting and diagnostic guidelines for HAM/TSP. *In*: BLATTNER, W (ed). **Human retrovirology:** HTLV. Raven, New York, 1990. p. 191-197.

POIESZ, B. J. *et al*. Detection and isolation of type C retrovirus particles from fresh and cultured lymphocytes of a patient with cutaneous T-cell lymphoma. **Proceedings of the National Academy of Sciences of the United States of America**, v.77, n. 12, p. 7315-7319. Dec. 1980.

CARNEIRO-PROIETTI, A.B. *et al.* HTLV in the Americas: challenges and perspectives. **Revista Panamericana de Salud Pública**, v. 19, n. 1, p. 44-53. Jan. 2006.

PUCCIONI-SOHLER, M. *et al*. HAM/TSP: association between white matter lesisons on magnetic resonance imaging, clinical and cerebrospinal fluid finding. **Arquivos de Neuro-psiquiatria**, v. 70, n. 4, p. 246-252. Apr. 2012.

RUDOLPH, D. L. *et al*. Detection of human T-lymphotropic virus type-I/II env antibodies by immunoassays using recombinant fusion proteins. **Diagnostic Microbiology and Infectious Disease**, v. 17, p. 35-39. Jul. 1993.

SANTOS, F. L. N., LIMA, F. W. M. Epidemiologia, fisiopatogenia e diagnóstico laboratorial da infecção pelo HTLV-1. **Jornal Brasileiro de Patologia e Medicina Laboratorial**, v. 41, n.2, p.105-116. Abril. 2005.

SCHÜTZE, M. *et al.* Brain metabolism changes in patients infected with HTLV-1. **Frontiers in Molecular Neuroscience**, v. 10, p. 1-8. Feb. 2017.

SILVA, M.T. *et al*. Neuropsychological assessment in HTLV-1 infection: a comparative study among TSP/HAM, asymptomatic carriers, and healthy controls. J**ournal of neurology, neurosurgery, and psychiatry**, v. 74, n.8, p. 1085-1089. Aug. 2003.

SILVA, C. M. S. *et al*. Prevalência de sorologia positiva para o HTLV-1 e HTLV-2 em gestantes atendidas em três serviços de pré-natal, São Luís, jul/08 a jul/09. **Cadernos de Pesquisa**, v. 16, n. 3. p. 39-44. Ago-Dez. 2009.

STARLING, A. L. *et. al*. Immunological signature of the different clinical stages of the HTLV-1 infection: establishing serum biomarkers for HTLV-1-associated disease morbidity. **Biomarkers: biochemical indicators of exposure, response, and susceptibility to chemicals**, v. 20, n. 6-7, p. 502-512. Oct. 2015.

STRUPP, M. *et al.* Bilateral vestibulopathy: diagnostic criteria consensus document of the classification committee of the Bárány Society. **Journal of vestibular research: equilibrium & orientation**. v. 27, n. 4, p. 177-189. 2017.

TANAJURA, D. *et al*. Neurological manifestations in human T-cell lymphotropic virus type 1 (HTLV-1)–infected individuals without HTLV-1–associated myelopathy/tropical spastic paraparesis: a longitudinal cohort study. **Clinical Infectious Diseases**, v. 61, n. 1, p. 49-56. Jul. 2015.

TAYLOR, G. P., MATSUOKA, M. Natural history of adult T-cell leukemia/ lymphoma and approaches to therapy. **Oncogene**, v. 24, n.39, p. 6047-6057. Sep. 2005.

UMEHARA, F. *et al*. Abnormalities of spinal magnetic resonance images implicate clinical variability in human T-cell lymphotropic virus type I–associated myelopathy. **Journal of Neurovirology**, v. 13, n.3, p.260-267. Jun. 2007.

WATSON, S.R.D.; COLEBATCH, J.G. Vestibular-evoked electromyographic responses in soleus: a comparison between click and galvanic stimulation. **Experimental Brain Research**, v. 119, n. 4, p. 504-510, 1998.

YAMANO, Y. *et al*. Correlation of human T-cell lymphotropic virus type 1 (HTLV-1) mRNA with proviral DNA load, virus-specific CD8_ T cells, and disease severity in HTLV-1–associated myelopathy (HAM/TSP). **Blood**, v.99, n.1, p. 88-94. Jan. 2002.

YOSHIDA, M.; JEANG, K. T. Preface to 25 years of HTLV-1 and ATL research. **Oncogene**, v. 24, p. 5925. Sep. 2005.

APÊNDICE A: S1 Appendix (Artigo 2)

QUESTIONNAIRE

IDENTIFICATION

ID _____ IDSEARCH _____ GIPH _____ DATE OF EXAMINATION __/__/____

NAME _____ SEX _____

ADDRESS _____

TELEPHONE _____/ _____ E-MAIL _____

DATE OF BIRTH _____/_____/_____ AGE _____ SCHOOLING YEARS _____

HOURS OF SLEEP IN THE PREVIOUS NIGHT _____ DOMINANT HAND _____ GROUP _____

GENERAL HEALTH

MEDICATION _____ WHICH _____

HEARING COMPLAINT _____ WHICH_____ TINNITUS _____

VESTIBULAR COMPLAINT _____WHICH_____CONVULSION _____

MEMORY COMPLAINT _____ COMPLAINT ATTENTION _____ COMPLAINT COMMUNICATION _____

APÊNDICE B: S2 Table (Artigo 2)

S2 Table. Descriptive variables of healthy controls, asymptomatic infection group, and HTLV-1-associated myelopathy group: age, disability scales (EDSS and OMDS), the latency (ms) of cervical VEMP (P13 and N23 waves) and ocular VEMP (N10 and P15 waves).

Variables		Control (n=26)	Asymptomatic (n=26)	HAM (n=26)
Age	Mean	53.27	53.73	55,69
	Standard deviation	3.39	7.65	4.44
	Median	53.00	58.50	57.00
	Minimum	46.00	32.00	45.00
	Maximum	59.00	60.00	60.00
EDSS	Mean	0.00	0.00	3.00
	Standard deviation	0.00	0.00	2.08
	Median	0.00	0.00	2.00
	Minimum	0.00	0.00	1.00
	Maximum	0.00	0.00	7.00
OMDS	Mean	0.00	0.00	2.30
	Standard deviation	0.00	0.00	1.85
	Median	0.00	0.00	1.00
	Minimum	0.00	0.00	1.00
	Maximum	0.00	0.00	6.00
Cervical VEMP P13 latency	Mean	12.80	13.73	14.83
	Standard deviation	0.91	1.03	3.22
	Median	12.73	13.85	13.85
	Minimum	11.15	11.25	12.00
	Maximum	14.70	16.40	23.00
Cervical VEMP N23 latency	Mean	22.30	23.04	25.75
	Standard deviation	1.36	2.44	4.43
	Median	21.88	22.63	24.63
	Minimum	20.50	20.50	20.50
	Maximum	24.80	33.00	33.00
Ocular VEMP N10 latency	Mean	10.49	10.38	11.51
	Standard deviation	0.65	0.92	2.80
	Median	10.70	10.33	10.38
	Minimum	8.75	9.00	9.05
	Maximum	11.45	13.55	20.00
Ocular VEMP P15 latency	Mean	15.40	15.74	18.17
	Standard deviation	0.66	1.35	3.30
	Median	15.44	15.68	16.85
	Minimum	14.10	13.75	14.20
	Maximum	16.60	20.90	25.00

ANEXO A: Treinamento USP

ANEXO B: Aprovação do COEP UFMG

UNIVERSIDADE FEDERAL DE MINAS GERAIS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Exames eletrofisiológicos para testar a cognição auditiva e equilíbrio postural na mielopatia associada ao HTLV-1 (HAM)

Pesquisador: Denise Utsch Gonçalves

Área Temática:

Versão: 2

CAAE: 92928518.3.0000.5149

Instituição Proponente: UNIVERSIDADE FEDERAL DE MINAS GERAIS

Patrocinador Principal: Financiamento Próprio
UNIVERSIDADE FEDERAL DE MINAS GERAIS

DADOS DO PARECER

Número do Parecer: 2.898.825

Apresentação do Projeto:

A proposta inicial deste projeto é avaliar e desenvolver ferramentas de diagnóstico e tratamento para as alterações causadas pelo HTLV-1 no sistema nervoso central. (Obs.: O vírus HTLV (sigla da língua inglesa que indica "vírus que infecta células T humanas") é um retrovírus isolado em 1980, a partir de um paciente com um tipo raro de leucemia de células T.) Em relação ao comprometimento cognitivo associado ao HTLV-1, O treinamento auditivo é um conjunto de estratégias utilizadas para desenvolver ou reabilitar as habilidades auditivas, as quais são necessárias para a compreensão da fala e melhorar a cognição. Técnicas específicas de treinamento auditivo podem aprimorar as habilidades auditivas e a melhor funcionalidade está diretamente relacionada com a capacidade de reorganização do substrato neural auditivo. Tal fenômeno é conhecido como plasticidade neural, que pode ser observada em adultos. Em relação ao comprometimento medular associado ao HTLV-1, a avaliação da resposta á reabilitação postural, feita através da estimulação vestibular galvânica, depende da comparação de dois grupos infectados pelo HTLV-1 com instabilidade postural; um será exposto a estimulação galvânica como estratégia de tratamento para a estabilidade postural enquanto o outro grupo não será submetido ao tratamento teste.

Inicialmente os integrantes da coorte do Grupo Interdisciplinar de pesquisa em HTLV-1 (GIPH) que aceitarem participar do estudo serão submetidos a avaliação clínica, neurológica e

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

otorrinolaringológica com a finalidade de serem divididos em três grupos: controle negativo, HTLV-1 assintomático e com mielopatia associada ao HTLV-1 (HAM). Em seguida, o exame Potencial evocado miogênico vestibular ocular(o-VEMP), cervical (c-VEMP) e solear (s-VEMP)será realizado com a finalidade de se avaliar a via vestíbulo-espinhal, que é relacionada ao reflexo postural. O objetivo é selecionar os indivíduos infectados pelo HTLV-1 com reflexo postural alterado e com reflexo normal. Os participantes terão o seu equilíbrio postural avaliado clinicamente através do teste de Romberg, Timedupandgo test, Escala de equilíbrio de Berg e Escala visual analógica. Além de submetidos ao VEMP, os participantes serão submetidos ao teste de processamento auditivo central - P300 para avaliar a cognição auditiva. Os participantes com todas as avaliações normais serão reavaliados após 6 meses (subprojeto 1). Os participantes com alteração no VEMP ou nos testes de estabilidade postural serão convidados a participar do subprojeto 2 cujo objetivo é avaliar o efeito da EVG na reabilitação da instabilidade postural. Os participantes com alteração no processamento auditivo serão convidados a participar do subprojeto 3 cujo objetivo é avaliar o efeito do treinamento auditivo na reabilitação das habilidades auditivas centrais.
Subprojeto 1: VEMP para avaliar o equilíbrio corporal na HAM - Serão convidados a participar da pesquisa 150 indivíduos, na faixa etária de 30 a 59 anos, compostos por um grupo de 50 indivíduos infectados pelo HTLV- 1 assintomáticos, 50 com diagnóstico definido de HAM e por um grupo controle de 50 indivíduos não infectados pelo HTLV-1. Tratar-se de um estudo comparativo transversal analítico do tipo caso-controle aninhado a coorte de infectados pelo HTLV1 acompanhados pelo Grupo Interdisciplinar de Pesquisa em HTLV-1 (GIPH) desde 1997. Os participantes serão submetidos a estimulação vestibular galvânica (EVG) para gerar o VEMP. A resposta eletrofisiológica será captada por eletrodos de superfície nos músculos oculares (o-VEMP) esternocleidomastóideo (c-VEMP) e sóleo da panturrilha (s-VEMP). Como etapa longitudinal, propõe-se a realização semestral dos VEMPs nos indivíduos infectados pelo HTLV-1 assintomáticos para se avaliar a evolução de resposta eletrofisiológica de normal para alterada visando selecionar indivíduos com possível evolução da fase subclínica para HAM. Subprojeto 2: Avaliação da estimulação vestibular galvânica na melhora da instabilidade postural associada à HAM - Trata-se de estudo experimental com 30 infectados pelo HTLV-1 entre 18 a 75 anos de idade com instabilidade postural que serão randomicamente divididos em dois grupos. O diagnóstico de instabilidade postural será baseado no exame neurológico, incluindo alteração na prova de Romberg, tempo superior a 10 segundos na realização da prova de marcha do Timed up and go test e pontuação menor ou igual a 49 pontos na Escala de equilíbrio de Berg, além de

alteração nos VEMPs. Um dos grupos será submetido á EVG que será realizada com eletrodos de superfície colocados na pele do osso da mastóide. O estímulo será gerado por um estimulador de corrente constante. Cada sessão terapêutica será constituída de dois ensaios de 60 estimulações. O intervalo entre os ensaios será de 5 minutos em cada sessão e os intervalos entre os estímulos serão randomizados entre 4 e 6 segundos. Os participantes serão acompanhados quanto ao equilíbrio postural pelo VEMP e testes neurológicos. Subprojeto 3: Alteração da cognição auditiva associada ao HTLV-1: avaliação comportamental, eletrofisiológica e da efetividade do treinamento auditivo para reabilitação. O treinamento auditivo será usado para melhorar a cognição auditiva de indivíduos infectados pelo HTLV-1 com alteração da cognição auditiva detectada pelo P300 e testes comportamentais. Trata-se de estudo experimental com 30 infectados pelo HTLV-1 e com P300 alterado que serão randomicamente divididos em dois grupos. Um dos grupos será submetido ao TA e o outro grupo será submetido a atividades com mesmo tempo de duração do TA mas que não tem ação em melhora da cognição auditiva (controle). Os grupos serão acompanhados pelo P300 e testes comportamentais para avaliar a cognição auditiva. O P300 é um teste eletrofisiológico que avalia o processamento auditivo central (PAC) e detecta alterações cognitivas que tem se mostrado frequentes na HTLV-1 (HAM). O treinamento auditivo (TA) poderá se apresentar como uma estratégia de tratamento com melhora na cognição auditiva dessa população. Estudos envolvendo medidas comportamentais, psicofísicas e eletrofisiológicas pré e pós intervenção demonstram associação positiva entre Treinamento Auditivo (TA) e desenvolvimento das habilidades auditivas neurocognitivas em diferentes populações.

Como critério de Inclusão o pesquisador descreve "Serão incluídos no estudo indivíduos de 18 a 75 anos de idade, de ambos os gêneros. Os grupos estudados serão:Grupo controle: Composto indivíduos com sorologia negativa para o HTLV-1 pelo teste ELISA (Enzyme-linked-immunosorbent -assay). Grupo com a infecção pelo HTLV-1: Composto por ex-doadores de sangue da Fundação Hemominas com soropositividade definida pelo teste ELISA e confirmado por meio do WB (Western Blot) ou testes moleculares (Reação em cadeia da polimerase - PCR). Os participantes foram subdivididos em dois subgrupos de acordo com o resultado da avaliação neurológica:Grupo assintomático: indivíduos sem sintomas clínicos de acordo com os critérios propostos pela Organização Mundial de Saúde (OMS) adaptado (GRASSI et al, 2011; CASTRO-COSTA, 2006), classificados conforme Escala de Incapacidade Funcional Ampliada adaptada (EDSS) e OSAME apresentando classificação zero em ambas as escalas (KURTZKE, 1983; OSAME, 1990).

Grupo HAM: indivíduos com sinais clínicos suficientes, de acordo com os critérios propostos pela OMS adaptado (GRASSI et al, 2011; CASTRO-COSTA, 2006), classificados conforme Escala de

Incapacidade Funcional Ampliada adaptada (EDSS) e OSAME apresentando classificação a partir de dois em ambas as escalas. Já os critérios de exclusão, serão indivíduos com documentação de sorologia positiva para vírus da imunodeficiência humana (HIV), vírus da hepatite B (HBV), vírus da hepatite C (HCV), teste Venereal Disease ResearchL aboratory (VDRL) positivo e participantes com história de acidente vascular encefálico e epilepsia.Para a realização do VEMP serão excluídos os participantes com incapacidade de permanecer na posição do exame e participantes com episódios recorrentes de vertigem ou história de vestibulopatia periférica já diagnosticada previamente. Para a realização da avaliação do processamento auditivo e testes comportamentais serão excluídos os participantes com perda auditiva superior a 25dBNA nas frequências de 1000Hz ou 2000Hz."

Objetivo da Pesquisa:

Objetivo Primário

Avaliar e desenvolver testes eletrofisiológicos de diagnóstico e de tratamento das alterações no equilíbrio corporal e na cognição auditiva e no equilíbrio causadas pelo HTLV-1.

Objetivos Secundários

Avaliar, por eletrofisiologia, utilizando-se o VEMP, as vias neuronais ascendentes (VEMP ocular) e descendentes (VEMP cervical e solear) associadas ao equilíbrio corporal de indivíduos infectados pelo HTLV-1 assintomáticos e com HAM; Avaliar a resposta ao tratamento com a EVG de pacientes com instabilidade postural; Avaliar e descrever o PAC através do P300 e de testes comportamentais relacionados a cognição auditiva; Avaliar a resposta ao TA em caso de alteração no PAC; Comparar os resultados do P300 com os resultados do VEMP.

Avaliação dos Riscos e Benefícios:

Segundo o pesquisador

Riscos: Os riscos dos exames são mínimos. Durante a estimulação galvânica, o paciente poderá sentir um leve formigamento no couro cabeludo; poderá sentir também um desequilíbrio passageiro durante o estímulo. Para a realização do VEMP, eletrodos de superfície para captar a resposta eletrofisiológica são colocados na perna ou pescoço do paciente.Para a realização do P300, um fone de ouvido em som de intensidade normal é oferecida para o paciente que deve estr atento para o que escuta.

Benefícios: O paciente será submetido a uma avaliação auditiva, exame neurológico, avaliação cognitiva. Todos esses procedimentos tem caráter preventivo se exames mostrarem-se normais e

o paciente será encaminhado para o devido diagnóstico e tratamento se os exames se mostrarem alterados.Para aqueles infectados pelo HTLV-1 com alteração do equilíbrio corporal, a estimulação galvânica será oferecida como uma opção de tratamento para melhorar o equilíbrio corporal. Vale ressaltar que não existe, até o presente momento, estudo controlado em pacientes com HTLV-1. A modalidade de estimulação elétrica do crânio tem se mostrado útil para intervenções em zumbido e depressão, mas com um custo muito elevado (estimulação transmagnética). Oferecemos uma opção a baixo custo, caso nossas pesquisas mostrem ganho, o que é a nossa expectativa.Para aqueles infectados pelo HTLV-1 que tiverem o diagnóstico de alteração na cognição auditiva por causa da presente pesquisa, ter a oportunidade de ser submetido ao treinamento auditivo é um privilégio, ao nosso ver. O treinamento auditivo é uma modalidade de reabilitação da cognição auditiva que não tem qualquer risco para o paciente e vem sendo usado para quadros de déficit de atenção em crianças, dentre outras indicações. O participante desse estudo não teria oportunidade de ter acesso a esse tipo de tratamento se não fosse por essa pesquisa.Por fim, a infecção do HTLV-1 é considerada pelo Ministério da Sáude como negligenciada e a HAM é uma mielopatia de diagnóstico tardio e sem tratamento definido. Essa pesquisa tem como foco o diagnóstico precoce e o tratamento da instabilidade postural e cognitiva na HAM. Ambas as ações são muito importantes no contexto de uma infecção que precisa de pesquisas clínicas para avançar nas questões citadas.

Comentários e Considerações sobre a Pesquisa:

A pesquisa não apresenta questionamentos éticos. Mostra-se importante para o campo de conhecimento, bem como tendo relevância social ao se tratar de método diagnóstico e de tratamento.

Considerações sobre os Termos de apresentação obrigatória:

Todos os termos foram apresentados de forma correta. Não havendo comentários sobre eles.

Conclusões ou Pendências e Lista de Inadequações:

Diante da resposta positiva aos questionamentos feitos na diligência do parecer de número 2.816.069, sou favorável, s. m. j., a aprovação do projeto "Exames eletrofisiológicos para testar a cognição auditiva e equilíbrio postural na mielopatia associada ao HTLV-1 (HAM)".

Considerações Finais a critério do CEP:

Aprovado conforme parecer.

Tendo em vista a legislação vigente (Resolução CNS 466/12), o COEP-UFMG recomenda aos

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pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1080446.pdf	21/08/2018 21:11:23		Aceito
Outros	Carta_resposta_COEP.jpg	21/08/2018 21:10:25	Denise Utsch Gonçalves	Aceito
Outros	Parecer_Departamento_HTLV_2018.pdf	21/08/2018 21:09:10	Denise Utsch Gonçalves	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_nova_versao.pdf	21/08/2018 21:06:38	Denise Utsch Gonçalves	Aceito
Declaração de Instituição e Infraestrutura	Parecer_EBSERH.pdf	09/03/2018 08:01:01	Denise Utsch Gonçalves	Aceito
Parecer Anterior	COEP_VEMP_GALVANICO_2005.pdf	09/03/2018 08:00:10	Denise Utsch Gonçalves	Aceito
Projeto Detalhado / Brochura Investigador	UniversalHTLV_2018.pdf	08/03/2018 19:33:48	Denise Utsch Gonçalves	Aceito
Folha de Rosto	FolhaRostroHTLV_2018.pdf	08/03/2018 19:28:58	Denise Utsch Gonçalves	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

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Continuação do Parecer: 2.898.825

BELO HORIZONTE, 17 de Setembro de 2018

Assinado por:
Eliane Cristina de Freitas Rocha
(Coordenador)

Endereço: Av. Presidente Antônio Carlos,6627 2º Ad SI 2005
Bairro: Unidade Administrativa II **CEP:** 31.270-901
UF: MG **Município:** BELO HORIZONTE
Telefone: (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

ANEXO C: Escala EDSS

ESCALAS DE INCAPACIDADE FUNCIONAL EDSS e OSAME (REVISADA)

ESCALA DE INCAPACIDADE FUNCIONAL AMPLIADA (EDSS)

(KURTZKE, 1965; KURTZKE, 1983)

0. Exame neurológico normal (grau 0) em todas as avaliações do sistema funcional - SF.

1,0. Nenhuma incapacidade; sinais mínimos em um SF (ou seja grau 1).

1,5. Nenhuma incapacidade; sinais mínimos em mais de um SF (mais de um SF grau 1).

2,0. Incapacidade mínima em um SF (um SF grau 2; outros graus 0 ou 1).

2,5. Incapacidade em dois SF (dois SF grau 2; outros graus 0 ou 1).

3,0. Incapacidade moderada em um SF (um SF grau 3 , outros grau 0 ou 1),ou discreta incapacidade em três ou quatro SF (três ou quatro SF grau 2 ;outros 0 ou 1) embora completamente ambulatorial.

3,5. Deambulação plena, com incapacidade moderada em um SF (um SF grau 3) e um ou dois SF grau 2; ou dois SF grau 3; ou cinco SF grau 2 (outros 0 ou 1).

4,0. Deambulação plena sem ajuda; auto-suficiente; ativo por cerca de 12 horas por dia, apesar da incapacidade relativamente grave consistindo de um SF grau 4 (outros 0 ou 1), ou combinações de graus menores excedendo os limites das etapas anteriores capaz de caminhar cerca de 500 metros sem ajuda ou descanso.

4,5. Deambulação plena sem ajuda; ativo durante grande parte do dia; capaz de trabalhar por um dia inteiro; porém, pode apresentar alguma limitação da atividade completa ou precisar de um pouco de ajuda; caracteriza-se por incapacidade relativamente grave, geralmente consistindo de um SF grau 4 (outros 0 ou 1), ou combinações de graus menores excedendo os limites das etapas anteriores; capaz de caminhar cerca de 300 metros sem ajuda ou descanso.

5,0. Deambulação sem ajuda ou descanso para caminhar cerca de 200 metros; incapacidade grave o suficiente para comprometer as atividades diárias (por exemplo, trabalhar o dia inteiro sem dispositivos especiais); os equivalentes comuns do SF são de grau 5, isoladamente (outros 0 ou 1),ou combinações de graus menores, geralmente excedendo os limites da etapa 4,0.

5,5. Deambulação sem ajuda ou descanso para caminhar por 100 metros; incapacidade grave o suficiente para impedir a realização de atividades diárias; os equivalentes comuns do SF são de grau 5, isoladamente (outros 0 ou 1), ou combinações de graus menores, geralmente excedendo os limites da etapa 4,0.

6,0. Assistência intermitente ou com auxílio unilateral constante (bengala, muleta ou suporte) para caminhar cerca de 100 metros com ou sem descanso; os equivalentes comuns do SF são combinações com mais de 2 SF grau 3+.

http://www.bibliotecadigital.ufba.br/tde_busca/arquivo.php?codArquivo=465.

6.5. Assistência bilateral constante (bengala, muleta, suporte) para caminhar cerca de 20 metros sem descanso; os equivalentes comuns do SF são combinações com mais de dois SF grau 3 +.

7.0. Incapacidade para caminhar além de cerca de 5 metros, mesmo com auxílio; restrito a cadeira de rodas; capaz de conduzir a cadeira de rodas comum sem auxílio, além de entrar e sair da cadeira sem ajuda; consegue permanecer em atividade, na cadeira de rodas, por cerca de 12 horas por dia; os equivalentes comuns do SF são combinações com mais de um SF grau 4+; muito raramente, função piramidal grau 5 isoladamente.

7.5. Incapacidade para dar mais do que alguns passos; confinamento à cadeira de rodas; pode precisar de ajuda para sair e sentar na cadeira; capaz de conduzir a cadeira sem ajuda, mas não consegue permanecer na cadeira de rodas comum o dia inteiro; precisa de cadeira de rodas motorizada; os equivalentes comuns do SF são combinações com mais de um SF grau 4+.

8.0. Restrito ao leito ou a cadeira, ou consegue se locomover com a cadeira de rodas, porém não consegue ficar fora da cama por muito tempo; consegue realizar algumas funções para cuidar da sua própria higiene e mantém o uso dos braços; os equivalentes comuns do SF são combinações com grau 4+ em diferentes sistemas.

8.5. Essencialmente confinado a cama na maior parte do dia; consegue realizar algumas funções para cuidar de sua própria higiene e mantém algum uso dos braços; os equivalentes comuns do SF são combinações com grau 4+ em diferentes sistemas.

9.0. Paciente acamado e desamparado; consegue se comunicar e comer; os equivalentes comuns do SF são combinações, em sua maioria, do grau 4+

9.5. Paciente totalmente desamparado e acamado; incapaz de se comunicar com eficácia ou comer/ engolir; os equivalentes comuns do SF são combinações, quase todos do grau 4+.

10. Morte devida a complicações da EM.

http://www.bibliotecadigital.ufba.br/tde_busca/arquivo.php?codArquivo=465.

ANEXO D: Escala OSAME

BASELINE
ESCALA DE INCAPACIDADE MOTORA REVISADA DE OSAME
IZUMO *et al.*, 1996

ESCALA OSAME	
0	Deambula e corre normalmente
1	Marcha normal mas corre lentamente
2	Marcha anormal(vacilante ou espástica)
3	Marcha anormal e incapacidade para correr
4	Necessita apoio para usar escadas mas deambula sem auxilio
5	Necessita apoio em uma das mãos para deambular
6	Necessita apoio nas duas mãos para deambular
7	Incapaz para deambular embora engatilhe
8	Incapaz de engatilhar embora mude posição no leito
9	Incapaz de mudar a posição no leito embora mova os dedos
10	Completamente restrito ao leito

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