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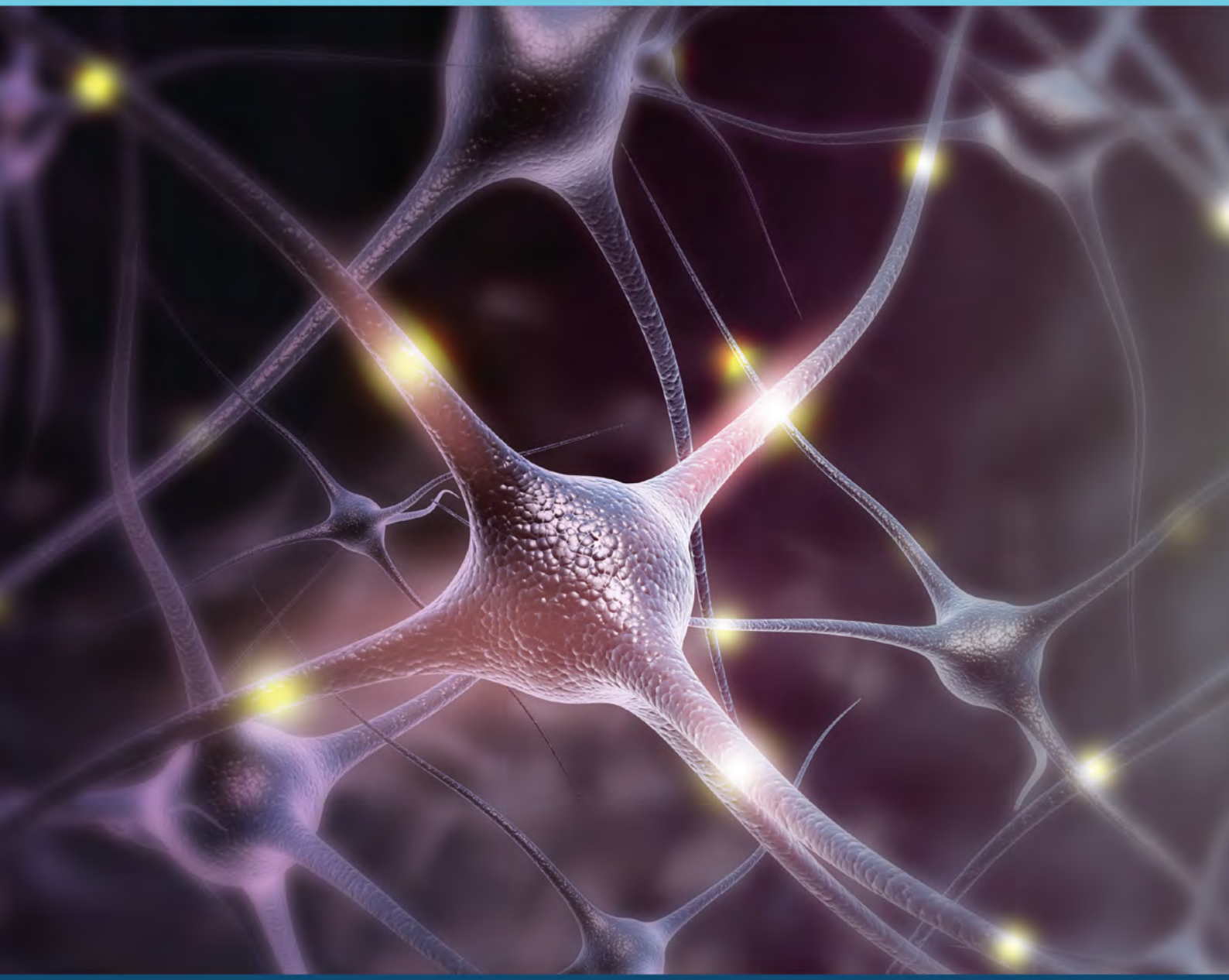

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CONSELHO EDITORIAL INTERNACIONAL

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Ricardo Ramina, MD, PhD
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Artigos de periódicos (COLOCAR DOI QUANDO EXISTENTE)

1. **Até 6 autores (citar todos)**
2. Harbell J, Terrault NA, Stock P. Solid organ transplants in HIV-infected patients. Curr HIV/AIDS Rep. 2013;10(3):217-25. http://dx.doi.org/10.1007/s11904-013-0170-z.
3. **Mais de 6 autores (citar 3 seguido de et al.)**
4. Patel MA, Kim JE, Theodros D, et al. Agonist anti-GITR monoclonal antibody and stereotactic radiation induce immune-mediated survival advantage in murine intracranial glioma. J Immunother Cancer. 2016;4:28. http://dx.doi.org/10.1186/s40425-016-0132-2.

Livros

Donald PJ, editor. Surgery of the skull base. Philadelphia: Lippincott-Raven; 1998.

Breedlove GK, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services; 2001.

Capítulos de livros

Meltzer PS, Kallioniemi A, Trent JM. Chromosome alterations in human solid tumors. In: Vogelstein B, Kinzler KW, editors. The genetic basis of human cancer. New York: McGraw-Hill; 2002. p. 93-113.

Dissertações e teses

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Trabalhos apresentados em congressos, simpósios, encontros, seminários e outros

Petersen R, Grundman M, Thomas R, Thal L. Use of titanium mesh for reconstruction of large anterior cranial base defects; 2004 July; United States, Philadelphia; 2004.

Artigos em periódicos eletrônicos

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

Textos em formato eletrônico

Instituto Brasileiro de Geografia e Estatística. Estatísticas da saúde: assistência médico-sanitária. Disponível em: http://www.ibge.gov.br. Acessado em: 5/2/2004.

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Review

Case Report


PDT
Responsável Técnico
Dr. André Giacomelli Leal
CRM-PR 21874
O Instituto de Neurologia de Curitiba foi pioneiro nas Américas ao utilizar a Terapia Fotodinâmica Intraoperatória (PDT) – LASER que destroi células tumorais cerebrais.
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Estimulação do Núcleo Anterior do Tálamo em Epilepsias Refratárias: metanálise

Stimulation of the Anterior Nucleus of the Thalamus in Refractory Epilepsies: meta-analysis

Gabriela de Paiva Ascani[1]
Gabriel Lima de Carvalho[2]
Marina Machado de Almeida[1]
Pedro Henrique Simm Pires de Aguiar[2]
Katie Senger[1]
Paulo Henrique Pires de Aguiar[3,4]

RESUMO

Introdução: *A epilepsia é um distúrbio neurológico crônico comum. Na maioria dos pacientes, as medicações antiepilépticas auxiliam no controle das convulsões, mas em aproximadamente 20 a 30% dos casos a doença é refratária ao uso de medicação. Nesses casos existem algumas modalidades terapêuticas, como o estímulo cerebral profundo, que tem como alvo o núcleo anterior do tálamo (NAT).* **Objetivos:** *Comparação de artigos sobre estimulação cerebral profunda em relação às complicações e resultados nas epilepsias refratárias a medicações.* **Métodos:** *Foram coletados 12 artigos publicados entre 2004 e 2019, nas bases de dados LILACS, PubMed e Scielo, sobre a estimulação cerebral profunda em epilepsia e comparados os seus resultados quanto ao sucesso e complicações da terapia utilizada.* **Resultados:** *A partir da metanálise dos dados analisados, foi observado que, em média, para um N=24,8, em um tempo de seguimento de 10,9 a 45,41 meses, com os parâmetros de estimulação de 122-145 Hz, 3,75-5.69 V, e 87,5-100 µs, houve uma redução da frequência mensal média de crises de 55,1%.* **Conclusão:** *Estimulação cerebral profunda do núcleo anterior do tálamo (ANT-DBS) para epilepsia refratária a medicamentos é uma terapia segura. Apesar disso, estudos clínicos em busca do alvo ideal, em populações bem definidas, ainda são importantes.*

Palavras-Chave: *Estimulação cerebral profunda; Núcleo anterior do tálamo; Cirurgia DBS; Epilepsia refratária*

ABSTRACT

Background: *Epilepsy is a common chronic neurological disorder. In most patients, antiepileptic medications help to control seizures, but in approximately 20% to 30% of cases, the disease is refractory to the use of medication. In these cases, there are some therapeutic modalities for refractory epilepsy, such as deep brain stimulation, which can target the anterior nucleus of the thalamus (ANT).* **Objectives:** *Comparison of articles on deep brain stimulation in relation to complications and outcomes in drug-resistant epilepsy.* **Methods:** *Twelve articles published between 2004 and 2019 in the LILACS, PubMed and Scielo databases were collected on deep brain stimulation in epilepsy and their results were compared regarding the success and complications of the therapy used.* **Results:** *From the meta-analysis of the data, it was observed that, on average, for an N = 24.8, in a follow-up time of 10.9 to 45.41 months, with the stimulation parameters of 122-145 Hz, 3.75-5.69 V and 87.5-100 µs, there was an average reduction of 55.1% in the monthly seizure frequency.* **Conclusions:** *Deep brain stimulation of the anterior thalamus nucleus (ANT-DBS) for drug-refractory epilepsy is a well-tolerated therapy. However, clinical studies in search of the ideal target, in well-defined populations, are still important.*

Keywords: *Deep brain stimulation; Anterior nucleus of thalamus; DBS surgery; Refractory epilepsy*

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INTRODUÇÃO

A epilepsia é um distúrbio neurológico crônico comum que afeta em torno de 70 milhões de pessoas em todo o mundo[1-3]. Na maioria dos pacientes, as medicações antiepilépticas auxiliam no controle das convulsões, mas em aproximadamente 20 a 30% dos casos a doença é refratária ao uso de medicação, o que é definido como sendo uma falha em alcançar um status sustentado de doença livre de convulsões, apesar do uso de dois medicamentos antiepilépticos escolhidos de forma apropriada[1,3-6]. A patogênese da epilepsia refratária ainda não consegue ser completamente explicada, mas sabe-se que pode estar associada tanto a mecanismos biológicos quanto a fatores ambientais[3]. As convulsões não controladas estão associadas a significativas taxas de morbidade e mortalidade, além de um impacto profundo na qualidade de vida de seus pacientes, uma vez que interfere diretamente em seu desempenho social e até financeiro[1].

Quando um foco de convulsão é identificado, a sua ressecção cirúrgica pode controlar as convulsões em aproximadamente dois terços dos pacientes, principalmente quando se identifica a patologia estrutural. Infelizmente, muitos pacientes não são candidatos à ressecção cirúrgica, devido à falta de um foco específico de convulsão, ou porque os focos de convulsão envolvem o córtex eloquente, ou devido à comorbidades que os tornam medicamente inaptos[2,7,8]. Para esses pacientes, algumas terapias alternativas como a dieta cetogênica, o estímulo do nervo vago, o estímulo cerebral profundo em circuito aberto e o estímulo cerebral profundo em circuito fechado têm sido realizadas em uma variedade de alvos cerebrais, incluindo os núcleos anterior e centro medial do tálamo, o núcleo subtalâmico, o hipocampo e o cerebelo[7,9].

O núcleo anterior do tálamo é o alvo mais estudado e validado do estímulo cerebral profundo em epilepsias não tratáveis, especialmente desde a publicação do estudo SANTE[1]. Como resultado desse estudo, em abril de 2018, o FDA pré-aprovou a realização da terapia de estímulo cerebral profundo como um tratamento adjuvante para a redução da frequência de crises epilépticas parciais, em indivíduos com 18 anos ou mais, que são refratários a três ou mais medicações antiepilépticas.

Apesar do sucesso dos múltiplos estudos da estimulação do núcleo anterior do tálamo, principalmente quanto ao estudo SANTE, o exato mecanismo pelo qual ocorre a redução da atividade convulsiva, relacionada à estimulação do ANT, continua não sendo completamente compreendido. Em 1985, Cooper e Upton levantaram a hipótese de que a estimulação do núcleo anterior do tálamo deveria produzir uma supressão da descarga neural anormal no sistema límbico[10]. Finalmente, baseado na observação de que alguns pacientes apresentavam melhora após a implantação, mas antes do início da estimulação propriamente dita, alguns autores sugeriram a possibilidade de um efeito microtalamotômico benéfico[5,8,9].

Assim, o objetivo do presente estudo foi de comparar os artigos sobre a estimulação cerebral profunda em relação a complicações e resultados nas epilepsias refratárias a medicação.

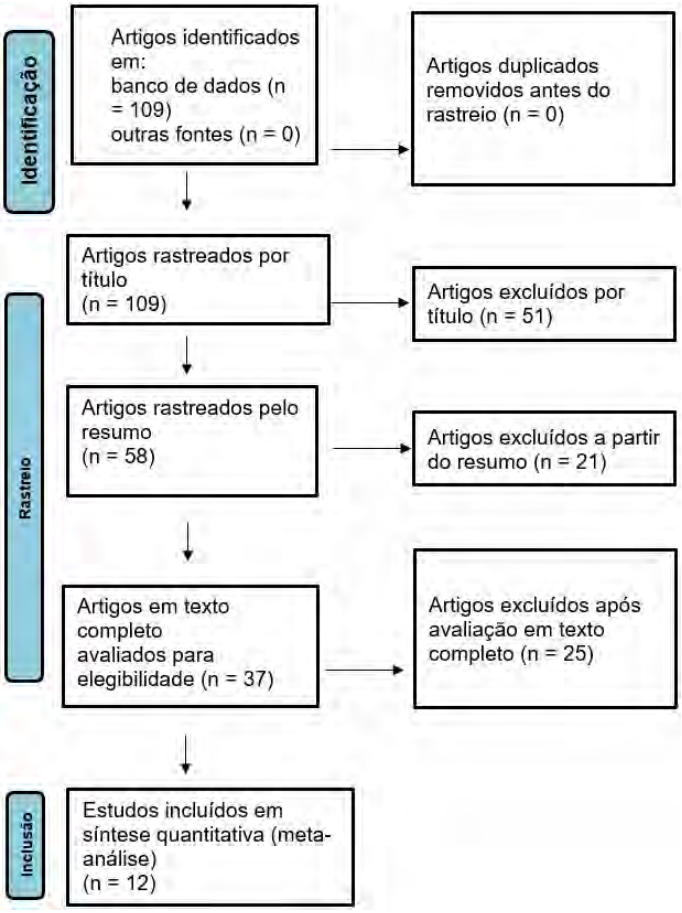
MÉTODOS

Foi feita uma revisão sistemática com meta-ánalise baseada na metodologia PRISMA (Preferred Reporting Project for Systematic Evaluation and Meta-Analysis) (Fluxograma 1). Foram coletados 12 artigos publicados entre 2004 e 2019 nas bases de dados LILACS, PubMed e Scielo, originalmente na língua inglesa, sobre a estimulação cerebral profunda em epilepsia e comparados os seus resultados quanto ao sucesso e complicações da terapia utilizada. Para isso foram utilizadas as seguintes palavras-chave individualmente ou combinadas: *deep brain stimulation, anterior nucleus of thalamus, DBS surgery, refractory epilepsy.*

Foram incluídos estudos prospectivos, retrospectivos e revisões de literatura realizados entre os anos de 2004 e 2019. Foram excluídos artigos de baixo impacto (Tabela 1).

RESULTADOS

Na Tabela 2 revisamos os principais artigos publicados na chamada "Era pré-SANTE" a partir do ano de 2004. Apesar das diferenças relativas aos parâmetros utilizados para a estimulação do NAT, assim como ao tempo de seguimento, todos os estudos



Fluxograma 1. PRISMA 2020 diagrama de fluxo para novas revisões sistemáticas que incluíram apenas buscas em bancos de dados e registros.

demonstraram melhora significativa da frequência mensal de crises epilépticas nos participantes analisados[5,9,11-13].

Já na Tabela 3, ao analisar o estudo SANTE, além dos artigos da era pós-SANTE, quanto ao número de pacientes, técnica de estimulação e tempo de seguimento, também foi observada, em todos os estudos, a redução média da frequência de de crises[1,2,4,6-8,14].

A partir da metanálise dos dados analisados, mostrada na Tabela 4, observou-se que em média, para um N = 24,8, em um tempo de seguimento de 10,9 a 45,41 meses, com os parâmetros de estimulação de 122-145 Hz, 3,75-5,69 V e 87,5-100 µs, houve uma redução de 55,1% da frequência média mensal de crises.

DISCUSSÃO

Apesar de os estudos abordados na Tabela 1 serem posteriores a 2004, devemos reforçar que já em 1985 os autores Cooper e Upton haviam criado a hipótese de que a estimulação do núcleo anterior do tálamo deveria produzir uma supressão da descarga neural anormal junto ao sistema límbico[10]. Em 2002, Hodaie et al. demonstraram que 5 participantes com epilepsia refratária, submetidos a implantes bilaterais de eletrodos de DBS

Tabela 1. Critérios de inclusão e exclusão, com base no método PICOS (PICOS: *population, intervention, comparison, outcome and study design*).

	Critérios de inclusão	**Critérios de exclusão**
Population (População)	Pacientes com epilepsia refratária, de qualquer sexo ou idade	Pacientes sem epilepsia refratária
Intervention (Intervenção)	Estimulação cerebral profunda no núcleo anterior do tálamo	Pacientes que não foram submetidos à DBS do núcleo anterior do tálamo
Comparison (Comparação)	Controle das crises epiléticas com e sem a estimulação efeitos adversos provenientes da terapia de estimulação	
Outcomes (Desfecho)	Frequência das crises epiléticas antes e após a terapia de estimular efeitos adversos provenientes da terapia de estimulaçãoção	
Study design (Desenho do estudo)	Estudos observacionais prospectivos e retrospectivos; revisões de literatura; revisões sistemáticas; série de casos; ensaios clínicos	Relato de caso e estudos transversais; estudos com animais; estudos não escritos na língua inglesa

Tabela 2. Artigos sobre estimulação do núcleo anterior do tálamo em epilepsias refratárias na era pré-SANTE.

Artigo	Autor, ano	N	Técnica de estimulação	Tempo de Seguimento (meses)	Redução média da frequência de crises (%)
Electrical stimulation of the anterior nucleus of the thalamus for the treatment of intractable epilepsy[11]	Kerrigan et al. (2004)	5	100 Hz 1 - 10 V 90 µs 1 min *on* / 10 min *off*	jun/36	48% (57-98%)
Chronic deep brain stimulation of subthalamic and anterior thalamic nuclei for controlling refractory partial epilepsy[12]	Lee et al. (2006)	3	130 Hz 1,5 - 7V 90 µs 1 min *on* / 5 min *off* alternando esq/dir	fev/30	75,4% (50-90,6%)
Long-term follow-up patients with thalamic deep brain stimulation for epilepsy[9]	Andrade et al. (2006)	6*	100 Hz 10 V 90 µs 1 min *on* - 5 min *off* alternando esq/dir	mar/60	63,7% (-2%-95,5%)**
High frequency thalamic stimulation for inoperable mesial temporal epilepsy[13]	Osorio et al. (2007)	4	175 Hz 4,1 V 90µs 1 min *on* - 5 min *off* (média)	jun/36	75,6% (53-92%)
Electrical stimulation of the anterior nucleus of the thalamus for intractable epilepsy: a long-term follow-up study[5]	Lim et al. (2007)	4	90 - 110 Hz 4 - 5 V 60 - 90µS contínuo	33 - 48	49% (35-76%)

*O número leva em conta apenas os pacientes cujos eletrodos elétricos de estimulação foram implantados no núcleo anterior do tálamo. ** Valores obtidos a partir do último ano de seguimento em relação a cada participante (4 anos para dois pacientes, 5 anos para 3 pacientes e 7 anos para um paciente).

no núcleo anterior do tálamo, tiveram diminuição estatisticamente significativa na frequência de crises (redução total média de 54% em um acompanhamento de 15 meses)[15].

Andrade et al. deram seguimento à análise de um ano feita por Hodaie et al. em cinco pacientes que tinham sido submetidos previamente à cirurgia de estimulação cerebral profunda, adicionando três novos participantes (um deles com implante de eletrodos do NAT, e os outros dois, com implantes do núcleo centro medial). No presente estudo, incluímos apenas os dados relativos aos participantes que receberam implantes no NAT. O único efeito adverso relatado foi o de letargia em um paciente, durante o período de quatro dias de estimulação contínua. Qualquer ganho adicional no controle das crises após o início do período de estimulação foi mínimo, levantando a possibilidade de que a resposta benéfica no controle das convulsões poderia estar primariamente relacionada à microtalamotomia causada pela inserção do eletrodo[9]. É possível, então, que a combinação entre a microtalamotomia e a estimulação crônica esteja implicada na resposta benéfica na frequência das crises.

Em 2007, Osório et al.[13] introduziram implantes no núcleo anterior do tálamo de quatro participantes voluntários, sendo que o estímulo elétrico teve início após 6 semanas do procedimento. Todos os

Tabela 3. Artigos sobre a estimulação do núcleo anterior do tálamo em epilepsias refratárias a medicação- estudo SANTE e era pós-SANTE

Artigo	Autores, Ano	N	Técnica de estimulação	Tempo de seguimento (meses)	Redução média da frequência de crises - último seguimento %
Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy[1]	Fisher et al., 2010	110 (54/55)	145 Hz; 5 V; 90 µs; 1 min *on* - 5 min *off* / sem estímulo	3-13	41%
Long-term outcome of anterior thalamic nucleus stimulation for intractable epilepsy[7]	Lee et al. (2012)	15	100-185 Hz; 1,5-3,1 V; 90-150 µs; contínuo	24-67	70,51% (0-100%)
Cognitive improvement after long-term electrical stimulation of bilateral anterior thalamic nucleus in refractory epilepsy patients[4]	Oh et al. (2012)	9	100-185 Hz; 1,5-3,1 V; 90-150 µs; contínuo	22-60	57,9% (35,6-90,4%)
Anterior thalamic nucleus deep brain stimulation (DBS) for drug-resistant complex partial seizures (CPS) with or without generalization: long-term evaluation and predictive outcome[2]	Piacentino et al. (2015)	6	140 Hz; 4 V; 90µs; contínuo	3 - 36	≥ 50%
Long-term efficacy and safety of thalamic stimulation for drug-resistant partial epilepsy[6]	Salanova et al. (2015)	105*	145 Hz; 5 V; 90 µs; 1 min *on* - 5 min *off* / sem estímulo	13 - 48	69%
Anterior nucleus deep brain stimulation for refractory epilepsy: insights into patterns of seizure control and efficacious target[8]	Krishna et al. (2015)	16	100 - 185Hz; 2,4 - 7 V; 90 µs; 1 min *on* - 5 min *off*	13 - 48	11,5% (-400-99%) **
Outcome based definition of the anterior thalamic deep brain stimulation target in refractory epilepsy[14]	Lehtimäki et al. (2016)	15	140 Hz; 5 V; 90 µs; 1 min *on* - 5 min *off*	3 - 60	50% (para 60% dos participantes)

*Durante o seguimento, 30 dos 105 participantes deixaram de ser acompanhados (incluindo 5 mortes, não relacionadas à implantação dos eletrodos e ou à estimulação elétrica). **Redução média na frequência de crises para todo o coorte (n=16).

Tabela 4. Metanálise de dados coletados (Média aritmética dos valores coletados nos 12 artigos)

N	Parâmetros	Tempo de seguimento (meses)	Redução média da frequência de crises
24,8	122 - 145 Hz 3,75 - 5,69 V 87,5 - 100 µs	10,9 - 45,41	55,1%

indivíduos completaram os estudo e não tiveram efeitos adversos graves, sendo que a redução média na frequência das crises foi de 75,6%, mostrando uma melhora importante da qualidade de vida.

Também em 2007, Lim et al.[5] propuseram um estudo a partir da implantação de um eletrodo estimulatório quadripolar bilateralmente no NAT de quatro pacientes. A localização do eletrodo foi confirmada, em todos os casos, por meio de exame

de RM pós-operatória e o estímulo elétrico foi ativado em 2 a 4 semanas após o procedimento de implantação, seguindo os parâmetros listados na Tabela 1. Os quatro pacientes (um homem com convulsões generalizadas, e três mulheres com convulsões parciais e generalização secundária) foram acompanhados por um período médio de seguimento de 43,8 meses e apresentaram 49% de redução na frequência mensal média de crises convulsivas. A simples inserção dos eletrodos de DBS produziu uma redução média mensal de 67% na frequência das crises. Um paciente permaneceu livre de convulsões por 15 meses, em uso de medicações anticonvulsivantes. Um paciente teve uma pequena hemorragia frontal e, um segundo paciente apresentou erosão expansiva ao longo do couro cabeludo.

Os vários resultados favoráveis publicados nos artigos da Tabela 1 encorajaram o planejamento do SANTE, um estudo controlado, duplo-cego randomizado, envolvendo 110 participantes com epilepsia refratária que se submeteram a implantes cerebrais profundos para a estimulação elétrica do NAT[1].

Um mês após o implante bilateral no NAT os pacientes foram randomizados para receber um regime de estimulação (n=54) ou de não estimulação (n=55). Os parâmetros utilizados para o grupo sob estimulação elétrica estão descritos na Tabela 2. Depois de um período de 3 meses de fase cega, todos os participantes passaram a receber estimulação (todos sob os mesmos parâmetros). A partir do 13º mês todos os participantes entraram na fase de seguimento, na qual os medicamentos antiepilépticos poderiam variar livremente, assim como os parâmetros de estimulação. No último mês da fase cega o grupo estimulado teve uma redução de 29% maior na frequência de crises, quando comparado com o grupo controle. Crises complexas parciais e convulsões "mais severas" foram significativamente reduzidas pela estimulação. Em 2 anos, houve redução percentual média de 56% na frequência de crises; 54% dos pacientes tiveram redução de convulsões de, pelo menos 50%, e 14 pacientes permaneceram livres de crises por pelo menos, 6 meses. Ocorreram 5 mortes, mas nenhuma devido à implantação ou estimulação. Nenhum participante apresentou hemorragia sintomática ou infecção cerebral. Dois participantes apresentaram crises convulsivas agudas e transientes associadas à estimulação. Não foram observadas diferenças de humor ou de cognição entre os dois grupos, mas os pacientes do grupo estimulado estavam mais susceptíveis a reportarem depressão ou problemas de memória como efeitos adversos[1].

A Tabela 2 mostra também um estudo relativo ao seguimento de longo prazo (5 anos) de alguns participantes (n=105 no início, sendo que 30 tiveram o acompanhamento descontinuado) do estudo SANTE. Nesse seguimento posterior, de Salanova et al., foi observado que a redução média na frequência mensal de crises epilépticas após 5 anos, quando comparada à frequência de base (pré-implantação) foi de 69%. A taxa de "respondedores" (pacientes que tiveram 50% ou mais de redução na frequência das crises) foi de 68% e 16% dos participantes tiveram um período livre de crises por, pelo menos 6 meses durante os 5 anos de seguimento. Não houve relatos de efeitos adversos relacionados ao implante do eletrodo ou hemorragias intracranianas[6].

Em 2012, Lee et al.[7] demonstraram que a frequência mensal de crises após 3 meses da cirurgia de DBS, assim como no período de seguimento final reduziu significativamente (p= 0,002 e p= 0,001, respectivamente). Não houve grandes complicações, como hemorragias intracranianas associadas ao procedimento.

Krishna et al.[8] descreveram três padrões de controle das crises, em relação aos pacientes que apresentaram resposta ao tratamento: o primeiro foi o de redução sustentada (> 50%) da frequência das crises sem que houvesse o início da estimulação (efeito de inserção prolongado); o segundo foi em relação ao efeito da estimulação imediata: um aumento na redução da frequência das crises imediatamente associado ao início da estimulação e, por fim, a estimulação de efeito retardado: uma diminuição na frequência média de crises com estimulação contínua, após falha inicial na redução das crises. Pode-se observar um efeito de inserção em 56% dos pacientes. Curiosamente, em uma série de casos relatando o resultado das crises após o fim da bateria, um paciente com ANT-DBS e 3 anos de estimulação contínua não demonstrou uma alteração na frequência das crises mesmo após 6 meses do ocorrido, o que denota um efeito de inserção prolongado, modulação definitiva da rede epiléptica ou ainda, o reflexo do curso natural da epilepsia. Lee et al.[7] observaram apenas um efeito de estimulação prolongado, pois o desenho do estudo exclui a possibilidade de um efeito de inserção prolongado, no qual os resultados a curto prazo estão notavelmente associados ao controle das crises a longo prazo. Em relação ao funcionamento cognitivo a longo prazo, Oh et al. relataram leve melhora nas tarefas de fluência e atraso na memória verbal[4].

A revisão da literatura de Li e Cook traz alguns pontos chave sobre o ANT-DBS como, por exemplo, que esse processo, assim como a estimulação do hipocampo, reduziu de 46% a 90% a taxa

de convulsões e de 48 a 95% entre metade de todos os pacientes estudados, sendo que a eficácia da estimulação profunda de outros sítios ainda permanece inconclusiva. Foi observado também que, em mais de 70% dos pacientes que receberam o ANT-DBS ou a estimulação do hipocampo, entre os estudos existentes, são respondedores. Por fim, notou-se que os efeitos colaterais e complicações do DBS para epilepsia resistente à medicação são similares aos observados na terapia com DBS para outras indicações.

CONCLUSÃO

A estimulação cerebral profunda do núcleo anterior do tálamo (ANT-DBS) para epilepsia refratária a medicamentos é uma terapia segura e bem tolerada, em que deve-se enfatizar o monitoramento da depressão e da função de memória. Além disso, o ANT-DBS é uma modalidade de tratamento eficaz, mesmo quando os procedimentos curativos ou técnicas neuromodulativas menos invasivas falham. Quando comparado a outras terapias como a estimulação do nervo vago (VNS), o ANT-DBS mostra uma resposta ao tratamento ligeiramente superior, o que exige testes comparativos diretos. Com base nas evidências disponíveis, as terapias com ANT-DBS e VNS são atualmente superiores em comparação às técnicas de neuromodulação não invasiva, como estimulação do nervo vago transcutânea (t-VNS) e estimulação magnética transcraniana repetitiva (rTMS).

Apesar de sua eficácia clínica, o ANT-DBS para epilepsia resistente a medicamentos ainda enfrenta grandes desafios. A otimização do protocolo DBS procedural, incluindo técnicas de imagem, procedimento cirúrgico e algoritmos para adaptação dos parâmetros de estimulação, poderia ajudar a reduzir a variabilidade da resposta ao tratamento. Pesquisas adicionais deverão fornecer uma melhor compreensão das redes neuronais fisiológicas normais em comparação com as redes epileptogênicas, a fim de obter mais informações sobre o mecanismo de ação ANT-DBS na epilepsia relacionada à localização. Idealmente, um conhecimento mais aprofundado das redes epileptogênicas pode explicar a resposta diferencial de DBS de diferentes alvos anatômicos em diferentes tipos de crises. Estudos clínicos randomizados em busca do alvo ideal em populações bem definidas de pacientes com epilepsia, possivelmente poderão permitir a estratificação ideal ao aplicar a terapia de neuromodulação intracraniana naqueles em que existe resistência à terapia medicamentosa.

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Early Deep Brain Stimulation of Globus Pallidus Internus in Primary Meige's Syndrome: a successful case report and literature review

Estimulação Cerebral Profunda Precoce do Globo Pálido Interno na Síndrome de Meige Primária: relato de caso bem sucedido e revisão da literatura

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ABSTRACT

Background*: Meige's Syndrome is cranial dystonia in adults that associates orofacial dystonia with blepharospasm. The whole pathophysiology has not been fully elucidated yet but it is already known that it courses with abnormal excitability of the sensorimotor cortex and brainstem interneuronal pathways associated with environmental factors and genetic predisposition. There are different types of possible therapies that include both pharmacological and invasive procedures as therapeutic proposals. The Deep Brain Stimulation of Globus Pallidus Internus (GPi-DBS) emerged as an established form of invasive neuromodulation for Meige's Syndrome which has been demonstrated to have a remarkable effect on symptoms improvement.* **Case presentation***: a case of Meige's Syndrome previously treated with conventional procedures for the condition, such as pharmacological treatment, blepharopexy, botulinum toxin, all without success, was reported. After multiple failures, the patient was submitted to a GPi-DBS, which evolved with an improvement of 80% of the symptoms, improving also the patient's quality of life. Also, a literature review of other cases of GPi-DBS, which almost 100% demonstrated a significant improvement of the condition was performed.* **Conclusion***: GPi-DBS has been used as an important tool to treat Meige's Syndrome, showing high efficacy in the symptoms improvement and quality of the patients' life.*

Keywords: *Deep Brain Stimulation; Meige's Syndrome; Globus pallidus internus; Blepharospasm; Dystonia*

RESUMO

Introdução: *A Síndrome de Meige é uma distonia craniana que acomete adultos e associa distonia orofacial com blefaroespasmo. Toda a fisiopatologia ainda não foi totalmente elucidada, mas já se sabe que cursa com excitabilidade anormal do córtex sensório-motor e vias interneuronais do tronco encefálico associadas a fatores ambientais e predisposição genética. Existem diferentes tipos de tratamentos possíveis que incluem tanto vias farmacológicas quanto invasivas como propostas terapêuticas. A Estimulação Cerebral Profunda do Globus Pallidus Internus (GPi-DBS) surgiu como uma forma estabelecida de neuromodulação invasiva para a Síndrome de Meige, demonstrando ter um efeito significativo na melhora dos sintomas.* **Relato de Caso***: um caso de Síndrome de Meige previamente tratado com procedimentos convencionais para a condição, como tratamento farmacológico, blefaropexia, toxina botulínica, todos sem sucesso. Após múltiplas falhas, o paciente foi submetido a um GPi-DBS, que evoluiu com melhora de 80% dos sintomas, melhorando também sua qualidade de vida. Além disso, também foi realizada uma revisão da literatura de outros casos de GPi-DBS, que, em quase 100% dos casos, foi demonstrada uma melhora significativa do quadro.* **Conclusão***: o GPi-DBS tem sido utilizado como uma importante ferramenta no tratamento da Síndrome de Meige, apresentando alta eficácia na melhora dos sintomas e na qualidade de vida dos pacientes.*

Palavras-Chave: *Estimulação cerebral profunda; Síndrome de Meige; Globo Pálido Interno; Blefarospasmo; Distonia*

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INTRODUCTION

Meige's syndrome is one of the segmental forms of cranial dystonia in adults that associates orofacial dystonia with involuntary eye closure. A complete understanding of the pathophysiology and underlying causes have not yet been fully elucidated in the literature. Abnormal excitability of the sensorimotor cortex and brainstem inter-neuronal pathways associated with environmental factors/triggers and genetic predisposition of unknown genes could be related to this condition according to several studies[1]. This proposed mechanism would, therefore, cause plastic changes and reduction of cortical inhibition[2]. Dystonias are also associated with an asymmetry of function within the basal ganglia, especially within the Globus Pallidus Internus (GPi).

There are two types for this condition: 1) primary or idiopathic, which has dystonia as the unique clinical sign associated with a genetic component[1], and 2) secondary, which is usually a late manifestation described as Tardive Dystonia (TD), in some cases associated with other neurological disorders or related to neuroleptic drugs causing a blockage of the dopamine receptors, altering its function causing denervation supersensitivity[2].

Treatment includes both pharmacological therapy and invasive procedures. Pharmacological therapy includes anticholinergic medications. The clinical effect varies for this type of dystonia, but it is widely accepted its low efficacy for most of the patients[3,4]. Another established and efficacious treatment for this condition is botulinum toxin[1,2,5,6]. When patients develop resistance, side effects to botulinum toxin or when this treatment losses efficiency over time, an adjunct or associated treatment is the Deep Brain Stimulation[2]. GPi Deep Brain Stimulation (DBS) of Globus Pallidus Internus (GPi) is an established form of invasive neuromodulation for Meige's Syndrome with a variable range of improvement reported in the literature[4,7,8].

In this study we will report a case of a patient diagnosed with Meige's Syndrome successfully treated with GPi-DBS, in addition to conducting a literature review about this alternative therapy, demonstrating its proven high efficacy in these conditions.

CASE PRESENTATION

White male patient, 66 years old. More than 3 years ago he started involuntary orofacial muscle contractions and constant blepharospasm which usually worsened with emotional distress (Figure 1). Past medical history of hypertension, dyslipidemia, benign hepatic nodule, hepatitis C and polycythemia vera.

After 1 year of the initial symptoms, he was given a formal diagnosis of Meige's Syndrome by a neurologist specialist in movement disorders. He failed medical treatment with Levodopa for 1 month, Trazodone (2 months of use) and Lorazepam. His neurological symptoms negatively impacted his quality of life and activities of daily living, leading him to seek a psychiatrist. Approximately 1.5 years after the initial symptoms he underwent a blepharopexy which resulted in no benefit. Among the conventional procedures for this condition, he was also treated with botulinum toxin injections (total 6 different and separate attempts every 2-3 months) which he was also refractory. Subsequently, he was referred to our Functional Neurosurgery DBS service and Multidisciplinary Meeting (MDT). The recommendation was to proceed with DBS procedure since he failed previous treatments. We underwent then a bilateral asleep posteroventral GPi DBS

Figure 1. Blepharospasm and orofacial dystonia before surgery.

implantation with microelectrode recordings (MER) on February 2021. In our department, we routinely use a 3 Teslas Magnetic Resonance Image of the brain with specific DBS sequences (Volumetric T1-, T2-weighted sequences, Susceptibility Weighted Image (SWI) and a Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) sequences to better visualize the target of choice (MRI is performed routinely in the same week the patient is operated on).

DBS planning is performed on the day before using direct target on the MRI confronted with the indirect target parameters of the atlas. For dystonia patients are anesthetized before the implantation of the stereotactic frame (in our unit Leksell Frame). Subsequently, a volumetric CT scan is taken and imaging fusion with the MRI is performed. In this case the implantation of the leads (Medtronic lead type 3387) was performed after a bilateral single MER needle passage followed by an intraoperative image intensifier. MERs, in this case, were consistent with the anatomical target. Internalization of the system with the extensions and Internal Pulse Generator (IPG) is routinely performed the same day after placing the leads. Subsequently, after the procedure, a volumetric CT scan without the frame is performed to fuse with the previous MRI scans and measure target precision and also to rule out complications (bleeding and pneumocephalus). We routinely use pre-operative antibiotics until day 5 of the procedure to minimize the risk of infection. In dystonia, we use rechargeable IPG which, in this case, was an Activa RC implanted in the left infraclavicular region. Skin non absorbable surgical sutures are removed in 2 weeks. This patient experienced a mild improvement of the symptoms following 2 weeks from his procedure due to micro lesioning effect from lead placement. (Figures 2 to 4). Initial programming 2 to 3 days after removal of the sutures as outpatient with the Neuromodulation team was performed and during this appointment lead contact test and mapping were completed. Phosphenes were observed for contact 0 bilateral and no side effects were recorded for the remaining contacts. The best contact was number 1 bilateral which was initially programmed with 80 microseconds (μs) of pulse width (PW), 1.5 milliamps (mA) and 130 Hz of frequency. In our center, we routinely use constant current as opposed to voltage-dependent.

The subsequent follow-up (FU) appointments occurred every 2-3 weeks in which adjustments of the parameters were carried out. On his last FU appointment an adjustment of the parameters was made keeping the same contacts bilaterally, 130 Hz, increased intensity to 2.4 mA and also PW to 140 μs since GPi is a large target and usually requires a large PW to stimulate more fibers. On every FU adjustment, he reported improvements in his symptoms. After more than four weeks, electrodes were set at

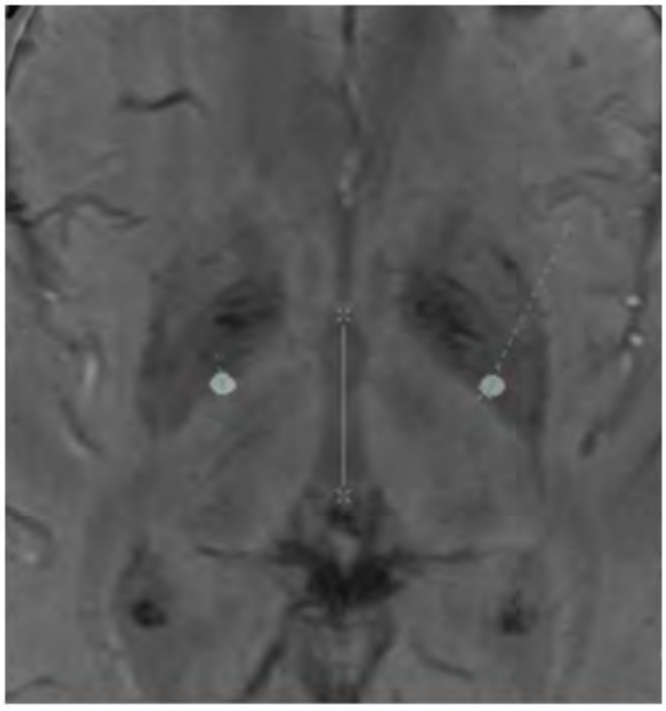

Figure 2. Post-operative fusion of the MRI and CT scans showing adequate placement of the DBS electrodes within the GPi on axial imaging sequences.

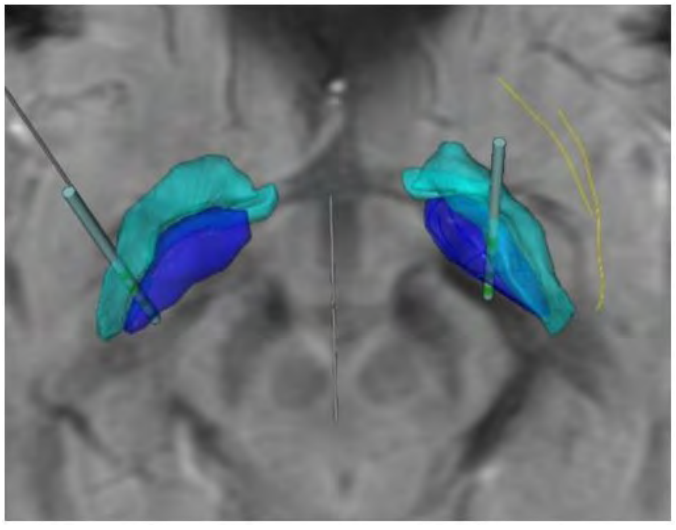

Figure 3. Post-operative fusion of the MRI and CT scans showing adequate placement of the DBS electrodes within the Gpi.

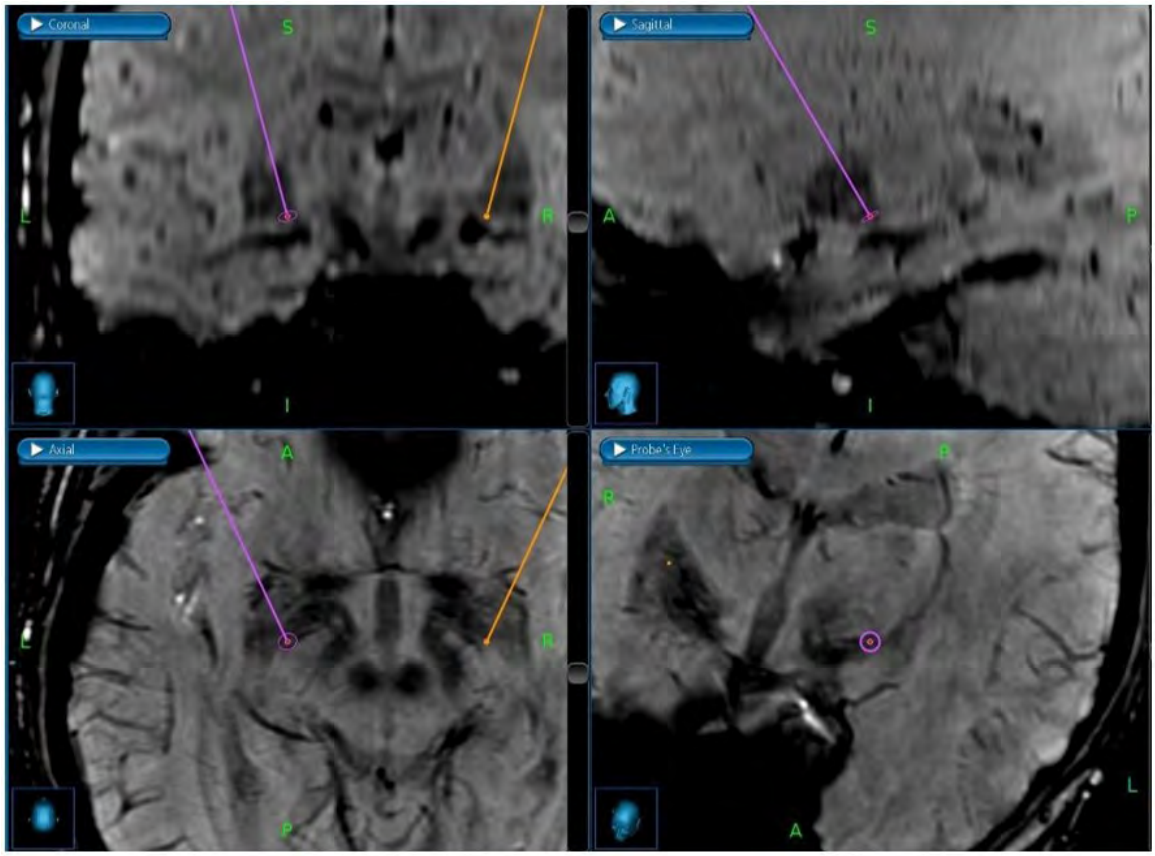

Figure 4. Preoperative planning on Stealth Station showing 3 Teslas MRI SWI sequences and direct visualization of the right and left GPi. In this case, indirect parameters based on the atlas were consistent with the GPi location. The right GPi parameters based on anterior commissure-posterior commissure line (ACPC line) were X: 21 mm, Y: 2 mm and Z: -4 mm. For the left GPi parameters were: X: -21 mm, Y: 2 mm and Z: -4 mm. The entry point (burr holes) for both sides was 3 cm lateral to the midline and 1 cm anterior to the coronal suture.

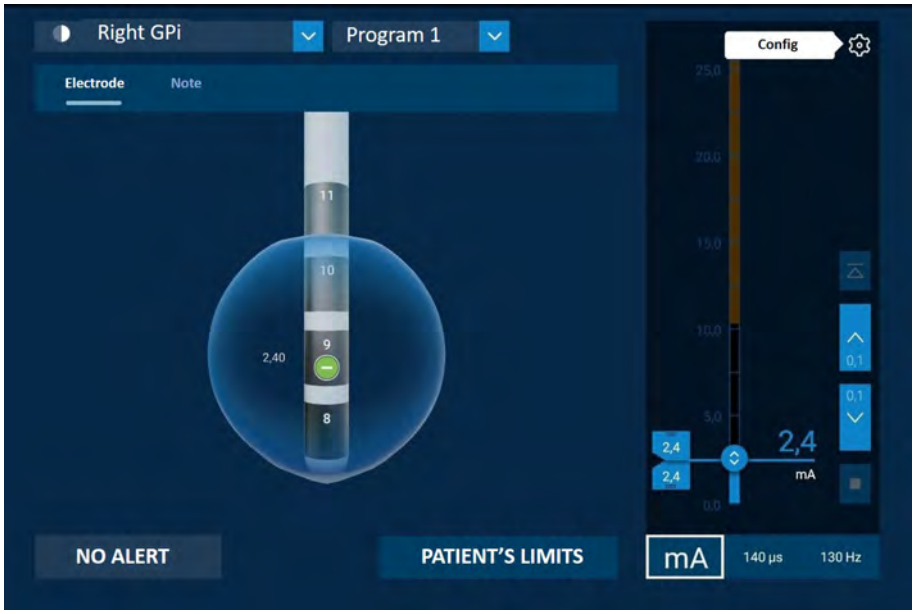

Figure 5. Right GPi-DBS programming settings.

Figure 6. Left GPi-DBS programming settings.

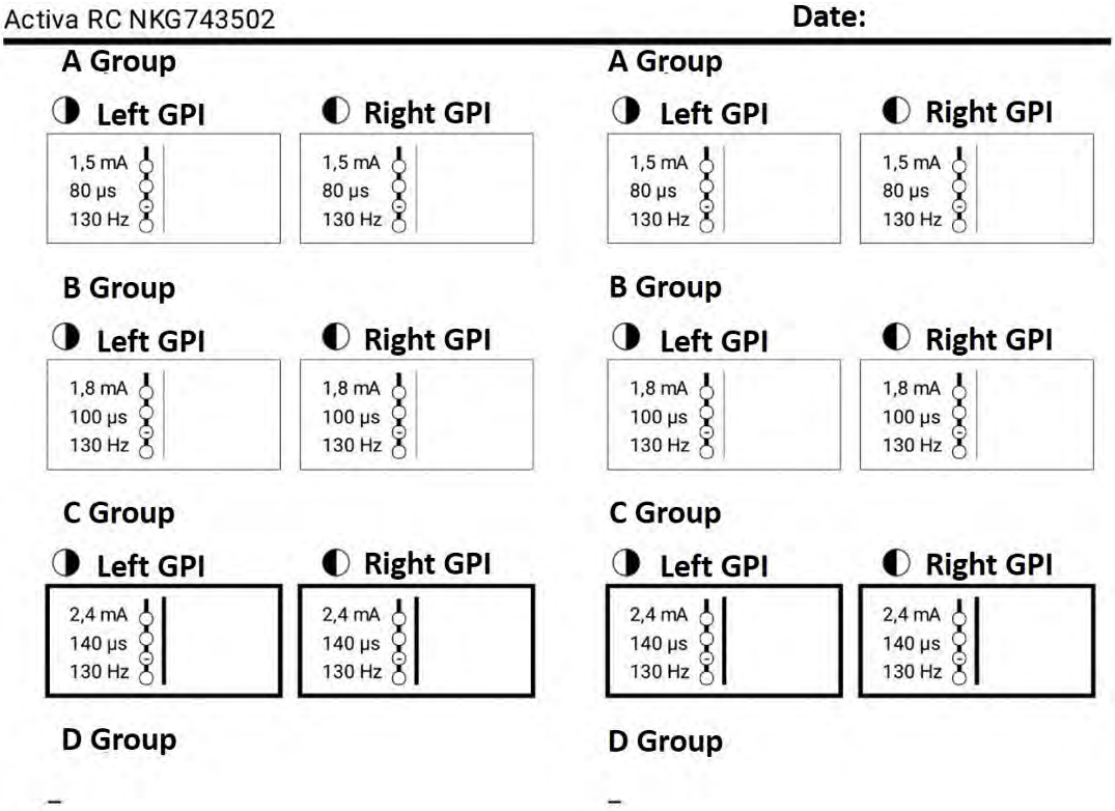

Figure 7. Active group C showing left and right DBS GPi programming and previous groups tested during FU.

Figure 8. Patient after surgery at his last follow-up with 80% improvement of his symptoms.

130 Hz, 140 μs and 2,4 mA bilaterally (Figures 5 to 7). At this moment, in time with this program, the patient subjectively reported an improvement of 80% of the symptoms (Figure 8), presenting only blepharospasm in situations of emotional distress, physical fatigue and during exposure to flashing lights.

BACKGROUND

Meige's syndrome was first described by Dr. Henri Meige in 1910, who initially observed and detailed the characteristic involuntary muscle movements of the face in patients with this condition[2]. This type of clinical presentation with blepharospasm and oromandibular dystonia combined, received the name of Meige's Syndrome[1]. Blepharospasm occurs, in most of the cases, bilaterally and synchronously, from excessive contraction of the orbicularis oculi and adjacent muscles, including conjugator supercilii and procerus[3,5]. Blepharospasm is the most common and incapacitating characteristic of this type of dystonia[2]. The oromandibular component involves the lower facial and masticatory muscles, generating characteristic tonic-clonic movements[1]. There are no diagnostic tests for Meige's Syndrome and neuroradiologic assessment or blood tests are unrevealing. Thus, making the diagnosis based on clinical and neurologic evaluation by the movement disorders specialist[3].

Patients with blepharospasm complain of eye irritation / dryness, burning sensation, and photophobia that increases during blinking or intermittent spasms[3,9,10]. Patients also report that blepharospasms become more intense with bright or flickering lights and they usually disappear during sleep[3,11]. Symptoms begin usually unilaterally and become bilateral in about 25% of the patients[2]. Blepharospasms normally have a tonic and/or clonic spasms. During tonic spasms, the eye stays closed for a prolonged time and for clonic spasms, the orbicularis oculi muscle contracts preventing full eye opening[2,6]. Patients normally develop sensory tricks to alleviate spasms such as singing, talking, touching eyelids or humming[2,9]. Spasms can progressively become worse and also involve cervical, limbs and oromandibular muscles or segments[2]. Over time, actions like lip pursing, chewing, jaw thrusting, grimacing, jaw opening, and jaw-closing/clenching become more difficult with involvement of lower facial muscles, and consequently affecting negatively the patient's quality of life and activities of daily living, for example, safe driving becomes a difficult activity[1,3]. In rare and more advanced or complex cases, spasms and progressively more severe symptoms can lead to the involvement of respiratory muscles[2].

Some studies suggested that patients with Meige's Syndrome are more likely to develop other movement disorders, like essential tremor, chorea, akathisia, palatal myoclonus or even Parkinson's Disease, since basal ganglia are affected in both situations[2]. These patients are also more likely to develop psychiatric conditions arising from poor health-related quality of life, for instance, depression, anxiety or social distance[6]. However, very few studies have reported changes in quality of life or mental status[6]. Alternatively, other studies suggest a connection between depression and Meige's Syndrome, possibly related to a genetically inherited abnormality of the monoamine metabolism[11,12].

CLASSIFICATION

The most recent classification of dystonia distinguishes primary and secondary forms. Primary dystonia usually appears without an

underlying identifiable cause[3], being idiopathic or caused by a genetic disorder[1]. Secondary dystonia is usually a tardive manifestation[2], related to stroke, trauma, neurodegenerative conditions or medications[3], like neuroleptics, antiemetics, dopamine agonists and antipsychotics, that cause a blockage of dopamine receptor altering its function causing denervation supersensitivity[2]. In the primary one, it is believed that there is no neuronal loss, unlike the acquired or secondary dystonia, in which neurological manifestation can result from brain lesions from multiple possible causes[13,14]. Some factors can be associated as predictors of the development of Meige's Syndrome, such as cranioencephalic trauma, age at onset (usually fifth to sixth decade), women[1], sunlight exposure or ophthalmology diseases[9]. In the most recent classification of dystonia from Albanese et al., age at onset, body distribution symptoms, temporal pattern, the presence or not of movement disturbances and other neurologic manifestations are important to correctly study and classify the movement disorder[1,14].

PHYSIOPATHOLOGY

Meige's Syndrome's physiopathology has not been completely elucidated yet, but many studies describe the hypothesis of an association between environmental triggers and genetic predisposition causing plastic changes, impairment of central sensorimotor integration[3,15] and reduction of cortical inhibition[2]. Thus, dystonia is associated with a lesion of a complex neural network involving basal ganglia, cerebellum, thalamus, globus pallidus and sensorimotor cortex, more specifically, the primary motor and ventral premotor cortex[1,2,8,13]. In this proposed mechanism, cerebral lesions cause hyperactivity in the striatum and hypothalamus and affect the sensitivity of the dopamine receptor, culminating in dopaminergic and cholinergic abnormalities, resulting in imbalances of excitatory and inhibitory pathways. The reduced inhibition causes uncontrolled muscle activity, which leads to symptoms and clinical presentation[1,16].

Dystonia is, therefore, a network disorder involving the basal ganglia, cerebellum and thalamo-cortical circuits[8,13], which is composed of a direct, indirect and a hyper direct pathway where both GPi and STN are situated. The unbalanced neurotransmitters in the basal ganglia and thalamus and the voluntary motor controlling dysfunction are involved in Meige's Syndrome, resulting in the imbalances of the inhibitory and excitatory pathways[6].

OUTCOME MEASURES

The most important clinical scales to study and graduate dystonias are the Burke-Marsden Dystonia Rating Scale (BFMDRS), Jankovic Rating Scale (JRS) and Global Dystonia Severity Rating Scale (GSDRS). BFMDRS is a universal tool commonly used in these cases that evaluate both movement and disability factors. The movement component of this scale divides the body into nine parts in which scores vary from 0 to 120 according to the degree of dystonia. The disability part includes assessment of daily activities, such as eating, hygiene, dressing, walking, speech, handwriting, swallowing and feeding; scores vary from 0 (complete independence) to 30 (complete dependence)[17]. JRS assesses blepharospasm, graduating severity and frequency of symptoms, rating both factors from 0 (no severity and no frequency) to 4 (severe, incapacitating spasms of eyelids and possibly other facial muscles / patients are functionally "blind" due to persistent eye closure more than 50% of the waking time)[18]. Finally, the GDSRS divides the body into 10 areas and rates each one from 0 (no dystonia) to 10 (severe symptoms). The body parts involved are eyes and upper and lower face, jaw, tongue, larynx, neck, shoulder and proximal arm, distal arm and hand, pelvis, upper leg, distal leg, foot and trunk[19].

DISCUSSION

In our literature review, we found 64 cases published since 2004. From the patients with Meige's Syndrome who underwent bilateral GPi-DBS, 52% were women[10,15,20-33]. And 60% of these patients were between 50 and 69 years old[6,20,21,23-25,27,29,31,32,34-37]. (Table 1). Almost 100% of the patients in our review, that had significantly improved clinically after DBS implantation, with only one case reported having a worsening of symptoms[24].

Treatment for dystonias includes pharmacological therapy and invasive procedures. Anticholinergic or dopaminergic drugs, as well as benzodiazepines, neuroleptic, Baclofen and atypical antipsychotic medications, can be partially effective for some patients[1-3]. Orofacial/Oromandibular dystonia typically responds poorly to oral medications, although Zolpidem may be helpful in some cases[3].

Table 1. Studies published reporting Deep Brain Stimulation in Meige's Syndrome patients.

Author	Diagnosis	Target	Gender	Age at first surgery	Duration of symptoms	Medications	BFMDRS	BFMDRS Improvement (%)
Aires et al.[20]	Meige's syndrome	Bilateral GPi- DBS	Female	76y-o	8y	Tetrabenazine and Botulinum toxin injections unsuccessfully for 5 years	After 24 months post operactive the BFMRDS-D score was 1/30, the BDS was 2/8 and JRS was 1/30	*
	Oromandibular dystonia	Bilateral GPi- DBS	Female	68y-o	18y	Clobazam, Trihexyphenidyl hydrochloride, Amantadine hydrochloride unsuccessfully for 4 years	After 24 months post- operactive BFMRDS-M was scoring 2 and BFMRDS-D was 3	*
Bain et al.[38]	Generalised dystonia and blepharospasm	GPi- DBS **	Male	48y-o	Began at 15y and at 40y was generalized	Levodopa, Trihexyphenidyl, Baclofen, Olanzepine, and Alcohol were unhelpful. Botulinum toxin improved cervical dystonia	BFMRDS decreasing from 72 pre-operatively to 16	77.77
Bereznai et al.[21]	Segmental dystonia	Bilateral GPi- DBS	Male	62y-o	4y	Botulinum toxin A, Diazepam, Clonazepam, Tetrabenazine, Tiapridex, Trihexyphenidyl, Baclofen, Levodopa, Apomorphine, Amantadine, Clozapine, and Pimozide were helpful for only a short period and were not continued	Dystonic arm and shoulder movements disappeared almost completely, Torticollis was significantly improved. When the patient sat or walked, there was still a slight bending of the trunk backwards	*
	DYT 1 generalized dystonia	Bilateral GPi- DBS	Female	22y-o	14y	Trihexyphenidyl, Tetrabenazine, Baclofen, and Levodopa caused no meaningful improvement	Significant decrease in muscular tension of the lower extremities but also of the upper limbs. Severe in-turning of the foot completely disappeared on the right side and markedly improved on the left side. The patient could stand and walk without canes, and could run for longer distances	*
	Segmental dystonia	Bilateral GPi- DBS	Female	78y-o	18y	Tetrabenazine, Trihexyphenidyl, and Tiapridex had no benefit; Tizanidine was not tolerated	Stimulation had no immediate effect on the patient's symptoms during the first 6 months, but a clear decrease of Meige's syndrome and cervical dystonia was seen thereafter, when stimulation amplitude was increased	*
	Segmental dystonia	Bilateral GPi- DBS	Male	50y-o	6y	Therapy with botulinum toxin A injections had no effect	After 24 hours of chronic stimulation, segmental dystonia disappeared almost completely. Over a period of 3 months some of the symptoms (laterocollis, blepharospasm, and upper limb dystonia) reemerged, but to a lesser extent	*
	Cervical dystonia	Bilateral GPi- DBS	Male	44y-o	6y	Numerous pharmacological and Botulinum toxin A treatments provided only modest improvement	Clonic movements were almost absent, whereas slight laterocollis was still present. Lorazepam was reduced to 1 mg daily	*
	Cervical dystonia	Bilateral GPi- DBS	Female	58y-o	15y	Trihexyphenidyl, Baclofen, Levodopa, and Clonazepam were not beneficial and therapy with Botulinum toxin A injections was helpful only for a short period	The patient's severe retrocollis disappeared completely after surgery. On examination 3 months after surgery there was only a slight horizontal tremor of the head, which had no clinical significance.	*
Bhoyar et al.[34]	Meige's syndrome	GP- DBS **	Male	60y-o	3y	Tetrabenazine and Clonazepine had no benefit	The patient showed dramatic improvement in his symptoms	*

y-o = years-old; y = year; mo = month; *Not cited by the article;** Not specified by the author.

Table 1. Continued...

Author	Diagnosis	Target	Gender	Age at first surgery	Duration of symptoms	Medications	BFMDRS	BFMDRS Improvement (%)
Blomstedt et al.[22]	Meige's syndrome	Bilateral GPi- DBS	Female	*	22y	Clonazepan, Baclofen, Botulinum toxin had no benefit.	BFMDRS improved from 34 to 6 in the post- operactive.	82.35
			Female	*	12y	Trihexyphenidyl, Clonazepan, Botulinum toxin had no benefit	BFMDRS improved from 28 to 6 in the post- operactive.	78.57
			Male	*	10y	Baclofen, Clonazepan, Botulinum toxin had no benefit	BFMDRS improved from 15 to 4 in the post- operactive.	73.33
Chung et al.[23]	Tongue dystonia	Bilateral GPi- DBS	Female	58y-o	7y	Trihexyphenidyl and Clonazepam had no benefit. Botulinum toxin injections on genioglossus muscle, it did not showed good response.	BFMDRS improved from 12.5 to 1 in the post- operactive. The patient improved 92% compared with its baseline.	92
	*dysarthia and mumbled when read and spoke	Bilateral GPi- DBS	Female	54y-o	9y	Medications (**) and Botulinum toxin injections had no benefit.	BFMDRS improved from 13 to 1 in the post- operactive. The patient improved 92.3% and become free from symptoms.	92.3
Evidente et al.[5]	Tardive blepharospasm	Bilateral GPi- DBS	Male	35y-o	2y (starts at 6y-o, stopped at 15y-o and returned at 33y-o)	Risperidone, Olanzapine, Quetiapine, Lurasidone and Clonazepam had no benefit. Also botulinum toxin A and B	BFM improved from 4 to 0 and JRS from 6 to 0 in the post- operactive	100
Foote et al.[39]	Meige's syndrome	Bilateral GPi- DBS	Male	47y-o	5y	Trihexyphenidyl, Baclofen, Lorazepam, Diazepam, Olanzapine, Quetiapine and Botulinum toxin (A and B) injections had no benefits.	Clinical examination revealed only a minimally notable increase in blinking rate and no visible craniofacial dystonia. The patient reported had a 75% improvement in all symptoms.	75
Hebb et al.[33]	Idiopathic cranial dystonia (Meige syndrome)	Bilateral GPi- DBS	Female	49y-o	10y	Clonazepan and Lorazepan had no benefit	GDRS scores: from 47 (preoperative) to 10 (1 year postoperative with bilateral GPi function) and 10 (5 years postoperative with left GPi and right on)	*
Houser and Waltz[10]	Blepharospasm and oromandibular dystonia (Meige's Syndrome). Preceded by a dry eyes sensation.	Bilateral GPi- DBS	Female	44y-o	*. The patient developed oromandibular dystonia 2y after the inicial blepharospasm	Trazodone, Anticholinergics, Benzodiazepines, Levodopa (L-dopa), Botulinum toxin had no benefit	BFM score changed from 44 to 10 (75% reduction) and the UDRS from 17 to 2.5 (85% reduction)	75
Inoue et al.[25]	Blepharospasm and oromandibular dystonia (Meige's Syndrome), trunk bending toward the right; mild dystonic tremor in the right arm.	Bilateral GPi- DBS	Female	61y-o	18y	Thalamotomy bilateral and sequential pharmacological trials unsatisfactory	Preoperative scores BFMDRS Movement and Disability Scales of 35 and 23, respectively. after the surgery, BFMDRS movement and disability scores of 5 and 4, respectively. Improvement more than 80% even of the 10-years follow-up	80
Kashyap et al.[26]	Orolingual dyskinesia; Parkinsonism	Bilateral STN- DBS	Female	75y-o	9y	Tetrabenazine, Benztropine, oral Lidocaine, Thioridazine, TBZ, Fluoxetine, Quetiapine, Trazodone, Propranolol, Amantadine, Sinemet, Pramipexole and Primidone had no benefit	Initial near-complete resolution of tremors. Two years after implantation, leg tremors not at all bothersome and able to feed herself. Able to exercising, but she still has a fear of falling and uses a walker for ambulation. Continued to need TBZ and Valbenazine	*

y-o = years-old; y = year; mo = month; *Not cited by the article;** Not specified by the author.

Table 1. Continued...

Author	Diagnosis	Target	Gender	Age at first surgery	Duration of symptoms	Medications	BFMDRS	BFMDRS Improvement (%)
Limotai et al.[27]	Blepharospasm and cranio-cervical dystonia (Meige's Syndrome); Limb dystonia.	Bilateral GPi- DBS	Male	48y-o	6y	History of medication refractory (**)	The patient improved more than 20% at a 6-month follow-up visit compared with it's baseline.	more than 20%
	Blepharospasm and cranio-cervical dystonia (Meige's Syndrome); Limb dystonia	Bilateral GPi- DBS	Male	26y-o	19y	*	Improved less than 20% at a 6-month follow-up visit. Post operactive presented improvement in his dystonia, but his speech and swallowing problems persisted	less than 20%
	Blepharospasm and cervical dystonia (Meige's Syndrome); Right arm dystonia; Myoclonus	Unilateral left GPi-DBS	Female	58y-o	18y	Botulinum toxin and Levetiracetam had no benefit	Improved more than 20% at a 6-month follow-up visit compared with the baseline	more than 20%
	Blepharospasm and cranio-cervical dystonia (Meige's Syndrome)	Bilateral GPi- DBS	Female	71y-o	10y	Botulinum toxin B had no benefit	Improved more than 20% at a 6-month follow-up visit, with little evidence of dystonia post-operactive	more than 20%
	Meige's syndrome	Bilateral GPi- DBS	Male	68y-o	5y	*	Improved less than 20% at a 6-month follow-up visit compared with the baseline	less than 20%
	Blepharospasm and cranio-cervical dystonia (Meige's Syndrome) and Head tremors.	Bilateral GPi- DBS	Male	67y-o	10y	*	Improved more than 20% at a 6-month follow-up visit compared with the baseline	more than 20%
Luthra et al.[6]	Blepharospasm and cranio-cervical dystonia, orofacial dystonia (Meige's Syndrome)	Bilateral GPi- DBS	Male	69y-o	8/9y	Botulinum toxin and Clonazepam had no benefit	BFMDRS and JRS scores improved from 8 do 0 (100% compared with baseline). BFMDRS total motor score improved from 15 to 1.5(90% compared with baseline). Improved BFMDRS neck subscore from 4 to 0.5 (88% compared with baseline)	100
Markaki et al.[28]	Bilateral blepharospasm and orofacial dystonia (Meige's Syndrome)	Bilateral GPi- DBS	Female	49y-o	7y	History of medication refractory (Dopaminergic, Anticolinergics drugs, Benzodiazepine, Dopamine depletors, Baclofen) and botulinum toxin injections had no benefit	BFMDRS movement score improved from 10 to 3 and the disability score imrpoved from 15 to 1. The patient showed 84% reduction of the total score	84

y-o = years-old; y = year; mo = month; *Not cited by the article;** Not specified by the author.

Table 1. Continued...

Author	Diagnosis	Target	Gender	Age at first surgery	Duration of symptoms	Medications	BFMDRS	BFMDRS Improvement (%)
Reese et al.[29]	Blepharospasm and oromandibular dystonia (Meige's Syndrome)	Bilateral GPi- DBS	Female	72y-o	12y	Trihexyphenidyl, Clonazepam, Tetrabenazine, Botulinum toxin had no benefit	BFMDRS improved from 22 baseline to 14 in a short-term follow-up and to 10 in a long-term follow-up	54.5
			Male	65y-o	6y	Levodopa, Lorazepam, Baclofen, Trihexyphenidyl and Zolpidem had no benefit.	BFMDRS improved from 22 baseline to 5 in a short-term follow-up and to 2.5 in a long-term follow-up	88.63
			Female	68y-o	12y	b	BFMDRS improved from 20 baseline to 9 in a short-term follow-up and to 8 in a long-term follow-up.	60
			Male	66y-o	4y	Trihexyphenidyl, Tetrabenazine and Botulinum toxin had no benefit	BFMDRS improved from 15 baseline to 7 in a long-term follow-up	53.33
			Male	62y-o	5y	Botulinum toxin and Trihexyphenidyl had no benefit.	BFMDRS improved from 26 baseline to 18 in a short -term follow-up and to 16 in a long-term follow-up.	38.46
			Male	71y-o	4y	Trihexyphenidyl had no benefit.	BFMDRS improved from 26 to 14 in a short-term follow-up	46.15
			Female	60y-o	5y	Botulinum toxin, Tiapride, Trihexyphenidyl and Zolpidem had no benefit	BFMDRS improved from 20 baseline to 12 in a long-term follow-up	40
			Male	64y-o	18y	Botulinum toxin and Trihexyphenidyl had no benefit	BFMDRS improved from 18 baseline to 8 in a long-term follow-up	55.55
			Female	61Years	7y	Tiapride, Trihexyphenidyl, Botulinum toxin and Levodopa had no benefit	BFMDRS improved from 22 baseline to 9 in a short-term follow-up and to 14 in a long-term follow-up	36.36
			Male	62y-o	13y	Trihexyphenidyl, Pimozid, Tetrabenazine, Botulinum toxin A and B and Lorazepamhad no benefit.	BFMDRS improved from 22 baseline to 16 in a short term follow-up and 11 in a long-term follow-up	50
			Female	66y-o	10y	Botulinum toxin A and B, Clozapin, Valproic acid, Clonazepam and Levodopa had no benefit.	BFMDRS improved from 20 baseline to 14 in a short and long-term follow-up	30
			Female	57y-o	7y	Trihexyphenidyl, Botulinum toxin and Biperiden had no benefit.	BFMDRS improved from 24 baseline to 5 in a long-term follow-up	79.16
Romito et al.[35]	Blepharospasm and oromandibular dystonia (Meige's Syndrome).	Bilateral GPi- DBS	Male	68y-o	12y	Benzodiazepines, Trihexyphenidyl and Botulinum toxin had no benefit.	BFMDRS improved from 66 to 4 at 12 moths postoperactive	81.81
Santos et al.[36]	Blepharospasm	Bilateral GPi- DBS	Male	63y-o	5y	Clonazepam and Botulinum toxin had no benefit	After 21 months the JRS of 1 (severity) and 2 (frequency) on the left eye and of 1 (severity and frequency) on the right eye.	*
Shu et al.[30]	Meige's syndrome	Bilateral GPi- DBS	Female	71y-o	4y	Drugs ** and Botulinum toxin had no benefit	BFMDRS decrease from 43 score to 19. The patient had a new decrease to 2 with bipolar stimulation	55.81
Tai et al.[31]	Meige's syndrome	Bilateral GPi- DBS	Female	66y-o	3y	Anticholinergics, Benzodiazepines, Neuroleptics, Valproic acid and Botulinum toxin had no benefit	Good clinical effect was observed even 60 months post operactive BFMDRS improved from 32 to 7.5.	76.56

y-o = years-old; y = year; mo = month; *Not cited by the article;** Not specified by the author.

Table 1. Continued...

Author	Diagnosis	Target	Gender	Age at first surgery	Duration of symptoms	Medications	BFMDRS	BFMDRS Improvement (%)
Reza Vagefi et al.[37]	Meige's syndrome	Bilateral GPi- DBS	Male	69y-o	10y	Levodopa, Baclofen, Clonazepam and Botulinum toxin had no benefit	He had some improvement of lower facial spasms and swallowing, with jaw and neck pain, but blepharospasm were worse. Nine months myedtomy surgery was indicated	*
Valálik et al.[32]	Meige's syndrome	Bilateral GPi- DBS	Female	66y-o	4y	Injections of botulinum toxin A and B and Sequential pharmacological trials refractory	BFMDRS improved to 25.5 to 2.5 in 6 months post operactive and to 3 after 3 years of the surgery	90.19
Zauber et al.[40]	Craniocervical dystonia; Blepharospasm	Bilateral GPi- DBS	Male	42y-o	8 mo	Oral medications and botulinum toxin had no benefit	BFMDRS improved to 20 to 6, showing a 70% improvement in the dystonia at the cost of mild parkinsonism	70
Horisawa et al.[24]	Meige's syndrome	bilateral GPi- DBS	Male	20	16y	Trihexyphenidyl, clonazepam	BFMDRS-M improved from 24 baseline to 1 in a short and long-term follow-up	95.8
			Male	33	1y	Botulinum toxin, monoclonal antibody	BFMDRS-M improved from 18 baseline to 1 in a short and long-term follow-up	94.4
			Male	51	2y	Tiapride, baclofen, clonazepam, etizolam, alprazolam, trihexyphenidy	BFMDRS-M improved from 23 baseline to 14 in a short and long-term follow-up	40.9
			Male	50	7y	Botulinum toxin, etizolam, haloperidol, clonazepam, trihexyphenidyl, quetiapine, baclofen, levodopa	BFMDRS-M improved from 26 baseline to 10 in a short and long-term follow-up	61.5
			Female	58	14y	Botulinum toxin, clonazepam	BFMDRS-M improved from 12 baseline to 11 in a long-term follow-up	8.3
			Male	60	9y	Botulinum toxin, trihexyphenidyl	BFMDRS-M improved from 11 baseline to 5 in a short and long-term follow-up	54.5
			Male	59	7y	Botulinum toxin, clonazepam, alprazolam, chlorproma-zine, haloperidol, trihexyphenidyl	BFMDRS-M improved from 22 baseline to 1 in a short and long-term follow-up	95.5
			Male	45	3y	Botulinum toxin, amantadine, tiapride, clonazepam	BFMDRS-M improved from 15.5 baseline to 3.5 in a short and long-term follow-up	77.4
			Male	43	6y	Botulinum toxin	BFMDRS-M improved from 7 baseline to 4 in a short and long-term follow-up	42.9
			Female	52	3y	Botulinum toxin	BFMDRS-M improved from 15.5 baseline to 2 in a short and long-term follow-up	87.1
			Female	50	5y	Botulinum toxin	BFMDRS-M improved from 10 baseline to 1 in a short and long-term follow-up	90
			Male	49	5y	Botulinum toxin, trihexyphenidyl, clonazepam	BFMDRS-M improved from 17.5 baseline to 2.5 in a short and long-term follow-up	85.7
			Female	40	1y	Botulinum toxin, trihexyphenidyl	BFMDRS-M improved from 14 baseline to 0.5 in a short and long-term follow-up	96.4
			Male	39	1y	Botulinum toxin	There was no BFMDRS-M improvement. It was 14 on the preop and 14 at the last follow-up	0
			Female	31	7y	Trihexyphenidyl, haloperidol, clonazepam, diazepam, botulinum toxin, monoclonal antibody	BFMDRS-M improved from 10 baseline to 8 in a long-term follow-up.	20
			Female	52	4y	Botulinum toxin, tiapride, baclofen, levodopa, biperiden	Worsening of symptoms was observerd, with BFMDRS-M from 22 to 29	-24.1

y-o = years-old; y = year; mo = month; *Not cited by the article;** Not specified by the author.

Invasive procedures include botulinum toxin injections into the involved muscles or surgical interventions like myotomy or myomectomy. Partial or full resection of the muscle can relieve symptoms in over 80% of patients. Nevertheless, these procedures are ablative, non-reversible and have complications including bruising, numbness, eyebrow or eyelash loss and since the neurologic component is not addressed there is a high chance of recurrence. Therefore, muscle procedures are reserved for patients with severe symptoms that are not controlled with toxin injections or for cases that failed other modalities[3].

Other procedures for dystonia include Neuromodulatory interventions or Deep Brain Stimulation (DBS), a reversible and non-ablative procedure as opposed to ablative and irreversible procedures to the brain named pallidotomy, which could be the best choice for some selected patients[3]. If patients are or become refractory to oral medication, botulinum toxin injection is usually the chosen therapy. Botulinum toxin is usually more effective for the blepharospasm component rather than oromandibular dystonia[1,2]. Despite improvement of the symptoms, some patients have a diminished response over time, and some may develop antibodies that make it difficult to continue this treatment modality[4]. In our review, around 70.83% of the patients have been treated with botulinum toxin injections before being referred to DBS surgery. Some cases didn't respond well to botulinum toxin or lost efficacy over time[5,6,10,20-23,27-32,35-39]. DBS is normally recommended when patients fail conservative management or botulinum toxin[1,12,13,41].

GPi-DBS treatment is level A of evidence according to the US Food and Drugs Administration (FDA)[41] for patients with primary generalized or segmental dystonia. Idiopathic or inherited, isolated, focal, tardive dystonia and myoclonus-dystonia overall have also good to excellent results with DBS[12]. Two different multicenter, randomized, controlled studies, demonstrated significant improvements at a 3-month follow-up after bilateral GPi-DBS[42,43].

Mechanisms of DBS for dystonia are multifactorial: long-term neuronal reorganization, and transient neuromodulatory effects and synaptic plasticity are involved[6]. In other words, DBS system works modulating the cortical excitability, interrupting the pathological activity which enables neuroplasticity phenomenon and promotes changes of the number and connections of the cortical neurons[13,15].

Preoperative higher BFMDRS scores indicate higher improvements. Studies showed a cut of improvement of 30% in symptoms. However, other studies demonstrate that severity of symptoms in the pre-surgical stage predicted poor outcome[6]. The effects of GPi-DBS on speech and swallowing are variable and not so beneficial when compared for blepharospasm[3,12,13,27]. Short-term follow-up in patients with Meige's Syndrome treated with DBS are positive[12,21,24,25,29,35], as well as for long-term FU. In a retrospective study from Reese et al.[29] 12 patients with Meige's Syndrome were analyzed[29]. The BFMDR improved 53% at 6.5 years from implantation. The BFMDR eyes improved 47%, BFMDR mouth 56% and BFMDR speech/swallowing improved 64%. Another study from Horisawa et al[24]. reported 58.9% improvement in BFMDR scores at 66-month FU. Bilateral GPi-DBS has been successful when patients become refractory conservative management[2].

Adverse effects of GPi-DBS can result from mispositioned lead or mistarget, since GPi is surrounded by the GP externus, putamen, internal capsule, ansia lenticularis, optical tract, amygdala, ventral pallidum, zona incerta (ZI) and MFB.

Beneficial effect from the DBS stimulation tend to occur on the long term since it requires neuromodulatory effect within the correct part of the GPi. Current spread outside the GPi can produce side effects when, for example, the internal capsule is stimulated, patients demonstrate long tract symptoms (tonic contraction of contralateral facial muscles) or stimulation-induced hypokinesia in non-dystonic body segments[6,12,13]. Bradykinesia, parkinsonism and freezing of gait are less frequent with GPi stimulation, however, can occur in 6 long-term follow-up[12], but most of which can be improved or completely resolved with DBS parameter adjustment[6]. Other side effects include dysarthria, sensory disturbances, cranial nerves deficits or phosphenes when there's current spread to the visual tracts which are ventral to GPi[7]. DBS is considered to be an efficient and low risk procedure, but it has possible complications including infections, hardware complications and neurological deficits.

The hypokinesis, bradykinesia or gait difficulties that some DBS patients present could be related to an exacerbated stimulation of the ventral portion of the GPi, even though it usually improves dystonic symptoms[7,13,41], by generating a suppression of the hyperkinesia induced by the levodopa. These mechanisms have not been completely elucidated yet, but the modification of neuronal activity in the ascending pallido-thalamofrontal

connections seems to have some relation in these symptoms[12]. The bradykinetic effect could be related to the frequency settings of the DBS postoperatively. Stimulation frequencies below 100 Hz were associated with fewer symptoms, but also to less clinical benefits[41].

GPi is still the most utilized target for DBS in dystonias. Neuromodulation of the posteroventral lateral portion of GPi is considered to be the best target for DBS, because is the area where the basal ganglia output pathways converge[41]. It is also based on good outcomes and knowledge of pallidotomy for dystonia[12]. The highest the volume of activated tissue (VTA) is stimulated in the GPi, better the results would be postoperatively[12]. Improvement of symptoms usually takes up to 6 months of FU[4], which depends on the postoperative programming of DBS[7]. Most of the Neurosurgical units still choose GPi over other targets such as STN for generalized or segmental dystonia including Meige's Syndrome. STN as target is also an effective and safe location according to some authors[8,44]. For primary dystonia, both targets were associated with important improvements on outcome measures in the short-term. STN is a smaller target and is also associated with more side effects due to the fibers and tracts surrounding this area[44]. Liu et al.[8] compared outcomes of GPi-DBS and STN DBS for primary dystonia and demonstrated that both of them improved this condition in the short-term, whereas STN-DBS was associated with more side effects.

Many centers have published their own DBS programming algorithm to facilitate doctors and health professionals when they start working with these patients postoperatively[7,44]. The first DBS programming normally varies from 2 days to 1 month after surgery[44].

The programming algorithms follows the same recommendations as for Parkinson's Disease (PD) or Essential Tremor with some modifications. For instance, a high frequency around 185 Hz has been recommended and demonstrated to be effective in GPi-DBS. There is also debate and discussion when selecting the best contact for chronic stimulation but usually after a lead mapping (test of every contact for side effects e benefits of stimulation), the most ventral contact is programmed since the VAT will probably be more efficient. Cheung et al.[45] recently identified a small area located squarely in the middle of the GPi as a potential specific therapeutic target for DBS for dystonia, whereas recent evidence from his group suggests that most efficient DBS electrodes displayed close anatomic proximity to the pallidothalamic tracts (*ansa* and *fasciculus lenticularis*) between the GPi and the pyramidal tract. Thus, stimulation is most commonly initiated in the ventral region of the GPi above the optic tract (contacts 0 and 1) with a short pulse width (60–120 μs), high frequency (130–185 Hz) and amplitude just prior to eliciting adverse effects. Due to the anatomical location of the target, delayed side effects are less likely to occur than with STN-DBS or VIM-DBS, therefor favoring a top-down approach and starting the stimulation with the highest tolerated voltage or current-mA. The use of high- vs. low-frequency stimulation in dystonia has shown mixed results. Alterman et al. suggested that the use of 60 Hz stimulation could be beneficial in some patients. Moro et al. concluded that high-amplitude and high-frequency stimulation predict better outcomes for cervical dystonia. Various pulse widths have been recommended in GPi-DBS as well. Coubes et al. recommend the using of a large pulse width of 450 μs to stimulate more fibers. However, another study comparing 60, 120, and 450 μs did not show any significant differences between the three groups[7]. In conclusion, an optimal combination of frequency, voltage and pulse width is always tailored to each patient and has to be done individually in the careful and time-consuming work of health professionals involved with movement disorders[46].

CONCLUSION

DBS for Meige's Syndrome using GPi as target is still an efficient and low risk invasive neuromodulatory modality of treatment for this condition. Early DBS for these patients, when they fail conservative treatment, could result in excellent improvements in outcome measures possibly related to prompt neuromodulation effect within the basal ganglia specially the GPi. The use of other targets such as the STN could still be efficient for this condition either as a primary target or as a rescue form of treatment when GPi fails.

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Amyotrophic Lateral Sclerosis and Cervical Myelopathy overlap: a concise review for the spine surgeon

Sobreposição de Esclerose Lateral Amiotrófica e Mielopatia Cervical: uma revisão concisa para o cirurgião de coluna

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ABSTRACT

Amyotrophic Lateral Sclerosis is a progressive condition caused by motor neuron deterioration in the spinal cord and brain. Cervical spondylotic myelopathy is a secondary spinal cord dysfunction, non-traumatic and progressive. Due to their similar initial symptoms and higher incidence in older individuals, it is not uncommon for an overlap of amyotrophic lateral sclerosis and cervical spondylotic myelopathy. The purpose of this paper is to differentiate amyotrophic lateral sclerosis of cervical spondylotic myelopathy and to elucidate, if possible, the overlap presentation of them. In summary, the amyotrophic lateral sclerosis and the cervical spondylotic myelopathy occur in similar epidemiology and can co-occur in almost half of amyotrophic lateral sclerosis patients. Their diagnosis must consider imaging exams, symptoms and clinical red flags that help to differentiate these two conditions, thus avoiding iatrogenic issues and misdiagnosis, which are associated with worse prognosis, inappropriate surgeries, and higher costs in healthcare.

Keywords: *Amyotrophic lateral sclerosis; Spine surgery; Cervical myelopathy*

RESUMO

A esclerose lateral amiotrófica é uma condição progressiva causada pela deterioração do neurônio motor na medula espinhal e no cérebro. A mielopatia espondilótica cervical é uma disfunção medular secundária, não traumática e progressiva. Devido aos sintomas iniciais semelhantes e maior incidência em indivíduos mais velhos, não é incomum a sobreposição de esclerose lateral amiotrófica e mielopatia espondilótica cervical. O objetivo deste trabalho é diferenciar a esclerose lateral amiotrófica da mielopatia espondilótica cervical e elucidar, se possível, a apresentação sobreposta destas. Em resumo, a esclerose lateral amiotrófica e a mielopatia espondilótica cervical ocorrem em pacientes com epidemiologia semelhante e podem coexistir em quase metade dos pacientes com esclerose lateral amiotrófica. O diagnóstico deve considerar os exames de imagem, sintomas e alertas clínicos que ajudam a diferenciar essas duas condições evitando, assim, iatrogenias e erros de diagnóstico, que estão associados a pior prognóstico, cirurgias inadequadas e maiores custos no atendimento.

Palavras-Chave: *Esclerose lateral amiotrófica; Cirurgia na coluna; Mielopatia cervical*

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INTRODUCTION

Amyotrophic Lateral Sclerosis (ALS) is a progressive condition caused by the deterioration of motor neurons in the spinal cord and brain, which epidemiology is large but geographically limited. In a literature review made by Chiò et al.[1], the most prevalent mean age of ALS onset was 62 years. ALS has a clinical spectrum that englobes spasticity, muscle atrophy, fasciculations, facial weakness, low palatal elevation, dysarthria, tongue fasciculations atrophy, slow speech, palm omental, and jaw jerk reflexes, as well as frontotemporal dementia[2]. Cervical Spondylotic Myelopathy (CSM) is a non-traumatic and progressive secondary spinal cord dysfunction. According to Young, it is the most common cause of spinal cord dysfunction in adults[3]. It presents clinical motor manifestations, similar to ALS symptoms, except for the absence of the bulbar deficits and frontal dementia.

Due to their similar initial symptoms and higher incidence in older individuals, it is not uncommon an overlap of ALS and CSM[4]. When that happens, it can be late for the proper ALS diagnosis, resulting in inadequate treatment and, consequently, a possibility of iatrogenic action. The purpose of this paper is to differentiate ALS from CSM and to elucidate, if possible, their overlap presentation.

MATERIAL AND METHODS

A non-systematic review was performed with search on public databases: PubMed, Medline, ScienceDirect, SciELO and Cochrane. The searching process was performed using keywords related to Amyotrophic Lateral Sclerosis, Cervical Spondylotic Myelopathy and overlap of Amyotrophic Lateral Sclerosis and Cervical Spondylotic Myelopathy. The most relevant papers written in English were selected.

RESULTS

Amyotrophic lateral sclerosis

ALS is a motor neuron disease (MND) characterized by degenerative changes of upper and lower motor neurons with the involvement of the brainstem and multiple spinal cord regions of innervation. ALS is caused by specific mechanisms of neuronal death that are currently unknown. Evidence supports the presence of autoimmune mechanisms that contribute to ALS pathogenesis[5].

Many clinical presentations of ALS have been described, including lower motor signs like weakness in members, muscle atrophy and fasciculations. Also, upper motor signs like spasticity, facial weakness, low palatal elevation, dysarthria, tongue fasciculations and tongue atrophy. Bulbar signs involve slow speech and palm omental and jaw-jerk reflexes[6]. According to Picher-Martel et al.[7], up to 50% of ALS patients may have symptoms of frontotemporal dementia, which include personality change, behavioral abnormalities, language dysfunction, and memory impairment.

Approximately 30% of patients with ALS have a cognitive impairment, and 10% of them have frontotemporal dementia, mostly the behavioral variant. The cognitive profile of ALS patients presents with deficits in fluency, language, social cognition, executive functions, and verbal memory with sparing of visual perception[8]. The higher-level executive impairment does not follow the same rate of declines as physical disability. Scientific evidence reveals that the relative resistance of pure oculomotor function is an objective mean of assessing extra motor cerebral involvement in ALS[9].

Diagnosis of ALS is primarily determined by clinical manifestations, electromyography (EMG) and laboratory testing. It requires at least one of the following: the progression of upper motor neurons and lower motor neurons dysfunction in at least one limb or body region or lower motor neuron dysfunction in 1 region identified by clinical examination and/or by EMG in 2 regions (lumbosacral, bulbar, thoracic, cervical). The EMG findings consist of sharp waves and/or fibrillation and neurogenic potentials[10]. Laboratory tests are done in patients with ALS to exclude other conditions.

ALS has no curative treatment, and there are no studies with significant scientific evidence for interventions to manage the symptoms resulting from lower motor signs. The cornerstones of the management of ALS patients are focused on symptom control: drug therapy in case of pain and/or spasticity, mechanical ventilation for supporting respiratory function, treatment for sialorrhea, enteral tube feeding for supporting nutrition, therapeutic exercise, and multidisciplinary care[11].

Cervical spondylotic myelopathy

Cervical Spondylotic myelopathy (CSM) is in the group of non-traumatic spinal cord injuries (NTSCI), which epidemiology varies around the globe. In a literature review made by New et al.[12], the vertebral column degenerative disorders, including CSM, contribute to 64% of the cases of NTSCI in North America, while in Europe, the incidence is 31%; in North Africa/Middle East is 27%. In Asia, the South shows 16%, the Pacific 59%, Australasia 22%, while in Southwest and Oceania there are no numbers. Moreover, finally, Africa brings 27% in the East, 13% in the East, 22% in the West, and 4% in the Southern. Latin America has no data in this study. Thus, there is a lack of data on the exact incidence of CSM, with few population-based studies, except for those covering rates and discussions on surgical treatments of the condition.

CSM is caused by non-traumatic, progressive, and chronic cord compression. In other words, it is a secondary spinal cord dysfunction, which involves spasticity, hyperreflexia, neck pain or stiffness, wide-based ataxic gait, ascending paresthesia in the upper or lower extremities, lower extremity weakness, finger/hand clumsiness, pathologic reflexes, clonus and Babinski sign. Besides, in severe disease, there is a sphincter dysfunction[13,14]. Degenerative disorders are more common at C5 and C6 or C6 and C7.

Diagnosis is suspected by one or more symptoms between hand clumsiness, gait imbalance, numbness, weakness, and bladder dysfunction besides cervical spinal cord signs like fine motor dysfunction of the hands, hyperreflexia, gait ataxia, sensory deficits, and focal weakness. Still, one must have the proof of compression on MRI[15], which is the standard criterion for current diagnosis, made by the view of the spinal cord and nerve. Computed tomography and radiographs are helpful only to bring information about dynamic changes, quality, and bone alignment, which can be used for surgical guidance. Electromyography, likewise, holds value in the differential diagnosis of other neurological disorders, excluding the hypotheses of peripheral disorders, neuropathy, amyotrophic lateral sclerosis, and multiple sclerosis. Furthermore, finally, the somatosensory evoked potential, due to the more direct assessment of spinal cord dysfunction, can collaborate to CSM diagnosis, as Milligan and the authors approached it in their review.

There are no studies with significant scientific evidence for its determination regarding treatment, but it is known that Cervical Spondylotic Myelopathy is a progressive disease. Therefore, at some point in the evolution of the disease, it will require surgical intervention, even with conservative treatment at first. Instead, it is empirical and presents scientific scarcity for further protocol, being made from physiotherapy, immobilization through the cervical collar, massages, medication with anti-inflammatories, and the removal of high impact activities[15,16]. In surgical treatment, functional and clinical improvement are achieved, with some authors even indicating it for all patients diagnosed with CSM. The indication of each surgery is performed and evaluated by the surgeon by analyzing the patient's physiological and pathological characteristics, which can be facilitated using the JOA and Nurick scales, for example. Likewise, the risks and complications of each surgery are identified and studied by the surgeon. In anterior approaches, with the advantage of shorter operation time and risk of infection, the most indicated surgeries are anterior cervical discectomy with fusion (ACDF), which is the standard for interventions for degenerative cervical diseases, anterior cervical corpectomy with fusion (ACCF), and cervical arthroplasty. In the posterior approach, laminectomy with fusion and laminoplasty present similar evidence of prognosis achieved by patients, with the advantage of the absence of technical problems compared to those found in the anterior approach, such as obesity and short neck. When multiple cervical levels are affected, the posterior approach is preferred, and in exceptional cases, one can intervene with combined approaches[17].

Cervical spondylotic myelopathy and amyotrophic lateral sclerosis overlap

As exposed, CSM and ALS are two clinical entities with very different natural histories. While ALS is usually a fatal condition with most patients dying in the first two years from diagnosis with variation depending on clinical phenotype and country of the patient, CSM is a treatable condition although a morbid one[18-21].

An overlap of CSM and ALS is not uncommon because they are two conditions with a higher incidence in older individuals. One study shows that 4.2% of patients with ALS are submitted to a surgical procedure before diagnosis. Retrospectively, 81% of patients' symptoms were classified as clearly related to ALS. An important feature was that unilateral foot drop represented the symptom that leads to surgery in 21% of the cases[4].

In a large national study in South Korea, it was found that ALS account for 0.19% of all myelopathies diagnosed patients, but 41.9% of ALS patients had concomitant myelopathy. CSM accounted

for 10% of these cases and associated higher surgery rates among other myelopathies diagnosed[22].

In another study, Yamada et al.[23] found similar results with a prevalence of 48% of CSM in patients who have already ALS diagnosis, showing that the overlap of the conditions is common, and the presence of one of them does not exclude the diagnosis of the other one. Another study found that 13% of patients with ALS undergo unnecessary surgery for many reasons, including CSM before ALS diagnosis[24].

A more recent study with a larger sample found that 8.6% received inappropriate surgery, with CSM being the second more common reason before lumbar spine surgery. Interestingly, most of the patients (41/43) who undergo surgery had a limb onset ALS, and the other two patients with a bulbar onset had a cervical spine one[25].

In the study of Kim et al.[22], it was found that 10% of patients with ALS undergo surgery, with the cervical spine being the second most common reason. In this study, it was found that 11% of the patients underwent conservative treatment for their symptoms, with a precise diagnosis made just for 24% of them. The other ones received treatment for their symptoms only[26].

Patients with ALS and myelopathy have higher surgery rates than patients with myelopathy isolated, showing that symptoms severity can mislead to inappropriate surgery[22]. A crucial piece of data found by Cellura et al.[27] brings that CSM was the most common misdiagnosis in ALS patients made by a neurologist, showing that even fellowship-trained neurologists are prone to diagnostic confusion between ALS and CSM. On the other hand, ALS diagnosed patients that had a cervical disease, although unusual, have been reported as well. In addition, patients first diagnosed with ALS were further evaluated to have CSM from various causes[28].

Surgery had no benefits in 89% of patients with ALS, and, obviously, even in the tiny sample that did refer to any benefits, these benefits were promptly overshadowed by ALS progression. Furthermore, the benefits of surgery in the small responsive sample were restricted to pain symptoms[4].

Clinical, electrodiagnosis, and other differentiation tools

It is essential to address that sensibility symptoms are well-known differentiators between ALS and CSM[4]. However, the important overlap of the two conditions can shadow these differences because ALS patients can have sensibility symptoms, especially pain due to muscle atrophy and weakness[29] or caused by CSM itself. Therefore, a careful sensory, physical examination can help to show a spine level characteristic pattern and help to support CM diagnosis over ALS, although it should not be the only sign to close the diagnosis[30,31].

With that in mind, it is essential to remember that CSM can have a pure motor onset with no sensory symptoms, which, in this setting, should be borne in mind a particular CSM phenotype, the Cervical Spondylotic Amyotrophy (CSA) that presents with no sensory signs and is associated with upper limb atrophy[30,32]. In these cases of CSA, the disease tends to be restricted to one upper limb, although bilateral disease can be present, and there is not such atrophy or symptomatology in the lower limbs[32.] In addition, the hand muscle atrophy pattern can help to differentiate ALS and distal type CSA[33].

In cases with no sensory affection and only motor presentation, the differentiation of ALS from CSM is clinically easier to be made when patients have a bulbar onset. In these cases, the misdiagnosis can occur but it is rarely made[26]. The problem is that only 23% of ALS have bulbar onset in disease, although bulbar symptoms are common with disease progression and should be actively investigated in older patients reaching a spine surgeon for cervical pathology complaints with limb weakness[6].

Other symptom that may help differentiate ALS from CSM is sphincter dysfunction, that points towards CSM in detrimental to ALS[30].

Although it is still challenging to be evaluated in inexperienced hands, an emerging picture that is growing is that of cognitive and executive function alterations in ALS[8]. As a neurodegenerative condition that shares pathophysiological mechanisms with frontotemporal dementia, ALS when presented with this board can be helpful in a diagnostic challenge between ALS and CSM. Among the signs, it presents deficits in verbal fluency, semantic memory, and in almost every other cognitive domain[29,34].

In this field, executive dysfunction – eye-tracking alterations, anti-saccadic tests, and other oculomotor alterations – can be altered in ALS patients compared to controls. Therefore, it may pose an additional sign to differentiate ALS and its mimics, even though further studies results are needed[9,35,36].

Usual imaging studies should not differentiate ALS and CSM once the overlap between these conditions is not uncommon[4,23]. However, diffusion coefficient in MRI evaluation apparently can differentiate CSM from ALS, as demonstrated in a study conducted by Koike et al.[37].

The main exam used to differentiate ALS and CSM is the electroneuromyography (EMG). With that aim, especially in lower limbs, EMG can show lower motor neuron degeneration in areas with clinically preserved function[38]. Important sensory nerve conduction alterations are not uncommon in ALS and should not exclude the diagnosis when present[39].

Hand muscle's pattern of affection in EMG is different in ALS and CSA and can help to differentiate the conditions. The ulnar/median compound muscle action potential (CMAP) ratio is a helpful tool as well. It is customary in patients with CM and less in patients with motor neuron disease[40]. The repetitive nerve stimulation with CMAPs decrements in at least one proximal muscle is again much more common in ALS patients (91%) than CSA patients (32.6%)[41].

In a recent study, Zheng et al.[42] evaluated the motor unit number index (MUNIX) to quantify the split hand phenomenon to help to differentiate CSA and ALS. The authors found a larger area under the curve using MUNIX when compared to CMAP.

DISCUSSION

ALS and CSM are conditions that occur in similar patient's epidemiology and can co-occur in almost half of ALS patients[19,23]. Once ALS is an inexorably severe condition, surgery in these patients brings no results except diagnostic delay and an iatrogenic procedure[4(22).] Surgery is associated with diagnostic delay as well[25].

As exposed earlier, ALS diagnosis is not simple, and confusion with CSM is not restricted to a single specialty and occurs even with fellowship-trained neurologists[27].

Limb-onset disease accounts for significant diagnostic errors and a higher risk of surgery. Specifically, orthopedists were associated with diagnostic delay in limb onset ALS patients, and it could be associated with a higher surgery rate in patients with ALS overlapped with CSM[22,25,43].

Even though ALS is an incurable condition nowadays, multidisciplinary care in reference is associated with lower costs in disease conduction and better outcomes for the patients[44].

This fact highlights the importance of being aware that symptoms can help to differentiate cervical spine affections from ALS, since spine surgeons are frequently the first or second physicians seen by an ALS patient. In addition, by relying solely on imaging techniques to diagnose, CSM can severely affect patients if they have ALS overlapped. Thus, spine surgeons should be aware of clinical aspects that help to differentiate these two conditions and their significant EMG alterations, thus preventing unnecessary surgery and improving care in such burdensome conditions.

Importantly, when facing a patient with signs of MND which might be attributed to a cervical myelopathy, the Ockham rule doesn't fit. Therefore, the only and simplest answer that addresses all the symptoms is perhaps the wrong one.

CONCLUSIONS

In conclusion, imaging studies cannot be the only reliable exam to diagnose CSM, especially in patients with suspected ALS. Misdiagnosis is associated with worse prognosis, inappropriate surgeries, and higher costs in ALS patients' care.

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Fratura do seio frontal. Condutas e desafios: uma revisão de literatura

Frontal sinus fracture. Conducts and challenges: a literature review

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RESUMO

Introdução: *A fratura do seio frontal (FSF) é uma entidade de grande importância devido à sua incidência e tratamentos complexos, ocorre em cerca de 5 a 15% dos traumas de face e se apresenta quatro vezes mais em homens. O tratamento da FSF varia da observação clínica até o processo cirúrgico de cranialização do seio.* **Objetivo:** *O presente estudo pretende nortear a comunidade médica a respeito do cenário atual do manejo das fraturas de seio frontal, principais condutas e desafios.* **Metodologia:** *Trata-se de uma revisão de literatura utilizando as bases de dados PubMed, Google Scholar e Scielo utilizando os termos: "Frontal sinus", "Frontal bone" e "Facial injuries". Foram selecionados artigos de 2006 a 2022, resultando em 52 artigos que foram submetidos à revisão sistemática.* **Resultados:** *Existe uma grande controvérsia com relação ao tratamento específico empregado nos casos de FSF, devendo-se levar em conta que mais benefícios têm se mostrado em técnicas conservadoras em detrimento das terapêuticas mais agressivas.* **Conclusão:** *A literatura tem demonstrado um melhor desfecho nos tratamentos conservadores em detrimento dos cirúrgicos quando estes são passíveis de eleição e os prejuízos da falta de uma classificação unificada para as fraturas de seio frontal em especial na população pediátrica.*

Palavras-Chave: *Seio frontal; Traumatismo cranioencefálico; Tratamento; Complicações*

ABSTRACT

Introduction: *The frontal sinus fracture (FSF) is an entity of great importance due to its incidence and complex treatment, it occurs in about 5-15% of facial traumas and presents four-fold number more in men. The treatment of FSF varies from clinical observation to the surgical process of sinus cranialization.* **Objective:** *The present study aims to guide the medical community regarding to the current scenario of the management of frontal sinus fractures, main conducts and challenges.* **Methodology:** *This is a literature review using PubMed, Google Schollar and Scielo databases using the terms: "Frontal sinus", "Frontal bone" and "Facial injuries". Articles from 2006 to 2022 were selected, resulting in 52 articles that were submitted to a systematic review.* **Results:** *There is a great controversy regarding to the specific treatment used in cases of FSF, considering that more benefits have been shown in conservative techniques at the expense of more aggressive therapies.* **Conclusion:** *The literature has shown a better outcome in conservative treatments over surgical ones when these are amenable to be chosen and the disadvantages of the lack of a unified classification for frontal sinus fractures, especially in the pediatric population.*

Keywords: *Frontal sinus; Traumatic brain injury; Treatment; Complications*

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INTRODUÇÃO

A fratura do seio frontal (FSF) é uma entidade de grande importância para a saúde pública devido à sua incidência e aos mecanismos de trauma implicados. Deste modo, a incidência tem predominância pelo sexo masculino[1-6], com uma proporção de 4:1 e entre a segunda e terceira décadas de vida[1-3,5]. Além disso, alguns estudos relatam uma relação íntima entre o trauma de face e a baixa escolaridade dos pacientes. Segundo Muller et al.[7], seu trabalho demonstrou uma taxa de 64% dos pacientes com ensino médio incompleto ou inferior a este[7-9]. Sabe-se atualmente que a grande maioria das FSF apresentam uma origem traumática, podendo ela estar relacionada a agressões físicas, ferimento por arma de fogo (FAF), acidentes automobilísticos e acidentes de trabalho, em especial na construção civil, sendo o acidente automobilístico a causa mais comum, acometendo cerca de 58,3% a 70% dos casos, e vale ressaltar que cerca de 41,7% dos pacientes estão associados ao consumo alcoólico antes do acidente[1-5,7,10-30]. Em contrapartida, estudos atuais têm apontado para uma redução das taxas correspondentes aos acidentes automobilísticos devido à obrigatoriedade por lei do uso do cinto de segurança e produção de carros constando com mecanismo de airbag. Sendo assim, associado a este fato, é possível perceber um aumento proporcional nas taxas correspondentes à violência interpessoal em detrimento dos acidentes automobilísticos[7,31,32]. Deste modo, o impacto social e econômico da FSF é algo que deve ser considerado, pois tais fraturas representam cerca de 5 a 15% de todas as fraturas faciais[5,8,10-18,21,23,24,26,27,29,30,33-41].

Apesar da rigidez da tábua externa do osso frontal, associado ao fato da mesma estar resguardada por estruturas como proeminência supraorbital a qual confere maior resistência a mesma, as lesões mais comuns acometem a tábua externa de forma associada ou não à tábua interna[13,27,42]. Deste modo, as fraturas ocorrem mais comumente nas tábuas externa e interna de forma conjunta em ⅔ dos casos; de forma isolada na tábua externa em ⅓; e de forma isolada na tábua interna em menos de 1% dos casos. Visto isso, as fraturas que apresentam maior gravidade são as que são as atingem a tábua interna do osso frontal ou assoalho do seio e ducto nasofrontal[8-11,13,18,21,24,27,41]. As FSF na população pediátrica são extremamente raras devido a alguns fatores, a exemplo da fiscalização dos pais, maior elasticidade do esqueleto, pneumatização incompleta do SF e proporção pequena entre face e crânio, tais fatores também acarretam uma maior taxa de condutas conservadoras para a população pediátrica[10,22].

METODOLOGIA

Trata-se de uma revisão de literatura realizada por meio de pesquisas nas bases de dados: PubMed, Scielo e Google Scholar. Foram utilizados como descritores: "Frontal sinus", "Frontal Bone" e "Facial Injuries", selecionando artigos com recorte temporal de 2006 a 2022, resultando em um total de 52 artigos que preencheram os critérios de inclusão levando em conta suas citações, seus respectivos impactos e conteúdo de acordo com o tema.

Embriologia e anatomia do SF

O seio frontal (SF) é uma estrutura de grande importância que está situada na transição do esplancnocrânio e neurocrânio articulando-se a partir das suturas frontozigomática, frontonasal e frontomaxilar[1,10]. Trata-se de uma estrutura derivada do recesso frontal que é parte do meato médio e células etmoidais, e encontra-se situada entre a tábua interna do osso frontal, que é uma estrutura laminar e fina contendo cerca de 0,1 a 4 mm de espessura, e tábua externa do osso frontal a qual apresenta cerca de 2 a 12 mm de espessura e forma parte das regiões da sobrancelha, glabela e fronte[10-13,33,36,43]. O SF está intimamente relacionado com estruturas nobres como o teto da órbita, células etmoidais, nariz e principalmente a fossa cerebral anterior[8,10,11,13-15,43-45]. Tem sua formação iniciada a partir da 4ª semana de gestação[16,17,33,43], porém geralmente está ausente ao nascimento sendo o último dentre os seios paranasais a se desenvolver completamente entre os 10 e 15 anos de idade, com sua máxima pneumatização dos 18 aos 20 anos[8,10,11,13,15,33-35,43]. Já é possível visualizá-lo radiograficamente desde os 3 aos 6 anos[11,17,33,43], e vale ressaltar que o SF é associado a algumas variações anatômicas. Assim, apenas 1 a 10% da população não apresenta SF[11,33,43] e 4 a 5% apresenta apenas uma célula aerada[11], além disso, apenas 15% da população apresenta o ducto nasofrontal verdadeiro[10].

Em sua morfologia, o SF possui altura de cerca de 28 a 32 mm, com largura e profundidade de 20 mm, formando um espaço de 5 a 16 ml[8,17,33], porém o tamanho e a forma do seio variam entre os indivíduos sobretudo nos lados direito e esquerdo de uma mesma pessoa, além disso, o mesmo apresenta paredes irregulares e recortadas em suas margens e um septo interno, podendo haver pequenas septações de osso completo, ou não, que o separam em múltiplos subcompartimentos[8,11,33]. Nota-se um vasto suprimento arterial o qual ocorre às custas dos ramos das artérias esfenopalatina, oftálmica, supraorbital, supratroclear e etmoidal anterior[17,33]. A drenagem venosa é de grande importância

devido à sua comunicação com o arcabouço intracraniano, sendo feita a partir das veias diploicas, já a inervação sensorial do SF é de responsabilidade de ramos do nervo trigêmeo[17,33].

Fisiopatologia da FSF

As lesões ocorrem quando a energia cinética transferida para o corpo excede a tolerância do tecido. A probabilidade de lesão está relacionada à quantidade de energia transferida e à condição do tecido subjacente[1-4,8,12,18-23]. O SF contém epitélio respiratório pseudoestratificado colunar ciliado recoberto por uma camada de mucina[8,12,17,21,36] e sabe-se que os cílios batem a uma taxa de cerca de 250 a 600 ciclos por minuto, direcionando o fluxo de mucina da face medial para a lateral do SF [8], a quantidade de drenagem de mucina é de cerca de 5 g/cm. A drenagem do SF é prejudicada quando o ducto nasofrontal fica danificado ou obstruído, pois o muco pode posteriormente acumular-se atrás do ducto obstruído e uma mucocele pode desenvolver-se e atuar como um tumor em expansão [8]. Dessa forma, o ambiente se torna propício ao desenvolvimento anaeróbio de bactérias, aumentando o risco de sinusite frontal envolvendo o conteúdo intracraniano[8].

É sabido, atualmente, que as FSF ocorrem por meio de mecanismos de alto impacto com grande dissipação de energia necessitando de um vetor de força com uma média de 360 a 990 kg, logo, nota-se que o trauma nessa região requer maior força para fraturar do que qualquer outro osso facial[8,10,11,14,17,33,35,36,42]. Segundo Buller et al.[46], há uma relação inversa entre o tamanho do seio e a força necessária para fraturá-lo. Logo, quanto maior o SF, menor a força necessária para lesá-lo[46]. As fraturas de SF de maior impacto frequentemente acometem a tábua interna do osso frontal e, infelizmente, tais fraturas estão intimamente ligadas a injúria da órbita ocular, sistema nervoso central, terço médio da face e partes moles adjacentes, sendo assim, com relação às fraturas da face associadas a fratura do SF temos: fraturas expostas (20,8%); fraturas nasais (16,7 a 41,7%); fraturas de arco zigomático (33,3%); fraturas maxilares (12,5%) e fraturas de mandíbula (8,4%)[7,11,18]. Em cerca de 76% dos pacientes que sofrem FSF com acometimento de tábua externa e interna cursam com alteração do nível de consciência, a qual pode-se associar com injúrias importantes do sistema nervoso como hemorragias intracranianas (10 a 20,9%); pneumoencéfalo (8 a 33%); fístulas liquóricas (12,5 a 25%); fraturas de base de crânio (12,5%) e compressão do nervo óptico (4,2%)[11,24,47]. Além disso, 42% dos pacientes acometidos pela fratura de tábua interna irão cursar com comprometimento neurológico permanente, 59% com comprometimento da órbita e 25% apresentarão mortalidade aumentada[24,25]. O paciente com FSF apresenta fratura panfacial na grande maioria dos casos. Assim, nas fraturas de seios frontal e seios etmoidais cerca de 70% destes irão apresentar fraturas compostas e 35% apresentarão anosmia[11,24].

Diagnóstico

A FSF deve ser suspeitada em qualquer paciente que apresente lesão na região superior da face[10] e deve ser manejada inicialmente como qualquer trauma a partir do protocolo de XABCDE garantindo via aérea pérvia, oxigenação e respiração adequada, estabilidade hemodinâmica e triagem neurológica rápida[14]. Após a triagem inicial segue-se com o exame clínico o qual apresenta dor, edema, equimose periorbital, hematoma, lacerações na fronte, alterações de sensibilidade, crepitações, irregularidades ósseas e outros achados menos comuns, como exoftalmia, enoftalmia e perda de projeção do terço médio da face[1,4,9,33,48]. Atualmente, tem-se o consenso de que o exame clínico associado a exames complementares, como radiografia simples, tomografia computadorizada (TC) e ressonância magnética (RM), são de essencial importância para guiar o tratamento do paciente com FSF[11,33]. A utilização de raios-X de crânio com incidências anteroposterior, perfil, Towne, Waters e Caldwell, é de fundamental importância para o atendimento inicial do paciente traumatizado[21], porém a utilização da TC de crânio e face com cortes sagitais, coronais e axiais somados à reconstrução tridimensional constituem-se como o padrão-ouro. Além disso, a videoendoscopia nasal promove uma melhor avaliação e melhor tomada de decisão para o desfecho do paciente[1,5,10,11,17,44].

Determinadas condutas devem ser tomadas na abordagem inicial do paciente no momento da admissão como, por exemplo, avaliação de sinais vitais e nível de consciência, assim como, realizar uma avaliação mais detalhada do acometimento do SF palpando a região da glabela, crista supraorbital e tecidos moles do fronte verificando a presença de afundamentos e lacerações, além de descrição de possíveis hemorragias intra e extracranianas, anestesia em região supraorbital e presença de equimose peripalpebral[8,10,11]. A presença de irregularidades na região da fronte no primeiro atendimento sugerem possível acometimento olfatório e a presença de lacerações é indicativo de lesão de estruturas mais profundas. Vale ressaltar que, quando existe afundamento na região supraorbital deve-se cogitar a injúria de SF, ducto nasofrontal, nervos supraorbitais e formação de fístula liquórica.

A suspeita da formação de fístula liquórica deve ser levantada em qualquer lesão de base de crânio, mas em especial na saída de secreção hialina da cavidade nasal "runny nose" e deve ser confirmada através de exames direcionados[1,19]. Um dos principais modos de diagnóstico inicial da fístula liquórica é por meio das fitas (*dipstick*) as quais são utilizadas no controle glicêmico da diabetes, a fita funciona mensurando a glicemia presente na secreção e seu resultado é dado a partir da comparação entre a glicemia da secreção e a glicemia sanguínea, caso a glicemia da secreção seja superior a 30 mg/dL ou represente ⅔ da glicemia sanguínea, o resultado aponta a favor de fístula liquórica[19]. Apesar da fita *dipstick* ser um método rápido e não invasivo, a mesma apresenta taxas consideráveis de falso-positivo e falso-negativo, seus resultados podem ser falseados na presença de lágrimas no momento da coleta da amostra e em vigência de quadro de meningite, o qual reduz a taxa de glicose presente no LCR, sendo assim, devido a tais motivos o método tem perdido credibilidade nos últimos anos[19].

De forma mais específica, temos o teste de dosagem de Beta 2-transferrina que tem se demonstrado nos últimos anos ser um teste de alta especificidade e sensibilidade para o diagnóstico preciso da fístula liquórica, sendo necessários apenas 50 microlitros para dosar a proteína específica do LCR. Sendo assim, é considerado o teste de escolha para conferir tal diagnóstico, porém infelizmente, trata-se de um método ainda indisponível em alguns centros o que dificulta a sua utilização[10,11,19,37].

Outros exames de imagem e métodos invasivos, os quais permitem uma maior assertividade quanto ao diagnóstico da fístula, são a TC de seios da face, endoscopia nasal, TC com cisternografia, RM de seios da face e a administração de fluoresceína intratecal para melhor visualização da lesão no ato cirúrgico. A utilização da fluoresceína intratecal é feita a partir da administração de 2 ml de fluoresceína a 5% no espaço subaracnoideo e o paciente é posicionado em Trendelenburg durante cerca de 30 min. Feito isso, o paciente é avaliado endoscopicamente sob a utilização de luz ultravioleta com o objetivo de discriminar locais de falha óssea em que a fluoresceína irá se apresentar com uma coloração amarelada. Vale ressaltar que a fluoresceína é passível de causar complicações, a exemplo de fraqueza em extremidades, convulsões, torpor e déficit de nervos cranianos, mas são complicações raras e reversíveis.

Classificação das fraturas de SF

Ainda nos dias atuais não dispomos de uma classificação universal para as FSF, porém alguns autores propõem algumas classificações baseadas na avaliação clínica, achados radiológicos, localização, extensão do trauma, grau de depressão da fratura e envolvimento do ducto nasofrontal[8,12,24,37]. Deste modo, temos a classificação de Gonty a qual classifica as fraturas em tipo 1, 2, 3 e 4 e seus subtipos (Quadro 1)[8]. Além disso, temos outras classificações mais diretas como a classificação proposta por Naidu et al.[37] em que as fraturas são dispostas em tipos A, B e C. A fratura tipo A envolve a parede anterior do SF, a tipo B envolve a parede posterior do seio e a tipo C acomete a região frontobasal, porém não compromete o SF[37]. Devido às diferenças anatômicas e o constante processo de desenvolvimento, os pacientes pediátricos possuem uma classificação própria, tal como a classificação proposta por Lopez et al.[22], na qual temos as fraturas classificadas em tipos I, II e III. Sendo assim, temos as fraturas tipo I nas quais é possível observar fraturas do osso frontal com base na calvária, sem extensão para a borda ou teto orbitário, as fraturas tipo II são fraturas do osso frontal estendendo-se até a borda supraorbitária e teto orbitário e, por fim, as fraturas tipo III que se apresentam como fraturas frontais com extensão caudal e/ou contralateral no terço médio da face, geralmente envolvendo a lâmina cribriforme, ossos nasais, complexo naso-órbito-etmoidal/zigomaticomaxilar, paredes orbitais medial ou inferior, seio em desenvolvimento ou via de saída nasofrontal (Quadro 1).

DISCUSSÃO

O tratamento da FSF varia da observação até o processo de cranialização do seio, o tratamento como um todo consiste basicamente no processo de redução da fratura e fixação óssea a qual pode necessitar de utilização de enxertos ósseos de osso parietal, gordura abdominal, fáscia temporal, pericrânio, fosfato de cálcio, hidroxiapatita e outros materiais, como prótese de polietileno prototipada e placas de titânio[3,11,12,19,26,31,34,38,48]. Deste modo, o tratamento da FSF deve ser realizado o quanto antes e ser pensado a partir da gravidade do trauma e o acometimento ou não das tábuas externa e interna, compartimento intracraniano e ducto nasofrontal[1,4,12,13,20,26,27,31,34,35,39,43,49]. As principais justificativas para o tratamento da FSF são proteção estrutural dos conteúdos intracranianos, isolamento do compartimento intracraniano do trato aerodigestivo, prover um seio funcional, restauração da função estética, prevenção de complicações de natureza infecciosa ou inflamatória pós-operatórias e redução do tempo de internamento[1,4,12,13,20,26,27,31,34,35,39,43,49]. O tempo até o tratamento é fator crucial para definir o prognóstico do paciente, pois o atraso

Quadro 1. Classificação de Gonty para FSF.

Tipo 1 – Fraturas da parede anterior
1. Fratura isolada da parede anterior
2. Acompanhada de fraturas do rebordo supraorbital
3. Acompanhada de fraturas do complexo nasoetmoidal
Tipo 2 – Fratura das paredes anterior e posterior
1. Fratura linear
a. Transversal
b. Vertical
2. Fraturas cominutivas
a. Envolvendo ambas as paredes
b. Acompanhada de fratura no complexo nasoetmoidal
Tipo 3 – Fratura de parede posterior
Tipo 4 – Fraturas cominutivas muito graves de toda a área frontal, envolvendo a órbita, a base nasal e o etmoide – Fratura do Seio Frontal "Through-and-Through"

Fonte: Castro et al.[9].

até a realização do mesmo em casos de indicação clara de conduta cirúrgica, maiores que 48 horas estão associadas ao maior risco de infecções severas. Além disso, fraturas com mais de 21 dias podem apresentar dificuldades no momento da redução, assim como fraturas com mais de 30 dias são tratadas como sequelas[5,19,36]. A profilaxia de infecções, a exemplo da meningite, têm se mostrado como um dos pilares para o tratamento, a profilaxia é realizada utilizando-se cefalosporinas de 3ª geração como Ceftriaxone 1g de 12/12h associado a vancomicina por via intravenosa; tal associação de fármacos torna-se necessária devido a crescente resistência bacteriana ao Ceftriaxone[19,36].

Ademais, a abordagem da FSF pode ser feita tanto por via aberta como por via endoscópica[10,45], esta última tem ganhado destaque nos últimos 20 anos devido à melhora da tecnologia que permeia a videoendoscopia, o acesso endoscópico pode ser realizado de forma transnasal, transorbital e transcraniana e é considerado o padrão-ouro para tratamento de falhas da base anterior do crânio[25,32,40,50]. A técnica endoscópica está atrelada a um tratamento menos invasivo com menores incisões, menor risco de complicações a exemplo das infecções, parestesia e cicatrizes, e uma melhor visualização intraoperatória em alguns casos, o que resulta em uma recuperação pós-operatória mais rápida e um resultado esteticamente satisfatório[17,21,24,40,50,51]. Devido à redução da visualização do seio em alguns casos, o método endoscópico sofre intensa variação devido a curva de aprendizado e experiência do cirurgião, sendo assim, trata-se de uma técnica desafiadora em casos de defeitos grandes e localizados muito lateralmente ou superiormente no SF[9,10,12,37,50]. Em casos de lesões grandes com anatomia desfavorável ainda são preferíveis as técnicas abertas com cranialização ou técnica de osteoplastia somada a obliteração do ducto nasofrontal, porém sabe-se que as técnicas abertas apresentam maiores taxas de complicações, sendo as principais de causa infecciosa ou obstrutiva. Sendo assim, há relatos na literatura de complicações em 10 a 17% dos pacientes, sendo a cefaleia crônica a complicação mais comum que se torna presente em cerca de 50% dos pacientes vítimas de trauma[24,27,50,51]. A abordagem endoscópica do SF pode ser planejada utilizando a classificação de sinusotomias de Wolfgang Draf, as quais podem ser divididas em 3 níveis sendo o segundo nível subdividido em A e B (Quadro 2). Deste modo, temos: Draf I: remoção completa das células etmoidais anteriores e processo uncinado que circunda o recesso frontal até o óstio do seio frontal; Draf II: ressecção do assoalho do SF do septo nasal até a lâmina papirácea, remoção da face anterior do recesso frontal; e Draf III: remoção da porção inferior do septo interfrontal, a parte superior do septo nasal, e o assoalho do SF entre as paredes mediais das órbitas[32,33,51]. Ademais, ambas as técnicas, tanto via endoscópica como via aberta, apresentam resultados satisfatórios e possibilitam a utilização de enxertos como gordura, pericrânio e substitutos sintéticos de dura-máter na presença de lesão dural[11] (Quadro 2).

Há uma grande controvérsia com relação ao tratamento específico, o qual deve ser empregado nos casos de FSF, mas

Quadro 2. Tabela de classificação das sinusotomias frontais de Wolgang Draf.

Tipo	Descrição
Draf I	Etmoidectomia anterior, sem instrumentação do seio frontal
Draf IIa	Limpeza de sinusotomia frontal padrão de tecido da lâmina papirácea até o corneto médio
Draf IIb	Abertura da lâmina papirácea ao septo
Draf III (Lothrop modificado)	Remoção do septo intersinusal frontal, bico frontal e septo superior, da lâmina papirácea para a lâmina contralateral

Fonte: Arnold e Tatum[33].

deve-se levar em conta que mais benefícios têm se mostrado em técnicas conservadoras. As técnicas mais agressivas, as quais têm como objetivo a cranialização do seio com enxerto de gordura e remoção de toda a sua mucosa rebatendo-a de modo a obliterar o ducto nasofrontal, ficam restritas a casos seletos em que haja fratura associada à lesão da pele e fragmentos ósseos insuficientes para realizar a reconstrução da tábua interna, devido à maior possibilidade de desenvolvimento de complicações pós-operatórias[9,11,25,28,32-34]. Nos últimos 30 ano,s têm-se observado a tendência por optarem por condutas mais conservadoras na grande maioria dos casos devido à maior conservação da forma, estética, função e drenagem do seio [10]. Outrossim, quando indicada a cirurgia, a mesma deve ser realizada o quanto antes visando a redução do risco de infecção, retração de cicatriz e distorção do esqueleto da face[10].

Fratura da tábua externa

O manejo da FSF de tábua externa é bem variado dentro das especialidades que a tratam e apresenta suas peculiaridades com relação aos níveis de acometimento[17]. As fraturas que cursam com pequenas irregularidades em adultos ou fraturas com moderada irregularidade em pacientes pediátricos podem ser tratadas de forma conservadora[10,22]. Sendo assim, em fraturas que apresentam deslocamento significativo, em geral maior que 2 mm, é sugerida a realização de cirurgia endoscópica sob anestesia geral ou local, porém atualmente a conduta conservadora é preferível para tais casos. Deve-se ponderar os riscos e benefícios da intervenção devido àpossibilidade de deslocamento do fragmento ósseo e agravamento do resultado estético[11,17,27]. A correção cirúrgica da fratura deve ser acompanhada de elevação e redução da mesma, seguida de elevação do periósteo e posicionamento de parafusos e miniplacas de titânio, porém alguns autores afirmam não ser necessária tal fixação, caso a fratura consiga ser reduzida a sua posição anatômica[10,12,18,24]. Ademais, em fraturas em que haja um deslocamento severo da tábua externa, geralmente > 6mm, ou fraturas cominutivas, está indicada a redução por via aberta e fixação interna para reduzir o risco de mucoceles e corrigir o deslocamento. Sendo assim, tal procedimento é realizado por meio de uma incisão hemicoronal ou bicoronal ou bitemporal ou em asa de borboleta para que seja visualizada toda a tábua externa e, assim, o seio seja copiosamente irrigado e a mucosa afetada excisada. Posteriormente, há a fixação dos fragmentos ósseos com microplacas bioabsorvíveis, vale ressaltar que tal procedimento está relacionado ao desenvolvimento de alopecia, atrofia do músculo temporal, parestesias e uma recuperação mais prolongada[10,11,19,23,27,32,34,35,40]. Algumas deformidades podem ocorrer no processo de reconstrução cirúrgica, devido à falha na organização dos fragmentos ósseos, atrofia do tecido ao redor devido ao trauma de alta energia e exposição das placas metálicas de fixação óssea. Assim, o intervalo de até 10 dias até a cirurgia de correção é crucial para um resultado estético satisfatório[17,24,31,36]. Nos casos em que haja uma depressão aparente da tábua externa, em geral de 4 a 6 mm, está indicada a técnica de "camuflagem" que consiste na inversão do fragmento ósseo como medida de reduzir o grau de depressão e melhorar o resultado estético para o paciente. Tal técnica está associada a redução ou ausência de necessidade de aplicação de enxertos e acesso direto ao SF para avaliação da perviabilidade do ducto nasofrontal, porém, apesar dos grandes benefícios, a mesma está atrelada a um alto custo o que torna sua aplicabilidade restrita a alguns serviços[12,27,40].

Fratura da tábua interna

Diferentemente das fraturas de tábua externa de SF, a fratura de tábua interna está condicionada a uma conduta cirúrgica mais agressiva, maior número de complicações e uma recuperação mais tardia do traumatizado. As FSF envolvendo a tábua interna estão comumente atreladas a um mecanismo de trauma mais severo e fratura concomitante de tábua externa. Sabe-se que a presença da lesão da tábua interna está extremamente relacionada a injúrias do sistema nervoso central e comunicação entre o SNC e a cavidade nasal. Além disso, há também relação com um maior tempo de tratamento com intensa dedicação ao manejo de complicações agudas[7,10]. Devido à maior severidade do quadro geral, trazido pela fratura de tábua interna, medidas drásticas são

propostas a exemplo da cranialização do SF[30], a qual é indicada na presença de fraturas com deslocamento maior que uma tábua ou > 6mm, ou fraturas envolvendo a tábua externa e interna, associado à impossibilidade de reconstrução de tábua interna ou fraturas acometendo uma área >25% da tábua interna[3,10,12,27,35]. A cranialização do seio consiste na remoção total da tábua interna, obliteração do ducto nasofrontal utilizando a mucosa presente no seio ou pericrânio, cauterização de toda mucosa do seio e reconstrução da base do crânio. Vale ressaltar que, o procedimento recebe tal nome por permitir que o lobo frontal ocupe a posição que antes pertencia ao SF[10,12], e que tal procedimento de correção da falha em vigência de lesão da dura-máter deve ser realizado num período de no máximo 3 a 4 horas devido ao aumento da proliferação bacteriana e maior predisposição a infecções[52]. Ademais, com o aumento das técnicas conservadoras para manejo das FSF é imprescindível que se cogite tal possibilidade, porém a conduta conservadora quando empregada na presença de acometimento de tábua interna está atrelada à necessidade de um acompanhamento intenso durante anos após o evento traumático, devendo ser indicada com cautela[10].

Fraturas associadas ao ducto nasofrontal

O ducto nasofrontal trata-se de uma estrutura tubular ou, em 85% dos casos, apenas um ósteo o qual se estende do SF até a região do meato médio e suas paredes são formadas por limites ósseos de estruturas anatômicas adjacentes; a grande importância dessa estrutura é a drenagem do SF propriamente dito[16]. As fraturas envolvendo o ducto nasofrontal podem ser observadas em 25 a 50% e podem ser cogitadas quando há o acometimento das células etmoidais, borda medial superior da órbita, teto da órbita, assoalho medial do SF, além de tomografia de crânio com sinais sugestivos de líquido dentro do seio[10,26,32]. As fraturas de ducto nasofrontal (FDNF) estão relacionadas a um maior número de complicações pós-operatórias quando comparados a grupos que não cursam com fratura de ducto nasofrontal[10,26,32]. Os ductos nasofrontais de formato tubular e de maior extensão apresentam maior suscetibilidade ao trauma. Tal fato é de extrema importância para o prognóstico do paciente já que quando obstruído o mesmo perde sua capacidade de drenagem, o que implica em chances expressivas de formação de mucoceles as quais expõem o paciente a um maior risco de desenvolvimento de meningite[16]. Portanto, as FDNF devem ser ponderadas no momento da escolha terapêutica do paciente, pois a maior predisposição a infecções e demais complicações leva a um prejuízo significativo no prognóstico do paciente. Na presença de trauma importante de tábua externa somado ao trauma do ducto nasofrontal deve se proceder com abertura do seio para correção da fratura e teste de patência do ducto nasofrontal, já nos casos de fraturas de tábua externa cominutivas menores que 4 mm, juntamente à fratura do ducto nasofrontal pode-se proceder com abordagem via endoscópica endonasal para correção da deformidade ductal[18]. Ademais, as FDNF não associadas a fraturas importantes de tábua interna e/ou externa, podem ser manejadas de forma conservadora, pois quando tratadas de forma expectante e associado a suporte medicamentoso com 4 semanas de antibióticos, corticoides orais e esteroides nasais tópicos, o restabelecimento da ventilação do SF ocorre em 71,4% dos pacientes, já com 6 semanas esses números atingem 88%[24,25,35].

Fechamento do seio frontal

O fechamento do SF deve ser feito de forma primorosa com uma escolha racional da técnica empregada para que se reduza a possibilidade de infecções e recidivas, além de defeitos estéticos[32]. Sendo assim, podem ser utilizados materiais como próteses prototipadas e enxertos ósseos de osso parietal, além de miniplacas de titânio, fios de mononylon e fios de titânio[11]. A presença de fístulas liquóricas em contato com cavidades contaminadas como a cavidade nasal, assim como acometimento do nervo óptico e órbita, predispõem ao desenvolvimento de infecções. Logo, é necessário que tais pacientes sejam operados dentro do período de 3 a 7 dias desde o seu diagnóstico, pois, infelizmente, as complicações por infecção não são incomuns dentro do ambiente intra-hospitalar. Nos casos em que há falhas maiores que 5 mm e formação de fístulas é válido utilizar uma técnica de reconstrução em três camadas, sendo elas intradural, epidural e extracraniana associada a enxerto de gordura, já os defeitos menores podem ser reparados usando técnica de duas camadas, sendo elas epidural e extracraniana[32]. É recomendado que se utilize uma inclinação de cabeceira de 30º associada ao uso de antibióticos com capacidade de transpassar a barreira hematoencefálica (BHE) e acetazolamida para manter a pressão intracraniana dentro dos níveis normais como medida de evitar recidivas[10,11,51].

Complicações da fratura de SF

As complicações da FSF estão diretamente relacionadas à presença de comorbidades no paciente, grau da lesão traumática e agilidade de execução do tratamento necessário[26]. Estudos, como o de Al-Moraissi et al.[26], apontaram que cerca de 7 a 11% dos pacientes apresentam complicações quando tratados cirurgicamente, já os pacientes com indicação de tratamento conservador complicam em cerca de 7% dos casos. Vale ressaltar que os pacientes submetidos à obliteração do SF cursam

com as maiores taxas de complicações encontradas, cerca de 10,6%[26]. A maior parte das complicações está relacionada à obstrução de um orifício de drenagem que foi preservado ou ao crescimento da mucosa do recesso frontal através de um orifício inadequadamente ocluído em um seio que foi obliterado[1]. Além disso, as complicações da FSF podem ser divididas temporalmente em transoperatórias, precoces e tardias, sendo assim, as complicações transoperatórias são representadas por sangramentos intracranianos, convulsões, danos neurológicos, formação de hematomas e lesões oftalmológicas. As complicações precoces ocorrem nos primeiros 6 meses após a FSF e correspondem a sinusites, fístulas liquóricas, meningites, irregularidades cosméticas, pneumoencéfalo, osteomielite, abscessos cerebrais e trombose do seio cavernoso. Por sua vez, as complicações tardias são aquelas que ocorrem 6 meses ou mais após lesão inicial, tendo como suas representantes mais expressivas a mucocele e mucopiocele[8,17,20,26,34-36,41].

Dentre as principais complicações transoperatórias temos a fístula liquórica que é definida como um vazamento persistente de fluido claro das narinas espontaneamente ou com inclinação da cabeça anteriormente por pelo menos 30 segundos que resulta da comunicação do espaço subaracnoideo com a cavidade nasal por meio de uma falha óssea na base do crânio[25,49,51], tal complicação normalmente se apresenta desde às 48 horas pós-injúria até 3 meses após[25]. As fístulas liquóricas impõem uma grande importância devido à dificuldade de realizar seu acesso cirúrgico[32] e à predisposição a gerar quadros de meningite de repetição. A fístula deve ser corrigida assim que detectada, pois quando detectada imediatamente no tempo intraoperatório e corrigida, as chances de fechamento da mesma são superiores a 90%, e quando consideramos uma reabordagem para revisão posterior as taxas de sucesso são superiores a 97%[25,43], além disso, algumas complicações podem ser ligadas com a presença de fístula liquórica como abscesso cerebral e mucocele[16].

Mucocele é uma das complicações mais frequentes, a qual ocorre devido à drenagem ineficaz do seio e pode se apresentar até anos após o trauma. Sendo assim, a mucocele resulta do crescimento da mucosa remanescente no seio e da sua produção de muco na condição de obstrução da drenagem, que deveria ser realizada pelo ducto nasofrontal, além disso, a secreção quando aprisionada pode ser infectada gerando quadros de mucopiocele e piocele[21,36,41]. Os sintomas da mucocele são benignos, a cefaleia é o sintoma mais comum encontrado neste quadro, já como outros sintomas menos comuns temos obstrução nasal, diplopia, coriza, edema na região frontal e estrabismo. O tratamento da mucocele consiste basicamente na remoção do foco infeccioso e restabelecimento da drenagem eficiente do seio, isso pode ser feito a partir da remoção completa da mucosa do seio somada à obliteração de ducto nasofrontal e, em alguns casos, cranialização do seio, porém estudos apontam taxas de recorrência de 6 a 25%[32,36].

Outra complicação da FSF é a osteomielite do osso frontal. Deste modo, esta é geralmente causada de forma secundária a um quadro de sinusite crônica. Após a introdução dos antibióticos no tratamento das fraturas de SF, as taxas de osteomielite têm decrescido de forma expressiva, sendo atualmente uma complicação rara. Ademais, o tratamento da osteomielite baseia-se no desbridamento do tecido necrótico como forma de melhorar a vascularização da região e, assim, permitir uma melhor cicatrização e penetração dos antibióticos. Posteriormente ao desbridamento pode-se realizar a reconstrução a partir de retalhos vasculares microcirúrgicos[36]. Além disso, temos a fratura de órbita com herniação da gordura orbital e aprisionamento dos músculos extrínsecos do olho, uma complicação grave, pois, além de levar a uma maior predisposição a infecções devido à exposição da órbita a cavidade nasal, a mesma tende a produzir uma limitação e distúrbios de mobilidade visual a curto e longo prazo[43].

CONCLUSÃO

A FSF ainda se mostra um grande desafio, pois quando tratada de forma incorreta ou em tempo inadequado a mesma está relacionada a um pior prognóstico e diversas complicações, como maior tempo de hospitalização, infecções e fístulas liquóricas. A literatura tem apontado para um melhor desfecho nos tratamentos conservadores em detrimento dos cirúrgicos. Além disso, a falta de uma classificação unificada para as FSF tanto em pacientes adultos quanto pediátricos gera uma variabilidade na tomada de decisão por parte do corpo de cirurgiões de diferentes centros de referência de tratamento. A falta de dados concretos a respeito do *follow-up* dos pacientes vítimas de FSF limita o conhecimento sobre a incidência das complicações tardias.

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Sexual Dysfunction After Traumatic Brain Injury: an integrative review

Disfunção Sexual Após Traumatismo Cranioencefálico: uma revisão integrativa

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ABSTRACT

Introduction: *Traumatic brain injury (TBI) is a major cause of morbidity and mortality in adults. Although sexuality issues following the lesions may cause a negative impact on rehabilitation, their epidemiological and treatment aspects are scarcely documented.* **Objective:** *This review intends to assess the published studies on aspects of sexuality related to TBI.* **Methods:** *This is an integrative review conducted in BVS and PubMed databases, during the period from 1980 and 2022, which presents the pathophysiology, incidence, methods of evaluation and treatment options of sexual dysfunction after TBI.* **Results:** *There are few studies evaluating sexuality and TBI relation, and the epidemiological aspects are controversial. Articles stress that discussing sexual issues with the patient is still a taboo and the best approach to be taken is yet undefined.* **Conclusion:** *Studies of sexuality in TBI patients are scarce, particularly on developing countries, such as Brazil. However, health professionals need to be aware of these matters, in order to better address the patient, improving his/her quality of life. Similarly, epidemiological studies on developing countries are of utmost importance.*

Keywords: *Traumatic brain injury; Sexuality; Sexual behavior*

RESUMO

Introdução: *O trauma cranioencefálico (TCE) é uma das principais causas de morbidade e mortalidade em adultos, podendo causar impacto negativo em aspectos relacionados à sexualidade.* **Objetivo:** *Nesta revisão, pretende-se avaliar os estudos publicados sobre aspectos da sexualidade em vítimas de TCE.* **Métodos:** *Trata-se de uma revisão integrativa realizada nas bases de dados BVS e PubMed, de 1980 a 2022, que apresenta a patofisiologia, incidência, métodos de avaliação e opções de tratamento para disfunção sexual após TCE.* **Resultados:** *Há escassez de estudos sobre sexualidade em doentes vítimas de TCE, não havendo acordo sobre sua incidência. Artigos demonstram que discutir esse assunto com os pacientes ainda é um tabu e a melhor abordagem para fazê-lo permanece indefinida.* **Conclusão:** *Os profissionais de saúde precisam estar cientes sobre tais problemas para melhor abordar o paciente, melhorando sua qualidade de vida. Estudos sobre sexualidade em TCE são necessários, especialmente os estudos epidemiológicos em países em desenvolvimento.*

Palavras-chave: *Traumatismo cranioencefálico; Sexualidade; Comportamento sexual*

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INTRODUCTION

Sexuality is an important aspect of human life and goes beyond the sexual act itself, involving psychological, physiological and social characteristics, which reflect the physical and mental health of people[1]. The term is not synonymous with intercourse and not merely the presence or absence of orgasm. Much more than that, it consists in a basic need, in thoughts, actions and interactions. Therefore, sexuality relates to physical and mental health, being an important marker of quality of life, motivating humans to seek satisfaction through contact, self-handling, welfare, orgasm, as well as by expressing affect and intimacy[2,3]. After a traumatic brain injury (TBI), sexuality can be compromised, causing remarkable alterations, and thus negatively influencing the quality of life[4]. However, this subject is rarely explored in the context of a person who suffered TBI, specially on non-developed and developing countries, where conversely, TBI is one of the leading causes of death and morbidity.

In Brazil, each year 500,000 people are hospitalized after TBI. A total of 75 to 100,000 people die a few hours after the event, whilst 70 to 90,000 progresses to an irreversible loss of some neurological function[5]. Due to its prevalence and the recognition of subtle disturbances even in patients with mild TBI, we decided to explore how sexuality is affected and addressed in such population. TBI can compromise both the "sexual performance" (in relation to physiological aspects of sexual performance) and the "sexual wellness" (which refers to the subjective sexual experience, for example, sexual satisfaction) of an individual[4]. Therefore, in this review we intend to assess those topics and to disclose the current status of sexual disorders after TBI, reporting the pathophysiology, incidence, methods of evaluation and treatment options.

METHODS

The studies in this review included original articles (Randomized Clinical Trials, Non-Randomized Clinical Trials, cohorts, case-control, cross-sectional, and case series studies). Review articles and meta-analyses were not included. The population of the studies was composed of adults. The articles selected contained data on epidemiology, pathophysiology, assessment tools, and treatment for sexual dysfunction related to TBI.

The literature research was performed comprising the period from January 1980 to December 2022, using the Medical Subjects Heading (MeSH) terms: "traumatic brain injury", "sexual dysfunction", "erectile dysfunction" and "sexuality" in Biblioteca Virtual em Saúde (BVS) database and Pubmed. Additional research based on these MeSH terms was made in the periodicals "The Journal of Sexual Medicine", "Archives of Sexual Behavior", "International Journal of Impotence Research", and "Journal of Sex Research".

Two authors (review), independently, reviewed the articles by title and abstract. The full text was obtained for the article whose title appeared to meet the inclusion criteria. The study authors then reviewed all of the full-text articles and independently determined whether they met the inclusion criteria. The disagreements were resolved by discussion.

It was performed a research of literature comprising the period from January 1980 to May 2022, in order to know the landscape of scientific literature on "post-trauma Sexual dysfunction traumatic brain injury." Literature review was performed in the Biblioteca Virtual em Saúde (BVS) crossing the keywords "Traumatismos encefálicos", "Disfunção sexual", "Função sexual", "Disfunção erétil", "Qualidade de vida" and "Sexualidade". In the PubMed database, we crossed the descriptors "Traumatic brain Injury", "Sexual dysfunction", "Sexual functioning", "Erectile dysfunction", "Quality of life", and "Sexuality". Moreover, we made a manual search on the periodicals "The Journal of Sexual Medicine", "Archives of Sexual Behavior", "International Journal of Impotence Research", and "Journal of Sex Research", crossing the same referred descriptors. A search for additional articles was also made looking for the reference of relevant articles papers. The selection of articles was made by reading the titles and abstracts, being an exclusion criterion those papers not related to sexuality on TBI, review papers, and those not written in English or Portuguese.

RESULTS

In the BVS search two articles in Portuguese were found, and both selected. A search on PubMed retrieved 203 articles in English, and 28 were selected. Three articles were retrieved from the pool for lack of relevance. In search of The Journal of Sexual Medicine four articles were found, and in the Archives of Sexual

Behavior, other three, but none had been selected. In search of the International Journal of Impotence Research and the Journal of Research, no article was found. At the end of the research, 33 articles were selected. These are analyzed in Table 1.

Pathophysiology

TBI can both, directly and indirectly, affect important aspects related to sexuality, after all, it involves different neurological parameters that include complex interactions between the neuroanatomical, neurochemical, neurophysiological, and neuropsychological systems. These contributions can be roughly distinguished in chemical messengers, spinal systems, brainstem-related structures, and cortical and subcortical systems[1,35].

Neurotransmitters such as dopamine have been associated with sexual desire by excitatory influences including the mesolimbic and mesocortical pathways. Serotonin has an inhibitory effect on sexual function, as extensions of the spine have a crucial role in the sexual response such as erection, ejaculation, fertility, and lubrication. The centers of the brainstem, which are important for alertness and arousal, play a role in the emotional and orgasm answers, enabling the excitement. Subcortical areas such as the hypothalamus and the pituitary gland are important structures involving the control and execution of human sexual response, through the action of hormones that are involved in reproduction, sexual desire, and also lubrication. Finally, the upper cortical regions, such as the limbic and frontal lobe and paralimbic regions are important for the regulation of sexual behavior[1,35].

Incidence

There is no consensus on the impact of changes in sexuality after TBI. Approximately 50-75% of individuals who have suffered TBI present cognitive and behavioral symptoms, and the consequences may occur even without motor or sensory sequelae, and the sexual behavior changes are serious complications[6]. The overall incidence of sexual disturbances in TBI patients vary from 29 to 60%[7-10,36,37]. Early after injury, sexual dysfunction is infrequent and occurs in less than 10% of patients[10].

Around 36-54% of sexual dysfunction after TBI is more prevalent in men with severe injuries. More than 50% of individuals suffering from TBI have decreased sexual arousal and women report more dyspareunia (genital pain during intercourse) and decreased vaginal lubrication. While men have more erectile and ejaculatory dysfunction, although, the prevalence is not well known[11,38].

One study investigated the incidence and types of sexual issues in men and women one year after TBI. The sample was comprised of 165 men and 58 women who have gone through the rehabilitation process and were living in their communities. Dissatisfaction with sexual functioning was reported (29%) mostly by men[12]. This finding was also reported by Gaudet et al.[13]. In another study, 255 people with TBI (187 men and 68 women), one year after the injury that underwent hospitalization and rehabilitation, and were living in the community were investigated. They concluded that the variables age, female gender, and having more serious injuries were associated with worse sexual dysfunction[14]. Both studies were prospective cohorts and used the scales Derogatis Interview for Sexual Functioning-Self-Report (DIFS-SR) and Global Sexual Satisfaction Index (GSSI).

However, not all studies report significant sexual dysfunction after TBI. A study examined the longitudinal changes in sexual functioning from 6 to 12 months after moderate and severe TBI through DIFS-SR and GSSI scales and evaluated 182 people (53 women and 129 men). After 6 months of trauma (72%) and 12 months after trauma (71%) subjects reported being satisfied with their sexual functioning, concluding that the sexual function and satisfaction appear to be stable in most of these subjects[39].

Risk factors and associated diseases

Sexuality can be influenced by neurological diseases and may lead to mood disorders, pain, paresis, loss of sensation, hypersensitivity, changes in sexual desire (which rarely happens to be hypersexuality, better known as an excessive sexual drive), anxiety, depression, musculoskeletal and self-image changes[38]. For example, lesions in the frontal region can generate apathy with decreased sexual desire, loss of pragmatic skills, self-neglect, and loss of interpersonal skills, interfering with sexual relationships. Different from what is stated above, a survey of 5 patients with high sex drive after TBI, states that this behavior is a complication that can occur after head injuries, and can be a source of great suffering for patients, partners, and close relatives[15].

The predictors generally reported of sexual dysfunction in TBI patients are older age, severe injuries, female gender, endocrine disorder, cognitive limitations, increased fatigue, depression, increased anxiety, changes in body image, motor limitations, and reduced self-esteem[14,16-18,40-42].

Table 1. Selected papers and data.

Author and date of publication	Paper	Journal	Study type (retrospective or prospective)	Study design (descriptive, cohort, cross-sectional or case-control)	Scales applied	Sample Size	Population group (mild, moderate or severe TBI)	Conclusions
Stolwyk et al.[4], 2011	Assessment of Sexuality Following Traumatic Brain Injury: Validation of the Brain Injury Questionnaire of Sexuality	The Journal of Head Trauma Rehabilitation	Retrospective	Cross-sectional	Brain Injury Questionnaire of Sexuality (BIQS), Derogatis Interview for Sexual Functioning-Self-Report version (DISF-SR).	865 (608M:257F)	Mild, moderate and severe	The study results reinforce the reliability and validity of BIQS as a measuring tool for future research
Ter Mors et al.[6], 2012	Evaluation of electrical aversion therapy for inappropriate sexual behaviour after traumatic brain injury: a single case experimental design study	BMJ Case Reports	Prospective	Descriptive	Analysis through behavioral observations	1 (1M:0F)	Severe	The EAT (Electrical aversion therapy) it was effective in a patient with inappropriate sexual behavior did not improve with conventional treatments
Ponsford[7], 2003	Sexual changes associated with traumatic brain injury	Neuropsychological Rehabilitation	Retrospective	Case-control	Structured questionnaire	208 (144M:64F)	Moderate and severe	Victims of TBI reported reduction of opportunities to have sexual activity, decline in ability to give sexual satisfaction to the partner, decreased libido, self-confidence, communication and quality in the relationship with sexual partner
Sandel et al.[8], 1996	Sexual functioning following traumatic brain injury	Brain Injury	Retrospective	Cross-sectional	Derogatis Interview of Sexual Function (DISF): Orgasm and Drive/Desire	52 (39M:13F)	Mild, moderate and severe	Patients with lesions in the frontal lobe and right hemisphere reported higher levels of satisfaction and sexual functioning than those with other injuries, and patients with more recent injuries reported higher arousal levels than those with longer lesions
O'Carroll et al.[9], 2001	Psychosexual and psychosocial sequelae of closed head injury	Brain Injury	Retrospective	Cross-sectional	Golombok Rust Inventory of Sexual Satisfaction-(GRISS), General Health Questionnaire (GHQ), Hospital Anxiety and Depression Scale (HAD)	36 (30M:6F)	Moderate and severe	Of patients suffering from TBI studied, 61% were classified with degrees of emotional distress, with a prevalence of symptoms of anxiety and depression that bring psychosocial and psychosexual losses

Table 1. Continued...

Author and date of publication	Paper	Journal	Study type (retrospective or prospective)	Study design (descriptive, cohort, cross-sectional or case-control)	Scales applied	Sample Size	Population group (mild, moderate or severe TBI)	Conclusions
Aloni et al.[10], 1999	Incidence of sexual dysfunction in TBI patients during the early post-traumatic in-patient rehabilitation phase	Brain Injury	Retrospective	Cross-sectional	Interdisciplinary assessment team and structured interview	44 (44M:0F)	Severe	It is suggested that sexual dysfunction in TBI patients that appear during later stages of recovery, are probably related behavioral changes
Kreutzer et al.[11], 1989	Psychosexual consequences of traumatic brain injury: methodology and preliminary findings	Brain Injury	Retrospective	Cross-sectional	Systematic observation	21 (21M:0F)	Mild, moderate and severe	Male patients TBI victims have negative changes in sexual behavior, including decreased sexual desire, erectile function and frequency of sex, and emotional changes, including depression, decreased self-esteem and decline in personal sex appeal
Sander et al.[12], 2012	Sexual Functioning 1 Year After Traumatic Brain Injury: Findings From a Prospective Traumatic Brain Injury Model Systems Collaborative Study	Archives of Physical Medicine and Rehabilitation	Prospective	Cohort	Derogatis Interview for Sexual Functioning-self-report (DISF-SR), Global Sexual Satisfaction Index (GSSI), structured interview regarding changes in sexual functioning, comfort level discussing sexuality with health care professionals	223 (165M:58F)	Moderate and severe	TBI victims with one-year injury time, living in their communities, had sexual difficulties after the evaluations. Thus, it is important to carry out interventions to improve the quality of sexual life of these people
Gaudet et al.[13], 2001	Self-reported consequences of traumatic brain injury: a study of contrasting TBI and non-TBI participants	Sexuality and Disability	Retrospective	Cross-sectional	Two Likert-type questionnaires: affective and behavioral	50 (26M:24F)	Mild, moderate and severe	TBI patients report having concerns about their cognition and aspects of sexuality, and men have greater concern

Table 1. Continued...

Author and date of publication	Paper	Journal	Study type (retrospective or prospective)	Study design (descriptive, cohort, cross-sectional or case-control)	Scales applied	Sample Size	Population group (mild, moderate or severe TBI)	Conclusions
Sander et al.[14], 2013	Predictors of Sexual Functioning and Satisfaction 1 Year Following Traumatic Brain Injury: A TBI Model Systems Multicenter Study	Journal Of Head Trauma Rehabilitation	Prospective	Cohort	Derogatis Interview for Sexual Functioning-Self-Report (DISF-SR), Global Satisfaction With Sexual Functioning (Global Sexual Satisfaction Index), Participation Assessment With Recombined Tools-Objective, Patient Health Questionnaire-9	255 (187M:68F)	Moderate and severe	The elderly and women appear to be at greater risk of sexual dysfunction after TBI and may benefit from assessment and specialist treatment services. They were identified relations between social participation and sexual function and between depression and sexual satisfaction, which can serve as indicators for future clinical assessments and interventions
Hanks et al.[10], 2013	Changes in Sexual Functioning From 6 to 12 Months Following Traumatic Brain Injury: A Prospective TBI Model System Multicenter Study	Journal of Head Trauma and Rehabilitation	Prospective	Cross-sectional	Derogatis Interview for Sexual Functioning-Self-Report (DIFS-SR), Global Sexual Satisfaction Index (GSSI)	182 (129M:53F)	Moderate and severe	Sexual function and sexual satisfaction may be stable in most of the victims of TBI, a fact that reinforces the importance of further studies in this field
Eghwrudjakpor et al.[15], 2008	Hypersexual Behavior Following Craniocerebral Trauma– an Experience with Five Cases	Libyan Journal Of Medicine	Prospective	Cross-sectional	Analysis through behavioral observations	5 (4M:1F)	Moderate and severe	Excessive sexual drive is a complication that can occur after head injuries, can be a source of great suffering for patients and people with whom they share significant relationships
Strizzi et al.[16], 2015	Sexual functioning, desire, and Satisfaction in women with TBI and healthy controls	Behavioural Neurology	Prospective	Case-control	Sexual Quality of Life Questionnaire (SQoL), Female Sexual Functioning Index (FSFI), Sexual Desire Inventory (SDI), Sexual Satisfaction Index (ISS)	29 (0M:29F)	Moderate and severe	Women victims of TBI have reduced sexual desire, arousal, orgasm, sexual satisfaction and lubrication, compared to healthy women

Table 1. Continued...

Author and date of publication	Paper	Journal	Study type (retrospective or prospective)	Study design (descriptive, cohort, cross-sectional or case-control)	Scales applied	Sample Size	Population group (mild, moderate or severe TBI)	Conclusions
Moreno et al.[17], 2015	The Relationship Between Postconcussion Symptoms and Sexual Quality of Life in Individuals with Traumatic Brain Injury	Sexuality and Disability	Retrospective	Case-control	Sexual Quality of Life Questionnaire, and postconcussion symptoms with the Post-concussion Symptom Scale.	41 (18M:23F)	Moderate and severe	The current study shows that sexual quality of life is significantly lower in individuals with TBI than in matched healthy controls, and that there is a strong association between sexual quality of life and postconcussion symptoms in individuals with TBI.
Hibbard et al.[18], 2000	Sexual dysfunction after traumatic brain injury	NeuroRehabilitation	Retrospective	Case-control	Semi structured interview	322 (193M:129F)	Moderate and severe	Individuals with TBI have physiological and emotional problems that impair sexual performance. The TBI men reported more difficulties to sustain an erection and symptoms of depression, while women reported more difficulty becoming sexually aroused, pain during sex or masturbation, hormonal changes and vaginal lubrication and depression
Downing et al.[19], 2013	Sexual changes in individuals with traumatic brain injury: a control comparison	The Journal Of Head Trauma Rehabilitation	Retrospective	Case-control	Brain Injury Questionnaire of Sexuality (BIQS), Hospital Anxiety and Depression Scale, Rosenberg Self-Esteem Scale	865 (608M:257F)	Moderate and severe	There was a significant difference related to sexual performance among participants with TBI and healthy, as after TBI subjects reported depression, anxiety, decreased self-esteem, fatigue, low confidence, pain and decreased mobility
Ponsford et al.[20], 2013	Factors associated with sexuality following traumatic brain injury	The Journal Of Head Trauma Rehabilitation	Prospective	Case-control	Brain Injury Questionnaire of Sexuality (BIQS), Hospital Anxiety and Depression Scale, Rosenberg Self-Esteem Scale	986 (676M: 310F)	Moderate and severe	Victims of TBI, sexual dysfunction most often are associated with depression, loss of self-esteem, social barriers to participation, reduction of sexual contact opportunities and impaired independence
Simpson et al.[21], 2013	Prevalence, clinical features, and correlates of inappropriate sexual behavior after traumatic brain injury: a multicenter study	The Journal Of Head Trauma Rehabilitation	Prospective	Cross-sectional	Overt Behavior Scale, Disability Rating Scale, Sydney Psychosocial Reintegration Scale-2, Health of the Nation Outcome Scale-Acquired Brain Injury, Care and Needs Scale	500 (250M:257F)	Severe	The prevalence and clinical characteristics of inappropriate sexual behavior. They represent a complex clinical challenge between a minority of patients with severe TBI

Table 1. Continued...

Author and date of publication	Paper	Journal	Study type (retrospective or prospective)	Study design (descriptive, cohort, cross-sectional or case-control)	Scales applied	Sample Size	Population group (mild, moderate or severe TBI)	Conclusions
James and Young[22], 2013	Clinical correlates of verbal aggression, physical aggression and inappropriate sexual behaviour after brain injury	European Journal Of General Practice	Retrospective	Cross-sectional	Brain Injury Rehabilitation Trust (BIRT), Aggression Rating Scale, complementary measures of inappropriate sexual behavior	152 (114M:38F)	Mild, moderate and severe	Verbal aggression, physical aggression and inappropriate sexual behavior after an acquired brain injury (TBI among them) seem to reflect clinical phenomena separate instead of general deregulation of behavior.
Goldin et al.[23], 2014	Sexual Functioning and the Effect of Fatigue in Traumatic Brain Injury	Journal of Head Trauma Rehabilitation	Prospective	Case-control	Fatigue Assessment Instrument, Global Fatigue Index, Beck Depression Inventory, SF-36 Health Survey.	220 (115M:105F)	Mild, moderate and severe	Fatigue affects more the performance of sexual activity for men and women with TBI than for those without brain injuries
Simpson et al.[24], 1999	Sex offen-ding as a psychosocial sequela of traumatic brain injury	The Journal Of Head Trauma Rehabilitation	Retrospective	Cross-sectional	Protocol to record data on demographic, injury, radiological and psychosocial variables and offensive behavior	445 (363M:82F)	Not specified	Sexual crimes are a significant clinical problem among a small minority of men after TBI (6.5% - n = 29)
Simpson and Long[25], 2004	An evaluation of sex education and information resources and their provision to adults with traumatic brain injury	The Journal Of Head Trauma Rehabilitation	Prospective	Cross-sectional	Two protocols with closed questions	49 (15M:34F)	Not specified	The resources of the sex education program were positively assessed by rehabilitation agencies and the community as a means to provide education and information to meet the sexual health concerns of people with TBI
Gill et al.[26], 2011	Exploring Experiences of Intimacy From the Viewpoint of Individuals With Traumatic Brain Injury and Their Partners (não possui os dados que buscamos)	The Journal Of Head Trauma Rehabilitation	Retrospective	Cross-sectional	Semi structured interview	18 (12M:6F)	Not specified	After TBI can occur commitments related to sexuality, so health workers should be educated about the difficulties that the victims and their partners may have, and how to make appropriate referrals to help them.

Table 1. Continued...

Author and date of publication	Paper	Journal	Study type (retrospective or prospective)	Study design (descriptive, cohort, cross-sectional or case-control)	Scales applied	Sample Size	Population group (mild, moderate or severe TBI)	Conclusions
Yang et al.[27], 2018	Risk of Erectile Dysfunction After Traumatic Brain Injury: A Nationwide Population-Based Cohort study in Taiwan	American Journal of Men's Health	Retrospective	Cohort	Not specified	72,642 male patients who were diagnosed with TBI, and 217,872 patients without TBI	Mild, moderate and severe	patients with TBI are associated with a high risk of developing subsequent ED especially organic ED, in comparison to the controls
Downing et al.[28], 2018	Sexuality in individuals with traumatic brain injury and their partners.	Neuropsychological Rehabilitation	Retrospective	Cross-sectional	Derogatis Interview for Sexual Function—Self-Report (DISF-SR)	55 couples	Mild, moderate and severe	It appears that individuals with TBI experience significant negative changes in sexual function, including problems with lubrication, as well as reduced sexual arousal.
Bivona et al.[29], 2016	A biopsychosocial analysis of sexuality in adult males and their partners after severe traumatic brain injury	Brain Injury	Retrospective	Cross-sectional	Sexual life was assessed with the Sexuality Evaluation Schedule Assessment Monitoring (SESAMO)	Twenty males with a history of severe TBI and 20 healthy controls (HC) and their respective partners	Severe	sexual life can be adversely affected in males after severe TBI for both survivors and their partners. However, sexual dysfunction is only one part of the sexual difficulties observed in survivors
Moreno and McKerral[30], 2017	Towards a taxonomy of sexuality following traumatic brain injury: A pilot exploratory study using cluster analysis	Neurorehabilitation	Retrospective	Cross-sectional	Sexual Quality of Life Questionnaire. and Sexual Desire Inventory (SDI-2	19 M:23F	Mild, moderate and severe	The group of individuals with TBI showing sexual problems was older, showed lower levels of sexual quality of life and sexual desire, with significant symptoms of anxiety and depression.
Bellamkond and Zollman[31], 2014	Relationship Between Employment Status and Sexual Functioning After Traumatic Brain Injury	Brain injury	Retrospective	Cross-sectional	Derogatis Interview for Sexual Functioning Self Report (DISF-SR) sum and sub-scale scores, Global Sexual Satisfaction Index (GSSI).	95 M: 37F	mild, moderate or severe	The results of this study show a relationship between lower quality sexual functioning and satisfaction in persons with TBI and concomitant unemployment or lower annual income.

Table 1. Continued...

Author and date of publication	Paper	Journal	Study type (retrospective or prospective)	Study design (descriptive, cohort, cross-sectional or case-control)	Scales applied	Sample Size	Population group (mild, moderate or severe TBI)	Conclusions
Simpson et al.[32], 2001	Social, Neuroradiologic, Medical, and Neuropsychologic Correlates of Sexually Aberrant Behavior After Traumatic Brain Injury: A Controlled Study	The Journal of Head Trauma Rehabilitation	Retrospective	Case control	Not specified	25 males with f sexually aberrant behavior (SAB) after traumatic brain injury (TBI) and 25 males in control group	mild, moderate or severe	In the assessment, no relevant risk factors for the development of SAB were identified
Anto-Ocrah et al.[33], 2019	Risk of Female Sexual Dysfunction Following Concussion in Women of Reproductive Age	Brain Injury	Prospective	Cohort	Brain Injury Questionnaire on Sexuality (BIQS)	31 female	mild TBI (concussion)	Our results suggest that women who have a concussion have a significantly increased risk of sexual dysfunction compared to those who have an extremity injury. A history of previous concussions was also associated with current sexual dysfunction, further substantiating our hypothesis that concussion is associated with decreased sexual functioning.
Sander et al.[34], 2016	Multicenter Study of Sexual Functioning in Spouses/ Partners of Persons With Traumatic Brain Injury.	Archives of Physical Medicine and Rehabilitation	Retrospective	Cross sectional	Derogatis Interview for Sexual Functioning Self-Report; Global Sexual Satisfaction Index	70 couples	mild, moderate or severe	Worse sexual functioning in spouses/partners was associated with older age and with worse sexual functioning in persons with TBI.

A study compared the sexuality of individuals with TBI and healthy people matched for age and sex with 865 participants with moderate to severe TBI were compared with 142 healthy people. A significant difference between participants with TBI and healthy people was found because the subject after TBI reported depression, anxiety, reduced self-esteem, fatigue, low confidence, pain and decreased mobility[19]. In another study, 986 moderate to severe TBI patients were evaluated. Those patients with sexual dysfunction, in most cases, presented with depression, loss of self-esteem, barriers to social participation, reduction of sexual opportunities, and impaired independence[20]. Both studies used the Brain Injury Sexuality Questionnaire (BISQ), Hospital Anxiety and Depression Scale, and Rosenberg Self-Esteem Scale.

In another study, 507 subjects with severe TBI were evaluated through the Overt Behavior Scale, Disability Rating Scale, Sydney Psychosocial Reintegration Scale-2, Health of the Nation Outcome Scale-Acquired Brain Injury, and Care and Needs Scale. The authors reported that occurred inappropriate sexual talk in 57.9% of cases, followed by touching and non-touching genital behavior (29.8%), and exhibitionism/public masturbation (10.5%)[21].

In order to explore the relationships between verbal aggression, physical aggression, and inappropriate sexual behavior after TBI, a study reviewed 77 people that were hospitalized after Acquired Brain Injury (ABI), mostly caused by TBI (66%). The patients were evaluated with the Brain Injury Rehabilitation Trust (BIRT) and Aggression Rating Scale during hospitalization. They concluded that 46 of the 77 participants had verbal aggression, 26 showed aggressive behavior and 26 had inappropriate sexual behavior, however, no correlation between sexual disturbance and aggressive behavior was found[22].

A recent study evaluated 200 adults from a community who suffered mild TBI and 83 subjects without brain injury. The aim was to examine specific aspects of sexual functioning (like frequency, desired frequency, importance, and satisfaction) and its relationship with fatigue. They applied the Fatigue Assessment Instrument, Global Fatigue Index, Beck Depression Inventory, and SF-36 Health Survey. As a result, we have that several aspects of sexual activity (frequency, desired frequency, and importance) were closely related to the specific features of fatigue among individuals with TBI. Women with TBI reported less frequent and minor sex than men. In subjects without brain damage, the impact of fatigue was limited to the frequency of sexual activity, with no differences between the sexes. The authors concluded that fatigue plays a different role in the subjective experience of sexual activity for men and women with TBI than for those without brain damage[23].

The Forensic Psychiatry has also studied this subject, reporting that individuals after TBI have more convictions for sexual offenses such as pedophilia, exhibitionism, and compulsive sexual behavior[38]. In a study evaluating 447 criminals with TBI, 6.5% (n = 29) committed some form of sexual crime[24].

Assessment

Sexual disorders after TBI is little discussed in the scientific literature and are complex to be evaluated[38]. There are relationships between social participation and sexual function and between depression and sexual satisfaction, which can serve as clinical indicators for further evaluation and intervention. However, more research is needed to elucidate these relationships and to identify effective clinical approaches[14].

Given the importance and difficulty of identifying and effectively managing the issues of sexuality after TBI, an Australian study recruited 865 people who had suffered traumatic brain injury to participate in the validation of the "Brain Injury Questionnaire of Sexuality," a tool that assesses problems of sexuality after TBI. The evaluation method consists of applying a questionnaire with 18 questions that compare sexual activity before and after the injury[4].

Another study evaluated the features designed to meet the sexual health concerns of people with TBI in two different multidisciplinary services; 37 subjects who had suffered trauma within the past 12 months and living in the community, answered two protocols with closed questions. The result is that the services showed attention to sexual health concerns of individuals through Sex Education (guidelines and monitoring issues related to sex, free from prejudices and taboos). In addition, they found that the 4 issues most addressed were: what is sexuality, which is sexual dysfunction, such as meeting people, and how to work the sexual adjustment issues in the context of relations after TBI[25].

In a study evaluating 223 subjects (165 men and 58 women) who were admitted, discharged, and were living in the community, the scales applied were Derogatis Interview for Sexual Functioning-self-report (DISF-SR), Global Sexual Satisfaction Index (GSSI), and a structured interview referring changes in sexual functioning. The results showed that 68% of patients would talk freely about issues of sexual difficulties with health professionals, while the rest

would talk only if asked, or not enter this subject. This reinforces the importance of providing education and information to address sexual concerns of people with TBI and education regarding the impact of TBI on intimacy should be integrated into rehabilitation[12]. A conclusion was also reached by another recent study[43].

Treatment

There's no consensus on treatment for the different types of sexual dysfunction. One study reported the results of a functional analysis that showed inappropriate sexual behaviors exhibited by a boy, 9 years old, who had been diagnosed with TBI. They found a significant improvement after an intervention consisting of functional communication training and the extinction of inappropriate behavior[44].

The two strategies most used in the treatment of excessive sexual drive after TBI are psychotherapy, with an emphasis on the cognitive-behavioral model, and when this does not present satisfactory results, it is added a pharmacological approach, which often includes selective serotonin reuptake inhibitors, such as citalopram[15].

It is also suggested as a treatment, through the description of a clinical case, that "Electrical aversion therapy" (EAT) is a behavioral treatment option that can be used in people with severe TBI, including behavioral changes, and inappropriate sexual behavior, when other therapies are not effective[6].

Another study sought to explore through qualitative interviews intimacy experience from the point of view of 18 couples in which the companion suffered TBI (average of 4 years after injury) and living in the community with their partners. Factors that were perceived that helped the relationship were: unconditional commitment, spending time together, open communication, facing the difficulties caused by injury together, social support, family ties, spirituality, and the experience of overcoming difficulties. Factors that were perceived as barriers to intimacy included: emotional reactions to change, sexual difficulties, conflict and tension in the social role, family issues, social isolation, and communication problems. Thus, the study concludes that health professionals should be sensitized to the needs that people with TBI and their partners have about intimacy and how to make appropriate referrals to help them[26].

Another study explored the perceptions and experiences of rehabilitation professionals to discuss sexuality with users who have TBI. It included 24 professionals (6 men and 18 women) in two medical institutions treating victims of TBI. In each institution, arrangement was in 4 focus groups, using a semi-structured interview schedule. Focus group data were transcribed and analyzed using thematic analysis. Six main themes were obtained from the analysis: 1) Sexuality after TBI is a matter of expertise: this item refers to the participants' perception that sexuality is a topic that requires specialized knowledge, skills, and training. Sometimes the lack of knowledge, skills, and experience prevented the professional to open sexuality discussions; 2) Sexuality is a sensitive subject: the subject relates to the participants' perception that sexuality is a delicate issue that needs to be approached carefully to avoid discomfort; 3) Practical aspects of discussing sexuality: this theme refers to 'difficulty' (with a questionnaire, explanatory material, individually or in groups?), 'when' (beginning, middle, end of treatment or when the person bringing the theme?) and 'where' (in the institution?) to raise issues of sexuality with the victims; 4) Roles and responsibilities: this theme refers to the aspect of professionals putting or not putting themselves in the role to address the issue; 5) Dilemmas about risks and vulnerabilities: this theme refers to the risks and vulnerabilities that the subject can be placed if the sexuality issues are not addressed, for example, risks associated with sexual exploitation and unprotected sex; and 6) Organizational and structural issues: This theme refers to the organization and structure that offers the service to address the issue[43].

CONCLUSION

The incidence of TBI with sexual changes varies among studies as well as if sexual problems occur more frequently in men or in women, or whether the excessive sexual drive is common or not. It was noted that the greater the severity of the lesion and the age of the person, the greater the risk of developing sexual difficulties. As for evaluation, professionals lack instruments that can be used to evaluate and to conduct sexuality issues related to TBI, and usually do not address these problems.

Unfortunately, the study and intervention of sexual dysfunction after TBI is still a neglected field in literature, and sexuality issues remain largely unsolved through the rehabilitation process, especially in non-developed and developing countries. Further studies are necessary to elucidate the sexual dysfunctions presented by the affected population, in order to allow the advent of new treatment strategies that address their needs, thus enhancing sexual satisfaction and improving quality of life.

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Spontaneous Spinal Epidural Hematoma: a descriptive systematic review

Hematoma Epidural Espinhal Espontâneo: uma revisão sistemática descritiva

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ABSTRACT

Spontaneous Spinal Epidural Hematoma (SSEH) is rare, with unknown etiology and devastating potential. Also, it is a pathology of difficult diagnosis, the exact knowledge of signs and symptoms is fundamental to allow a good prognosis. A systematized review of the literature was performed selecting articles published until 2021 in Pubmed, Embase, Web of Science, and Scopus databases about SSEH resulting in 2325 clinical studies related to the main diagnosis, and its etiologies, treatments and outcomes were described. A thorough search of these articles suggests that vascular malformations, anticoagulant therapy, neoplasms, and previous spinal surgery are the most common causes of SSEH and the main diagnostic method of SSEH is a thorough patient history and imaging studies, mainly MRI. Moreover, surgical treatment is indicated for most of cases, consisting of surgical decompression and hematoma evacuation, with conservative treatment recommended for fewer, selected cases with pieces of evidence suggesting that surgical timing influences the prognosis.

Keywords: *Spinal epidural hematoma; Spinal hematoma; Spontaneous hematoma; Spontaneous spinal hematoma; Spontaneous spinal epidural hematoma*

RESUMO

O hematoma epidural espinhal espontâneo (HEEE) é raro, com etiologia desconhecida e potencial devastador. Além disso, é uma patologia de difícil diagnóstico, sendo fundamental o conhecimento exato dos sinais e sintomas para permitir um bom prognóstico. Realizamos uma revisão sistemática da literatura selecionando artigos publicados até 2021 nas bases de dados da Pubmed, Embase, Web of Science e Scopus sobre HEEE resultando em 2325 estudos clínicos relacionados ao diagnóstico principal, em que foram descritas etiologias, tratamentos e desfechos. Uma busca minuciosa desses artigos sugere que malformações vasculares, terapia anticoagulante, neoplasias e cirurgia espinhal prévia são as causas mais comuns de HEEE. O principal método diagnóstico de HEEE é uma história completa do paciente e exames de imagem, principalmente a ressonância magnética. Além disso, o tratamento cirúrgico é indicado para a maioria dos casos, consistindo em descompressão cirúrgica e evacuação do hematoma, com tratamento conservador recomendado para poucos casos selecionados com evidências, sugerindo que o tempo cirúrgico influencia o prognóstico.

Palavras-Chave: *Hematoma epidural espinhal; Hematoma espinhal; Hematoma espontâneo; Hematoma espinhal espontâneo; Hematoma epidural espinhal espontâneo*

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INTRODUCTION

Spontaneous spinal epidural hematoma (SSEH) is a rare, acute condition, with an incidence of 0.1 per 100,000/year[1,2]. SSEH is caused by the accumulation of blood in the epidural space, which can mechanically compress the spinal cord[3,4]. Since the first case of SSEH in the 19th century, more than 600 cases with various aetiologies have been reported in the literature[5-7] and, in cases where progressive neurological deficits appear, urgent neurosurgical evacuation of the hematoma and spinal cord decompression may be required[8,9]. Comprehensive and broad reviews of this diagnosis are relatively lacking in the literature. Our aim is to conduct a thorough review of the literature in order to address the main scientific evidence on SSEH and summarize the main diagnosis, treatments, and outcomes of this disease.

MATERIALS AND METHODS

Our review was based on the guiding question: "what are the most relevant aspects in pathophysiology, diagnostics, treatment, and outcomes in relation to the spontaneous spinal epidural hematomas in the general population?" A comprehensive literature review was performed using Pubmed, Embase, Web of Science, and Scopus databases using as keywords: "spontaneous spinal hematoma" OR "spontaneous spinal epidural hematoma." Information collecting included etiology, pathophysiology, clinical signs and symptoms, diagnosis, treatments, and outcomes.

Eligibility criteria considered involved all articles in English from current literature. Letters to the editor and commentaries were excluded from the review. Studies involving hematomas occurring after trauma, epidural anesthesia, lumbar puncture, or surgery, SSEH in association with subdural and/or spinal subarachnoid hemorrhage, or vertebrae or spinal canal tumors were excluded.

The search strategy revealed a total of 5551 initial articles, with 1612 being excluded due to duplications. A total of 3939 articles were selected by title by a reviewer (SB), excluding 2325. Two reviewers (SB and JM) performed the analysis and extraction of data following abstract and full-text of 1614 remaining articles, with disagreements of inclusion settled by a senior author (DZ). After this final selection, a total of 18 references were included in this review.

RESULTS

Although etiology of SSEH has not been completely elucidated, a number of factors such as hypertension, anticoagulation therapy, straining, sneezing, lifting, coagulation disorders, cavernous angiomas, and spinal vascular anomalies have been hypothesized to predispose to SSEH[1,4,7]. In a meta-analysis of 613 patients with spinal hematoma it was verified that in approximately a third of the cases, no etiological factor can be identified as the cause of the bleeding[5]. Bleeding diathesis and arterial hypertension are conditions often associated with SSEH, however, the pathogenesis of those conditions remains obscure[10]. Coagulation disorders, arteriovenous malformations, antiplatelet therapy, surgery trauma, and conditions causing increased intrathoracic-intra-abdominal pressure (coughing, Valsalva maneuver) may act as predisposing factors[1,6,11].

The pathogenesis and bleeding mechanism of SSEH are still unclear. However, two mechanisms for the development of SSEH have been considered in the literature: the rupture of epidural vessels, and hemorrhage from vascular anomalies[5,7]. The most widely accepted hypothesis is that spinal hematoma is caused by rupture of epidural veins (venous bleeding)[5]. The pathophysiological mechanism involves a *locus minoris resistentiae* that ruptures upon transmission of increased intra-abdominal or intrathoracic pressure due to its connection with the valveless veins of epidural venous plexus. Since epidural veins are valveless, they have no protection against the variations of abdominal or thoracic veins' pressure[5,7]. Some researchers see the epidural venous plexus as an alternative path for blood amid the inferior and superior vena cava, which explains why there is a vascular bed that is much larger than would be necessary for the perfusion of the meninges alone[5]. In cases of increased intrathoracic or intra-abdominal pressure, this alternate route is utilized. If such pressure variations operate on acquired or congenital abnormalities of vascular walls, a place of less resistance (*locus minoris resistentiae*), rupture can occur[5,12]. Epidural veins' rupture could happen during coughing, sneezing, defecation, coitus, straining (e.g. lifting of weights), pregnancy, and intrapartum in newborns[5,7]. However, these insignificant physiological processes are numerous in daily life,

and the relative development of SSEH in these straining-associated activities is rare[5,7].

Alternatively, another hypothesis is that SSEH may be originated from an arterial hemorrhage, since the venous plexus pressure is lower in the epidural space, theoretically insufficient to cause a hematoma, as proposed by Beatly and Winston, mainly at the cervical level[12]. Most SSEH are localized in the dorsal portion of epidural space and this supports the hypothesis of venous bleeding because the internal epidural venous network consists of a more prominent dorsal and a smaller ventral part, whereby the ventral portion is partially covered by the posterior vertebral longitudinal ligament and separated from the epidural space[5].

However, the "venous hypothesis" will be unlikely to be applicable in the cervical region. Firstly, venous pressure is lower than intrathecal pressure[13]. Secondly, the cervical epidural hematoma usually produces rapid deterioration[13]. Anastomotic arteries that run in the epidural space and are also connected with radicular arteries are a possible origin for arterial bleeding[13]. The pressure of arterial bleeding is sufficient to compress the spinal cord, and such bleeding would likely not be tamponade by the counter-pressure of the thecal sac[14]. Prior literature has shown that the more mobile segments of the cervical spine (C6-C7) were the most common sites of hemorrhage, in which movement at this level might stretch the arteries beyond their limits, leading to rupture, thus making this a common location of spinal epidural hematomas[13].

Spinal compression involving SSEH occurs due to the limitation of the hemorrhage by epidural fat tissue and by coagulation of the blood so that additional bleeding does not spread into the relatively large epidural space that measures 3 to 6 mm on average[5]. The interval between the initial lesion and symptom onset could correspond to the gradual collection of blood in the epidural space that will later cause direct compression of the spinal cord or secondary ischemic injury of the spinal cord due to compression of spinal blood vessels[5].

Venous epidural hemorrhages are believed to be self-limited due to compression before they become mass lesions, which has led some authors to believe that there should be an arterial source for SSEH[5]. Moreover, most hematomas are located dorsolaterally and often present with radicular pain, which suggests a lesion in the radicular arteries, which are also located laterally and run along with the nerve roots[5]. The radicular arteries accompany the nerve roots into the spinal canal and may form longitudinal bridging arteries that could be easily injured by mechanical forces[5]. Since most hematomas are localized laterally (at the nerve root) and, similarly to epidural arteries, surrounded by a venous network, intraoperative observations would possibly support the hypothesis of arterial bleeding[5]. Beatty and Winston[13] verified that their patients' hematomas were predominantly lateral and surrounded by a net of epidural veins, where epidural arteries would be found.

Clinical presentation of SSEH is usually an acute and severe onset of pain in the location of hemorrhage that may be radiated to limbs, and sometimes there is radicular paraesthesia, similarly to vascular lesions[4,5]. Radicular pain may precede spinal pain, and subsequently, signs of the spinal cord or root compression ensue[4,5,15]. Symptom onset may vary from several minutes to several days[4]. Rarely, patients may present with slowly progressive, chronic, or relapsing symptoms or with neurological signs and symptoms that mimic an acute intervertebral disc herniation[15]. In most cases of SSEH, severe neck and back pain at the segment of bleeding is more prominent, but pain with radiation into the extremities is verified in many cases[5]. Hematomas in the superior cervical region are marked by onset with nuchal pain, while the hematomas in the inferior cervical spine present with interscapular pain[5]. The severity and progressiveness of sensory and motor deficit depend on the severity and rapidity of bleeding[16].

In high cervical regions, SSEH could cause spinal shock, leading to fatal conditions. Hematomas occurring at the lower levels (thoracic and lumbar spine) tend to have a subacute or chronic course[13,17].

Diagnosis of SSEH is made by prompt imaging examsand clinical suspicion[1,18]. Patients with back pain and acute or subacute neurological deficits with no apparent cause or secondary to minor trauma or a physiological effort should be suspected and an investigation for underlying coagulopathies and arteriovenous malformations (AVMs) should be performed. Differential diagnoses should include neoplasia, epidural abscesses, and lipomas[1,18]. SSEH on MRI scans may be seen as isointense lesions that progress to hyperintense on T1-weighted[18] or heterogeneous hyperintensities on T2-weighted images with focal hypointense areas, seemingly associated with deoxyhemoglobin or too fibrous septa that attach to the dura to the walls of the spinal canal.

The latter finding can help to differentiate between SSEH and malignant lesions of the epidural space[1].

Despite of common characteristics of T1-weighted images, some cases in the literature show atypical presentations on MRI, such as hypointensity and persistent isointensity for more than 48 hours. In these cases, clinical history is essential for differential diagnosis, and T2-weighted imaging seems to be of utmost importance for differential diagnosis, especially when patient history is confusing. Similarly, T1 contrast-enhanced images show peripheral enhancement in most cases, in sharp contrast with neoplastic alterations that usually show central enhancement[18].

According to reports from the literature, surgical decompression and evacuation of hematoma will be necessary in the majority of patients[7,10,14]. Although in some cases, conservative treatment could be a feasible alternative[15]. As an acute or subacute condition with severe potential complications, SSEH with neurological deficits should be immediately surgically treated. It is worth noting that patients treated within 48 hours (if incomplete deficits) or 36 hours (if total deficits) have been reported to have better outcomes[10]. Some studies suggest the ideal timing for treatment to be within 12 hours of onset. This may suggest a narrower therapeutic window and increased necessity of celerity in diagnosis and management[4,12]. As shown by Liao et al.[7], operated patients had a complication rate of 2.9% and no deaths were reported in their series, compared to the disease-related mortality rate of 5.7%.

Interestingly, according to Groen et al.[14], in 1996, the mortality seems to be higher in patients with cervical hematomas when compared to other segments (thoracic and lumbar segments) ($p < 0.05$) and it was observed that a possible major cause of mortality in this series was thromboembolic events, such as pulmonary embolism and myocardial infarction, which may be secondary to the perioperative interruption of previous anticoagulant therapy.

Even so, there seems to be a growing trend in literature to adopt conservative treatment for SSEH. According to Groen et al.[15], this effectiveness may correlate with increased use of MRI imaging for the diagnosis of SSEH, which may have led to higher diagnostic rates and patients with milder symptoms being more frequently diagnosed and treated conservatively. Another interesting point observed by Groen[15], in 2003, is that patients with conservative treatment usually have longer-lasting symptoms than patients treated with operative treatment. This may be correlated to the "spreading theory" of spontaneous cure of SSEH, which hypothesizes that the hematoma spreads on the epidural space before being absorbed, which leads to spinal decompression and neurological amelioration[15].

Surgical approaches remain the primary therapeutic intervention, with high rates of neurological recovery (88.9% complete recovery in patients with incomplete neurological deficit and 37.5% in those with a complete deficit[10]), being possibly replaced with conservative treatment in cases of a benign course with mild symptomatology and earlier improvement of sensorimotor symptoms[15].

In patients who underwent surgery, the main factor related to the postoperative outcomes was the time since ictus to surgery, average Frankel grade, initial neurological deficit, size of the hematoma, and level of spinal cord compression. The average Frankel grade in numerical equivalents (5 as grade E, 4 as grade D, etc.) was 4.7 in patients treated before 6 hours, compared to an average grade of 3.7 in patients treated after 24 hours, and a decrease from 67% to 12% of complete recovery between these intervals[1]. Complete recovery was seen in 65,9% of patients treated before 12 hours of onset and 64% of deaths, severe neurological outcome, or no improvement in symptoms in patients treated between 13-24 hours[5]. Approximately 25% of patients who had total recovery were Frankel Grade A and 83% of these patients were Frankel grade of D[1]). Lower affected levels (thoracic and lumbar) and smaller hematomas were associated with better recovery of neurologic function[1] and cervical hematomas were associated with higher mortality rates[10]. Additionally, the use of anticoagulants was associated with a worse prognosis[2].

CONCLUSION

SSEH has an extremely low incidence in the population. Although studies suggest that its main etiologies may be vascular malformations, anticoagulant therapy, neoplasms, and trauma, remains unclear. There is evidence that cervical hematomas may carry higher mortality rates than hematomas in other spine segments. Regarding prevalence, there is no significant difference between genders and some studies suggest that it may be more common in people over 50 years of age. The primary diagnostic method is the combination of a well-documented medical

history and magnetic resonance imaging. Furthermore, in most cases, surgical treatment is indicated. In a few selected cases conservative treatment might be an option. Future prospective studies are necessary to better understand the natural history, potential outcomes of this disease, and how treatment could be tailored for each case.

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Neoadjuvant Chemotherapy to Reduce Morbidity and Improve Surgical Resection in a Skull Base Ewing's Sarcoma: case report

Quimioterapia Neoadjuvante para Redução de Morbidade e Melhora de Ressecção Cirúrgica em Sarcoma de Ewing de Base de Crânio: relato de caso

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Gustavo Fabiano Nogueira[4]
Ricardo Ramina[5]

ABSTRACT

Ewing's Sarcoma (ES) affects skull base in 1-6% of the cases. Involvement of orbit, optic nerve and the brain may preclude complete surgical resection without severe morbidity. Neo-adjuvant chemotherapy is part of the standard care in extracranial ES. Imaging suggesting a different, more common diagnosis or urgent need to decompression of neural structures are commonly reasons by which neoadjuvant chemotherapy is not used in skull base ES. We present a case of a 3-year-old patient presenting a skull base ES where in spite of the fast progressing visual decline, neoadjuvant chemotherapy had demonstrated to be a valuable tool to symptoms improvement and reduce surgical morbidity without compromising radical surgery.

Keywords: *Ewing; Sarcoma; Skull base; Tumor*

RESUMO

O Sarcoma de Ewing (SE) afeta a base do crânio em 1-6% dos casos. O envolvimento da órbita, do nervo óptico e do cérebro pode impedir a ressecção cirúrgica completa sem morbidade grave. A quimioterapia neoadjuvante faz parte do cuidado padrão no SE extracraniano. Exames de imagem sugerindo um diagnóstico diferente, mais comum ou sob necessidade urgente de descompressão de estruturas neurais são comumente as razões pelas quais a quimioterapia neoadjuvante não é usada em SE da base de crânio. Apresentamos um caso de um paciente de 3 anos com SE da base de crânio onde, apesar do rápido declínio visual, a quimioterapia neoadjuvante demonstrou ser uma ferramenta valiosa para melhora dos sintomas e redução de morbidade cirúrgica sem comprometer a cirurgia radical.

Palavras-chave: *Ewing; Sarcoma; Base de crânio; Tumor*

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INTRODUCTION

The Ewing's sarcoma family of tumors (ESFT) is an entity that encompasses 3 highly aggressive forms of childhood cancer: Ewing's sarcoma, Askin tumor, and peripheral primitive neuroectodermal tumor[1]. While Ewing's sarcoma is most commonly found in pelvis, chest, femur, tibia, vertebrae and humerus; skull base involvement is extremely uncommon[2-5]. Therefore, management is usually extrapolated from other locations. Surgical resection is the initial treatment in most cases, as imaging usually suggest a different, more common diagnosis, or due to the need of decompression of neural structures[4]. We present a case of an extensive Ewing's sarcoma of the anterior skull base in a pediatric patient that was treated with neoadjuvant chemotherapy followed by surgery.

CASE PRESENTATION

A 3-year-old girl was presented with a history of fifteen days of progressing proptosis in the left eye associated with visual impairment and anosmia. She had unremarkable past medical history. MRI showed a contrast-enhancing mass in the anterior skull base, centered in the ethmoid sinus with intracranial extension and extending into the left orbit (Figure 1). The patient underwent an endonasal endoscopic biopsy due to the uncertainty of the diagnosis, with frozen section compatible with a small blue round cell tumor, and definitive pathology consistent with Ewing's sarcoma. Immunohistochemistry was positive for CD99, S100 and EMA, and fluorescent in-situ hybridization was positive for ESWR1 rearrangement of the chromosome 22q1, confirming ES. PET Scan and whole body MRI excluded metastatic disease.

The patient underwent induction chemotherapy with vincristine, doxorubicin and cyclophosphamide, alternating with ifosfamide and etoposide (VDC-IE protocol). Follow-up MRI after 8 weeks showed significant reduction of the contrast-enhancing mass, with residual lesion in the ethmoid bone (Figure 2). Due to the patient's age, surgery of the remaining mass was preferred over radiation therapy.

A combined approach (transcranial and endonasal) was chosen to effectively decompress the infero-medial wall of the optic canal as well as medial wall of the orbits. Reconstruction is also more effectively harvesting pericranium plus bilateral temporal facia graft superiorly and a nasal septum flap or lateral wall, allowing a three-plane reconstruction.

Through a bifrontal craniotomy, the anterior cranial base was exposed extradurally, with transection of the olfactory fibres. The tumor was seen at the level of planum sphenoidale and left orbital roof. The bulk of the tumor was resected, as well as the cribriform plate and planum. The left optic canal was unroofed along with the orbit, and the periorbit was also resected. Adjacent dura mater and both olfactory bulbs were also removed. Endonasally, both middle and superior turbinates were removed bilaterally along with the remaining ethmoid cells and lamina papyracea. Decompression of the left optic canal was achieved in a 360-degree fashion by removing the medial and inferior walls. Frozen section confirmed negative surgical margins (Figure 3). Reconstruction of the skull base was performed with a large pericranial plus temporal muscle fascia flap, titanium mesh and nasal septum flap. Postoperative MRI demonstrate a complete surgical resection (Figure 4).

The early postoperative period was unremarkable, however, on postoperative day 5, the patient developed paraparesis due to symptomatic vasospasm on the anterior cerebral arteries, that was managed with intra-arterial milrinone followed by intravenous milrinone for 48 hours, with complete relieve of the simptoms. The patient was discharged on postoperative day 10.

Afterwards, the patient received 9 cycles of the VDC-IE protocol starting fourteen days after discharge. At one year follow-up the patient is in complete remission.

DISCUSSION

Ewing's sarcoma is thought to involve the skull in 1-6% of cases[6,7], and due to the rapid growth, most patients present with compressive neurological symptoms, or sinonasal complaints such as nasal obstruction, rhinorrhea and epistaxis. In particular, patients with periorbital extension may present with proptosis, periorbital edema and decreased visual acuity[8,9].

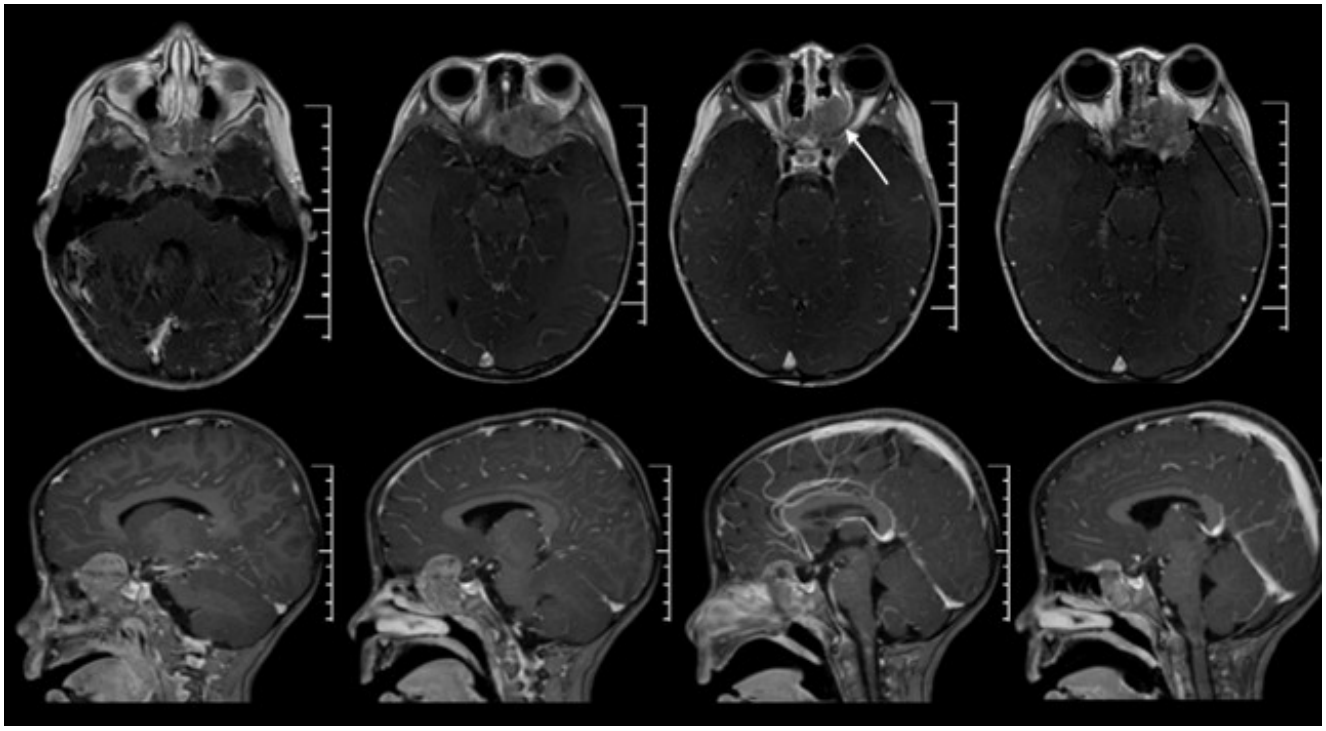

Figure 1. Axial and sagittal T1WI post gadolinium MRI demonstrating an enhancing tumor mass extending from upper clivus to anterior cranial fossa cantered at the cribriform plate, ethmoid and sphenoid bone extending into right and left orbital cavity, compressing the optic nerve (white arrow) and invading the periorbit (black arrow). A proptosis is seen in the left eye.

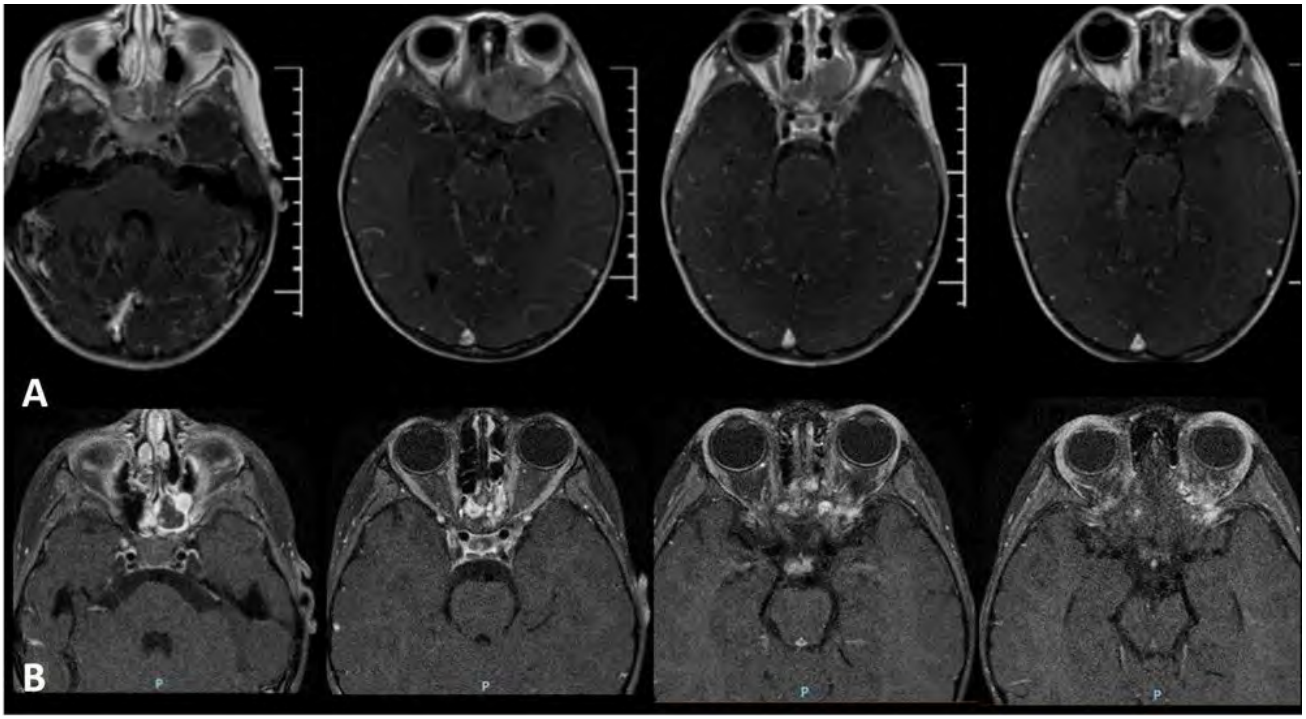

Figure 2. Comparative T1WI post gadolinium MRI (**A**. pre adjuvant chemotherapy; **B.** post adjuvant chemotherapy after 8 weeks of adjuvant chemotherapy) demonstrating a significant reduction in the tumor mass, absence of periorbit involvement and resolution of the proptosis in the left eye.

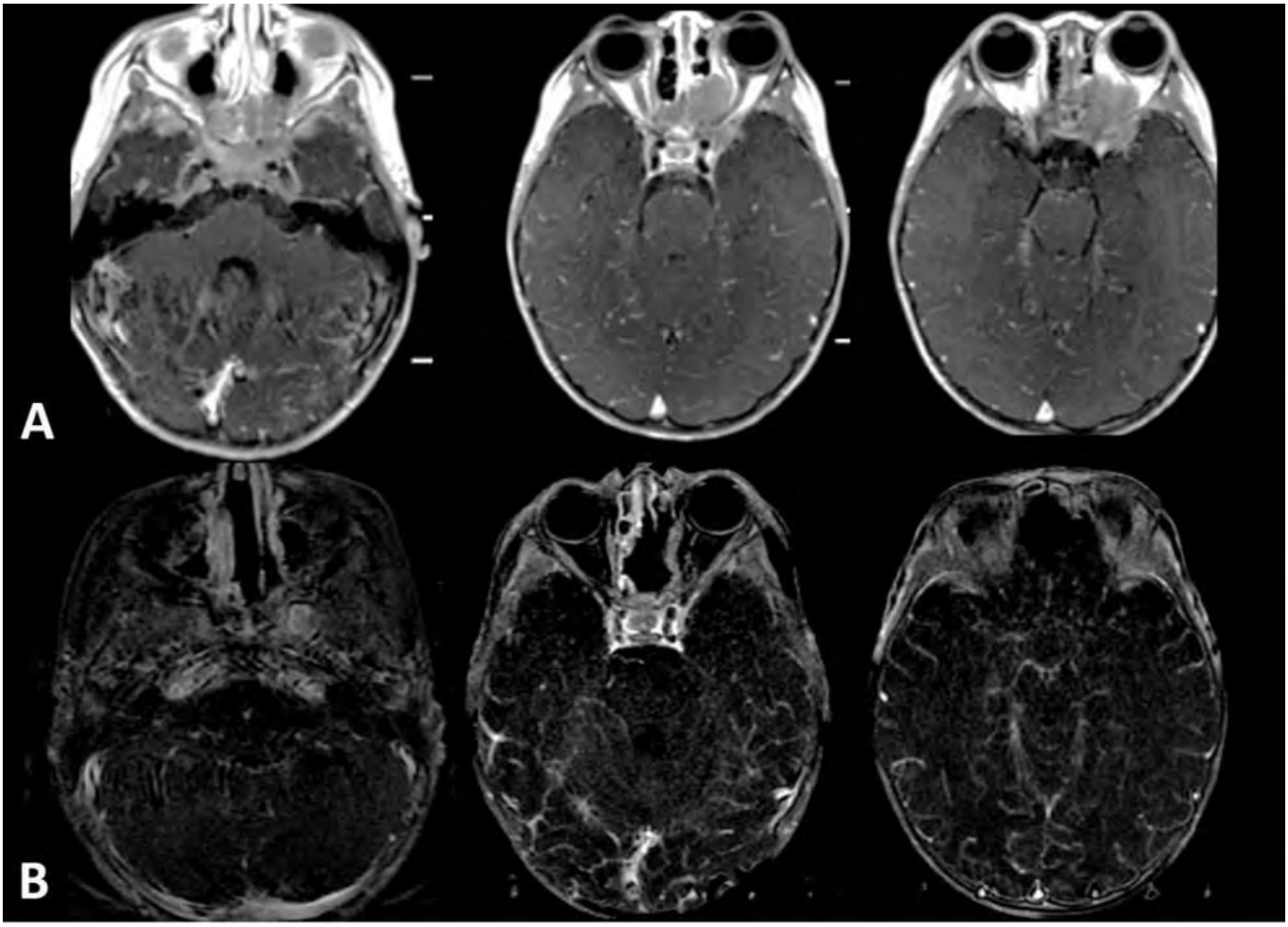

Figure 3. Comparative images. **A.** preoperative T1WI post gadolinium MRI.; **B.** postoperative T1WI post gadolinium with subtraction MRI demonstrating complete surgical resection of the residual tumor. An adequate decompression of the orbit as well as the optic canal can be seen.

Current treatment for Ewing's sarcoma relies on multi-drug chemotherapy[10,11], which has improved overall survival from 10 to 75% for localized disease[1]. Chemotherapy may be associated with surgery and/or radiation therapy for local control. Neoadjuvant chemotherapy has been increasingly used for, but no report on its use for skull base disease has been reported[12].

Ewing's sarcoma involving the skull base possesses a unique challenge, as location, size, extension, and effect on neurological structures dictate the need of urgent volume reduction. Moreover, imaging is usually non-diagnostic, and may suggest a primary lesion such as meningioma. Therefore, the need of surgical resection must be weighted toward the possibility of achieve negative surgical margins, which has been shown to reduce local recurrence rates[13]. Induction chemotherapy in this setting provides an interesting opportunity to optimize both goals, as in responding cases, cytoreduction is rapidly achieved, potentially sparing structures that would otherwise be resected, such as the optic pathway. Moreover, by controlling microscopic disease adjacent to the bulk of the tumor, we believe that also improves the rate of negative margins achieved by surgery, which is exemplified by our case, where induction chemotherapy achieved rapid improvement of visual acuity, mass reduction, and allowed us to achieve negative margins without the need of orbit exanteration, which would have been probably needed otherwise.

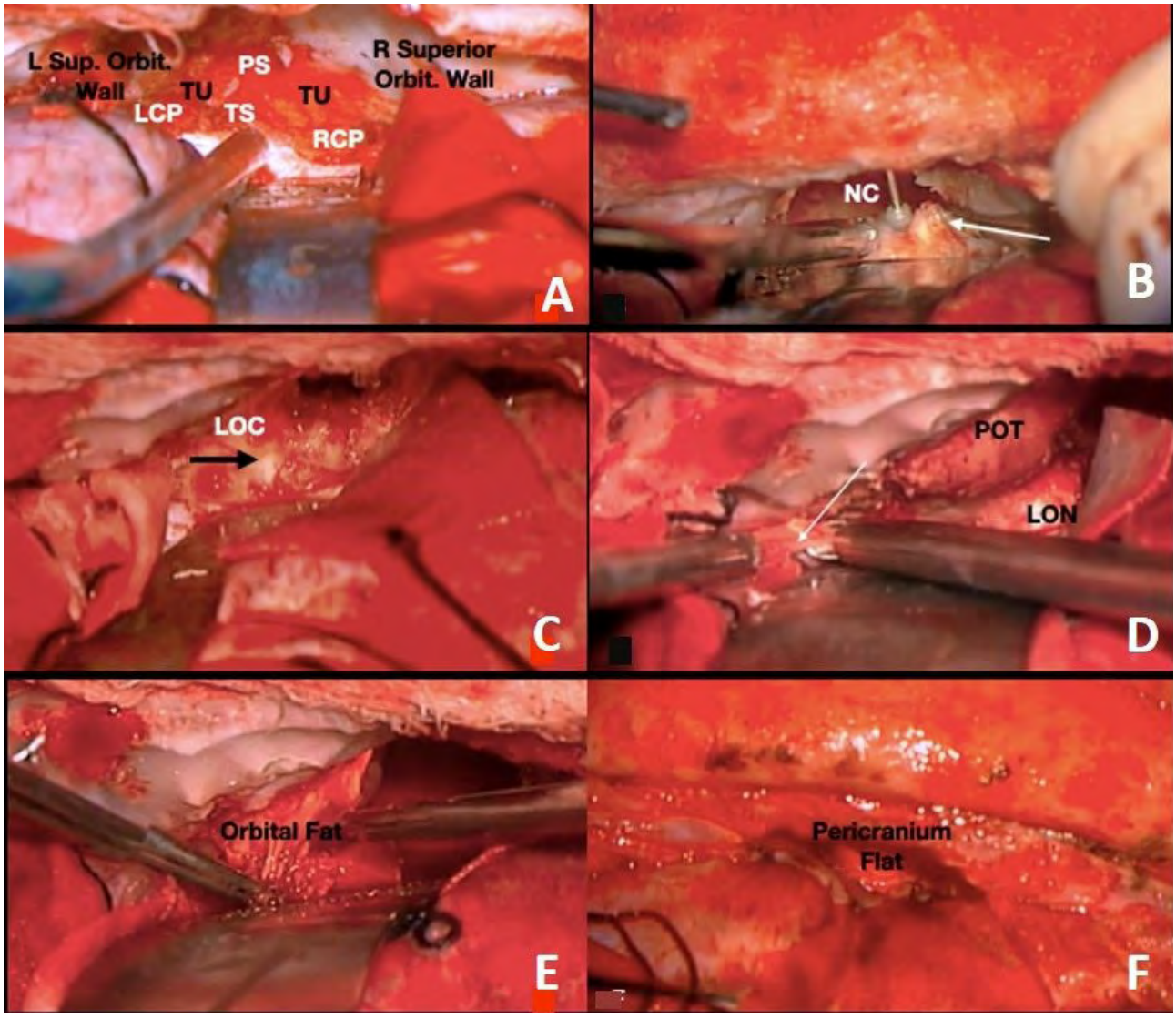

Figure 4. Intraoperative view. **A.** Transcranial exposure of the anterior skull base demonstrating tumor extending from the cribriform plate up to the tuberculum sellae in the coronal plane, and affecting upper wall of both orbit cavity. **B.** Transcranial view after partial resection of the anterior skull base. Endonasally, the infero-medial portion of the right optic canal is been drilled. **C.** Transcranial view of the left optic canal (LOC) and the extradural portion of the optic nerve (black arrow) after bone removal. **D.** Complete decompression of the left orbit and optic canal exposing the periorbital tissue (POT) and the optic nerve (LON). The lesser sphenoid wing is been removed. **E.** Transcranial view of the surgical cavity demonstrating a complete surgical resection of the tumor mass. The orbital fat is exposed after removal of the periorbital tissue. **F.** Reconstruction of the surgical cavity with large pericranium flap and temporal muscle fascia covering the titanium mesh.

CONCLUSION

In conclusion, induction chemotherapy is a feasible approach to manage Ewing's sarcoma of the skull base, possibly improving the rate of negative margins after surgery.

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2022

Lançamento

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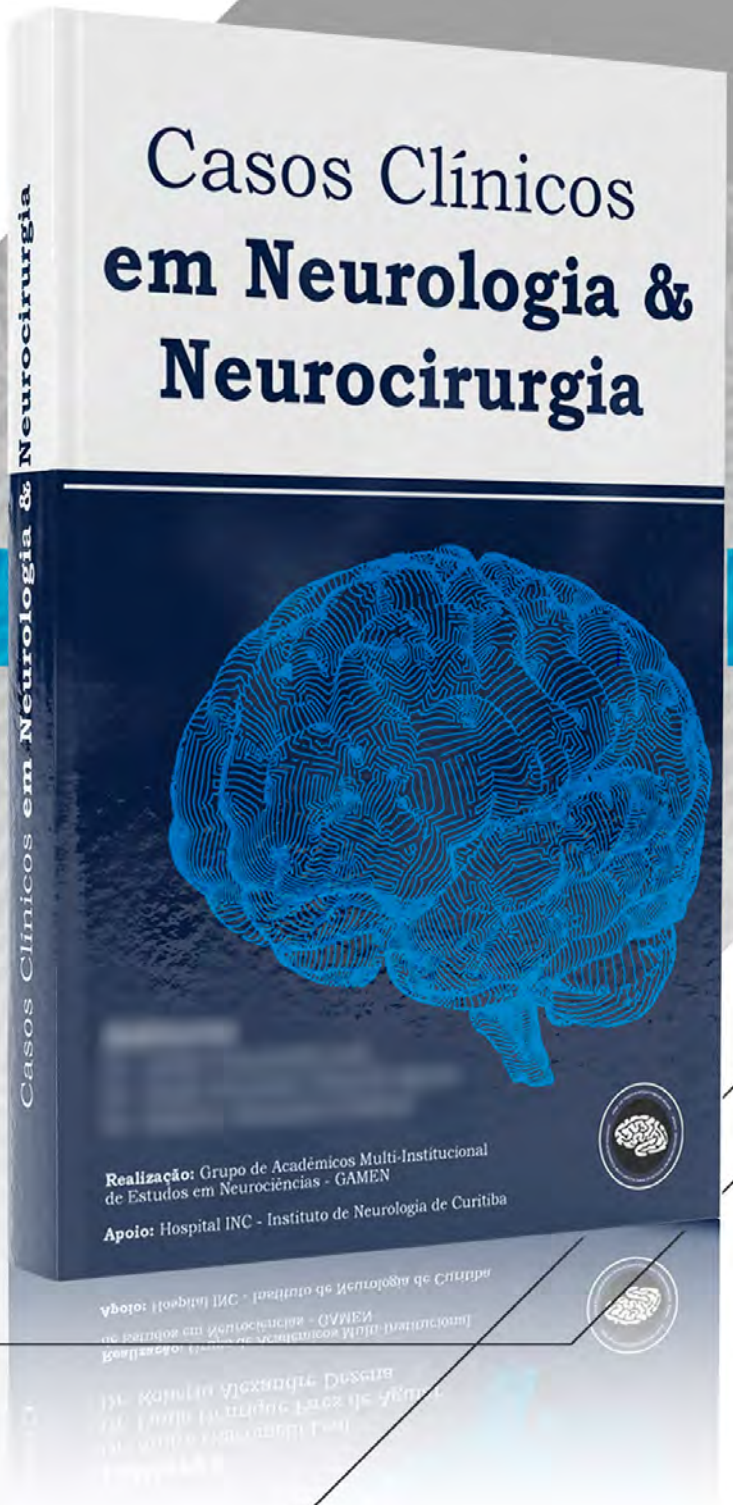

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DBS Treatment in a 18-Year-Old Patient with Refractory Dystonia Due to DYT1 Mutation: a case report

DBS em um Jovem de 18 Anos com Distonia Refratária por Mutação no Gene DYT1: relato de caso

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ABSTRACT

Purpose*: To present a case of an infrequent refractory dystonia due to DYT1 gene mutation in an 18-year-old male patient that was later treated with Deep Brain Stimulation (DBS).* **Case presentation***: Male 18-year-old patient, affected by torsion dystonia of the neck and upper limbs is reported. Genetic analysis identified a DYT1 gene superexpression mutation. Previous therapies had included physiotherapy, botulinum toxin injection, drugs such as primidone and clonazepam, but all with little improvement. The patient underwent two neurosurgeries in order to insert Deep Brain Stimulation (DBS) on his left and right internal Globus Pallidus (GPi). The electrodes inserted were Medtronic® 3389 and the generator was Activa RC rechargeable. The postoperative period of both procedures were successful, without any identified deficits. After a 2-year follow-up period, the patient presents a normal life compared to the average of his age, without any of the symptoms or complications that he had before.* **Conclusions***: DYT1-dystonia is a disabling disease that can affect young patients but shows good prognosis with DBS therapy. The reported case presented an excellent outcome particularly because it involves a young patient with DYT1-related dystonia.*

Keywords: *DYT1; Dystonia; DBS*

RESUMO

Objetivo*: Apresentar um caso de uma infrequente distonia refratária por mutação no gene DYT1 em um menino jovem que foi tratado com estimulação cerebral profunda (DBS – da sigla em inglês).* **Relato do caso***: Jovem de 18 anos do sexo masculino afetado por uma distonia de torção cervical do pescoço e membros superiores. A análise genética identificou uma mutação de superexpressão no gene DYT1. Terapias prévias incluíram fisioterapia, injeções de toxina botulínica, drogas como primidona e clonazepam, mas todas com pouca ou nenhuma melhora. O paciente foi submetido a duas neurocirurgias para inserção do DBS no lado esquerdo e direito do Globo Pálido interno (GPi). Os eletrodos inseridos foram da Medtronic® 3389 e o gerador foi Activa RC rechargeable. O pós-operatório de ambos os procedimentos foi de sucesso, sem nenhum déficit identificado. Após um seguimento de 2 anos, o paciente apresenta vida normal comparada à média de sua idade, sem nenhum sintoma ou complicação que apresentava antes.* **Conclusão***: O caso apresentado mostrou excelente evolução por se tratar de jovem com distonia por DYT1. Esse tipo de distonia é uma doença que pode acometer jovens, mas tem bom prognóstico com a inserção do DBS.*

Palavras-chave: *DYT1; Distonia; DBS*

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INTRODUCTION

Dystonia may be defined by abnormal involuntary movements or postures due to sustained or intermittent muscle contractions. It is a highly stigmatizing and disabling condition, just as other movement disorders. One of the most common aetiologies of early onset, dystonia — with symptoms beginning in childhood of adolescence — is due to the mutation in the DYT1 gene: up to 53% of all cases in non-Jewish populations and about 80% in Ashkenazi Jewish population, because of a founder mutation. The penetrance of this autosomal dominant gene is 30%, meaning that 70% of all gene carriers have no signs or symptoms of dystonia[1].

Typically, the clinical manifestation of this type of dystonia will begin at the average age of 13 years, involving more likely a limb or, less frequently, the trunk, cervical or cranial muscles. More than half of these cases will progress to a generalized dystonia, involving other limbs and/or the trunk[2].

The pathophysiology of DYT1-dystonia involves a GAG deletion in the coding region of the TOR1A gene located on chromosome 9, resulting in a disorder of anomalous regulation of transcription and neuronal circuit development. The mutant gene product — torsinA — has been found to be stocked intracellularly and interact abnormally with other proteins. Overall, the outcome of this mutation is a neurodevelopmental circuit disorder involving the cortico-striato-pallido-thalamo-cortical and cerebello-thalamo-cortical pathways[3].

The objective of this report is to present a case of a severe refractory dystonia due to DYT1 mutation in an 18-year-old boy, who was later treated with Deep Brain Stimulation (DBS). Also, the possible treatments for this disease will be discussed.

CASE PRESENTATION

Male patient, 18-year-old, affected by segmental cervical dystonia was reported. First, he exhibited symptoms when he was 15 years old and, within one year through the course of the disease, and he had a number of complications including severe pain, recurrent pneumonia and social isolation due to his condition. Physical examination revealed a bilateral torsion dystonia of the neck and proximal third of the upper limbs, with more prominent signs on his right side (Figure 1). His genetic analysis identified a DYT1 gene superexpression mutation. In previous medical care, he was oriented towards treatments such as physiotherapy, botulinum toxin injections, drugs such as primidone and clonazepam, but all with little improvement.

The attending neurosurgeon indicated a procedure to treat initially the symptoms of the right side, as it was the more severely affected. A Magnetic Resonance Imaging (MRI) of the patient's head was done in order to make the surgical planning. The neurosurgery was performed in March 2018 to implant a DBS on the left internal globus pallidus (GPi) posteromedial area with general anesthesia. The generator was implanted on his right side, under the skin in the upper chest. The electrodes inserted were Medtronic® (Minneapolis - MN, EUA) 3389 and the generator was Activa RC rechargeable, with 0.5 mm spacing. The following programming was set: current of 3 mA, frequency of 130 Hz and pulse width of 90 μs. The procedure was successful and the patient was discharged from the hospital 4 days post-operative (PO) (Figure 2A).

After 10 months, in January 2019, the same procedure was performed in the right GPi, aiming to treat his dystonic tremors located in the left part of the body. The procedure was also successful, without any deficit, with the patient being discharged from the hospital at the PO day 2 (Figure 2B).

During a 2-year follow-up period, the patient presented a normal life compared to the average of his age, without any of the symptoms or complications he had before. He regularly attends to physiotherapy and fitness centers to maintain muscle training.

DISCUSSION

The patient presented a severe refractory dystonia due to DYT1 mutation. Regarding the recommended treatment for early onset dystonia, it aims mostly at relieving the symptoms. The first option of therapy are botulinum toxin injections, mainly if it is a focal or segmental dystonia. If refractory to this step or in case of a generalized dystonia, the next option are oral medications,

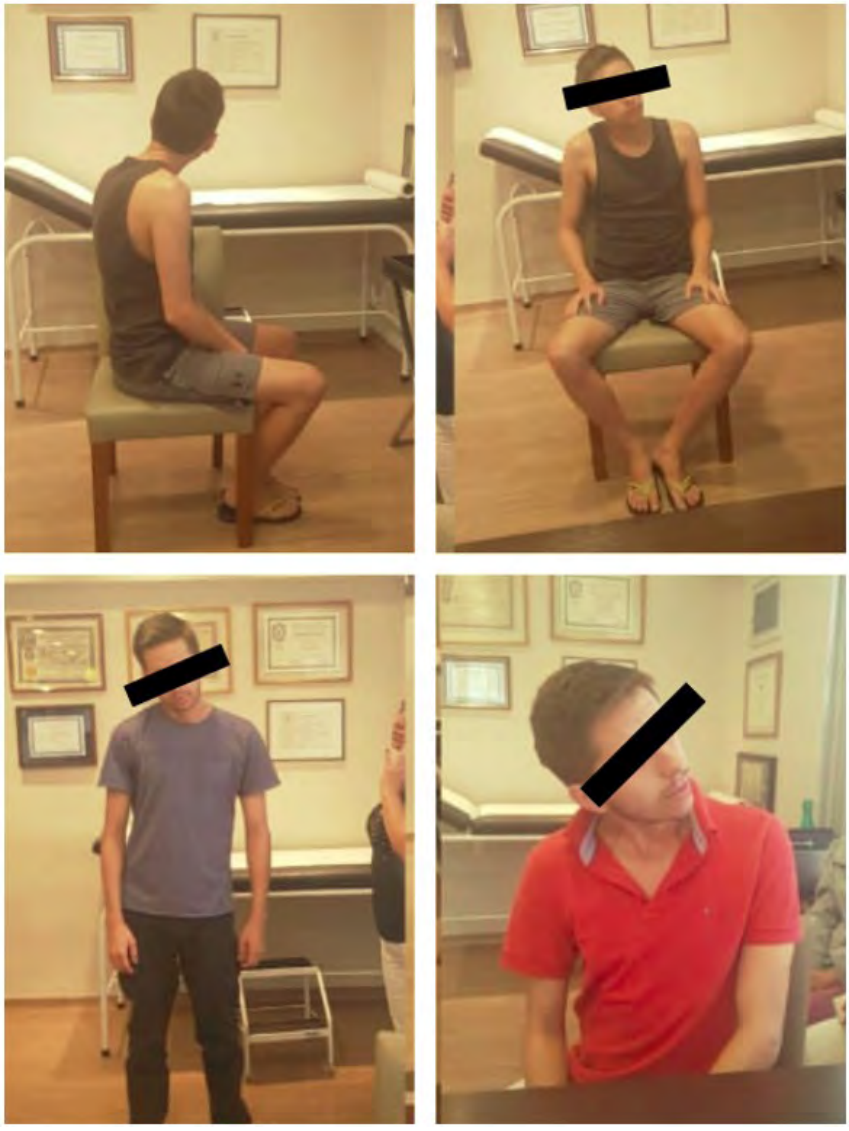

Figure 1. Dystonic presentation of the patient.

such as anticholinergics or benzodiazepines. Once more, if the disease is refractory to the previous therapies, a surgical treatment can be tempted: a system called Deep Brain Stimulation (DBS) consists in the insertion of an electrode in a specific part of the brain, in order to modulate the patterns of electrical activity[1].

Our patient went through clinical therapies including physiotherapy, botulinum injections and oral medications, but not only he still presented the dystonia symptoms of intermittent muscle contractions but also complications due to the disease: severe pain, recurrent pneumonia and social isolation. The respiratory disease most likely resulted from the decrease of the size of his thoracic cavity, due to the dystonic posture. As for the social isolation, it can be analyzed as a collateral effect of the severity of his disease: Junker et al.[4] demonstrated significant correlations between Health-Related Quality of Life (HRQoL) subscales such as social functioning and emotional role functioning, and dystonia severity. Those complications exhibited by our patient are within the most common of this disease, including chronic pain, depression, anxiety, social stigma, and reduced self-esteem, all leading to an impaired HRQoL[5].

The adequate management of the disease is important to avoid the decreased well-being and that is the main idea brought

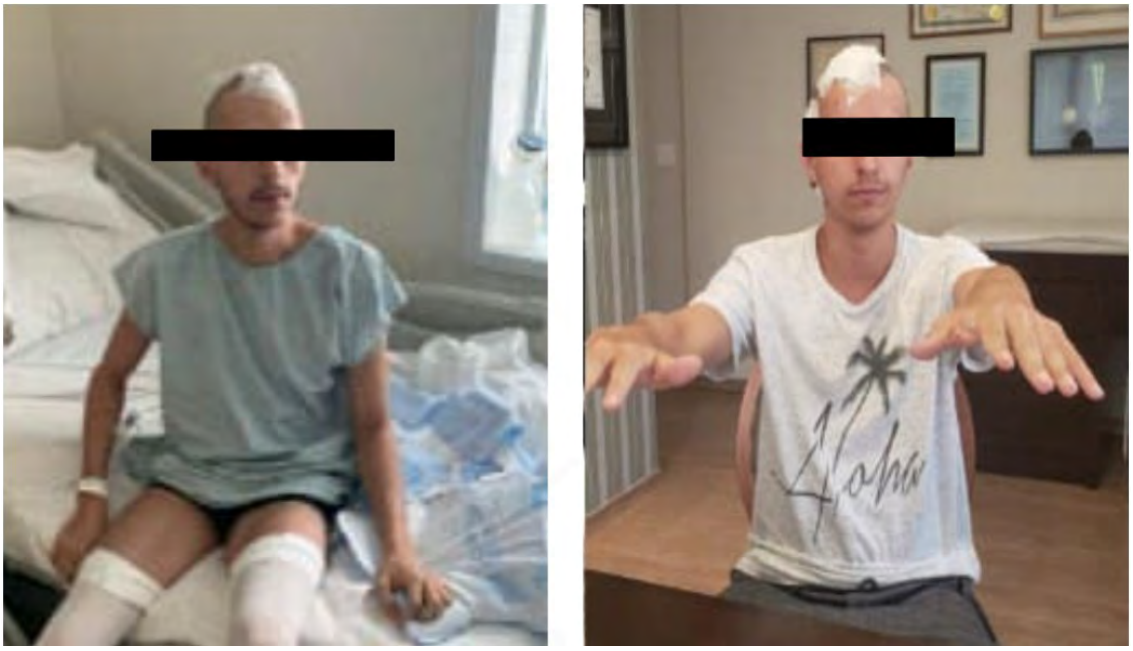

Figure 2. Clinical presentation. **A.** after the first surgery to implant the DBS and **B.** after the second surgery.

by this report: young patients with refractory dystonia may have more lifetime with higher quality of life when there is an early approach of DBS, specially if there is a presumption of a DYT1 mutation.

Supporting this statement, Tsuboi et al.[5] showed in a systematic review that patients with inherited isolated dystonia reported significant improvement in motor function and pain after DBS surgery, leading to an improved overall life satisfaction.

Our patient had important symptoms regarding physical and social spheres, but after the insertion of DBS bilaterally, he claimed to have an immeasurable improvement in both of the complaints.

As for the medical literature, the results from the last five years in PubMed database with the keywords "Dystonia", "DBS" and "DYT1" are scarce, with 12 papers in the English language, seven from which correlate with this report. Mainly, their data showed that the surgical stimulation is efficacious and can potentially prevent disease progression in the long term[6-8], and also a great improvement in motor and disability scores post-operatively[9,10]. From all dystonias, the one with the best prognosis is DYT1-related[9]. Other positive predictive factors for good prognosis after DBS insertion are short disease duration and isolated idiopathic dystonia[11]. One study even showed that 8% of their DYT1-dystonia cohort presented suboptimal response after DBS implantation (less than 30% of improvement over baseline), but still the long-term follow-up demonstrated beneficial effects of the stimulation, compared to before the procedure[12]. All of these data are in line with our case report, showing significant improvement after DBS implantation in young patients with severe DYT1-dystonia.

CONCLUSION

DYT1-dystonia is a disabling disease that can affect young patients but it has good prognosis with DBS therapy. The reported case showed an excellent outcome particularly because it involves a young patient with DYT1-related dystonia.

Finally, the surgical treatment with DBS should not be delayed in refractory dystonia patients, specially in the DYT1-type, as it has great prognosis and leads to a great difference in their quality of life.

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Perimesencephalic Cerebral Arteriovenous Malformation (AVM): case report

Malformação Arteriovenosa Cerebral Perimesencefálica (MAV): relato de caso

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ABSTRACT

Background*: Cerebral arteriovenous malformation (AVM) evolves asymptomatically and can cause serious injuries, most of the time irreversible, with difficult diagnosis, controversial treatment and restricted access to reference therapeutic centers.* **Case Presentation***: a case of intraparenchymal hemorrhagic stroke with presence of a left perimesencephalic AVM in a 66-year-old male patient is reported. Regarding the therapeutic approach, the AVM correction procedure through micro neurosurgical resection is described here.* **Conclusion***: With this in mind, the present study aimed to meet this expectation, as well as to describe the correction of silent AVM after intraparenchymal hemorrhagic accident.*

Keywords: *Arteriovenous Malformation; AVM; Intraparenchymal hemorrhage; Treatment*

RESUMO

Introdução*: A malformação arteriovenosa cerebral (MAV) evolui de forma assintomática e pode causar lesões graves, na maioria das vezes irreversíveis, com diagnóstico difícil, tratamento controverso e acesso restrito a centros terapêuticos de referência.* **Relato de caso***: relato de um caso de acidente vascular cerebral hemorrágico intraparenquimatoso com presença de MAV perimesencefálica esquerda, em paciente do sexo masculino de 66 anos. Em relação à abordagem terapêutica, descreve-se aqui o procedimento de correção da MAV por meio de micro-ressecção neurocirúrgica.* **Conclusão***: Pensando nisso, o presente estudo teve como objetivo discorrer a história clínica, bem como descrever a correção da MAV silenciosa após acidente hemorrágico intraparenquimatoso.*

Palavras-Chave: *Malformação Arteriovenosa; MAV; Hemorragia intraparenquimatosa; Tratamento*

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BACKGROUND

Vascular malformations are categorized as capillary, arterial, venous or lymphatic, being that the coexistence of different vessels in the same lesion may be common. According to the blood flow, can be divided in high or low. Those with high flow comprise arterial malformation (AM), arteriovenous fistula (AVF) or arteriovenous malformation (AVM). The low flow ones are venous malformation (VM), lymphatic malformation (ML) and capillary malformation (MC). In addition, there may be complex combined malformations, e.g. lymphatic capillary (MCL), venous capillary (MVC), lymphatic venous (MLV), arterial capillary (MAC), capillary venous lymphatic (MCLV), capillary venous arterial (MCAV) and lymphatic venous arterial capillary (MCAVL). They can also be classified as localized or diffuse[1,2]. When ruptured, the subsequent risk of death increase, depends on association with aneurysms, deep locations, deep drainage, age and others risk factors[3,4].

Regarding the diagnosis, it can occur by means of angioimaging, revealing the delimitation of the malformation. These morphological changes consequently lead to functional changes directly and indirectly on the affected tissue. Regarding the prognosis, these may be non-modifiable or generate structural and/or functional sequels, and may even cause risk of death[4,5].

The diagnosis, treatment and follow-up of the patient is multidisciplinary and interprofessional, increasing resolution and effectiveness[6]. Thereby, the actions to be carried should be clear and disclosing, for those better protocols diagnosis and therapeutical can be executed and better prognostics can be reached.

CASE PRESENTATION

This case report description was approved and accepted by the research Ethics Committee (CEP – Plataforma Brasil), under register 4,947,483. The participant and any identifiable individuals consented to publication of his image.

A 66-year-old male patient arrived at the service with right hemiplegia, dysarthria, lowered level of consciousness and Glasgow eleven, and in the following hours was seven, resulting in intubation. At the first cranial computed tomography (CT) imaging exam, left mesencephalic hemorrhage and presence of blood in the ventricle was revealed (Figure 1A). His previous morbid history indexed to the medical record did not present any comorbidity. Thus, in line with the previous findings, arteriography was performed in which perimesencephalic AVM could be seen on the left SM3 (Figures 1B and C).

With the diagnosis of intraparenchymal hemorrhagic stroke with the presence of a left perimesencephalic AVM, the chosen therapeutic approach was to perform microsurgery for resection of the AVM in the posterior fossa. The surgical procedure took place with the patient in a sitting position, head in flexion, without rotation or lateral flexion (Figure 2A). Straight incision of approximately 12 cm was performed in the sub-occipital region in the midline from IO to C1. The upper portion of the incision was curved to avoid a superficial pressure ulcer. The muscular plane was dissected through the nuchal ligament until the exposure of the external occipital protuberance, superior nuchal lines, external occipital crest, posterior border of foramen magnum (opistium), posterior atlanto-occipital membrane and posterior C1 arch (Figure 2B). Supra and infratentorial suboccipital craniotomy was performed using three burr holes, one of which located in the midline 2 cm above the external occipital protuberance and the other two holes located just below the superior nuchal line, every 5 cm apart of the midline. With the posterior arch of C1 preserved, V-shaped durotomy was performed, thus allowing the flaps to be folded upwards and the suboccipital surface of the two cerebellar hemispheres to be exposed (superior and inferior semilunar lobes, biventral lobe, pyramid and uvula) (Figure 2C).

To reach the AVM, the tentorium-pontine-cerebellar veins were cauterized, allowing the visualization and identification of the uvula, pyramid, lobes of the cerebellar hemispheres and arachnoid membrane. The cistern arachnoid was then dissected, thus revealing the AVM (Figure 3A). Nidus and afferent branches of the AVM were identified (Figure 3B) and cauterized, in the same way, the main drainage vein (precentral cerebellar vein). With the completion of the resection process, hemostasis of the quadrigeminal cistern region was verified and the cavity was revised and it was identified the maintenance of pulsation of vascular structures (Figure 3D).

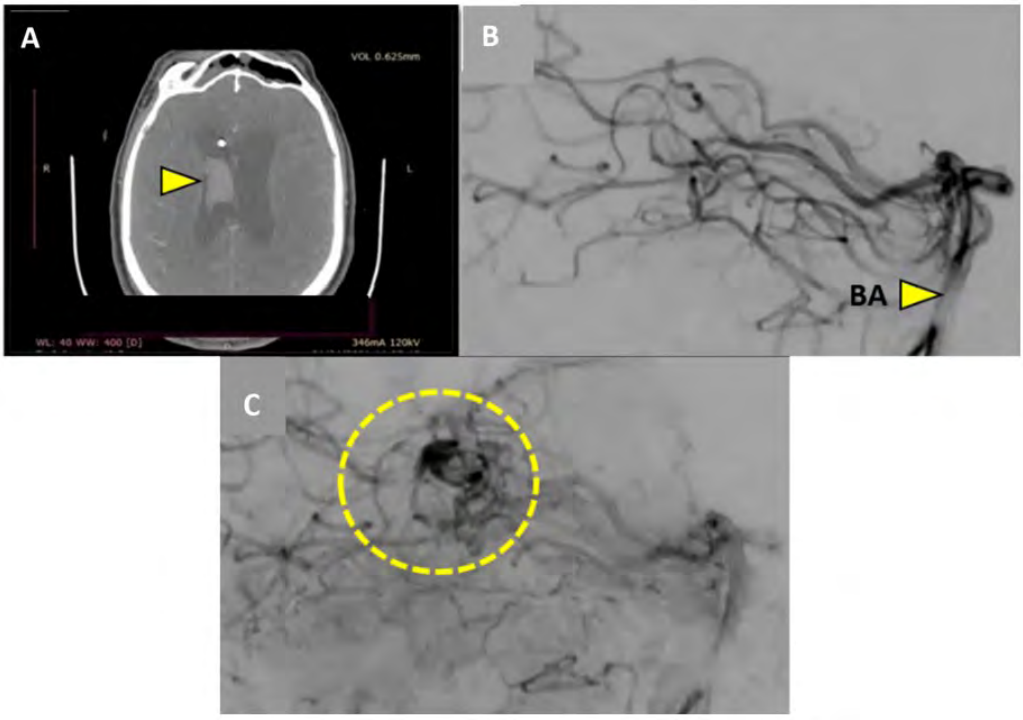

Figure 1. A. Angiotomography showing intraventricular hemorrhage and cannula shunt on the left. **B**. beginning of contrast flow in the left posterior cerebral artery (LPCA). **C**. evidence of contrast accumulation in the center of the third branch of the LPCA, AVM of the SM3.

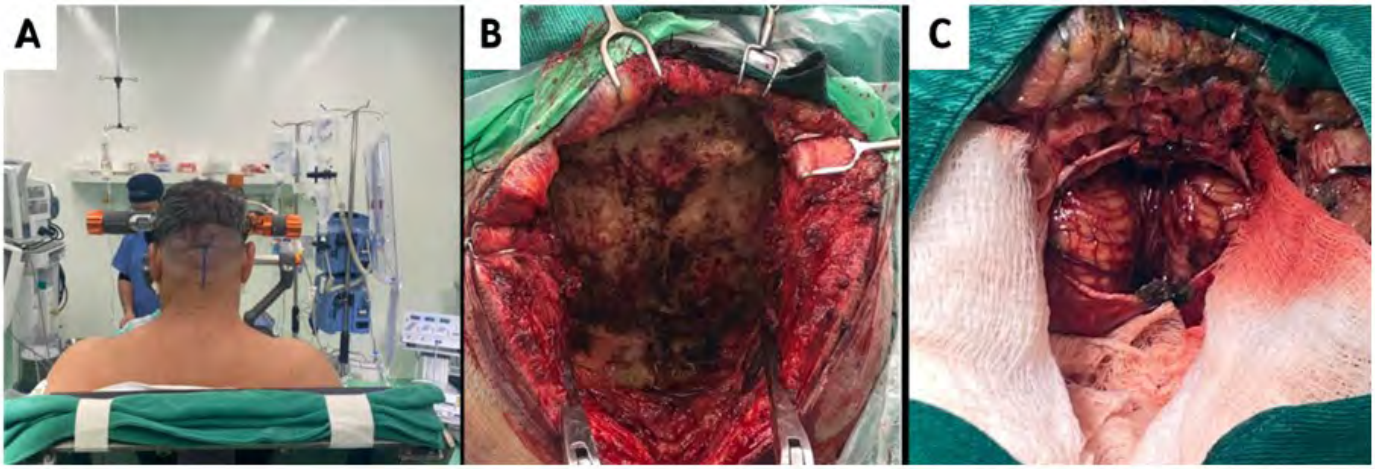

Figure 2. A. Positioning the patient in a seated position with head in flexion. **B**. dissected muscular plane with exposure of the occipital bone. **C**. Craniotomy and durotomy completed with exposure of the cerebellar hemispheres.

After resection, cranioplasty was performed. The surgical procedure was uneventful. In the postoperative evaluation, the patient was bedridden, non-compacting, afebrile, in a persistent vegetative state, and had a sacral decubitus ulcer. A new postoperative arteriography was then performed, which revealed normal anatomy of the basilar artery (BA), the posterior cerebral artery (PCA), the superior cerebellar arteries (SCA), the antero-inferior cerebellar artery (AICA) and the postero-inferior cerebellar artery (PICA), and the absence of perimesencephalic AVM was also observed (Figures 4A-C).

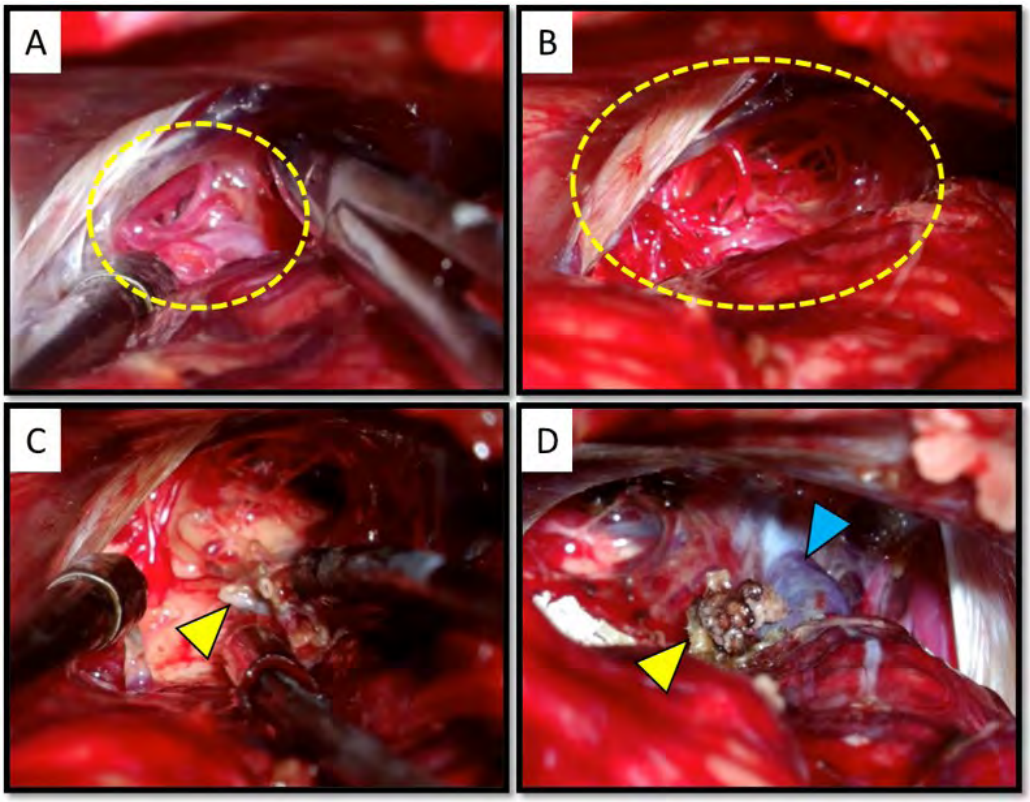

Figure 3. A and **B**. AVM afferents can be visualized through the branches of the posteromedial and lateral choroidal arteries of the posterior cerebral artery. **C**. nidus coagulation; and **D**. extraction of the AVM nidus and draining vein with normal staining.

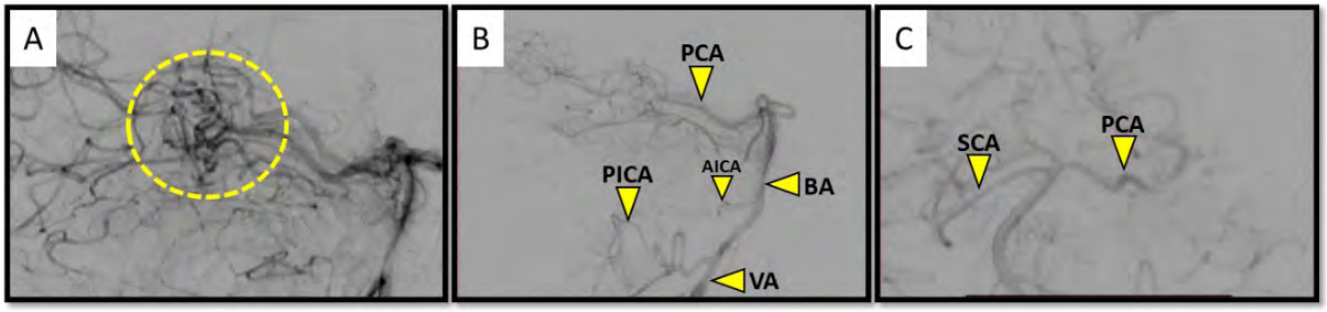

Figure 4. A. Preoperative arteriography, with the yellow dotted circle demarcating the perimesencephalic AVM area. **B**. arteriography showing the preservation of PCA, AICA, PICA, BA, and VA; and. **C**. Arteriography showing preservation of SCA.

DISCUSSION

The AVM case reported was a silent condition, which, after an hemorrhagic accident, caused irreversible damage to the healthy patient and who had no previous comorbidities. Cases like this call for early diagnosis and resolute therapies, since due to the complicated screening of vascular irregularities, the diagnosis usually occurs only after vessel dehiscence[7]. In this patient the intraparenchymal hemorrhagic episode have been caused by rupture of the AVM, generating the beginning of the signals and symptoms. With this scenario, the initial diagnostic hypothesis was stroke, so there was a delay between the differentiation between hemorrhagic stroke and confirmation of AVM (hours). The structure of the health system was very important for

achievement of results, the possibility of significant results for medical care.

Cerebral hemorrhage is a condition with low resolution that demonstrates high morbidity and mortality, in which patients who have injury may acquire focal motor deficits, functional sequelae, epilepsy, in addition to a permanent vegetative state and, in most severe cases, progress to death[8,9]. The present report goes according to the evolution to severe sequelae and death.

Early diagnosis is usually due to clinical investigation of other vascular comorbidities, as well as the presentation of nonspecific neurological manifestations (mainly due to bleeding episodes), seizures, headache and focal losses that can be motor, visual or somatosensory[10-13]. Therefore, the identification by neuroimaging and angiographic exams is essential, as well as diagnostic confirmation[14,15]. At the service where the patient was admitted, the diagnostic method used was initially computed tomography angiography, that indicated the lesion and facilitated the decision of the therapeutic approach. Microsurgery is the most widespread and used method, and the technique consists of anatomical exposure, occlusion of the feeding arteries, preservation of the vessels that pass through the region, circumferential dissection of the lesion, cessation of venous drainage and finally the removal of the nidus[16,17].

The treatment and follow-up of the case was microsurgical, but other treatment options have the following modalities: conservative and interventional, which are divided into surgery, microsurgery, stereotaxic radiosurgery and endovascular embolization[18-20].

Surgical resection presents high risk post-operatively, but this and the benefit colide when comparing with outcome of surgeries performed when total resection is achieved, in this context there is elimination of hemorrhagic danger and prolonged durability of hemostatic stabilization[19,21]. Complications of these methods consist mainly of hospital risks due to the long stay, stroke, intraoperative injury in the case of microsurgery, intraoperative or postoperative ischemic or hemorrhagic stroke in the case of embolization, and hemorrhagic risk in the latency period (time between radiation and tissue response with respect to radiosurgery)[11,12,22]. Therefore, in the present case no identification of new hemorrhagic focus or others complications were seen, however, the long stay was necessary for the other systemic issues. The post-surgical vegetative state resulted in decompensatory systemic complications and culminated in death.

CONCLUSION

The correction of AVM by microneurosurgery is a therapeutic approach widely used in referral and high complexity centers. The description of resection procedures leads to the presentation of access and correction approaches that can contribute to clinical vision and therapeutic designs. With this in mind, the present study aimed to meet this expectation, as well as to describe the correction of silent AVM after intraparenchymal hemorrhagic accident.

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Central Nervous System Involvements of the Lemierre Syndrome: case report and mini-review of the literature

Envolvimentos do Sistema Nervoso Central na Síndrome de Lemierre: relato de caso e mini-revisão da literatura

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ABSTRACT

Lemierre syndrome is a rare disease with fulminant course observed in healthy young adults. After an oropharyngeal infection, it is characterized by internal jugular vein thrombophlebitis, septicemia, and necrotic abscesses in distant organs. Mostly its causative microorganism is the Fusobacterium necrophorum. In these cases mortality rate used to be around 90%, but today this rate has decreased to 5% with early diagnosis and appropriate antibiotic treatment. Although the Lemierre syndrome, which was described in 1936, was widely observed in the pre-antibiotic period, the number of cases decreased dramatically after the widespread use of antibiotics in 1950s and 1960s. Facing this situation the Lemierre syndrome started being called the "forgotten disease" in the relevant years. In 1970s, it was observed its cases tended to increase according to the developments in radiological imaging techniques. Hovewer, the reviews in literature showed a remarkable increase in the incidence of Lemierre syndrome cases, especially in the last 15 years. In this article, a case of Lemierre Syndrome with sequelae of left abducens nerve palsy was presented with a literature review.

Keywords: *Human necrobacillosis; Internal jugular vein thrombosis; Jugular septic thrombophlebitis; Postanginal sepsis; Suppurative jugular thrombophlebitis*

RESUMO

A síndrome de Lemierre é uma doença rara com curso fulminante observada em adultos jovens saudáveis. Após uma infecção orofaríngea, caracteriza-se por tromboflebite da veia jugular interna, septicemia e abscessos necróticos observados em órgãos distantes. O microrganismo causador é principalmente Fusobacterium necrophorum. A taxa de mortalidade nesses casos costumava ser em torno de 90% e hoje reduziu para 5% com o diagnóstico precoce e o tratamento antibiótico adequado. Embora a síndrome de Lemierre, descrita em 1936, tenha sido amplamente observada no período pré-antibiótico, o número de casos diminuiu drasticamente após o uso generalizado de antibióticos nas décadas de 1950 e 1960. Esta situação a levou a ser chamada de "doença esquecida" nos anos relevantes. Na década de 1970, observou-se que os casos de síndrome de Lemierre tendiam a aumentar segundo o avanço das técnicas de imagem radiológica. No entanto, as revisões feitas na literatura mostram que houve um aumento notável na incidência de casos de síndrome de Lemierre, principalmente nos últimos 15 anos. Neste artigo, foi apresentado um caso de Síndrome de Lemierre com sequelas de paralisia do nervo abducente esquerdo com revisão da literatura.

Palavras-Chave: *Necrobacilose humana; Trombose da veia jugular interna; Tromboflebite séptica jugular; Sepse pós-anginosa; Tromboflebite jugular supurativa*

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INTRODUCTION

Lemierre Syndrome (LS), also called as human necrobacillosis, jugular septic thrombophlebitis, suppurative jugular thrombophlebitis, and postanginal sepsis, is a rare disease observed in healthy young adults[1-6]. LS was quite common and quickly became fatal within 7 to 15 days before the development of antibiotic drugs[7]. In the majority of cases, the septic thrombophlebitis develops in the jugular vein following the acute pharyngitis or tonsillitis. In fewer cases, the odontogenic infections, sinusitis, otitis and mastoiditis can be considered as primary infection foci. The most common microorganism in the sepsis, originating from the oropharynx, is *Fusobacterium necrophorum* (F. *necrophorum*), which is found in the normal oral flora. F. *necrophorum* is rod-shaped and is a gram-negative and obligate intracellular anaerobic bacterium[1,7]. Although more rarely, LS cases in which other causative microorganisms – such as F. *nucleatum*, *Staphylococcus aureus*, *Streptococcus viridans*, *Streptococcus pyogenes*, *Porphromonas asaccharolytica* and common anaerobic oral cavity bacilli – are responsible were also reported.

CASE PRESENTATION

A 46-year-old male patient was admitted to our Neurosurgery Department with a complaint of frontal headache. The patient's frontal headache complaint had been intermittent for 1 week. During his neurological examination a "lateral gaze restriction" was found, on the left, as a sign of *abducens* nerve palsy. However, diplopia was not detected. No abnormality was detected in laboratory tests. Since our patient did not have symptoms that could indicate infection, such as high fever and chills, and no abnormality was detected in laboratory tests, no causative microorganism research was performed. In the brain MRI was depicted a lesion in the left cavernous sinus, which was hypointense in T1- and hyperintense in T2- sequence, compatible with cavernous sinus thrombosis (Figure 1A). In the brain MR-angiography, a left internal carotid artery occlusion was detected and that the left anterior cerebral artery and middle cerebral artery were filling through the anterior communicating artery (Figure 1B). In addition, in the neck CT-angiography, the left internal carotid artery was found thrombosed along the entire tracing by starting from the proximal part, and no flow was observed (Figure 1C). In the brain MR-venography, an advanced decrease in the calibrations was detected depending on the partial thrombosis of the left internal jugular vein, sigmoid sinus and transverse sinuses (Figure 1D).

According to the patient, when he was 5 years old, he was referred to an external center with complaints of headache and fever, and was first diagnosed with sinusitis and then meningitis. The patient received antibiotic treatment for 2 months, and after this, the patient developed "double vision". During this period, the patient had developed a posture of looking by turning his head and neck to the opposite side in order to see the objects single. It was understood that ophthalmological surgical treatment was applied for the extraocular muscle weakness detected in the patient, and after this treatment, no complaints were observed in the patient for 11 years. When the patient reached the age of 17, he developed a pain starting from the left half of the neck, radiating to the left half of the head and face, and to the left eye. At the age of 20, the complaints of difficulty in looking outward and "double vision" in the left eye of the patient recurred, and these complaints continued for 5 years. At the age of 25, the patient was diagnosed with ophthalmic venous thrombosis and underwent ophthalmic surgery for the second time. Two years after this operation, the patient's complaint of "double vision" was completely resolved.

The patient was evaluated in detail by the Department of Infectious Diseases and Clinical Microbiology and Deapartment of Interventional Radiology. As a result of the 'multidisciplinary expert consultation', the final diagnosis of the patient was made as "left abducens nerve palsy permanent sequelae of Lemierre Syndrome". Anticoagulant therapy with Coraspin 100 mg/day per oral treatment and analgesic therapy was administrated. In the 1st, 6th and 12th months follow-ups of the patient there was no frontal headache complaint. In the neurological examination performed during the follow-ups; no other pathological finding was detected in the left eye other than 'lateral gaze restriction'.

DISCUSSION

The incidence of Lemierre syndrome (LS) is estimated to be 1 case per 1 million annually[1,8]. Among the reasons for this low

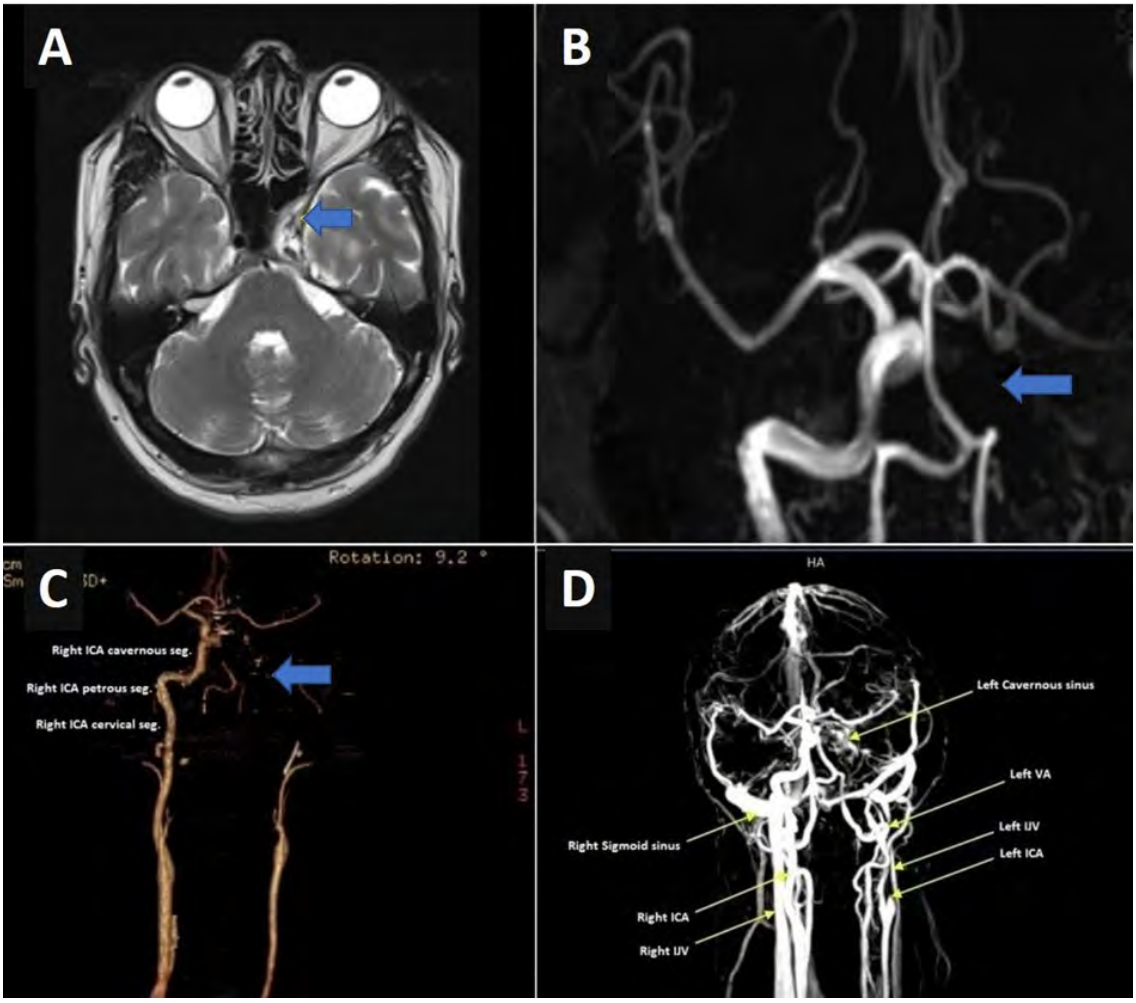

Figure 1. A. Brain MRI with hyperintense heterogeneous lesion observed in the left cavernous sinus on T2 sequences compatible with the cavernous sinus thrombosis (arrow). **B.** brain MR-angiography of the patient, the left internal carotid artery occlusion was detected (arrow) and it was determined that the left anterior cerebral artery and middle cerebral artery were filling through the anterior communicating artery. **C.** neck CT-angiography revealed left internal carotid artery thrombosed throughout the entire tracing, starting from the proximal part, and no flow was observed (arrow). **D.** brain MR-venography, a severe decrease in calibrations was detected depending on the partial thrombosis of the left internal jugular vein, sigmoid sinus and transverse sinuses.

incidence, the difficulties in diagnosing LS can be accounted due to both the fact that LS is a less well-known syndrome by clinicians and the multisystemic clinical course of the syndrome[9]. The fact that a case of LS was not reported in the literature between 1950 and 1960 caused this disease to be called as "forgotten disease"[10]. In 1970s, it was observed that LS cases reported in the literature tended to increase depending on the developments in diagnostic imaging techniques. In 2008, Hagelskjaer Kristensen and Prag[4] reported 3.6 cases per 1 million people per year. In 2019, Nygren and Holm[11] compared the cases between 2010-2013 and 2014-2017 and also emphasized that the its incidence increased from 1 case per 1 million of people to 1.7 cases per year, and this increase was statistically significant. In addition, it was also reported that the incidence of F. *necrophorum* infections increased from 2.9 to 5 cases.

Natural history and updated diagnostic criteria

The first patient with F. *necrophorum* infection was reported in 1900. In 1936, 20 cases with postanginal septicemia showing a fatal course were reported by Andre Lemierre, who nominated the disease. The symptoms observed in LS clinic such as sore throat ache, neck swelling, and sepsis were described in detail in this study[1,12]. The clinical triad of LS, which includes oropharyngeal infection, F. *necrophorum* bacteremia, and internal jugular vein

thrombosis (IJV) was described by Vogel and Boyer in 1980. In this description, the presence of at least two parameters was considered enough to diagnose LS, provided that only one of F. *necrophorum* bacteremia and IJV thrombosis were detected[13]. The causative microorganisms, which have a high potential to cause tissue necrosis, advance from the primary infection focus to the lateral pharyngeal space, where they are mostly located in the IJV via the lymphatics. In this localization, after ulceration and abscess formation, the causative microorganism invades the adjacent vascular structures in the head and neck region and it causes septicemia course along with the IJV thrombophlebitis and/or venous thrombosis within 1 to 3 weeks[14]. A number of invasion mechanisms were reported in the literature, which state that the hematogenous pathway – via the tonsillar vein, the lymphatic pathway through the jugular lymphatic system, and the local neighborhood pathway – were also responsible for the spread of the causative microorganism to the IJV. In particular, *in-vitro* studies showed that F. *necrophorum*, which enters ito the venous structure, activates platelets by producing leukotoxin and causes thrombus formation. In addition, it was observed that the exotoxin produced by F. *necrophorum* increased the production of tumor necrosis factor-α, which is responsible for inflammation in the clinical picture of LS[7]. As a result, a multisystemic infection picture occurs as a result of the metastatic spread of the septic emboli to the distant organs. The most exposed organ to the septic embolisms are the lungs and they often present with pulmonary thromboembolism. However, it may develop in the septic arthritis, osteomyelitis, pericarditis, meningitis and hepatic abscesses as a result of the metastatic infection[15].

However, many LS cases in which IJV thrombophlebitis was not observed after an oropharyngeal infection and metastatic lesions were detected in distant organs, only with F. *necrophorum* bacteremia, were also reported in the literature. On top of that, in 2014, Riordan[1] and Olson et al.[16] revised LS diagnostic criteria and reported that the presence of IJV thrombophlebitis was not essential. The authors described that the presence of a history of oropharyngeal angina in the previous 4 weeks and the detection of F. *necrophorum* in the blood culture would be enough for the diagnosis of LS in the patients with distant organ lesions. Similarly, a case report of LS with oropharyngeal Fusobacterium infection in which the infection spread to adjacent air sinuses, followed by cavernous sinus thrombosis, superior ophthalmic vein thrombosis, and meningitis was reported by Dasari et al.[17] Here, it was assumed that the causative microorganism caused bacteremia and septic emboli from this focus after spreading from the oropharyngeal region to the adjacent sinuses. It was reported that the main factors responsible for the fulminant course of LS were sepsis and pulmonary thromboembolism.

Central nervous system involvements

Papers reporting central nervous system (CNS) involvement caused by LS are summarized in Table 1. In LS case reviews, observed after 2010, it was reported that the CNS involvement due to LS was lesser than other organ involvement (1.9%, 3.6% and 4.9%)[2,12,18]. This occurred due to the fact that the IJV was located more inferiorly than the CNS and to the reverse flow. However, thrombosis of the sigmoid sinus, cavernous sinus and/or other intracranial venous sinuses secondary to LS were also reported in the literature[19]. Similarly, cavernous sinus thrombosis and internal carotid artery (ICA) cavernous segment partial thrombosis were determined in our case with the IJV total occlusion. The complaint of diplopia observed in the history in our case was caused by abducens nerve palsy secondary to the cavernous sinus thrombosis.

Although *Fusobacterium* meningitis is a rare observed complication secondary to LS, it is a poor prognostic sign[17]. Riordan et al.[1] reported that meningitis due to the *Fusobacterium ssp* or other anaerobic bacteria was observed in only 3 (1.3%) LS cases when they examined the data of 222 cases between 1970 and 2007. Kupppalli et al.[7] analyzed the data of a total of 91 LS cases between 1974 and 1999, reporting that *Fusobacterium* meningitis picture was observed in 7 (7.7%) LS cases as the most common CNS complication. These patients aged 5 to 26 years also had subdural empyema, venous sinus thrombosis, cranial nerve palsies, carotid and cerebral artery stenosis. From these, 3 patients had recovered, and the sequelae of different cranial nerve palsies were reported to be permanent in 3 patients. In this study, recurrence was observed in 1 patient, as in our case[7]. Similarly, in the case of LS with *Fusobacterium* meningitis reported by Dasari et al.[17], the patient was discharged with the residual findings such as abducens nerve palsy and diplopia, which we observed in our case.

Another LS complication characterized by the residual cranial nerve palsies is cavernous sinus thrombophlebitis (CST) followed by thrombosis picture. The cavernous sinuses, which have a high degree of vascularity, are highly sensitive structures especially in the head and neck region due to localized infection-induced septic embolism[20]. The CST picture still has a high mortality rate despite current antimicrobial treatments. It is caused by the retrograde flow of IJV thrombosis into the intracranial dural

Table 1. Lemierre Syndrome with Central nervous system complications.

Compilation Studies	Riordan (2007)[1]	Karkos et al. (2009)[8]	Kuppalli et al. (2012)[7]	Johannesen and Bodtger (2016)[2]	Nygren and Holm (2020)[11]	Moretti et al. (2021)[18]
Date range during compilation is made	1970 –2007	1950-2007	1980-2010	2010-2015	2010-2017	2013-2019
Number of cases (n)	222	114	91	137	104	64
Complication of the Central Nervous System (%)	16.7%	30%	24.1%	3.6%	1.9%	4.6%
Cavernous sinus thrombosis (%)	-	3.5%	2.1%	-	-	-
Cavernous sinus thrombosis & Carotid artery stenosis (%)	-	-	1%	-	-	-
Cavernous sinus thrombosis and Meningitis (%)	1.8%	-	-	0.7%	-	-
Cavernous sinus thrombosis, Meningitis & Carotid artery stenosis (%)	-	-	4.3%	-	-	-
Cranial nerve palsy (%)	-	3%	4.3%	-	-	-
Meningitis (%)	-	-	7.7%	-	-	-
Brain abscess (%)	1.8%	-	1%	-	-	-
Epidural and Subdural empyema (%)	-	-	6.5%	0.7%	-	-
Cerebral infarction (%)	-	-	8.7%	-	-	-
Ophthalmic complication (%)	-	5%	3.3%	0.7%	-	-

venous sinuses. Additionally, in the literature was reported that the air sinus infections such as maxillary, paranasal, ethmoidal and sphenoidal sinuses cause CST with the venous spread. Involvement of the anatomical structures within the cavernous sinus and adjacent to the sinus constitutes the main clinical presentation of the disease. Although the CST is often accompanied by the meningitis, the epidural/subdural empyema, cerebritis, cerebral abscess, ICA stenosis and cerebral infarction can also be observed less frequently[21,22]. In the CST clinic picture, high fever, frontal headache, ocular pain, and periorbital edema are frequently accompanied by the limitation of eye movements and diplopia, which is developed secondary to the ocular cranial nerve palsies[23]. Dasari et al.[17] and Shibuya et al.[19] also reported LS cases in which *Fusobacterium* meningitis and cavernous sinus thrombosis were observed together. They found the importance of early diagnosis in the cavernous sinus thrombosis, which can have a fatal course, was particularly emphasized, and they reported that the initiation of antibiotic and anticoagulant treatment as early as possible significantly affected prognosis of the disease[23]. It is also very important to investigate the primary focus in LS cases complicated by the cavernous sinus thrombosis and to plan surgical intervention in the cases with chronic sinusitis and oropharyngeal abscess[20]. In 2009, Karkos et al. [8] reviewed 114 cases of Fusobacterium-induced thrombophlebitis, between 1950 and 2007, and reported the overall CNS involvement rate as 30%, including cavernous, transverse, and sigmoid sinus thrombosis. In this study, the rate of ophthalmic complications, including paralysis of the 3rd, 4th and 6th cranial nerves innervating the extraocular muscles, was reported to be 5%.

Clinical manifestations and complications

LS clinic aspects usually starts with the complaint of sore throat, which is a common finding of the oropharyngeal infections such as pharyngitis and tonsillitis. High fever can be observed in addition to other nonspecific symptoms such as vomiting, fatigue and weight loss approximately 1 week after the onset of this localized infection in the primary focus[24]. After, a neck pain, mostly unilateral, and swelling in the neck, and to a lesser extent, trismus findings arew developed[25]. In cases complicated by septic pulmonary thromboembolism, the chest pain and shortness of breath dominate the clinical presentation. In addition to all these complaints, the patients with LS diagnosis often are referred to the emergency department with the systemic sepsis findings and shock[24].

In a review conducted in 2020 on 27 patients diagnosed with LS between 2009 and 2019, it was reported that the ophthalmic complications were detected in 88.9% of the cases. In these cases, there was limitation of

extraocular muscle movements due to paralysis of the 3rd, 4th and 6th cranial nerves and diplopia among the most common complaints. They reported IJV thrombosis in 81.5%, cavernous sinus thrombosis in 70.4%, diplopia due to 6th cranial nerve palsy in 50%, and decreased visual acuity in 29.6%[26]. The cases complicated by the partial or total thrombosis of the cavernous, sigmoid, and other intracranial venous sinuses can show an asymptomatic course, as well as a symptomatic course ranging from the cranial nerve palsies to the venous infarctions[27].

Diagnosis: laboratory and radiological parameters

Investigation of the diagnostic criteria such as radiological imaging of IJV thrombosis, showing F. *necrophorum* in blood cultures and detecting multisystemic metastatic infected lesions is a detailed and long process. The fact that the defined diagnostic criteria are not fully met and the disease has a multisystemic course are the most important issues that make the diagnosis difficult in LS. Delayed diagnosis causes late initiation of the treatment and a two-fold increase in mortality[2]. In this context, the most important issue in the diagnosis of LS is the high clinical suspicion that should be shown in patients with oropharyngeal infection. Especially, in case of persistent high fever observed in early stages of the disease, skepticism should be treated and further research should be done[7].

In the early stages of the disease, nonspecific sore throat depending on the oropharyngeal infection and infectious mononucleosis findings such as Leukocytosis, C-reactive protein (CRP) and Erythrocyte sedimentation rate (ESR) elevation are observed in the laboratory. Especially in this period, the blood cultures should be sent to determine the causative microorganism before starting antibiotic treatment so that LS cases are not overlooked. However, since F. *necrophorum* has long incubation period such as 5 to 8 days causes blood cultures to be seen as sterile in the early stages of LS, resulting in a false confidence picture for clinicians. Therefore, Polymerase chain reaction (PCR) test should also be performed to detect F. *necrophorum* in the cases with negative culture results in the early stages of the disease[1,2,7,16].

The neck/jugular venous system Doppler USG and/or neck contrast-enhanced CT (computed tomography) to detect IJV thrombosis in cases with suspection of LS, and thorax CT in the diagnosis of the septic pulmonary embolism are vital tests for the diagnosis[1]. In addition, the presence of pulmonary infiltrates on chest radiographs is a valuable finding. However, the contrast-enhanced CT and MRI are the most accurate diagnostic tools for detecting metastatic infected lesions and their localization such as venous thrombus formation, pulmonary embolism, osteomyelitis, arthritis and abscess (brain, kidney and liver abscess)[1,2,25].

Antimicrobial therapy

In patients who are referred to the Emergency Department with pulmonary embolism and shock, supportive treatment for the respiratory and cardiovascular systems should be planned first. The mortality rate in the patients who do not receive appropriate antibiotic treatment during this period until definitive diagnosis is around 90%[24]. Rapid diagnosis and initiation of antibiotic treatment as soon as possible is the most important factor to reduce morbidity and mortality in LS cases[1,28]. Therefore, the treatment with the broad-spectrum antibiotics such as Ceftriaxone, which is also effective against the anaerobic bacteria, should be started until F. *necrophorum* is identified in the blood cultures, especially in the patients with significant swelling and tenderness in the neck, symptoms of sepsis, and high fever. This treatment should be continued for 4 to 6 weeks[17,25]. In addition, there are other antibiotic options that are effective against the anaerobic bacteria, such as ticarcillin-clavulanate, ampicillin-sulbactam, clindamycin and flagyl[24]. In cases with the peritonsillar abscess, high-dose intravenous penicillin treatment can also be preferred[3]. Where Fusobacterium strains are identified in the blood cultures, Metronidazole, which penetrates well into the CNS and has excellent antimicrobial effect, should be preferred. Johannessen et al. reported that a 98% success rate was achieved by using Metronidazole together with Carbapenem or Piperacillin/Tazobactam combination treatment for an average time of 1 month[2].

Anticoagulation therapy

The anticoagulation treatment is still a controversial issue due to its potential risks such as bleeding in the treatment of jugular venous thrombophlebitis, intracranial vein and dural sinus thrombosis observed in LS[8,24]. In the review of Johannesen and Bodtger[2], 64% of the patients who received anticoagulant treatment were compared to 34% of the patients who did not receive anticoagulant treatment, and found no difference in mortality between two groups. On the other hand, in a prospective study conducted by Stam in 2005[23], the rate of recovery in the patients with the sinus thrombosis was 79% with the anticoagulation treatment with Heparin, whereas major morbidity was 5% and mortality was 8%. Riordan et al. [1] suggested that 21 to 23% of the patients included in their study were treated with the anticoagulants, and consequently, the anticoagulant treatment should be used only in the cases where there is no response to the antibiotics and thrombus spreading continuously including the cerebral sinuses. Kuppalli et al.[7] emphasized that the cases with the cerebral sinus thrombosis such as IJV thrombosis and cavernous sinus thrombosis should be divided into subgroups first and then an aggressive treatment strategy including the anticoagulant treatment should be decided for these subgroups. However, it is observed that the views on the use of

the anticoagulant treatment gain more weight in the literature, as it facilitates the resolution of venous thrombosis and allows antibiotics to have a better penetration in septic embolisms[15,17,23].

Surgical therapy

The mortality rate in the localized infections such as necrotic abscesses, septic arthritis and empyema observed in LS and infected in the deep neck region is around 5%. Therefore, drainage of the infected lesions in the relevant localization is an important factor determining the prognosis of the disease[1]. The surgical drainage of the abscesses detected in primary foci is also very important to provide better penetration of the antibiotics and better control of the infection[2,13]. In this case, the surgical drainage of the abscess should be performed first and then the treatment with the broad-spectrum intravenous antibiotics should be continued. In these cases with excessive pulmonary secretion and severe shortness of breath, the respiratory support should be given by the intubation first. On the other hand, the surgical drainage should be preferred in the abscesses observed in the lateral pharyngeal space and retropharyngeal space. Similarly, in the treatment of the peritonsillar abscesses, the abscess drainage should be performed by the surgical intervention to prevent the airway obstruction that will be able to develop with the abscess enlargement, aspiration pneumonia that will be able to be developed as a result of the spontaneous abscess rupture, and the dissection of the abscess into the lateral retropharyngeal space. Both anaerobic and aerobic culture studies should be performed on the materials taken during the surgery[3]. In addition, the cases who underwent multiple air sinus operations such as maxillary antrostomy, ethmoidectomy and sphenoidectomy to remove infected materials in the air sinuses were reported in the literature[17].

Combination therapy

In the review conducted by Dasari and Jha[26], 2020, it was reported that all three treatment methods were applied in 27 patients with LS diagnosed with the IJV thrombosis and cavernous sinus thrombosis. In this study, while 40.7% of the cases were treated with metronidazole and 25.9% with ceftriaxone antibiotic treatment, both anticoagulant and surgical treatment were applied in 51.8% of the cases.

CONCLUSION

The reviews found in the literature showed a remarkable increase in the incidence of LS cases, especially in the last 15 years. This increase is thought to be due to more limited use of the antibiotic applications in patients with sore throat in recent years. Early diagnosis of the focus of the infection and "multidisciplinary treatment approach" are vital in Lemierre Syndrome cases. Thus, the focus of the infection can be eradicated with both surgical treatment and appropriate antibiotic treatment. The anticoagulant treatment indication and duration of the administration were still not standardized. In order not to overlook LS, which is less well-known by clinicians and shows a fulminant course, LS should be considered especially in patients with oropharyngeal infection and presenting a picture of the sepsis.

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Fístula Liquórica Rinogênica por Iatrogenia Pós-Teste de *Swab* para Covid-19: revisão e relato de caso

Iatrogenic Liquor Fistula After Swab Test for Covid-19: review and case report

Milena de Souza Melo[1]
Felipe Marchi[1]
Danilo Magnani Bernardi[2,3]
Sérgio Aydar Quadrado[4]

RESUMO

Introdução: *As fístulas liquóricas nasais são comunicações do espaço subaracnoide com a cavidade nasal ou seios paranasais, de etiologia traumática ou não-traumática. A descontinuidade na base craniana resulta em escape de líquor através da nasofaringe. Os sintomas mais frequentes são rinorreia hialina unilateral, que piora ao abaixar a cabeça ou realizar algum esforço físico, cefaleia, náuseas e vômitos.* **Relato de caso:** *Caso de fístula liquórica rinogênica por iatrogenia pós teste para covid-19 por swab nasal, na qual houve a necessidade de fechamento cirúrgico. Paciente de 56 anos encaminhada ao serviço hospitalar após iniciar com quadro de rinorreia hialina após teste com swab nasal para covid-19, que resultou na formação de uma fístula liquórica nasal à esquerda. Após dias em tentativas de tratamento conservador, sem resolução do quadro, a paciente foi submetida a uma septoplastia com confecção de retalho septal para fechamento posterior da fístula.* **Conclusões:** *Diante do cenário atual de pandemia, é de grande relevância a documentação de casos de fístula liquórica para a preparação de profissionais que realizam os testes, frente ao uso demasiado destes durante a pandemia, pois pode acarretar graves prejuízos e riscos à saúde dos pacientes.*

Palavras-Chave: *Iatrogenia; Fístula liquórica; Swab nasal; Septoplastia*

ABSTRACT

Background: *Nasal cerebrospinal fluid fistulas are communications from the subarachnoid space with the nasal cavity or paranasal sinus, of traumatic or non-traumatic etiology. A discontinuity in the cranial base results in cerebrospinal fluid escape through the nasopharynx. The most common symptoms are unilateral hyaline rhinorrhea, which worsens by lowering the head or performing some physical exertion, headache, nausea, and vomiting.* **Case presentation:** *A case of rhinogenic liquic fistula by iatrogenic post-test for covid-19 by nasal swab, given the high frequency of these tests in the current pandemic scenario is reported. A 56-year-old patient referred to the hospital after starting with hyaline rhinorrhea after a test with nasal swab for covid-19, which resulted in the formation of a nasal cerebrospinal fluid fistula on the left nasal cavity. After days of attempting conservative treatment, without resolution of the condition, the patient was submitted to a septoplasty with septal flap for posterior closure of the fistula.* **Conclusions:** *Given the current pandemic scenario, it is of great relevance to document cases of nasal cerebrospinal fluid fistula for the preparation of professionals who perform the tests, given the use of these during the pandemic, as it can bring serious damage and risks to the health of patients.*

Keywords: *Iatrogenic; Cerebrospinal fluid fistula; Nasal swab; Septoplasty*

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INTRODUÇÃO

As fístulas liquóricas nasais são comunicações do espaço subaracnoide com a cavidade nasal ou seios paranasais, de origem traumática ou não-traumática. As fístulas traumáticas podem ocorrer por iatrogenia ou traumas de crânio[1-3]. As fístulas liquóricas podem levar à hipotensão intracraniana, sendo a manifestação mais frequente, sendo cefaleia ortostática intensa com piora na vertical[3,4]. Outros sintomas frequentes são: rinorreia hialina, unilateral, que acontece ao abaixar a cabeça ou realizar algum esforço físico, a quantidade pode variar de poucas gotas até a saída profusa. Pode ser acompanhado de gosto metálico, náusea, vômito[4,5]. A principal complicação das fístulas liquóricas são as infecções do sistema nervoso central, em especial, a meningite, por atuar como possível porta de entrada para diversos microrganismos[4,5]. São referidos como iatrogenia, os efeitos colaterais e os riscos associados a intervenções médicas. Segundo a Organização Mundial da Saúde (OMS) iatrogenia pode ser definida como qualquer efeito nocivo não intencional e indesejado de uma droga, que ocorre em doses usadas em humanos para profilaxia, diagnóstico ou terapia[6,7]. Essa definição tende a subestimar incidentes ocorridos durante procedimentos diagnósticos que possuem uma natureza mecânica[6,8], como os exames que utilizam *swab* para a coleta do material analisado, como o relatado no presente trabalho. No presente relato de caso, o fator causador da fístula foi a realização do exame RT-PCR por meio do *swab* nasal para detecção do novo coronavírus (COVID-19).

O diagnóstico precoce é de suma importância para a realização da profilaxia de infecções, que podem ter desfechos graves. Em certos casos, o diagnóstico de fístula é óbvio, entretanto, em muitos outros casos se torna um desafio[9]. A história do paciente com fístula é característica, manifestando-se como descarga nasal de líquido claro e intermitente que emana do nariz quando o paciente se inclina para a frente, de quantidade variável, muitas vezes associada a algum trauma ou após algum procedimento médico, porém, o diagnóstico não é tão simples quando a etiologia não é tão clara, como nas fístulas não traumáticas[2,4,10]. Foram registrados outros 8 casos de fístulas liquóricas secundárias a injúrias causadas por *swab* utilizados nos testes de RT-PCR para o diagnóstico de COVID-19; como no relato de caso em que se conseguiu uma remissão a partir do tratamento conservador[9].

RELATO DE CASO

Paciente feminina, 56 anos, parda, hipertensa, diabética tipo II ecardiopata. Paciente encaminhada ao serviço hospitalar com queixa de cefaleia, êmese, otalgia, xeroftalmia, vertigem e dificuldade para deambulação, apresentando uma fístula liquórica rinogênica de etiologia iatrogênica (traumática) em narina esquerda após a realização de um teste RT-PCR por suspeita de infecção COVID-19.

Decorreu-se uma semana dos sintomas supracitados para que a paciente recebesse o diagnóstico de fístula liquórica rinogênica. Com internação imediata a paciente foi submetida a um exame de tomografia computadorizada (Figura 1) que confirmou o diagnóstico.

O tratamento inicial de escolha foi realizado de forma clínica conservadora, com antibioticoterapia: amoxicilina 875mg + ácido clavulânico 125mg para profilaxia de infecção, acetazolamida, repouso no leito com elevação da cabeceira 45 graus, recomendação para evitar movimentos da cabeça e outros fármacos para alívio dos sintomas, além da administração da medicação de uso contínuo da paciente.

Outra tentativa de tratamento consistiu na colocação de um dreno peridural lombar, utilizado por 7 dias, sem eficácia necessária. Após 80 dias de internação, sem resolução do caso, a paciente foi submetida a uma septoplastia com confecção de retalho septal para fechamento posterior da fístula (Figura 2). Sob efeito de anestesia geral foi introduzido um cateter peridural, e aplicada a fluoresceína, feito uma solução hipodensa, na concentração de 5%. Realizou-se antrostomia maxilar esquerda, etmoidectomia anterior à esquerda, etmoidectomia posterior à esquerda, onde evidenciou a fístula liquórica nasal à esquerda, no teto do etmoide. Em seguida, foi escarificada a borda da fístula e inserido substituto de dura. Fixado o enxerto livre sobre a região da fístula e colocado Surgicel® (hemostático absorvível) em todo o bordo do enxerto. Para finalizar, aplicou-se a cola biológica sobre o enxerto e colocado um tampão anterior em fossa nasal esquerda para segurar o enxerto. Paciente passou por três consultas de seguimento onde se evidencia a ausência da fístula, permanecendo assintomática.

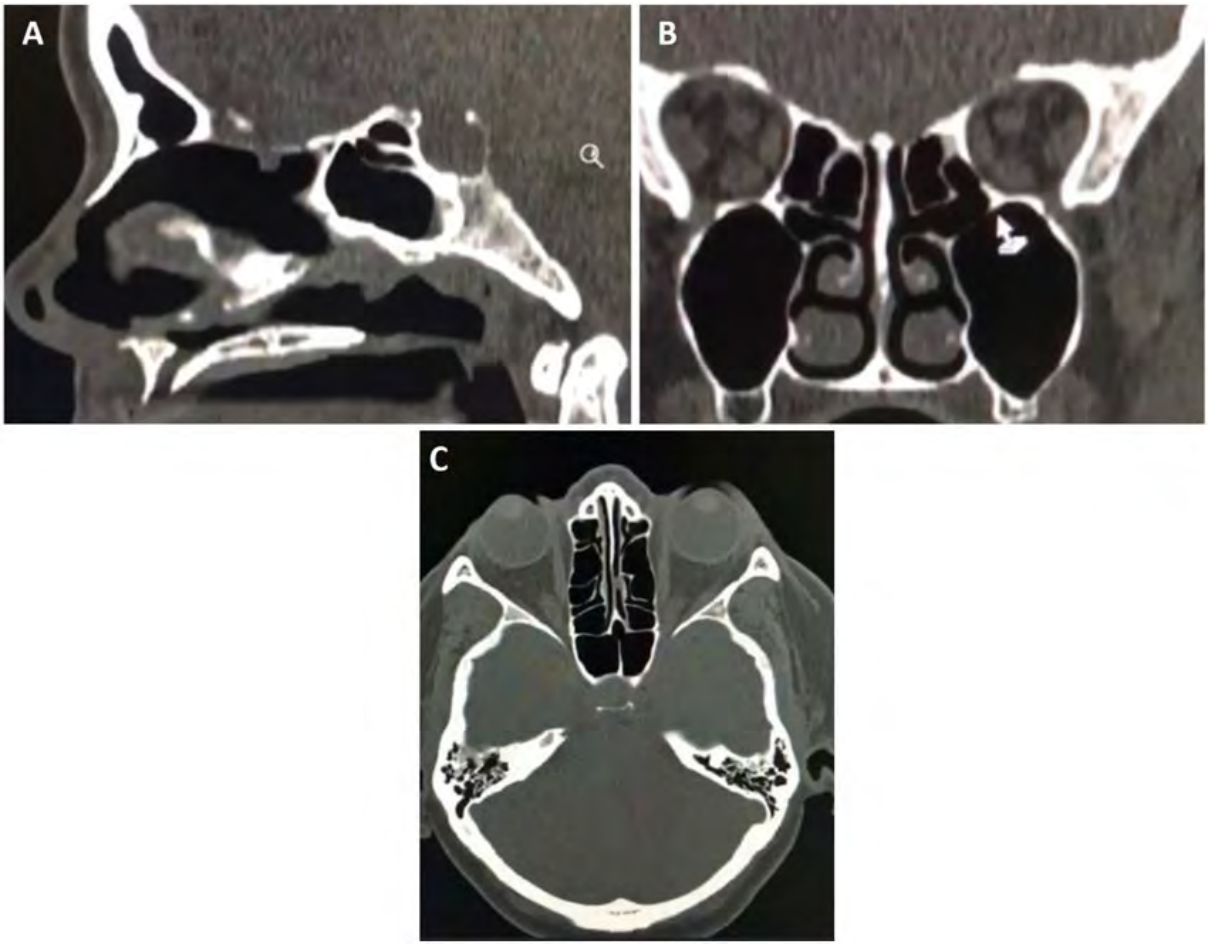

Figura 1. Tomografia de seios da face pré-operatório. Fístula liquórica entre septo e concha média, transição entre etmoide anterior e posterior. **A**. corte sagital. **B**. corte coronal. **C**. corte axial.

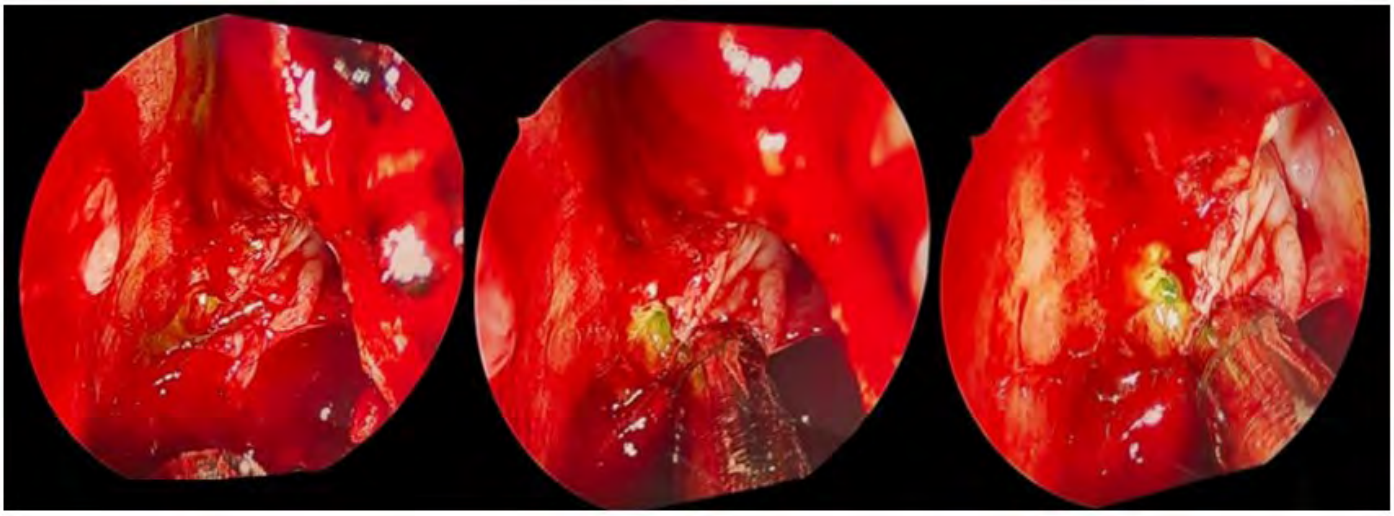

Figura 2. Imagem intraoperatória em vídeo com fístula localizada com coloração com contraste de fluoresceína.

DISCUSSÃO

As fístulas liquóricas nasais se caracterizam por uma comunicação do espaço subaracnoideo com os seios paranasais e o lúmen nasal. A descontinuidade na base craniana resulta em escape de líquor através da nasofaringe, que pode ser profuso ou discreto[2,11]. As fístulas liquóricas nasais são comumente localizadas no osso etmoide (37%) e no seio esfenoidal (33%). A maior parte dos pacientes que apresentam uma fístula liquórica, a possuem devido a uma etiologia traumática (2/3 dos pacientes)[12]. O mecanismo de trauma do caso relatado caracteriza-se pela ruptura da base anterior esquerda na lâmina cribriforme posterior através da aplicação de força excessiva durante a introdução do *swab* para a coleta do material nasal, levando à formação de uma fístula liquórica com o extravasamento imediato de líquido cefalorraquidiano pela narina esquerda.

Este exame, padrão-ouro para detecção do vírus COVID-19, que é realizado através de um cotonete longo e estéril, introduzido na fossa nasal até atingir a resistência natural da parede posterior da nasofaringe, com movimentos rotatórios suaves, evitando sangramento. A execução do teste e leitura dos resultados devem ser realizadas por profissionais da saúde de nível médio, com supervisão, e/ou de nível superior[13], no entanto, é realizado principalmente por profissionais que podem não entender completamente a anatomia da cavidade nasal e da nasofaringe[14]. Ao exercer uma força desproporcional, o profissional que realizava o *swab*, perfurou a lâmina cribriforme causando o extravasamento de líquor, responsável por toda a sintomatologia da paciente. As fístulas liquóricas são comumente causadas por eventos traumáticos, como em acidentes automotivos, ou por procedimentos médicos, como punções durais e epidurais. Contudo, apenas 30% dos pacientes com fístula liquórica conseguem identificar um evento iniciante ou trauma, como a maioria dos pacientes, sendo incapazes de rastrear a causa dos sintomas[2-4]. A confirmação do diagnóstico se faz com exames de imagens, incluindo radiografia simples, tomografia computadorizada, ressonância magnética, mielograma-TC, cisternogramas de radionuclídeos e ressonância magnética com gadolínio intratecal[5,15]. O fechamento da fístula ocorre espontaneamente em 60% dos pacientes, caso não haja progressão dos sintomas, nos primeiros meses o tratamento deve ser conservador, com fármacos para alívio dos sintomas, antibioticoprofilaxia e repouso. Há necessidade de intervenção cirúrgica, caso não haja remissão espontânea[5,16-18]. Em casos em que o tratamento conservador não é suficiente, os pacientes submetidos a uma cirurgia reparadora apresentam uma taxa de sucesso de 97%[12]. O tratamento mandatório é o fechamento cirúrgico é através da técnica endonasal ou transesfenoidal, preferencialmente endoscópica, por essa ser uma estratégia segura e eficiente, com taxas de mortalidade e morbidade inferiores à técnica por craniotomia[3].

CONCLUSÃO

Diante do cenário atual de pandemia, a realização de exames para detecção do novo coronavírus por meio do *swab* nasal tornou-se rotina. O RT-PCR por *swab* é considerado padrão-ouro para diagnosticar infecções agudas pela Covid-19, causada pelo SARS-CoV-2[8,12]. Ainda não são bem conhecidas as possíveis complicações do esfregaço nasal, contudo, como em qualquer outro procedimento existem riscos ao paciente, e portanto, os testes devem ser realizados com cautela[13]. Por conseguinte, é de grande importância a documentação de casos de fístula liquórica para a preparação de profissionais que realizam os testes, frente ao uso demasiado destes durante a pandemia. O tratamento das fístulas é realizado, na maioria das vezes, de forma conservadora, porém, em alguns casos como o da paciente em questão, é necessário o fechamento cirúrgico[15,17,18].

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Chronic Encapsulated Intracrerebral Hematoma

Hematoma Intracerebral Crônico Encapsulado

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ABSTRACT

Chronic intracerebral encapsulated hematomas (CEIH) correspond to a very rare neurosurgical pathology. To date, there are about 57 cases described worldwide, especially in Japan, where the disease is more prevalent. To data, until the moment we wrote this report, according to a review on the Pubmed website, there was no case described in South America. It is a condition of difficult preoperative diagnosis because its form of presentation is very similar to brain neoplasms. Only about 20% of cases are diagnosed during pre-operative period.

Keywords: *Chronic encapsulated intracerebral hematoma; Cerebral neoplasms, Tumor-like brain lesion*

RESUMO

Os hematomas encapsulados intracerebrais crônicos (CEIH) correspondem a uma patologia neurocirúrgica bastante rara. Até a presente data existe cerca de 57 casos descritos em todo o mundo, especialmente no Japão, onde a doença é mais prevalente. Para registro, até o momento em que escrevemos este relato, segundo a revisão levantada no site da Pubmed, não existe nenhum caso descrito na América do Sul. Trata-se de uma condição de difícil diagnóstico pré-operatório, pois sua forma de apresentação assemelha-se bastante com as neoplasias cerebrais. Somente cerca de 20% dos casos são diagnosticados no pré-operatório.

Palavras-Chave: *Hematomas intracerebrais crônicos encapsulados; Neoplasias cerebrais; Lesões tumor-like*

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CASE PRESENTATION

Male patient, 22 years old, born in the city of Urucará, state of Amazonas. According to the anamnesis – collected from the mother and partner, he was born by normal delivery with uneventful pregnancy, therefore born at term. According to the mother, he presented a good neuropsymotor development without any data that drew attention to a possible abnormality. He performed well at school.

He had no previous pathologies. About 3 years ago, he presented head trauma after physical aggression. After this episode, he developed seizures with a tonic-clonic pattern. He was attended to in his hometown and the medication Phenobarbital 200mg / day was started. Initially, he presented a good response with adequate control of seizures.

After this accident, he started to present headache with tension pattern, frontal-occipital headache, under weight, lasted less than 4h with good response to analgesics.

Mother says that over the years these pain symptoms have worsened. Becoming disabling, and about two months ago, he presented drowsiness and disorientation with occasional nausea episodes. At this moment, he was sent to the capital of the State of Amazonas for specialized evaluation.

He entered the emergency room with support for neurosurgery. He was admitted to the emergency room of the Hospital with Glasgow coma scale of 13, with severe headache, visual alteration (referring partial loss of visual field). He was initially taken for a brain tomography that showed an expansive lesion located in the topography of the temporal lobe D, circular in shape with well-defined edges. The image was contrasted and maintained a pattern very suggestive of a neoplasm with a glial pattern.

After the brain Magnetic Resonance imaging showed the same pattern with elliptical, temporal D image with contrast enhancement in the capsular region and a cleavage plane between the lesion and brain tissue (Figures 1-4).

Due to the urgency requiered by the staff, he was transferred on an emergency basis to the Hospital Universitário Getúlio Vargas for surgical treatment.

The initial diagnosis of this patient was a neoplasm of glial origin. We believed that we were treating a brain tumor, so a wide right fronto-temporo-parietal craniotomy was planned. After that, a corticectomy was performed in the right superior temporal gyrus.

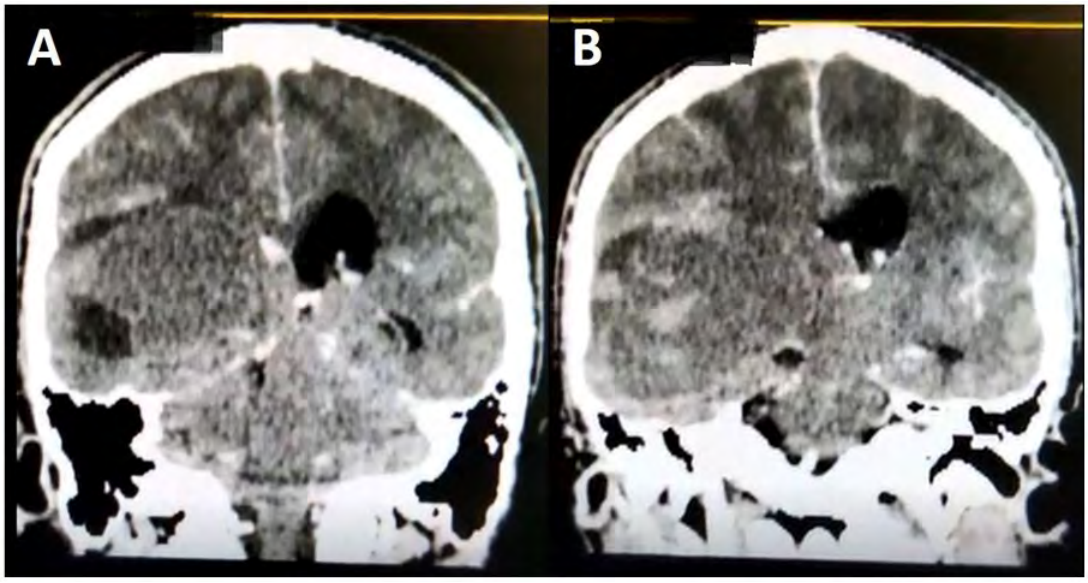

Figure 1. A, **B**. Pre-operative CT. Coronal view.

To our surprise, it was a liquid, bloody collection, permeated by some small clots, which were well organized in a yellowish capsule. After drainage, the cerebral cortex collapsed, requiring its internal filling (inside the capsule) with physiological solution. Gelfoam was also used to help not to pull the vein bridges. During the surgery, material from the capsule was collected and it was chosen not to remove its most posterior portion as it was adhered to the Middle Cerebral Artery.

The patient was extubated in the immediate postoperative period and evolved with complete recuperation of the level of consciousness on the same day (Figures 5-7).

After 2 days, he was discharged asymptomatic.

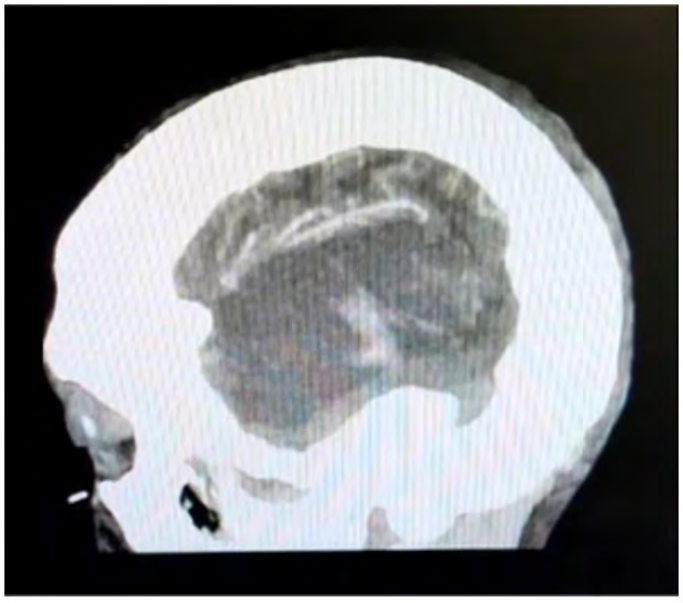

Figure 2. Pre-operative CT. Sagittal view.

BACKGROUND

Chronic encapsulated intracerebral hematoma (CEIH) is a rare condition. About 60 cases have been described worldwide[1]. It was first described in 1981 by Hirsch et al in Pennsylvania in the United States[2].

It is a slow-growing lesion, with a mass effect, which resembles a neoplasm of the central nervous system. This pattern of behavior makes it a nosological entity with difficult preoperative diagnosis, so that only about 20% of cases are diagnosed prior to surgery[3].

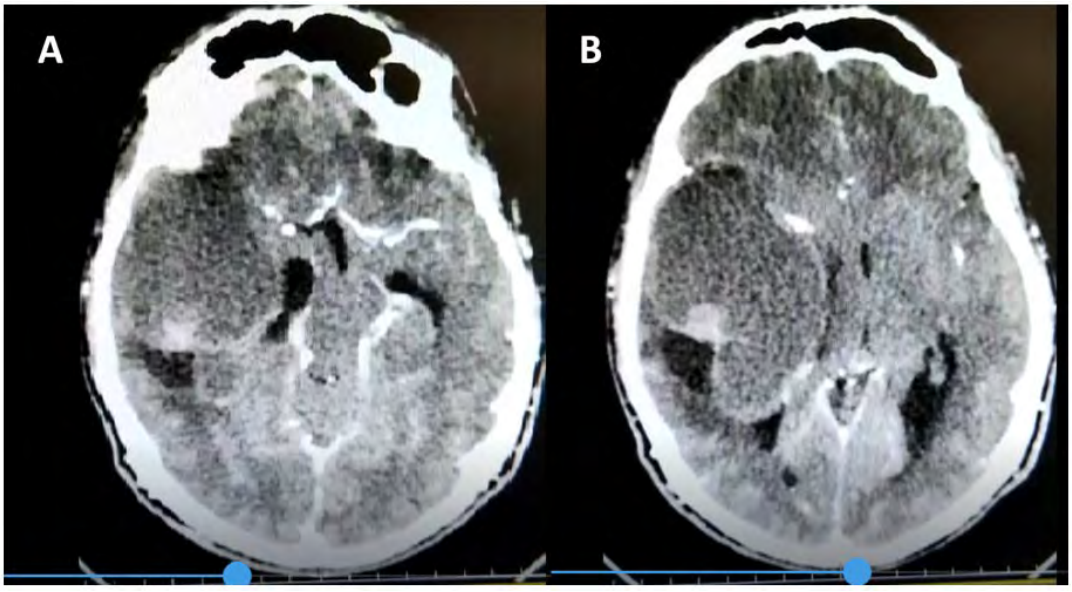

Figure 3. A, **B**. Pre-operative CT. Axial view.

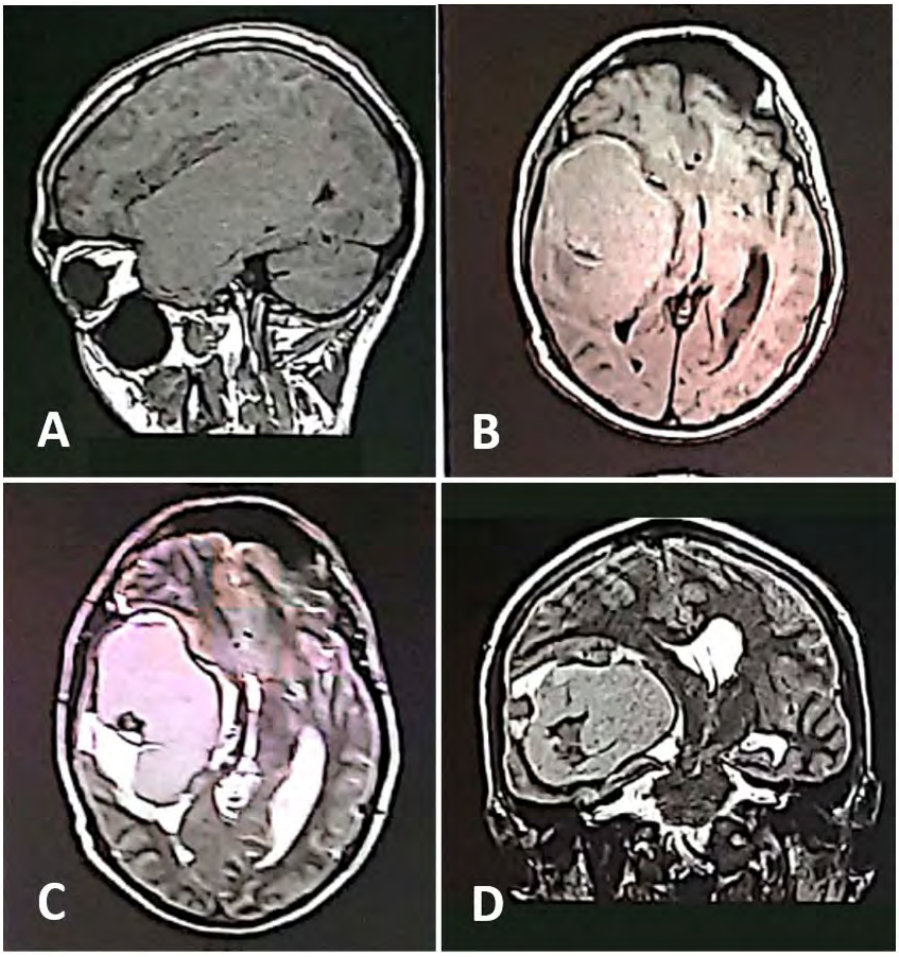

Figure 4. Pre-operative CT. **A**. T1, sagittal view. **B**. Flair, axial view. **C**. T2, axial view. **D**. T2, coronal view.

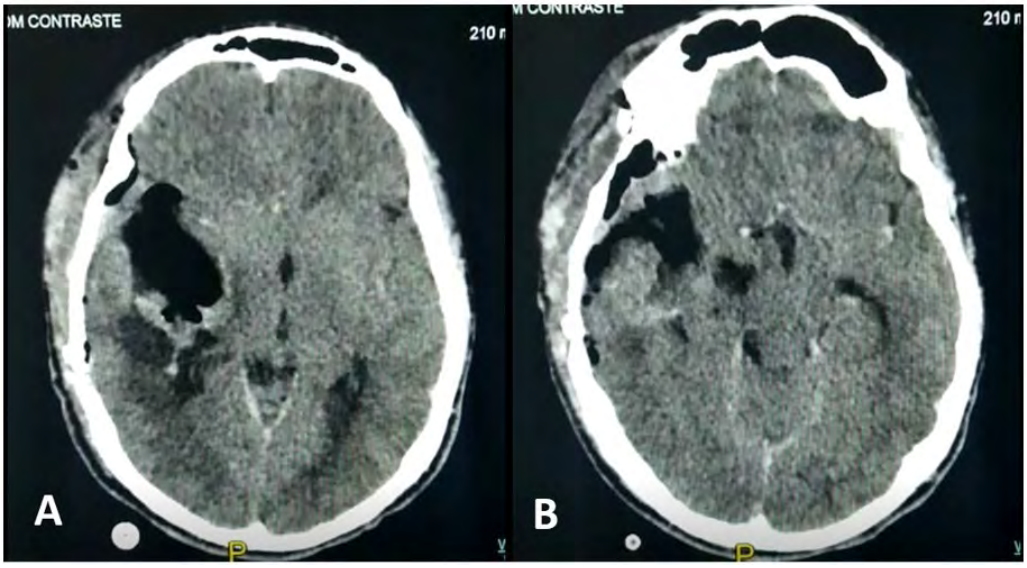

Figure 5. A, **B**. Post-operative CT (Day 1).

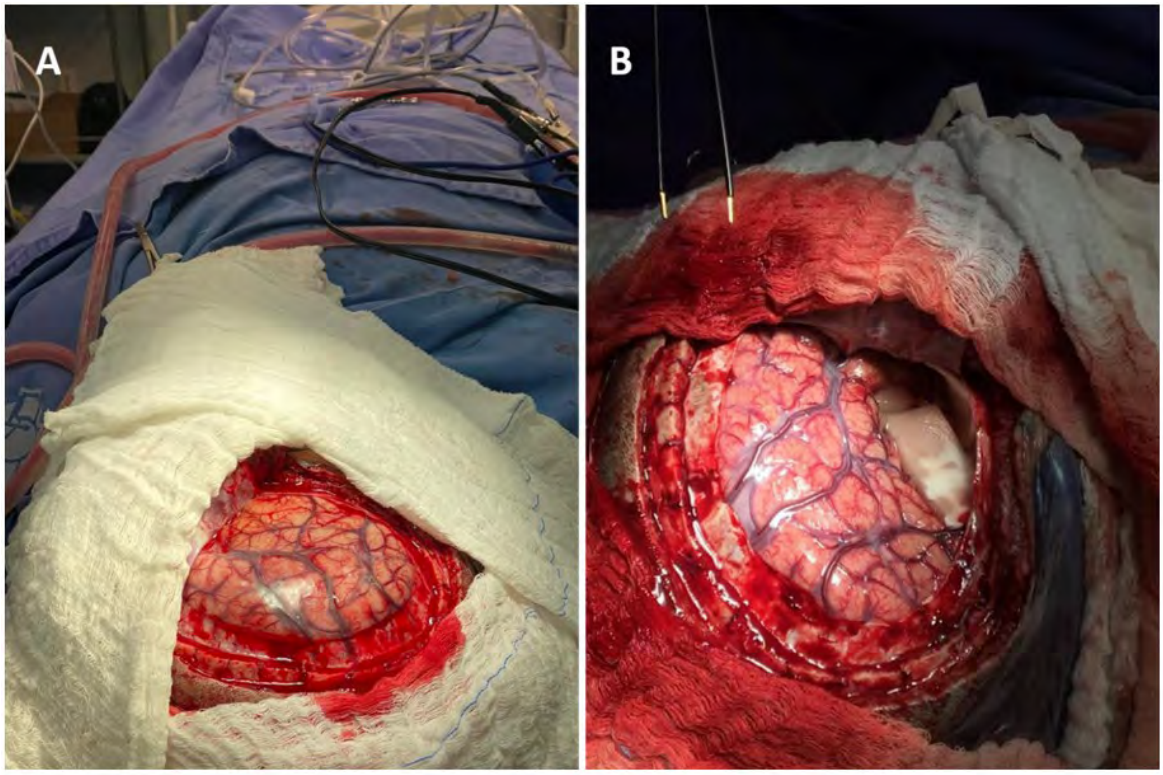

Figure 6. A. Pre-operative image. **B**. post-operative image.

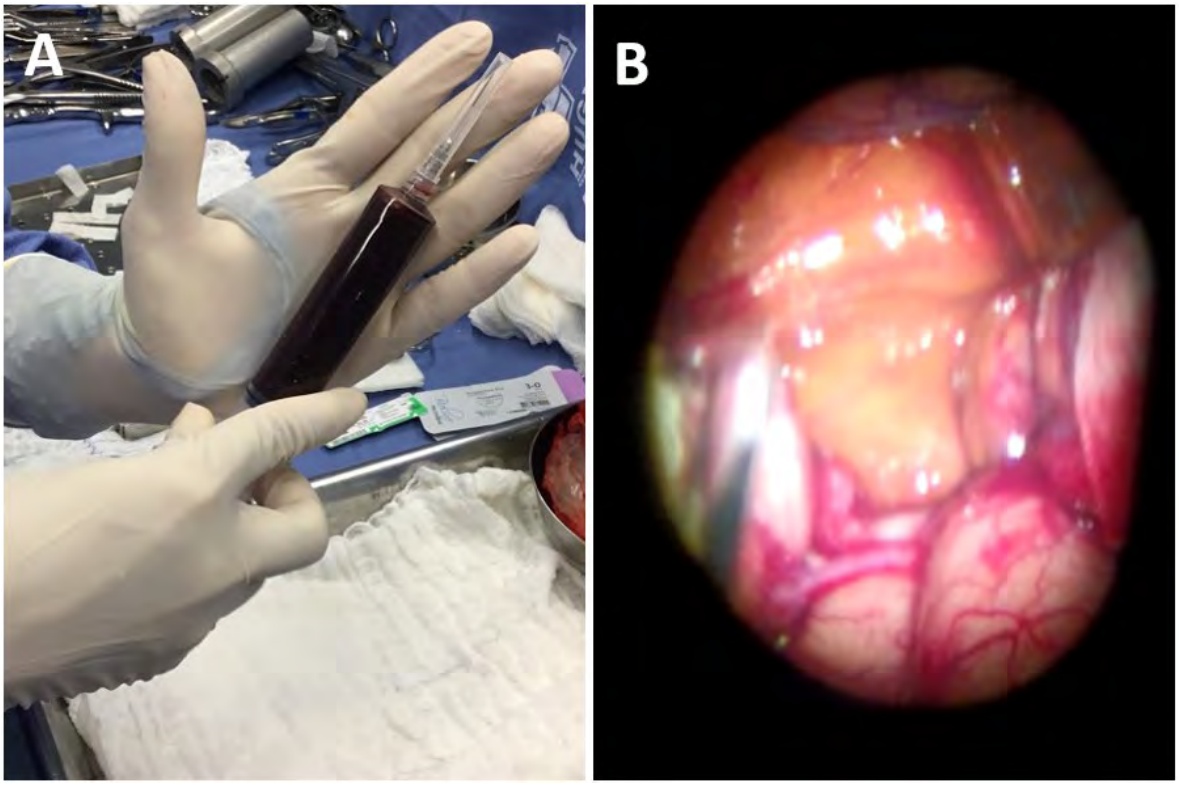

Figure 7. A. Intra-capsular content (blood). **B**. hematoma capsule after hematoma drainage.

Such pathology presents slow growth which allows the formation of a fibrous capsule, rich in fibroblasts that ends up isolating the hemorrhagic content and preventing its absorption. Such a capsule is quite similar to that seen in chronic subdural hematomas, both from a macroscopic and histological point of view.

Of all reported cases, it is clear that it is an entity that is found in all age groups. Cases have been described in individuals aged 2 years and 80 years. Men are more affected (37 men, 20 women). The mean age of diagnosis is 44 years[3]. There is a small difference in the presentation of these cases. Subdural hematomas have a more acute presentation, with neurological deficits of more evident onset. Chronic encapsulated intracerebral hematomas (CEIH) have a slower pattern. It is characterized by a more incipient evolution of intracranial hypertension syndrome[4]. About 30% of patients starts the picture with a seizure crisis.

About 80% of CEIH cases are diagnosed as a neoplasm, the main ones being glioblastoma and metastasis[3]. This is due to the fact that this type of lesion presents with perilesional edema and the appearance of a progressive neurological deficit. This is not common in vascular cases. It is widely observed in neoplasms.

CEIH cases are related to arteriovenous malformations (AVM), micro-aneurysms, cavernomas and venous angiomas[5-7].

CT images of CEIH always show quasi-circular or elliptical cystic lesions. Most of the cysts are of uniform low density. Cysts can vary depending on diferent manifestations and diferent periods of bleeding, and can be of high or mixed density. On enhanced CT, granulation tissue with rich neovascularization can be observed as a ring enhancement pattern that is similar to that of brain abscesses[8,9]. Thus, CEIH is easily misdiagnosed as glioma tumor, stroke or brain abscess. A small proportion of capsular hematomas can be multi-lobed and few cases showed visible calcification[9,10].

Regarding the images generated by MRI, we observed the bright signal capsule, as it is formed by chronic or subacute bleeding. Therefore, it presents bright signal as in T1 as in T2. T2 shows that more clearly as a black 'ring sign'[8], which is specific for CEIH. This data is extremely important, since when we encounter an intense T2 signal on MRI and a hemosiderin halo, we must strongly consider the hypothesis of CEIH.

Hemorrhage in cases of CEIH occurs slowly and progressively[4]. Thus, the initial symptoms hardly attract the patient's attention. They are usually mild symptoms that do not make the subjects to seek for medical help. Therefore, as the blood capillaries bleed, the hematoma volume and mass effect increase. At this moment, when they have undoubted symptoms of intracranial hypertension syndrome, that patients seek medical help[3,11,12].

It is not yet clear why this hematoma is not absorbed. It is believed to be a continuous and repeated bleeding, associated with a continuous inflammatory process. The capsule is characterized by processes of gliosis and neovascularization. In the outer portion of these capsules, the presence of abnormal vessels and capillaries is observed[8,11,13].

Currently, the most accepted theories are that VEGF is the route of formation of the capsule[6,12,14].

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Astrocitoma Difuso de Mesencéfalo e Diencéfalo: um relato de caso de localização rara

Diffuse Astrocytoma in Mesencephalon and Diencephalon: a case report of rare localization

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RESUMO

O astrocitoma difuso grau II, IDH-mutante, é um tumor de crescimento relativamente lento com um tempo médio de sobrevida de 3,9 a 10,8 anos. Contudo, sua infiltração no parênquima cerebral dificulta a ressecção total, cuja taxa bruta é em apenas 14 a 17% dos casos. Estes tumores apresentam desdiferenciação para tumores de alto grau com facilidade, com alto índice de mortalidade. A localização em tronco e diencéfalo constitui evento raro, visto que 90% das manifestações são supratentoriais. Há uma suscetibilidade genética ao desenvolvimento dos astrocitomas de baixo grau, e em 66% destes casos há mutações no gene p53. Os fatores de mau prognóstico destes tumores são: idade avançada, status de desempenho de Karnofsky (KPS) <70, déficits neurológicos anteriores, tumor maior que 6 cm, tumor cruzando a linha média e tumores não hemisféricos. Apresentamos relato de caso de paciente feminina, 54 anos, que procurou atendimento por quadro de cefaleia intensa e progressiva hemicraniana direita, tipo pulsátil, de início recente, associado a vertigem e soluços, sem outros déficits neurológicos focais. Posterior progressão do quadro clínico com estrabismo convergente e diplopia, disartria severa, disfagia grave, paresia grau 2 de predomínio proximal em dimídio direito, tremor em repouso, clônus esgotável em membros inferiores e Babinski positivo. Exames de neuroimagem com evidência de lesão glial em tronco e diencéfalo, com predomínio mesencefálico. A localização em tronco cerebral inviabiliza a total ressecção da lesão dado conjunto de estruturas nobres locais. Desta forma, a paciente é submetida à biópsia sendo evidenciado astrocitoma difuso IDH-mutante grau II (OMS). Apesar dos avanços no tratamento dos gliomas difusos, com estudos comparativos mostrando ganho de 5,5 anos de sobrevida com associação de quimioterapia e radioterapia, não há terapias curativas, podendo haver progressão tumoral e desfechos desfavoráveis.

Palavras-chave: *Astrocitoma difuso; Astrocitoma de diencéfalo; Glioma de linha média*

ABSTRACT

Grade II diffuse astrocytoma (IDH-mutant) is a relatively slow-growing tumor with median survival time of 3.9 to 10.8 years. However, its infiltration into the brain parenchyma makes total resection difficult, and gross rate is only 14 to 17% of cases. These tumors dedifferentiate to high-grade tumors easily, with a high mortality rate. The location in the brainstem and diencephalon is a rare event, since 90% of the manifestations are supratentorial. There is a genetic susceptibility to the development of low-grade astrocytomas, and in 66% of these cases there are mutations in the p53 gene. Poor prognostic factors for these tumors are advanced age, Karnofsky performance status (KPS) <70, previous neurological deficits, tumor larger than 6 cm, tumor crossing the midline, and non-hemispheric tumors. We present a case report of a 54-year-old female patient who was presented due to a recent onset of intense and progressive right hemicranial headache, pulsatile, associated with vertigo and hiccups, without other focal neurological deficits. Later, progression of the clinical picture with convergent strabismus and diplopia, severe dysarthria, severe dysphagia, grade 2 paresis predominantly in the proximal right side, resting tremor, exhaustible clonus in the lower limbs, positive Babinski. Neuroimaging exams with evidence of glial lesion in the brainstem and diencephalon, with mesencephalic predominance. The location in the brainstem makes the total resection of the lesion impossible, given the set of local noble structures, in this way, the patient is submitted to a biopsy, which shows diffuse IDH-mutant astrocytoma grade II (WHO). Despite advances in the treatment of diffuse gliomas, with comparative studies showing a 5.5-year gain in survival with the combination of chemotherapy and radiotherapy, there are no curative therapies, and there may be tumor progression and unfavorable outcomes.

Keywords: *Diffuse astrocytoma; Diencephalon astrocytoma; Midline glioma*

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INTRODUÇÃO

Dentre todos os tumores do sistema nervoso, os tumores gliais correspondem a menos de um terço das lesões cerebrais, e a 80% das lesões malignas primárias. Aproximadamente três quartos são derivados dos astrócitos, os quais representam grande parte da neuroglia. Dos astrocitomas em adultos, 10-15% são do tipo difuso, e cuja incidência anualmente é de 0,55-0,75 novos casos para cada 100.000 pessoas, com predominância homem:mulher 1,18:1, e idade entre 20 a 50 anos (média de 36 anos). A lesão, geralmente, tem localização em qualquer região do sistema nervoso central, no entanto, é mais comum na região supratentorial, predominando nos lobos frontais[1-3].

Os astrocitomas bem diferenciados são caracterizados por pleomorfismo nuclear variável e uma região reticular de finos processos celulares astrocíticos positivos para proteína ácida fibrilar glial (GFAP), à medida que avança o processo de desdiferenciação, torna-se difícil a distinção entre tecido doente e sadio, bem como o aparecimento de plano de fundo densamente celularizado, piora do pleomorfismo nuclear, surgimento de mitoses, necrose (núcleo em pseudopaliçada) e angiogênese com proliferação endotelial. Histologicamente diferenciam-se entre astrocitomas difusos ou circunscritos, e os difusos entre protoplásmico e gemistocítico com base na expressão da GFAP – escassa no protoplásmico e proeminente no gemistocítico[4].

De acordo com a Organização Mundial da Saúde (OMS) os astrocitomas podem ser classificados entre: 1) grau I (pilocítico e células gigantes subepêndimárias) – sobrevida de mais de 10 anos; 2) grau II (difuso de baixo grau; atipias celulares) – sobrevida de mais de 5 anos; 3) grau III (anaplásico; atividade mitótico proeminente) – sobrevida de 2 a 5 anos; e 4) grau IV (gliobastoma; necrose e/ou angiogênese com hiperproliferação endoteliais) – sobrevida de até 1 ano. Os avanços nos estudos genéticos e moleculares aprimoraram a classificação destes tumores. Uma das formas mutantes mais comuns alteram a atividade enzimática de isoformas da enzima metabólica isocitrato desidrogenase (IDH 1 ou IDH 2), importante no ciclo do ácido cítrico para metabolização do isocitrato em alfa-cetoglutarato. Desta forma, são diferenciados em: astrocitoma localizado/circunscrito (IDH negativo); astrocitoma IDH-mutante (90% das lesões grau II e III); astrocitoma com IDH-selvagem/triplo negativo (raro)[1,5].

A manifestação clínica vai depender do local no parênquima cerebral em que o tumor se insere, contudo, o sintoma mais comum é a crise convulsiva. Nos estudos de neuroimagem, o astrocitoma difuso aparece como lesão hipodensa mal definida e não captante ao contraste tomográfico. Na ressonância magnética, observa-se hipointenso em T1Wi e hiperintenso em T2/FLAIR, não há restrição à difusão no DWi, alteração em T2* na vigência de calcificações (20% dos casos) e hipocaptação de gadolíneo. A espectroscopia mostra pico de colina e 2-hidroxiglutarato (2,25 ppm), aumento na taxa inositol/creatinina e baixa de N-acetilaspartato[2,6].

RELATO DE CASO

Paciente feminina, 54 anos, admitida em pronto socorro por quadro de cefaleia intensa e progressiva, hemicraniana à direita, tipo pulsátil, de início recente associado a vertigem e soluços, sem outros déficits focais motores, sensitivos e em pares cranianos.

Ressonância magnética de crânio (Figuras 1-4) evidencia extensa lesão infiltrativa e expansiva, hidratada (alto sinal T2/FLAIR), heterogênea, com áreas focais de impregnação irregular, sem restrição a difusão ou necrose, localizada na região centro-encefálica. Está centrada no mesencéfalo, onde envolve praticamente a sua totalidade, preservando apenas a placa quadrigeminal. Há maior expansão do pedúnculo cerebral esquerdo e um pequeno foco hemorrágico na substância negra mesencefálica direita. Estende-se cranialmente aos tálamos, núcleos da base (sobretudo globos pálidos bilaterais e putâmen esquerdo), cápsulas internas e cápsula externa direita. Há maior progressão cranial à esquerda, onde atinge até a coroa radiada e o corpo do núcleo caudado. Anteriormente, a lesão atinge o quiasma óptico. Lateralmente atinge a haste temporal e as regiões amigdalianas, bilaterais. Caudalmente, atinge os pedúnculos cerebelares superiores e o tegmento pontino. O efeito de massa apaga o aqueduto cerebral, deforma o III ventrículo e o ventrículo lateral esquerdo, sem hidrocefalia. Outros achados: sinais de atrofia cerebelar, com alargamento dos sulcos adjacentes e do IV ventrículo. Estruturas da junção crânio-vertebral de aspecto anatômico preservado. O diagnóstico etiológico é incerto e podem ser consideradas as principais possibilidades: vasculites (por exemplo, neuro-Behçet), neoplasia primária (especialmente glioma difuso da linha média) e romboencefalite infecciosa.

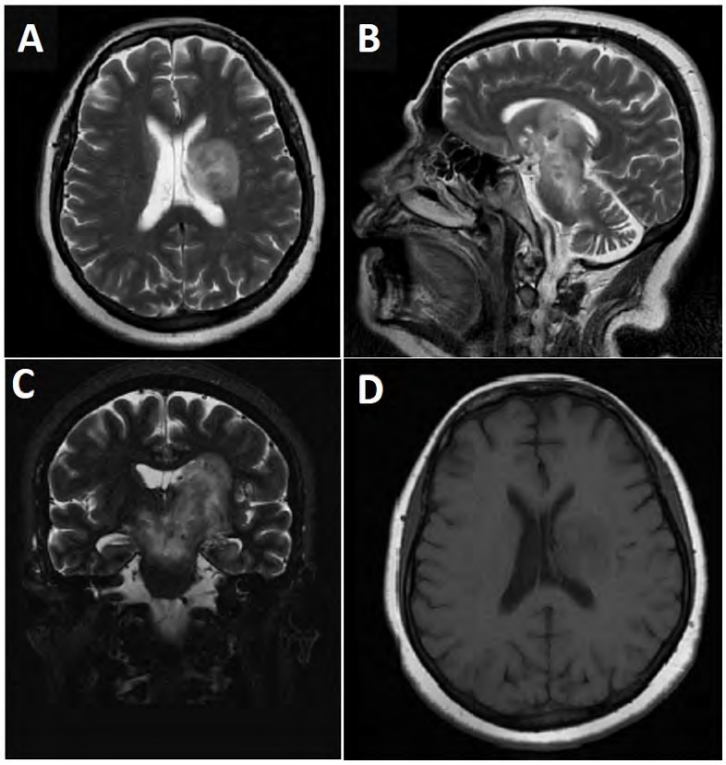

Figura 1. Ressonância magnética de crânio: A. Axial T2; B. Sagital T2; C. Coronal STIR; e D. axial T1.

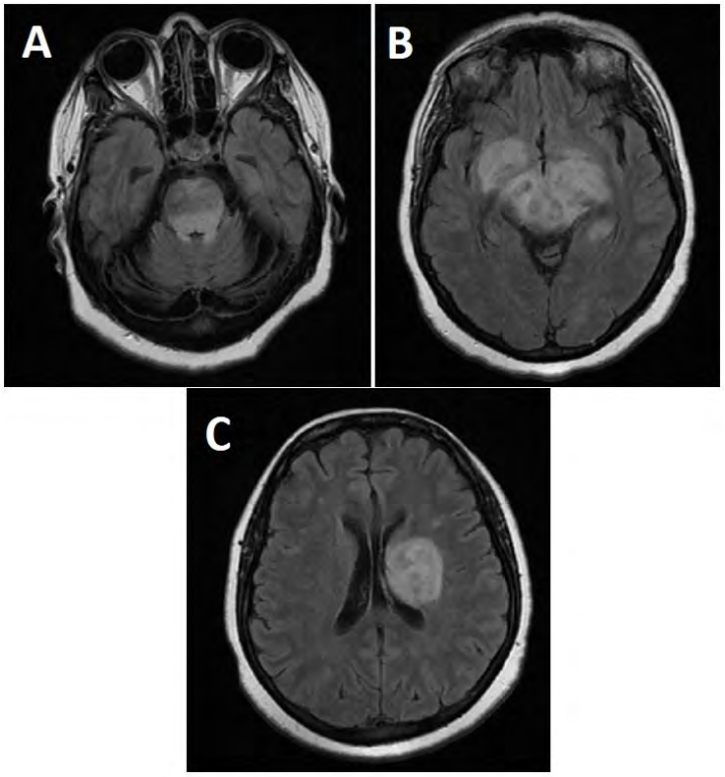

Figura 2. Ressonância magnética de crânio: A, B, C. axial FLAIR.

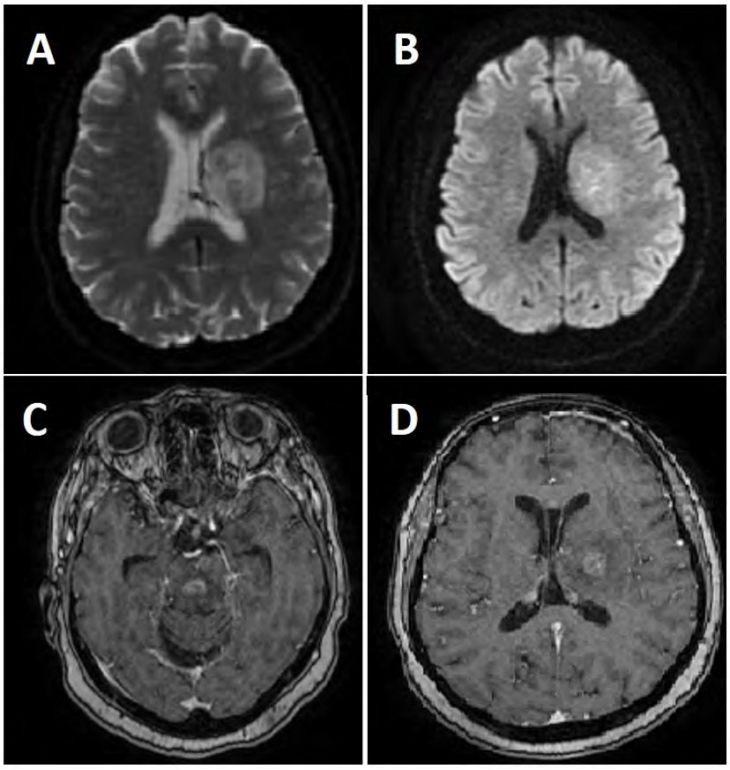

Figura 3. Ressonância magnética de crânio: A, B. DWi; C, D. Volumétrico T1 com contraste.

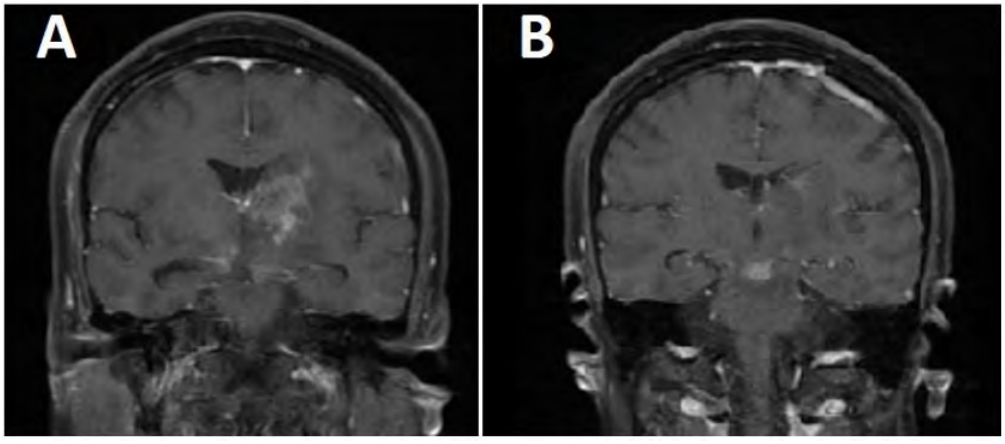

Figura 4. Ressonância magnética de crânio: A, B. Coronal T1 FS com contraste.

Exame de espectroscopia de prótons demonstrou aumento acentuado do pico de colina/creatina e colina/N-acetil-aspartato, estimado em até 2,3. Este achado é indicativo de aumento do turnover celular. Acentuada redução do N-acetil-aspartato na lesão (redução da viabilidade neuronal). Estudo de perfusão: considerando a curva de contrastação subótima, não se identifica aumento significativo do fluxo ou do volume sanguíneo cerebral relativo na lesão. Os achados na espectroscopia favorecem processo com proliferação celular, tipicamente de origem neoplásica. Ressalta-se que processos inflamatórios ativos e acentuados também podem se apresentar com este padrão. O estudo perfusional não foi típico de neoangiogênese neoplásica.

Paciente evoluiu com progressão do quadro clínico, estrabismo convergente e diplopia, disartria severa, disfagia grave com necessidade de gastrostomia, paresia grau 2 de predomínio proximal em dimídio direito tornando-se acamada (Steinbrocker IV / Karnofski 30), tremor em repouso de baixa amplitude e alta frequência no membro superior esquerdo, clônus esgotável em membros inferiores e Babinski positivo. Submetida à biópsia da lesão através de craniotomia frontal esquerda com neuronavegação direta sob auxílio de ultrassonografia perioperatória. Estudo anatomopatológico sugestivo de glioma de baixo grau, sendo confirmado por imuno-histoquímica que evidenciou: GFAP – proteína glial (clone Policlonal) positivo difusamente; Proteína S-100 (clone policlonal) positivo; IDH-1 (clone R123H-GenomeMe) positivo; proteína P53 (clone D07) positivo em 60% das células; Ki-67 (clone MIB-1) positivo em 2% das células. O painel imuno-histoquímico associado aos aspectos histológicos condiz com o astrocitoma difuso IDH-mutante grau II da OMS; mutação H3 K27M não pesquisado por indisponibilidade.

Encaminhada para tratamento oncológico, sendo optado por radioterapia radical com plano de 4005Gy divididas em 15 sessões 267Gy, devido ao baixo KPS. Pela fragilidade do quadro base, a paciente evoluiu com desfecho fatal após aproximadamente 11 meses do início dos sintomas, não conseguindo completar o plano de terapia oncológica.

DISCUSSÃO

Os gliomas são os tumores encefálicos primários mais comuns do sistema nervoso central. Dentre eles, temos os astrocitomas, oligodendrogliomas e os ependimomas. Destes, o astrocitoma infiltrativo destaca-se, sendo responsável por cerca de 80% das neoplasias encefálicas primárias em adultos[4]. Os astrocitomas infiltrativos apresentam um espectro de diferenciação histológica que possui estrita relação com o curso e a resposta clínica da doença. A classificação da OMS (2016) classifica-os em graus de I a IV, baseada na presença histológica de atipia nuclear, mitoses, proliferação microvascular e necrose. Sendo assim, são chamados astrocitomas grau II ou astrocitomas difusos aqueles que apresentam apenas atipia nuclear. Ademais, a nova classificação da OMS de 2016 considera a evolução nos estudos genéticos e moleculares, complementando a classificação de acordo com a presença da mutação IDH 1 ou IDH 2. Desta forma, são diferenciados em: astrocitoma localizado/circunscrito (IDH negativo); astrocitoma IDH-mutante (90% das lesões grau II e III); e astrocitoma com IDH-selvagem/positivo (raro)[1,7].

Além do marcador IDH, outro de grande importância, especificamente para lesões gliais de linha média, é a mutação da lisina em metonímia no códon 27 do gene que codifica o isomorfismo 3 da histona. Através deste marcador, houve uma reclassificação pela OMS, em 2016, dos gliomas difusos intrínsecos da ponte em gliomas difusos de linha média H3 K27M-mutante. Com a alteração dos aminoácidos em K27M há o bloqueio do complexo PRC2 (complexo repressivo policombo de metiltransferase 2) em modificar a lisina no códon 27 na cauda da histona 3, resultando em diminuição da trimetilação das proteínas H3 com consequente interrupção da diferenciação glial, levando a um estado oncogênico primitivo, semelhante a células-tronco. Apesar de as mutações terem sido descobertas em gliomas difusos intrínsecos da ponte em crianças (incidência 80%), houve associação do astrocitoma difuso de linha média, sobretudo aqueles de diencéfalo, cerebelo e medula espinhal, com a mutação H3 K27M nos adultos (incidência 15 a 60%). Devido ao pior prognóstico nos casos em que o marcador é positivo nas crianças, a classificação da OMS 2016 definiu estas lesões como grau IV, independente da apresentação de necrose ou proliferação microvascular. Contudo, faltam dados para correlacionar a presença do marcador e o prognóstico em adultos[8,9].

O astrocitoma difuso (DA) grau II, IDH-mutante, como apresentado pela paciente relatada, é um tumor de crescimento relativamente lento com um tempo médio de sobrevida de 3,9 a 10,8 anos. Contudo, sua infiltração no parênquima cerebral dificulta a ressecção total, cuja taxa bruta é em apenas 14 a 17% dos casos. Diferentemente de quando acomete crianças, em adultos – faixa etária de maior prevalência desse tumor – há a desdiferenciação para tumores de alto grau com maior facilidade, com rápida progressão e alto índice de mortalidade[10]. Devido ao comportamento infiltrativo e eventual progressão para tumores de grau III e IV lhe é conferido um grau de malignidade[11].

Os efeitos locais do astrocitoma são resultado de vários mecanismos celulares. Desde a invasão direta e competição por oxigênio, levando à lesão hipóxica do parênquima cerebral normal, bem como emissão de radicais livres, neurotransmissores e mediadores inflamatórios que prejudicam a homeostase neuronal. Além da lesão no local de infiltração, o efeito de massa do tumor é responsável por diversos sinais e sintomas clínicos, os quais são divididos em gerais e focais. Os gerais incluem cefaleia, náuseas, vômitos, dificuldades cognitivas, alterações de personalidade e

distúrbios da marcha, enquanto os focais envolvem convulsões (em 90% dos pacientes), afasia ou defeitos do campo visual[2].

A localização do astrocitoma difuso em tronco cerebral e diencéfalo, como relatado no presente artigo, constitui-se de um evento pouco frequente, visto que 90% das manifestações são supratentoriais[1-3]. Em se tratando de gliomas difusos de linha média, uma série de casos com 60 pacientes, evidenciou o diencéfalo como local mais comum (57% no tálamo), seguido por medula espinhal, e menos frequentemente o tronco[9]. A paciente que inicialmente apresentava sintomas gerais inespecíficos, progressivamente evoluiu com alterações correlacionadas a sua localização. A paresia em dimídio direito, possivelmente deve-se a: acometimento do pedúnculo cerebral esquerdo; tremor em repouso de baixa amplitude e alta frequência em membro superior decorrente da lesão em núcleos da base; diplopia pelo acometimento das vias da conjugação do olhar bem como da região pontina, local do núcleo do nervo abducente; e disartria, pela invasão de gânglios da base e pedúnculos cerebelares.

O único fator de risco estabelecido para desenvolvimento do astrocitoma difuso foi a exposição à radiação ionizante. Crianças que recebem radiação profilática para leucemia linfocítica aguda (LLA) podem ter 22 vezes mais chance de desenvolver malignidade do sistema nervoso central em cerca de 5 a 10 anos. A radioterapia para adenoma hipofisário acarreta 16 vezes mais risco de desenvolvimento de gliomas. Salienta-se que nossa paciente não relatou ter sido exposta à radiação. Há uma suscetibilidade genética ao desenvolvimento dos astrocitomas de baixo grau, e em 66% destes casos há mutações no gene p53. Os fatores de mau prognóstico destes tumores são: idade avançada, status de desempenho de Karnofsky (KPS) <70, déficits neurológicos anteriores, tamanho do tumor maior que 6 cm, tumor cruzando a linha média e tumores não hemisférico – estando as três últimas presentes em nosso caso[2,5].

Com relação aos achados na neuroimagem, a ressonância magnética (RM) revela diversos aspectos e padrões tumorais característicos do astrocitoma de baixo grau. Assim, a RM é a modalidade de escolha na avaliação diagnóstica do astrocitoma difuso, pois além da avaliação anatômica nos fornece dados quantitativos e informações moleculares e metabólicas da lesão[12].

As imagens de RM multiparamétrica quantitativa diferenciam de forma mais precisa os gliomas de baixo grau dos de alto grau, com sensibilidade de 84,2% e especificidade de 100%. Esta abordagem envolve tanto as sequências T2, FLAIR, T1 pré e pós contraste – as quais são primordiais para identificar a localização do tumor e sua relação com as estruturas cerebrais adjacente (evidência de nível II) –, somado às técnicas avançadas: imagem ponderada por suscetibilidade (SWI) – identifica calcificações e sangramentos intratumorais; imagem ponderada por difusão (DWI) associada a ADC – revelam a heterogeneidade tumoral; imagem ponderada por perfusão (PWI) como Ktrans, Vp, rCBV, Espectroscopia (MRS) – revelam a heterogeneidade das lesões contribuindo para os diagnósticos diferencias. A partir destas técnicas avançadas de ressonância magnética são evidenciados alterações imaginológicas que definem os gliomas de baixo grau, sendo elas: hipodensidade celular evidenciado pela difusividade média mínima e ADCmin mais alto; valores de anisotropia fracionária baixos e valores medianos de curtose – quando comparado com as lesões de alto grau; parâmetros de perfusão mais baixos devido à menor secreção do fator de crescimento endotelial, baixa proliferação microvascular, ausência de neo-microvascularidade hiperpermeável e imaturidade celular; bem como a extensa lesão infiltrativa e expansiva com hipersinal em T2. Além dos benefícios supracitados da RM, através das análises imaginológicas é possível extrair dados prognósticos e evolutivos. Valores iniciais de ADCmin, rCBVmax e Ktrans quando baixos são indicativos de pior desfecho. Valores da razão Cho/Cr intratumoral > 2,4 e de rCBVmax > 1,52–1,75, bem como a taxa de crescimento maior que 3 mm por ano estão correlacionados com progressão tumoral e desdiferenciação em lesão de alto grau[11,13].

Invariavelmente, todos os pacientes devem ser submetidos ao procedimento neurocirúrgico para identificação histológica da lesão. Ressecções amplas se mostram melhor do que as parciais/biópsias com relação à sobrevida. E os gliomas IDH-mutante possibilitam maior ressecabilidade devido ao menor padrão infiltrativo[14]. Todavia, a localização em tronco cerebral e diencéfalo inviabiliza a total ressecção da lesão dado o conjunto de estruturas nobres presentes. A terapia adjuvante é reservada para pacientes com lesão residual após a cirurgia e/ou características que indicam pior prognóstico. Estudos comparativos mostram melhor desfecho quando associado radioterapia (50-54 Gray em 1.8 Gray/fração) com quimioterapia (temozolomida ou procarbazina, lomustine e vincristina - PCV) com ganho de 5,5 anos de sobrevida quando comparado à radioterapia isoladamente[15]. Apesar dos avanços no entendimento e tratamento dos gliomas difusos, nenhuma terapia é curativa, e o tumor eventualmente irá progredir. Estudos promissores estão sendo conduzidos para abordagem terapêutica direcionada à mutação IDH, por ser específica e uniformemente expressa pelos gliomas difusos (exceto IDH-selvagem)[16].

CONCLUSÃO

A importância do relato do caso reside em sua localização pouco frequente e extensa, reforçando o auxílio da neuroimagem no diagnóstico, prognóstico e programação terapêutica. Apesar dos esforços terapêuticos e dos tratamentos suplementares com quimioterapia e radioterapia, as lesões difusas com envolvimento de estruturas como o tronco cerebral e diencéfalo continuam um desafio gigantesco.

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LANÇA MEN TO

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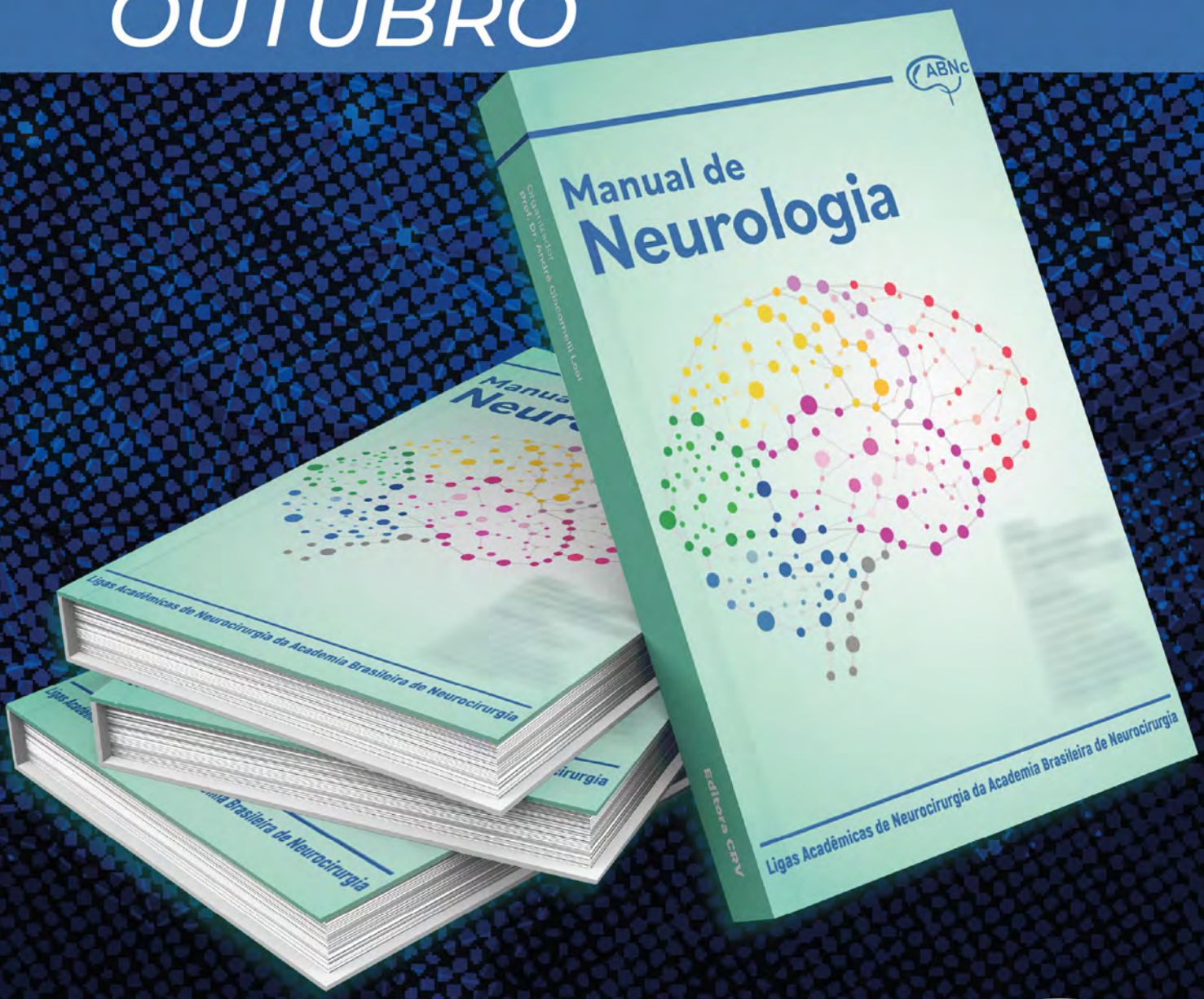

ABNc

Ondine's Syndrome as a Postoperative Complication of High Cervical Cordotomy: a case series review

Síndrome de Ondine Como Complicação Pós-operatória da Cordotomia Cervical Alta: uma revisão de série de casos

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ABSTRACT

Ondine's curse is the term used to describe sleep apnea caused by damage to the spinal cord pathways of respiratory control. Despite presenting several causes for this syndrome, Ondine's syndrome is recognized as a common and fatal postoperative complication of upper cervical cordotomy for malignant pain control. Our objective is to carry out a historical review based on papers linked to PubMed and Scielo databases in order to analyze the frequency and evolution of sleep apnea in patients undergoing upper cervical cordotomy, in addition to observing the anatomical and functional mechanism that triggers it. The results revealed that postoperative Ondine's syndrome is caused by sectioning of the lateral spinothalamic and spinoreticular tracts, which are located in the anterolateral portion of the spinal cord.

Keywords: *Ondine's syndrome; Sleep apnea; Cordotomy; Respiratory automaticity; Breathing control*

RESUMO

A maldição de Ondine é o termo usado para descrever a apneia do sono causada por danos nas vias da medula espinhal de controle respiratório. Apesar de serem apresentadas várias causas, a síndrome de Ondine é reconhecida como uma complicação pós-operatória comum e fatal da cordotomia cervical superior para o controle da dor maligna. Nosso objetivo é realizar uma revisão histórica baseada em artigos ligados às bases de dados PubMed e Scielo, de forma a analisar a frequência e evolução da apneia do sono em pacientes submetidos a cordotomia cervical superior, além de observar o mecanismo anatômico e funcional que a desencadeia. Os resultados obtidos revelam que a síndrome pós-operatória de Ondine é causada pela seção dos tratos espinotalâmicos e espiroreticulares laterais, que estão localizados na porção anterolateral da medula espinhal.

Palavras-Chave: *Síndrome de Ondine; Apneia do sono; Cordotomia; Automaticidade respiratória; Controle de respiração*

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INTRODUCTION

In one of the interpretations of a Greek myth, Ondine is a water spirit who, by falling in love with a human, gives up his immortality to share life with her beloved. At one point, due to her husband's betrayal, Ondine curses him to lose involuntary control of his breathing, so that he dies as soon as he falls asleep[1,2]. Due to the correlation with this fanciful story, Ondine Syndrome is the eponym attributed to sleep apnea induced by impairment of the neurological centers of respiration, consisting of loss of respiratory automaticity that culminates in alveolar hypoventilation during the period of sleep[3].

Regarding the etiology of Ondine's syndrome, the congenital origin occurs through mutation of genes intrinsic to the autonomic nervous system, especially the PHOX2B gene considered the gene that causes the syndrome[4]. In addition, the medical literature has documented several acquired causes of Ondine syndrome[5], including the postoperative complication of cordotomy[6,7].

Cordotomy is based on the surgical section of the lateral spinothalamic tract and spinoreticular tract, the ascending pathways responsible for the transmission of painful stimuli[8], with the objective of producing the absence of contralateral pain perception and, thus, treating patients with chronic pain[9,10]. The aim of this study is to review the anatomo-functional mechanisms that explain Ondine's curse as a postoperative complication of the cordotomy procedure through a series of case reports.

METHODS

The proposed design is a historical literature review. The keywords designated for this study are: Ondine's Syndrome Sleep apnea Cordotomy Respiratory automaticity Breathing control. Thus, the selection of articles to support this review was carried out from the PubMed and Scielo databases between January 2022 and February 2022, using the following search terms: Sleep Apnea AND Chordotomy, Ondine's Curse AND Chordotomy, Respiratory Syndrome AND Chordotomy. The use of the "boolean operator" "AND" proved to be essential to find intersection and correlation between related terms. Inclusion criteria were Research and case reports addressing a correlation between Ondine syndrome and upper cervical cordotomy, written in Portuguese, English or Spanish and published in academic journals. In addition, linked articles were added as a bibliographic reference to other articles present in the databases following the same inclusion criteria to expand the available repertoire. A total of 25 articles were found in the databases, and 7 were considered. The search in the bibliographic references resulted in 6 articles, totaling 13 articles chosen for this analysis.

RESULTS

From the selected 13 articles, according to Table 1, it was highlighted the following aspects of each study: author, method used and final result obtained.

In general, the papers mentioned, mostly case reports, pointed to a correlation between upper cervical cordotomy and sleep apnea through the disruption of pathways that circulate in the anterolateral portion of the spinal cord, such as the spinoreticular tract, which are responsible for involuntary breathing control.

DISCUSSION

Ondine's syndrome is characterized by the automatic deactivation of breathing during sleep and is one of the main postoperative complications of cordotomy, a procedure that aims to treat patients with chronic pain.

Cordotomy is usually performed using two techniques: the open technique and the percutaneous technique. Open technique cordotomy requires general anesthesia and hemilaminectomy or total laminectomy to access the patient's spinal cord in the contralateral portion and 3 to 4 spinal cord levels above which pain attenuation is desired. Then, the anterolateral segment of the spinal cord is exposed and a cordotomy hook[24], as shown in Figure 1. The percutaneous cordotomy technique is more used and less invasive when compared to the open technique, consisting of disruption of the spinal pain through radiofrequency ablation

Table 1. Results of selected studies.

Author	Method	Result
Lahuerta et al.[11]	Case reports of 12 patients who died after unilateral cordotomy	Unilateral high cordotomy causes destruction of spinoreticular tract fibers in the anterior and lateral cords of the spinal cord that are related to the process of reticular activation of the respiratory center of the brainstem
Krieger et al.[12]	Case reports of 10 patients who developed sleep apnea after bilateral cervical cordotomy	The upper cervical cordotomy is responsible for causing the rupture of ascending reticular fibers in the anterolateral cord of the spinal cord that establish a connection with the respiratory center of the brainstem
Kanpolat et al.[13]	Retrospective study of 207 patients who underwent CT-guided cordotomy between 1987 and 2007	CT-guided cordotomy is associated with considerable pain relief on the Karnofsky scale for patients with malignant conditions and intractable pain, requiring 1 week interval between procedures if it is a bilateral approach
Polatty et al.[14]	Case report of a 33-year-old man who developed Ondine's syndrome after cordotomy to treat chronic pain	Cordotomy causes injury to the involuntary descending pathways of respiratory control in the anterolateral segment of the spinal cord, predisposing to Ondine's syndrome
Chevrolet et al.[15]	Case report of a 46-year-old man who developed ventilatory disorders after bilateral cordotomy	Bilateral cordotomy usually presents with apnea due to respiratory control dysfunction or respiratory muscle dysfunction, which are reversed with the administration of aminophylline
Tranmer et al.[16]	Retrospective study of 112 patients who underwent upper cervical cordotomy since 1977	About 5% of the 112 patients evaluated developed sleep apnea due to injury to the afferent and/or efferent respiratory fibers of the spinal cord
Nathan[17]	Retrospective analysis of eight case reports	Most of the descending fibers responsible for respiratory activity are located in the most anterior part of the lateral cord of the spinal cord and are partially or totally interrupted in the cordotomy procedure
Hitchcock and Leece[18]	Case reports of respiratory functions through spirometry in 14 patients before and after upper cervical cordotomy	Voluntary and involuntary control of breathing occurs through distinct nerve pathways, which corroborates the fact that many patients develop sleep apnea after high cervical cordotomy
Mullan and Hosobuchi[19]	Case reports of 9 patients who died due to upper cervical cordotomy	Vital pathways for respiratory control circulate in the anterior portion of the anterior cord of the spinal cord and are extremely compromised during the cordotomy procedure, with sleep apnea being the most common manifestation during the first 5 nights after the procedure
Lema and Hitchcock[20]	Case reports about changes in breathing patterns in patients with opioid-resistant pain after surgery at the upper cervical level	Involuntary airways are affected during upper cervical procedures, which led to changes in breathing pattern in 11 of the 15 patients evaluated
Tenicela et al.[21]	Case report of ventilatory changes in 13 patients who underwent cervical cordotomy at C2 level	Of the 13 patients, 3 developed sleep apnea in the period after bilateral cordotomy, showing that the level of respiratory failure and the number of respiratory fibers affected are directly associated
Belmusto et al.[22]	Case reports of 20 patients who underwent cervical cordotomy with observation of respiratory functions	Bilateral upper cervical cordotomy is contraindicated for patients with previous lung disease because it causes changes in breathing pattern through injury to the descending airways
Rosomoff et al.[23]	Randomized study to evaluate changes in respiratory functions in 48 patients undergoing cervical cordotomy	Both unilateral and bilateral cordotomy promoted a reduction in respiratory capacity and respiratory muscle strength and an increase in respiratory rate

guided by fluoroscopy or computed tomography in patients under local anesthesia[25].

By injuring the respiratory control pathways in the anterolateral segment of the spinal cord, respiratory control or respiratory muscle dysfunction may occur[17]. This occurs because when sectioning the spinoreticular tract, chronic pain would be relieved, but this tract contains fibers that establish the connection with the respiratory center of the brainstem and, when injured, causes apnea[12].

Depending on the number of respiratory fibers affected, respiratory compromise can be variable[21]. Bilateral upper cervical cordotomy, for example, consists of sectioning more than one fiber pathway, which can cause more severe respiratory failure and, therefore, is contraindicated in patients with lung disease[22]. In some cases, a one-week interval between procedures may be necessary[13].

Unilateral cordotomy, despite breaking a smaller number of fibers compared to bilateral, also causes respiratory dysfunction, as the fibers of the spinoreticular tract in the anterior and lateral cords of the spinal cord are sectioned in the same way[11].

Both the bilateral and the unilateral approach affect the fibers responsible for respiratory activity and can cause varying degrees of respiratory failure, but mainly sleep apnea, which characterizes Ondine's syndrome. The Lema Ane Hitchcock study (1986)[20] found that about 74% of the patients undergoing the procedure suffered from some alteration in their breathing pattern.

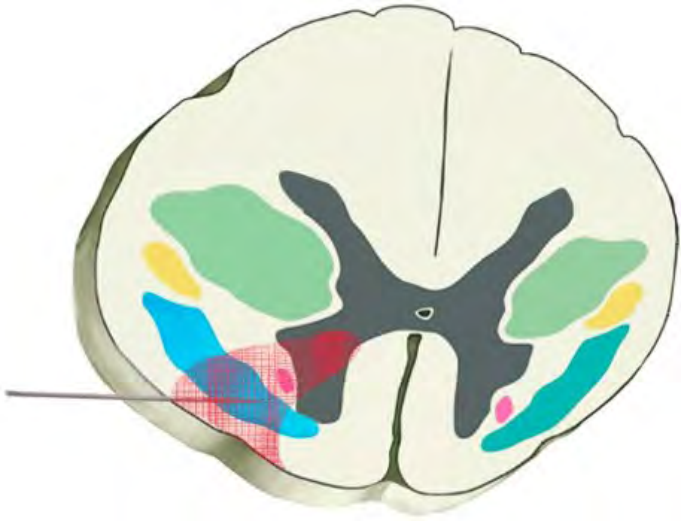

Figure 1. Medullary pathways affected by the cordotomy procedure

Despite the dysfunction of respiratory control after the procedure, the use of bronchodilators, such as aminophylline, can reverse apnea[15].

CONCLUSION

Cordotomy is a procedure aimed at relieving chronic pain, either unilaterally or bilaterally, and consists of sectioning the lateral spinothalamic and spinoreticular tracts (Figure 1), at the level of the lateral and anterior cord of the spinal cord. Such tracts contain fibers that are directly related to the respiratory center and their section can cause different degrees of respiratory dysfunction, depending on the number of fibers affected. Although there is a difference in the degree of respiratory distress, sleep apnea or Ondine's curse is the main postoperative complication of cordotomy.

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Chronic Subdural Hematoma Following Spinal Anesthesia: case report

Hematoma Subdural Crônico Após Raquianestesia: relato de caso

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ABSTRACT

The authors report the case of a 34-year-old female patient who underwent spinal anesthesia for a cesarean delivery and developed CSF hypotension headache for 7 days, presenting, then, persisted continuous daily headache. Submitted to a Brain MRI, it showed subacute subdural hematoma in the right fronto-temporo-parietal area, and was, then, submitted to surgical drainage with total resolution of the hematoma. In this paper, the authors discuss the pathophysiology of the formation of this type of hematoma and emphasize the infrequency of this occurrence in the medical literature.

Keywords: *Chronic subdural hematoma; Spinal anesthesia*

RESUMO

Os autores relatam o caso de uma paciente de 34 anos submetida à raquianestesia para submeter-se a um parto do tipo cesariana e evoluiu com cefaleia do tipo hipotensão liquórica por sete dias e, em seguida, persistiu com cefaleia contínua e diária. Foi submetida à ressonância magnética do encéfalo que evidenciou hematoma subdural subagudo fronto-têmporo-parietal à direita sendo, então, submetida à drenagem cirúrgica com resolução do hematoma. Discute-se a fisiopatologia da formação deste tipo de hematoma e ressalta-se a infrequência desta ocorrência na literatura médica.

Palavras-chave: *Hematoma subdural crônico; Anestesia espinal*

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INTRODUCTION

Chronic subdural hematomas (CSDH) represent one of the most frequent conditions in the daily practice of Neurosurgery. Its incidence increases proportionally with age, reaching up to 58 cases per 100,000 inhabitants in the elderly, 65 years old or over[1], and in Japan it is estimated that there are 20.6 cases per 100,000 inhabitants per year between 70-79 years and 127.1 cases for every 100,000 inhabitants per year over 80 years old[2].

Most cases can be related to a history of trauma, but as most traumas are minor or trivial, patients may not report that trauma has occurred. The thin wall of the bridging veins and the lack of support on these veins in the subarachnoid space may explain their fragility and their ruptures related to minor trauma to the skull[3].

Besides trauma, other etiologies may be associated with the occurrence of chronic subdural hematomas such as coagulopathies, use of anticoagulants, antiplatelet agents and, less frequently, associated with intracranial hypotension due to CSF loss after spinal surgery, spinal anesthesia or CSF fistula[3].

The authors, in this paper, report the case of a young patient who developed a chronic subdural hematoma, diagnosed 40 days after undergoing spinal anesthesia for a cesarean section, discussing the pathophysiology of chronic subdural hematomas and the infrequency of this occurrence after spinal anesthesia.

CASE PRESENTATION

A 34-year-old patient at 38 weeks gestation underwent a cesarean delivery because the fetus was in breech presentation. Spinal anesthetic block (spinal anesthesia) was performed for the surgery, with puncture at L3-L4 level, with the patient in a sitting position. The CSF obtained was clear and with normal pressure, and anesthetic block was obtained up to T6 level.

The delivery was uneventful and lasted about 60 minutes. The patient and the newborn were discharged 30 hours after delivery, with no symptoms.

On the second day after delivery, the patient started to have a low CSF pressure headache, which persisted for seven days and then, changed its characteristics, becoming daily, continuous and progressive, with short periods of improvement with common analgesics. On the thirtieth postoperative day, the patient noticed mild hypoesthesia in the left hemibody, but she only sought neurological care on the fortieth postoperative day, when it was requested a Brain MRI, which showed hyperintense extra-axial subdural collection at T1 and T2 weightings, with isointense areas in between, in the right fronto-temporo-parietal area, with mass effect, compressing the right lateral ventricle and shifting the midline to the left, compatible with chronic subdural hematoma (Figure 1).

After preoperative preparation, the patient had undergone neurological surgery to drain the hematoma, through two trepanations located one in the frontal and the other on the parietal areas, irrigation of the cavity with saline solution and subdural drainage with a closed system for 48 hours. She had complete resolution of the symptoms, and a Head CT scan performed on the 38th day after the hematoma drainage showed complete resolution of the hematoma (Figure 2).

DISCUSSION

Subdural hematomas can be classified according to the evolution time into: acute (occur within 3 days after trauma), subacute (4 to 20 days after trauma) and chronic (after 20 days)[4]. Chronic subdural hematomas consist of an encapsulated collection of fluid, blood, or blood breakdown products between the arachnoid and the dura mater[5].

One of the theories about the formation of CSDH would be the rupture of bridging veins that drain the cerebral cortex to the venous sinuses, leading to an accumulation of venous blood in the subdural space over the days following the trauma[6]. But this theory has been challenged for years for several reasons. First, because we know that most CSDH become symptomatic on an average of four to seven weeks after trauma and a subdural hemorrhage of venous origin would lead the patient to have symptoms in just a few days. Second, in the current days with the increased access of patients to CT scans after a head injury, we often see cases where the initial CT scan is completely normal, with no signs of hemorrhage and

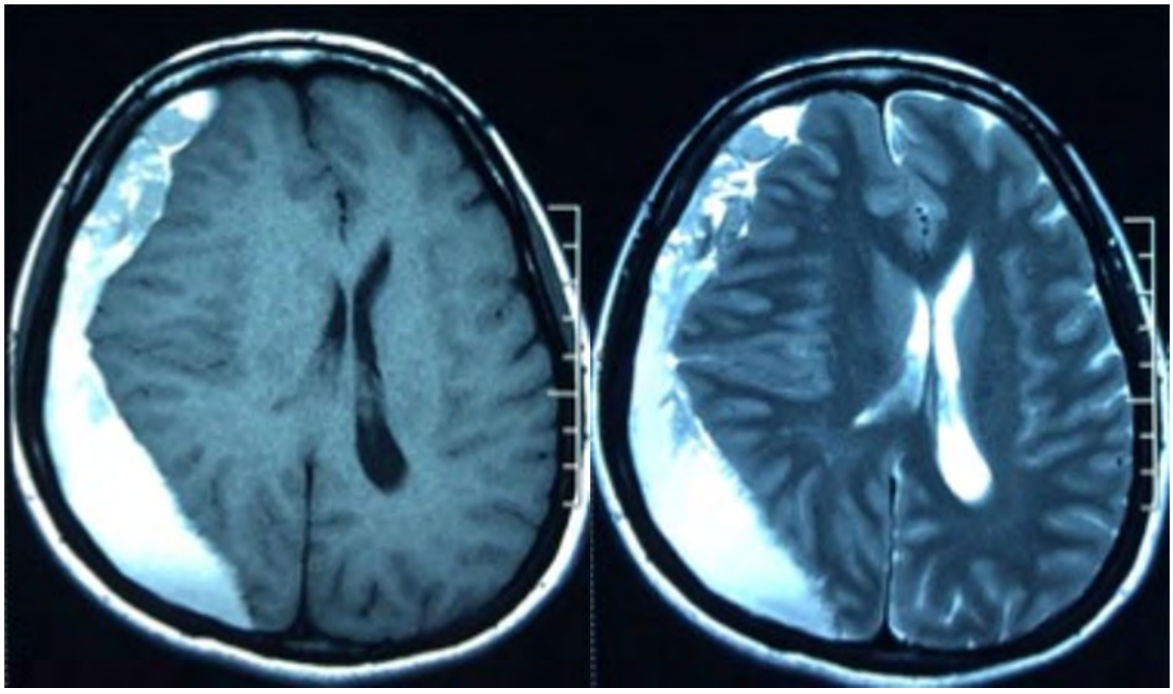

Figure 1. MRI in T1 and T2 showing an extense fronto-temporo-parietal subdural collection on the right.

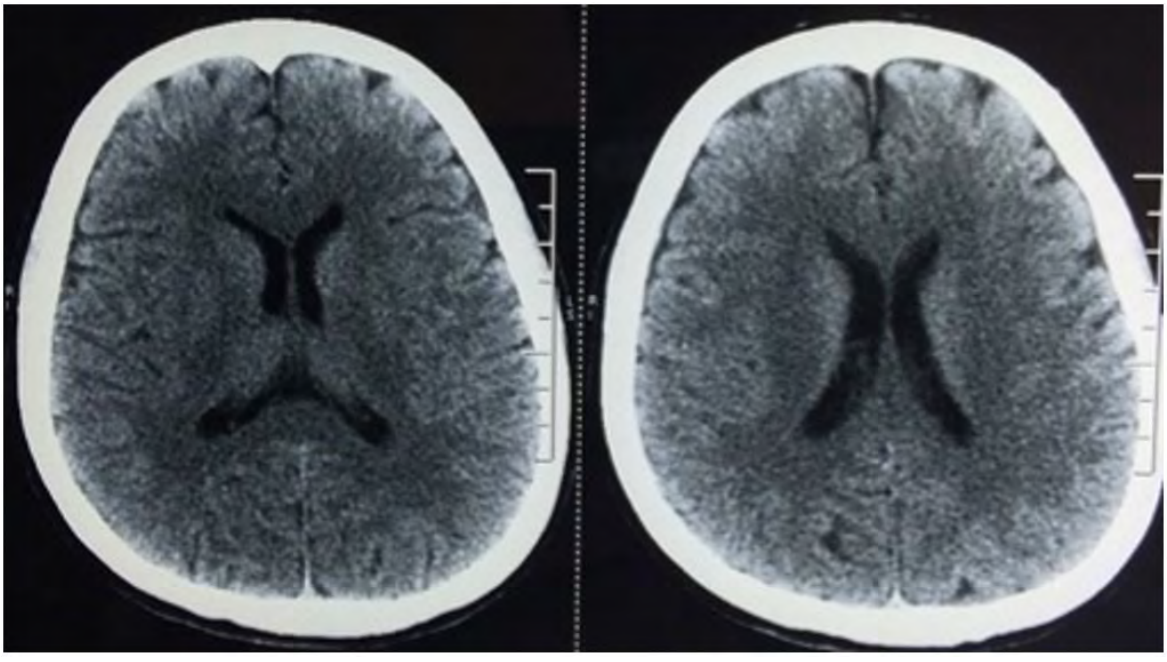

Figure 2. Head CT Scan, without contrast, performed on the 38th post-operative day showing total resolution of the subdural hematoma.

yet the patient develops a CSDH weeks or months later[5]. Therefore, more recently, several authors have discussed inflammation as a key process in the development of CSDH.

In 1857, Virchow referred to this condition as "pachymeningitis haemorrhagica interna", because he believed that the hematoma would be originated from a chronic inflammatory response of the

dura mater, resulting in fibrin exudation and the development of new capillaries[5,6].

In 1946, Inglis, after histological analysis of several cases of CSDH, identified that the dura mater is lined with a layer of specialized, modified connective tissue cells, which more recently has been called "dural border cells". These cells have two essential functions, which are: phagocytize; and also become fibro-cellular connective tissue, allowing the formation of new membranes as seen in CSDH[7,8]. Damage to the "dural border cells" besides an acute hemorrhage, could also initiate inflammation, recruiting inflammatory cells into the subdural space in order to repair this layer of cells. However, what actually happens is a differentiation and proliferation of these cells resulting in the formation of new membranes[5]. Thus, with the delamination of the dural border cells, two new membranes are formed, one internal, in contact with the arachnoid, and the other external, in contact with the dura mater, thereby creating a new subdural cavity which will be filled with fluids and blood, once, mainly the outer layer contains fibroblasts and collagen fibers, in addition to cells such as neutrophils, lymphocytes, macrophages and eosinophils, capillaries with very thin walls and extremely thin or absent basement membrane, highly permeable, which allow the migration of erythrocytes, leukocytes and plasma from these vessels to the subdural cavity, favoring the increase of the subdural collection. In addition, there are several studies that analyzed the membranes of CSDH as well as the fluid from these hematomas, and have showed that in the process of formation and progression of these hematomas there are fibrinolysis, angiogenesis and inflammation[9-13].

Subarachnoid anesthesia is a type of anesthetic block, safe and widely used in daily practice, and the incidence of serious complications is approximately 0.05%[14]. Intentional or inadvertent puncture of the dura mater, even if done with fine needles and adequate bevels, can leave the puncture orifice open from 14 days to a few weeks and could lead to the drainage of up to 240 mL[15] of CSF per day, through an orifice of 0.6 mm. The loss of CSF leads to a reduction in its volume, which initially decreases spinal pressure and, more dangerously, intracranial pressure. These changes result in a movement of the spinal cord and brain in a caudal direction, which, thus, pulls pain-sensitive structures such as the dura mater, cranial nerves, and blood vessels[16]. In the literature, we can find several factors that enhance this mechanism and contribute to the genesis of subdural hematoma after puncture of the subarachnoid space. Among these factors, we have the excessive loss of CSF due to the use of thick needles, a sharp bevel, as well as multiple attempts to puncture the subarachnoid space. However, the use of fine gauge needles and/or with a non-cutting bevel, reduces the chance, but does not totally prevent the appearance of this complication.

The venous drainage of the brain is done through short, almost perpendicular venous branches, called bridge veins, which pass directly from the brain to the dural sinuses, which adhere to the internal bone plate of the skull[17]. Between these two points, the bridging veins have a straight course, without tortuousness, therefore favoring their rupture when they are pulled or there are movements of anteroposterior acceleration and deceleration of the brain, culminating in the formation of subdural hematomas.

Headache is the most frequent complication after intentional puncture of the dura mater for diagnostic purposes or for spinal anesthesia. It is a headache that starts 15 minutes after the individual sits or stands and improves in a similar time after lying down, starting up to 5 days after lumbar dural puncture, usually associated with sensation of noises in the ears and cervical pain. It disappears spontaneously after one week or, 48h after epidural blood patching[18]. When headache persists beyond one week or changes its characteristics, some complication associated with CSF hypotension resulting from spinal anesthesia should be considered. The average time elapsed between the loss of CSF leading to headache and the development of hematoma varies from two hours to 44 days[19,20]. According to literature review, the earliest diagnosis occurred after two days of anesthesia and the latest after 20 weeks[19]. In the case reported, the change in the characteristics of the patient's headache after the 8th day became clear, becoming a continuous headache that was no longer influenced by her posture. Attention is also drawn to the symptomatology presented by the patient on the thirtieth day postpartum of altered sensation over the left hemibody, which could suggest some cortical dysfunction in primary sensory areas, but she only sought neurological care four weeks after delivery and spinal anesthesia.

CONCLUSION

We recommend that all patients who underwent any kind of procedure related to puncture of the subarachnoid space and who present headache for more than one week, with different characteristics to headache due to low CSF pressure, should be evaluated by specialists and submitted to imaging exams to rule out bleeding complications resulting from CSF hypotension.

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