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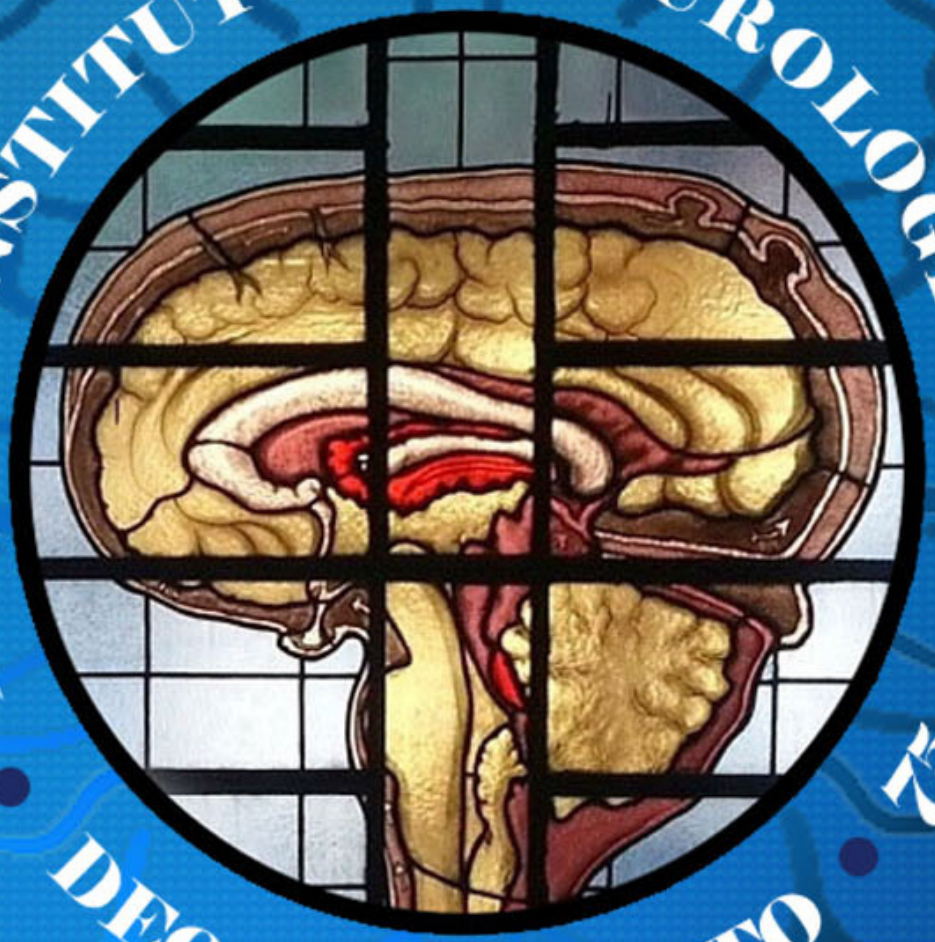

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Editorial

A Revista Brasileira de Neurologia (RBN), revista tradicional da medicina brasileira, tem como objetivo publicar os trabalhos produzidos na área da Neurologia e áreas afins.

A RBN é indexada no LILACS, o que significa que a informação nela contida alcança um largo território científico, na América Latina e Caribe, abrangendo 21 países e 890 periódicos, permitindo grande visibilidade do material divulgado, dos autores e de suas instituições.

O periódico encontra-se em portais de fácil acesso, da própria RBN (https://revistas.ufrj.br/index.php/rbn), assim como da ABN-RJ (ANERJ) (http://neuro.org.br/) e da BVS (Biblioteca Virtual em Saúde) (https://lilacs.bvsalud.org/), vinculada à OPAS e OMS. As publicações encontram-se em caráter aberto, disponível para os autores e os leitores interessados nessa área de conhecimento.

São aceitos para avaliação especializada por revisores os seguintes tipos de manuscritos:

- Artigos Originais: pesquisa clínica ou experimental
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- Comunicações Breves
- Relatos de Casos
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Os profissionais de ensino e de pesquisa da área da neurologia e conexas, acadêmicos ou não, podem e devem publicar seus achados e seus conhecimentos e partilhá-los com a comunidade científica.

Os Editores

Desfechos clínicos e funcionais de pacientes com hemorragia subaracnóidea aneurismática em UTI

Clinical and functional outcomes of patients with aneurysmatic subarachnoid hemorrhage in the ICU

Ana Paula Rabelo Nespolo[1], Lucas Lima Ferreira[2].

ABSTRACT

Introduction. Rehabilitation has recently been discussed in patients with subarachnoid hemorrhage (SAH) caused by a ruptured aneurysm.
Objective. To compare clinical and functional outcomes of surviving and non-surviving patients with aneurysmal SAH in a neurosurgical ICU.
Methods. This is a retrospective documentary study. Medical records of patients with SAH admitted to the neurosurgical ICU of a teaching hospital between July 2014 and July 2019 were analyzed. Data were divided according to the outcomes into survivors group (SG) and non-survivors group (NG).
Results. 103 patients were analyzed, 72% female, mean age 55 years, 62% had high ICU outcome. The SG had significantly lower age, SAPS III score, Fisher and Hunt-Hess scales and time on mechanical ventilation (MV) than the NG, in addition, they had a Glasgow Coma Scale (GCS), on admission and discharge from the ICU and length of hospital stay, significantly higher ($p \leq 0.05$) than NG. The SG showed significantly higher functionality ($p \leq 0.05$) than the NG on admission and a significant increase ($p \leq 0.05$) in functionality between admission and discharge from the ICU.
Conclusion. Surviving patients with aneurysmal SAH had lower age, SAPS III score, neurological scales and time on MV, higher GCS scores at ICU admission and discharge, and longer hospital stay than non-survivors. Surviving patients had better functionality than non-survivors on admission, and, evolved with functional improvement from admission to discharge from the ICU.

Keywords: Subarachnoid hemorrhage, Mobility limitation, Physiotherapy.

RESUMO

Introdução. Recentemente tem sido discutido quanto à reabilitação em pacientes com hemorragia subaracnóidea (HSA) causada pelo rompimento de um aneurisma.
Objetivo. Comparar desfechos clínicos e funcionais de pacientes com HSA aneurismática, sobreviventes e não sobreviventes em uma UTI neurocirúrgica.
Métodos. Trata-se de um estudo documental retrospectivo. Foram analisados prontuários de pacientes com HSA internados na UTI neurocirúrgica de um hospital escola, entre julho de 2014 e julho de 2019. Os dados foram divididos de acordo com os desfechos em grupo sobreviventes (GS) e grupo não sobreviventes (GN).
Resultados. Foram analisados 103 pacientes, 72% do sexo feminino, idade média de 55 anos, 62% apresentaram alta da UTI como desfecho. O GS apresentou idade, escore SAPS III, escalas de Fisher e Hunt-Hess e tempo de ventilação mecânica (VM) significativamente menores ($p \leq 0,05$) que o GN, além disso, apresentaram escala de coma de Glasgow (ECG), na admissão e na alta da UTI e tempo de internação hospitalar, significativamente maiores ($p \leq 0,05$) que o GN. O GS apresentou funcionalidade significativamente maior ($p \leq 0,05$) que o GN na admissão e incremento significativo ($p \leq 0,05$) da funcionalidade entre a admissão e alta da UTI.
Conclusão. Pacientes com HSA aneurismática sobreviventes apresentaram menores idades, escore SAPS III, escalas neurológicas e tempo de VM, maiores escores de ECG, na admissão e na alta da UTI e maior tempo de internação hospitalar que os não sobreviventes. Os pacientes sobreviventes apresentaram melhor funcionalidade que os não sobreviventes na admissão, e, evoluíram com melhora funcional da admissão até a alta da UTI.

Palavras-chave: Hemorragia subaracnóidea, Fisioterapia, Limitação de mobilidade.

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INTRODUÇÃO

A terceira causa de mortalidade no Brasil são as doenças cerebrovasculares, a maioria associado ao acidente vascular encefálico (AVE), que pode ser classificado como isquêmico ou hemorrágico[1]. A estimativa é que em 2030 as doenças cerebrovasculares cheguem a 12,1% da mortalidade mundial[2]. O AVE hemorrágico pode ocorrer em diversos espaços: no cérebro, tronco cerebral ou meninges, quando atinge a meninge aracnoide tem-se a hemorragia subaracnóidea (HSA), que apresenta incidência de 5 a 10% de todos os AVEs[1,2].

A principal etiologia da HSA é o rompimento de um aneurisma[1,3], extravasando sangue no espaço subaracnoide[4]. O aneurisma cerebral é a dilatação da parede de uma artéria, decorrente da fragilidade congênita da musculatura lisa da parede do vaso, ou devido a infecção ou trauma da parede vascular[5]. A presença de sangue e produtos de degradação da hemoglobina no espaço subaracnóideo é responsável pela irritação meníngea, meningismo e vasoespasmo[6].

A HSA representa de 6 a 8% de todas as doenças vasculares cerebrais agudas[4], apresenta morbidade e mortalidade globalmente altas[3,4], mas apesar disso é potencialmente curável[4]. Ela ocorre principalmente entre 40 e 60 anos de idade, com incidência maior no sexo feminino[6]. Até 12% dos pacientes que sofrem de HSA não são diagnosticados devidamente ou evoluem a óbito antes de chegarem ao hospital, cerca de 30% dos que chegam vivos ao hospital falecem nos primeiros dias e a morbidade chega a 50% dos sobreviventes[4].

Os principais fatores de risco para o desenvolvimento de aneurismas são: tabagismo, abuso de álcool, hipertensão[7], risco genético, drogas simpaticomiméticas, sexo feminino e terapia antitrombótica[6].

A ruptura de um aneurisma está associada a altas taxas de mortalidade e incapacidades, mais de um terço dos que sobrevivem têm grandes déficits neurológicos[8], somente 30% conseguem retornar à vida independente[3]. A gravidade do sangramento é um determinante importante na taxa de mortalidade e resultado funcional[6]. Além disso, complicações como ressangramento, hidrocefalia, hiperglicemia, distúrbios metabólicos, complicações cardiopulmonares e repouso prolongado no leito estão associadas ao aumento da probabilidade de mau prognóstico[6].

Apenas recentemente que tem sido discutido quanto à reabilitação e seus resultados em pacientes com HSA[8]. A neurorreabilitação demonstra benefícios interessantes como a melhora da capacidade funcional, redução da mortalidade dos pacientes com AVE, diminuição do tempo de internação hospitalar com redução de custos, aumento da rotatividade de pacientes e reintegração do paciente à comunidade[8].

Sendo pouco conhecido qual o comportamento físico desses pacientes após a HSA, a proposta do presente trabalho foi comparar os desfechos clínicos e funcionais de pacientes com HSA aneurismática, sobreviventes e não sobreviventes, e o desfecho funcional entre a admissão e a alta dos sobreviventes em uma UTI neurocirúrgica.

MATERIAIS E MÉTODOS

Amostra e tipo de estudo

Trata-se de um estudo documental retrospectivo, realizado através da análise de prontuário eletrônico (MV PEP). Foram analisados os prontuários de pacientes com HSA que ficaram internados na UTI Neurocirúrgica do Hospital de Base de São José do Rio Preto.

Procedimentos éticos

O projeto foi submetido ao comitê de ética em pesquisa (CEP) da Faculdade de Medicina de São José do Rio Preto (FAMERP) com número do Certificado de Apresentação de Apreciação Ética (CAAE) 19887819.6.0000.5415 e aprovado sob parecer número 3.646.047. Foi solicitado e autorizado pelo CEP, dispensa do termo de consentimento livre e esclarecido por se tratar de um estudo documental com análise de prontuários. O estudo seguiu as diretrizes e os princípios éticos em pesquisas envolvendo seres humanos presentes na Resolução número 466/2012 do Conselho Nacional de Saúde.

Delineamento da pesquisa

Os dados foram coletados no mês de junho de 2020 e foi selecionado o período de julho de 2014 a julho de 2019 para as coletas nos prontuários eletrônicos. Esse período foi definido, pois a UTI neurocirúrgica foi aberta em julho de 2014.

Critérios de inclusão e exclusão

Foram incluídos pacientes maiores de 18 anos, de ambos os gêneros, com diagnóstico de HSA aneurismática confirmado por angiografia cerebral. Foram excluídos pacientes com HSA traumática e aqueles que apresentavam distúrbios ou doenças neurológicas prévias.

Procedimentos

As variáveis coletadas dos prontuários clínicos dos pacientes foram: sexo, idade, localização topográfica do aneurisma, escore *Simplified Acute Physiology* Score 3 (SAPS III), escala de Fisher, escala de Hunt-Hess, escala de coma de Glasgow (ECG), tempo de permanência em ventilação mecânica invasiva, e período de internação na UTI, em dias, nível de funcionalidade na admissão e na alta da UTI, por meio da ICU *Mobility Scale*, desfecho alta ou óbito na UTI

e tempo de internação hospitalar, em dias.

Para fins de análise estatística das variáveis de desfecho, os dados coletados foram divididos em dois grupos sobreviventes e não sobreviventes e, posteriormente, o grupo sobrevivente foi subdividido em dois momentos admissão e alta da UTI.

O SAPS III foi desenvolvido para ser um índice prognóstico, é composto de 20 variáveis que são mensuráveis de forma fácil na admissão do paciente na UTI[9]. Essas variáreis são divididas em três partes, variáveis demográficas, razões pela admissão na UTI e variáveis fisiológicas e representam o grau de comprometimento da doença e a avaliação do estado de saúde prévio à admissão hospitalar, sendo indicadora da condição pré-doença[9]. É atribuído um peso para cada variável analisada com base na gravidade do distúrbio fisiológico, o menor valor concedido pelo escore é 16 e o maior 217 pontos[9].

As escalas para avaliação neurológica da HSA utilizadas no presente estudo foram a de Hunt-Hess e Fisher. A escala Hunt-Hess tem como objetivo avaliar o grau de comprometimento clínico de pacientes com hemorragia em alguma meninge, logo na admissão hospitalar e quanto maior a graduação, maior o acometimento clínico[10]. Na escala de Fisher, a graduação é feita de acordo com os achados tomográficos, a partir da quantificação da presença de sangue no espaço subaracnóideo por meio da tomografia computadorizada de crânio e quanto maior a graduação, maior a quantidade de sangue observado no exame[10].

Amplamente utilizada para avaliação de pacientes comatosos em cuidados intensivos, a ECG desenvolvida por Teasdale e Jennett em 1974, na Universidade de Glasgow, através da observação de comportamentos e atribuindo um valor numérico a essas observações, define o nível de consciência do paciente, auxilia na determinação da gravidade do trauma, na interpretação do estado clínico e prognóstico do paciente e nas pesquisas clínicas de profissionais da área da saúde[11]. Essa avaliação é realizada através da observação de três parâmetros: abertura ocular, reação motora e resposta verbal, cada um deles recebe um escore, e a soma dos três pode variar de três a quinze[11].

A mobilização precoce compõe o desenvolvimento da reabilitação de pacientes internados em UTI, é considerada estratégia de prevenção de fraqueza muscular adquirida em UTI e da decadência da função física, além disso, alguns estudos a relacionam com a redução de tempo de permanência na UTI e no hospital, diminuição do tempo de ventilação mecânica e promoção de melhora funcional[12]. Há uma variedade de escalas para avaliar os aspectos funcionais dos pacientes internados em UTI, com base nisso, foi validada em 2016 a escala ICU Mobility Scale, no português, escala de mobilidade em UTI (EMU) por Kawaguchi et al.[12], que foi desenvolvida para mensurar a mobilidade dos pacientes internados em UTI, sua pontuação varia entre zero e dez, em um único domínio, sendo que a pontuação zero significa uma baixa mobilidade (paciente que realiza apenas exercícios passivos no leito) e a pontuação 10 significa uma alta mobilidade (paciente que apresenta deambulação independente, sem auxílio)[12]. Tal escala foi utilizada para a avaliação da funcionalidade na admissão e na alta da UTI e para nortear o protocolo de mobilização precoce aplicado pela equipe de fisioterapia na UTI neurocirúrgica.

Os pacientes com diagnóstico de HSA aneurismática, internados na UTI neurocirúrgica, foram submetidos a um protocolo de mobilização precoce composto por três fases evolutivas: Fase I, mudanças de decúbitos e posicionamentos funcionais, mobilização passiva e sedestação passiva fora do leito. Fase II, exercícios ativo-assistidos e ativos, uso de cicloergômetro no leito, sedestação beira leito, transferência ativa da cama para a poltrona e exercícios na poltrona. Fase III, ortostatismo, marcha estacionária e deambulação. Foi avaliada a evolução funcional dos pacientes incluídos nesse estudo através da descrição no prontuário do tipo de atividades físicas desenvolvidas na admissão e na alta hospitalar, de acordo com o protocolo citado acima. Foi coletado ainda, o número de sessões de atendimentos fisioterapêuticos realizados desde o momento da internação na UTI neurocirúrgica até a alta hospitalar ou óbito.

Análise estatística

Foi constituído um banco de dados no programa Microsoft Excel® e realizada estatística descritiva com apresentação das variáveis em médias, desvios-padrão, números absolutos e percentuais. Foi aplicado teste de Kolmogorov-Smirnov para analisar a normalidade de distribuição dos dados e após, aplicada estatística inferencial com teste t não pareado de Student ou teste de Mann-Whitney para comparação das variáveis entre sobreviventes e não sobreviventes e teste t pareado de Student ou teste de Wilcoxon para comparação entre os períodos admissão e alta nos sobreviventes. As análises estatísticas foram realizadas do programa SPSS versão 17.0 para Windows® e foram considerados estatisticamente significativos valores de $p \leq 0,05$.

RESULTADOS

O presente estudo analisou dados retrospectivos de 103 pacientes diagnosticados com HSA aneurismática, internados na UTI neurocirúrgica, com idade média de 55,13±13,7 anos, destes, 72% foram do sexo feminino. Verificou-se que os pacientes não sobreviventes apresentaram idade significativamente ($p<0,0001$) maior que os sobreviventes (Tabela 1).

Tabela 1. Características sociodemográficas dos pacientes sobreviventes e não sobreviventes.

Variável	Sobreviventes (n=64)	Não sobreviventes (n=39)	p-valor
Idade (anos)	50,40 ± 11,99	62,89 ± 13,05	< 0,0001*
Sexo			
-masculino	n = 17 (27%)	n = 12 (31%)	0,65†
-feminino	n = 47 (73%)	n = 27 (69%)	

*Teste t não pareado. †Teste exato de Fisher

As variáveis clínicas e desfechos dos pacientes demonstraram que o escore de funcionalidade médio na admissão foi de 1,62±0,64 e na alta foi de 2,00±0,94, o desfecho alta contabilizou 62% dos pacientes e a topografia do HSA demonstrou 40% de aneurismas em artérias não especificadas (Tabela 2).

Tabela 2. Desfechos clínicos dos pacientes incluídos no estudo.

Variável	Média ± DP	Mediana	Mínimo-Máximo
Escore SAPS 3	49,33 ± 19,5	45	[16 – 93]
Escala de Fisher	3,44 ± 0,86	4	[1 – 4]
Escala de Hunt-Hess	2,91 ± 1,05	3	[1 – 5]
Topografia do aneurisma		-	-
Artéria cerebral média	n = 9 (9%)	-	-
Artéria comunicante anterior	n = 6 (6%)	-	-
Artéria comunicante posterior	n = 6 (6%)	-	-
Artéria basilar	n = 3 (3%)	-	-
Outras artérias	n = 39 (38%)	-	-
Artéria não especificada	n = 40 (39%)	-	-
Glasgow admissão	10,2 ± 5,3	13	[3 – 15]
Glasgow alta/óbito	10,4 ± 5,3	14	[3 – 15]
Internação na UTI (dias)	11,22 ± 9,98	8	[2 – 46]
Tempo de VM (dias)	4,88 ± 7,6	1	[0 – 43]
Internação Hospitalar (dias)	17,31 ± 14,2	13	[3 – 68]
Desfecho Alta (A) / Óbito (O)	A n = 64 (62%) O n = 39 (38%)	-	-
Sessões de Fisioterapia UTI	19,16 ± 22,87	12	[0 – 110]
Funcionalidade admissão	1,62 ± 0,64	2	[1 – 3]
Funcionalidade alta	2,00 ± 0,94	2	[1 – 3]

SAPS 3 = *Simplified Acute Physiology* Score 3; UTI = unidade de terapia intensiva; VM = ventilação mecânica.

Nas comparações entre os grupos por desfecho, alta ou óbito (Tabela 3), verificou-se que os pacientes não sobreviventes apresentaram índices significativamente maiores (p<0,05) de idade, escores SAPS III, Fisher e Hunt-Hess, pior ECG na admissão e no desfecho, maior tempo de permanência no hospital, maior tempo de VM e pior escore de funcionalidade.

Tabela 3. Comparações por desfecho entre sobreviventes e não sobreviventes das variáveis do estudo em valores de média ± desvio padrão ou mediana [mínimo e máximo].

Variável	Sobreviventes (n=64)	Não sobreviventes (n=39)	p-valor
Escore SAPS III	39,84 ± 14,07	64,89 ± 17,44	< 0,0001*
Escala de Fisher	3,5 [1–4]	4 [3–4]	0,0008‡
Escala de Hunt-Hess	2 [1–5]	3 [2–5]	0,0009‡
Glasgow (admissão)	15 [3–15]	3 [3–15]	< 0,0001‡
Glasgow (alta)	15 [6–15]	3 [3–12]	< 0,0001‡
Internação na UTI (dias)	8 [2–46]	6 [2–45]	0,43‡
Tempo de VM (dias)	0 [0–19]	6 [1–43]	< 0,0001‡
Internação Hospitalar (dias)	15,5 [3–68]	9 [3–60]	0,0017‡
Funcionalidade (admissão)	2 [1–3]	1 [1–3]	< 0,0001‡

*Teste t não pareado. t Teste de Mann-Whitney.

Na comparação dos desfechos neurológico e funcional na admissão versus alta, verificou-se melhora extremamente significativa (p<0,0001) no Glasgow e na funcionalidade dos pacientes que evoluíram para alta (Tabela 4).

Tabela 4. Comparações por desfecho admissão vs alta da UTI das variáveis neurológica e funcional em valores de mediana [mínimo e máximo] nos pacientes sobreviventes.

Variável	Admissão	Alta	p-valor*
ECG	15 [3–15]	15 [6–15]	< 0,0001
Funcionalidade	2 [1–3]	3 [1–3]	< 0,0001

ECG = escala de coma de Glasgow; *Teste de Wilcoxon.

DISCUSSÃO

No presente estudo a HSA foi predominante no sexo feminino, com idade média de 55 anos. A taxa de mortalidade foi de 38%. Na comparação dos desfechos clínicos verificou-se que os pacientes com HSA aneurismática sobreviventes apresentaram idade, escore SAPS III, escala de Fisher, escala de Hunt-Hess e tempo de VM, em dias, significativamente menores que os não sobreviventes, além disso, apresentaram escala de coma de Glasgow, na admissão e na alta da UTI e tempo de internação hospitalar, em dias, significativamente maiores que os não sobreviventes. Na comparação dos desfechos funcionais verificou-se que os sobreviventes apresentaram escore de funcionalidade significativamente maior que os não sobreviventes na admissão. Verificou-se ainda, que os sobreviventes evoluíram com incremento significativo da funcionalidade entre a admissão e alta da UTI.

Os acometimentos aneurismáticos são distúrbios neurológicos significativos, a incidência de HSA aguda foi estimada em 2–22 casos por 100.000 pessoas por ano e 60% de todas as HSA surgem em pessoas entre 40 e 60 anos[3]. Os pacientes que apresentam aneurismas graves necessitam de atendimento cuidadoso em UTIs, além de apresentarem taxas elevadas de morbimortalidade[13] e risco de desenvolver repercussões neurológicas importantes[14].

A literatura sobre rompimentos de aneurismas e HSA demonstra que há predomínio de acometimentos no sexo feminino, e que a idade média fica entre a quarta e a quinta década de vida[8,13,15-17] , assim como observado no presente estudo, no qual 72% dos pacientes foram do sexo feminino e a idade média foi de 55 anos. A pesquisa bibliográfica de Godeguez e Waters[14] levanta a hipótese de que se pode explicar essa predominância no sexo feminino devido ao período do climatério (períodos: pré-menopausa, peri-menopausa e pós-menopausa), que ocorre em torno dos 40 anos e pode se prolongar até os 65 anos. A menopausa gera menor secreção de estrogênio, essa diminuição atua no endotélio vascular gerando uma disfunção endotelial que acarreta desequilíbrio na disponibilidade de substâncias ativas podendo gerar inflamação, vasoconstrição e maior permeabilidade vascular[14]. Portanto, construindo essa vulnerabilidade endotelial que pode propiciar a formação de aneurismas, no entanto, ainda não foi possível tirar conclusões reais sobre essa explicação[16]. Além disso, a faixa etária mais acometida pode estar relacionada ao tempo de exposição aos fatores risco e ao desgaste natural do corpo[14].

No presente estudo, a média encontrada da escala Hunt-Hess foi de 2,91, em conformidade com o estudo de Silva et al.[18], em que a média foi de 2,33. A escala de Fisher foi de 3,44 e no estudo[18] citado anteriormente foi de 2,57, que indica achados tomográficos mais sutis comparados ao desse estudo.

Os resultados encontrados demonstram que os pacientes com HSA não sobreviventes apresentavam piores índices (escala de Fisher, escala Hunt-Hess, ECG, avaliação de função física conforme protocolo de mobilização precoce, maior idade e mais dias de VM) logo no momento da admissão, em comparação aos que evoluíram a alta. Porém, os que tiveram alta apresentaram mais dias de internação hospitalar. Se tratando aos dias de internação na UTI não houve diferença estatística entre os grupos, assim como ocorre no estudo de Silva et al.[18], no qual, a maioria dos pacientes (59,2%) apresentou tempo de internação na UTI inferior a sete dias e todos os pacientes que evoluíram a óbito permaneceram mais de seis dias internados na UTI (40,2%), no entanto essa diferença não foi significativa. Um dado relevante com significância estatística que se pode observar é que os pacientes que ficaram mais de seis dias internados na UTI apresentaram maior índice de infecção[18], tal complicação pode contribuir para a extensão do tempo de internação e evolução desfavorável[19]. Nesse estudo foi realizada a comparação entre os pacientes sobreviventes e não sobreviventes somente quanto ao tempo de internação (de 0 a 6 dias e de 7 a 66 dias), intervalo entre ictus e cirurgia e o uso de dexametasona, não sendo apresentadas diferenças estatísticas entre os dois grupos[18].

O rompimento de um aneurisma pode gerar alterações gravíssimas em um cérebro saudável, além de ocasionar altas taxas de mortalidade[8]. Cerca de 40% dos pacientes hospitalizados evoluem a óbito um mês após o evento, e mais de um terço dos que sobrevivem têm grandes déficits neurológicos[8]. As alterações neurológicas mais comuns encontradas nesse tipo de paciente são: confusão mental, déficit motor, afasia e crise convulsiva[14].

Apenas recentemente a reabilitação e seus resultados em paciente com HSA vêm sendo estudados e discutidos[8]. A realização de exercícios passivos e o auxílio na deambulação irão gerar melhora no retorno venoso e a prevenção da atrofia muscular, além de a deambulação proporcionar maior independência para o paciente[14]. Estudos realizados com pacientes que sofreram um AVC demostram que o treinamento físico melhora a função motora e a capacidade cognitiva[20] e que a reabilitação feita de forma adequada tem o potencial de melhorar a estabilização proximal, melhorando assim o equilíbrio e reduzindo o risco de quedas[21]. Pessoas com alguma deficiência neurológica constantemente necessitam fazer várias modificações no seu estilo de vida para acomodar suas deficiências e são propensas ao desenvolvimento de condições secundárias, como depressão, dor, imobilidade e descondicionamento geral, sendo o exercício físico um meio para suavizar essas condições secundárias[22].

As evidências sobre o benefício funcional da fisioterapia realizada precocemente em pacientes críticos vêm aumentando nos últimos dez anos, no entanto, essa prática habitual ainda não é rotineira[23]. No Brasil apenas 10% dos pacientes são mobilizados fora do leito[19]. A European Respiratory Society (ERS) e a European Society of Intensive Care Medicine (ESICM) aconselham a realizar a mobilização precoce o mais cedo possível[23]. As Diretrizes Brasileiras de Mobilização Precoce em Unidade de Terapia Intensiva enfatizam que é responsabilidade do fisioterapeuta definir o melhor modelo de intervenção, sua intensidade, periodicidade, continuidade ou interrupção da mobilização[23].

Visando padronizar a mobilização dentro da UTI neurocirúrgica e para fins educativos, foi criado o protocolo de mobilização precoce citado anteriormente. Quanto maior a fase, melhor a função física desse paciente. Como resultado do estudo foi observado que houve diferença estatisticamente significativa neste item ($p \leq 0,05$), comparando o primeiro atendimento fisioterapêutico motor e o último relatado em prontuário, ou seja, houve melhora da função física desses pacientes.

Um estudo semelhante utilizou a medida de independência funcional (MIF) um instrumento de avaliação do estado funcional e cognitivo para avaliar o grau de independência dos pacientes, para analisar os pacientes com HSA admitidos no Hospital das Clínicas da Universidade Estadual de Campinas[8]. Como resultados obtiveram melhora significativa dos escores da MIF entre a admissão e a alta, apresentando evolução relevante e melhora generalizada em todos os pacientes[8]. Neste mesmo estudo é enfatizado que o paciente que apresenta algum déficit motor na admissão provavelmente necessitará de mais cuidados/supervisão na alta, sendo então a condição motora um preditivo de prognóstico[8], esse fato foi observado no presente estudo, pois, quando comparamos a avaliação de função física conforme protocolo de mobilização precoce entre o grupo que recebeu alta e o grupo que evoluiu a óbito, o segundo grupo apresentou piores índices (médias: 1,90 vs 1,15 respectivamente).

É importante frisar a relevância da mobilização precoce dentro das UTIs, visando a melhora funcional dos pacientes e a redução do tempo de internação[23]. Dessa forma, a criação de um protocolo de mobilização precoce como a utilizada na UTI Neurocirúrgica, alvo do presente estudo, se expõe como guia tanto da avaliação da função física, quanto da própria mobilização precoce.

Limitações do estudo

O estudo realizado apresentou limitações quanto a busca dos dados no prontuário eletrônico, visto que, por ser um estudo retrospectivo, em muitos prontuários principalmente os mais antigos, não havia todos os dados necessários para a inclusão do paciente no estudo, portanto, o número da amostra foi menor. Além disso, a literatura referente a evolução funcional dos pacientes com HSA é escassa, o que dificulta a comparação dos resultados obtidos com outras pesquisas.

CONCLUSÃO

Pacientes com HSA aneurismática sobreviventes apresentaram menores idades, escore SAPS III, escala de Fisher, escala de Hunt-Hess e tempo de VM, maiores escores de escala de coma de Glasgow, na admissão e na alta da UTI e maior tempo de internação hospitalar que os não sobreviventes. Os pacientes sobreviventes apresentaram melhor funcionalidade que os não sobreviventes na admissão, e, evoluíram com melhora funcional da admissão até a alta da UTI.

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General, verbal, and non-verbal cognitive functioning of children and adolescents with 22q11.2 Deletion Syndrome

Funcionamento cognitivo geral, verbal e não verbal de crianças e adolescentes com Síndrome de Deleção 22q11.2

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ABSTRACT

Background: Cognitive dysfunctions are frequently found in the 22q11.2 Deletion Syndrome, being an aggravating factor in the impairment of social relationships and communication, strongly impacting the functionality of the individual. Increasing the knowledge regarding cognitive skills may provide contributions to the diagnostic process and the intervention planning.

Objectives: To estimate the general, verbal, and non-verbal cognitive functioning of children and adolescents with 22q11.2 Deletion Syndrome.

Methods: This is a cross-sectional, descriptive, and case series study regarding 15 individuals between 7-18 years-old diagnosed with 22q11.2 Deletion Syndrome. An assessment of the cognitive functions was performed using the Wechsler Abbreviated Scale of Intelligence (WASI). For data analysis we used a descriptive statistics analysis, having absolute frequencies for variables, and mean, median, standard deviation, minimum and maximum values for numerical variables.

Results: In the group analysis, we observed an important cognitive impairment degree. Most of the sampling (n=8; 53.33%) presented a considerably low total intelligence quotient score. Cases showing lower performances also presented greater difficulties regarding Visual Motor and Visuospatial coordination. Regarding the intelligence quotient representative punctuation in the WASI scale, the sample showed a large variability in the results (between 40 and 92 points), with the median total of 83.

Conclusions: We observed important dysfunctions, cognitive difficulties, and intellectual, verbal, and non-verbal disabilities in the population studied. These findings indicate the need for an early intervention to assist not only the cognitive aspect, but also the socio-emotional development of children with the 22q11.2 Deletion Syndrome, aiming at their participation in society.

Keywords: DiGeorge Syndrome; Velocardiofacial Syndrome; Cognition; Neuropsychology; Wechsler Scales

RESUMO

Fundamento: Disfunções cognitivas são frequentemente encontradas na Síndrome de Deleção 22q11.2, sendo um agravante no comprometimento das relações sociais e da comunicação, impactando fortemente na funcionalidade do indivíduo. O aumento do conhecimento sobre as habilidades cognitivas pode trazer contribuições no processo diagnóstico e no planejamento da intervenção.

Objetivo: Estimar o funcionamento cognitivo geral, verbal e não verbal de crianças e adolescentes com Síndrome de Deleção 22q11.2.

Métodos: Estudo transversal, descritivo, tipo série de casos, com 15 indivíduos entre 7-18 anos com diagnóstico da Síndrome de Deleção 22q11.2. A avaliação das habilidades cognitivas foi realizada com a Escala Wechsler Abreviada de Inteligência (WASI). Para análise dos dados, foi utilizada análise estatística descritiva, com frequências absolutas para variáveis, e média, mediana, desvio padrão, mínima e máximo para variáveis numéricas.

Resultados: Na análise do grupo, observou-se um importante grau de comprometimento cognitivo. A maior parte da amostra (n=8; 53,33%) mostrou quociente de inteligência total extremamente baixo. Os casos com desempenhos mais baixos apresentaram maiores dificuldades em relação às habilidades de coordenação visuomotora e visuoespacial. Em relação à pontuação representativa do quociente de inteligência na escala WASI, a amostra apresentou uma grande variabilidade de resultados (entre 40 a 92 pontos), com mediana total de 83 pontos.

Conclusões: As dificuldades cognitivas encontradas indicam a necessidade de uma intervenção precoce para auxiliar não só no desenvolvimento cognitivo, mas socioemocional de crianças com a Síndrome de Deleção 22q11.2 visando sua participação na sociedade.

Palavras-chave: Síndrome de DiGeorge; Síndrome Velocardiofacial; Cognição; Neuropsicologia; Escalas de Wechsler.

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INTRODUCTION

22q11.2 Deletion Syndrome (22q11.2del), also known as DiGeorge Syndrome or Velocardiofacial Syndrome, is the most common microdeletion identified in humans, and its populational prevalence is approximately 1:4000 born alive.[1] This syndrome possesses more than 180 clinical manifestations, both physical and behavioral, highlighting language and communication alterations, intellectual disability and learning difficulties.[2]

In general, cognitive dysfunctions are frequently found in 22q11.2del patients and tend to increase during adolescence[3, 4], being on several occasions, a case of late diagnosis. These cognitive problems are described in the literature as aggravating factors in the impairment of social relationships and communication, strongly impacting the functionality of the individual.[5,6,7]

Increasing the knowledge regarding cognitive skills in 22q11.2del children and adolescents may provide relevant contributions to the diagnostic process and the intervention planning, which is crucial for reducing secondary conditions to the inherent alterations of the genetic condition, thereby promoting an improvement to the quality of life and health of this population.[8,9]

Therefore, this study aims at estimating the general, verbal, and non-verbal cognitive functioning of 22q11.2del children and adolescents, thus contributing to the understanding of this population cognitive phenotype.

METHODS

Cross-sectional, descriptive and case series study, regarding 15 individuals between 7-18 years-old with confirmed diagnosis for 22q11.2del by means of positive result in the Fluorescent in Situ Hybridization (FISH) technique and/or CGH-array. Children and adolescents presenting severe degrees of speech intelligibility alterations or associated neurological dysfunction were excluded. The total number of participants was established by convenience sampling, where participants were selected by consulting the database of the Medical Genetics Center of a landmark hospital of the Rio de Janeiro State, and by indication of medical geneticists from Rio de Janeiro municipality.

The study was approved by the Ethic in Research Committee of the Instituto Nacional de Saúde da Mulher, da Criança e do Adolescente Fernandes Figueira (IFF/Fiocruz) under the number 3.557.676 and CAAE nº 99733418.0.0000.5269. All the children and adolescents' guardians signed the Information Consent Form and the children and adolescents themselves, the Informed Assent.

The assessment of the cognitive functioning was performed at a pre-scheduled time at the outpatient clinic of a Rio de Janeiro State landmark hospital, with an average duration of 90 minutes each session, which started by interviewing the guardians, where we collected: clinic data, education level and therapy realization. Subsequently, the Wechsler Abbreviated Scale of Intelligence (WASI)[10] evaluation was conducted with the participating children and adolescents.

The WASI aims to meet the need for a brief intelligence measurement in ages ranging from 6 years-old children to 89 years-old elders. The test was applied individually in a reserved environment with the sole presence of the examiner and the child. Application timewas around fifty minutes for the four subtests. The WASI test provides the Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ) and Full-Scale Intelligence Quotient (FSQI) scores. This scale comprises four subtests: Vocabulary, Block Design, Similarities and Matrix Reasoning. Administration of these four subtests is a quick way to estimate the individual's general cognitive, verbal, and non-verbal functioning. The WASI also allows the assessment of several cognitive aspects, such as verbal knowledge, visual information processing, spatial and non-verbal reasoning, fluid, and crystalized intelligence in diverse contexts.[10] The application of this test was performed in agreement to the instructions of the scale manual, following all recommendations made by the authors.

IQ classification was carried out according to the Wechsler Intelligence Scale for Children - Fourth Edition (WISC IV), since the Brazilian WASI Manual does not contain a qualitative description corresponding to the IQ scores. Thus, the classification used was "extremely low" (standard scores <70); "very low" (standard scores 70-80); "low average" (standard scores 80-90); "average" (standard scores 90-110); "high average" (standard scores 110-120); "very high" (standard scores 120-130); "extremely high" (standard scores> 130).

After application, the data was plotted in an Excel spreadsheet and transported to the EPIINFO data bank for the proper treatment of the data. For the data analysis, we performed a descriptive statistics analysis with absolute frequencies for variables, and mean, median, standard deviation, minimum and maximum values for numerical variables.

RESULTS

Our sample comprised of 15 children/ adolescents with an average (mean) age of 12.13 years-old (standard deviation = 3.42), varying from 7 to 18 years-old, and a median of 13.

All children/adolescents attended school, and 13 (86.7%) reported having school difficulty. Still on the school issue, little more than half of the sample (9; 60%) is not in the school year expected for their age.

In relation to the presence of other comorbidities, 13 children/adolescents possessed associated comorbidities, the most frequent being: heart (10; 76.9 %) and respiratory (2; 15.3%) problems, and other alterations (cataract or Noonan Syndrome) (2; 15.3%).

Most part of the sample (13; 86.67%) was undergoing some kind of therapy in the time of the interview, especially psychotherapy and speech therapy.

Table 1 presents the classification of the sample performance regarding Verbal Intelligence Quotient (VIQ), Performance Intelligence Quotient (PIQ) and Full-Scale Intelligence Quotient (FSQI). Regarding the representative IQ score on the WASI scale, the sample presented a large variability of results.

Table 1. Sample distribution regarding the IQ classification obtained from the WASI test.

	Verbal IQ	Performance IQ	Full Scale IQ
Classification			
Average	1 (6.67%)	3 (20.00%)	1 (6.67%)
Low Average	5 (33.33%)	2 (13.33%)	4 (26.67%)
Very Low	4 (26.67%)	5 (33.33%)	2 (13.33%)
Extremely Low	5 (33.33%)	5 (33.33%)	8 (53.33%)
Representative Score			
Variation (Min – Max)	45-91	45-101	40-92
Mean (Standard Deviation)	72.8 (15.23)	73.93 (15.06)	70 (15.12)
Median	78	78	83

Source: Authors' own elaboration
Note: IQ = intelligence quotient; categorical result expressed by the absolute number and frequency in parentheses.

Table 2 presents the sample results in each WASI subtest. This analysis was performed through weighted scores presented by children and adolescents in each subtest. The abilities measured were knowledge and understanding of the word's meanings (Vocabulary subtests); verbal and logical analogy (Similarities subtest); visual motor and visuospatial coordination (Block Design subtest); non-verbal reasoning and general intellectual skill (Matrix Reasoning subtest).

Table 2. Sample distribution regarding the weighted score on the WASI subtests.

	Vocabulary	Similarities	Block Design	Matrix Reasoning
Variation (Min – Max)	1 - 9	1 - 11	1 - 8	1 - 13
Mean (Standard Deviation)	5.27 (2.23)	5.3 (2.98)	4.3 (2.09)	6.53 (3.20)
Median	6	5	4	6

Source: Authors' own elaboration

In the group analysis, in general, an important degree of cognitive impairment was observed. The case with the best performance compared to the entire sample, with a FSQI of 92 and classified as average, presented cognitive performance adequate to what was expected for his age, highlighting the non-verbal reasoning and general intellectual skills, assessed by Matrix Reasoning subtest, in which obtained higher average as result. On the other hand, the cases with lower performances, generally presented greater difficulties in relation to the Visual Motor and Visuospatial skills, evaluated from the Block Design subtest.

DISCUSSION

Despite our small sampling size, given this disease incidence within the population, it is possible to observe important issues regarding cognitive functioning. The results mostly showed an extremely low general cognitive functioning, with some variation of results in the intelligence quotient among the sample of children and adolescents with 22q11.2del. These findings corroborate with previous reports that indicated a great variation of cognitive alterations related to 22q11.2del.[11,12,13] From a meta-analysis with cross-sectional studies, Moberg et al.[14] highlighted robust findings concerning cognitive deficits in the intellectual functioning of individuals with 22q11.2del, being influenced by factors such as the comparison group; age; sex and clinical status. Studies describe this alteration with disparities, ranging from the presence of intellectual deficiency to moderate,[15,16,17] or within the normality parameters.[18,19] According to Fiksinski[3] in order to understand the phenotypic variability found, it is worth reflecting on additional factors that influence it – as the gene-environment interaction; variability in the assessment; age-depending phenotypes; and standardization of the diagnostic criteria.

It is important to consider that the cognitive disturbances constitute one of the most difficult psychosocial aspects for patients and their families.[20] Moreover, early cognitive decline in 22q11.2del children is a robust indicator of the risk of developing a psychotic illness,[9] [17]and there is a discussion of the possibility of both phenotypes presenting the same pathological process in different development stages;[11] highlighting the importance of monitoring the cognitive development of children and adolescents.

Results regarding the representative IQ score in the total index of the WASI[10] scale presented variation between 40 and 92 and mean of 70. These data corroborate the study of Pimenta et al.[21] also conducted with Brazilian children and adolescents with 22q11.2del, which pointed out IQ variation from 42 to 104 and mean of 73.0 following Wechsler Scale of Intelligence for Children – Fourth Edition (WISC-IV). Results from international studies also presented similar variation concerning IQ, as the one conducted by De Smedt et al. [19] with a large sample of children from Belgium, indicating variation between 50-109 and mean of 73.48 in IQ following the third edition of Wechsler Scale (WISC-III). Similar to the results of these studies, the qualitative descriptions of Full-Scale IQ of the present sample varied between 'extremely low' to 'average', whereas Jacobson et al.,[22] assessing children and adolescents from United Kingdom, found an average IQ of 65.4 and varying from 44 to 80, indicating a slightly inferior classification.

Despite the variability referent to the Intelligence Quotient, the sample classification regarding Full Scale IQ was mostly extremely low (53.33%). This result may be

related to school difficulties, presented by most of the sample, considering the cognitive functioning as a key factor for a school life and, therefore, must be taken in consideration when planning the development of individuals with 22q11.2del.[23] 23 Learning difficulties are also reported in this genetic condition, [24] and may be related to the school delay seen in this study. In this sense, we emphasize the importance of the educational intervention, covering the training of verbal and non-verbal skills.[13]

Discrepancies between verbal and non-verbal skills of individuals with 22q11.2 Deletion Syndrome are discussed in the literature. Moberg et al.[14] did not find significative differences between the verbal and non-verbal intellectual functioning in the cross-sectional studies analyzed in the review, whereas Jacobson et al.[22] and Pimenta et al.[21] pointed out superiority of the verbal intelligence over non-verbal one as an apparent characteristic of the cognitive phenotype of 22q11.2del. In the present study, the children and adolescents' performances in verbal and non-verbal tasks did not present great discrepancy, with average Verbal IQ of 72.8 and average Performance IQ of 73.9. Variation in the qualitative descriptions, in both, was from 'extremely low' to 'average', however, with higher frequency of 'average' classifications in the Performance IQ (20%) in comparison to the Verbal IQ results (6.67%).Another finding of this research was the presence of comorbidities, all consistent with the 22q11.2 Deletion Syndrome, especially the heart problems. According to the literature, 22q11.2del is the second biggest cause in the developmental delay and of congenital heart defects, behind only to Down Syndrome.[25]

Our small sample was a limitation of this research and can be explained by the diagnostic commonly being realized just after birth due to the associated comorbidities, mostly heart problems, or during adolescence when the psychological problems appear,[3,4] and there is no segment flow of this population in public services. Thus, it is understandable to face difficulties finding and convening children for this research, because many phone numbers and addresses were outdated in the health service. Still, we emphasize the importance of descriptive statistics, such as those performed here, to evaluate the needs and health trends of the population, and for the planning and allocation of resources and interventions.[26,27]

Cognitive and communication problems have a significative impact on the disability and functionality of individuals, being those of great social and economic relevance for most countries and of dramatic proportions considering the existence of millions of disabled people in the world. Thus, considering the cognitive and adaptive functioning as key factors in the school and professional life of individuals with 22q11.2del,[23] studies that discuss the impact of the cognitive functioning on the functionality of the individuals are necessary.

CONCLUSION

In conclusion, this study highlights that the presence of cognitive dysfunction and intellectual, verbal, and non-verbal disabilities are predominant in the 22q11.2 Deletion Syndrome, which reinforces the importance of its investigation. It is also essential to discuss the results found in the WASI related to functionality, aiming to guarantee the children and adolescents greater coverage in health care.

Also, the cognitive impairments found indicate the need for an early intervention to assist not only the cognitive development, but also the socioemotional development of children with 22q11.2 Deletion Syndrome aiming towards its participation in the society.

Key Messages:
- 22q11.2 Deletion Syndrome (22q11.2del) possesses more than 180 clinical manifestations, both physical and behavioral, highlighting language and communication alterations, intellectual disability and learning difficulties
- Presence of cognitive dysfunction and intellectual, verbal, and non-verbal disabilities are predominant in the 22q11.2del
- The cases with lower performances generally presented greater difficulties concerning Visual Motor and Visuospatial coordination
- Cognitive and communication problems have a significative impact on the disability and functionality of individuals, being those of great social and economic relevance for most countries
- The cognitive and adaptive functioning are key factors in the school life and professional career of individuals with 22q11.2del

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Treatments for Tourette syndrome in children and young adults: A systematic review

Tratamento da síndrome de Tourette em crianças e jovens adultos: Uma revisão sistemática

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ABSTRACT

Introduction: Tourette's Syndrome (TS) is a neurodevelopmental disorder characterized by motor and / or vocal tics for more than 12 months. TS affects about 0.8% of pediatric patients and is associated with great functional impairment and psychological distress. The present study aims to list and compare the effectiveness of therapies used in children and young people with TS.
Methods: PubMed / MEDLINE, Cochrane Library, ScienceDirect, SciELO and Lilacs were used from September 2020 to April 2021 to search for randomized clinical trials with pharmacological, behavioral, physical or alternative interventions for tics in children and young people with ST.
Results: 13 clinical trials were included, of which six pharmacological, six behavioral and one of other conformation. The global score on the Yale Global Tic Severity Scale showed evidence in favor of Habit Reversal Training (HRT) and Comprehensive Behavioral Intervention for Tics (CBIT). Evidence from two studies suggests that antipsychotic medications improve tic scores. Evidence from other interventions has shown no conclusive benefit.
Conclusions: The present study identified benefits with the use of antipsychotics. The study also found that HRT and CBIT showed improvement in reducing the severity of tics, in addition to not having any adverse effects. These therapies showed significant clinical improvement, but there is no comparison between the use of these isolated approaches in relation to their use associated with medications. In view of the different forms of therapy, further studies are needed to identify the effectiveness and the profile of adverse effects of these interventions.

Keywords: Tourette Syndrome, Therapeutics, Tics, Child, Adolescent.

RESUMO

Introdução: A Síndrome de Tourette (ST) é um distúrbio do neurodesenvolvimento caracterizado por tiques motores e/ou vocais por mais de 12 meses. A ST afeta cerca de 0,8% dos pacientes pediátricos e associa-se a grande comprometimento funcional e sofrimento psíquico. O presente estudo tem como objetivo listar e comparar a eficácia das terapias utilizadas em crianças e jovens com ST.
Métodos: PubMed/MEDLINE, Cochrane Library, ScienceDirect, SciELO e Lilacs foram usados desde setembro de 2020 até abril de 2021 para a busca de ensaios clínicos randomizados com intervenções farmacológicas, comportamentais, físicas ou alternativas para tiques em crianças e jovens com ST.
Resultados: 13 ensaios clínicos foram incluídos, dos quais seis farmacológicos, seis comportamentais e um de outra conformação. A pontuação global na Yale Global Tic Severity Scale, apresentou evidências a favor do Treinamento de Reversão de Hábito (TRH) e Intervenção Comportamental Abrangente para Tiques (ICAT). As evidências de dois estudos sugerem que medicamentos antipsicóticos melhoram os escores de tiques. Evidências de outras intervenções não mostraram nenhum benefício conclusivo.
Conclusões: O presente estudo identificou benefícios com o uso do antipsicóticos. O estudo também identificou que a TRH e a ICAT apresentaram melhora na redução da gravidade dos tiques, além de não apresentarem efeitos adversos. Essas terapias mostraram importante melhora clínica, mas não há comparação entre o uso dessas abordagens isoladas em relação ao seu uso associado com medicamentos. Diante das diferentes formas de terapia, mais estudos são necessários para identificar a eficácia e o perfil de efeitos adversos dessas intervenções.

Palavras-chave: Síndrome de Tourette, Terapêutica, Tiques, Criança, Adolescente.

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INTRODUCTION

Tourette's syndrome (TS) and Chronic tic disorder (CTD) are disorders characterised by the presence of combined or singular motor and vocal tics for more than 12 months with the onset before the age of 18 years[1]. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), tics are sudden, fast, recurring, non-rhythmic movements or vocalisations usually preceded by a feeling of urgency, which is described as an intense desire to move or an internal tension before the movement[2,3]. The prevalence in paediatric patients has been estimated as 0.4%-0.8%, and both TS and CTD are associated with great functional impairment and psychological distress[4]. In general, tics start at around 6 to 7 years old, with clinical worsening between the ages of 8 and 12 years old. From adolescence and early adulthood tics decrease in severity, with a comparatively lower prevalence in adult life[5]. Tics can be simple or complex movements and, although they can affect any part of the body, they are more prominent on the face. Vocal tics include a variety of sounds and words, including coprolalia - inappropriate or involuntary use of words, sounds or phrases[3].

About 85% of patients with TS have one or more neuropsychiatric disorders, such as Obsessive-Compulsive Disorder (OCD), Attention Deficit Hyperactivity Disorder (ADHD), anxiety and depression[6,7]. The pathophysiology associated with TS is still not well understood, but it is probably caused by striatal-thalamic-cortical circuit interruption due to aberrant neural activity and consequent inhibition of somatosensory impulses and movements [8].

Cognitive-behavioural and pharmacological therapies are indicated for young people with TS who have, due to tics, impaired quality of life and daily functioning[8]. The cognitive-behavioural therapy and the psychoeducation is based on improve the knowledge of the patient and their families about TS, as a result, the knowledge deconstructs misconceptions about the syndrome, prepares the patient for possible more invasive therapeutic approaches, and educates the patient and his family [9].

Pharmacological approaches are based on experience *one on one,* but it is also influenced by the comorbidities of the paciente and the way of the spectrum of TS. In general lines, a pacient with TS may be treated with antipsychotic drugs first and second-generations, α-2-agonists, botulinum toxin or Δ-9-tetrahydrocannabinol showing different levels of evidence, quality of treatment and recommendation[8,9].

Most of the time these therapies show significant improvement in TS[9], however, there are other treatment options in cases of refractoriness, such as deep nerve stimulation, provided it meets a list of criteria based on recommendations of North American and European groups of study[10]. When choosing the treatment for TS, the interaction between tics and other comorbidities, such as OCD and ADHD, should be considered[11].

Systematic reviews and meta-analyzes on the treatment of tics are rarely found. Some studies have evaluated the effectiveness of treatments in both children and adults[12, 13], but it is known that children and adults may have different responses to the same drugs, both in terms of effectiveness and in susceptibility to adverse effects[14].

The current review aimed to list and compare the efficacy of the therapies used in children with TS, as well as their benefits and damages.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA).

Data base

The keywords used for the search in databases were obtained from Health Sciences Descriptors in the Virtual Health Library. The databases used for the research were PubMed/MEDLINE, Cochrane Library and ScienceDirect, with the keywords “Tourette syndrome”' and “Treatment”, and in the Scientific Electronic Library Online (SciELO) and Latin American and Caribbean Literature in Sciences of Health (Lilacs) with the same keywords in Portuguese, Spanish and English. Searches were conducted from September to December 2020 and updated in April 2021. Articles published in national and international journals in the last 20 years in English, Portuguese and Spanish were included. Book chapters, editorials, case reports and review studies were excluded from the analysis.

Eligibility criteria

PICO strategy was used to determine the inclusion and exclusion criteria.

Population: aged < 19 years old with a clinical diagnosis of TS or chronic tics disorder, according to DSM-5 criteria. Patients with transient tics (duration < 12 months) were excluded. Studies that included patients older than 19 years were not enrolled even if the average age of the study was < 19 years, due to possible associated biases.

Intervention: pharmacological treatments, psychological, behavioural, educational and psychosocial therapies, as well as physical and alternative therapies.

Comparison: placebo or other pharmacological therapies, psychological, behavioural, educational and psychosocial therapies, as well as physical and alternative therapies. Head-to-head studies were excluded.

Outcome: severity of tics assessed by the Yale Global Tic Severity Scale (YGTSS).

Only Randomised Clinical Trials (RCTs) were considered eligible. Decisions about inclusion criteria and classification of interventions were agreed by all authors before data extraction.

Eligibility criteria

Relevant data for the research were added to a table by one of the reviewers and this information was later verified by a second reviewer using a pilot form in Microsoft Excel 2017. As several scales have been described, the analysis priority has been given to YGTSS, which is the most used. After searching and choosing the articles, the risks of bias were analysed for each of the studies, evaluating whether any source of bias had a significant impact on the results.

Yale Global Tic Severity Scale (YGTSS)

The main subscale used for comparison was the YGTSS - total tic score (YGTSS-TTS), since most of the articles analysed used the values resulting from this assessment as their main result. When this value was not available in the study, YGTSS motor tic severity and YGTSS phonic tic severity were used, but this does not affect the comparison between the effectiveness of treatments, since YGTSS total tic score derives from YGTSS motor tic severity and YGTSS phonic tic severity [15].

YGTSS was the tool chosen because it is the score most commonly used for TS and it is also considered the gold standard in the tics evaluation[12]. YGTSS includes a symptom validation list for motor and vocal tics[15]. Tics are assessed for the number, frequency, intensity, complexity and interference of symptoms on a scale of 0–5. The scores for each dimension are totaled to reflect the severity of motor tics (range 0–25), vocal tics (range 0–25) and combined tics (range 0–50)[16]. YGTSS also includes a classification of general impairment such as experienced suffering and disability in the interpersonal, academic and occupational spheres[17].

RESULTS

After excluding duplicate texts, 916 articles were identified and, of these, 254 were selected for full text screening. Thirteen articles published between 2001 and 2021 met eligibility criteria (Figure 1). Of the 13 selected clinical trials, six articles were pharmacological interventions, six were behavioural interventions and one was physical intervention.

The characteristics of these studies, as well as the benefits and potential damages of each therapy, are present in Tables 1, 2 and 3. All the studies analysed involved patients diagnosed with TS or chronic tics, with targeted treatment for these conditions

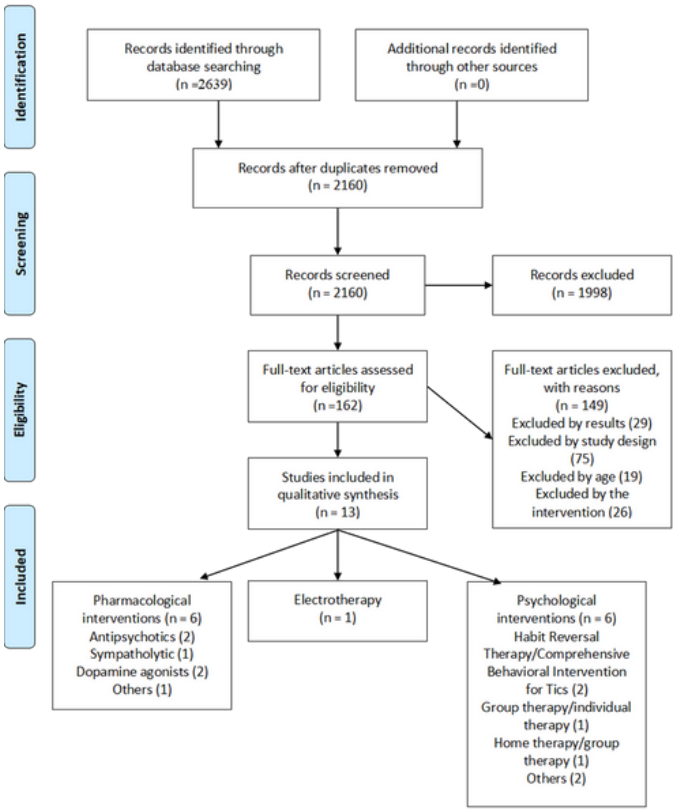

Figura 1. Flow diagram of preferred reporting items for systematic and meta-analysis.

Pharmacological interventions

Aripiprazole[18] in high dose (n = 45) and low dose (n = 44) compared to placebo (n = 44) resulted in significant clinical improvement. Patients were treated for 8 weeks and followed up for an average period of 30 days thereafter. There was a significant improvement in YGTSS-TTS in patients who used a low dose of aripiprazole (p = 0.002; 95% CI = -10.2 to -2.3) and in those who used high doses (p <0.0001; 95% CI = - 13.8 to -5.9) compared to placebo. Patients who used high doses of aripiprazole had a statistical difference in the improvement of tics according to YGTSS-TTS compared to placebo during all 8 weeks of treatment, and except for the second week of treatment, low doses of aripiprazole also showed this improvement. At the end of the 8th week, patients who used a low dose of aripiprazole had a mean change from baseline in YGTSS-TTS of - 13.4 ± 10.36, while those who used high doses had a change of -16.9 ± 9, 46. Patients who used placebo had a mean variation of -7.1 ± 10.36 in YGTSS-TTS. There was an improvement of 45.9% and 54.2% in YGTSS-TSS with the use of low and high doses of aripiprazole, respectively.

Ecopipam[19] showed significant results compared to placebo after 16 days (p = 0.01; 95% CI = 0.9 to -6.5) and 30 days of treatment (p = 0.03; 95% CI = -6.1 to 0.3). The mean was reduced from 32.8 ± 7.1 at baseline to 27.7 ± 8.8 in 16 days and to 27.2 ± 9.1 in 30 days with the use of ecopipam. With the placebo, the results varied from 33.7 ±

6.7 to 31.6 ± 7.7 and 30.3 ± 8.6, respectively, in the same periods of time. Both motor and vocal tics showed significant improvement with the use of ecopipam.

Guanfacine[20] did not show promising results when compared to placebo. In the group that used guanfacine (n = 16), the YGTSS-TTS decreased from 26.25 ± 6.61 to 23.56 ± 6.42 (p = 0.08), after 8 weeks of treatment, while in the control group (n = 18) there was a similar reduction from 27.67 ± 8.7 to 24.72 ± 10.54 after the same period of time. Thus, there was no significant reduction between the two groups in the YGTSS-TTS.

N-acetylcysteine[21] (n = 17) did not show any significant reduction in tics assessed by YGTSS-TTS compared with the control group (n = 14) after 12 weeks of treatment. The group that used N-acetylcysteine showed a variation from 27.1 ± 7.2 before treatment to 24.3 ± 7.9 after 12 weeks, while the placebo group varied from 26.3 ± 7.7 to 21.3 ± 4.6 (p = 0.815) in the same period of time.

Pergoline[22] showed a small improvement of symptoms in YGTSS-TSS. There was an average reduction of 8.8 points in the YGTSS-TSS (p = 0.05; 95% CI = 0.1 to 17.6) in the group that used pergoline (n = 36), varying from 50.6 ± 13.1 before treatment to 36.4 ± 16.5 after 8 weeks. In the placebo group (n = 15) there was a decrease in YGTSS-TTS from 45 ± 13 to 39.6 ± 19.4 in 8 weeks. The decrease in symptoms with pergoline did not reach clinically significant levels.

Psychological / psychosocial interventions

In the study by Yates et al.[23], patients were divided into 2 groups, one group (n = 17) participated in the Habit Reversal Training (HRT) and another (n = 16) in the educational group treatment. There was a reduction from 16.31 ± 3.03 to 15.88 ± 2.28 in the YGTSS motor tic severity (percentage improvement of 2.6%) and from 12.63 ± 5.93 to 11.13 ± 5.82 in the YGTSS phonic tic severity (improvement of 10.5%) in patients who participated in the educational group after 6 therapy sessions. In the HRT group, there was a change from 17.65 ± 4.74 to 15.12 ± 4.3 in the YGTSS motor tic severity (improvement of 14.5%) and from 12.71 ± 6.99 to 12.71 ± 5.61 in the YGTSS phonic tic severity (without percentage improvement) after the eighth session.

In the study by Dabrowski et al.[24], 28 of the 33 participants in the study by Yates et al.[23] were reevaluated, comparing YGTSS motor tic severity and YGTSS vocal tic severity after one month and after 12 months of treatment. Thirteen participants from the educational group and 15 from the HRT group were reevaluated. In the educational group there was a reduction from 15.54 ± 2.33 (95% CI = 14.13 - 16.95) to 13.77 ± 2.24 (95% CI 11.08 - 16.46 in the motor YGTSS tic severity and from 11.15 ± 6.35 (95% CI 7.32 - 14.99) to 9.23 ± 7.28 (95% CI 4.83 - 13.63) in the YGTSS phonic tic severity. In HRT group there was a decrease from 12.33 ± 5.64 (95% CI = 9.21 - 15.46) to 10 ± 7.1 (95% CI = 6.07 - 13.93) in the YGTSS phonic tic severity, while the YGTSS motor tic severity went from 14.73 ± 3.83 (95% CI = 12.61 - 16.85) to 12.2 ± 5.07. An average reduction of 8 points in the YGTSS-TSS was observed between the first evaluation (one month before the starting treatment) and the last one (12 months later) in those in HRT group, while in the educational group there was a reduction of 6 points in the same period of time.

One of the studies compared the effectiveness of behavioural therapy (n = 25), psychoeducational therapy (n = 24) and pharmacological treatment (n = 47) with risperidone or aripiprazole[25]. Patients who used Behavioural Therapy (BT) and pharmacology therapy showed a reduction in the severity of tics according to YGTSS-TTS (and its subscales), while the group that underwent psychoeducational therapy did not show considerable improvement. The volunteers were evaluated three times, the first (T0) before the starting treatment, the second (T1) after 10 weeks and the third (T3) 3 months after the end of BT or psychoeducational therapy and 5 months after starting pharmacological therapy. Patients who participated in BT had a reduction from 35.4 ± 17.78 at T0 to 19.84 ± 14.38 at T1 and 19.96 ± 13.68 at T2 at YGTSS-TTS, while those who used pharmacological treatment increased from 36.38 ± 16.70 in T0 for 23.47 ± 12.64 in T1 for 22.26 ± 11.23 in T2 with p <0.05 in both approaches. On the other hand, patients who used psychoeducational therapy went from 34.25 ± 14.34 in T0 to 35.00 ± 14.89 in T1 to 33.12 ± 13.88 in T2 in YGTSS-TTS.

One of the studies compared the effectiveness of individual therapy with group therapy[26], using in both approaches HRT and tic exposure therapy. Individual therapy group used HRT (n = 31) and the group that received group therapy was submitted to exposure therapy (n = 28). Patients who participated in individual therapy (n = 31) had an average of 51.52 13.04 in YGTSS-TTS before the beginning of treatment, while those who were allocated for group therapy (n = 28) had an average of 48 12.12. After eight therapy sessions, there was a decrease of 9.48 7.84 points in individual therapy and 7.48 5.44 points in group therapy. Both treatments presented clinical improvement (p < 0.0001). There was no significant difference in the clinical response between the two groups considering YGTSS-TTS.

A research by Singer, McDermott, Ferenc, Specht and Mahone[27] produced videos and an instructional guide that should be administered by parents (based on home psychotherapy) and compared its effectiveness with therapy administered by a therapist after 10 weeks of treatment. The patients who used the first method (n = 8) had, on average, in YGTSS-TTS, 27.75 ± 3.62 points before treatment and 18.75 ± 5.7 after 10 weeks of treatment (p <0.001) . Patients who had the therapy administered in person by a therapist had a score of 28.2 ± 4.56 before the start of treatment and 20.70 ± 6.34 after 10 weeks of treatment (p = 0.010).

The study by Piacentini et al.[28] compared Comprehensive Behavioural Intervention for Tics (CBIT)

(n = 61) in relation to educational and supportive therapy (n = 65) in the reduction of chronic tics for 10 weeks. The CBIT group had an average of 24.7 ± 6.2 points in YGTSS-TSS before the starting treatment and 17.1 ± 2 after the 10 weeks of treatment, while those who participated in the control group had 24.6 ± 6 before treatment and 21.1 after 10 weeks. There was an average decrease of 7.6 points in YGTSS-TTS in patients undergoing HCT compared to a decrease of only 3.5 points in the other group (p <0.001; 95% CI = 2 to 6.2).

Other types of interventions

A study conducted by Wen-Jun et al.[29] evaluated the effectiveness of electrotherapeutic stimulation in reducing tics compared to a false procedure ("sham procedure"). Patients who underwent electrotherapeutic stimulation (n = 29) scored an average of 30.41 ± 5.89 on the YGTSS-TTS before the starting treatment and 20.62 ± 6.44 after 40 sessions. Patients who participated in the sham procedure scored 30.04 ± 5.52 before the starting the procedure and 23 ± 7.37 after 40 sessions. Participants who underwent electrotherapy showed an average improvement of 31.66% in YGTSS-TTS, while the sham group had an improvement of 23.96%, which resulted in a non-significant difference between the groups.

A study by Zheng et al.[30] compared 5-ling-granule (5-LGr), a herbal medicine, (n = 363) with tiapride (n = 123) and placebo (n = 117) for 8 weeks, evaluating the clinical response in the 2nd and 8th week. In the 2nd week of treatment, there was no statistical difference between the groups evaluating the YGTSS-TSS, but in the 8th week a significant difference was found. Patients who used tiapride showed a variation in the YGTSS-TSS from 23.1 ± 6.9 before treatment to 10.1 ± 6.4 after the 8th week of treatment (p <0.001 compared to placebo). The 5-LGr group varied the YGTSS-TSS score from 23.7 ± 6.8 to 10.6 ± 6.8 (p <0.001 compared to placebo and 0.489 compared to tiapride). Variation in the placebo group was 22.7 ± 6.7 to 14.4 ± 7.5 after the 8th week of treatment initiation.

Adverse effects associated with treatment

Given the relatively small samples found in the studies, every evidence that there was an increased risk for adverse effects was considered. Although antipsychotics are associated with increased risks of sedation and extrapyramidal side effects[31] the studies analysed did not associate any serious adverse effects to antipsychotics when compared to placebo. Patients who used high doses of aripiprazole had more side effects, with thirty-four participants experiencing at least one adverse effect. Twenty-nine patients who used low doses of aripiprazole and eighteen of the placebo group had at least one adverse effect.

Guanfacine also had considerable adverse effects compared to placebo, especially fatigue, drowsiness, headache, abdominal pain, decreased appetite, depressed mood, dry mouth, and irritability. These symptoms were most frequently reported within the first four weeks of treatment. Other drugs analysed in this research, as well as electrotherapy, did not present statistically significant adverse effects when compared to placebo.

Some studies did not provide information on adverse effects caused by the treatments applied, and therefore, it was not possible to assess their safety profile.

DISCUSSION

HRT is considered the first treatment line for TS and for CTD in children and young people[32]. Our results support this recommendation, with evidence that other Behavioural therapies, such as CBIT, have a similar magnitude of effect to medications. CBIT approach basically consists of awareness training for tics and premonitory desire, competitive response training to provide tic substitutive behaviour and functional intervention to help identify changes in daily activities that could be beneficial in reducing tics. The absence of collateral damage is a factor that benefits CBIT practice[7, 33, 34], as well as its long term effect of reducing tics. The main guidelines of the United States, European Union and Canada recommend HRT as the first line of treatment for tics[32, 33, 35]. Despite this, for many people with tics and TS, pharmacological treatment should be considered either because of the lack of treatment response to HRT or limited access to therapy. Antipsychotics are widely used for TS and aripiprazole, in our results, showed an important clinical response compared to placebo, even at low doses. In comparison to the control group, there was no increased risk of clinically significant adverse effects. These findings may suggest that aripiprazole is a useful and safe drug for children with tics, with a similar effect to other antipsychotics. Educational therapies presented no significant clinical improvement, especially when compared to Behavioural therapies and pharmacological treatment. Treatment combining both HRT and exposure therapy was effective in individual and group therapy.

Antipsychotics, such as olanzapine, have not been evaluated in RCTs, only in head-to-head studies, which have a low comparative potential for effectiveness. Thus, to assess its efficacy, as well as its safety profile in paediatric patients with TS, further studies are needed.

Ecopipam showed an important clinical improvement in patients with tics, reducing both vocal and motor tics. In addition, ecopipam appears to be well tolerated in TS, with the absence of neuroleptic conditions common in other dopamine antagonists. Alpha-2-agonists, such as clonidine and guanfacine, are commonly used in children with CTD and are even considered first-line for TS[36-41]. The selection of clonidine and guanfacine occurs

partly because of their more favourable side effect profile when compared to antipsychotics[13]. The study analysed in this review[20] differed from other findings in the literature, since it concluded that there was no significant clinical improvement in patients who used guanfacine compared to placebo. However, this study had a sample of only 34 participants and, therefore, it may not have considerable statistical power to conclude the effectiveness of guanfacine. Another drug that did not show significant clinical improvement in TS in children and adolescents, according to the results obtained in this research, was N-acetylcysteine. Other previous studies concluded that N-acetylcysteine has a significant clinical benefit in the treatment of trichotillomania in adults, however, the same efficacy results were not observed in children with TS evaluated in Bloch's research[37].

5-LGr provided a significant clinical improvement over the placebo, in addition to demonstrating an efficacy in reducing tics similar to what occurs with tiapride. The effectiveness of 5-LGr observed in this study may be related to its multiple pharmacological and therapeutic properties. Preclinical studies have shown that this substance was able to decrease the affinity of the striatal D2 receptor and decrease the metabolic level of dopamine, while suppressing tics-like behaviour in mice [30].

It is important to highlight the scarcity of evidence for alternative treatments that are often used for CTD and TS. The only research found that assessed the efficacy of acupuncture was a head-to-head study[42] compared to haloperidol and had a low impact of evidence. No studies were found on the use of dietary supplements, vitamins or yoga.

There is no evidence of the effectiveness of electrotherapeutic stimulation in reducing tics in children and adolescents. Although the study by Wu et al.[29] concluded that this approach is safe, there was no significant improvement in relation to the sham group. It should also be considered that, in addition to a small sample, the patients in this study continued to use medications for tics, which may explain the clinical improvement in both groups - even in those who did not undergo electrotherapy.

It should be noted that the great effectiveness of behavioural therapies was due to the research that used CBIT, since it was the study with the most significant sample. Despite consistent evidence of the efficacy of Behavioural therapies and the low risk of associated adverse effects, difficulties with access and financial constraints may make it impossible to adhere to this type of treatment. An alternative proposed for these situations is home psychotherapy. Usually little used in practice, this approach consists of an instructional video based on HRT and written instructions to be followed by patients and parents at home[7]. One study concluded that there is a significant clinical improvement in tics using videos and, despite being a small sample study, this alternative is promising, especially for cases where there is no possibility of face-to-face therapy. Further studies are needed to prove the effectiveness of this approach.

Associated disorders are very common in TS and in patients with chronic tics. These conditions were identified in 10 of the 13 RCTs evaluated in this review, it is noteworthy that the three studies did not include comorbidities in the data analysis.

Psychoeducational therapy showed no improvement when compared to pharmacological treatment and Behavioural therapy. The psychoeducational approach uses cognitive behavioural strategies to work on topics that interfere in the quality of life of these patients, such as the tics themselves and the TS, self-esteem, school, anger and anxiety. The objective is to reinforce coping strategies, reduce anxiety and emphasise the patient's strengths[43].

Thus, the approach chosen to treat tics depends on the degree and types of disability[4]. A commonly used approach is behavioural therapy, often HRT. With regard to pharmacological therapy, alpha-adrenergic agonists are indicated as the first line, these being clonidine and guanfacine. Other therapeutic options include risperidone, aripiprazole, tetrabenazine, pimozide, haloperidol and fluphenazine[3].

Some limitations must be considered, mainly the number of studies and the sample of some of these studies, and this diminishes the strength of the evidence and conclusions. In addition, many of the interventions were only studied on a short-lived RCT, with modest sample sizes. The number of studies and the size of the samples were reduced, so there is doubt about which treatments are the best and the magnitude of their effects. Many interventions had poor quality evidence. Most studies have compared the short-term post-treatment effects, and the long-term effectiveness of interventions is not well known.

Most studies did not report changes in comorbid conditions, focusing on changes in tics. Thus, it is not possible to conclude the effect of interventions on symptoms of comorbidity related to TS. Adverse effects were not considered in all studies evaluated, thus preventing a more detailed critical assessment of the studies. Finally, as long as there is evidence to support the effectiveness of various treatments, knowledge gaps remain and there is still a great need for controlled RCTs for tic interventions to assess long-term efficacy and safety.

CONCLUSION

Regarding pharmacological therapies, the present study identified benefits with the use of aripiprazole and ecopipam. Pergoline shows a slight improvement in tics compared to placebo. The results showed no benefit in the use of guanfacine, considered a first-line medication for the treatment of tics in children and young people, diverging

from other findings in the literature. Similarly, no reduction in tics was observed when evaluating the effectiveness of N-acetylcysteine. HRT has been shown to be slightly superior to educational therapy, being a good alternative due to the absence of adverse effects. It was also noted that behavioural and pharmacological therapy (risperidone and aripiprazole), when compared to psychoeducational intervention, rates expressive reductions in symptoms.

Given, as likely, some behavioural and pharmacological options, it seems reasonable to consider the patient's choice and financial possibilities when choosing therapy. Other treatments may become the option after the lack of response to the therapies mostly commonly used. A therapy considered an alternative, 5-LGr, obtained good results – similar to tiapride. Considering that young people and their parents can seek alternative treatments, it is important to emphasise that their use is not supported by strong evidence to date. We conclude that among the various forms of therapy, the most studies are indicated to identify the efficacy and the profile of adverse effects of these actions, in order to guide the best method for each patient and their comorbidities.

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Efeito da Pandemia por Covid-19 nos Cuidados de Indivíduos com Distrofia Muscular de Duchenne

Covid-19 Pandemic's Effect on the Care of Individuals with Duchenne Muscular Dystrophy

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ABSTRACT

Introduction: Since December 2019, the scientific community has been mobilized to contain the COVID-19 pandemic. Although individuals with Duchenne Muscular Dystrophy (DMD) have restrictive lung disease, risk of immunosuppression and associated cardiomyopathy, they are not considered to be a risk group for COVID-19. DMD is a neuromuscular, genetic and progressive disease, with early childhood development. In order to manage the disease, multidisciplinary follow-up is necessary to improve this patient's quality of life.
Objective: Identify the impact of the pandemic on the care of patients with DMD and its repercussions.
Method: This is a cross-sectional, quantitative and descriptive study. The sample consisted of patients diagnosed with DMD aged between 4 and 18 years, followed up at the neuropediatrics service. Data collection was carried out by an interview with those responsible for the patient and evaluation of the medical records, using a questionnaire. Statistical analysis was descriptive using central tendency and dispersion measures.
]**Results:** Among the 44 patients included, the median age was 12 years and the predominant type of gene mutation was deletion (56.8%). The median age of first symptoms was 4 years. Thirteen patients had contact with family members positive for COVID-19 and tested positive for the disease. Eleven received the vaccine against COVID-19. Medical follow-ups suffered a great reduction in the pandemic period, as well as respiratory and motor physiotherapy.
Conclusion: The pandemic interfered with multidisciplinary care for patients with DMD. As a chronic and degenerative disease, individuals with DMD require ongoing care, which was interrupted by the pandemic scenario.

Keywords: Duchenne muscular dystrophy, COVID-19, SARS-CoV-2.

RESUMO

Introdução: Desde dezembro de 2019, a comunidade científica está mobilizada para a contenção da pandemia pela COVID-19. Embora indivíduos portadores de Distrofia Muscular de Duchenne (DMD) apresentem doença pulmonar restritiva, risco de imunossupressão e cardiomiopatia associada, não são grupo de risco para a COVID-19. DMD é doença neuromuscular, genética e progressiva, de início na infância. Para manejo da doença, faz-se necessário acompanhamento multidisciplinar para melhora da qualidade de vida.
Objetivo: Identificar o impacto da pandemia nos cuidados aos pacientes com DMD e suas repercussões.
Métodos: Trata-se de um estudo transversal, quantitativo e descritivo. A amostra foi composta por pacientes com diagnóstico de DMD com idade entre 4 e 18 anos acompanhados no serviço de neuropediatria. A coleta de dados foi realizada por entrevista com responsáveis e avaliação do prontuário, a partir de um questionário. A análise estatística foi descritiva com uso de medida de tendência central e dispersão.
Resultados: Dentre os 44 pacientes incluídos, a mediana de idade foi de 12 anos e o tipo de mutação gênica predominante a deleção (56,8%). A mediana de idade dos primeiros sintomas foi de 4 anos. Treze pacientes tiveram contato com familiares positivos para COVID-19 e testaram positivo para a doença. Onze receberam a vacina contra COVID-19. Os acompanhamentos médicos sofreram grande redução no período pandêmico, bem como a fisioterapia respiratória e motora.
Conclusão: A pandemia interferiu nos atendimentos multidisciplinares aos pacientes com DMD. Como uma doença crônica e degenerativa, os indivíduos com DMD necessitam de cuidados contínuos, o que foi interrompido pelo cenário pandêmico.

Palavras-chave: Distrofia muscular de Duchenne, COVID-19, SARS-CoV-2.

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INTRODUÇÃO

Desde dezembro de 2019, após a emergente infecção viral causada pelo coronavírus surgir na China, a comunidade científica está mobilizada para a contenção da pandemia. No mundo, segundo o último relatório da Organização Mundial da Saúde (OMS) de fevereiro de 2022[1], há mais de trezentos e oitenta milhões de casos confirmados com mais de 5 milhões de mortes relacionadas à doença causada pelo coronavírus 19 (COVID-19). No Brasil, o Ministério da Saúde relata cerca de 26 milhões de casos confirmados e cerca de 628 mil mortes, tendo como foco pandêmico a região sudeste com mais de 10 milhões dos casos confirmados[2]. Com a crescente taxa de contaminação por coronavírus, a aplicação de medidas de restrição social, como o distanciamento físico, é proposta para permitir que os sistemas de saúde possam expandir e responder aos casos da doença, bem como reduzir a transmissão viral[3].

Em relação à apresentação clínica do COVID-19, pessoas acima de 60 anos e/ou com comorbidades associadas possuem maior predisposição para o desenvolvimento de formas graves da doença. Embora indivíduos portadores de Distrofia Muscular de Duchenne (DMD) apresentem doença pulmonar restritiva, risco de imunossupressão por uso prolongado de corticoesteroides e cardiomiopatia associada, não estão presentes no grupo de risco[4]. A DMD é a doença neuromuscular mais frequente em crianças, estima-se cerca de 1 para cada 5.000 recém-nascidos do sexo masculino[5]. É uma doença genética recessiva ligada ao cromossoma X de cunho progressivo, causada pela mutação no gene DMD, que codifica a distrofina, proteína responsável direta pela preservação da fibra muscular. Estas mutações levam à ausência ou diminuição de distrofina, o que acarreta perda da função muscular que evolui para uma limitação motora significativa, progredindo para a perda completa da função com consequente perda da marcha por volta dos 12 anos evoluindo para as complicações cardiorespiratórias que levam a morte antes dos 20 anos e requer cuidados contínuos[6].

Os indivíduos com DMD requerem cuidados globais que envolvem o acompanhamento ortopédico e da saúde óssea, respiratório, gastrointestinal, cardiológico, endócrino, neuromuscular e serviços de reabilitação com fonoaudiólogo, terapeuta ocupacional e fisioterapeuta, além de suporte psicossocial. O Consenso Brasileiro[7,8] indica a necessidade de acompanhamento multidisciplinar e aplicação de corticoides em uso prolongado como primeira linha de ação no tratamento com objetivo de desacelerar a perda na função muscular e obter maior qualidade de vida.

No cenário pandêmico, os indivíduos portadores de doenças raras são uma incógnita para a comunidade científica e pouco se discute sobre as implicações do coronavírus neste grupo. As medidas de proteção contra a infecção que foram adotadas pelas unidades de saúde e pelas famílias dos pacientes com DMD podem ter implicações nos cuidados e acompanhamento da doença. No presente trabalho, busca-se entender se a atual pandemia teve impacto nos cuidados multidisciplinares aos pacientes com DMD, bem como descrever as repercussões, se houver.

METODOLOGIA

Trata-se de um estudo transversal, quantitativo e descritivo. A amostra foi composta por pacientes com diagnóstico de DMD com idade entre 4 a 18 anos acompanhados no serviço de neuropediatria de uma unidade hospitalar universitária de referência para doenças neuromusculares em crianças e adolescentes. O projeto foi aprovado pelo CEP da Instituição pelo número 466.12621.7.0000.5264. Durante as consultas de rotina, os responsáveis e pacientes foram convidados a participar da pesquisa e assinaram o termo de consentimento livre e esclarecido e o termo de assentimento.

A coleta de dados foi realizada no período de Agosto/2021 a Novembro/2021, a partir da entrevista com responsáveis para obtenção de informações do acompanhamento da doença antes do início da pandemia (entre 2019 a Abril de 2020) até Novembro/2021. Para corroborar com as informações fornecidas pelos responsáveis e a fim de evitar informações incorretas, os dados coletados na entrevista foram confrontados com as registradas em prontuário pelos médicos ou através de exames anexados aos prontuários. A coleta foi guiada por um questionário elaborado pelos autores, dividido em informações de (a) caracterização do paciente como: idade atual, idade de diagnóstico, fase da doença, tipo de mutação gênica, idade dos primeiros sintomas e descrição dos primeiros sintomas observados; (b) informações sobre contexto familiar relacionados ao grau de instrução do cuidador, renda familiar, número de pessoas que coabitam a mesma residência perda ou não da renda durante pandemia, tipo de escola frequentada, uso de rede privada ou pública para atendimento médico; (c) informações sobre COVID-19 se houve contágio por COVID-19 pelo paciente ou residentes, tratamento realizado, se houve óbito ou necessidade de hospitalização; (d) informações sobre acompanhamento multidisciplinar (data de última consulta com especialistas e terapeutas, bem como alterações no acompanhamento, se houver); (e) informações sobre desempenho escolar (acompanhamento com pedagogo e impacto da pandemia na escola); (f) uso de medicação e vacinas.

A análise estatística foi descritiva, com uso de medida de tendência central e dispersão. A frequência em percentuais foi aplicada aos dados não numéricos.

Tabela 1. Características dos pacientes com DMD incluídos no estudo.

Variáveis	DMD (*N*= 44)
Idade (anos) mediana (variação)	12 (4 – 18)
Mutação genética	
Duplicação	7 (15,9%)
Deleção	25 (56,8%)
Mutação de ponto	10 (22,72%)
Outros	2 (4,54%)
Fase da DMD	
Fase 2	1 (2,27%)
Fase 3	8 (18,18%)
Fase 4	15 (34,0%)
Fase 5	20 (45,45%)
Uso de cadeira de rodas	
Sim	27 (61,36%)
Não	17 (38,64%)
Perda de deambulação na pandemia	
Sim	6 (22,22%)
Não	21 (77,78%)
Idade de perda da deambulação (anos) mediana (variação)	9 (8 – 12)
Prova de função respiratória	
Sim	25 (57%)
Não	19 (43%)
< 50%	3 (12%)
> 50% < 70%	8 (32%)
< 70%	14 (56%)
Ecocardiograma	
Sim	38 (87%)
Não	6 (13%)
FE < 60%	5 (13%)
Ecocardiograma (ano de realização)	
Anterior à 2019	5 (13,15%)
Jan/2019 à Dez/2019	14 (36,84%)
Jan/2020 à Dez/2020	8 (21,05%)
Jan/2021 à Nov/2021	11 (28,94%)
Uso de medicação	
Sim	31 (70%)
Não	13 (30%)
Tipo de medicação cardiológica	N= 31
iECA	16 (51,61%)
iECA associado a beta-bloqueador	3 (9,67%)
iECA associado a diurético	6 (19,35%)
iECA associado a beta-bloqueador e diurético	5 (16,12%)
iECA associado a antiarrítmico	1 (3,22%)
Informações sobre frequência escolar antes da Pandemia	
Escola Pública em 2019	30 (68,18%)
Escola Particular em 2019	7 (15,90%)
Não frequentavam escola em 2019	7 (15,90%)
Informações sobre frequência escolar depois da Pandemia	
Escola Pública em 2020	29 (65,90%)
Escola Particular em 2020	4 (9,09%)
Não frequentavam escola em 2020	11 (25%)

DMD, Distrofia muscular de Duchenne; iECA, inibidor da enzima conversora da angiotensina.
Fonte: Elaborada por autores.

RESULTADOS

Dentre os 44 pacientes incluídos, a mediana de idade dos pacientes foi de 12 anos (variação entre 4-18 anos), sendo o tipo de mutação gênica predominante a deleção (56,8%), seguido por mutação de ponto (22,7%) e duplicação do gene da distrofina (15,9%) (Tabela 1). A idade média dos primeiros sintomas reportados pelos responsáveis de 3 anos e 7 meses de idade (mediana: 4, desvio-padrão: 1,73). Dentre os primeiros sintomas, a maior queixa relatada foram as quedas frequentes com 22,73%, seguidos do não conseguir pular, correr e subir escadas. A marcha miopática e dificuldade para levantar do solo, bem características nos pacientes com DMD, foram relatadas mais notoriamente em pacientes que vieram a primeira consulta já com mais de 7 anos de idade.

A média na idade do diagnóstico foi de 6 anos e 6 meses (mediana: 7, desvio-padrão: 2,28) e nota-se que o diagnóstico foi mais comum na faixa entre os 5 a 7 anos de idade, o que evidencia o diagnóstico tardio. Este diagnóstico genético coincide com a idade com que estes pacientes buscam a primeira consulta com o especialista neuropediatra, passando dos 50% para essa faixa de idade (52,27%). Em sua maioria os pacientes encontravam-se nas fases 4 e 5 da doença (79%), portanto eram cadeirantes, mesmo se a informação do uso de cadeira de rodas (61%) não alcance o mesmo valor.

Aproximadamente 86,3% das famílias recrutadas recebem até três salários mínimos, tendo uma média de três pessoas coabitando na mesma residência, outro grupo (13,63%) apresenta renda superior a 4 salários mínimos e cerca de 3,3 pessoas na mesma situação de coabitação. Cerca de 56,81 % dos pacientes não possui plano de saúde, necessitando do atendimento público para a realização de consultas e exames. Quanto ao uso de corticóide, 95,46 % dos pacientes estão em uso desta medicação, apenas dois pacientes não fazem uso de corticóide por decisão familiar. Destes 42 pacientes, seis em uso de Atalureno, sendo quatro através de ensaios clínicos em andamento e dois pacientes via judicialização, o corticóide vem sendo usado paralelamente. Dentre os pacientes passíveis de fazer uso de Eteplirsen, dois não fazem uso do fármaco. Já para o Atalureno, dois pacientes não fazem uso.

Apesar do avanço da COVID-19, dentre os pacientes entrevistados, 13 pacientes relataram ter tido contato com familiar que contraiu a infecção e tiveram diagnóstico de COVID-19 através da realização de PCR (oito pacientes) ou teste rápido (cinco pacientes). Nenhum paciente necessitou de internação ou evoluiu a óbito, porém em dois casos de familiares houve necessidade de internação e um óbito de familiar registrado. Como a vacinação para COVID-19 ainda não se encontrava aprovada para todas as faixas etárias, até o momento, dentre os 19 pacientes passíveis de serem vacinados, 11 receberam o imunizante.

Durante o período da pandemia, seis pacientes iniciaram o uso de cadeira de rodas, estes com idades entre 8 e 12 anos. Mais da metade dos pacientes (n= 23; 52,27%) não apresentaram em prontuário informações claras sobre consultas ortopédicas, exames relacionados, indicação e uso de órteses. Apenas 8 (38,09%) pacientes reportam o uso regular da órtese conforme orientação médica. Dos 15 pacientes que não fazem uso regular de órtese, 60% relatam que a criança não quer usar pelo desconforto que sentem, mesmo quando indicadas para uso noturno, 40% informam que a órtese não está mais adequada e que com a pandemia não conseguiram realizar a confecção de uma nova. O acompanhamento neurológico destes pacientes também sofreu impacto. Entre 2019 a Março/2020, 38 pacientes realizaram ao menos uma consulta com a Neurologia, enquanto no período da pandemia, entre Abril/2020 a 2021, somente 16 foram consultados (Gráfico 1).

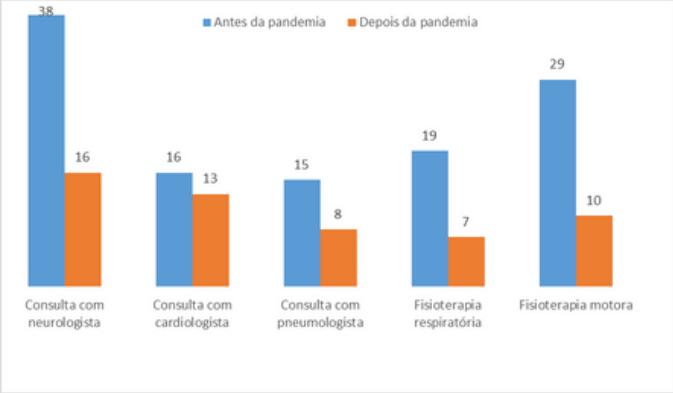

Gráfico 1. Impacto da pandemia nas consultas médicas e acompanhamento com fisioterapia (Fonte: Elaboração própria).

Os registros de acompanhamento da cardiologia mostram que dos 38 pacientes que possuem algum registro sobre consultas e ou exame de ecocardiograma realizado, cinco (13,15%) destes são anteriores ao ano de 2019. Aproximadamente 37% dos exames foram realizados entre Janeiro de 2019 à Dezembro de 2019, 21% realizados no decorrer de 2020 e aproximadamente 29% de Janeiro à novembro de 2021. Antes da pandemia, 16 pacientes realizaram consultas e exames com o cardiologista, enquanto no período pandêmico, 13 realizaram consultas, mas somente três conseguiram realizar os exames complementares. Como resultado dos ecocardiogramas, cinco pacientes da amostra apresentam fração de ejeção abaixo de 60% . Quanto as medicações cardiológicas prescritas, cerca de 31% dos pacientes entrevistados estão em uso de medicação inibidora da enzima conversora de angiotensina associada ou não beta-bloqueadores, diuréticos ou antiarritmicos.

Em 2019, cerca de 15 (34%) pacientes haviam realizados a consulta com o médico pneumologista, 12 (80%) destes, realizaram a prova de função respiratória (PFR). Já em 2020, devido a pandemia apenas oito pacientes compareceram as consultas agendadas e três (18%) conseguiram realizar a PFR. Até o momento apenas cinco pacientes haviam conseguido realizar os exames em 2021. Os pacientes com resultados de PFR anteriores à 2019 somam cinco pacientes. Dentro deste período de 2019 à Novembro de 2021, cerca de 12% dos indivíduos apresentavam como resultado da capacidade pulmonar valores inferiores a 50% , 32% com resultado de PFR entre 50 e 70% da capacidade vital funcional e 56% com valores dentro dos limites considerados normais. Em relação a atendimento com pneumologista, em 2019, 14 pacientes realizaram consultas e 11 tiveram acesso a exames complementares – enquanto no período de pandemia entre 2020 e 2021, o número de pacientes consultados diminuiu para nove consultas e quatro com exames realizados.

Dentre as outras recomendações de cuidados com pacientes portadores de DMD, as terapias desempenham fundamental ação no intuito de miniminar e retardar a evolução da doença do estudo. A ausência de fisioterapia respiratório por parte dos pacientes em 2019 era de 25% dos pacientes entrevistados, já em 2020 este número aumentou para 45,4%. Antes da pandemia, 22 pacientes realizavam periodicamente a fisioterapia respiratória, sendo: 19 com terapia semanal e três com terapia duas vezes na semana. Com a pandemia, o número reduziu para sete, sendo: cinco com terapia semanal e dois com terapia duas vezes na semana. Na fisioterapia motora, observou-se que em 2019, tinhamos 29 (65,9%) pacientes em terapia motora uma ou duas vezes na semana. Já em 2020, este número caiu para dez (22,7%) pacientes. Houve uma redução de 43,2% no número de pacientes que realizaram as sessões de fisioterapia motora em casa e quatro realizaram a fisioterapia via homecare. Destes dez pacientes que seguiram de alguma forma com a atividade motora pelo menos uma vez por semana, seis tiveram os exercícios realizados pelos pais sob orientação do fisioterapeuta, dois continuaram com atendimentos domiciliares pelo profissional de homecare, e dois informaram que não houve interrupção completa nos atendimentos, apenas a redução no número de sessões semanais. Os demais relatam que ou não foram orientados a realizar os exercícios ou sentem receio de machucar o paciente durante a atividade.

Apesar de necessário para alguns pacientes com DMD devido ao seu déficit intelectual, a grande maioria não dispõe deste auxílio nas escolas, principalmente nas escolas públicas. Dos quatro pacientes que vinham em acompanhamento pedagógico nas escolas públicas, apenas um conseguiu receber auxílio no decorrer do ano letivo de 2020.

DISCUSSÃO

As medidas restritivas impostas para controle da pandemia levaram a repercussões na perda de acompanhamento multidisciplinar de pacientes com DMD. A fim de reduzir o impacto da transmissão viral em larga escala, a comunidade científica identificou a necessidade de aplicação de medidas de restrição social, como distanciamento físico para população geral, isolamento social aos infectados e, de forma mais radical, o lockdown de cidades e estados. Ao diminuir a curva exponencial dos casos confirmados, o sistema de saúde é capaz de se expandir, receber insumos necessários (ventiladores mecânicos, equipamentos de proteção individual, importação de kits, por exemplo) para o combate a pandemia[3]. No Brasil, estas medidas foram regulamentadas a partir da Lei n. 13.979, de 6 de Fevereiro de 2020, "Lei da Quarentena", que discorre sobre as medidas de saúde pública relacionadas ao coronavírus e a possibilidade de restrição de direitos fundamentais, como o de ir e vir [9,10] . Com estas medidas para contenção do avanço da pandemia, o acompanhamento periódico de pacientes crônicos foi comprometido.

As orientações de cuidados preconizados para pacientes com DMD incluem o acompanhamento médico e terapias com fisioterapia, fonoaudiólogos, terapeutas ocupacionais e acompanhamento psicológico periodicamente de acordo com o quadro clínico do paciente. A fisioterapia é essencial para retardar a progressão, garantir maior qualidade de vida e prover funcionalidade para as atividades diárias do paciente[11]. No cenário pandêmico, a fisioterapia sofreu impacto importante, visto que a terapia respiratória sofreu redução de 45,4% enquanto a fisioterapia motora, 43,2%. Ainda que parte dos pais tivessem acesso as atividades fisioterapeuticas que poderiam desenvolver junto aos seus filhos em casa, a falta de segurança para realizá-las foi fator determinante para esta redução. O incentivo a prática da fisioterapia por pais e responsáveis deve ser realizada desde o começo do acompanhamento, a fim de garantir mais autonomia dos pais no manejo da criança e também maior frequência de realização dos estímulos motores e cardiorrespiratórios.

Igualmente, os acompanhamentos médicos, em especial com o cardiologista, neurologista e pneumologista também foram duramente atingidos. A importância do acompanhamento cardiorrespiratório destes pacientes está relacionada a morbimortalidade pelas causas cardíacas e respiratórias, em especial em fases mais avançadas da doença, como da presente amostra. A perda de seguimento dos pacientes nos serviços de pneumologia e cardiologia pode ser um fator de risco importante para o desfecho de mortalidade, bem como de complicações da doença.

Dentre os 44 pacientes da amostra, somente 13 apresentaram diagnóstico para COVID-19 com manifestação leve da doença. Embora os pacientes com DMD apresentem risco de imunossupressão por uso prolongado de corticoides, diminuição da capacidade funcional e cardiopatias associadas, a faixa etária assume papel protetor e sobrepõe o risco de complicações da COVID-19[12]. Indica-se que pacientes com DMD devem manter o tratamento com corticoides ou terapias modificadoras específicas, de acordo com o quadro clínico, bem como inibidores da ECA ou bloqueadores do receptor de angiotensina para cardiopatia[13]. Ainda, recomenda-se que os cuidados sejam ofertados de maneira ininterrupta, de foma a garantir o acompanhamento e impedir progressão precoce da doença[13]. Os cuidadores responsáveis pelos pacientes com DMD também devem ser orientados quanto aos cuidados contínuos, uma vez que, com as restrições pela pandemia, há maior dependência dos pacientes com seus cuidadores tanto para cuidados de saúde quanto para o acompanhamento e auxílio nas atividades escolares[14]. Da mesma forma, os profissionais de saúde também podem se adaptar, utilizando recursos como telemedicina e telereabilitação para auxiliar os cuidadores e garantir o acompanhamento dos pacientes[15].

A amostra deste estudo foi composta por pacientes com DMD em fases mais avançadas da doença e, com isso, maior comprometimento sistêmico e com maiores demandas de equipe multiprofissional. Embora grande parte da amostra tenha deleção como mutação genética, o tipo de mutação por si só não prediz diferenças na progressão da doença[16]. A fase avançada da doença deve estar relacionada com a idade da amostra em torno de 12 anos, tendo em vista que as crianças com DMD perdem a capacidade de deambulação e ficam confinados a cadeira de rodas em torno desta idade[17]. Embora a doença tenha início antes dos 3 anos da idade, usualmente o diagnóstico é realizado após 5 anos de idade[18,20]. O diagnóstico tardio também é uma realidade desta amostra, o que também contribui para a pior prognóstico da doença.

O tratamento padrão para DMD é o uso de corticoides e grande parte da amostra faz uso da medicação para retardar a progressão da doença e melhora do desfecho, principalmente relativo a deambulação[21]. Medicamentos voltados para a restauração da produção da distrofina são emergentes para o tratamento da DMD, com o objetivo de preservação da massa muscular e mitigação dos sintomas[22]. Entretanto, os medicamentos são mutação-dependentes, o que interfere na quantidade de indivíduos elegíveis para seu uso, sendo evidenciado no estudo pelo baixo número de pacientes em uso de Eteplirsen (registro na ANVISA não aprovado) e Atalureno (registro aprovado na ANVISA em 2019, http://antigo.anvisa.gov.br/novos-medicamentos-e-dicacoes). Como centro de referência, a maior parte da amostra em uso destas medicações de ponta consegue acesso a partir da participação do ensaio clínico.

O comprometimento cardiorrespiratório também foi majoritariamente presente na amostra, o que condiz com o estadiamento da doença e confere a amostra maior fator de risco presumidos para complicações da COVID-19. O uso de medicamentos cardioprotetores, como beta-bloqueadores e inibidores de ECA, em pacientes assintomáticos amplia em 5 a 7 anos a curva de sobrevivência[23], o que justifica o número elevado de pacientes em uso de medicações para intervenção cardiológica. Cabe ressaltar que 13% da amostra não realizou ecocardiograma, o que dificulta a avaliação cardiológica do ponto de vista funcional e morfológico.

CONCLUSÃO

Como uma doença crônica e degenerativa, os indivíduos com DMD necessitam de cuidados contínuos e acompanhamento multidisciplinar constante, o que foi interrompido pelo cenário pandêmico. No presente estudo foi possível evidenciar que a pandemia teve impacto não somente nos cuidados de saúde, mas também no desenvolvimento escolar. Uma epidemia, assim como uma intercorrência externa não infecciosa a pacientes com doenças crônicas progressivas, que requerem cuidados contínuos, impacta em seus cuidados multidisciplinares e potencialmente acelera a progressão de sua história natural.

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Dream-Reality confusion: differential psychiatric diagnosis in narcoleptic subjects

Confusão sonho-realidade: diagnóstico psiquiátrico diferencial em narcolépticos

Helio Rocha Neto[1,3] , Antonio E. Nardi[1], Marleide da Mota Gomes[2]

ABSTRACT

Dream-reality confusion (DRC) is the consequence of hypnagogic content confusion with real events and memories. Narcoleptic subjects eventually have DRC and can be misdiagnosed as schizophrenic or with another disorder with delusional or hallucinatory symptoms. Although dream-related experiences and hallucinatory perception share neurophysiological pathways, they are phenomenologically distinct. The lack of phenomenological intentionality in Dream-related perceptions, the different cognitive pathways for delusion generation, and other differences between mental disorders psychopathology, and DRC-related phenomena are here discussed. The lived world and awake experience interpretation, and dream neurobiology in narcoleptic subjects related to DRC, might indicate some hints for the mind-brain gap issue that still exists in neurology and psychiatry.

Keywords: Dreams, Parasomnias, Delusion, Sleep, Narcolepsy

RESUMO

A confusão entre realidade e sonho(CRS) é a consequência da confusão do conteúdo hipnagógico com eventos e memórias reais. Sujeitos narcolépticos eventualmente têm CRS e podem ser diagnosticados erroneamente como esquizofrênicos ou com outro transtorno com sintomas delirantes ou alucinatórios. Embora as experiências relacionadas ao sonho e à percepção alucinatória compartilhem vias neurofisiológicas, elas são fenomenologicamente distintas. A falta de intencionalidade fenomenológica nas percepções relacionadas ao sonho, as diferentes vias cognitivas para a geração do delírio e outras diferenças entre a psicopatologia dos transtornos mentais e os fenômenos relacionados à CRS são discutidos aqui. A interpretação do mundo vivido e da experiência de vigília, e a neurobiologia dos sonhos em sujeitos narcolépticos relacionados à CRS, podem indicar algumas dicas para a questão do gap mente-cérebro que ainda existe na neurologia e na psiquiatria.

Palavras-chave: Sonhos, Parassonia, Delusões, Sono, Narcolepsia

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INTRODUCTION

Psychiatry and neurology diseases are operationally defined. Psychiatry follows DSM/ICD descriptive operational systems, with "criteria" composed of psychopathological signs. A diagnosis is set when a specific quantity is met (e.g. 2 of 4 major criteria and 2 of 8 minor is necessary for depression). Neurology follows the anatomopathological system used in general medicine: a disease is defined by a syndrome (signal plus symptoms) with an organic lesion and a "natural history".[1] Operational systems increase reliability but, as signs and symptoms are not exclusive for a single disease, misdiagnosis happens eventually. Hallucinatory and delusional phenomena related to abnormal dream physiology are examples of this confusion.

Modern dream research focuses on the manifest content abnormalities of dreams. The Dream-Reality Confusion (DRC) is an event or an experience that is difficult to separate from the conscious or dream period. These experiences are confounded with psychopathological signs, like hallucinations and delusions, resulting in misdiagnosis.

Some mental disorders are more related to DRC, like Post-traumatic Stress Disorder nightmares,[2] and dream-related self-disorder in schizophrenia.[3] However, narcoleptic patients also present these experiences and suffer from DRC.[4]

The boundaries of wakefulness, sleep, and dreams are loose in psychiatric disorders and narcolepsy, but other neurological conditions present the same problem. Consequently, it affects how reality is experienced by the subject, raising questions about its influence on creativity or the presence of psychopathology.

Reality experience is related to neurologic hybridity. In the case of creativity, the remote associations between memories and reality experience depend upon neural activation and dissemination.[5] Those connections variations might also relate to altered subjective experiences and evolutionary benefits to high creativity and "out of the box" thinking, as seen in schizotypy and autistic savant phenomena.[6]

We will here discuss hypnagogia, a hallucinatory state caused by prolonged sleep deprivation, sensory isolation, and drug use.[7] The fundamentals of this subject are presented through the definition of perceptions and dreams, neuroanatomy, and dreams physiology, besides DRC that occurs in narcoleptic patients.

DREAM FUNDAMENTALS

Dream recall and constitution according to sleep stages

Dreaming is possible in all stages of sleep, while principally associated with rapid eye movement sleep (REM). REM is consistently associated with higher dream recall than non-REM, but dream study methodology variations, sleep stage duration, and night period influence the content or increase the frequency of dream recall from non-REM. In general, the quality of non-REM and REM dream reports differs consistently. Non-REM dreams are typically shorter, more fragmented, and thought-like.[8] In contrast, REM dreams are longer, more emotional, and bizarre. Dreams length, bizarreness, and perceptual vividness for non-REM and REM reports increase across the night[8]. However, REM dreams continue to be more emotionally and perceptually vivid than non-REM dreams.

Narcolepsy

Narcolepsy is classified as type I or II according to the International Classification of Sleep Disorders 3rd edition. The presence or absence of cataleptic attacks, different degrees of somnolence, and sleeping crisis are the main differences. Both types might present many parasomnias, altering dream subjective experience (Figure 1).

Narcolepsy impairs the general behavior and functioning of the patient. Some of its symptoms, like cataplectic attacks, are triggered by emotions, such as joy or anger, limiting daily activities and social interaction. Cataplexy neuropathophysiology and neurochemical findings suggest the involvement of emotional brain circuitry.[9] Impaired emotion processing in narcolepsy-cataplexy, can be a coping strategy behavior to prevent or reduce the frequency of cataplexy attacks.[9]

Patients with Type 1 narcolepsy have frequent rapid transitions to REM. Successful dream recall is associated with increased EEG desynchronization in REM and non-REM corresponding areas.[4] Narcoleptic patients have frequently associated sleep-wake symptoms such as sleep paralysis, hallucinations (visual, auditory, and tactile), increased frequency of dreams, nightmares, lucid dreams, and enacted dreams.[10]

Some patients confuse the memory of a dream with real experience and form sustained delusions about significant events, a phenomenon called "dream delusions''.[11] These are false memories induced by a vivid dream leading to false beliefs and could persist for days or weeks. These memories are pervasive and severe in patients with narcolepsy. Still, "dream delusions" are semiologically distinct from hypnagogic and hypnopompic hallucinations. Dream delusion is an altered content idea, while hypnagogic and hypnopompic hallucinations are perceptual disturbances occurring in sleep/wake transition.

Perceptions, hypnagogia, and dreams

Perception is the process of regulating and subjectively understanding sensory input. Explaining subjective experiences in terms of brain processes is a major issue in consciousness science. It is unknown if the neural basis of perceptual consciousness and the neural basis of cognitive mechanisms of conscious experiences are independent. Particularly, DRC of dreamed events and real experiences, suggests the occurrence of attribution errors between these systems.

Illusory and hallucinatory phenomena may either be or not be related to diseases. However, hallucinations have real perception qualities, indicating a common neurological pathway between perception input and this psychopathological event.[7] The DRC results from these shared neuroanatomical and neurochemical bases.[11]

However, dream sensory perceptions and hallucinations are distinctly experienced, even if sharing an anatomical basis. Dreams sensory events are immersive and primarily detached from reality, while hallucinations are discrete and overlap with real perceptions.

Dreams and hallucinatory activity are also related to different consciousness states.[7] Sleep is a physiological state of reduced consciousness, which decreases the ability to integrate perceptions. So, sleep sensations are possibly the consequence of a perceptual engram, where the physically stored memory of a previously perceived object becomes represented as a perceptual experience.

Non-physiologic reduced consciousness states such as sleep deprivation, sensory isolation, and sub-hallucinatory doses of LSD or mescaline are also associated with hallucinations. Some organic stressful situations, like toxemia, stress, exhaustion, and dehydration are also related to hallucinations, despite awake consciousness activity.

Hallucinations are not uncommon in healthy individuals. It can be experienced in awake states as an isolated feature without pathological meaning.[12] However, it is also a symptom of psychosis.

Clinically significant hallucinations can manifest as a consequence of combined factors. Hereditary and cultural predispositions, excessive excitement in anxiety, panic, and dissociative mechanisms are some examples. Those factors harm or distort perceptions as a frightening or threatening social environment.[2]

Despite dreams and hallucinations similarities, they are fundamentally different, subjective and phenomenologically. Wake experiences are apprehended through the lenses of intentionality, and qualitatively different from the altered sensorium phenomena in dreams. Such qualitative difference is the reason for thought processes in the hypnagogic state, to be radically different from ordinary wake thought. Many artists, writers, scientists, and inventors attributed their creativity to hypnagogia-related states, as a consequence of the altered perceptive states lived during the wake-sleep transition.[6]

From a biologically oriented approach, waking and dreaming experiences share brain activity similarities. The differences are observed in neuroimaging and EEG studies, comparing wake brain activity with REM sleep. In this state, subjects are most likely to report dreams with perceptive content, while some areas are active, and others inactive.[13]

Particularities about the reality monitoring processes also contribute to dream/reality sensory discrimination. In particular, the medial prefrontal cortex is an important region for reality monitoring and is activated during the retrieval of self-generated information. Such cerebral regions may be responsible for discriminating information generated internally from externally.

Many people with narcolepsy have hypnagogic/hypnopompic hallucinations. Those hallucinations might be similar to those of the REM dream perceptions but occur when someone is only half awake. Likewise, many people with narcolepsy have very vivid and intense dreams and nightmares while sleeping and, for young children with narcolepsy, it is difficult to differentiate vivid dreams from reality.[11]

Like sense-perceptive phenomena and hallucinations in dreams, dream delusions are not the same experience as true delusions. Dream delusions originate from vivid dream experiences confounded with memories. True delusions may arise from a delirious interpretation, as observed in memory disturbances related to self-disorders. However, that is not the usual pathway for delusion formation.[14]

True delusions seem to be the final consequence of many logical processes trying to explain self-disorders and other common-sense disturbances.[14,15] Consequently, true delusions are usually permanent in schizophrenia spectrum disorders and oscillate with the treatment in mood disorders. Dream delusions are solved once their oniric origins are perceived by patients or by social calling to a shared reality, being ontologically diverse from true delusion. The organic pathway for both disturbances must be elucidated to clarify this mind-brain gap issue.

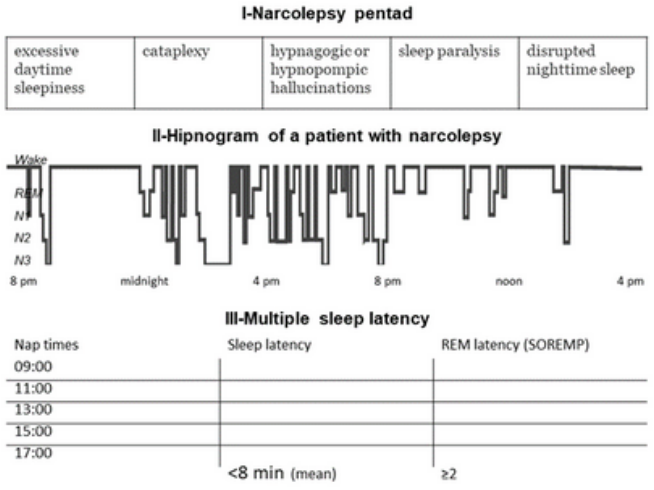

Figure 1. Narcolepsy-cataplexy, clinical and polysomnographic aspects (Narcolepsy type 1). I-Clinical symptomatology; II-Hipnogram shows fragmented sleep, rapid entry into Sleep-Onset REM Period (SOREMP), and numerous naps during the day that include REM sleep. III-Multiple sleep latency test results in patients with narcolepsy, in which patients are asked to take five short naps separated by 2 hours over a day. Narcolepsy type 2 is a diagnosis of exclusion requiring ancillary tests ruling out other causes of excessive daytime sleepiness.

CONCLUSIONS

The hypnagogia can be confused with a realistic perception, or a misunderstanding of dreams and memories confounded with real experiences. Hypnagogia is a common occurrence in patients with narcolepsy due to frequent episodes of SOREMP. These patients´ perception experiences contribute to a better understanding of the mechanisms of the levels of consciousness and their different perceptions, including hallucinatory ones, from the simplest to the most complex.

Authors Contributions: Helio Rocha Neto did the search, selection and review of papers about phenomenology and semiology, and took equally part writing the final manuscript. Marleide da Mota Gomes did the research, selection and review of papers about neurobiology of sleep, narcolepsy and dream reality confusion, being also the designer of presented figures and one of the proponents of the draft. Antonio E Nardi reviewed the selected papers, reviewed and proposed arguments in discussion section, and equally written the approved final draft.

Data Availability Statement: All data generated or analyzed during this study are included in this article [and/or] its supplementary material files. Further enquiries can be directed to the corresponding author

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The carotid and vertebral arteries discovery – initial findings

A descoberta das artérias carótidas e vertebrais – achados iniciais

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ABSTRACT

The studies on the vascular system, including the cervicocephalic arteries (carotid and vertebral arteries), present a long trajectory, having their deep roots in the far past, considering the Western authors, having as representatives the Greek sages Alcmaeon, Diogenes, Hippocrates, Aristoteles, Rufus, and Galenus. They produced pivotal knowledge dissecting mainly cadavers of animals, and established solid bases for the later generations of scholars. The information assembled from these six authors makes it possible to build a quite clear picture of the vascular system, here specifically focused on the cervicocephalic arteries, and mainly of the extracranial segments. Thus, the carotid system became fairly well identified, origin, course, and name, as well as the origin of the still unnamed arteries running through the orifices of the transversal processes of the cervical vertebrae, and entering into the cranium. Almost all that was then known about human anatomy, since this period, and then throughout the Middle Ages, was extrapolated from animal dissections. This state of affairs was maintained until the 14th century, when human corpses dissections were again allowed.

Keywords: arteries, cervicocephalic, carotid, vertebral, discovery

RESUMO

Os estudos do sistema vascular, incluindo as artérias cervicocefálicas (artérias carótidas e vertebrais), apresentam um longo percurso, tendo suas raízes profundas no passado distante, considerando os autores ocidentais, tendo como representantes os doutos gregos Alcméon, Diógenes, Hipócrates, Aristóteles, Rufus e Galenus. Eles produziram conhecimento pivotal, dissecando principalmente cadáveres de animais e estabelecendo bases sólidas para as gerações futuras de estudiosos.

A informação reunida desses seis autores permite construir um quadro bastante claro do sistema vascular, aqui focado especificamente nas artérias cervicocefálicas e principalmente nos seus segmentos extracranianos. Assim, o sistema carotídeo ficou bastante bem identificado, origem, trajeto e nome, assim como a origem das ainda não nomeadas artérias que percorrem os orifícios dos processos transversos das vértebras cervicais e entrando no crânio.

Quase tudo que era conhecido sobre anatomia humana, desde esse período, e depois ao longo da Idade Média, foi extrapolado a partir de dissecções de animais. Esse estado de coisas foi mantido até o século 14, quando a dissecção de cadáveres humanos foi novamente permitida.

Palavras-chave: artérias, cervicocephalicas, carótidas, vertebrais, descoberta

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INTRODUCTION

The encephalic blood supply is delivered by the cervicocephalic arteries that comprise four vessels, two internal carotid and two vertebral arteries, which course in the neck and then ingress into the cranial cavity, where they ramify.[1] (Figure 1) (Box)

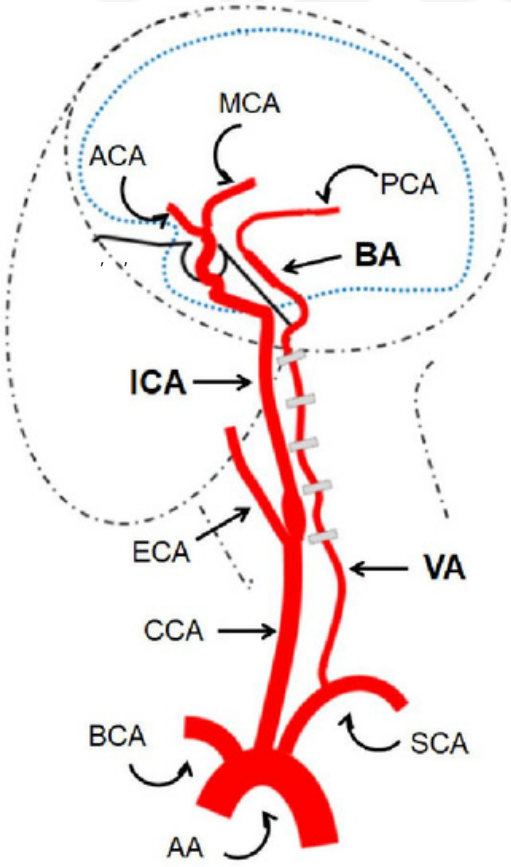

Figure 1. Simplified schema of the head and neck with projection of the cervicocephalic arteries [left side vew].

AA=aortic arch, BCA=brachiocephalic artery, SCA=subclavian artery, CCA=common carotid artery, ICA=internal carotid artery, ACA=anterior cerebral artery, MCA=middle cerebral artery, VA=vertebral artery, BA=basilar artery, PCA=posterior cerebral artery

Box. Anatomic characteristics of the cervicocephalic arterial system (carotid and vertebrobasilar arteries).

The encephalic structures are supplied by the cervicocephalic arterial system (carotid and vertebrobasilar arteries), which arises directly or indirectly from the aortic arch.[1]
The carotid system is formed by the internal carotid arteries and their branches.
The **internal carotid arteries** [ICA] arise in the neck, resultant from the bifurcation of the 'common carotid arteries' [CCA] (about the level of C4). The latter have different origin on each side – on the right, it stems from the brachiocephalic artery [BCA] (or innominate artery), ramification of the aortic arch [AA], while on the left, it arises directly from the aortic arch. At the origin, the internal carotid arteries are somewhat dilated – segment known as the 'carotid bulb' or 'carotid sinus'. Both arteries, from their origin, progress to the base of the skull [cervical segment], enter through the ostium that leads to the 'carotid canal', a passage localized inside the petrous part of the temporal bone [petrous segment], entering into the cranial cavity through the 'foramen lacerum', pierce the dura mater, and pass into the 'cavernous sinus' [cavernous segment], lateral to the sella turcica. Inside the cavernous sinus they present a sinuous route, leave the sinus perforating the dura-mater [cerebral segment]. There, after the ophthalmic artery is released, emerge in the suprachiasmatic cistern, emit the 'posterior communicating artery' [PCoA], and finally their two terminal branches, the 'anterior cerebral artery' [ACA] and the 'middle cerebral artery' [MCA].[1,33]
The vertebrobasilar system is established by the vertebral and basilar arteries, and their branches.
The **vertebral arteries** [VA] have a similar origin on both sides – the subclavian arteries [SCA]. After a short course, they pass through orifices of the transversal processes from C6 (or C5) to C3 cervical vertebrae, then forming a loop, enter through the transverse foramen of C2 (axis), continue through the transverse foramen of C1 (atlas) [cervical segment], pierce the dura mater, and finally ingress into the cranial cavity through the occipital aperture (foramen magnum) [intracranial segment]. There, they progress anterolaterally to the medulla oblongata, and at the lower border of the pons merge to form the **basilar artery** [BA], which runs in the central groove of the pons, and behind the dorsum of the sella, bifurcates to form its two terminal branches, the 'posterior cerebral arteries' [PCA].[1,34]
Such is the usual pattern, existing also a number of variations of this configuration.[32,33]
Once at the base of the brain, the ramifications of the carotid and the vertebral-basilar systems anastomose, forming an arterial circle – the 'circle of Willis'.[31,35]

These vascular systems have been studied since ancient times. Initially, such studies were performed mainly by animal dissections, and should be regarded as pivotal, as they laid the bases of this knowledge.

The present paper intends to review the discovery of the cervicocephalic arteries, from their origin, throughout the course in the neck, until the entrance into the skull, and finally their terminal intracranial branching, as seen by the early Western authors. The representative authors, for the present purpose, stem from the ancient Greek civilization, from the Archaic to the Roman period of its history.[2]

The late Archaic or pre-Classical period (ca 600-500 BCE) is best represented by the pre-Hippocratic scholars, Alcmaeon and Diogenes, who opened the paths of such studies.[2,3]

Alcmaeon of Croton (born ca 540-510 [fl ca 490-450 BCE]), was a Greek physician whose apparently important anatomic production, including 'On Nature' (De Natura) (written between 500 and 450 BCE), was mostly lost. However, scanty extant fragments may be found in writings of later authors. There, it can be learned that he performed dissections, probably of animals only, and he is seen by some as the first one to perform such activity. Further, it is argued by some that in the course of dissections, he observed that in the dead animal certain vessels were bloodless, or contained very little blood, concluding that it was also so in the living animal. Thus, it was maintained that he drew a distinction between 'veins' ('blood-flowing vessels') and 'bloodless vessels' ['arteries']. Alternatively, others consider that he simply distinguished between larger and deeper blood vessels as opposed to smaller ones close to the surface, based on the differential blood flow in his theory of sleep.[3,4,5,6,7]

Alcmaeon is credited by some for distinguishing between two kinds of vessels - 'veins' ('blood-flowing vessels') and 'bloodless vessels' ['arteries'].

Diogenes of Apollonia (5th century BCE [fl ca 440]), was a Greek natural philosopher, whose works, most of them, were also lost. But, in his extant fragments of 'On Nature' there is a description of the distribution of the blood vessels in the human body, later quoted by Aristoteles in the 'History of Animals' (On Veins). He did not distinguish between arteries and veins, both being called 'veins' (or 'vessels') (*phlebes* - *φλέβες*). He begins: "...the body contains two large veins [vessels] that stretch through the abdomen along the vertebral column, on the right ['cava'?] and on the left ['aorta'?], extending to the corresponding leg and reaching to the head". Then: "The blood-vessels that run to the head along the throat can be seen as large ones in the neck ['internal jugular'?]; and from each of the two, at the point where it terminates, a number of blood-vessels branch off to the head...and each set finishes up beside the ear ['external jugular'?]. There is another blood vessel in the neck running nearby the large one, on either

side of the neck, but it is a little smaller [CCA?], and the majority of vessels coming from the head converge on it, and these [two vessels] extend inward through the throat and from each of them vessels branch off, passing underneath the shoulder blade [SCA?] in the direction of the hands…".[3,8,9,10]

Diogenes identified two main vessels coursing along the body, one at the right side ('cava') and another at the left ('aorta'), and vessels which they gave origin, some to the head (jugular? and carotid?), and others to the arms (subclavian). Apparently, he was the first to make the initial description of the vascular system.

The above authors were followed by Hippocrates, and Aristoteles, of the Classical period, and then by Rufus and Galenus, of the early Roman period, obligatory names to be cited as fundamental of this period of achievements.

Hippocrates of Kos (ca 460-370 BCE), Greek physician (and Corpus Hippocraticus), described aspects of the blood circulation in his numerous writings, as the 'Epidemics II and V', 'Nature of Man', 'On Anatomy', and others. His Epidemics II (section IV - chapter 'On Veins' [*Περι φλεβων*]) mentions that the 'hepatic' [vein] (*ipatites*) (*ήπατϊτις*) ('cava vein', according to Galenus' interpretation) ascends [descends?] until the heart, and from there some [branches] go to the neck ['jugulars'?], while others go to the shoulder blade ['subclavians'?].[11,12,13] The 'Nature of Man' (chapter XI) deals with veins [and/or arteries], as follows: "The large veins [comprise]… There are four pairs in the body. One pair extends from behind the head through the neck, and on either side of the spine externally reaches to the loins and legs, and then stretches through the shanks to the outside of the ankles and to the feet ['cava vein' and 'aorta']…The other pair of veins extend from the head by the ears through the neck, and are called jugular (throat, neck) veins ['jugular veins'? 'carotid arteries'?]. They stretch right and left by the side of the spine [vertebral column] internally ['cava' and 'aorta'] along the loins…The third pair of veins passes from the temples through the neck under the shoulder-blades, then they meet in the lungs and reach, the one on the right the left side, and the one on the left the right. The right one reaches from the lungs under the breast both to the spleen and to the kidneys [branches of the cava'?], and the left one [branches of the aorta'] to the right from the lungs under the breast both to the liver and to the kidneys…The fourth pair begin at the front of the head and eyes [external 'jugular' or 'carotid'], under the neck and collarbones ['brachiocephalic' and 'subclavian'], passing on the upper part of the arms to the elbows, then through the forearms to the wrists and fingers…".[14,15]

The description is complex, and far from unambiguous, revealing a mix-up of arterial and venous vessels, as he did not (clearly) distinguish between them. The large vessels have an upper segment (superior cava, and ascending and arch of the aorta), and a lower one (inferior cava, and descending aorta), the first related to the head, neck, and upper limbs, the second to the rest of the body. Thus, it is possible to infer that these vessels (veins and arteries), passing along the neck to supply the head, could be understood as the 'jugular veins' (external and internal) and 'carotid arteries' (common, external, and internal). The vessels passing throughout the neck under the collarbones could represent the 'brachiocephalic'/'subclavian' veins/arteries.[15] Additionally, the short treatise 'On Anatomy' also contains information about the vascular system. There, he describes the heart, and a vein that rises from its base, which trembles loudly [pulsation?], and courses to the liver, named the 'large vein' ['aorta artery'?], which nourishes the entire body, descending further to the kidneys, ureters, and bladder. Next, in "On the Heart", he mentions that from this organ arise two veins ('cava vein' and the 'large artery' ['aorta']). Further, in 'On Veins', he describes that the 'aorta' artery leaves the heart, and divides into an ascending and a descending segment.[15]

It should be considered that Hippocrates knowledge on anatomy was probably based on observation on animals [kind not specified], possibly corroborated by some human dissection, perhaps aborted foetus, or exposed infants, in conjunction with opportunistic observation of war wounded and accident victims.[16] There is a great difficulty in understanding Hippocrates' description of the vascular system, as he did not distinguish (clearly) between 'arteries' and 'veins', using the same term frequently for both. It should be highlighted that the term 'artery' (*άρτηριη*) is used more often, in his writings, for the 'rough artery' (*τραχεϊα άρτηρία*) ('tracheia-arteria') [trachea] and 'bronchi' [Note 1]. The term 'vessels' (*aggeia [αγγεία]*) was usually preferred, as they carry blood, air, and possibly other fluids. Finally, the starting point and direction of these vessels (e.g., 'come from the heart" and "come from the head") is varied, derived only by a simple observation, sometimes seen as originating from the heart, other times, from the head, liver, and/or spleen.[11,16,17]

Aristoteles of Stagira (384-322 BCE), Greek philosopher and biologist, obtained his anatomical knowledge dissecting animals. In his 'The History of Animals' (*Historia Animalium*) and 'The Parts of Animals' (*De Partibus Animalium*), he considers aspects of the circulatory system. In the *Historia* he writes: "There are two blood-vessels in the thorax by the backbone [vertebral column], and lying to its inner side, and of these two the larger one is situated to the front, and the lesser one is to the rear of it, and the larger is situated rather to the right-hand side of the body ['cava vein'], and the lesser one to the left, and by some this 'vein' ['artery'] is termed the 'aorta' [*άορτή*]…". Further: "These blood-vessels have their origins in the heart, for they traverse the other viscera, in whatever direction they happen to run, without in any way losing their distinctive characteristic as blood-vessels…owing to the fact that these two veins are above and below ['cava' and 'aorta'], with the heart lying midway". Proceeding:

"...the parts of the lesser vein, named the 'aorta', branch off, accompanying the branches from the large vein ['cava'] And: "...the vein that emerges from the heart ['superior cava'] branches off in two directions ['brachiocephalic veins']...extend to the sides and to the collarbones ['subclavian veins']...The 'jugular veins' ...run alongside the trachea-arteria... they branch off into four veins...each branch of the other pair ['internal jugular'] stretches from the region of the ear to the brain ... the remaining veins that branch off from the last-mentioned vein, some encircle the head ['superficial temporal vessels'], others ['maxillary vessels'] end their courses...at the teeth... ['external jugular veins' and 'external carotid']".[18,19,20] In *Partibus* (II and III), there are additional information: "... however, that it [the brain] may not itself be absolutely without heat, but may have a moderate amount, branches run from both blood-vessels, that is to say from the 'large vessel' ['cava'] and from what is called the 'aorta', and end in the membrane [meninges] which surrounds the brain... [internal 'jugular veins' and 'carotid arteries']...".[20,21]

Aristoteles did not discriminate (clearly) between veins and arteries, both being called veins (*phlebes*), but recognized the different natures of the vessels, those being larger and membranous and those narrower and sturdy, and also those that contained or not blood. He acknowledged two main blood vessels - the 'large vein', corresponding to the 'cava', and the lesser veins, or 'aorta'. However, he did not distinguish between their functions, holding that both alike nourish the body by carrying the blood to all parts of it. Branches from the 'large vein' and 'aorta' accompany each other throughout the entire body, emitting twigs to the head ('jugulars' and 'carotids'), supplying the external structures ['external jugular' and 'external carotid'] and the brain ['internal jugular' and 'internal carotid], and both providing branches to the upper limbs ('brachiocephalic veins' and 'subclavian artery']).[20,21]

Aristoteles writings are somewhat clearer, in comparison to those of Hippocrates. He introduced the term 'aorta' to designate the 'lesser vein' [Note 2]. The excerpts above permit to suspect that Aristoteles meant, arising from the 'aorta', and ascending in the direction of the head, the existence of cervicocephalic arteries (carotid and vertebral arteries), and also those directed to the upper limbs (subclavian arteries).

[Note 1: arteria= from Greek *arteria* ('windpipe')] (https://www.etymonline.com/word/artery) [28-04-2022]
[Note 2: aorta=from Greek *aorte* 'a strap to hang (something by)', a word applied by Aristoteles to the large artery of the heart, literally 'what is hung up', probably from *aeirein* 'to lift, heave, raise'. Used earlier by Hippocrates to designate the bronchial tubes] (https://www.etymonline.com/word/aorta) [28-04-2022]

Rufus of Ephesus (fl late 1st and early 2nd centuries CE), Greek physician, acquired most of his knowledge on anatomy by dissecting varied animals (mainly monkey cadavers). He wrote numerous books, but most of his works were lost. However, preserved writings and fragments were rescued and published, including his principal work on anatomy, 'On Names of the Parts of the Human Body', where information about the state of pre-Galenic anatomy may be found. He distinguished veins from arteries, arguing that veins are vessels that contain blood, while arteries contain a certain amount of blood and a larger amount of 'spirit' (*pneuma*). He mentions that Aristoteles named the large artery which runs down the spine as 'aorta'. Regarding the origin of the term 'carotid' he affirms: "In the past, the name 'somniferous' (*carotides*) (*καροτίδες*) was applied to the vessels which ascend through the neck, because by compressing them, drowsiness [stupor] (*karódeis*) (*καρώδεις*) (derived from the Greek word *karos* [*κάρος*], meaning 'to stun, stupefy, or fall into deep sleep') is produced. ..." ['carotid artery' (common? internal?)]. And added: "The carotid [artery] (*καρωτίδας*) provides blood to the brain, and interruption to its flow results in loss of consciousness (*καρώδεις*)".[19,22,23]

Rufus' contribution is important, as he reminds the origin of the term 'carotid', and clarifies that the term was in use for a relatively long time. However, it was not possible, until now, to trace the ancient origin of this term.

Claudius Galenus of Pergamon (ca 130-ca 210 CE), Greek physician and philosopher, explained in his varied books aspects of the circulatory system. He recognized the differences between arteries and veins, and argued that not only the veins but also the arteries contain blood. He described the arterial system [mostly in monkeys, preferentially the tailless Barbary ape (*Macaca inuus*)], beginning with the 'large artery' or 'aorta' (according to Aristoteles), which rises from the left ventricle of the heart and soon forms the arch and the descending segment. From the arch emerge two unequal branches. One, which ascends to the sternum [right side] where it splits into two unequal divisions, a lesser at the left side, form the left [common] 'carotid artery' [left CCA], and the other sturdier, at the right side [BCA], ascends obliquely, and form the right [common] 'carotid artery' [right CCA] (*carotides* – "term according to the old times", as he affirmed), and the remaining part runs to the right shoulder and upper limb [right SCA]. Another, slimmer branch arising from the arch, at the left side, goes to the shoulder and upper limb [left SCA].[19,24,25,26] Each [common] 'carotid artery', in the neck, divides into two branches - one posterior, and one anterior. Each 'posterior branch' divides to supply external parts of the head [ECA]. The internal branch [ICA] runs through a 'channel' [carotid canal] in the 'petrous bone' [part of the temporal bone], where it makes a bend like a 'spun', and ramifies into minute twigs to form the 'retiform plexus' (*rete mirabile*). Further, an artery runs to the brain, providing the 'choroid plexus', another to the

ocular orbit ['ophthalmic artery'], and the extremities of the posterior ramifications [PCoA?] join with those [branches] that came from the orifices of the cervical vertebrae [VA] (see below). From there, he explained, that out of the 'retiform plexus', the small ramifications, are again reunited, and constitute 'two larger arteries' that ascend and encircle the brain together with the delicate meninx [pia-mater], "in the fashion of a girdle" [ACA? and MCA?].[24,25,26,27,28] He also detailed the origin and course of other deep seated arteries, describing that the branches destined to the upper limb [SCA] emit rami that run to the vertebral column, and route through the lateral vertebral [transvers processes] orifices of the lower six cervical vertebrae [VA], ascending in the direction of the cranium. There, after crossing over the 1st vertebra, each divide into two branches, one of them enters the cranium [intracranial VA], and course in the direction of the posterior encephalon.[24,25,26,29]

Galenus studies were performed mainly by dissecting and vivisecting varied kinds of animals (monkeys, oxen, pigs, sheep, dogs). He also obtained information from injured gladiators, as he acted as physician to this class of wrestlers.[20,25,26,29]

Galenus provided the first detailed description of the cervicocephalic arteries, including the extra- and intracranial segments of the carotid and vertebral arteries, from their origin in the cervicothoracic region, their course in the neck, and their arrival and branching in the intracranial cavity (Figure 2). Despite some inaccuracies derived from the fact that his studies were performed mostly in animals [monkeys, oxen, etc.), and that he attributed to one animal the structures found in another, and extrapolated his findings to the human body, as he claimed that there were no marked differences between them, his findings were influential for more than one and a half millennium, even when, in the 14th century, human corpses dissection was reinstituted.[30]

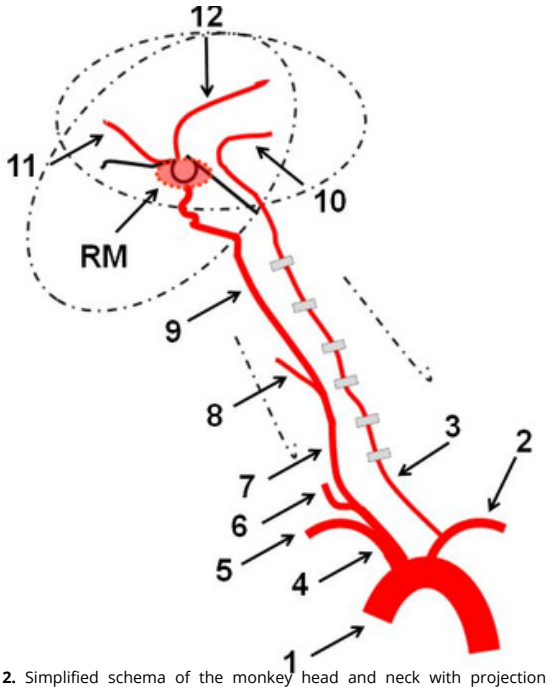

Figure 2. Simplified schema of the monkey head and neck with projection of the cervicocephalic arteries [left side view], drawn according to Galenus description[24,27,29]. Obsevation. The carotid RM is inexistent in the monkey.

1=aorta, 2=small branch to the left upper limb [left SCA], 3=branch that ascends to the head through the transversal process orifices of the lower six cervical vertebrae [VA], 4=large common trunk that ramifies into 5=branch to the right upper limb [right SCA], and a trunk that bifurcates to form the 6=right [common] carotid artery [right CCA] (cut), and 7= left [common] carotid artery [left CCA], which divide to form 8=a posterior branch [ECA], 9=an anterior branch [left ICA], 10=branch to the posterior encephalon of the [intracranial VA], RM=plexiform net (*rete mirabile*), 11=[anterior] branch resulting from the reunion of the small vessels of the RM [ACA?], 12=[posterior] branch resulting from the reunion of the small vessels of the RM [MCA?]

COMMENTS

The studies on the vascular system, including the cervicocephalic (carotid and vertebral arteries), have a long trajectory, having their deep roots in the far past, considering the Western civilization. Thus, it can be stated, without perpetrating a mistake, that initially Alcmaeon and Diogenes, then Hippocrates and Aristoteles performing their studies many centuries later, still BCE, and later Rufus and Galenus, flourishing in the first centuries of the CE, are obligatory names to be cited. They produced pivotal knowledge on this (and other subjects), dissecting mainly cadavers of animals, and laid solid bases for the next generations of scholars. It should be stressed, that the above-mentioned pioneers, mainly Galenus, continued to be cited, and their teachings continued to be followed during the Middle Ages, and at the Renaissance, and further, even with the reinstitution of human corpses dissection, by the pre-Vesalian anatomists, and by Vesalius proper, who relied on or criticized Galenus, as well as by anatomists that appeared later.[3,9,31]

Almost all that was then known about human anatomy, since Alcmaeon until Galenus, and then throughout the Middle Ages, with exception of the recovered information of the Alexandrian anatomists, was extrapolated from animal dissection and vivisection - the distinction between non-human animal and human anatomy was probably not regarded as significant. This state of affairs was maintained until the 14th century, when human corpses dissections were again allowed.[26,32]

The writings on the vascular anatomy of pre-Classic and Classic authors are not clear, as they did not distinguish clearly between veins and arteries. Thus, some descriptions are confusing, and it is necessary to 'decode' what they meant. The few extant writings of Rufus, and the many books of Galenus, which appeared centuries later, show a clearer description, and nomenclature.

Summing-up the information gathered from these six authors, native of varied regions of an extended Greece (Figure 3), makes it possible to build a quite clear picture of the vascular system, here specifically focused on the cervicocephalic arteries, and mainly of the extracranial

segments. Thus, the carotid system became fairly well identified, with its components (common, external, internal), origin, course, and name, as well as the origin of the still unnamed arteries that run through the transversal processes of the cervical vertebrae [VA], and enter into the cranium.

These studies lasted more than a half millennium, from Alcmaeon to Galenus, and laid solid bases for the forthcoming authors, one and a half millennium later, to begin the final steps for the obtention of the present-day knowledge on the subject.

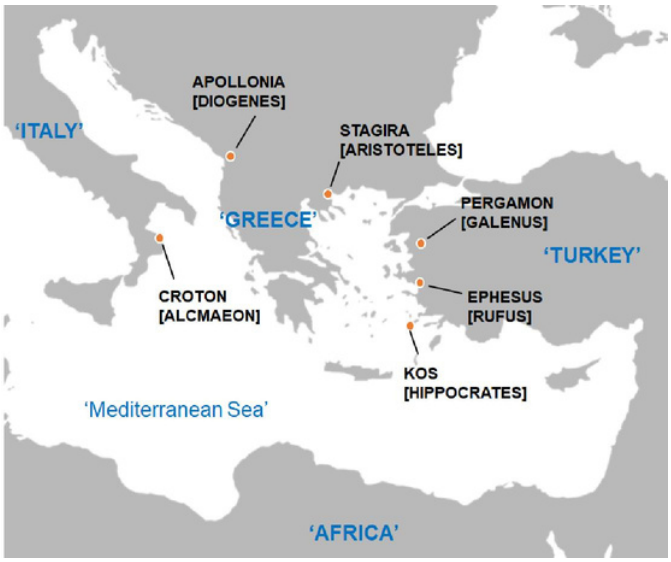

Figure 3. Map of the Mediterranean Sea region, where the cities [red circles] of the six authors [between square brackets] are localized in an extended Greece. Present day names of the countries and the sea written in blue colour, and in simple quotation marks.

Blank map (part):
https://commons.wikimedia.org/wiki/File:Blank_Map_of_Mediterranean_Sea_region.svg
Localization of the cities: varied sources

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Imagens em NEUROLOGIA

Membrana aracnoide espinhal – Diagnóstico pela ressonância magnética

Spinal arachnoid web – Magnetic resonance Diagnosis

Mayara Oliveira Da Silva[1],Marcio Luís Duarte[2], Leonardo Furtado Freitas[3]

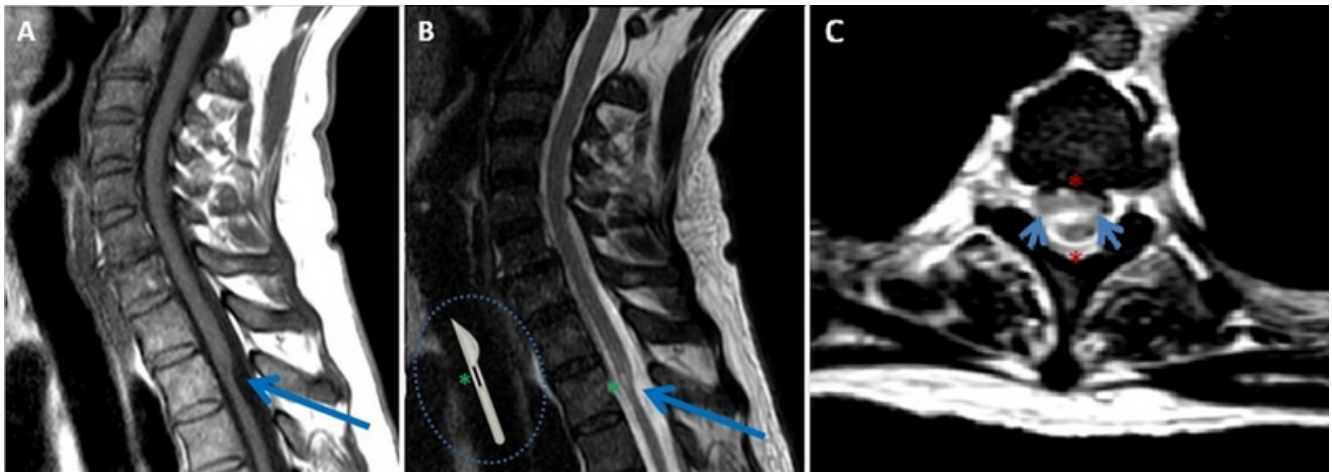

Figura. Imagens de RM da coluna cérvico-torácica em sagital T1 (A), sagital T2 em alta resolução (B) e axial T2 em alta resolução (C) demonstrando deformidade na superfície medular posterior (seta azul) no nível T2-T3 com aspecto em "bisturi" (vide representação em B) compatível com web (membrana) aracnoide, com destaque para a pequena cavidade hidrossiringomiélica (asterisco em verde) local. No plano axial (C), também podemos observar essa deformidade (setas azuis) e presença de coluna liquórica promovendo artefatos de fluxo (asteriscos vermelhos) posterior e anteriormente, afastando o diagnóstico diferencial de herniação transdural anterior da medula.

A membrana aracnoide espinhal é uma malformação idiopática de uma membrana no espaço subaracnoide.[1,2] Os pacientes apresentam dor nas costas de caráter neuropático, características mielopáticas compressivas e radiculopatia incluindo fraqueza episódica da extremidade inferior e sintomas de incontinências intestinal e vesical.[1,2] Um total de 43 casos foram documentados, sendo sua maioria na região torácica.[3]

Os achados são sutis, porém, quando não tratada, esta lesão pode causar efeitos devastadores na função neurológica do paciente.[1,2] Estudos referem lesões traumáticas e cirurgias de coluna como possíveis fatores para o seu desenvolvimento.[1,2] O tratamento mais utilizado atualmente é a técnica cirúrgica a qual, deve ser individualizada levando em consideração a gravidade dos sintomas e os achados clínico-radiológicos.[1,2]

Este caso demonstra um homem de 73 anos em tratamento de adenocarcinoma de próstata com dorsalgia subaguda refratária à analgesia, sem histórico de radio ou quimioterapia. Ao realizar a ressonância magnética (RM) da coluna cérvico-torácica, foi visualizada uma deformidade na superfície posterior na medula espinhal – sinal do "bisturi" – no nível T2 e com alteração de sinal medular, sem realce pelo contraste, compatível com membrana aracnóide e pequena cavidade hidrossiringomiélica. A RM é o exame padrão-ouro, mas tem uma baixa sensibilidade devido ao tamanho relativamente fino das membranas comparado ao tecido adjacente, requerendo, portanto, muita atenção dos radiologistas e protocolo otimizado do exame, incluindo sequências de alta resolução (3D-CISS).

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