REVISTA BRASILEIRA DE

NEUROLOGIA

Órgão Oficial do Instituto de Neurologia Deolindo Couto

JUL/AGO/SET - 2021

Vol. 57 N°3

INSTITUTO DE NEUROLOGIA DEOLINDO COUTO • UFRJ • 75 ANOS •

ABN-RJ
ANERJ
ACADEMIA BRASILEIRA DE NEUROLOGIA
REGIONAL RIO DE JANEIRO

UFRJ
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DO RIO DE JANEIRO

ISSN 0101-8469 CODEN RBNEES ISSN eletrônico: 2447-2573 Acesso pelo LILACS-Express

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NEUROLOGIA
Órgão Oficial do Instituto de Neurologia Deolindo Couto

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CIP-Brasil - Catalogação na Fonte
Sindicato Nacional dos Editores de Livro - RJ

R349 Revista Brasileira de Neurologia/Instituto de Neurologia Deolindo Couto, Universidade Federal do Rio de Janeiro
[vol 1 - nº 1 (1949)]

Continuação do:
Jornal Brasileiro de Neurologia [vol 19 - nº 6 (1983)] Trimestral a partir do vol 37 - nº 1 (2001) [descrição
baseada no vol 34 - nº 6 (1998)]

1. Neurologia - Periódicos brasileiros.
I. Universidade Federal do Rio de Janeiro. Instituto de Neurologia Deolindo Couto. II. Título: Jornal Brasileiro de Neurologia.

98-1980 CDD 616.8 CDU 616.8

ISSN 0101-8469
CODEN RBNEE

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RBN: http://revistas.ufrj.br/index.php/rbn

Editorial

Esta edição da Revista Brasileira de Neurologia, e as próximas quatro, serão especiais, com capa comemorativa em homenagem aos 75 anos da criação do Instituto de Neurologia Deolindo Couto (INDC) da Universidade Federal do Rio de Janeiro (UFRJ).

A galeria de Diretores do INDC se inicia com o próprio Prof. Deolindo Couto, seguido por Bernardo Couto (seu irmão), Clóvis de Oliveira, Helcio Alvarenga, Gianni Temponi, José Luiz Cavalcanti e Leôncio Feitosa. Todos nobres professores e médicos, que se dedicaram à instituição e à Revista Brasileira de Neurologia.

O INDC, vinculado ao Centro de Ciências da Saúde da UFRJ, e com nobre localização no campus da Praia Vermelha, desempenha funções de ensino, assistência e pesquisa na áreas de Neurologia, Neurocirurgia, Fisioterapia, Fonoaudiologia, Neuropsicologia e Enfermagem.

O INDC foi criado em 1946, pelo empenho pessoal do Prof. Deolindo Couto, que convenceu a Cátedra de Clínica Médica da Faculdade de Medicina da UFRJ a respeito da necessidade de expansão das atividades neurológicas com a criação de um instituto próprio. O INDC foi então criado em 16 de dezembro de 1946, por ato do Conselho Universitário, que reconheceu a necessidade de ampliar as dependências da Cátedra de Clínica Neurológica da Faculdade de Medicina.

Os Profs. Deolindo Couto e José Ribe Portugal, patronos da Neurologia e Neurocirurgia brasileiras, respectivamente, constituíram os pilares fundamentais na formação de centenas de profissionais e professores espalhados pelo país e exterior, que continuaram e replicaram o legado do conhecimento neurológico. Ao longo de sua existência, nesses 75 anos, o INDC permaneceu como um importante centro de difusão do conhecimento neurológico, tendo sido enriquecido, mais recentemente, com outras áreas do conhecimento, quando passou a agregar as Faculdades de Fisioterapia e Fonoaudiologia.

Não podemos deixar de citar a COVID-19, que se tornou pandemia e, no Brasil, em 03 de fevereiro de 2020, foi declarada, por meio de Portaria n° 188 do Ministério da Saúde, “Emergência em Saúde Pública de Importância Nacional”, com mais de 232 milhões de casos no mundo, sendo mais de 21 milhões no Brasil, com a triste marca de 600 mil óbitos até o momento no país. A pandemia escancarou a necessidade de hospitais e instituições de saúde bem montados, aparelhados e com recursos humanos adequados e do Sistema Único de Saúde em pleno funcionamento.

Cesar Fantezia Andraus, Diretor geral do INDC

Avaliação da influência dos marcadores inflamatórios na mortalidade de pacientes com AVC isquêmico

Evaluation of the influence of inflammatory markers on the mortality of patients with ischemic stroke

Gabriela Gobo Nogueira[1], Mariana Gobo Nogueira[1], Talita Egevardt De Castro[2], Ana Claudia Paiva Alegre-Maller[1]
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ABSTRACT

Introduction: As the population ages and life expectancy increases, the global incidence and prevalence of ischemic stroke tends to rise significantly. In this context, the need arises to evaluate new predictive markers of mortality, such as absolute monocyte count, lymphocyte-to-monocyte ratio, neutrophil-to-lymphocyte ratio and C-reactive protein (CRP) levels which, besides being easily accessible and affordable, manage to predict the outcome in patients with acute stroke.
Objectives: the aim of this study was to evaluate the association between inflammatory markers and the mortality in ischemic stroke patients.
Methods: this is a retrospective observational study based on the analysis of electronic medical records and laboratory tests of in-patients who suffered an ischemic stroke in Cascavel/PR. A descriptive statistical analysis was conducted to determine patients´ profile according to the outcome and a logistic regression model was applied in order to verify the variables associated with mortality. Only data with a p-value <0,05 was considered.
Results: Out of the 65 patients who suffered an ischemic stroke included in the study, 50 were discharged and 15 died in hospital. Among the inflammatory markers, the neutrophil-to-lymphocyte ratio (OR 1.55; p-value <0,01) was associated with a greater chance of death. Patients who died presented with higher levels of ultra-sensitive CRP, higher absolute monocyte count, lower lymphocyte-to-monocyte ratio and higher neutrophil-to- lymphocyte ratio.
Conclusion: the elevated neutrophil-to-lymphocyte ratio may be significantly associated with negative outcomes following an ischemic stroke.

Keywords: Ischemic stroke, inflammatory markers, neutrophils, monocytes, lymphocytes, CRP

RESUMO

Introdução: À medida que a população envelhece e a expectativa de vida aumenta, a incidência global e a prevalência de AVC isquêmico tendem a aumentar significativamente. Nesse contexto, surge a necessidade de avaliar novos marcadores preditores de mortalidade, como a contagem absoluta de monócitos, relação linfócitos sobre monócitos, relação neutrófilos sobre linfócitos e níveis de proteína C reativa ultrassensível, que além de serem de fácil acesso e baixo custo, sugerem indicar desfecho no paciente com AVC agudo.
Objetivos: o objetivo deste estudo foi avaliar a associação dos marcadores inflamatórios com a mortalidade de pacientes com AVC isquêmico.
Métodos: trata-se de um estudo retrospectivo observacional a partir de prontuários eletrônicos e exames laboratoriais de pacientes com AVC isquêmico em uma unidade hospitalar de Cascavel/PR. Uma análise estatística descritiva foi conduzida para determinar o perfil dos pacientes segundo o desfecho e aplicado um modelo de regressão logística para verificar as variáveis associadas a mortalidade. Foram considerados significativos apenas os dados com p-valor <0,05.
Resultados: Dos 65 pacientes que foram admitidos no estudo, 50 receberam alta hospitalar e 15 foram a óbito no hospital. Entre os marcadores inflamatórios, a relação de neutrófilos sobre linfócitos (OR 1,55; p-valor <0,01) mostrou-se significativamente associada a maior chance de óbito. Os pacientes que faleceram apresentaram níveis superiores de PCR ultrassensível, maior contagem absoluta de monócitos, relação linfócitos sobre monócitos diminuída, e relação neutrófilos sobre linfócitos elevada.
Conclusão: a relação de neutrófilos sobre linfócitos elevada pode estar significativamente associada ao desfecho desfavorável após um AVC isquêmico.

Palavras-chave: AVC isquêmico, marcadores inflamatórios, neutrófilos, monócitos, linfócitos, PCR.

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Declaração conflito de interesses: não há conflito de interesse.
Declaração de financiamento: não há fonte de financiamento.

INTRODUÇÃO E OBJETIVO

Segundo a American Stroke Association, o acidente vascular cerebral (AVC) é caracterizado por um déficit neurológico súbito, decorrente de uma lesão focal aguda de origem vascular, no sistema nervoso central[1] . O AVC pode ser classificado em dois grandes grupos: isquêmico – causado por trombose, embolia ou hipoperfusão sistêmica – ou hemorrágico, como consequência de hemorragia intracerebral (HIC) ou hemorragia subaracnóidea (HAS)[2] . Na população caucasiana, aproximadamente 80% dos AVCs são isquêmicos e 20% são hemorrágicos, sendo de 10 a 15% por hemorragia intracerebral e 5% por hemorragia subaracnóidea[3] .

Mundialmente, os acidentes cerebrovasculares são a segunda maior causa de morte e a terceira maior causa de incapacidade[4] e, em algumas regiões do Brasil, ainda figuram como a principal causa de morte[5] . À medida que nossa população envelhece e a expectativa de vida aumenta, a incidência global e a prevalência de AVC isquêmico tendem a aumentar significativamente[6]. Nas últimas quatro décadas, a incidência de AVC em países de baixa e média renda dobrou[4] .

Alguns marcadores, como a homocisteína, ácido úrico, micro RNAs e adipocinas ajudam a prever o desfecho de pacientes com AVC isquêmico, entretanto, devido a incerteza no mecanismo ou ao alto custo dos exames, apresentam aplicação restrita[7] . Nesse contexto, surge a necessidade de avaliar novos marcadores precoces preditores de prognóstico e mortalidade, como a contagem absoluta de monócitos, relação linfócitos sobre monócitos, relação neutrófilos sobre linfócitos e níveis de PCR ultrassensível, que além de serem de fácil acesso e baixo custo, sugerem indicar desfecho no paciente com AVC agudo[8, 9].

Estudos prévios mostraram que inúmeros fatores inflamatórios podem afetar significativamente no desfecho hospitalar de um AVC, devido ao fato de causarem não apenas inflamação local nas áreas isquêmicas, mas também ativarem a resposta imune periférica, que por si só pode influenciar na progressão da doença[7] .

Esse estudo corresponde a primeira pesquisa brasileira com o objetivo de avaliar a influência dos marcadores inflamatórios como preditores de mortalidade nos pacientes com AVC isquêmico.

METODOLOGIA

Desenho do estudo

Foi realizado um estudo retrospectivo a partir da análise de prontuários eletrônicos e exames laboratoriais de pacientes com AVC isquêmico em uma unidade hospitalar de ensino. Os casos de AVC foram identificados no banco de dados do sistema de registro eletrônico do hospital a partir do Código internacional de doenças (CID-10). O estudo foi aprovado pelo comitê de ética local (4.353.927) e cumpriu todas as normas éticas aplicáveis.

População do estudo

Inicialmente, foram identificados um total de 194 pacientes com AVC isquêmico constatado através de exame de imagem (tomografia computadorizada ou ressonância magnética de crânio), maiores de 18 anos, que foram admitidos nas dependências do Hospital São Lucas, em Cascavel (PR), entre os anos de 2014 e 2020. Esses pacientes foram submetidos aos seguintes critérios de exclusão:
(1) Internação no hospital 24 horas após o AVC; (2) Histórico de infecção até 2 semanas antes do AVC; (3) Histórico de doenças autoimunes, inflamatórias, hematológicas ou câncer; (4) Uso de drogas imunossupressoras; (5) AVC prévio dentro de 3 meses; (6) Síndrome coronariana aguda dentro de 3 meses; (7) Registros médicos incompletos. Portanto, dos 194 pacientes iniciais, apenas 65 foram inclusos no estudo.

Os pacientes inclusos foram, então, divididos em 2 grupos de acordo com o seu desfecho hospitalar: grupo de pacientes com desfecho favorável e que receberam alta hospitalar (50 pacientes) e grupo de pacientes com desfecho desfavorável que foram a óbito em ambiente hospitalar após o evento isquêmico agudo (15 pacientes).

Variáveis do estudo

Foram recolhidos os seguintes dados dos prontuários dos pacientes: idade, sexo, comorbidades prévias, glicemia da admissão, pressão arterial sistólica da admissão, Glasgow da admissão e tempo de internação. Em seguida, foram obtidos dados a partir de amostras sanguíneas dos pacientes, coletadas dentro de 24 horas da admissão, contendo: PCR ultrassensível e hemograma completo (visando analisar contagem absoluta de monócitos, relação linfócitos/monócitos e relação neutrófilos/linfócitos).

Análise estatística

Os dados foram tabulados no pacote office por meio do software Excel. Foi realizada uma análise estatística descritiva para determinar o perfil dos pacientes segundo o desfecho favorável ou desfavorável, isto é, entre pacientes que vieram a óbito e aqueles que sobreviveram. Realizou-se o teste de Mann-Whitney para testar que duas amostras independentes são de populações com a mesma distribuição. Além disso, foram realizados[9] modelos de regressão logística com diferentes especificações para verificar as variáveis determinantes de mortalidade em pacientes com AVC isquêmico. O modelo que apresentou o melhor ajuste segundo o critério de informação de Akaike (Akaike Information Criterion – AIC) foi o modelo 6. Foram considerados significantes apenas os coeficientes com p-valor <0,05. A análise estatística foi realizada com o programa Stata.[14]

RESULTADOS

Dos 65 pacientes admitidos no estudo, 50 receberam alta hospitalar (grupo 1) e 15 foram a óbito em ambiente hospitalar (grupo 2), configurando uma taxa de mortalidade de 23,07%. Do total de inclusos, 38 eram homens (58,46%) e 27 eram mulheres (41,53%). As principais comorbidades associadas foram hipertensão (78,46%), diabetes (32,3%), fibrilação atrial (18,46%) e dislipidemia (16,92%).

Em comparação com o grupo de pacientes que receberam alta, os pacientes que foram a óbito apresentaram, segundo suas respectivas medianas [intervalo interquartil]: glicemia admissional maior (159 mg/dL [117 –200] vs. 125 mg/dL [114 – 156]), escala de coma de Glasgow admissional menor (10 pontos [3 –12] vs. 15 pontos [12–15]), níveis maiores de PCR ultrassensível (1,26 mg/dL [0,6 – 4,62] vs. 0,57 mg/dL [0,22 – 1,65]), maior mediana da contagem absoluta de monócitos (315 células/mm 3 [150 – 705] vs. 242,5 células/mm 3 [154 – 464]), menor mediana da relação linfócitos/monócitos (5,8 [3 – 9] vs. 6,41 [4,33 – 8,5]), maior mediana da relação neutrófilos/linfócitos (6,16 [3,85 – 11,25] vs. 3,19 [2,42 – 5,6]) e mediana do tempo de internação maior (9 dias [8 – 14] vs. 4 dias [2 – 12]), como mostra a Tabela 1**.** As variáveis com nível de significância no teste Mann-Whitney foram: escala de coma de Glasgow admissional (p-valor <0,01) e relação neutrófilos/linfócitos (p-valor <0,05).

Tabela 1. Perfil dos pacientes segundo o desfecho favorável ou desfavorável

Variável	Óbito	Observações	Média	Mediana	Q1	Q3	Iqr	Desvio padrão	Mínimo	Máximo
Idade (anos)	Sim	15	75	72	64	88	24	11,21	57	89
	Não	50	73,18	75	64	82	18	13,99	35	95
		P_valor = 0,8151								
Glicemia Admissional (mg/dL)	Sim	15	171,6	159	117	200	83	78,38	83	406
	Não	43	140,82	125	114	156	42	50,02	76,5	280
		P_valor = 0,0968								
PAS Admissional (mmHg)	Sim	15	149,26	140	120	170	50	39,60	80	226
	Não	50	151,74	144,5	132	169	37	31,13	90	240
		P_valor = 0,6844								
ECG Admissional	Sim	15	8,6	10	3	12	9	4,51	3	15
	Não	48	13,25	15	12	15	3	2,93	3	15
		P_valor = 0,0001								
PCR ultrassensível (mg/dL)	Sim	15	4,11	1,26	0,60	4,62	4,02	6,85	0,07	22,16
	Não	43	1,34	0,57	0,22	1,65	1,43	1,98	0,085	11,23
		P_valor = 0,0647								
Monócitos (células/mm3)	Sim	15	428,2	315	150	705	555	401,21	47	1398
	Não	50	323,98	242,5	154	464	310	215,5	73	888
		P_valor = 0,7202								
Linfócitos/ Monócitos	Sim	15	6,49	5,8	3	9	6	5,20	0,8	20
	Não	50	8,36	6,41	4,33	8,50	4,16	6,77	1,20	34
		P_valor = 0,3540								
Neutrófilos/ Linfócitos	Sim	15	7,74	6,16	3,85	11,25	7,40	5,77	1,4	22,75
	Não	50	4,71	3,19	2,42	5,60	3,17	4,33	0,04	23,5
		P_valor = 0,0304								
Tempo de internamento (dias)	Sim	15	15,6	9	8	14	6	16,03	0	54
	Não	50	7,6	4	2	12	10	7,08	1	35
		P_valor = 0,0188								

PAS: Pressão arterial sistólica; ECG: Escala de Coma de Glasgow; PCR: proteína C reativa ultrassensível. Q1: quartil 1. Q3: quartil 3. Iqr: Intervalo interquartil. O P_valor representa o nível de significância do teste Mann-Whitney.

O modelo 6 de regressão logística – considerado o de melhor ajuste de acordo com o Critério de Informação de Akaike (Tabela 2) – mostrou que maior idade (OR 1,20; p-valor <0,05; IC 1,02 – 1,41), maior glicemia admissional (OR 1,01; p-valor <0,05; IC 1,00–1,03) e maior relação neutrófilos/linfócitos (OR 1,56; p-valor <0,01; IC 1,14 – 2,14) estão significativamente associados a maior chance de óbito em pacientes com AVC isquêmico agudo (Tabela 3). Níveis de PCR ultrassensível, contagem absoluta de monócitos e a relação linfócitos/monócitos não mostraram associação significativa com mortalidade.

DISCUSSÃO

Nosso estudo apresentou taxa de mortalidade de 23,07% e maior prevalência de AVC isquêmico no sexo masculino. Em publicações anteriores, a taxa mundial de mortalidade estimada em 30 dias após o primeiro AVC isquêmico variou de 16 a 23%[10] e o estudo de Benjamin et al., indicou que em idades mais jovens, a incidência de AVC é mais alta nos homens, mas, a partir dos 75 anos há inversão, tornando-se maior no sexo feminino[11]. As principais comorbidades encontradas no estudo foram hipertensão, diabetes, fibrilação atrial e dislipidemia. Dados da literatura mostraram que os fatores de risco tradicionais do AVC incluem, além dos citados, doenças cardiovasculares, sedentarismo, tabagismo e consumo de álcool[12] .

No presente estudo buscou-se avaliar a influência dos marcadores inflamatórios como preditores de mortalidade nos pacientes com AVC isquêmico. De acordo com Bustamante et al., a aplicação desses novos marcadores poderia ser explicada devido as células da área isquêmica e da área peri-infartada liberarem sinais que ativam a microglia local e os leucócitos periféricos, resultando na liberação maciça de mediadores pró-inflamatórios que, quando em excesso, aumentam os danos cerebrais e contribuem para complicações secundárias, como edema, transformação hemorrágica e infecções[13] .

Nossa pesquisa detectou correlação positiva entre a relação neutrófilos/linfócitos ao desfecho desfavorável, indicando que os pacientes com uma relação maior nas primeiras 24 horas da admissão, apresentam maior risco de mortalidade. A literatura recente relata que como resposta inicial ao dano cerebral isquêmico, os neutrófilos são as primeiras células a migrar para a área danificada e podem se acumular nas áreas isquêmica e reperfundida, promovendo a liberação de enzimas proteolíticas e produtos reativos de oxigênio[14] . O estudo de Lux et al.[14] , relatou que a elevação do número basal de neutrófilos aumenta a gravidade do dano isquêmico e piora o prognóstico neurológico.

Por outro lado, após o AVC, os pacientes podem apresentar linfopenia ou redução na contagem absoluta de linfócitos, um fenômeno de imunodepressão que pode contribuir para o aumento da incidência da morbimortalidade secundária a infecção[15] . Os linfócitos têm papel dominante na inflamação crônica. Eles expressam interleucina 10 para as áreas isquêmicas e reperfundidas e podem ter papel importante na cicatrização[16] .

O modelo 8 de regressão logística incluiu apenas 5 variáveis (ECG da admissão, relação neutrófilos/linfócitos, tempo de internação, idade e glicemia da admissão) e mostrou que maior pontuação na ECG admissional está associada a menor mortalidade (OR 0,77; p-valor <0,05; IC 0,63 – 0,94), enquanto maior relação neutrófilos/linfócitos (OR 1,35; p-valor <0,05; IC 1,03 – 1,75) está associada a maior chance de óbito (Tabela 2).

Tabela 2. Modelos de regressão logística para os determinantes de mortalidade de pacientes com AVC.

Variável	Modelo 1	Modelo 2	Modelo 3	Modelo 4	Modelo 5	Modelo 6	Modelo 7	Modelo 8	Modelo 9
ECG Adm	0,74*** (0,06) [0,62-0,88]	0,73*** (0,07) [0,59-0,88]	0,70** (0,11) [0,56-1,01]	0,75* (0,11) [0,56-1,01]	0,72** (0,11) [0,53-0,98]	0,56* (0,16) [0,32-1,00]	0,74*** (0,07) [0,60-0,91]	0,77** (0,08) [0,63-0,94]	
Monócitos		1,00 (0,00) [0,99-1,00]	1,00 (0,00) [0,99-1,00]	1,00 (0,00) [0,99-1,00]	1,00 (0,00) [0,99-1,00]	1,00 (0,00) [0,99-1,00]			
Linfócitos/Monócitos		0,97 (0,09) [0,80-1,18]	0,96 (0,12) [0,75-1,23]	0,98 (0,13) [0,75-1,28]	0,97 (0,09) [0,80-1,18]	0,91 (0,09) [0,74-1,13]			
Neutrófilos/linfócitos		1,11 (0,081) [0,97-1,28]	1,12* (0,08) [0,97-1,29]	1,13* (0,07) [0,99-1,29]	1,09 (0,08) [0,94-1,27]	1,56*** (0,25) [1,14-2,14]		1,35** (0,18) [1,03-1,75]	1,19** (0,08) [1,02-1,37]
PCR us			1,06 (0,13) [0,84-1,35]	1,14 (0,15) [0,87-1,48]	1,12 (0,14) [0,87-1,44]	1,13 (0,17) [0,84-1,52]			
Tempo de internação				1,05* (0,03) [0,99-1,12]	1,05 (0,03) [0,98-1,13]	1,09** (0,04) [1,00-1,18]	1,05* (0,02) [0,99-1,11]	1,05 (0,03) [0,98-1,13]	1,06** (0,02) [1,01-1,12]
Comorbidades					1,55 (0,44) [0,88-2,73]	1,34 (0,43) [0,71-2,53]			
Sexo feminino						0,13 (0,21) [0,00-3,05]			
Idade						1,20** (0,10) [1,02-1,41]	0,99 (0,03) [0,93-1,06]	1,04 (0,04) [0,95-1,14]	1,00 (0,03) [0,93-1,08]
Glicemia						1,01** (0,00) [1,00-1,03]	1,01** (0,00) [1,00-1,02]	1,01** (0,00) [0,99-1,02]	1,00 (0,00) [0,99-1,02]
PAS						0,99 (0,01) [0,96-1,01]	1,00 (0,01) [0,99-1,02]		
Constante	9,14** (10,29) [1,00; 83,14]	3,97 (7,93) [0,07; 198,90]	5,32 (15,26) [0,01; 1473,12]	0,87 (2,61) [0,00; 305,28]	0,30 (1,02) [0,00; 232,54]	0,00** (0,00) [0,00; 0,16]	0,19 (0,57) [0,00; 70,74]	0,00 (0,01) [0,00; 11,38]	0,01 (0,02) [0,00; 2,82]
N	63	63	56	56	56	51	57	57	58
Pseudo	0,21	0,28	0,3	0,35	0,39	0,54	0,3	0,36	0,2
AIC	58,02	59,41	57,22	5610	55,38	52,04	57,95	53,54	62,96

Razão de chances (OR). Erros-padrão robustos entre parênteses; Intervalos de confiança entre colchetes; *** p-valor < 1%, ** p-valor < 5%, * p-valor < 10%. Estimaram-se nove modelos com diferentes especificações. O modelo que apresentou o melhor ajuste segundo o critério de informação de Akaike (Akaike Information Criterion – AIC) foi o modelo 6.

Tabela 3. Modelo 6 de regressão logística para os determinantes de mortalidade de pacientes com AVC

Variável	Coeficiente	Razão de chances (OR)	Intervalos de confiança (IC)
Sexo feminino	-2,0027	0,1349	[0,00 – 3,05]
	(1,5913)	(0,2147)	
Idade em anos	0,1858**	1,2042**	[1,02 – 1,41]
	(0,0838)	(0,1009)	
Glicemia Adm	0,0156**	1,0158**	[1,00 – 1,03]
	(0,0076)	(0,0077)	
ECG Adm	-0,5642*	0,5687*	[0,32 – 1,00]
	(0,2905)	(0,1652)	
PCR us	0,1245	1,1326	[0,84 – 1,52]
	(0,1503)	(0,1702)	
Monócitos	0,0033	1,0034	[0,99 – 1,00]
	(0,0025)	(0,0025)	
Linfócitos/monócitos	-0,0833	0,9199	[0,74 – 1,13]
	(0,1080)	(0,0994)	
Neutrófilos/Linfócitos	0,4485**	1,5660***	[1,14 – 2,14]
	(0,1609)	(0,2520)	
Tempo de internação	0,0870**	1,0909*	[1,00 – 1,18]
	(0,0430)	(0,0469)	
Número de comorbidades	0,2978	1,3469	[0,71 – 2,53]
	(0,3231)	(0,4352)	
Constante	-14,5623**	0,0000*	
	(6,5251)	(0,0000)	
Pseudo R^2	0,5461	0,5461	
AIC			

Erros-padrão robustos entre parênteses; *** p-valor < 1%, ** p-valor < 5%, * p-valor < 10%. PAS adm: Pressão arterial sistólica admissional; ECG adm: Escala de Coma de Glasgow admissional; PCR us: proteína C reativa ultrassensível.

O estudo de Tokgoz et al., demonstrou que a razão neutrófilos/linfócitos (RNL) elevada (>4.81) no momento da admissão hospitalar pode ser preditor de mortalidade a curto prazo (dentro de 30 dias), independente do volume do infarto em pacientes com AVC isquêmico agudo [17].

Apesar de, no nosso estudo, os outros marcadores inflamatórios, tais como níveis de PCR ultrassensível, contagem absoluta de monócitos e a relação linfócitos/monócitos, não terem mostrado com relevância estatística associação com a mortalidade, estudos prévios evidenciaram que esses marcadores podem afetar significativamente no desfecho do acidente isquêmico agudo.

O estudo de Cai et al.[18] demonstrou que níveis plasmáticos elevados de proteína C reativa ultrassensível (PCR-us) na admissão estão associados com deterioração neurológica e pior desfecho em pacientes com AVC isquêmico. No estudo de coorte de Itrat et al. [19], pacientes que sofreram AVC com PCR-us >10mg/L tiverem risco 2,65 (IC 95%: 1,99 - 3,53) maior de todas as causas de mortalidade em comparação com os pacientes com PCR-us ≤10 mg/L.

Já os monócitos, embora componham apenas cerca de 5% dos glóbulos brancos no sangue periférico, são parte importante do sistema imunológico inato vascular e podem produzir grandes quantidades de citocinas inflamatórias [20]. Liberale et al. sugeriram que a contagem absoluta de monócitos poderia ser preditor independente de pior prognóstico pós-AVC, além de ser um parâmetro prático e de baixo custo [21] . Enquanto o estudo de Dong et al., demonstrou que a maior parte dos pacientes com desfecho funcional desfavorável, após 90 dias do AVC, apresentaram contagem elevada de monócitos ($\geq 0{,}53 \times 10^9$ /L)[7] .

Por último, a relação linfócitos sobre monócitos foi estudada por Ren et al., que sugeriram que taxas de linfócitos sobre monócitos iguais ou inferiores a 3,48 na admissão são fatores de risco independente para desfechos desfavoráveis em pacientes com AVC[22] . No estudo conduzido por Ren et al.[23] , taxas de linfócitos sobre monócitos baixas foram correlacionadas com maior gravidade do AVC.

A principal limitação do nosso estudo foi o tamanho da amostra relativamente pequeno, o que aumentou a probabilidade de um viés de seleção. Outra limitação inclui o desenho retrospectivo e centralizado do estudo, o qual levou em conta apenas os casos de AVC isquêmico de pacientes internados em um hospital de referência de Cascavel. Portanto, a extrapolação destes resultados pode não ser adequada. Além disso, nós não levamos em consideração o volume do infarto nos pacientes com AVC, o que poderia influenciar na magnitude da resposta inflamatória. Embora tenhamos obtido conclusões positivas sobre a associação entre a relação neutrófilos/linfócitos e o desfecho do AVC, os resultados seriam mais convincentes em um estudo prospectivo, com uma amostra maior e que considerasse o volume do infarto.

CONCLUSÃO

O presente estudo demonstrou que a relação de neutrófilos sobre linfócitos elevada é um marcador inflamatório, presente no sangue periférico, que pode estar significativamente associado a um desfecho desfavorável após um AVC isquêmico. Portanto, o monitoramento dessa taxa pode ajudar os neurologistas e intensivistas a prever o resultado do evento isquêmico no ambiente hospitalar. Embora os mecanismos subjacentes ainda precisem ser elucidados e mais estudos sejam necessários, esse marcador pode, no entanto, ser um preditor de mortalidade barato e prático em pacientes com AVC isquêmico. O estudo não possui conflitos de interesse e fontes de financiamento.

REFERÊNCIAS

1. Sacco L, Kasner , Broderick , Caplan LR, Connors JJ. An Updated Definition of Stroke for the 21st Century. Stroke. 2013 May 7; 44(7): p. 2064–2089.
2. Caplan R. UpToDate. [Online].; 2019 [cited 2020 January 24. Disponível em:https://www.uptodate.com/contents/etiology-classification-and-epidemiology-of-stroke?search=stroke&source=search_result&selectedTitle=3~150&usage_type=default&display_rank=3.
3. Truelsen T, Begg S, Mathers C. World Health Organization. [Online].; 2006 [cited 2020 January 25. Disponível em: https://www.who.int/healthinfo/statistics/bod_cerebrovasculardiseasestroke.pdf.
4. Johnson , Onuma , Owolabi M, Sachdeva S. Stroke: a global response is needed. Geneva: World Health Organization; 2016.
5. Hospital Sírio-Libanês. [Online]. São Paulo; 2018 [cited 2020 01 25 .Disponível em:https://www.hospitalsiriolibanes.org.br/institucional/gestao-da-qualidade/Documents/2018-11-01-protocolos/Protocolo%20Gerenciado%20de%20Acidente%20Vascular%20Cerebral/Protocolo%20AVC_VF.pdf.
6. McDermott M, Jacobs T, Morgenstern L. Critical care in acute ischemic stroke. Handbook of Clinical Neurology. 2017; 140: p. 153-176.
7. Dong X, Nao J, Gao Y. Peripheral Monocyte Count Predicts Outcomes in Patients with AcuteIschemic Stroke Treated with rtPA Thrombolysis. Neurotoxicity Research. 2019; 37(2): p. 469-477.
8. Goyal N, Tsivgoulis , Chang „Alexandrov V. Admission Neutrophil-to-Lymphocyte Ratio as a Prognostic Biomarker of Outcomes in Large Vessel Occlusion Strokes. Stroke. 2018; 49(8): p. 1985-1987.
9. Lippi G, Targher G, Montagnana M, Guidi GC. Relation between red blood cell distribution width and inflammatory biomarkers in a large cohort of unselected outpatients. Archives of Pathology & Laboratory Medicine. 2009 Abril; 133(4): p. 628-632.
10. Edwardson A, Kasner E, Dashe F. UpToDate. [Online].; 2020 [cited 2021 Janeiro 22. Disponível em: https://www.uptodate.com/contents/overview-of-ischemic-stroke-prognosis-in-adults?search=stroke%20mortality&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1.
11. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR. Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017 March 7; 135(10): p. e146–e603.

12. Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. The Lancet. 2010 July; 376(9735): p. 112-123.
13. Bustamante A, Simats, Vilar-Bergua, García-Berrocoso, Montaner. Blood/Brain Biomarkers of Inflammation After Stroke and Their Association With Outcome: From C-Reactive Protein to Damage-Associated Molecular Patterns. Neurotherapeutics. 2016 Outubro; 13(4): p. 671–684.
14. Lux D, Alakbarzade V, Bridge , Pereira. The association of neutrophil-lymphocyte ratio and lymphocyte-monocyte ratio with 3-month clinical outcome after mechanical thrombectomy following stroke. Journal of Neuroinflammation. 2020 Fevereiro; 17(1).
15. Gu L, Jian Z, Stary C, Xiong X. T Cells and Cerebral Ischemic Stroke. Neurochemical research. 2015 Setembro; 40(9): p. 1786-1791.
16. Frangogiannis G, Smith W, Entman. The inflammatory response in myocardial infarction. Cardiovascular Research. 2002 Janeiro; 53(1): p. 31–47.
17. Tokgoz S, Keskin S, Kayrak M, Ogmegul. Is neutrophil/lymphocyte ratio predict to short-term mortality in acute cerebral infarct independently from infarct volume? Journal of Stroke and Cerebrovascular Diseases. 2014 Setembro; 23(8): p. 2163-2168.
18. Cai Z, He , Zhuang FJ, Chen. The role of high high-sensitivity C-reactive protein levels at admission on poor prognosis after acute ischemic stroke. International Journal of Neuroscience. 2019; 129(5): p. 423-429.
19. Itrat A, Griffith D, Alam S, Thompson N, Katzan L. The role of very high high-sensitivity C-reactive protein levels on mortality after stroke. Journal of the neurological sciences. 2017 Janeiro; 372: p. 1-5.
20. Dutta P, Nahrendorf M. Monocytes in myocardial infarction. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015 Março; 35(5): p. 1066–1070.
21. Liberale L, Montecucco F, Bonaventura A, Carbone F. Monocyte count at onset predicts poststroke outcomes during a 90-day follow-up. European Journal of Clinical Investigation. 2017 Outubro; 47(10): p. 702-710.
22. Ren H, Han , Liu , Wang L, Gao Y. Decreased Lymphocyte-to-Monocyte Ratio Predicts Poor Prognosis of Acute Ischemic Stroke Treated with Thrombolysis. Medical science monitor: international medical journal of experimental and clinical research. 2017; 23: p. 5826–5833.
23. Ren H, Liu X, Wang L, Gao Y. Lymphocyte-to-Monocyte Ratio: A Novel Predictor of the Prognosis of Acute Ischemic Stroke. Journal of Stroke and Cerebrovascular Diseases. 2017 Novembro; 26(11): p. 2595-2602.

Associação entre classes funcionais da insuficiência cardíaca com fração de ejeção preservada e comprometimento cognitivo

Association between the functional classification of heart failure with preserved fraction ejection and cognitive impairment

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ABSTRACT

Introduction: Heart failure (HF) is a syndrome resulting from structural and functional defects of cardiac pump, more than 80% of the patients are elderly with diverse associated comorbidities. The dementia is defined by any disorder where the significant decline of the previous cognition level of the patient intervene on his independence and social, domestic or occupational functioning. The link between light cognitive impairment and HF is already well documented in literature, however recent studies point a possible relation of HF in pathogenesis and deteriorating of dementia.
Objetive: Rank functional limitation of volunteers with HF with preserved ejection fraction and to apply the Montreal Cognitive Assessment (MoCA) memory test to analyse if there is a association between HF functional limitations and dementia onset/worsening.
Methods: Transversal observational study, 27 patients with HF with preserved ejection fraction were assessed in Universidade Luterana do Brasil's heart failure clinic.
Results: Assessing 27 patients, with average age of 72.4 years (+/-7.3), being 18 (66.6%) female, we found 24 (88.8%) with MoCA score lower to 26, being the average score 20.4. Between the 27 patients, 4 had functional class NYHA I, 15 NYHA II, 3 NYHA III and 5 NYHA IV.
Conclusion: The present study shows a tendency to lower performance in MoCA on patients with worse HF functional classification (NYHA I-II: MoCA 21.4 +/- 4.9 e NYHA III-IV MoCA: 18 +/- 4.2 p:0. 0.087).

Keywords: Dementia; Heart failure; Montreal Cognitive Assessment (MoCA)

RESUMO

Introdução: A insuficiência cardíaca (IC) é uma síndrome resultante de defeitos estruturais e funcionais da bomba cardíaca, mais de 80% dos pacientes são idosos, com diversas comorbidades associadas. A demência é definida por qualquer desordem onde o declínio significativo do nível prévio de cognição do paciente interfere em sua independência e funcionamento social, doméstico ou ocupacional. A relação entre o comprometimento cognitivo leve e a IC já é bem estabelecida na literatura, porém estudos recentes apontam uma possível relação da IC na patogênese e no agravo da demência.
Objetivos: Classificar a limitação funcional de voluntários com IC com fração de ejeção preservada (FEp) e realizar o teste Montreal Cognitive Assessment (MoCA) de memória para analisar se há associação entre as limitações funcionais da IC e o deterioramento cognitivo do paciente.
Métodos: Trata-se de um estudo observacional transversal, foram avaliados 27 pacientes com história de ICFEp no ambulatório de Insuficiência Cardíaca do Hospital da Universidade Luterana do Brasil.
Resultados: Foram avaliados 27 pacientes, com idade média de 72.4 anos, sendo 18 (66.6%) do sexo feminino, 24 (88.8%) obtiveram escore no MoCA inferior a 26, sendo a média da escala 20.4. Entre os 27 pacientes, quatro apresentavam classe funcional NYHA I, 15 NYHA II, 3 NYHA III e 5 NYHA IV.
Conclusão: O estudo mostra uma tendência de pior desempenho no MoCA entre pacientes com pior classe funcional de IC (NYHA I-II: MoCA 21.4 +/- 4.9 e NYHA III-IV MoCA: 18 +/- 4.2 p:0. 0.087).

Palavras-chave: Demência; Insuficiência cardíaca; Avaliação Cognitiva de Montreal (MoCA)

Conflito de Interesse: Os autores declaram não ter conflito de interesse.
Declaração de Financiamento: Não houve financiamento.
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INTRODUÇÃO

A insuficiência cardíaca (IC) é definida como "uma síndrome clínica complexa queresulta de qualquer comprometimento estrutural ou funcional do enchimento ventricular ou da ejeção de sangue". Suas manifestações clínicas mais comuns são: dispneia, fadiga e intolerância ao exercício. [1]

A IC possui variadas classificações, a classificação funcional da NYHA (*New York Heart Association*) é uma das mais utilizadas na prática clínica devido a sua fácil aplicabilidade e sendo uma ferramenta validada para relacionar a IC e seu prejuízo nas atividades de vida diárias do paciente.[2] A classificação da NYHA estima a gravidade da IC através de 4 estágios de possível sintomatologia do paciente: I – sem limitação da atividade física. Exercício físico rotineiro não causa fadiga, palpitação ou dispneia. II – Leve limitação da atividade física. Atividade física rotineira resulta em fadiga, palpitação ou dispneia. III – Evidente limitação da atividade física. Leves atividades físicas causam fadiga, palpitação ou dispneia. IV – Incapacidade de realizar atividade física sem desconforto. Sintomas de IC mesmo ao descanso.[3]

A demência, por sua vez, é definida por qualquer desordem onde o declínio cognitivo significativo do nível prévio do paciente interfere em sua independência e funcionamento social, doméstico ou ocupacional. A demência deve ser tratada como uma síndrome, e não uma doença específica, visto que é causada por um misto de fatores como condições médicas, sociais, neurológicas e psiquiátricas. [4] Com a publicação do Manual Diagnóstico e Estatístico de Transtornos Mentais (DSM-V), a síndrome demência foi incorporada ao recém nomeado "transtorno neurocognitivo maior", embora não tenha sido excluído o uso do termo "demência" ao referir-se aos seus subtipos etiológicos como Demência de Alzheimer (DA), Demência Vascular (DVa) e Demência com Corpos de Lewy (DCL).[5]

O estabelecimento do prejuízo cognitivo, e posteriormente a demência, afeta os indivíduos de maneira heterogênea, dependendo de diversos fatores de risco como severidade do comprometimento vascular, obesidade, hipertensão arterial sistêmica, diabetes e tabagismo.[6, 7] No diagnóstico de demência se faz uso de testes que avaliam o desempenho cognitivo, como o Mini Exame do Estado Mental (MEEM) e o Montreal Cognitive Assessment (MoCA). [8] Ao comparar a eficácia entre o MEEM e o MoCA na detecção de demência e comprometimento cognitivo leve (CCL), precursor de demência, o MoCA obteve resultados substancialmente superiores ao MEEM no rastreamento de demência.[9] Resultados semelhantes foram obtidos na detecção de sintomas iniciais de prejuízo cognitivo, onde o teste MoCA foi particularmente superior ao MEEM.[10] Em um estudo de validação com o objetivo de comparar a sensibilidade entre o MEEM e o MoCA (com pontuação de corte de 26) na detecção de demência moderada o MEEM teve uma sensibilidade de 78%, e o MoCA obteve sensibilidade de 100%, detectando assim, pacientes que o MEEM classificava como dentro da normalidade. [11]

A IC tem sido alvo promissor na investigação da patogênese da demência, resultados que sugerem que a IC é associada a maior risco de desenvolver demência, independente do histórico de acidente vascular cerebral. [12] Diversos mecanismos têm sido estudados a fim de elucidar a relação entre a IC e seu papel na patogênese da demência. A relação entre IC e fluxo sanguíneo cerebral (FSC) reduzido foi estabelecida há mais de 50 anos.[13] Em uma coorte de pacientes acima de 60 anos, encontrou-se relação entre baixo índice cardíaco (débito cardíaco dividido pela massa corpórea) e risco de desenvolvimento de demência e DA. [14] O índice cardíaco estima a quantidade total de sangue enviada à circulação, e consequentemente ao cérebro, o que explica sua relação íntima com a hipoperfusão cerebral e demência. Anormalidades vasculares cerebrais decorrentes de sofrimento vascular crônico frequentemente ocorrem em conjunto com a demência, e podem ter papel crítico no início e agravo da demência, visto que a eliminação da proteína β-amiloide através do leito vascular é uma importante rota no mecanismo de depuramento da proteína β-amiloide a fim de evitar o acúmulo de placas amiloides no cérebro, que é o principal mecanismo neurodegenerativo responsável pela DA.[15]

O objetivo deste artigo é avaliar a associação entre o escore do teste de memória MoCA em pacientes com IC com fração de ejeção preservada (FEp) de acordo com sua classe funcional segundo a classificação da NYHA.

MATERIAIS E MÉTODOS

Foram avaliados 27 pacientes com história de IC com fração de ejeção preservada (FEp) em acompanhamento no ambulatório de Insuficiência Cardíaca do Hospital da Universidade Luterana do Brasil, em Canoas, Rio Grande do Sul, no período de 1º de março de 2019 a 1º de novembro de 2019. Foram incluídos pacientes com idade maior ou igual a 60 anos, que tinham diagnóstico de ICFEp, comprovada por ecocardiograma, segundo critérios da Sociedade Brasileira de Cardiologia. Indivíduos com dificuldades graves de comunicação foram excluídos da amostra.

As seguintes variáveis foram analisadas: idade, sexo, anos de estudo, escore no teste MoCA, classe funcional segundo a classificação da NYHA e fração de ejeção do ventrículo esquerdo na última ecocardiografia.

Os pacientes foram submetidos ao teste Montreal Cognitive Assessment (MoCA), versão validada para a língua portuguesa, que analisa diversos domínios cognitivos do paciente. O teste é divido em oito áreas testadas (visuoespacial/cognitiva, nomeação, memória, atenção, linguagem, abstração, evocação diferida e orientação;) onde a partir do desempenho obtido na execução das tarefas do teste, é gerado um escore. O escore obtido é de nota máxima 30 (trinta) e terá como ponto de corte 26 (vinte e seis), sendo abaixo dessa pontuação considerado alterado.[16]

Os indivíduos foram divididos em dois grupos de acordo com a classe funcional da insuficiência cardíaca segundo a classificação NYHA (New York Heart Association), sendo o Grupo A (NYHA I-II) e Grupo B (NYHA III-IV). [3]

Os dados coletados foram digitados em planilhas no programa Microsoft Excel e analisados no software Statistical Package Social Sciences SPSS-21.0 (Chicago, Illinois). As variáveis qualitativas serão descritas por n (%) e as quantitativas por média (+/- desvio padrão). O teste T Student foi usado para comparações entre esses dois grupos. O nível de significância foi considerado p< 0,05.

A coleta de dados iniciou-se após a aprovação da pesquisa no Comitê de Ética e Pesquisa (CEP) da Universidade Luterana do Brasil (ULBRA), com número do Certificado de Apresentação de Apreciação Ética (CAAE): 13698819.2.0000.5349.

RESULTADOS

Avaliando 27 pacientes com IC com fração de ejeção preservada, a média de idade foi de 72.4 anos (+/-7.3), sendo 18 (66.6%) do sexo feminino, 24 (88.8%) dos voluntários obtiveram escore no MoCA inferior a 26, sendo a média da escala 20.4. Entre os 27 pacientes, 4 apresentavam classe funcional NYHA I, 15 NYHA II, 3 NYHA III e 5 NYHA IV. Comparando os indivíduos da classe funcional NYHA I e II com os de classe funcional NYHA III e IV, verificamos que não existe diferenças de idade, sexo e escolaridade entre os dois grupos. Os dados demográficos são apresentados na Tabela 1.

Verifica-se que existe uma tendência de pior desempenho no MoCA entre os pacientes com classe funcional III e IV de acordo com a NYHA.

Tabela 1. Diferenças entre paciente com IC classe funcional I-II e III-IV:

	NYHA I-II	NYHA III-IV	P
Idade	72,6 +/- 6,9	72 +/- 8,8	0,85
Sexo			0,766
Masc	31,60%	37,50%	
Fem	64,40%	62,50%	
Escolaridade	7,1 +/- 1,3	7,4 +/- 1,1	0,872
FE	64,7 +/- 8,6	63,8 +/- 7,7	0,81
MoCA	21,4 +/- 4,9	18 +/- 4,2	0,087

*FE: fração de ejeção

DISCUSSÃO

Após o diagnóstico de demência, a média de anos de vida até a morte do paciente é de aproximadamente 3,8 anos.17 Uma coorte populacional realizada entre 1990-2015 mostrou que intervenções bem sucedidas em adiar o aparecimento de demência podem resultar em 24- 60% de redução nos anos vividos com demência.[18]

Sendo assim, é de vital importância a identificação de sintomas iniciais de comprometimento cognitivo e prejuízo de memória (sintomas iniciais mais comuns na demência) a fim de promover medidas que desacelerem o pleno estabelecimento da patologia.[19]

Em 2012, os gastos relacionados ao tratamento de IC nos EUA chegaram a US$ 20,9 bilhões, e estimativas indicam que as despesas diretas relacionadas à IC chegarão a US$ 53,1 bilhões, sendo 80% desse valor relacionado à internação hospitalar. 20 Apesar dos altos gastos, não houve diminuição da mortalidade no ano posterior à internação, indicando que o tratamento necessita de otimização.[21] Um estudo conduzido em pacientes hospitalizados por IC descompensada observou que 80% dos pacientes possuíam declínio em pelo menos um domínio cognitivo (memória, velocidade de processamento e função executiva) e 17% em todos os três domínios. [22]

A situação hemodinâmica entre o coração e o cérebro parece ser uma importante e subestimada causa de comprometimento cognitivo vascular.[23] Durante muitos anos, a ocorrência de prejuízo cognitivo em pacientes com IC foi vista como circunstancial devido a ambas as síndromes serem muito prevalentes na população idosa. Buscando estabelecer relação de causalidade entre a IC e a demência em pacientes idosos, uma coorte acompanhou voluntários acima de 75 anos, durante um período de 9 anos, tendo como resultado a IC como fator de risco no estabelecimento da demência.[24]

O uso de biomarcadores cardíacos (principalmente as troponinas e os peptídeos natriuréticos) são largamente utilizados para mensurar danos clínicos e subclínicos ao miocárdio.[25]Sendo o coração responsável pelo suprimento sanguíneo do cérebro, um estudo demonstrou que troponinas e peptídeos natriuréticos foram associados a lesões vasculares subclínicas no cérebro, indicando que o sofrimento cardíaco contribui também para o stress neuronal através de mecanismos como hipoperfusão crônica e microlesões vasculares.[26] Em estudos com ressonância magnética foi constatado que pacientes com IC possuíam maior acometimento vascular cerebral e tinham perda do parênquima cerebral e atrofia da substância cinzenta aceleradas.[27]Esses achados sustentam a ideia de que o stress neuronal prejudica a capacidade do cérebro de regular o fluxo sanguíneo cerebral, entrando num ciclo vicioso de baixa perfusão tecidual e resposta vascular insuficiente.[28]

A hipoperfusão cerebral crônica e seu consequente stress oxidativo desencadeia a chamada "depleção energética neuronal", que aumenta o risco de neurodegeneração, levando ao acúmulo de substratos que participam na patogênese da demência, incluindo a proteína precursora amiloide e a proteína tau hiperfosforilada.[29, 30]

No presente estudo descrevemos uma tendência de pior desempenho no MoCA entre indivíduos que pertencem a classes funcionais III e IV de IC com fração de ejeção preservada em relação a indivíduos das classes funcionais I e II. Uma limitação do estudo trata-se do número de pacientes avaliados; entretanto, cabe ressaltar que o perfil desses pacientes não é tão freqüente uma vez que foram avaliados indivíduos com IC com fração de ejeção preservada. Outra questão importante a ser destacada foi a preferência por apresentarmos os resultados do MoCA através da média de seus resultados nos dois grupos; uma vez que o ponto de corte de tal instrumento pode variar de acordo com a população estudada. A inter-relação de doenças cardíacas com distúrbios neurológicos é muito conhecida, mas mais descrita no Acidente Vascular Cerebral causado por mecanismos cardioembólicos.[31- 34]

CONCLUSÃO

No presente estudo, ao avaliar a classe funcional de 27 pacientes com insuficiência cardíaca com fração de ejeção preservada e correlacionar com o seu desempenho no teste de memória de Montreal, foi possível detectar uma tendência de piores resultados entre os pacientes com classes funcionais mais sintomáticas (NYHA III-IV) de IC.[31] O estudo teve como principal limitação o número amostral obtido, uma vez que houve uma tendência à associação, porém estatisticamente insignificante, necessitando assim de mais dados para estabelecer associação entre as classes funcionais e seu escore no MoCA.[32] O tema ainda carece de estudos definitivos, portanto, pesquisas posteriores são necessárias a fim de verificar uma relação direta entre acometimento funcional da insuficiência cardíaca e sua relação com a patogênese e agravo da demência.[33, 34]

REFERÊNCIAS

1. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure. J Am Coll Cardiol [Internet]. 2013;62(16):e147–239.
2. Bennett J, Riegel B, Bittner V, Nichols J. Validity and reliability of the NYHA classes for measuring research outcomes in patients with cardiac disease. Heart Lung. 2002;31(4):262-270.
3. https://www.heart.org/en/health-topics/heart-failure/what-is-heart-failure/classes-of-heart-failure.
4. Gale S, Acar D, Daffner K. Dementia. Am J Med. 2018;131(10): 1161-1169.
5. American Psyquiatric Association. DSM-V. Manual Diagnóstico E Estatístico De Transtornos Mentais - DSM-V. 2013. Hjalmarson A, Goldstein S, Fagerberg B.
6. Baumgart M, Snyder HM, Carrillo MC, Fazio S, Kim H, Johns H. Summary of the evidence on modifiable risk factors for cognitive decline and dementia: A population-based perspective. Alzheimer's Dement [Internet].2015;11(6):718–26.
7. Zhong G, Wang Y, Zhang Y, Guo J, Zhao Y. Smoking Is Associated with an Increased Risk of Dementia: A Meta-Analysis of Prospective Cohort Studies with Investigation of Potential Effect Modifiers. PLoS One. 2015;10(3):e011833.
8. Panegyres PK, Berry R, Burchell J. Early dementia screening. Diagnostics. 2016;6(1):1–13.
9. Freitas S, Simões MR, Alves L, Santana I. Montreal Cognitive Assessment Validation Study for Mild Cognitive Impairment and Alzheimer Disease. Alzheimer Dis Assoc Disord [Internet]. 2013;27(1):37–43.
10. Roalf D, Moberg P, Xie S, Wolk D, Moelter S, Arnold S. Comparative accuracies of two common screening instruments for classification of Alzheimer's disease, mild cognitive impairment, and healthy aging. Alzheimers Dement. 2013;9(5): 529-537.
11. Nasreddine Z, Phillips N, BÃ©dirian V, Charbonneau S,Whitehead V, Collin I et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. J Am Geriatr Soc. 2005;53(4):695-699.
12. Vogels RLC, Scheltens P, Schroeder-Tanka JM, Weinstein HC. Cognitive impairment in heart failure: A systematic review of the literature. Eur J Heart Fail. 2007;9(5):440–9.
13. Sensenbach W, Madison L, Eisenberg S. Cerebral Hemodynamic and Metabolic Studies in Patients with Congestive Heart Failure. Circulation. 1960;21(5):697-703.
14. Jefferson A, Beiser A, Himali J, Seshadri S, O'Donnell C, Manning W et al. Low Cardiac Index Is Associated With Incident Dementia and Alzheimer Disease. Circulation. 2015;131(15):1333-1339.
15. Cermakova P, Lund L, Fereshtehnejad S, Johnell K, Winblad B, Dahlström U et al. Heart failure and dementia: survival in relation to types of heart failure and different dementia disorders. Eur J Heart Fail. 2015;17(6):612-619.
16. Freitas S, Simões M, Santana I, Martins C. Estudo de adaptação do Montreal Cognitive Assessment (MOCA) para a população portuguesa. Avaliação Psicológica. 2010;9(3):345-357.
17. Mayeda ER, Glymour MM, Quesenberry CP, Johnson JK, Pérez-Stable EJ, Whitmer RA. Survival after dementia diagnosis in five racial/ethnic groups. Alzheimer's Dement. 2017;13(7):761–9.
18. Wolters F, Tinga L, Dhana K, Koudstaal P, Hofman A, Bos D et al. Life expectancy with and without dementia: a population-based study of dementia burden and preventive potential. American Journal of Epidemiology. 2018;.
19. Plassman B, Langa K, Fisher G, Heeringa S, Weir D, Ofstedal M et al. Prevalence of Dementia in the United States: The Aging, Demographics, and Memory Study. Neuroepidemiology. 2007;29 (1-2):125-132.
20. Paul A. Heidenreich, Nancy M. Albert, Larry A. Allen, David A. Bluemke JB, Gregg C. Fonarow, John S. Ikonomidis, Olga Khavjou, Marvin A. Konstam, Thomas M. Maddox, Graham Nichol, Michael Pham, Ileana L. Piña JGT. Forecasting the Impact of Heart Failure in the United States : Circ Hear Fail. 2013;6(3): 606–19.

21. Chen J, Normand S, Wang Y, Krumholz H. National and Regional Trends in Heart Failure Hospitalization and Mortality Rates for Medicare Beneficiaries, 1998-2008. JAMA. 2011;306(15):1669.
22. Levin S, Hajduk A, McManus D, Darling C, Gurwitz J, Spencer F et al. Cognitive status in patients hospitalized with acute decompensated heart failure. Am Heart J. 2014;168(6):917-923.
23. Hooghiemstra A, Bertens A, Leeuwis A, Bron E, Bots M, Brunner-La Rocca H et al. The Missing Link in the Pathophysiology of Vascular Cognitive Impairment: Design of the Heart-Brain Study. Cerebrovasc Dis Extra. 2017;7(3):140-152.
24. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L. Heart Failure and Risk of Dementia and Alzheimer Disease. Archives of Internal Medicine. 2006;166(9):1003.
25. Bettencourt P. NT-proBNP and BNP: biomarkers for heart failure management. European Journal of Heart Failure. 2004;6(3):359-363.
26. Dadu R, Fornage M, Virani S, Nambi V, Hoogeveen R, Boerwinkle E et al. Cardiovascular Biomarkers and Subclinical Brain Disease in the Atherosclerosis Risk in Communities Study. Stroke. 2013;44 (7):1803-1808.
27. Vogels R, van der Flier W, van Harten B, Gouw A, Scheltens P, Schroeder-Tanka J et al. Brain magnetic resonance imaging abnormalities in patients with heart failure. European Journal of Heart Failure. 2007;9(10):1003-1009.
28. de la Torre J. Cerebral Hemodynamics and Vascular Risk Factors: Setting the Stage for Alzheimer's Disease. Journal of Alzheimer's Disease. 2012;32(3):553-567.
29. de la Torre J. Pathophysiology of Neuronal Energy Crisis in Alzheimer's Disease. Neurodegenerative Diseases. 2008;5 (3-4):126-132.
30. Jefferson A. Cardiac Output as a Potential Risk Factor for Abnormal Brain Aging. Journal of Alzheimer's Disease. 2010:20(3): 813-821.
31. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology.Eur Heart J. 2008; 29 (19): 2388-442.
32. Cesar KG, Yassuda MS, Porto FHG, Brucki SMD, Nitrini R. MoCA Test: normative and diagnostic accuracy data for seniors with heterogeneous educational levels in Brazil. Arq Neuropsiquiatr. 2019;77(11):775-781.
33. Marrone LCP, Diogo L P, de Oliveira FM, Trentin S, Scalco RS, de Almeida AG, Gutierres LCV, Marrone ACH, da Costa, J. C. Risk factors among stroke subtypes in Brazil. Journal of stroke and cerebrovascular diseases.2013; 22(1), 32-35.
34. Porcello Marrone LC, Farina Brunelli JP, Lutzky Saute R, Henrique Tomasi G, Cecchele Madeira B, Alves Martins W, et al. Thromboembolic sources in stroke patients in South of Brazil. Thrombosis. 2014;2014:753780.

Familial Amyloid Polyneuropathy: A Proposal for an Epidemiological Study Through the Creation of a Virtual Platform

Polineuropatia Amiloidótica Familiar: Uma proposta de Estudo Epidemiológico por meio da Criação de uma Plataforma Virtual

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ABSTRACT

Amyloidosis are characterized by mutations in the gene coding for transthyretin (TTR), located on chromosome 18. TTR is a set of four 127-aminoacid polypeptides structured as homo-tetrameric protein of 56 kDa with a secondary ß sheet structure. It plays the role of thyroxin (T4) carrier, and has a binding domain for retinol (vitamin A). It is synthesized in the liver, although a small quantity is also produced by the choroid plexus, and retinal cells. Mutations of this gene result in loss of tetramer stability. Insoluble amyloid fibrils (AF) are formed and deposited in tissues and organs. The abnormal aggregation of TTR protein trigger several syndromes, such as familial amyloid polyneuropathy (FAP-TTR), cardiomyopathies (CMP), and senile systemic amyloidosis (SSA). It is estimated there are 5,000 to 10,000 cases of FAP-TTR globally.

Objective: The study intends to develop an online platform for the diagnosis of FAP-TTR. The aim is to facilitate the diagnosis process and promote a tool for epidemiological study.

Methods: The project was based on a literature review featuring clinical and epidemiological evidence for the development of a practical platform (applied research).

Results: It was elaborated a platform containing a questionnaire to allow a more dynamic, cheaper, and efficient operation, mediated by a better characterization of the disease to enable its early diagnosis.

Conclusion: The platform might become a valuable resource for the characterization, diagnosis, and future epidemiological study of FAP-TTR.

Keywords: Amyloidosis. Mutation. Transthyretin. Polyneuropathy. Epidemiology

RESUMO

As amiloidoses se caracterizam por mutações no gene codificante da transtirretina (TTR) no cromossomo 18. A proteína TTR compõe-se de uma corrente de polipeptídios de 127 resíduos, que constituem uma proteína homotetramérica de 56kDa com estrutura secundária de folha ß, que serve como proteína de deslocamento para a tiroxina (T4), e uma proteína de ligação ao retinol (vitamina A). O principal local de produção dessa proteína é o fígado, embora uma pequena quantidade seja produzida pelo plexo coroide e pelas células retinianas. O gene codificante da TTR (18q11.2-12) é pequeno (7 kb) e contém quatro éxons. As mutações convertem-se em perda do equilíbrio do tetrâmero proteico. Surgem assim, fibrilas amiloides (FA) em cadeias não ramificadas de 10 a 12 nm de diâmetro e fibrilas indissolúveis, que se condensam nos tecidos e órgãos. As síndromes concernentes ao acúmulo da proteína TTR são: polineuropatia amiloidótica familiar (PAF-TTR), miocardiopatias (MCP) e amiloidose sistêmica senil (ASS). Estimativa recente relatou a existência de 5.000 a 10.000 casos de PAF-TTR no mundo.

Objetivo: O estudo objetiva elaborar uma plataforma de diagnóstico PAF-TTR *on-line* para auxiliar como ferramenta de contribuição para o estudo da epidemiologia e facilitar o diagnóstico.

Métodos: O projeto baseou-se em uma pesquisa bibliográfica capaz de levantar evidências clínicas e epidemiológicas na elaboração de uma plataforma facilitadora (pesquisa aplicada).

Resultados: O resultado alcançado foi a elaboração da plataforma contendo um questionário, que tornará o trabalho dos profissionais mais dinâmico, barato e eficiente, caracterizando melhor a doença e promovendo um diagnóstico precoce.

Conclusão: A plataforma poderá tornar-se recurso valioso para caracterização, diagnóstico e futuro estudo epidemiológico da PAF-TTR.

Palavras-chave: Amiloidoses. Mutação. Transtirretina. Polineuropatia. Epidemiologia

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Conflict of interests: the authors declare no competing interests.
Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

INTRODUCTION

Familial Amyloid Polyneuropathy (FAP) due to transthyretin (TTR) gene mutation is the most common presentation among hereditary amyloidosis and is characterized by high morbidity and mortality rates. It is a rare and progressive autosomal dominant disease caused by transthyretin (TTR) instability, leading to fibrillar protein aggregates and consequent deposits of amyloid fibrils. Once accumulated in the peripheral nervous system, it results in sensory-motor polyneuropathy with dysautonomia[11].

FAP was first reported in the north of Portugal, where the missense variant was most prevalent. Later, the disease was observed in large groups of individuals in Japan and Sweden. It was also reported in Brazil. However, epidemiological data in this country are still very scarce[8, 9]. The diagnosis of FAP-TTR is confirmed by biopsy/genetic test, which allows the identification/visualization of amyloid deposits or amyloidogenic mutation, respectively[2] . The assumed difficulty to access research centers and the need for preliminary treatment reinforce the importance of a facilitating tool for the FAP-TTR diagnosis.

Therefore, a questionnaire was developed based on the literature review, considering the disease's primary clinical and epidemiological aspects. The objective of the questionnaire is to aid in screening FAP-TTR patients. The tool is easy and quick to use. Free access was made available at an online diagnostic platform for FAP-TTR at www.neuropatia.com.br.

METHODOLOGY

This study used two specific techniques: bibliographic and applied research.

Bibliographic research was used to fundament the essential knowledge for the comprehension, analysis, and discussion of the topic in question. To achieve this goal, academically recognized research instruments such as PUBMED and Academic Google platforms were used. The expression familial amyloid polyneuropathy (polineuropatia amiloidótica familiar) was used as the main descriptor.

An exploratory applied research, also called Pilot Study, was necessary at a second moment to achieve the main specific goal: to create an online platform directed to help professionals based on a quick, precise, and low-cost diagnosis of FAP-TTR.

It is important to emphasize that this study aims only at creating a tool that may help in the diagnosis of FAP-TTR. Furthermore, its applicability, sensitivity, and accuracy can be evaluated along with major research reference centers such as CEPRAM (Centro de Pesquisas Antonio Rodrigues de Melo) located in Rio de Janeiro.

A questionnaire was organized to establish the main criteria for the identification of the clinical condition in question. The questionnaire (Attachment 1) contains 11 questions – the first one being only additional information (if the patient has a diagnosis of diabetes mellitus type 2 — DM2, and if they are on a glycemic control).

For the following ten questions, different scores were established, totaling the maximum result of 13 points. The higher the score, the greater the possibility of a positive diagnosis for FAP-TTR. The questions were based on the most relevant symptoms mentioned in the leading scientific studies, also considering the hereditary character of the comorbidity. The weight of each question does not depend on the patient's particular characteristic since the objective is to find similarities in the cases based on standardized data.

Inclusion criteria

- For neurologists who will use the platform in the future:

a) Active neurologists;
b) Neurologists with patients suspected of FAP-TTR diagnosis;

- For participating patients:

a) Patients with suspected diagnosis of FAP: small-fiber neuropathy, symmetric and progressive axonal sensory-motor polyneuropathy, autonomic symptoms, positive family history, bilateral carpal tunnel syndrome which may be associated with non-ischemic cardiomyopathy, ophthalmopathy, and kidney injury of undetermined cause.
b) No age restriction;
c) Both genders

Exclusion criteria

- For neurologists:

a) If the patient's signed consent form (ICF-Informed Consent Form) was not presented by the neurologist;
b) If the acceptance form from the patient was not presented (patient ICF);

- For participating patients:

Patients with a suspected diagnosis of FAP-TTR who do not show written evidence of acceptance (ICF).

An exclusive virtual environment was developed by a programmer linked to a private company so that the Familial Amyloid Neuropathy Platform was made available to any interested professional at www.neuropatia.com.br.

Every time a questionnaire is answered, the results will be sent directly to the Researcher, and will be possible to be analyzed in real-time. A collaborative and networked approach to FAP-TTR management, associated with further epidemiological knowledge, will allow the consistent sharing and the use of new data to improve the prognosis and quality of life of the patients and knowledge about the epidemiology of this disease in Brazil.

This study is in line with resolution number 196/96 and the 1988 Medical Code of Ethics. Since the research is based purely on developing a virtual diagnostic aid platform for FAP-TTR, there is no need for contact or evaluation of the patients by the physicians of the research team. This project was approved by the Antonio Pedro Hospital's Institutional Review Board under number 07284818.0.0000.5243.

RESULTS

The result of this study was the creation of a free, online tool of easy access that physicians can use whenever they suspect the diagnosis of FAP-TTR for a patient.

The platform will provide a structure capable of synthesizing symptoms and generating data that will promote low-cost diagnosis. This resource will also allow the identification of groups that are more likely to present familial amyloid polyneuropathy, and the endemic areas. Hopefully, it will contribute to timely treatment, thereby reducing expenses for patients, government or health insurance.

Plans of a future partnership with the Brazilian reference center CEPRAM and other institutions for applying this platform will allow statistically quantifying its sensitivity and accuracy.

The data collected may be insufficient to predict the risks of developing the disease. However, in the future, the platform will aid the physicians to quantify the minimum chance of the patient being a carrier. This will work as a screening tool to highlight patients at higher risk of developing the disease and who need closer monitoring. The platform as a screening and surveillance tool will also foster the generation of objective features to estimate the probability of disease development.

DISCUSSION

Familial amyloid polyneuropathy (FAP) is a hereditary, rare, progressive condition with high morbidity and mortality. It originates from the instability of the transthyretin protein, generating fibrilar protein aggregates, culminating in a widespread accumulation of amyloid.

Amyloidoses are classified according to the type of amyloid protein that causes the disease: TTR, apolipoprotein A1 (APLA1), or gelsolin (GL)[8].

The PNS and the heart are frequently affected, and most patients show sensory-motor polyneuropathy and dysautonomia. It can also affect leptomeninges and eyes and, less frequently, the kidneys.

Amyloidosis is relatively rare and can be systemic or punctual, spontaneous or hereditary.

TTR is the most common form of hereditary amyloidosis. Pathogenic substitution frequently occurs by the substitution of valine for methionine in position 50 of the gene TTR (Val50Met), nevertheless, other pathogenic substitutions have already been described. Currently, 119 punctual mutations have been identified, including 113 pathogenic variants in TTR gene 20 .

TTR is a plasmatic tetrameric transport protein; each monomer consists of a single polypeptide chain of 127 amino acid residues of about 14,000Da. The entire structure is approximately 56,000Da. The tetrameric structure has surface receptors for retinol-binding proteins (vitamin A), and binding sites for thyroxine (T4). The protein breakdown leads to inadequate aggregation and deposition of amyloid in various systems and organs. Most of the plasma TTR protein is synthesized by the liver, but some are produced in the pigment epithelium of the retina and in the choroid plexus of the brain.

Recently studies have reported TTR synthesis in Schwann cells of the peripheral nervous system (PNS). In humans, the TTR gene has been found in chromosome 18 in *locus* 18p11.1-q12.3. Its size is approximately 7kb, and it has four exons[2] . Most mutations are the product of a single substitution of nucleotides in the TTR gene. The abnormal amyloid fibrils (AF) were found to result from a replacement of valine by methionine at position 50 of the TTR gene (Val50Met). Since then, several other missense variants in the TTR gene have been described, but Val50Met remains the most common mutation.

FAP-TTR was first described by Andrade (1952)[1] in northern Portugal and was later observed in Japan and Sweden. Initially, its occurrence was believed to be restricted to endemic areas, but with the advanced techniques developed by immunohistochemistry and molecular biology, the diagnosis became less underestimated and could be observed even in sparsely isolated cases[2] . In the Brazilian population, the most common mutation is the TTRVal50Met, which is due to the Portuguese colonization[3, 4]. To date, four other missense variants have been reported: TTRVal71Ala[5] , TTRIle107Val[3], TTRAla19Asp[6] , and TTRAsp38Tyr[7] . The age at onset of symptoms varies from the second to the ninth decade of life.

Sensory-motor polyneuropathy occurs in patients with familial amyloid polyneuropathy due to mutation of the transthyretin gene (FAP-TTR) associated with autonomic disorders and non-neurological manifestations. Patients may have different patterns of neuropathy such as focal neuropathies, sensory-motor polyneuropathy, autonomic neuropathy, or any combination of all these types. The most common is length-dependent polyneuropathy. However, the disease may manifest as focal deficits resulting from local amyloid deposits. The medium nerve of the wrist is a place affected by FAP. Some patients present an early deterioration due to autonomic disfunction[9] .

The initial symptoms are burning of the feet, numbness, and loss of thermal sensibility. Symptoms begin in the lower limbs and may extend to the upper limbs.

Motor alterations are related to loss of strength and muscular atrophy in the feet and legs, occurring after sensitive symptoms and usually associated with suppression of deep tendon reflexes[1°].

Cardiovascular, genitourinary and gastrointestinal symptoms are also frequent and there may be orthostatic hypotension, dizziness, fatigue, and blurred vision. Gastrointestinal symptoms include postprandial diarrhea alternating with constipation[19].

The diagnosis of FAP-TTR should be considered in the presence of progressive sensory-motor polyneuropathy associated with at least one of the following: family history of small-fiber neuropathy, autonomic dysfunction, cardiac involvement, diarrhea or constipation, weight loss, bilateral carpal tunnel syndrome, renal involvement, or vitreous opacities[11].

The accepted tools for the definitive diagnosis are tissue biopsy and genetic tests. However, the diagnosis should be guided by clinical findings, followed by investigation with additional tests such as electroneuromyography (ENMG), electrocardiogram (ECG), Holter, and two-dimensional echocardiographic scan should be performed during the follow-up to screen for cardiac involvement.

Genetic tests detect specific amyloidogenic TTR mutations. When patients have suspected FAP, some differential diagnoses should be considered: light chain amyloidosis, chronic inflammatory demyelinating polyneuropathy, and other neuropathies (Fabry disease, leprosy neuropathy, among others). The diagnosis by tissue biopsy/genetic test is based on the identification/visualization of amyloid deposits or amyloidogenic mutation[2]. The FAP mutant gene is detected by DNA sequence analysis in exons 2, 3, and 4 of the TTR gene. It can determine whether the sequences found show mutations compared to the original template deposited in the NCBI (National Center for Biotechnology Information) – Reference Sequence: NG_009490.1. This analysis is performed by PCR (polymerase chain reaction), using the donated biological material as the substrate to confront the template[12]. Genetic testing and tissue biopsy of affected organs are performed in few places in Brazil and are usually expensive, often forcing patients to travel long distances to obtain a definitive diagnosis[13]. There are specific drugs for FAP-TTR that minimize or block amyloid deposits, aiming to better offer quality of life and reduce morbidity and mortality. Gene therapy comes up as promising[2, 9].

Previously, the only treatment was orthotopic liver transplantation (OLT). However, candidates for this therapy were patients with an early diagnosis (before age 50), confirmation of the TTRVal50Met mutation, minimum duration of the disease and greater modified body mass index (mBMI). Innovative procedures have gained prominence in recent years, such as tetramer stabilizers and gene therapies[14].

The classification of the FAP-TTR stages is based on different scores 2.

1. Clinical staging of FAP-TTR:
Stage 0: Asymptomatic;
Stage 1: Light; able to walk; symptoms limited to lower limbs;
Stage 2: Moderate; able to walk but needs assistance;
Stage 3: Serious; confined to a wheelchair or bed with diffuse weakness

2. Polyneuropathy Disability score (PND score):
I: Sensory alterations in the extremities, but able to walk (stage 1)
II: Difficulty walking, but still does not need assistance (stage 1)
IIIa: Walks with unilateral support (stage 2)
IIIb: Walks with bilateral support (stage 2)
IV: Confined to a wheelchair or bed (stage 3).

Considering the mentioned data and the importance of a tool that may help in the diagnosis of patients presenting FAP-TTR, the project focused on elaborating a questionnaire which takes into account the main clinical and epidemiological aspects of the illness as well as its hereditary and an easy access to the virtual environment.

The selection of the questions was based on a previous bibliographic review done before the elaboration of the questionnaire. It was based on the most relevant signs and symptoms of the disease —mentioned in the leading scientific studies— besides valuing the hereditary characteristic of the comorbidity.

The initial question is just an additional information and does not interfere with the final score of the questionnaire. It questions whether the patient presents a diagnosis of *diabetes mellitus* type 2 (DM2), and if there is glycemic control since this disease promotes a small-fiber neuropathy which also figures as a characteristic for FAP diagnosis, therefore being of great importance the previous knowledge whether or not the patient has DM2 in order to exclude factors that might bias in the final result.

Question 01. "Is FAP family history confirmed? —First- or second-degree kinship"— was rated 2. It was considered relevant due to the hereditary characteristic of FAP already identified by Corino de Andrade in 1952, and later having its autosomal dominant inheritance genetically elucidated.

Question 02. "Neuropathic pain? Ex: burning pain, stabbing or shock" —was also rated 2. Initial manifestations are related to sensitive symptoms (small-fiber neuropathy), which mainly affect lower members with numbness or neuropathic pain (burning). Initially, the types of sensitivity committed are pain and temperature, highlighting the importance of valuing such an nonspecific symptom regarding such a crippling disease. Initially, it appears to be a small-fiber neuropathy[17].

Question 03. "Dysautonomia? —Orthostatic hypotension, thermal alterations at extremities—hyperemia/cyanosis, constipation/diarrhea, erectile dysfunction" —was also rated 2.0 as, according to the analyzed literature, a significant amount of patients present dysautonomia. The characterization of these symptoms is described in between brackets in the question, highlighting the fact that the presence of dysautonomia as an initial symptom of the disease tends to make us think of a phenotype of a faster

and more severe progression of the disease, thus justifying the importance of a high score for this question. "Autonomic neuropathy is followed by the installation of sensitive neuropathy and less frequently can present itself as the initial symptom of the disease".[19]

The following questions were valued at 1.0 point each, being considered less significant for the diagnosis although necessary for a deeper view of the disease. When question 04 was elaborated—"Nonischemic cardiopathy? Do not include patients with hypokinesia, segmental akinesia"—it was considering cardiac amyloid deposit, which is observed in patients with ATTR.

Question 05. "Bilateral carpal tunnel syndrome?" — Was a must since it refers to a frequently described symptom of FAP-TTR patients due to the component of amyloid deposit on the median nerve, which generates a bilateral compressive syndrome. The amyloid deposits can accumulate in specific areas generating focal lesions such as bilateral carpal tunnel syndrome—more severe and less responsive to decompression surgery than idiopathic forms, described as an early symptom of ATTR[19].

Question 06. "Progressive symmetric sensorimotor polyneuropathy?"—The objective is to identify the main routine and clinical aspect of the disease, a neuropathy that initially affects the lower limbs with sensitive symptoms, evolving to motor findings and later affecting the upper limbs. It is an axonal length-dependent sensory-motor neuropathy associated with autonomic symptoms with initial impairment of small fibers.

Question 08. "Probable ophthalmopathy?—Abnormal vessels in the conjunctiva, alteration of the shape of the iris, amyloid deposition in the retina/vitreous/crystalline/conjunctiva, not including isolated ischemic or hypertensive retinopathy, or glaucoma"—seemed relevant since not too rarely amyloid deposit occurs in the vitreous body justifying the ophthalmological symptoms in the general context of such entity.

Question 09. "Doubtful family history? Family of Portuguese origin, first degree relative with a history of severe restrictive heart failure at a young age/affected with an inability to walk by severe sensory-motor polyneuropathy"—is justified in the same way as Question 01; however, in this case, the family diagnosis is suspected, not established.

Question 10. "Weight loss of undetermined cause?"—the choice of this question is imperative since weight loss of undetermined cause is highly related to this disease. Dysautonomia contributes to the alternation between diarrhea and constipation, leading patients to a significant weight loss. Besides the dysautonomic symptoms, throughout the disease's progression, the patient presents sustained weight loss that is not justified solely by their gastrointestinal symptoms [9].

The questionnaire was prepared in a structured way to elucidate the ethnic aspects of the patient, hence trying to identify his/her origin and the clinical aspects of the disease.

Regarding the evaluation criteria, the score chosen for each question does not rely on the patient's particular characteristics, since the aim is finding whatever there is in common in the analysis, allowing thus to build a platform that will present the data in a standardized manner.

The FAP-TTR diagnosis platform can be accessed easily through a link available online containing assertive questions about the condition, scoring the answers in different scales, and generating a data bank for future characterization of the clinical/epidemiological aspects of the disease.

The description of the processes used is relevant. Although there are no other similar instruments for comparison, it reveals knowledgeable strategies based on scientific evidence on the methodological easiness and challenges found in different events and studies. It is often impossible to obtain a satisfactory result through traditional data collection approaches, such as by presential interviews, by telephone or by written questionnaires. These methods do not generate results quickly and efficiently, and also may be expensive In addition, there is the magnitude of the technological resources available nowadays and the fact that the participation rates in epidemiological studies drop when they are not implemented through modern means and methods[21].

With the expansion of internet access throughout the world, studies using virtual environment have shown a fruitful trend in data collection, being the preferred method by most research participants[22]. Even though the use of the internet in research groups is done mainly by young people, the use of this tool has grown lately. Furthermore, it is a resource that allows those involved in the study to establish agile and rigorous contact with the predictions, answers, data, probabilities, and other theories raised.

In Europe, about 85% of homes have access to the internet. In Brazil, the proportion reached 120.7 million people in 2017. According to the study, in 2008, users were no more than 34%, and in 2017 they were already 74.9%. Considering these data, virtual questionnaires are an alternative method for obtaining answers in scientific research. The use of a virtual tool also disseminates the necessary information, enabling the development of research in the area of epidemiology of FAP-TTR. Thus, the objective of this study was to develop the FAP-TTR diagnostic platform through an online questionnaire and

disseminate it in a virtual environment, to systematize data collection related to the disease.

CONCLUSION

Knowledge about Portuguese heritage, the difficulty of access to large diagnostic centers, the high cost of the confirmatory tests, and the high morbidity and mortality rates of this condition support that this tool can contribute to an early diagnosis and an adequate and timely treatment. Moreover, it is worth highlighting the advent of new therapeutic approaches based on genetic replacement. Therefore, all hypotheses of the need for the applicability of this tool in the near future are justified.

Concluding, this platform will serve as an analysis tool that considers the disease itself and the diseased patient. Due to its low cost and great benefit, it can be used constantly in the daily routine of specialists. Hopefully, the platform will contribute to the improvement and agility of the diagnosis definition, facilitating both early treatment onset and the budget estimation for the patient, the government/the health insurance. In addition, the platform might enable the monitoring of the therapeutic response after the diagnosis determination.

REFERENCES

1. Andrade C. A peculiar form of peripheral neuropathy: Familial atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain. 1952; 75:408-427.
2. Ando Y. et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis. 2013; 8-31.
3. Cruz MW. Regional differences and similarities of familial amyloidotic polyneuropathy (PAF) presentation in Brazil. Amyloid. 2012;19:65-67.
4. Saporta MA, Zaros C, Cruz MV, André C, Misrachi M, Bonaiti-Pellié C, Panté-Bordeneuve V. Penetrance estimation of TTR familial amyloid polyneuropathy (type I) in brazilian families. Eur J Neurol. 2009;16:337-341.
5. Marques WJ, Borghetti VS, Marques VD, Neder L, Ruiz FBJ, Barreia AA. Clinical and electrophysiological correlates of TTRala71 amyloid neuropathy. Arq Neuropsiquiatr. 2010;68: 303-305.
6. Ferreira P, Dant´anna O, Varjão N, Lima C, Novis S, Barbosa RV, Caldeira CM, Rumjanek FD, Ventura S, Cruz MW, Foguel D. Structure-base analysis of a A19D a variant of transthyretin involved in familial amyloid cardiomyopathy. PLoS One. 2013; 824.
7. Lavigne-Moreira C, Marques VD, Lourenço CM, Cabrini DI, Nunez JC, Herrera RF, Maqrues WJ. Transthyretin Aps38Tyr: a new mutation associated to a late onset neuropathy. J Peripher Nerv Syst. 2015; 20:60-62.
8. Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. J Neurol Neurosurg Psychiatry. 2015; 86:1036-1043.
11. Conceição I. et al. Red-flag symptom clusters in transthyretin familial amyloid polyneuropathy. J Peripher Nerv Syst. 2016; 21:5-9.
12. Zhen DB, Swiecicki PL, Dispenzieri A, Mauermann ML, Gertz MA. Frequencies and geographic distributions of genetic mutations in transthyretin- and non-transthyretin-related familial amyloidosis. Clin Genet. 2015; 88:396-400.
13. Costa J, Swash M, Carvalho M. Awaji criteria for the diagnosis of amyotrophic lateral sclerosis: a systematic review. Arch Neurol. 2012; 69:1410-1416.
14. Carr AS, Pelayo-Negro AL, Evans MRB, Laurà M, Blake J, Stancanelli C, Iodice V, Wechalekar AD, Whelan CJ, Gilmore JD, Hawkins PN, Reilly MM. A study of the neuropathy associated with transthyretin amyloidosis (ATTR) in the UK. J Neurol Neurosurg Psychiatry. 2006;0:1-8.
15. Connors LH, Lim A, Prokaeva T, Roskens VA, Costello CE. Tabulation of human transthyretin (TTR) variants. Amyloid: J. Protein Folding Disord. 2003; 10:160-184.
16. Takei Y, Hattori T, Yazaki M, Tokuda T, Urasawa N, Kanai S, Ikeda S. Transthyretin Tyr69-to-Ile mutation (double-nucleotide substitution in códon 69) in a Japanese familial amyloidosis patient with cardiomyopathy and carpal tunnel syndrome. Amyloid. 2003;10:25-28.
17. Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. Muscle Nerve. 2007;36:411-423.
18. Ikeda S. et al. Familial transthyretin-type amyloid polyneuropathy in Japan: clinical and genetic heterogeneity. Neurology. 2002; 58:1001-1007.
19. Planté-Bordeneuve V, Gerard S. Familial amyloid polyneuropathy. Lancet Neurol. 2011; 10:1086-1097.
20. Giampaolo M, Wechalekar AD, Palladini G. Systemic light chain amyloidosis: An update for treating physicians. Blood. 2013;121(26):5124-30.
21. GALEA Sandro, Tracy Melissa. Participation rates in epidemiologic studies. In: AnnEpidemiol. Sep; 17(9), p.643-53, 2007.
22. VAN GELDER, Marleen M H J; BRETVELD, Reini W, ROELEVELD Nel. Webbased questionnaires: the future in epidemiology? In: Am J Epidemiol. Dec 1, 172(11), p.1292-8, 2010.

Attachment 1

STRUCTURED QUESTIONNAIRE
Title of the project: Familial Amyloid Polyneuropathy: A Proposal for Epidemiological Study Through the Creation of a Virtual Platform

Researcher: Osvaldo José M. do Nascimento

IDENTIFICATION:
Referred by Dr.: _____
Physician's phone: (___)_____
Patient's name: _____
Gender: (__) F (__) M
Patient's phone: (___)_____
Date of birth: ___/___/___ (dd/mm/yyy or mm/dd/yyy)
Address: _____

ADDITIONAL INFORMATION:
1) Diagnosed for Type 2 Diabetes mellitus? If YES, Classify by:
WELL CONTROLLED: fasting blood glucose <140 mg/dL and/or Hb <7;
PARTIALLY CONTROLLED: fasting blood glucose between 140-200mg/dL and/or Hb between 7-8;
UNCONTROLLED: fasting blood glucose >200mg/dL and/or Hb>8;
NOT POSSIBLE TO CLASSIFY

Questions		Points
1	Family history of PAF confirmed? (first or second degree relationship)	2
2	Neuropathic pain? (ex.: burning pain, pang pain or shock pain)	2
3	Dysautonomia? (orthostatic hypotension, thermal alterations in extremities—hyperemia/cyanosis, constipation/diarrhea, erectile dysfunction)	2
4	Non-ischemic cardiopathy? (do not include patients with hypokinesia, segmental akinesia)	1
5	Bilateral carpal tunnel syndrome?	1
6	Progressive symmetrical sensory-motor polyneuropathy?	1
7	Kidney injury? (microalbuminuria of undetermined cause, exclude diabetic patients)	1
8	Suspected ophthalmopathy? (abnormal conjunctiva vessels, iris shape alteration, amyloid deposition in retina/vitreous/iris/crystalline/conjunctiva; do not include isolated ischemic or hypertensive retinopathy or glaucoma, familial carpal tunnel syndrome?)	1
9	Suspicious family history? (Family of Portuguese origin, first degree relative with history of serious illness with severe restrictive cardiac insufficiency at young age and/or inability to walk due to severe sensory-motor polyneuropathy)	1
10	Weight loss of undetermined cause?	1
TOTAL		(_____)

Parkinson's disease and periodic limb movement in sleep

Doença de Parkinson e movimentos periódicos dos membros durante o sono

Lucas Lima Najar[1]; Leonardo Figueira Pouchucq[2]; Iara Louise Marques Alves[2]; Júlio Bernardo Ferreguett[2]; Lucas Rodrigues Diniz[2]; Marleide da Mota Gomes[3]

ABSTRACT

Parkinson's disease is a neurodegenerative disease understood as a complex syndrome with motor and non-motor symptoms, including sleep-related conditions, such as periodic limb movements in sleep (PLMS). This paper presents issues regarding Parkinson's disease, motor and non-motor symptoms, sleep physiology, and PLMS. In conclusion, both conditions seem to be correlated through impairment of the dopaminergic system.

Keywords: Parkinson's disease, nonmotor symptoms, sleep, periodic limb movement.

RESUMO

A doença de Parkinson é uma doença neurodegenerativa entendida como uma síndrome complexa com sintomas motores e não motores, incluindo condições relacionadas ao sono, como movimentos periódicos dos membros durante o sono (MPMS). Este artigo apresenta questões relacionadas à doença de Parkinson, sintomas motores e não motores, fisiologia do sono e MPMS. Em conclusão, ambas as condições parecem estar correlacionadas por comprometimento do sistema dopaminérgico.

Palavras-chave: Doença de Parkinson, sintomas não motores, sono, movimento periódico dos membros.

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Conflict of interest: There's no conflict of interest to declare.
Funding: There's no funding to declare.

INTRODUCTION

Patients with Parkinson's disease (PD) have a plethora of motor and non-motor symptoms. These last include periodic limb movements in sleep (PLMS) that are repetitive movements, most typically in the lower limbs. However, periodic limb movement disorder (PLMD) happens when patients with PLMS have associated clinical sleep disturbance or a complaint of daytime fatigue. Both PD and PLMD may respond to dopamine agonists. This association raises many issues regarding shared pathophysiology, as will be unfolded [1] .

PARKINSON'S DISEASE

PD is a progressive neurodegenerative disease capable of causing various motor and non-motor symptoms which usually develop slowly, mainly affecting people over 65 years of age, with a predominance of males over females.

The diagnosis of PD depends on the motor symptoms caused by clinical effects of dopamine deficiency, so most patients are usually diagnosed when the disease progression is advanced and about 50% of dopaminergic neurons in the substantia nigra (SN) are already absent, with treatment start delay [2] .

Clinical effects of dopamine deficiency include bradykinesia, rigidity, and tremor at rest, usually manifesting asymmetrically, besides postural instability [2]. Non- motor symptoms include mood disorders, autonomic dysfunctions, fatigue, pain, cognitive changes, gastrointestinal dysfunctions, perceptual distortions, attention deficit and sleep disorders, which is one of the commonly reported non-motor markers in patients with PD, as well as in other neurodegenerative disorders (atypical parkinsonian syndromes) 3 . Many of these symptoms are included in Figure 1.

Olfactory loss, REM sleep behavior disorder, constipation and subtle motor parkinsonism are among the strongest predictors to clinical PD presentation, and the period lag between the onset of these symptoms and the onset of PD varies from 5 years, for motor symptoms, to over 20 years, for autonomic symptoms [2] .

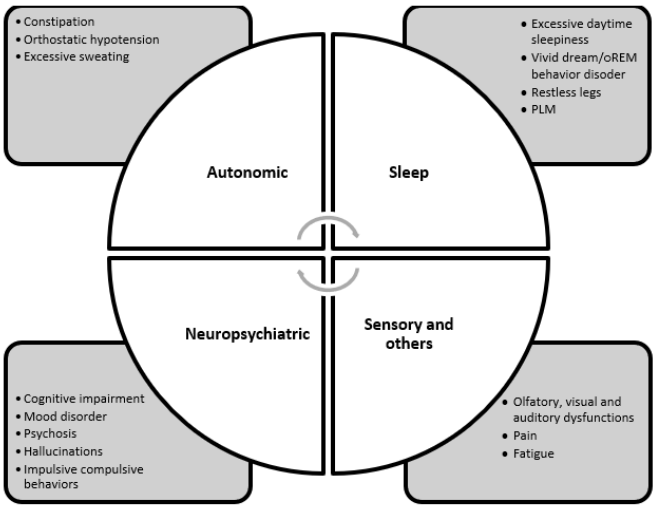

Figure 1. Parkinson disorders non-motor symptoms[2].

The etiology of PD is poorly understood, but the interaction between genetic factors and environmental risk factors seems to contribute to its neuropathogenesis. Probably multiple etiologies contribute jointly to the disease's development.

Neuroimaging testing can provide diagnosis confirmation and prevent possible misdiagnosis due to PD's overlapping symptoms with other neurodegenerative disorders, and DaTscan enables assessment of affected nigrostriatal dopaminergic neurons terminals for PD investigation. PD patients tend to have *striatum* (caudate and putamen) minor signal on DaTscan related to dopamine deficiency [4].

The predominant symptoms of PD are caused by the loss of dopaminergic neurons in the substantia nigra, and the nigrostriatal degeneration is a result of the depletion and final loss of the neurotransmitter dopamine at the synaptic terminals of striated neurons. As a result, replacement therapy is required. Other functional brain networks are also usually affected, such as those of mood, behavior, and cognition. Also, PD is linked to the abnormal presence of Lewy bodies, insoluble fibrillar aggregates formed by a protein present in the human brain called alpha-synuclein[4].

As presented in Figure 2, based on Braak et al. 2003 apud Keo et al. [5] the PD degenerative process would begin in non-dopaminergic structures that ascends caudo-rostrally from the lower brainstem and forebrain, into the cerebral cortex. Six PD Braak´s stages are presented sequentially depending on the accumulated Lewy bodies during disease progression. This staging model implicates environmental factors, such as toxins or inflammatory agents, which can trigger the aggregation of α-synuclein, the Lewy body, that come into contact with olfactory and/or enteric neurons. The aggregated α-synuclein spreads toward the central nervous system via the olfactory bulb and the vagus nerve, but probably genetic factors are likely to contribute to PD.

It is beyond the scope of this article to discuss the mechanisms of formation and spread of the misfolded prion-like alpha-synuclein through the brain and synaptically coupled neuroanatomical tracts. However, this would justify much earlier symptomatology when compared to the classical one. It is illustrated in six different stages. The former are marked by non-motor symptoms, then motor symptoms often displayed around the mid-stage state, and cognitive symptoms arising later.

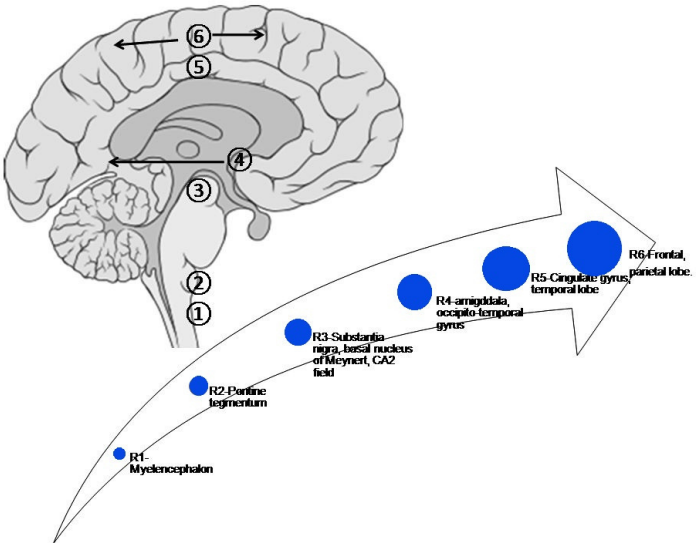

Figure 2. Staging system PD progression proposed by Braak et al. based on Keo et al. findings[5].

SLEEP CHARACTERISTICS

Sleep has an essential role in health, and around one-third of the day is usually dedicated to it. Sleep allows brain restoration when many sleep processes are carried out, such as defence against oxidative stress and clearance of waste proteins from the brain through the glymphatic system. Its lack induces many negative repercussions, e.g., in heart, kidney disease, high blood pressure, diabetes mellitus, memory loss, and stroke[1].

Most adults need around 8 hours of sleep, but with aging, due to decreased proportion of slow-wave sleep periods, the propensity to sleep, as well as its duration, decreases, and sleep become more fragmented.

Sleep progresses through 4-6 cycles, each of between 90 and 110 min, in a series of 4 stages of sleep included in two main types of sleep, with brain wave patterns particular to each one. There is Non-rapid eye movement sleep (NREM sleep – N1, N2, and N3), and REM sleep is characterized by rapid eye movement (REM), increased breathing and brain activity[1].

Within the 24 hours of the sleep-wake circadian cycle, determined by external and internal determinants, there is also the ultradian cycle – sleep phases immersed in 4-6 cycles each night. The light/dark cycle resets the activity of the suprachiasmatic nucleus (SCN), master pacemaker, via the retina and the retinohypothalamic tract. Other environmental stimuli can also entrain the SCN. Control of the peripheral clocks mainly by the central pacemaker occurs via a combination of neural and hormonal signals[1].

Paradoxical sleep is characterized by the brain and other body systems higher activation accompanied by higher muscle relaxation. This results in the expression of dreams due to increased brain activity, but with voluntary muscles immobilized. At the beginning of the night, NREM sleep is more profound and proportionally higher. However, as the night progresses, NREM sleep becomes more superficial, with a relatively higher presence of REM sleep compared to the beginning of the night.

The sleep-wake rhythm is one of the circadian rhythms that include it and almost all other bodily processes such as temperature, blood pressure, heart rate, hormone secretion, physical, mental, and behavioral changes. These rhythms respond to internal or external stimuli, mainly to ambient lighting[1].

The SCN internally controls the circadian system. It is the body's central biological clock in 24 hours of body functions. The input to SCN comes from specialized retinal ganglion cells that introduce light input and contribute to the restart of the sleep-wake cycle. However, these pathways are damaged in PD, as it occurs in dopaminergic retinal degeneration[1].

Melatonin levels increase at the end of the day, signaling the night and preparing for sleep. Sleep and basal ganglia disorders may have a common substrate, and Hasegawa et al. suggest that the latter may play an integral role in the sleep-wake cycle, specifically contributing to an oscillatory network in slow-wave sleep, which favors neural plasticity, besides the activity during REM sleep would allow the action of cognitive and emotional connections[6].

Periodic limb movement in sleep and Parkinson's disease

PD patients frequently present sleep disorders as nonmotor symptoms, which have a great impact on their quality of life. In Zhu et al's[7] cross-sectional study, approximately one-quarter of the PD patients suffered from sleep disturbances with a high prevalence of cognitive dysfunction (39.8%). In these patients, a higher percentage of sleep disorders was observed. In those with cognitive dysfunction, the nonmotor symptoms – hallucinations/delusions score was the most critical risk factor for sleep disorders. Nonmotor symptoms in early-stage PD are highly associated with the level of sleep quality[7].

The correlation between sleep disorders and PD is reinforced by studies that show REM sleep behavior disorder (RBD) as an early indicator for PD diagnosis before motor symptoms, with present data insinuating that up to 90% of patients with RBD develop some form of parkinsonism. Studies also point out that excessive daytime sleepiness may be present in both the early and late stages of PD[4].

PLMS is diagnosed on a clinical and neurophysiological basis, and it is recorded during Nocturnal Polysomnography using anterior tibialis Electromyogram (EMG) recordings. Besides, according to the American Academy of Sleep Medicine (AASM), its diagnosis may be given if the limb movements[8-12]: i. 0.5–10 sec in duration; ii. Amplitude > 8 μV above baseline; iii. In a sequence of ≥ 4 movements; iv. Onsets of consecutive leg movements ≥ 5 and ≤ 90 sec. The PLMS must be distinguished from leg movements that occur if the patient is waking up for other reasons, like sleep apnea.

Besides, there is Restless Legs Syndrome (RLS) that is commonly associated with sleep disturbance and with PLMS. PLMS and RLS are not the same. While the majority of RLS patients also have PLMS, many patients with PLMS do not have RLS. There are four main criteria for diagnosing RLS: irresistible need to move legs that feel uncomfortable; symptoms occur or worsen when there is inactivity; symptoms are relieved by moving the legs or rubbing them; symptoms worsen at night.

As already mentioned, PLMS presents as repetitive leg movement during night sleep, which is recorded through PSG (Figure 3). A study performed on 1107 subjects recruited from the German population showed, regarding PLMSI >15/hour: 32.4% prevalence, besides a positive association, in at least one of the cohorts, of factors like age, male gender, RLS, physical inactivity, current smoking, diabetes, antidepressant use and lower serum magnesium. PLMS indices were higher in men, as also occurs in PD[9].

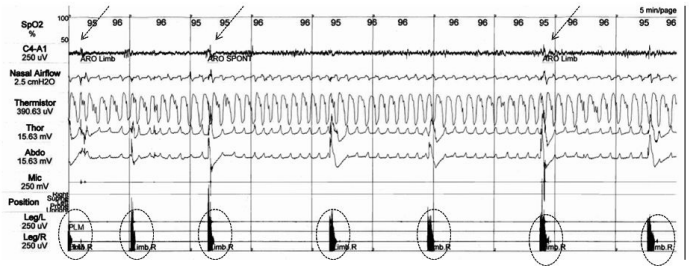

Figure 3. Periodic leg movements during sleep (PLMS) were recorded on a 5-minute polysomnogram page, demonstrating 7 PLMs (circles) with arousal peaks (arrows).

Zhang et al.[10] performed a systematic review of the literature exploring differences in PSG between PD patients and controls and they concluded that PD patients have poor quantity and quality of sleep. That work revealed an increased PLMI in PD patients when compared to healthy controls [10], and in the study by Covassin et al.[11] it was found to be more common in patients with PD of higher severity.

PLM has been suggested to be associated with a shallower and fragmented sleep in the general population, such as an increased amount of stage N1 and decreased slow-wave sleep (SWS). This is consistent with the findings that increased PLMI of PD patients is associated with increased N1 and decreased SWS percentage in PD patients when compared to controls, suggesting that PLMS is a significant contributor to PSG measured sleep abnormalities in PD patients.

The pathophysiology of PLMS is unknown, but there are reports of a negative correlation between the binding of the striatal tracer and PLMI, as reported in a study of PSG and SPECT [4]. As for the pathophysiology of PLMS during PD sleep, it is also not fully understood. However, a reduction in striatal dopamine transporter binding has been suggested in PD patients with PLMS compared to those without PLMS. Furthermore, given the importance of the dopaminergic system in sleep-wake regulation, sleep quality may be worse in parkinsonian patients with PLMS compared to those without it. Thus, the affected dopaminergic system could impact on sleep of PD patients, by increasing PLMI[10].

However, more evidence suggests common pathophysiological pathways, as nigrostriatal degeneration can promote PLMS as well as PD, and there is also a relationship between the number of leg movements and the loss of nigrostriatal dopaminergic cells. In addition, dopaminergic drugs provide benefits for PD and PLMS.

Although RLS and PD are both related to central dopaminergic dysfunction, there is no definitive evidence of an association between both conditions[4]. There is no clear pharmacological management of PLMS in PD available, but the treatment of RLS includes avoidance of medications known to exacerbate RLS and iron replacement in individuals with proven iron deficiency. Dopamine agonists are commonly used, but there is concern regarding the possibility of augmentation phenomenon[1].

CONCLUSION

There is a higher prevalence of PLMS in PD and similar pathophysiology between them.

REFERENCES

1. Keir Lindsay, Breen D. New awakenings: current understanding of sleep dysfunction and its treatment in Parkinson's disease. Journal of Neurology 2019; 267. 10.1007/s00415-019-09651-z.
2. Hustad E, Aasly JO. Clinical and Imaging Markers of Prodromal Parkinson's Disease. Front Neurol. 2020 May 8;11:395.
3. Bhattacharya A, Lenka A, Sunny A, Kamble N, Pal P. Overview of sleep disturbances and their management in Parkinson plus disorders. Journal of the Neurological Sciences 2020; 415. 116891. 10.1016/j.jns.2020.116891.
4. Yousaf T, Pagano G, Wilson H, Politis M. Neuroimaging of Sleep Disturbances in Movement Disorders. Front Neurol. 2018:767.
5. Keo A, Mahfouz A, Ingrassia AMT, et al. Transcriptomic signatures of brain regional vulnerability to Parkinson's disease. Commun Biol 2020;3(1):101.
6. Hasegawa H, Selway R, Gnoni V, et al. The subcortical belly of sleep: New possibilities in neuromodulation of basal ganglia? Sleep Medicine Reviews 2020; 52. 101317. 10.1016/j.smrv.2020.101317.
7. Zhu J, Zhong M, Yan J, et al. Nonmotor Symptoms Affect Sleep Quality in Early-Stage Parkinson's Disease Patients With or Without Cognitive Dysfunction. Front Neurol. 2020 Apr 21;11:292.
8. Stefani A, Högl B. Diagnostic Criteria, Differential Diagnosis, and Treatment of Minor Motor Activity and Less Well-Known Movement Disorders of Sleep. Curr Treat Options Neurol. 2019 19;21(1):1.

9. Szentkirályi A, Stefani A, Hackner H, et al. Prevalence and associated risk factors of periodic limb movement in sleep in two German population-based studies. Sleep 2019;42(3): zsy237.
10. Zhang Y, Ren r, Sanford LD, et al. Sleep in Parkinson's disease: A systematic review and meta-analysis of polysomnographic findings. Sleep Medicine Reviews 2020; 51: 101281, ISSN 1087-0792.
11. Covassin N, Neikrug AB, Liu L et. al. Clinical correlates of periodic limb movements in sleep in Parkinson's Disease. J Neurol Sci. 2012. May 15; 316(1-2): 131–136.
12. Choi JW, Song JS, Lee YJ, Jeong DU. Periodic Limb Movements in Sleep is Associated with Increased Mortality. Psychiatry Investig. 2017. 14(5):669-673.

Relato de Caso

5p13.2 Chromosomal duplication syndrome: case report and literature review

Síndrome de duplicação cromossômica 5p13.2: relato de caso e revisão da literatura

Carollina Tinoco [1] , Eduardo Silva [1] , Gabriela Carvalho [1] , Claudia Utagawa [1] ,

ABSTRACT

Chromosome 5p13 duplication syndrome represents a contiguous gene syndrome involving duplication of several genes on chromosome 5p13. Some clinical phenotypes are related to it, such as: obsessive-compulsive behavior, small palpebral fissures, intellectual disability, global development delay and ocular hypertelorism. The exact mechanism behind these changes has not well known and further studies are needed for this purpose. Since it is a rare and uncommon clinical situation, the case report contributes to the knowledge of the disease and early diagnosis. This condition mainly affects the cognitive neuromuscular system. We describe an 8-year-old Brazilian patient with the duplication of chromosome 5p13.2, karyotype, whose neurodevelopmental evaluation presented cognitive impairment, severe language delay and atypical physical examination, with ocular hypertelorism, right auricular tags, congenital heart defect and long fingers. The patient was diagnosed by comparative genomic hybridization (CGH)-array revealing a 204Kb of DNA duplication. The exact mechanism behind these structural disorders is still unclear and further studies are needed for this purpose. Nevertheless, the diagnostic suspicion of this genetic alteration that, in general, presents late diagnosis, should be considered to enable better clinical support to the patients and family genetic counseling..

Keywords: 5p13.2 duplication, genomic segmental duplications, Comparative Genomic Hybridization.

RESUMO

A síndrome da duplicação do cromossomo 5p13 representa uma síndrome genética contígua envolvendo a duplicação de vários genes contidos nesta região. Alguns fenótipos clínicos estão relacionados com ela, tais como: comportamento obsessivo-compulsivo, fissuras palpebrais pequenas, déficit intelectual, atraso no desenvolvimento global e hipertelorismo ocular. Por ser uma situação clínica rara, o relato do caso contribui para a disseminação do conhecimento acerca da condição, assim como para seu diagnóstico precoce. Descrevemos uma paciente brasileira de oito anos com a duplicação do cromossomo 5p13.2, que na avaliação do neurodesenvolvimento apresentou comprometimento cognitivo, grave atraso da linguagem e dismorfismos como hipertelorismo ocular, apêndice auricular direito, sopro cardíaco, relacionado a defeito do septo ventricular, e dedos alongados. A paciente foi diagnosticada por meio da pesquisa molecular (CGH)-array com ganho de 204Kb de DNA. O mecanismo exato por trás dessas alterações estruturais ainda não está claro e são necessários mais estudos para este fim. Não obstante, a suspeita diagnóstica dessa alteração genética que, em geral, apresenta diagnóstico tardio, deve ser
aventada para viabilizar melhor suporte clínico aos pacientes e aconselhamento genético familiar.

Palavras-chave: Duplicação 5p13.2, Duplicações Segmentares Genômicas, Hibridização Genômica Comparativa

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Conflict of interest: The author reports no conflicts of interest in this work.
Funding statement: The authors declare that this study has received no financial support
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INTRODUCTION

Chromosome 5p13 duplication syndrome represents a contiguous gene syndrome involving duplication of several genes on chromosome 5p13, including NIPBL[4] . Some clinical phenotypes are related to it, such as obsessive-compulsive behavior, short palpebral fissures, intellectual disability, global development delay and ocular hypertelorism[5] .

It is noteworthy that neurological development disorders such as intellectual disability and autistic spectrum disorders (ASD) are often caused by genomic copies variants, thus the phenotype and its clinical consequences are not easily determinable [6] . Therefore, in order to classify new CNVs the application of molecular genetic tests, such as comparative genomic hybridization (CGH) or chromosomal microarray (CMA) is desirable. [2]

CASE REPORT

The patient was an 8-year-old Brazilian girl, first referred to the clinical genetics outpatient service by the neurology service at the age of eight months, due to hypotonia, facial dysmorphisms, ventricular septal defect, autism spectrum disorder (ASD) and delayed neuropsychomotor development. Pregnancy and the neonatal period were unremarkable. The birth weight and height were 2870g and 46cm, respectively. The head circumference was 36cm and the Apgar score was 9 at 1 min and 10 at 10 min of age. She was born at term (39 weeks and 5 days).

On physical examination, anthropometric measurements showed a weigh of 28,5Kg (50th and 85 th centile), a height of 126cm (15 th and 50 th centile), head circumference of 51cm (50th centile) and an inner canthal distance of 4,2 cm (>+2SD). The patient presented peculiar facies, upslanting palpebral fissures, ocular hypertelorism, preauricular tags in the right side, heart murmur and elongated fingers. Thus, the first diagnostic hypothesis was a malformation syndrome, and a karyotype was requested. Nevertheless, the next contact with the patient was at 5 years of age, with a normal 46, XX karyotype and a diagnosis of global developmental delay was given.

A microarray comparative genomic hybridization approach was recommended, and the analysis revealed a microduplication in chromosomes 5p13.2 of 204Kb of DNA. Small copy number variations in 10p15.2, 11p15.5 and 11p15.4 with no clinical significance were present and considered non-specific. Based on clinical the clinical findings and the array-CGH results, the diagnosis of a 5p13.2 duplication syndrome was established.

The genetic diagnosis was made at the age of 8 years. Nowadays, she presents a cognitive deficit and a severe speech delay approached through multidisciplinary follow-up care.

DISCUSSION

The 5p13 duplication is categorized as a recognizable syndrome (OMIM #613174) that it represents a contiguous gene syndrome involving duplication of several genes on chromosome 5p13, including NIPBL (608667)[4] .

Most patients with this chromosome abnormality present with development delay and facial dysmorphisms. Micrognathia and hypertelorism are the most frequent findings in this group of patients. No single specific dysmorphic characteristic or development trait is common to all patients. Even though ocular anomalies such as proptosis, epicanthic folds and short palpebral fissures are present in most patients, including upslanting palpebral fissures seen in our patient as other two patients reported. Furthermore, ear malformations are described as a common finding of the syndrome, but only our patient presented with a right preauricular tag (Box).

Hypotonia is one of the most frequent clinical findings, but over half of the patients show some limb abnormalities, especially long fingers, present in five patients. Other described clinical finding was the single palmar crease. Our patient presented with all neurodevelopmental clinical findings (Box).

Regarding mechanisms involved in the formation of 5p13 duplication, most patients have a microduplication of a small region in the chromosome 5. Nonetheless, one of them differs, showing a small supernumerary marker chromosome (sSMC), derived from the chromosome[5] . This implies that more than one physiopathologic process might be related to the 5p13.2 syndrome (Box).

NIPBL is a gene involved in most 5p13.2 duplication syndrome and it is probably the main feature responsible for the clinical picture[6 - 9] , even though the small amount of 5p13.2 duplication cases hampers to establish a clear genotype-phenotype correlation[1°] . There seems to be an association foremost likely with autism spectrum disorder (ASD), but the process behind the genetic mechanism varies and most of the phenotypic characteristics largely differ among them[8, 10].

SLC1A3 gene also seems to play an important role as a possible ASD risk factor[6] , currently being described in nine patients [6 - 8, 11, 12] . Also, sixteen out of seventeen patients found in the literature presents some features observed in ASD, such as development delay even with different genes duplicated in the 5p13 region. As shown in some other cases, our patient received an ASD diagnosis during childhood (Box).

NIPBL seems to be the most dosage-sensitive gene and that CNV of these genes, such as 7q11.23, 16p13.11 and 22q11, relates to a variety of phenotypes[9] and ten patients share a critical region including the NIPBL gene. For that, it is considered the main candidate gene for the 5p13.2 duplication findings [6, 8, 9] . Hence, nowadays only a few reports of NIPBL duplications are available in the literature[1°] . It is likely that multiple genes are involved in phenotype characteristics determination.

CONCLUSION

Analyzing current available data on 5p13.2 duplication syndrome, it is not possible to categorically state which gene is responsible for any specific phenotype. Also, we could not find any relationship between the size of the duplication and the clinical expression of the syndrome. Furthermore, different mechanisms involved may alter the syndrome. More studies are necessary to characterize the clinical phenotype of 5p13.2 patients and which genes are of relevance in this microduplication syndrome. The pathophysiology in this syndrome still remains unknown.

Abbreviations

ASD, autism spectrum disorder; ADHD, Autism or Attention deficit hyperactivity disorder; CNV, Copy number variations; CGH, comparative genomic hybridization.

Ethical Approval

The research was approved by Ethical Committee of the Plataforma Brasil (CAAE 37118620.7.0000.5237). The patient's mother has signed informed assent forms. She also signed forms giving their consent for the use of case details and images for publication and for scientific purposes.

REFERENCES

1. Yang X, Song Z, Wu C, et al. Constructing a database for the relations between CNV and human genetic diseases via systematic text mining. BMC Bioinformatics. 2018;19 (S19) :528. doi:10.1186/s12859-018-2526-2
2. Robson SC, Chitty LS, Morris S, et al. Evaluation of Array Comparative genomic Hybridisation in prenatal diagnosis of fetal anomalies: a multicentre cohort study with cost analysis and assessment of patient, health professional and commissioner preferences for array comparative genomic hybridisation. Effic Mech Eval. 2017;4(1):1-104. doi:10.33 10/eme04010
3. do Nascimento PM, Medeiros IG, Falcão RM, Stransky B, de Souza JES. A decision tree to improve identification of pathogenic mutations in clinical practice. BMC Med Inform Decis Mak. 2020;20(1):52. doi:10.1186/s12911-020-1060-0
4. L. Kniffin C. Online Mendelian Inheritance in Man, OMIM. CHROMOSOME 5p13 DUPLICATION SYNDROME. omim.org. Published December 1, 2016. Accessed November 26, 2020. https://www.omim.org/entry/613174
5. Chromosome 5p13 Duplication Syndrome. malacards.org. Published July 26, 2010. Accessed November 26, 2020. https://www.malacards.org/card/chromosome_5p13_ duplicati on_syndrome
6. van Amen-Hellebrekers CJM, Jansen S, Pfundt R, et al. Duplications of SLC1A3: Associated with ADHD and autism. Eur J Med Genet. 2016;59(8):373-376. doi:10.1016/j.ejmg . 2016.06.003
7. Yan J, Zhang F, Brundage E, et al. Genomic duplication resulting in increased copy number of genes encoding the sister chromatid cohesion complex conveys clinical consequences distinct from Cornelia de Lange. J Med Genet. 2009;46(9):626-634. doi:10.1136/jmg.2008.062471
8. Lucarelli E, Pasca MG, Fanizza I, Trabacca A. Electroclinical characteristics and neuropsychological profile of a female child with chromosome 5p13.2 duplication syndrome. Neurol Sci. 2017;38(5):915-917. doi:10.1007/s10072-017-2825-9
9. Novara F, Alfei E, D'Arrigo S, et al. 5p13 microduplication syndrome: A new case and better clinical definition of the syndrome. Eur J Med Genet. 2013;56(1):54-58.doi:10.1016/j. ejmg.2012.10.002
10. Camerota L, Pitzianti M, Postorivo D, et al. A Small Supernumerary Marker Derived from the Pericentromeric Region of Chromosome 5: Case Report and Delineation of Partial Trisomy 5p Phenotype. Cytogenet Genome Res. 2017;153(1):22-28. doi:10.1159/000481331
11. Romero MCC, Hoyo RG, Calvente M, Cano MB, Castillo LG, Suela J. Neonatal detection of 5p13.2 duplication and delineation of the phenotype. Am J Med Genet A.2012;158A (4):877-881. doi:10.1002/ajmg.a.35237
12. Walters-Sen LC, Windemuth K, Angione K, Nandhlal J, Milunsky JM. Familial transmission of 5p13.2 duplication due to maternal der(X)ins(X;5). Eur J Med Genet. 2015;58(5): 305-309. doi:10.1016/j.ejmg.2015.03.004
13. NIPBLNipped-B homolog. gene.sfari.org. Accessed December 17, 2020. https://gene.sfari.org/database/human-gene/NIPBL

Box. Clinical characteristics of the 5p13.2 chromosomal duplication syndrome (present case and cases from the literature).

Patients	Sex Age	Overweight	Developmental delay	Psychomotor delay	ASD	Hypotonia	Upslanting palpebral fissures	Hypertelorism	Micrognathia	Preauricular tags in right side	Congenital heart defect	Limbs anomalies
Present case	F; 06 Y	+	+	+	+	+	+	+	+	+	+	+
Yan et al., 2009	F; 18 Y	+	+	-	-	-	+	-	-	-	N/A	+
	F; 6 Y	+	+	-	-	+	N/A	N/A	N/A	-	N/A	+
	F; 30 Y	-	+	-	-	+	-	-	+	-	N/A	+
	M; 08 M	-	N/A	-	-	+	-	+	N/A	-	N/A	+
	F; 5 Y	-	+	-	-	+	-	N/A	N/A	-	N/A	+
Walters-sens et al., 2015	M; 17 Y	+	+	-	+	+	-	-	+	-	N/A	-
	M; 8 Y	+	+	-	+	+	-	-	+	-	N/A	+
Camerota Romero et al., 2010	M; neonate	-	+	+	-	+	-	+	+	-	+	+
Dede et al., 2011	M; 17 Y	+	+	+	-	+	-	-	+	-	+	+
Van Amen- Hellebrekers et al., 2016	F; 7 Y	-	+	+	-	-	N/A	+	-	N/A	N/A	+
	F; 09 M	-	+	-	-	+	-	+	+	-	N/A	+
	F; 3 Y	-	+	+	+	+	N/A	-	-	N/A	N/A	N/A
	M; 12 Y	-	+	+	-	N/A	-	-	-	-	N/A	N/A
Lucarelli et al., 2017	F; 5 Y	+	+	+	-	+	-	-	+	-	N/A	+
Camerota et al., 2017	F; 17 Y	+	+	+	+	-	+	+	+	-	-	N/A
Novara et al., 2012	F; 2Y	-	+	+	-	+	-	-	-	-	N/A	+

White Matter Hyperintensities: repercussion on grey matter structures of the brain

Hiperintensidades da Substância Branca: repercussão em estruturas da substância cinzenta do cérebro

Eliasz Engelhardt [1]

ABSTRACT

The extensive white matter of the brain, which comprises about one half of its volume, is constituted by an intricate and interwoven assemble of nerve fibers. The WMH (leukoaraiosis) represent the most frequent ischemic type of lesion of SVD, affecting the white matter. These lesions may be apparent or normal appearing on neuroimaging. In both cases such lesions may interrupt the affected white matter fibers, with consequent disconnection syndromes, and atrophy of the denervated grey matter structures. These conditions affect the structural neural networks (connectome), with functional repercussion on the cognitive and behavioral domains.

Keywords: white matter, hyperintensities, leukoaraiosis, denervation, disconnection

RESUMO

A extensa substância branca do cérebro, que compreende cerca da metade do seu volume, é constituída por um intricado e entrelaçado conjunto de fibras nervosas. As HSB (hiperintensidades da substância branca) (leucoaraiose) representam o mais frequente tipo de lesão isquêmica da DPV (doença dos pequenos vasos) que afeta a substância branca. Essas lesões podem ser aparentes ou de aparência normal na neuroimagem. Em ambos os casos tais lesões podem interromper essas fibras da substância branca, com consequente síndromes por desconexão e atrofia de estruturas de substância cinzenta desnervadas. Essas condições afetam as redes neurais estruturais (conectoma), com repercussão funcional nos domínios cognitivo e do comportamento.

Palavras-chave: substância branca, hiperintensidades, leucoaraiose, desenervação, desconexão

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Conflict of interest: none
Funding statement: none
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INTRODUCTION

The cerebral white matter is a very frequent target of "small vessel diseases" (SVD), which appear under varied kinds of ischemic lesions (white matter lesions [WML]), comprising "white matter hyperintensities" (WMH), "lacunar infarcts" (lacunes), and "enlarged perivascular spaces" (EPS), and also hemorrhagic lesions, the "micro-hemorrhages" (MI), as visualized on magnetic resonance imaging (MRI)[2,3,4] . The WMH are the most common among the ischemic WML, and are also designated by the term "leukoaraiosis" (leuko=white and araios=rarefaction), "meaning a diminution of the density of representation of the white matter"[5,6] . They appear hyperintense on MRI and hypointense (hypodense) on CT, the latter with a lesser sensitivity in comparison to MRI[7,8] .

The WMH (leukoaraiosis) are the most common visible kind of lesions of the white matter, and occur frequently in adults over 65 years old with a prevalence rate of ~60 - 80% in the general population[9] , and are even more extensive in those with cerebrovascular or Alzheimer's diseases, where they may reach ~90% when compared with cognitively normal older adults[10]. Currently, there is accumulating evidence pointing to the clinical relevance of the WMH[11] .

Additionally, lesions of the white matter not visible with the conventional MRI sequences (e.g., FLAIR), the "normal appearing white matter" (NAWM), was identified by DTI, and have also an important role in the pathophysiology, as they affect the nerve fibers and their function[12,13,14].

As already seen, the severity and the spatial distribution of WMH vary, as can be assessed by several metrics, as the Fazekas scale and others[15] .

THE WHITE MATTER

The white matter makes up approximately one half of the human brain volume, and appears relatively homogeneous as seen on gross anatomical sections and sectional MRI (e.g., on T1 sequence), where some regions can be distinguished (e.g., internal, external and extreme capsules, corpus callosum (body, genu and splenium), centrum semiovale, gyral white matter [blades]), without further detail[4,16] .

However, it is known that the white matter is constituted by a very large number of interwoven nerve fibers (axons) of variable thickness, unmyelinated and myelinated. These fibers form assembles, constituting fascicles, bundles or tracts of diverse lengths and directions. Their course varies according to the brain axis, many in a predominantly medial-lateral direction (e.g., commissural, thalamic-cortical-thalamic, and cortical-striatal), and others mainly in an anteroposterior direction (e.g., long association tracts)[16,17,18,19,20] .

These tracts were identified by anatomical dissection in the human brain by numerous authors, who provided an apparently complete picture of the macro-connections of the brain [3,16,21,22,23] . They were also revealed and identified by virtual dissection with special MRI sequences in vivo, the diffusion tensor imaging (DTI), with the obtention of color-coded fractional anisotropy (FA) mapping and tractography[17,24] .

A general classification of these bundles of fibers, mostly localized between the lateral ventricles, cerebral cortex, and deep basal nuclei, as association (short, long), commissural, and projection tracts, was established a long time ago by Meynert (1872)[25] , which endures until the present days[4,16,17].

These fascicles, bundles or tracts are responsible for connecting the varied superficial (cortical) and deep (basal nuclei) gray matter formations, and underpin, when interrupted by apparent (visible) lesions or NAWM on MRI, the concept of disconnection syndromes[25,27].

Important to stress is that these fiber assembles that interconnect varied grey matter formations represent the material substrate of the varied structural and functional networks. Among the structural networks stands out the "connectome", a concept and term first defined as a "network of elements and connections forming the human brain", fundamentally important in cognitive neuroscience and neuropsychology[28,29].

WHITH MATTER LESIONS AND NERVE FIBERS DEGENERATION

As already mentioned, the white matter is formed by nerve fibers (axons) afferent or efferent from a given cortical (laminar) and/or subcortical (nuclear) structures (e.g., thalamo-cortical, cortico-thalamic, cortico striatal, cortico-cortical)[16,30]. Lesions of these axons cause denervation (deafferentation, deefferentation) of the interconnected gray structures. The "deafferentation" is caused by "anterograde degeneration" (Wallerian), which impacts on near and/or distant target regions, with deprivation of incoming information. On the other side, the "deefferentation" results from "retrograde degeneration", which affects the neuron body (pericarion, soma), leading to its reaction, eventually harm, and in some cases even to its death (via apoptosis). Such reactions also affects the synapses that contact the affected neurons, beside the related neuroglial elements. Additionally, transneuronal (trans-synaptic) degeneration, which affect nearby related structures, increases the extension of the damage, may also be seen[31,32,33,34,35].

The result of such changes of the grey matter structures (laminar or nuclear), and loss of nervous elements, may produce disorganization of their microstructure (e.g., cerebral cortex, thalamus), grossly represented by atrophy, with reflection on the local activity, of nearby, and of distant related structures.

THE DENERVATED STRUCTURES AND THEIR CHANGES

Many studies have focused on changes of the cerebral cortex and subcortical nuclei after WML (e.g., WMH) using several kinds of metrics.

Several isolated and systematic studies have shown brain volume and cortical thickness (CT) changes among patients with symptomatic SVD (WMH), interpreted as secondary to axonal degeneration. Some studies revealed a significant decrease in CT found in specific cortical areas connected to white matter focal lesions (regional cortical atrophy), while areas with undamaged connections remained relatively unchanged. Other studies showed that higher total WMH load was associated with lower global cortical thickness (and lower cognitive performance)[36,37,38,39].

It was demonstrated a correspondence of the localization of WMH and the affected cortical regions, which revealed that the most common sites of WMH are related to frontal and parieto-occipital regions. The frontal WMH affect fibers related to frontal cortical areas, while parieto-occipital WMH affect fibers related to posterior cortical regions, including parietal and temporal areas[40]. In consequence, there is a more accentuated volume loss of the frontal lobes cortex, followed by the temporal lobes, and less by parietal and occipital cortices[41].

Another MRI study analyzed the spatial distribution of WMH in a more detailed manner, and revealed an inhomogeneous distribution of the WMH. There, among 333 cases, 56.66% were frontal, 37.54% parietal, 7.21% temporal, and 3.30% occipital. Among those, there were also 43.84% in the basal ganglia, and lesser percentages in other regions[42], certainly reflecting proportional atrophy of the related gray matter structures.

Interestingly, it was also shown that regardless their location, the lesions of the white matter impacts the function of the frontal areas[43], certainly explained by the several longitudinal tracts that converge on the frontal lobes[24,25].

Confluent WMH (leukoaraiosis) affecting large parts of the white matter, as seen in cases of Binswanger disease, permitted further information. The neuropathological examination of brains revealed global brain volume reduction, and histological analysis of the white matter revealed areas of axonal and myelin loss with gliosis, and lacunar infarcts[44]. The examination of the cerebral cortex showed occasional isolated apoptotic neurons in layers 3 and 5 of the frontal and occipital cortex, and few apoptotic neurons were present also in the hippocampus of the long-lasting cases[45].

Regarding specifically the medial temporal region, studies of patients with SVD with WML (lacunes, WMH) showed, beside a reduction of the volume of the cortical grey matter, also of the entorhinal cortex and the hippocampus, in comparison to cognitively normal controls[46,47,48]. Another study of SVD, with post-mortem analysis, showed a volumetric global brain reduction, including the hippocampus and subiculum. The neuronal count revealed a substantial loss of pyramidal neurons of the CA1 region of the hippocampus, possibly due to damage to cerebral microvasculature and neuronal apopotosis[49].

A special consideration is deserved by studies of cases of CADASIL, the traditional model of monogenic illness, which produces a slowly developing subcortical ischemic vascular disease. There, a progressive cortical atrophy, revealed by MRI, associated with progressive cognitive decline, was seen. One the studies was performed on post-mortem material, with histological and immunohistochemical techniques, aiming the identification of varied apoptosis markers. Those revealed widespread apoptotic neurons (cell death), mostly in neocortical layers 3 and 5, place of large numbers of pyramidal neurons, which was more severe in frontal and occipital lobes. The severity correlated semi-quantitatively with the extent of ischemic lesions and axonal damage in the underlying white matter, and the apoptosis of cortical neurons could be credited to the resulting denervation (deafferentation or retrograde neuronal degeneration). This supports the view that neuronal apoptosis may contribute to cortical atrophy and cognitive impairment in patients with CADASIL and that it may, at least partly, result from axonal damage in the underlying white matter. Neuronal apoptosis was minimal in hippocampus where the underlying white matter was usually devoid of ischemic lesions. Apoptosis of neurons was milder in the basal nuclei (lenticular nuclei and thalamus)[34,45]. A recent CADASIL study analyzed the hippocampal formation with histological and immunehistochemical techniques, and stereological metrics of CA1 and CA2 regions, and layer 5 of the entorhinal cortex (EC). The results showed hippocampal volume decrease as demonstrated by neuroimaging studies, related to a selective loss of neurons in the hippocampal formation (CA1 and mainly CA2)[50]. Such findings also suggest that white matter integrity in the temporal stem is compromised and is a factor in the observed cell loss in the hippocampal formation, particularly in the layer 5 of the EC[51].

Other kinds of studies in human beings (stroke and diaschisis), and on experimental laboratory animals (stroke, cortical undercutting), which affect the white matter, analyzed by neuroimaging and/or neuropathology, were not presently considered, bearing in mind that they produce acute effects, and although they may provide useful information, they are not entirely comparable to the slow developing lesions produced by the WMH and their repercussion on grey matter structures. Such studies will be focused in another opportunity.

COMMENTS

The extensive white matter of the brain, which comprises about one half of its volume, is constituted by an intricate and interwoven assemble (fascicles, bundles, tracts) of myelinated and unmyelinated nerve fibers, interconnecting gray matter formations. The WMH (leukoaraiosis) represent the most frequent kind of ischemic lesion due to SVD,

acquired or genetic, affecting the white matter. They vary in severity, size and spatial localization. These lesions may be apparent on neuroimaging (MRI-FLAIR) or be NAWM (MRI-DTI) [1,3,13] .

Such kinds of lesions interrupt, in variable degree and extension, the affected fiber assembles of the white matter. The consequence of such situation is double: [1] interruption of the connection among grey matter structures (cortical, subcortical), a situation generating disconnection syndromes, and [2] volume reduction of the denervated (deafferented, deefferented) grey matter structures, as thinning of the affected areas of the cerebral cortex, and/or atrophy of the affected subcortical nuclei. These condition appear to have a broader effect, as the affected grey matter structures are frequently connected with others, which also become compromised, enhancing the dysfunctional effect [31,33] .

The nervous fiber system interconnecting varied gray matter structure represents the structural basis of the "connectome". The WMH, lesions that affect these fibers in diverse extension, are responsible for varied degrees of connectome disruption with consequent repercussion of cognitive and behavioral functional disorders [28,29] .

REFERENCES

1. Pantoni L. Cerebral small vessel disease: from pathogenesis and clinical characteristics to therapeutic challenges. Lancet Neurol 2010;9(7):689-701.
2. Rosenberg GA, Wallin A, Wardlaw JM, Markus HS, Montaner J…Hachinski V. Consensus statement for diagnosis of subcortical small vessel disease. J Cerebral Blood Flow Metabol 2016;36(1):6-25. doi: 10.1038/jcbfm.2015.172
3. Schmahmann JD, Smith EE, Eichler FS, Filley CM. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. Ann NY Acad Sci 2008;1142, 266.
4. Wang Y, Yang Y, Wang T, Nie S, Yin H, Liu. Correlation between White Matter Hyperintensities Related Gray Matter Volume and Cognition in Cerebral Small Vessel Disease. J Stroke Cerebrovasc Dis 2020;29(12):105275.
5. Hachinski V, Potter P, Merskey H. Leuko-Araiosis: An Ancient Term for a New Problem. Can J Neurol Sci / J Can Sci Neurol 1986;13(S4):533-534.doi: 10.1017/S0317167100037264
6. Kim KW, MacFall JR, Payne ME. Classification of white matter lesions on magnetic resonance imaging in elderly persons. Biological Psychiatry 2008;64(4):273-280.doi:10.1016/j.biopsych.2008.03.024
7. Bigler ED. Structural neuroimaging in neuropsychology: History and contemporary applications. Neuropsychology 2017;31(8):934-953. doi: 10.1037/neu0000418.
8. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR Signal Abnormalities at 1.5 T in Alzheimer's Dementia and Normal Aging. AJR 1987;149:351-356.
9. De Leeuw F, de Groot JC, Achten E, Oudkerk M, Ramos L… Breteler MMB. Prevalence of cerebral white matter lesions in elderly people:a population based magnetic resonance imaging study. The Rotterdam scan study. J Neurol Neurosurg Psychiatry 2001;70:9-14. doi: 10.1136/jnnp.70.1.9
10. Bombois S, Debette S, Delbeuck X, Bruandet A, Lepoittevin S…Pasquier F. Prevalence of subcortical vascular lesions and association with executive function in mild cognitive impairment subtypes. Stroke 2007;38:2595-2597. doi: 10.1161/STROKEAHA.107.486407
11. Frey BM, Petersen M, Mayer C, Schulz M, Cheng B, Thomalla G. Characterization of White Matter Hyperintensities in Large-Scale MRI-Studies. Front Neurol 2019;10:238. doi: 10.3389/fneur.2019.00238
12. Gouw AA, Seewann A, Van Der Flier WM, Barkhof F, Rozemuller AM, Scheltens P, Geurts JJ. Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. J Neurol Neurosurg Psychiatry 2011;82(2):126-135.
13. Maniega SM, Hernández MCV, Clayden JD, Royle NA, Murray C, Morris Z ...Wardlaw JM. White matter hyperintensities and normal-appearing white matter integrity in the aging brain. Neurobiology of Aging 2015;36(2):909-918.
14. Wardlaw JM, Valdés Hernández MC, Muñoz-Maniega S. What are white matter hyperintensities made of? Relevance to vascular cognitive impairment. J Am Heart Ass 2015;4(6):e001140.
15. Engelhardt E, Sudo FK, Alves GS, Moreira DM. White Matter Hyperintensities: Initial Assessments. Rev Bras Neurol 2021;57(2):14-17.
16. Wycoco V, Shroff M, Sudhakar S, Lee W. White matter anatomy: what the radiologist needs to know. Neuroimaging Clinics 2013; 23(2):197-216.
17. Catani M, De Schotten MT. Atlas of human brain connections. Oxford: Oxford University Press, 2012.
18. Mandonnet E, Sarubbo S, Petit L. The nomenclature of human white matter association pathways: proposal for a systematic taxonomic anatomical classification. Frontiers in Neuroanatomy 2018;12, 94.
19. Matute C, Ransom BR. Roles of white matter in central nervous system pathophysiologies. ASN Neuro 2012;4(2):AN20110060.
20. Sporns O. The human connectome: origins and challenges. Neuroimage 2013; 80: 53-61.
21. Engelhardt E, Moreira DM. A substância branca cerebral. Localização dos principais feixes com anisotropia fracionada direcional [The cerebral white matter. Localization of the main tracts with directional fractional anisotropy]. Rev Bras Neurol 2008;44 (2):19-34.
22. Dziedzic TA, Balasa A, Jeżewski MP, Michałowski Ł, Marchel A. White matter dissection with the Klingler technique: a literature review. Brain Structure and Function 2021;226(1):13-47.

23. Ludwig E, Klingler J. Atlas cerebri humani: the inner structure of the brain demonstrated on the basis of macroscopical preparations. Boston: Little, Brown and Co.1956.
24. Engelhardt E, Moreira DM. A substância branca cerebral. Dissecção virtual dos principais feixes: tratografia [The cerebral white matter. Virtual dissection of the main tracts: tractography]. Rev Bras Neurol 2008;44(4):19-34.
25. Meynert T. Von Gehirn der Säugethiere. In: Handbuch der Lehre von den Geweben des Menschen und der Thiere. 2 Band. Stricker S ed. Leipzig: Wilhelm Engelman, 1872 , pp 694-808.
26. Catani M, Ffytche DH. The rises and falls of disconnection syndromes. Brain 2005;128(10):2224-2239.
27. Langen CD, Zonneveld HI, White T, Huizinga W, Cremers LGM, de Groot M, Ikrama MA, Niessen WJ, Vernooij MK. White matter lesions relate to tract-specific reductions in functional Connectivity. Neurobiology of Aging 2017; 51:97-103.
28. Sporns O, Tononi G, Kötter R. The human connectome: a structural description of the human brain. PLoS computational biology2005;1(4), e42.
29. Sporns O. The human connectome: Origins and challenges. NeuroImage 2013;80:53-61.
30. Wakana S, Jiang H, Nagae-Poetscher LM, Van Zijl PC, Mori S. Fiber tract–based atlas of human white matter anatomy. Radiology 2004;230(1):77-87.
31. Holly Bridge H, Gordon T. Plant GT. Conclusive Evidence for Human Transneuronal Retrograde Degeneration in the Visual System. Clin Exp Ophthalmol 2012;S:3. doi:10.4172/2155-9570.S3-003
32. Beatty RM, Sadun AA, Smith LEH, Vonsattel JP, Richardson EP. Direct demonstration of transsynaptic degeneration in the human visual system: a comparison of retrograde and anterograde changes. J Neurol Neurosurg Psychiatry 1982;45(2):143-146.
33. Nagappan PG, Chen H, Wang D-Y. Neuroregeneration and plasticity: a review of the physiological mechanisms for achieving functional recovery postinjury. Military Medical Research 2020;7:30.
34. Viswanathan A, Gray F, Bousser M-G, Baudrimont M, Chabriat H. Cortical Neuronal Apoptosis in CADASIL. Stroke 2006;37:2690-2695. doi: 10.1161/01.STR.0000245091.28429.6a
35. Yamada K, PateI U, Shrier DA, Tanaka H, Chang J-K, Numaguchi Y. MR Imaging of CNS Tractopathy: Wallerian and TransneuronalDegeneration. AJR 1998;171:813-â18.
36. Cheng B, Schulz R, Bönstrup M, Hummel FC, Sedlacik J… Thomalla G. Structural plasticity of remote cortical brain regions is determined by connectivity to the primary lesion in subcortical stroke. J Cerebr Blood Flow Metabol 2015;35:1507-1514.
37. Reid AT, van Norden AGW, de Laat KF, van Oudheusden LJB, Zwiers MP… Kötter R. Patterns of Cortical Degeneration in an Elderly Cohort with Cerebral Small Vessel Disease. Human Brain Mapping 2010;31:1983-1992. doi: 10.1002/hbm.20994
38. Rizvia B, Narkhedea A, Lasta BS, Budgea M, Tostoa G… Brickman AM. The effect of white matter hyperintensities on cognition is mediated by cortical atrophy. Neurobiol Aging 2018; 64: 25–32. doi:10.1016/j.neurobiolaging.2017.12.006
39. Tuladhar AM, Reid AT, Shumskaya E, de Laat KF, van Norden AG, van Dijk EJ ...de Leeuw FE. Relationship between white matter hyperintensities, cortical thickness, and cognition. Stroke 2015;46(2):425-432.
40. Rossi R, Boccardi M, Sabattoli F, Galluzzi S, Alaimo G, Testa C, Frisoni GB. Topographic correspondence between white matter hyperintensities and brain atrophy. J Neurol 2006;253:919-927. doi 10.1007/s00415-006-0133-z
41. Raji CA, Lopez OL, Kuller LH, Carmichael OT, Longstreth Jr WT…Becker JT. White Matter Lesions and Brain Gray Matter Volume in Cognitively Normal Elders. Neurobiol Aging 2012;33(4):834.e7834.e16.doi:10.1016/j.neurobiolaging.2011.08.010
42. Zhuang F-J, Chen Y, He W-B, Cai Z-Y.Prevalence of white matter hyperintensities increases with age. Neural Regen Res 2018;13(12):2141-2146. doi: 10.4103/1673-5374.241465.
43. Tullberg M, Fletcher E, DeCarli C, Mungas D, Reed BR, Harvey DJ ... Jagust WJ. White matter lesions impair frontal lobe function regardless of their location. Neurology 2004; 63(2):246-253..
44. Révész T, Hawkins CP, Du Boulay EP, Barnard RO, McDonald WI. Pathological findings correlated with magnetic resonance imaging in subcortical arteriosclerotic encephalopathy (Binswanger's disease). J Neurol Neurosurg Psychiatry 1989;52(12):1337-1344.
45. Gray F, Polivka M, Viswanathan A, Baudrimont M, Bousser M-G, Chabriat H. Apoptosis in Cerebral Autosomal-Dominant Arteriopathy 2007;66(7):597-607.
46. Appelman APA, Exalto LG, van der Graaf Y, Biessels GJ, Mali WPTM, Mirjam I. Geerlings MI. White Matter Lesions and Brain Atrophy: More than Shared Risk Factors? A Systematic Review. Cerebrovasc Dis 2009;28:227-242. doi: 10.1159/000226774
47. Du AT, Schuff N, Laakso MP, Zhu XP, Jagust WJ…Weiner MW. Effects of subcortical ischemic vascular dementia and AD on entorhinal cortex and hippocampus. Neurology 2002; 58(11):1635-1641.
48. Godin O, Maillard P, Crivello F, Alpérovitch A, Mazoyer B, Tzourio C, Dufouil C. Association of White-Matter Lesions with Brain Atrophy Markers: The Three-City Dijon MRI Study. Cerebrovasc Dis 2009;28:177–184. doi: 10.1159/000226117
49. Kril JJ, Patel S, Harding AJ, Halliday GM. Patients with vascular dementia due to microvascular pathology have significant hippocampal neuronal loss. J Neurol Neurosurg Psychiatry 2002;72:747-751.
50. O'Sullivan M, Ngo E, Viswanathan A, Jouvent E, Gschwendtner A…Dichgans M. Hippocampal volume is an independent predictor of cognitive performance in CADASIL. Neurobiol Aging 2009;30:890-897.
51. Yamamoto Y, Hase Y, Ihara M, Khundakar A, Roeber S, Duering M, Kalaria RN. Neuronal densities and vascular pathology in the hippocampal formation in CADASIL. Neurobiology of Aging 2021; 97:33-40.

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