UNIVERSIDADE FEDERAL DA BAHIA
FACULDADE DE MEDICINA DA BAHIA
Programa de Pós-graduação em Ciências da Saúde
Largo do Terreiro de Jesus – Pelourinho

Aspectos Clínicos e Prognósticos de Pacientes com Diagnóstico de Doença do Espectro da Neuromielite Óptica

Thiago Gonçalves Fukuda

Tese de Doutorado

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Professor Orientador: Jamary Oliveira Filho

Tese apresentada ao Colegiado do PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE, da Faculdade de Medicina da Universidade Federal da Bahia, como pé-requisito obrigatório para a obtenção do grau de Doutor em Ciências da Saúde, da área de concentração em medicina.

Salvador (Bahia), 2024

COMISSAO EXAMINADORA

Membros Titulares: Prof. Dr. Jamary Oliveira Filho, UFBA (Presidente/ Orientador);

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"Faça ou não faça. A tentativa não existe.

Que a força esteja com você." **Mestre Yoda**.

Extraído do Filme "Star Wars: Episódio V – O Império Contra-ataca" (1980).

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Lista de Abreviaturas

Anti-AQP4 -Anticorpo anti-aquaporina 4

Anti-DNA -Anticorpo contra o nucleossomo

Anti-La -Anticorpo contra o antígeno La

Anti-MOG- Anticorpo contra a glicoproteína da mielina do oligodendrócito (do inglês myelin oligodentrocyte glicoprotein)

Anti-Ro -Anticorpo contra o antígeno Ro

Anti-SM - Anticorpo anti-Smith

Anti-TPO - Anticorpo antiperoxidase tireoideana

AP -Área Postrema

AQP4 -Aquaporina 4

AV -Acuidade visual

AZA- Azatioprina

BOC -Bandas oligoclonais

CBA -Ensaio baseado em células (do inglês cell-based assay)

DENMO Doença do Especto Neuromielite Óptica

EDSS -Escala Expandida do Estado de Incapacidade (do inglês Expanded Disability Status Scale)

EM- Esclerose Múltipla

FAN -Fator anti-nuclear

FLAIR - Método de aquisição de imagem magnética (do inglês fluid-attenuated inversion recovery)

HIV -Vírus da imunodeficiência humana

(do inglês Internacional Pediatric Multiple Sclerosis Study Group)

IVIG- Imunoglobulina humana intravenosa (do inglês intravenous immunoglobulin)

IDH- índice de desenvolvimento Humano

LCR - Líquido cefalorraquidiano

LES - Lúpus Eritematoso Sistêmico

MMF - Micofenolato de mofetila

MOGAD- Doença associada ao anticorpo anti-MOG (do inglês MOG associated disease)

MT -Mielite transversa

MTLE -Mielite transversa longitudinalmente extensa

MTX -Metotrexato

NMO - Neuromielite Óptica

NO- Neurite Óptica

RM - Ressonância Magnética

RTX- Rituximabe

TAS - Taxa anualizada de surtos

I. Resumo

Introdução: A doença do espectro da neuromielite óptica (DENMO) é uma doença inflamatória e desmielinizante rara do sistema nervoso central (SNC), mais frequente em mulheres e afrodescendentes. Nenhum estudo epidemiológico ou prognóstico prévio foi realizado na região do estado da Bahia, Nordeste brasileiro. **Objetivo:** Identificar características demográficas e fatores associados a maior progressão da doença em pacientes com DENMO no Estado da Bahia.

Material e Métodos: Foi realizado um estudo retrospectivo unicêntrico com pacientes consecutivos diagnosticados com DENMO. Foram descritas as características clínicas e epidemiológicas. O grau de incapacidade foi expresso pela Escala Expandida de Status de Incapacidade (EDSS). O desfecho principal do estudo foi o índice de progressão, definido pela razão entre o EDSS e a duração da doença em meses. Os preditores de progressão da doença foram identificados por meio de regressão binomial negativa ajustada para a duração da doença.

Resultados: Noventa e um pacientes foram incluídos, sendo 72 (79,1%) do sexo feminino e 67 (73,6%) afrodescendentes. A média da idade de início foi de 36 (± 14) anos e 73,3% eram positivos para o anticorpo anti-aquaporina-4. Mielite transversal isolada (32,9%) e neurite óptica isolada (22,4%) foram as síndromes clínicas iniciais mais frequentes. Após análise multivariada, neurite óptica (RR = 0,49; IC 95%=0,29 – 0,84; p = 0,009) e

dislipidemia (RR = 0,50; IC 95%=0,26 – 0,96; p= 0,038) foram associadas à progressão mais lenta da doença. O envolvimento da área postrema (RR = 6,59; IC 95% = 3,56 – 12,21; p < 0,001) e a idade de início (RR = 1,01; IC 95% = 1,00 – 1,03; p = 0,047) foram associados a uma progressão mais rápida da doença. **Conclusões:** No primeiro estudo clínico e prognóstico no nordeste do Brasil, identificamos o acometimento da área postrema e a idade mais avançada de início como fatores associados à progressão da doença; e a neurite óptica como síndrome inicial e a dislipidemia como os principais fatores protetores.

Palavra Chave: Transtornos do espectro da neuromielite óptica; Fatores prognósticos; Nordeste brasileiro; Aquaporina-4.

II. Introdução

A Doença do Espectro da Neuromielite Óptica (NMO) foi historicamente considerada uma variante mais grave da Esclerose Múltipla (EM), sendo categorizada como uma doença desmielinizante com manifestações clínicas mais severas. Contudo, nas últimas décadas, avanços significativos no campo da neuroimunologia revelaram que a NMO é, na verdade, uma astrocitopatia autoimune, caracterizada pelo ataque seletivo aos astrócitos que expressam a proteína aquaporina-4 (AQP4). Essa descoberta, possibilitada pela identificação do anticorpo NMO-IgG, que apresenta alta

sensibilidade e especificidade, transformou radicalmente nossa compreensão da doença, distinguindo-a, de forma clara, da Esclerose Múltipla.

Atualmente, a NMO é reconhecida como uma entidade clínica e patológica única, com fisiopatologia distinta e um curso clínico diferente da EM. Esse entendimento mais profundo sobre a doença abriu portas para o desenvolvimento de terapias direcionadas, que têm impactado de maneira significativa o manejo e o prognóstico dos pacientes.

Epidemiologicamente, a NMO apresenta padrões contrastantes em relação à EM, sendo mais prevalente em populações afrodescendentes e asiáticas, o que sugere influências genéticas e ambientais no desenvolvimento da doença. No contexto brasileiro, essa diferença é particularmente relevante. Regiões como o Nordeste, onde há uma maior concentração de afrodescendentes e uma diversidade racial notável, permanecem subestudadas quanto às características clínicas e epidemiológicas da NMO. Apesar das especificidades dessa população, que incluem fatores genéticos, ambientais e sociais, o conhecimento sobre a NMO no Nordeste, e especialmente na Bahia, ainda é limitado.

Este trabalho busca preencher essa lacuna, oferecendo uma análise detalhada das manifestações clínicas, epidemiológicas e prognósticas da NMO na Bahia, uma região com peculiaridades raciais e determinantes sociais únicos. Ao esclarecer esses aspectos, espera-se contribuir para um melhor entendimento da NMO no Brasil e, potencialmente, fornecer bases para o

desenvolvimento de estratégias terapêuticas e de saúde pública mais adequadas para essa população.

III. Revisão de Literatura

1. Evolução histórica do conceito e critérios da DENMO

A primeira descrição clínica relacionada à Doença do Espectro Neuromielite Óptica (DENMO) remonta a 1870, quando o médico Thomas Clifford Allbutt relatou uma série de 30 pacientes com acometimento medular, dos quais oito apresentavam comprometimento visual. Embora a ligação entre a mielite e a neurite óptica já estivesse sugerida, a definição precisa da condição ainda não havia sido estabelecida na época (1).

A descrição clínica detalhada, contudo, é atribuída ao médico francês Eugène Devic, em 1894. Devic apresentou um relato abrangente de uma síndrome caracterizada por inflamação aguda da medula espinhal (mielite) e do nervo óptico (neurite óptica), resultando em perda de visão e paraplegia. O diferencial observado por Devic foi o rápido desenvolvimento simultâneo desses sintomas, em contraste com doenças neurológicas típicas, cujo curso era mais gradual e progressivo. Juntamente com seu aluno Fernand Gault, Devic cunhou o termo “neurite optique aiguë avec myélite subaiguë” para descrever esses casos. Seu trabalho foi publicado no mesmo ano na revista

francesa Revue Neurologique, relatando uma série de 12 pacientes com a combinação dos dois sintomas (1).

A partir dessas observações iniciais, a condição recebeu o epônimo de "Doença de Devic". No entanto, com os avanços no entendimento da Neuromielite Óptica, sabemos hoje que a doença se apresenta de forma recorrente em mais de 90% dos casos e pode afetar diversas outras áreas do sistema nervoso central, além do nervo óptico e da medula espinhal. Por essa razão, o termo "Doença de Devic" tornou-se inadequado, sendo substituído por "Doença do Espectro Neuromielite Óptica (DENMO)" para descrever melhor o espectro clínico da doença (2).

Em 1930, o neurologista britânico Russel Brain revisou os achados neuropatológicos de pacientes com Esclerose Múltipla (EM) e com a Doença de Devic. Ele concluiu que a diferença entre ambas as doenças residia apenas na intensidade do acometimento, sugerindo que a Doença de Devic seria uma variante mais grave da Esclerose Múltipla (3). Essa visão prevaleceu por muitas décadas, até que novos avanços em pesquisa imunológica desafiaram essa noção.

Foi apenas em 1999 que critérios diagnósticos mais precisos começaram a ser desenvolvidos. Brian G. Weinshenker e Dean M. Wingerchuk criaram os primeiros critérios de revisão para a Neuromielite Óptica. No entanto, na ausência de um biomarcador específico na época, muitos pacientes que não

apresentavam os sintomas típicos de neurite óptica e mielite foram excluídos, o que pode ter levado a diagnósticos equivocados (4).

A descoberta do anticorpo anti-aquaporina-4 (AQP4) pela Dra. Vanda Lennon, em 2004, foi um marco crucial na diferenciação entre a Neuromielite Óptica (NMO) e a Esclerose Múltipla (EM). A identificação do anticorpo anti-AQP4, altamente específico para NMO, permitiu não apenas uma distinção precisa entre essas duas doenças, mas também uma melhor compreensão da evolução clínica e do prognóstico da NMO. Esse biomarcador tornou-se fundamental tanto para o diagnóstico quanto para o desenvolvimento de novas estratégias terapêuticas, além de abrir portas para uma maior elucidação dos mecanismos patológicos subjacentes (5).

Com a descoberta do anticorpo anti-AQP4, os critérios diagnósticos para a NMO foram revisados, e passaram a incluir a presença desse biomarcador. Pacientes que anteriormente eram diagnosticados com síndromes incompletas de neurite óptica ou mielite, mas com teste positivo para o anticorpo, foram reclassificados dentro do espectro da NMO. Essa revisão representou uma mudança significativa no entendimento da doença, ampliando seu espectro clínico e garantindo uma abordagem diagnóstica mais abrangente (6,7)

Os critérios diagnósticos atuais, estabelecidos em 2015 pelo Painel Internacional de Diagnóstico da NMO (IPND-2015), formalizaram o uso de

seis síndromes clínicas associadas à NMO, além da presença (ou ausência) do anticorpo anti-AQP4, como elementos fundamentais no diagnóstico. Esse avanço permitiu uma maior precisão diagnóstica e reforçou a recomendação do uso do ensaio baseado em células (Cell-Based Assay, CBA) como o método preferido para a detecção do anticorpo anti-AQP4 (8). **(Quadro 1)**

Quadro 1. CRITÉRIOS DIAGNÓSTICO PARA DENMO EM PACIENTES ADULTOS

Critérios para Diagnóstico de NMOSD com AQP4-IgG

1. Pelo menos 1 dos sintomas centrais no quadro clínico
2. Dosagem positiva para AQP4-IgG usando o melhor método disponível
3. Exclusão de outros diagnósticos

Critérios para Diagnóstico de NMOSD sem AQP4-IgG ou NMOSD com status desconhecido de AQP4-IgG

1. Ao menos 2 características clínicas centrais resultado de um ou mais crises agudas e todos os seguintes requisitos:
    a. Ao menos 1 das características clínicas centrais devem ser Neurite óptica, mielite aguda com METL ou síndrome da área postrema
    b. Disseminação no espaço (2 ou mais características clínicas diferentes)
    c. Preenche critérios na RNM se possível
2. Testes negativos para AQP4-IgG usando o melhor método disponível ou teste indisponível
3. Exclusão de outros diagnósticos

Características clínicas centrais

1. Neurite óptica
2. Mielite aguda
3. Síndrome da Área Postrema: episódios de soluços ou náuseas/vômitos sem outras explicações
4. Síndrome do tronco cerebral encefálico aguda
5. Narcolepsia sintomática ou síndrome diencefálica aguda com RNM de crânio característica de NMOSD
6. Síndrome cortical sintomática com lesões encefálicas típicas de NMOSD

Achados na RNM necessários para NMOSD sem AQP4-IgG e NMOSD com status desconhecido de AQP4-IgG

1. Neurite Óptica Aguda: RNM de crânio mostrando (a) achados normais ou apenas lesões inespecíficas da substância branca, OU (b) RNM com nervo óptico com lesões hiperintensas em T2 ou lesão que é contrastada em T1 abrangendo >1/2 da extensão do nervo óptico ou envolvendo o quiasma óptico.

2. Mielite Aguda: RNM com Mielite transversa longitudinalmente extensa – MTLE (lesões intramedulares estendendo por >3 segmentos contínuos) OU >3 segmentos contínuos com atrofia focal da medula espinal em pacientes com história compatível com mielite aguda

3. Síndrome da área postrema: requer lesões associadas da medula dorsal/área postrema

4. Síndrome do tronco encefálico: requer lesões associadas na região periependimal do tronco encefálico

Abreviações: AQP4 = aquaporina-4; IgG = imunoglobulina G; MTLE = Mielite transversa longitudinalmente extensa; NMOSD = Doenças do Espectro Neuromielite Optica.
Adaptado da *International consensus diagnostic criteria for neuromyelitis optica spectrum disorders*.

2. Epidemiologia

A Doença do Espectro Neuromielite Óptica (DENMO) é uma doença rara, mais prevalente em indivíduos do sexo feminino e não-caucasianos. O diagnóstico é geralmente feito entre os 35 e 45 anos, com uma média de 39 anos, superior à média de 29 anos observada na Esclerose Múltipla. Embora possa acometer uma ampla faixa etária, incluindo crianças e idosos, esses grupos não representam a maioria dos casos (9).

Há uma clara influência racial na prevalência da DENMO. Estudos realizados em países com predominância de populações caucasianas mostram uma prevalência inferior a 1 para cada 100.000 habitantes. Em contraste, a prevalência entre asiáticos é em torno de 3,5 para cada 100.000 habitantes, e entre afrodescendentes, a prevalência pode ser ainda maior, chegando a 10 para cada 100.000 habitantes, como observado na ilha da Martinica, onde cerca de 90% da população é afrodescendente (9–11).

Quando comparamos as características baseadas na ancestralidade, observa-se uma tendência de início mais precoce da doença em pacientes negros, com a média de idade de início entre 28 e 33 anos, enquanto para pacientes brancos a média é de 44 anos. Além disso, exacerbações agudas tendem a ser mais graves em pacientes negros (9).

Em um estudo populacional conduzido nos Estados Unidos, pesquisadores observaram que o quadro inicial da Neuromielite Óptica frequentemente se apresenta como uma neurite óptica, com sinais medulares surgindo nos dois anos seguintes ao início dos sintomas. A média de idade dos pacientes foi de 41,1 anos, com uma predileção significativa pelo sexo feminino (6:1). Além disso, 52,4% da amostra era composta por indivíduos não-caucasianos. Embora as doenças desmielinizantes sejam mais prevalentes em populações brancas, os casos em pacientes negros mostraram-se mais graves e de maior duração (12).

Na França, a média de idade dos pacientes com NMO é de 34,5 anos, sendo a maioria caucasiana. A proporção mulher/homem é de 3:1, e uma relevante diminuição da acuidade visual foi observada nessa população (13).

Em Cuba, a prevalência da NMO é de 0,52 por 100.000 habitantes, sem grandes diferenças entre as raças. No entanto, os pacientes negros apresentaram uma maior recorrência da doença e sinais medulares mais graves (14). Na América Latina, a prevalência estimada da NMO varia de 0,37 a 4,2 casos por 100.000 habitantes. Em Caracas, Venezuela, 43,3% dos pacientes com doenças desmielinizantes foram diagnosticados com NMO, enquanto Buenos Aires, Argentina, apresentou uma proporção significativamente menor, com apenas 2,1% dos casos sendo de NMO (15,16).

2.1 Epidemiologia no Brasil

No Brasil, ainda há poucos estudos sobre a prevalência da Doença do Espectro da Neuromielite Óptica (DENMO), com metodologias variadas aplicadas nas pesquisas.

Na região Sudeste, três estudos tentaram estimar a prevalência em cidades dessa região. O primeiro estudo, realizado em Volta Redonda, Rio de

Janeiro, em 2015, utilizou uma metodologia de busca ativa em registros médicos privados e públicos, centros de dispensação de medicamentos e centros de imagem. Apenas um paciente com diagnóstico de DENMO foi identificado, e com base na população total da cidade, estimou-se uma prevalência de 0,37/100.000 habitantes. O segundo estudo foi realizado na cidade de Belo Horizonte, Minas Gerais, e foi baseado no conhecimento prévio da prevalência de Esclerose Múltipla (EM) em 2001 (18,1/100.000 habitantes) e na proporção de pacientes com EM e NMO em um centro único, no período de 2000 a 2019. Nesse estudo, foram identificados 69 pacientes com NMO e 208 pacientes com EM, resultando em uma estimativa de prevalência de 4,52/100.000 habitantes em Belo Horizonte (17,18). O terceiro estudo, mais recente, foi publicado em 2023 e estimou a prevalência de NMO na cidade de São Paulo, utilizando uma metodologia semelhante ao estudo anterior. No Hospital das Clínicas da Universidade de São Paulo, foram detectados 133 pacientes com NMO e 968 com EM, resultando em uma prevalência estimada de 2,1/100.000 habitantes na cidade de São Paulo (19).

Na região Centro-Oeste, um estudo publicado em 2021 no estado de Goiás, realizado entre 2017 e 2020, incluiu 48 pacientes. Considerando o estado como um centro de referência único e a população estimada de 6.003.788 habitantes em 2010, a prevalência foi estimada em 0,79/100.000 habitantes. (20)

Em 2015, um estudo sobre a epidemiologia das doenças desmielinizantes na América do Sul incluiu pacientes de Santa Catarina (região Sul), Recife (região Nordeste) e Belém (região Norte do Brasil). No entanto, o número de pacientes com NMOSD e as características clínicas e epidemiológicas das regiões não foram descritos (15)

Até o momento, não foram encontrados estudos publicados sobre as características clínicas e epidemiológicas da DENMO na região Nordeste do Brasil.

3. Fisiopatogenia e o anticorpo anti-aquaporina na DENMO

Em descrições anteriores DENMO era classificada como uma doença desmielinizante, após a descoberta do anticorpo anti-AQP4 passamos a entendê-la como um astrocitopatia autoimune.

Os canais de aquaporina são proteínas transmembrana que formam poros específicos para a passagem de água e outros pequenos solutos através das membranas celulares. São encontrados em diversos tipos de células e tecidos, incluindo as células do sistema nervoso central, dos rins, dos pulmões e do trato gastrointestinal. Elas são responsáveis por controlar o fluxo de água através das membranas celulares, permitindo que as células mantenham o equilíbrio hidroeletrolítico e os processos fisiológicos adequados. Além disso, as aquaporinas também desempenham um papel

importante na regulação do volume celular, na secreção e absorção de líquidos e na manutenção da pressão osmótica adequada. (21)

Existem 13 tipos diferentes de aquaporinas conhecidas, designadas como AQP0 a AQP12. Essas proteínas são encontradas em diferentes tecidos e desempenham funções específicas. A AQP4 se localiza em diversos órgãos como os rins, o músculo esquelético, estômago e glândulas exócrinas. É o principal canal de água do sistema nervoso central, com uma grande concentração nas células ependimárias e nos podócitos dos astrócitos. (22,23)

Existem evidencias fortes de que o Anti-AQP4 é produzido perifericamente, ainda que poucos pacientes possam ter uma detecção exclusiva no LCR. As células B e às células plasmáticas desempenham um papel importante na patogênese da DENMO. Existe uma expansão clonal seletiva de CD19, CD27, CD38 e CD180 que participam tanto na produção do anti-AQ4 e quanto na liberação de citocinas e quimiocinas inflamatórias como IL-6 com uma interação patogênica entre as células B e T. (24)

A ligação do anti-AQP4 ao epítopos extracelulares nas membranas plasmáticas do astrócitos gera, através da imunidade inata, um dano celular dependente de complemento com a formação do complexo de ataque a membrana (MAC) com ativação de complemento que produz fatores C3a e C5a produzindo a permeabilidade vascular e o recrutamento de células

imunes efetoras como neutrófilos, basófilos, eosinófilos, mastócitos e macrófagos. (24)

Essa inflamação persistente gera um dano neuronal grave e tanto a imunidade adquirida como células B (CD19, CD20), ativação de complemento e o IL-6, que tem sido alvos de novas terapias para DENMO.

4. Manifestações Clínicas:

Apesar da importância histórica das descrições iniciais feitas por Eugene Devic de uma paciente com acometimento de nervo óptico e medula espinhal de curso monofásico, sabemos que em torno de 90% dos casos de DENMO associados com anticorpos Anti-AQP4 são recorrentes e que outros sítios anatômicos que não apenas o nervo óptico e a medula como a área postrema do bulbo, o tronco encefálico, diencéfalo e outras estruturas cerebrais podem ser acometidos. E diferente da Esclerose Múltipla na qual sabemos existir formas progressiva de doença como o fenótipo progressivo primaria e secundária ou mesmo progressões independentes de surtos ou atividade inflamatória aguda, no caso da NMOSD os casos de progressão são considerados raros, representando menos de 1-2% dos casos (25).

As manifestações clínicas da NMOSD ocorrem geralmente em exacerbações agudas, conhecidas como surtos, gerando sintomas que caracterização os principais sintomas clínicos conhecidos da doença que são a neurite óptica

aguda, a mielite aguda, a síndrome de área postrema aguda, a síndrome aguda de tronco encefálico, a síndrome narcoléptica ou diencefálica aguda e síndrome cerebral sintomática. (8)

4.1 Neurite Óptica Aguda

A neurite óptica aguda ocorre em mais de 50% dos pacientes do NMOSD, geralmente se manifesta com quadro de dor ocular seguido de dificuldade para enxergar, na maioria das vezes grave com comprometimento de acuidade visual pior que 20/200. Apesar de ser mais comum o acometimento unilateral do nervo óptico a rápida progressão para o olho contralateral ou o acometimento bilateral simultaneamente são características que chamam atenção para o diagnóstico. (27)

Caracteristicamente a neurite associada a DENMO tende a ter longitudinalmente extensa, acometendo geralmente 3 de 5 segmentos do nervo ou ao menos 17,6mm do nervo óptico com extensão para regiões posteriores do nervo como o quiasma óptico ou o trato óptico (**Figura 1).** Já na neurite da Esclerose Múltipla são mais comuns neurites retrobulbares curtas com acometimento mais anterior e na doença associado ao anti-MOG, MOGAD, apesar de extensas as neurites acometem predominantemente os segmentos anteriores do nervo óptico. (27) (**Figura 1)**

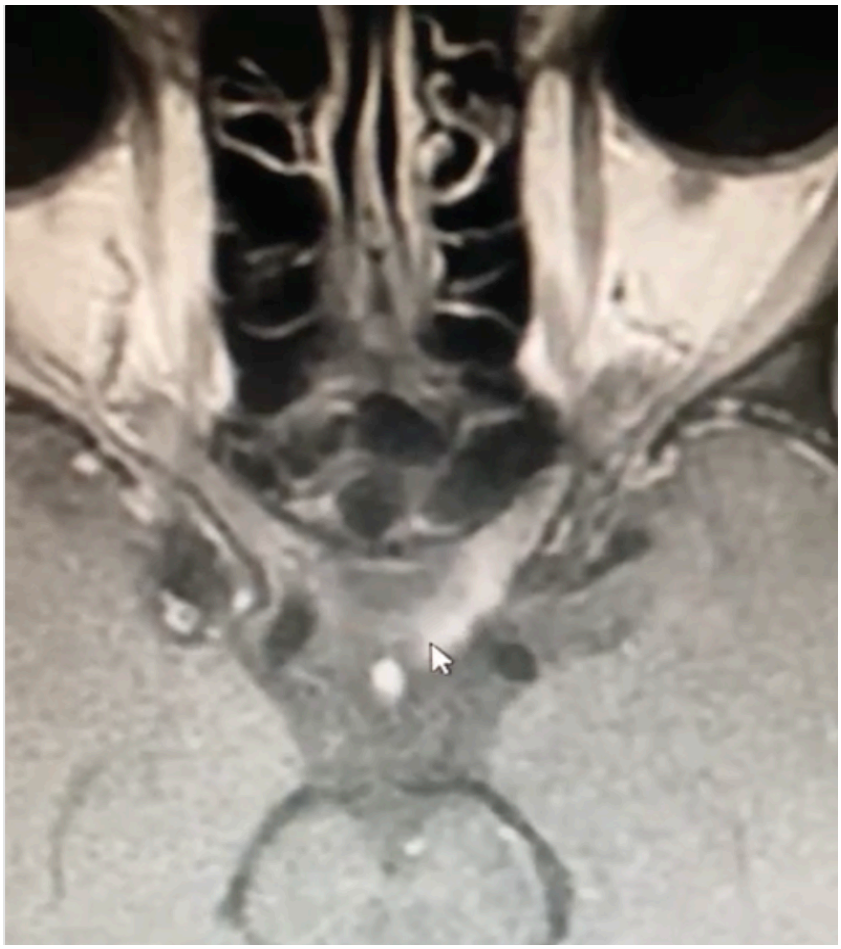

Figura 1- RM de encéfalo com cortes axiais em sequência T1GD, demostrando intensa captação de contraste em porção posterior de nervo óptico esquerdo e quiasma. Paciente feminino, 38 anos, DENMO Anti-AQP4+.

Quando se avalia o comprometimento de fibras retinianas e peripapilares pela tomografia de coerência óptica, OCT, é visto também uma maior perda neuronal quando comparado a pacientes saudáveis ou paciente com EM. (28)

4.2 Mielite Aguda

Outra manifestação central da NMOSD é a mielite aguda que tipicamente manifesta-se clinicamente como uma mielite transversa aguda grave com

acometimento motor (paraparesia/plegia ou tetraparesia/plegia), sintomas sensitivos (parestesias, hipoestesias, dor) e sintomas autonômicos (incontinência ou retenção fecal e urinária), mas em outros casos podemos ter acometimentos parciais da medula.

Diferente da Esclerose Múltipla na qual temos na maioria das vezes manifestações de uma mielite parcial, e acometimento focais e periféricos da medula, na NMOSD o acometimento mais característico é uma mielite longitudinal extensa grave com acometimento de mais de 3 seguimentos contíguos com comprometimento preponderantemente central e sendo mais frequente nos segmentos cervicais muitas vezes incluindo a transição bulbomedular **(Figura 2).** Na MOGAD a mielite também pode ser longitudinal extensa, mas com um predomínio de acometimento de seguimentos medulares mais baixos com acometimentos lombares e sacrais. (29)

É importante lembrar que até 14% dos pacientes podem apresentar um quadro de uma mielite curta e que em 40% desses pacientes essa pode ser a primeira manifestação e ser um fator de confusão importante com EM. Nas exacerbações subsequentes mais de 90% dos pacientes apresentaram uma mielite longitudinalmente extensa. (30)

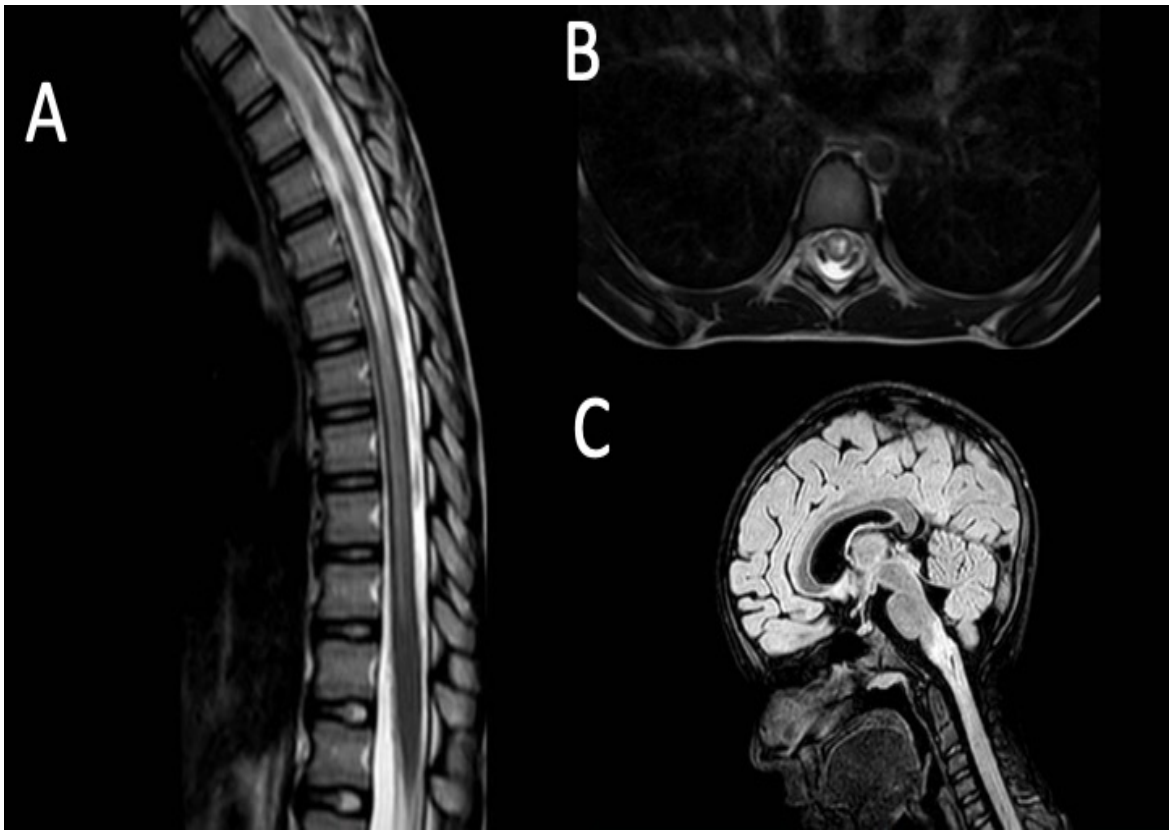

Figura 2. A- Imagem de RM em sequência T2 com cortes sagitais demostrando mielite longitudinal extensa em região dorsal; **B –** Imagem de RM de coluna dorsal sequencia T2 em cortes axiais demostrando mielite central com "Bright Spot Lesions" ; **C –** RM Imagem de RM encéfalo em sequência FLAIR axial demostrando alteração de sinal em bulbo e transição bulbomedular. Paciente 18 anos DENMO anti-AQP4+.

4.3 Síndrome da área postrema

A síndrome da aérea postrema é caracterizada por sintomas de náuseas vômitos e soluços incoercíveis, com duração de ao menos 48 hora, e associados ao acometimento documentado em RM de comprometimento de

região dorsal do bulbo **(Figura 3).** Em séries da literatura estima-se que mais de 30% dos pacientes com NMOSD irão apresentar um episódio de síndrome de área postrema durante o curso da doença, e em mais de 50% dos casos podem preceder em menos de 30 dias o aparecimento de outras síndromes típicas como mielite ou neurite. (30–33) A APS é um fator importante de diferenciação do MOGAD, no qual a APS ocorre em apenas 1,9% dos pacientes durante o curso de doença. (34) Quando ocorre como primeira manifestação da doença pode ser confundida muitas vezes com patologias gastrointestinais ou outras causas de vômitos. (35)

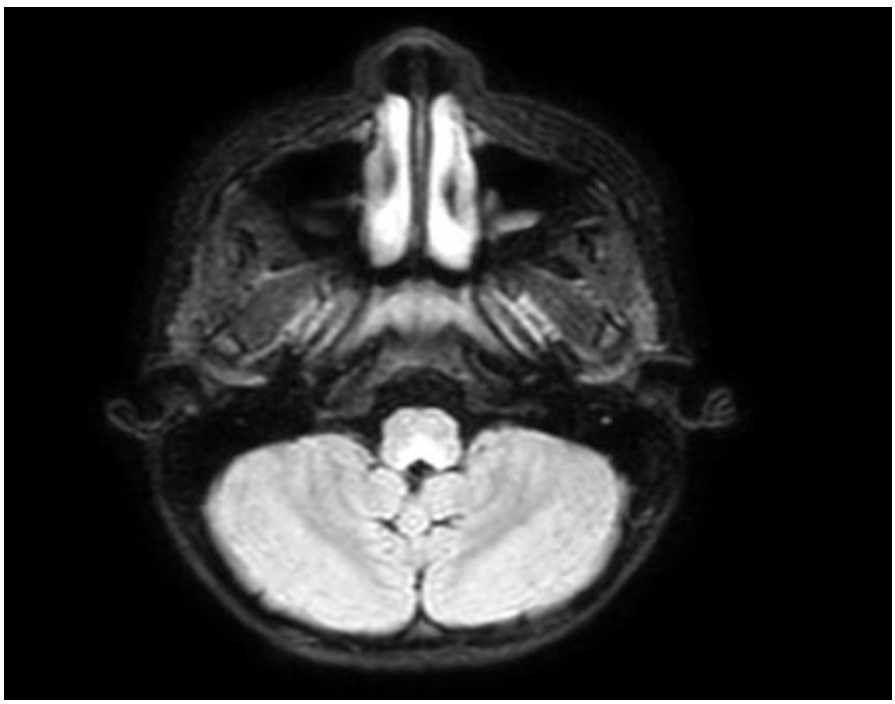

Figura 3. Imagem de RM de encéfalo em sequência FLAIR com cortes axiais, demostrando alteração de sinal em região dorsal do bulbo (Área postrema). Paciente 18 anos DENMO Anti-AQP4+.

4.4 Síndrome de tronco encefálico

Além dos sintomas relacionados a APS, outros sintomas agudos de acometimento de tronco encefálico podem ocorrer em pacientes com NMOSD associados a lesões em regiões periependimárias do quarto ventrículo no tronco encefálico e cerebelo. **(Figura 4)**

As manifestações mais comuns fora os relacionados a APS são alterações relacionados a disfunção oculomotora, paresia facial, disartria e sintomas vestibulares. (36)

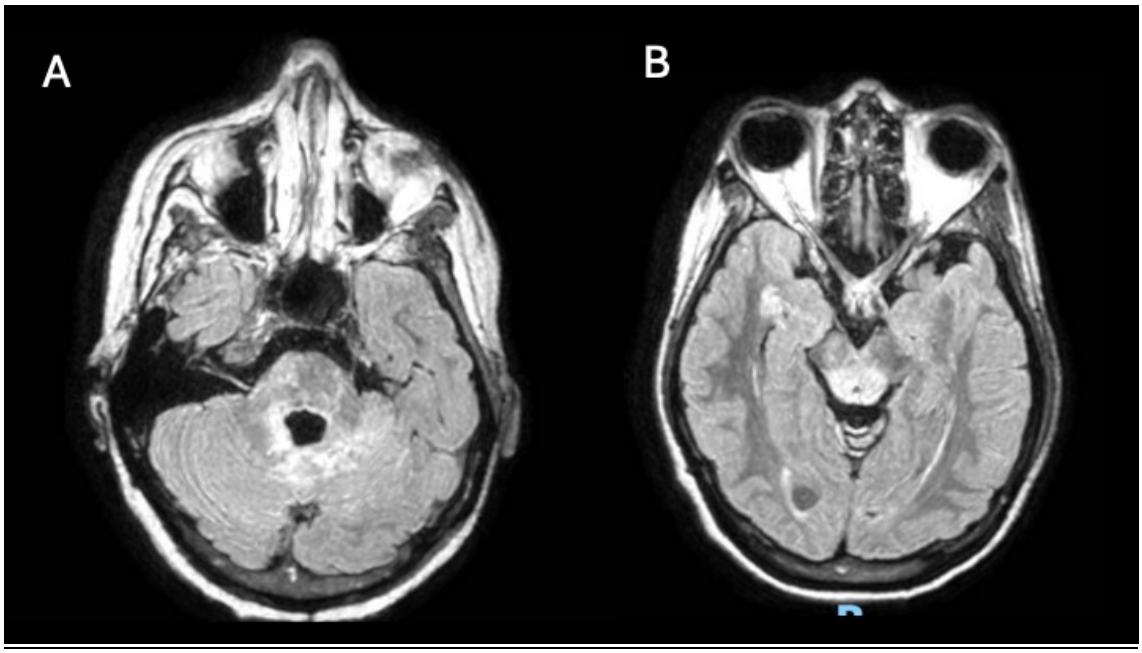

Figura 4. Imagem de RM de encéfalo em sequência FLAIR com cortes axiais demonstrando: **A-** Alteração de sinal em tronco encefálico Peri-quarto ventrículo. B- Alteração de sinal em tegmento mesencefálico e peri-arqueductal. Paciente 35 anos DENMO Anti-AQP4+.

4.5 Síndrome Diencefálica ou narcolepsia aguda com imagens típicas de NMOSD.

A região diencefálica é uma região do encéfalo com grande concentração de canais de aquaporina-4, e apesar das manifestações clínicas serem menos frequentes pode ser um alvo nos pacientes com NMOSD em aproximadamente 3% dos casos. Dentre as manifestações mais frequentes temos a síndrome narcoléptica aguda com uma apresentação de uma hipersonolência de rápida instalação, mas também sintomas como amenorreia, hipotensão e síndrome da secreção inapropriada de hormônio antidurético. (37) Para caracterização da síndrome é importante a confirmação por ressonância magnética do acometimento de áreas de hipotálamo, tálamo ou regiões periependimárias adjacentes ao terceiro ventrículo. **(Figura 5)**

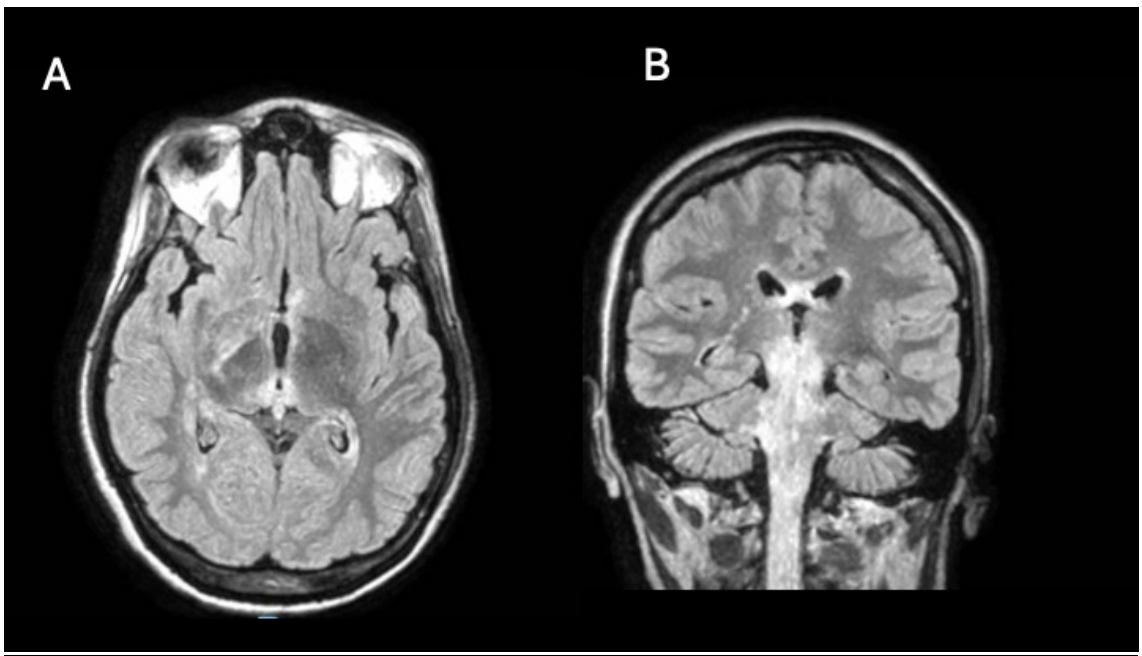

Figura 5. Imagem de RM de encéfalo em sequência FLAIR com **A-** corte axial; **B-** corte coronal: demostrando alteração de sinal em região em diencéfalo, região Peri-terceiro ventrículo e tronco encefálico e medula cervical. Paciente 35 anos DENMO Anti-AQP4+.

4.6 Síndrome Cerebral Sintomática com imagens típicas de NMOSD

Apesar de lesões cerebrais assintomáticas em NMOSD serem comuns, em torno de 18% dos pacientes com NMOSD apresentam sintomas.(38) Dentre as apresentações possíveis dessa síndrome estão quadros com estado confusional agudo ou comprometimento de nível de consciência, crises epilépticas e déficits motores ou sensitivos com acometimentos de vias longas também são encontrados.(7) Lesões grandes, confluentes, unilaterais ou bilaterais subcorticais ou profundas da substância branca são as imagens mais características associadas a essa síndrome. (8)

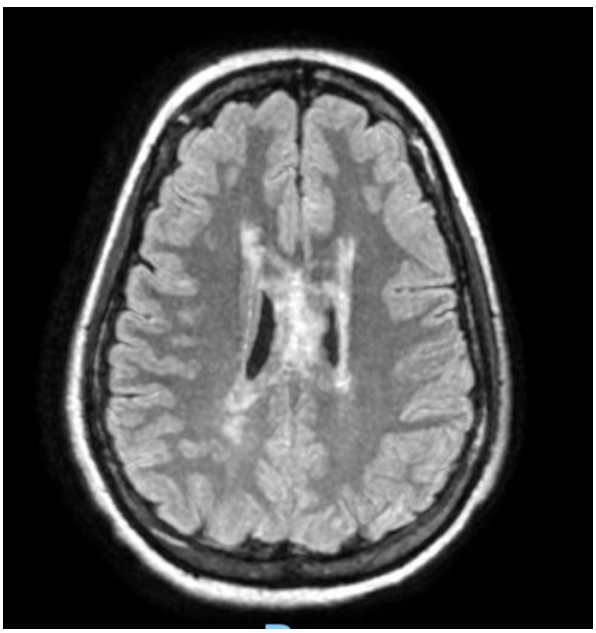

Figura 5. Imagem de RM de encéfalo em sequência FLAIR com corte axial com alteração de sinal periventricular e corpo caloso com lesão em "arco de Ponte". Paciente 35 anos DENMO Anti-AQP4+.

5. Tratamento

A DENMO é uma doença grave, estima-se que não tratada 50% dos pacientes estarão em cadeira de rodas ou cegos em um período de 5 anos e neste mesmo período em torno de 33% virão a óbito. (39)

O tratamento da DENMO possui dois fundamentos principais: a gestão dos episódios agudos de piora e a terapia crônica de modificação da doença. Para controlar os surtos agudos, a abordagem mais comum é a pulsoterapia intravenosa, que envolve o uso de altas doses de corticosteroides geralmente 1 grama por dia de 3 a 7 dias consecutivos ou plasmaferese, que é um processo no qual o plasma é separado dos componentes inflamatórios, como imunoglobulinas auto reativas circulantes, o sistema complemento e citocinas. O objetivo terapêutico desse procedimento reside na eliminação desses agentes mediadores dos processos patológicos, e quando realizado de forma precoce em surtos graves de DENMO leva um desfecho mais favorável. (40)

A terapia de manutenção tem como o objetivo de reduzir a frequência de exacerbações agudas e consequentemente a piora de incapacidade.

Estudos observacionais demostram algum benefício de drogas imunossupressores gerais como a azatioprina (2-3mg/kg/dia) combinada com prednisona oral (1mg/kg/dia), micofenolato mofetil (41) Os resultados de estudos abertos com uso de terapia Anti-CD20, rituximabe, demostronstraram que ele pode também reduzir a taxa da taxa se surtos e incapacidade. (42)

Recentemente estudos clínicos randomizados foram publicados demostrando redução significativas de surtos com uso de terapias anti-CD19 (Inebilizumabe), anti-Il6r (Satralizumabe) e anti-complemento C5 (Eculizumabe e Ravulizumabe) (43–46). Tendo início finalmente uma nova era para DENMO com medicação aprovadas pelas agências regulatórias.

IV. Objetivos

1- Gerais

Identificar aspectos clínicos, demográficos e fatores associados a maior progressão da doença em pacientes com DENMO no Estado da Bahia.

2- Específicos

Descrever características clínicas, demográficas e sociais de pacientes com DENMO em um centro de referência no Estado da Bahia.

Avaliar a taxa anualizada de surto e escores de progressão de doença nos pacientes com DENMO.

Analisar fatores associados a pior prognósticos em pacientes com paciente com DENMO no Estado da Bahia.

Descrever a terapêutica utilizada em pacientes com DENMO no Estado da Bahia.

Comparar características clínicas e radiológicos de pacientes com DENMO aquaporina-4 positivos e negativos.

Analisar presença de doenças autoimunes associadas e outros marcadores imunológicos na população estudada.

V. Casuística Material e Métodos

Foi realizado um estudo retrospectivo no qual foram incluídos 91 pacientes com DENMO, com base nos critérios de 2015 (8), atendidos consecutivamente entre 2017 e 2020. Os dados foram colhidos antes do período pandêmico que culminou com interrupção de atendimentos presenciais e atividades de pesquisa no período de 2020 a 2021.

Todos os pacientes foram acompanhados no centro de referência em NMOSD e MS da Universidade Federal da Bahia, localizado no nordeste do Brasil. Este é o único centro de referência público no estado da Bahia.

Todos os pacientes que preencheram os critérios e concordaram em participar do estudo assinaram o termo de consentimento livre e esclarecido

que inclui o acesso aos prontuários pelos pesquisadores. Para pacientes menores de 18 anos também foi assinado por um responsável.

Dados

Os dados foram obtidos prospectivamente por meio de entrevista no dia da consulta ambulatorial e complementados por revisão retrospectiva dos prontuários por meio de questionário padronizado aplicado pelo grupo de pesquisadores. Dados clínicos, demográficos, laboratoriais e de RM foram coletados de todos os pacientes que preencheram os critérios de inclusão.

Os seguintes fatores foram avaliados: idade de início, sexo, etnia, escolaridade, primeira síndrome de início, número de ataques, taxa de recidiva anualizada, sequelas da doença, comorbidades, doenças autoimunes concomitantes e status de AQP4-IgG (por metodologia CBA, TBA, ELISA ou Facs). A duração da doença foi definida como o intervalo de tempo entre a apresentação da doença e o último seguimento. Considerou-se atraso até o diagnóstico quando o tempo entre o início dos sintomas e o diagnóstico foi superior a 12 meses.

As informações relacionadas à análise por RM foram obtidas por meio de um laudo fornecido pelo neurorradiologista com base no primeiro exame realizado após o início dos sintomas. As informações foram coletadas com base na topografia do encéfalo e da lesão medular (cervical, torácica e lombar) e na extensão da lesão medular (número de segmentos vertebrais). As lesões na área postrema foram analisadas separadamente das demais

topografias de medula oblonga. Definimos mielite longitudinalmente extensa quando a lesão acometeu três ou mais segmentos vertebrais contínuos.

O grau de incapacidade foi quantificado pela *Expanded Disability Status Scale (EDSS)* (46) aplicada no momento da admissão do paciente no estudo por um neurologista certificado, a pontuação EDSS foi realizada pelo menos 30 dias após o último ataque.

Para controlar o viés devido à inclusão de pacientes com diferentes durações da doença, foram utilizados parâmetros como índice de progressão, taxa de recidiva anualizada e regressão binomial negativa.

O índice de progressão foi definido pela relação entre EDSS e a duração da doença em anos (47), enquanto a taxa de recidiva anualizada foi definida como a razão entre o número de ataques e a duração da doença em anos.

Aprovação ética e consentimento para participar:

Este estudo foi aprovado pelo Comitê de Ética em Pesquisa do Hospital da Universidade Federal da Bahia com base na Resolução nº 466/2012 do Conselho Nacional de Saúde do Brasil, que regulamenta a pesquisa com seres humanos no Brasil. Todos os métodos foram realizados de acordo com as diretrizes e regulamentos relevantes. O consentimento informado foi obtido de todos os sujeitos e/ou seu(s) responsável(is).

Análise estatística

A análise estatística foi realizada utilizando-se o software estatístico STATA versão 14.1 (StataCorp, College Station, TX). Os dados categóricos foram descritos em frequências e proporções simples (%). As variáveis contínuas de distribuição normal foram descritas como média e desvio-padrão; e mediana e intervalo interquartil (IQR) para aqueles com distribuição não normal. A distribuição das variáveis quantitativas foi observada por inspeção visual do histograma e pelo teste de Kolmogorov-Smirnov.

Utilizou-se regressão binomial negativa para avaliar a associação entre cada variável independente com o desfecho da progressão da incapacidade ao longo do tempo (EDSS como variável dependente e duração da doença em meses como variável offset). As variáveis com possível associação nas análises univariáveis ($p<0,1$) foram incluídas em um modelo final de regressão binomial negativa multivariável, que foi utilizado para estimar os riscos relativos (RR) e intervalos de confiança de 95%. A significância estatística foi estabelecida em um nível alfa de 5%.

VI. Artigo

Artigo 1

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RESEARCH Open Access

Clinical and prognostic aspects of patients with the Neuromyelitis Optica Spectrum Disorder (NMOSD) from a cohort in Northeast Brazil

Thiago Gonçalves Fukuda[1,2,3*], Ivã Taiuan Fialho Silva[2], Tayla Samanta Silva dos Santos[2], Marcos Baruch Portela Filho[3], Fernanda Ferreira de Abreu[2] and Jamary Oliveira-Filho[1,2]

Abstract

Introduction: Neuromyelitis optica spectrum disorders (NMOSD) is a rare inflammatory and demyelinating disease of the central nervous system (CNS) more frequent in women and Afro-descendants. No previous epidemiological or prognostic study has been conducted in the region of the state of Bahia, Brazilian Northeast.

Objective: To evaluate clinical and prognostic aspects in patients with NMOSD from a cohort in northeastern Brazil.

Material and methods: A single-center retrospective study was conducted with consecutive patients diagnosed with NMOSD. Clinical and epidemiological characteristics were described. The degree of disability was expressed by the Expanded Disability Status Scale (EDSS). Worsening disability were analyzed through negative binomial regression adjusted for disease duration.

Results: Ninety-one patients were included, 72 (79.1%) female and 67 (73.6%) afro descendants. Mean age at onset was 36 (± 14) years and 73.3% were anti-aquaporin-4 antibody positive. Isolated transverse myelitis (32.9%) and isolated optic neuritis (22.4%) were the most frequent initial clinical syndromes. After multivariate analysis, optic neuritis ($RR = 0.45$; 95% CI = 0.23 – 0.88; $p = 0.020$) and dyslipidemia ($RR = 0.40$; 95% CI = 0.20 – 0.83; $p = 0.014$) were associated with slower disease progression. Area postrema involvement ($RR = 6.70$; 95% CI = 3.31 – 13.54; $p < 0.001$) and age at onset (RR = 1.03; 95% CI = 1.01 – 1.05; $p = 0.003$) were associated with faster disease progression.

Conclusions: In the first clinical and prognostic study in northeastern Brazil, we identified area postrema involvement, age at onset, optic neuritis at fist syndrome and dyslipidemia as the main prognostic factors associated with disease progression.

Highlights

- Isolated transverse myelitis was the most frequent initial clinical syndrome.
- Optic neuritis as first clinical syndrome was independently associated with better prognostic.

*Correspondence: thiagofukuda@gmail.com
[1] Post-Graduate Program in Health Sciences, Federal University of Bahia (UFBA), Salvador, Bahia, Brazil
Full list of author information is available at the end of the article

- Age at onset were associated with faster disease progression.
- Hashimoto's thyroiditis was the most frequent autoimmune disease in NMOSD.

Keywords: Neuromyelitis optica spectrum disorders, Prognostic factors, Brazilian Northeast, Aquaporin-4

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) is an inflammatory and demyelinating disease of the central nervous system (CNS). The pathophysiology of NMOSD results from the autoimmunity against water channels (aquaporin-4) that are widely distributed in the CNS [1, 2]. The most recent diagnostic criteria recognize six core clinical characteristics of presentation during an attack, which the most common are optic neuritis (ON), longitudinally extensive transverse myelitis (LETM) and area postrema syndrome (APS) [3].

The natural history of the disease is variable, with most cases presenting a relapsing remitting course. It leads to accumulation of neurologic deficits from attacks with slow or partial recovery, which results in functional disability due to visual and motor sequelae [4]. Because of the variability and severity within the course of the disease, the ability to predict risk factors associated with poor outcomes can be useful to help physicians choosing therapeutic approaches.

NMOSD is a rare disease with an estimated prevalence of 0.3–4.4/100,000, more frequent in women and Afro-descendants [5]. Few epidemiological studies have been carried out in Europe, Asia, the United States and Latin America [6–12]. No studies were found in northeastern Brazil or in the State of Bahia, State with the highest percentage of blacks outside Africa [13].

Previous studies have evaluated epidemiologic and clinical features as predictors of disease outcomes. Optic neuritis as initial clinical presentation has been associated with poor visual acuity outcomes, whereas the seropositive to AQP4-IgG and poor recovery from the first attack have been shown to predict greater severity in the course of the disease [8, 14, 15]. Other known predictors of worse prognosis include age at disease onset, afro descendent ethnicity, higher number of attacks before and after immunosuppressive treatment and association with other autoimmune diseases [14–19].

In the present study, we aim to evaluate clinical, demographic, radiologic and laboratory data from 91 patients in order to foresee possible features of worst disease progression.

Material and methods

Study design

A retrospective study was conducted in which 91 patients with NMOSD were included, based on 2015 criteria [3], attended consecutively between 2017 and 2019. All patients were followed-up at the NMOSD and MS references center from Federal University of Bahia, located in northeastern Brazil. This is the only reference center in the state of Bahia.

All patients who met the criteria and agreed to participate in the study signed the consent form that includes access to medical records by researchers. For patients under the age of 18 was also signed by a guardian.

Data

Data were obtained prospectively through an interview on the day of the outpatient consultation and complemented by retrospective review of medical records through a standardized questionnaire applied by the group of researchers. Clinical, demographic, laboratory and MRI data were collected from all patients who met the inclusion criteria.

The following factors were evaluated: age at onset, sex, ethnicity, educational level, first syndrome at onset, number of attacks, annualized relapse rate, disease sequelae, co-morbidities, concurrent autoimmune diseases, and AQP4-IgG status. Disease duration was defined as the time interval between disease presentation and last follow-up. Delay until diagnosis was considered when the time between the onset of symptoms and diagnosis was greater than 12 months.

The information related to MRI analysis was obtained through a report provided by neuroradiologist based on the first examination performed after the onset of symptoms. Information was collected based on topography of brain, and spinal cord lesion (cervical, thoracic, and lumbar) and extension of spinal cord lesion (number of vertebral segments). Lesions in the area postrema were analyzed separately from the other medulla oblongata topographies. We defined longitudinally extensive myelitis when the lesion affected more than three continuous vertebral segments.

The degree of disability was quantified by the Expanded Disability Status Scale (EDSS) [20] applied at the time of patient admission to the study by a certified neurologist, EDSS scoring was performed at least 30 days after last attack.

To control bias due to the inclusion of patients with different disease durations, parameters such as progression index, annualized relapse rate and negative binomial regression were used.

Progression index [21] was defined by the ratio between EDSS and the duration of the disease, whereas annualized relapse rate was defined as the ratio between the number of attacks and the disease duration in years.

Statistical analysis

Statistical analysis was performed using STATA Statistical Software version 14.1 (StataCorp, College Station, TX). Categorical data was described in simple frequencies and proportions (%). Continuous normally distributed variables were described as means and standard deviations; and median and interquartile range (IQR) for those with non-normal distribution. The distribution of quantitative variables was observed by visual inspection and with the Kolmogorov–Smirnov test.

We used negative binomial regression to assess the association between each independent variable to the outcome of disability progression over time (EDSS as the dependent variable and disease duration in months as the offset variable). Variables with a possible association in univariable analyses ($p < 0.1$) were included in a final multivariable negative binomial regression model, with was used to estimate relative risks (RR) and 95% confidence intervals. Statistical significance was set at an alpha level of 5%.

Results

General description of the sample (Table 1)

Ninety-one outpatients were included in this study, 72 (79.1%) were female and 67 (73.6%) afro descendants. The mean age at the interview was 45 (± 14) years, while the mean age at onset of the disease was 36 (± 14) years. The other sociodemographic data can be found in Table 1.

Among the clinical syndromes presented in the first event, isolated transverse myelitis (32.9%) and isolated optic neuritis (22.4%) were the most frequent, followed by ON and TM simultaneously (21.2%) and area postrema syndrome (5.9%). In the 75 outpatients with information on anti-aquaporin-4 antibody (AQP4) status, 73.3% were positive. Of the aquaporin-4 negative patients we tested only 7 patients; two additional patients with seropositivity only for Anti-MOG were excluded from the analysis. No patients positive for aquaporin 4 were tested. The median EDSS at the first interview was EDSS of 4.0 [interquartile range (IQR): 2.62–6.50]. The recurrent course was more frequent (83.5%), and the average number of attacks was 4.0 (± 3.6). The mean annualized relapse rate was 1.3 (± 1.6) and the mean progression index was 2.3 (± 4.1).

The most frequent comorbidity was systemic arterial hypertension (29.8%), followed by depression (24.4%), dyslipidemia (22.0%), diabetes mellitus (15.7%) and smoking (10.8%). Other autoimmune diseases were present in nine (10.2%) patients, such as Hashimoto's thyroiditis (four patients), systemic lupus erythematosus (three patients), Sjögren's syndrome (one patient) and vitiligo (one patient).

Brain lesions were found in 52/73 (71.2%) patients who underwent brain magnetic resonance imaging (MRI). Most lesions were periventricular (17.8%), followed by

Table 1 General characteristics of 91 patients with neuromyelitis optica spectrum disorders

Characteristics	Total
Age at onset (years), average ± SD	36.3 ± 13.6
Female, n (%)	72 (79.1)
Afro-descendants, n (%)	67 (73.6)
First syndrome, n (%)	
Optic neuritis	19 (22.4)
Transverse Myelitis	28 (32.9)
Area postrema syndrome	5 (5.9)
ON + TM	18 (21.2)
ON + TM + APS	5 (5.9)
ON + APS	3 (3.5)
TM + APS	7 (8.2)
EDSS, median, (interquartile)	4 (2.62–6.50)
AQP4-IgG +, n (%)	55 (73.3)*
Autoimmune disease, n (%)	9 (10.2)
Recurrence, n (%)	71 (83.5)
Number of attacks, average ± SD	4.0 ± 3.6
Disease time (years), average ± SD	7.8 ± 6.9
Relapse rate, average ± SD	1.3 ± 1.6
Progression index, average ± SD	2.3 ± 4.1
Brain MRI lesions, n (%)	57 (75.0)
Spinal cord MRI lesions, n (%)	68 (90.7)
Number of affected vertebral bodies, median, (interquartile)	5 (3.0–7.0)
Longitudinally extensive lesion, n (%)	51 (78.5)
Spinal cord lesion topography, n (%)	
Cervical	25 (38.5)
Thoracic	10 (15.4)
Cervical and thoracic	18 (27.7)
Thoracic and lumbar	2 (2.9)
Lumbar and sacral	1 (1.5)
Without injury	9 (13.8)
Type of treatment, n (%)	
Azathioprine and glucocorticoid	37 (50.7)
Azathioprine	30 (41.1)
Rituximab	6 (8.2)

ON Optic Neuritis, *TM* Transverse Myelitis, *APS* Area postrema syndrome

* We had 55/75 (73.3% of those tested) AQP4-positive patients, 20/75 (26.6% of those tested) patients with NMOSD Aquaporin 4 negative and 16 met diagnostic criteria but had unknown aquaporin status (not tested or results not yet available)

area postrema (16.4%) and in the cerebellum (13.7%). In 65 patients who underwent spinal MRI, 51 (78.5%) had a longitudinally extensive lesion. The topography most affected was cervical (38.5%), followed by cervical and thoracic involvement (27.7%) and only thoracic (15.4%). The median number of affected vertebral bodies was 5.0 (IQR: 3.0–7.0).

Comparison of demographic, clinical and radiological characteristics between NMOSD patients with positive and negative aquaporin 4 status was performed and no statistically significant difference was found (Supplementary Table 1).

Association of age of onset of symptoms and worse rate of progression (Fig. 1)

When comparing patients in terms of progression index, older age at disease onset was seen in fast (>1 per year) vs slow (≤1 per year) progression index (43.0±13.8 vs 33.3±11.5 years of age, respectively). Similarly, three other findings were more frequent among patients with fast vs slow progression index: transverse myelitis as the initial presentation of the disease (50.0% vs 21.7%), diagnosis of autoimmune disease (22.6% vs 4.3%) and area postrema lesions (33.3% vs 2.7%).

Univariable predictors of worse disability progression over time (Table 2)

Older age at disease onset was associated with worse disability progression [$RR=1.07$; 95% CI (1.01–1.12); $p=0.020$]. Patients with dyslipidemia had a milder progression [$RR=0.09$; 95% CI (0.18–0.51); $p=0.006$].

Regarding the core syndrome of the first attack, outpatients who were affected only optic neuritis had a slower disability progression when compared to those who had only transverse myelitis [$RR=0.06$; 95% CI (0.01–0.44); $p=0.006$]. Similarly, those who had transverse myelitis and optic neuritis simultaneously at the first attack had slower progression [$RR=0.10$; 95% CI (0.01–0.66); $p=0.017$] when compared to those who had only transverse myelitis. Delay until diagnosis was associated with worse prognosis [$RR=12.53$; 95% CI (3.12–50.26); $p<0.001$].

There was no difference in progression regarding the positivity of the AQP4-IgG antibody [$RR=1.26$; 95% CI (0.24–6.59); $p=0.781$]. Outpatients with lesions in the area postrema tended to worse disability progression [$RR=6.55$; 95% CI (0.98–43.58); $p=0.052$].

Multivariable analysis (Table 3)

In the multivariable analysis, optic neuritis [$RR=0.45$; 95% CI (0.23 – 0.88); $p=0.020$] and dyslipidemia [$RR=0.40$; 95% CI (0.20 – 0.83) $p=0.014$] were associated with slower disability progression. Area postrema lesion [$RR=6.70$; 95% CI (3.31 – 13.54); $p<0.001$] and age at onset [$RR=1.03$; 95% CI (1.01 – 1.05); $p=0.003$] were associated with worse disease progression.

Discussion

This study is the first to evaluate clinical and demographic features in the Brazilian northeast region. Although our study is not population-based, we believe that we were able to investigate a significant proportion of patients with NMOSD in the state of Bahia since our study center is the only reference center in the state.

Despite methodological differences and disparities in the definition of NMOSD over the years, we have a similar average age at onset compared to most studies,

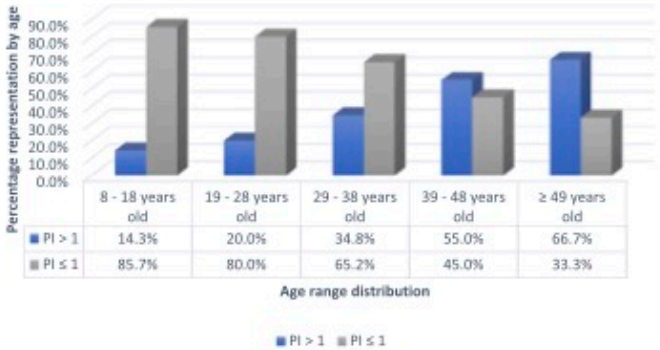

Fig. 1 Percentage distribution of the progression index by age group at onset of symptoms

Table 2 Univariable predictive clinic factors for early progression in neuromyelitis optica (negative binomial regression)

Variable	Relative risk	95% confidence interval	*P*-value
Sex			
Male	1.61	0.30 – 8.63	0.578
Female	Reference	–	–
Skin color			
Black	0.757	0.16 – 3.58	0.726
Others	Reference	–	–
Age at onset (years)	1.07	1.01 – 1.12	**0.020**
Co-morbidities			
Autoimmune disease	3.37	0.45 – 25.50	0.239
Hypertension	0.90	0.20 – 4.16	0.896
Diabetes mellitus	0.40	0.05 – 3.16	0.383
Dyslipidemia	0.09	0.18 – 0.51	**0.006**
Depression	0.20	0.04 – 1.12	0.067
Smoking	0.56	0.06 – 4.90	0.597
First syndrome			
Optic neuritis	0.06	0.01 – 0.44	**0.006**
Area postrema	0.38	0.02 – 6.28	0.497
Optic neuritis + transverse myelitis	0.10	0.01 – 0.66	**0.017**
Others	0.94	0.30 – 2.92	0.917
Transverse myelitis	Reference	–	–
AQP4-IgG +	1.26	0.24–6.59	0.781
Number of brain injuries on MRI	1.13	0.66–1.92	0.657
Topography of brain lesions on MRI			
Midbrain	1.07	0.00–5.97	0.276
Pons	2.10	0.24–18.08	0.500
Medulla Oblongata	2.45	0.37–16.04	0.349
High cervical spinal cord	2.94	0.39–22.35	0.298
Cerebellum	0.82	0.10–6.69	0.852
Periventricular	4.35	0.69–27.66	0.119
Area Postrema	6.55	0.98–43.58	**0.052**
Optic nerve MRI lesions	0.13	0.00–8.71	0.346
Delay until diagnosis (> 12 m)	12.53	3.12–50.26	< 0.001

Table 3 Multivariable predictors of early progression in optic neuromyelitis (negative binomial regression)

Variable	Relative risk	95% confidence interval	*P*-value
Optic neuritis at first syndrome	0.45	0.23 – 0.88	0.020
Area postrema involvement	6.70	3.31 – 13.54	< 0.001
Dyslipidemia	0.40	0.20 – 0.83	0.014
Depression	1.14	0.56 – 2.32	0.702
Age at onset (years)	1.03	1.01 – 1.05	0.003
Delay until diagnosis (> 12 m)	1.14	0.56 – 2.30	0.712

as well as the higher prevalence in women, with female: male proportions > 3:1[6–8, 10, 22–24]. Our sample has a higher percentage of afro-descendant patients (73.6%) compared to other international studies and even compared with other studies in Brazil. [6–8, 10, 22–24]. This could be due to the population profile of the study location, the city of Salvador, state of Bahia, which concentrates the highest proportion of black people outside Africa [13]. The higher prevalence of NMOSD among Afro-descendant populations explains the sample size of this study, which is comparable to prior multicenter studies that evaluated epidemiological aspects of entire countries [10, 11].

Despite this peculiarity, we did not find a significant association between the race of patients and worst clinical outcomes. This association shows a great divergence in the literature. A previous study demonstrated that race is not an independent factor of worse motor or visual prognosis [17]. Another author demonstrates that there is an association between the white race and worse visual outcomes and higher EDSS scores [14]. In addition, some papers found worse prognosis in Afro-Caribbean patients [18, 25]. Due to the wide miscegenation of the population it's difficult to define race in this Brazil, thus the racial stratification analyzed in this study was based on the patients' phenotype.

The guideline of the Brazilian Academy of Neurology, which is the main representative entity of neurologists in Brazil, on NMOSD is currently in progress. There is a manual published by this entity in 2016 that guides as first line—first option (rituximab, azathioprine or azathioprine plus corticoids), first line—second option (mycophenolate) and second line (methotrexate and cyclosporine) [26]. All our patients were using first line, first option medications.

The AQP4-IgG seropositivity was observed in 73.3% of patients, in accordance with prior studies [6, 7, 22, 24]. Other authors found a lower frequency of AQP4-IgG seropositivity [8, 11]. This divergence can be attributed to the methodology used and the timing of the antibody test. Although in some studies the seropositivity of AQP4-IgG antibody has been associated with more severe impairment [15, 27, 28]. Others, similar to our results, showed no association [11, 22].

According to many studies transverse myelitis was the most prevalent syndrome of initial attack (32.9%) [7, 10, 29]. The classic presentation of simultaneous ON and TM was observed in 21.2% of the patients, a percentage that is in agreement with other samples [7, 8, 22]. However, it was smaller than the percentage observed in other cohorts [6, 10]. Another important feature of our sample is that 5.9% of the patients had ON, TM and APS simultaneously in the initial presentation. This data can

be explained by another study that demonstrated that combined initial clinical syndromes are more frequent in Afro-American and Afro-European populations [17].

With regards to comorbid autoimmune diseases, the frequency in our sample is similar (10.2%) to what was shown in some previous studies [6, 8]. When compared to others studies, however, where up to a third of patients presented this type of comorbidity, our percentage was lower [10, 11, 22]. In our study, we observed that Hashimoto's thyroiditis was the most frequent autoimmune disease, followed by systemic lupus erythematosus, comorbidities that were previously associated with NMOSD [30]. Furthermore, the percentage of comorbid autoimmune diseases tended to be higher in patients with disease progression, but this association was not statistically significant in the multivariate analysis. A prior study described an association between concomitance of other autoimmune diseases and greater disability [31].

The annualized relapse rate as well as the frequency of relapsing remitting phenotype among patients were similar to the described in the literature. However, we found a progression index of 2.3 (±4.1), an index higher than the one reported in a previous southeastern Brazilian study [8]. Regarding the treatment options, the most frequent type of maintenance therapy used was the combination of azathioprine and glucocorticoid, which is accordant to other studies [8, 11, 22].

Concerning the prognostic factors, a higher age at the initial symptomatic presentation was associated with worst clinical outcome, as reported previously [32, 33]. Our findings also suggest that patients who had area postrema lesions could have worst disease outcomes. Previous studies indicate the medulla oblongata is a highly frequent CNS structure involved in NMOSD (prevalence varying between 12.8% and 91.3%), with lesions usually occurring in its dorsal part [34–37]. One study demonstrated that patients with medullary lesions were more likely to have a higher number of brain injuries, as well as disease with elevated clinical activity and rapid progression, hence reporting higher EDSS and annualized relapse rate scores [38]. To explain this more severe behavior among patients with area postrema injuries, we speculate that: 1) the signs and symptoms resulting from lesions in this topography can more severely increase the EDSS; 2) these patients are more often affected by a greater number of brain and extensive spinal cord injuries, which could have an impact on the severity of the disease.

Although it is not clear if the initial clinical syndrome type has an influence on prognosis, our study found that optic neuritis as first presentation was associated with slow disease progression. A recent retrospective study demonstrated that optic neuritis as initial presentation of NMOSD correlated to worst visual outcome, with no differences regarding EDSS [14]. One study showed that patients with optic neuritis as an initial symptom of multiple sclerosis took more years to achieve EDSS 4.0, 6.0 and 7.0 when compared to patients without neuritis [39]. Similarly, another study reported that patients who had optic neuritis as initial attack (clinically isolated syndrome) had a lower rate of conversion to multiple sclerosis, when compared to other types of first disease presentation [40]. However, this type of optic neuritis differs from atypical optic neuritis, as generally seen in NMOSD and further prospective studies are needed to investigate the real influence of the initial syndrome on the prognosis of patients. One of the limitations presented by the study was the low percentage of patients tested for anti-MOG and a possible association of patients with ADEM-like phenotype and/or concomitant neuritis and myelitis not being associated with a worse prognosis.

One of the most unexpected aspects of the present study was the finding of dyslipidemia as a factor associated to a better prognosis, a feature that was not analyzed in most of the previous epidemiological cohorts. This result is contrary to a previous observation that hypertriglyceridemia may be related to a worse recovery from the first demyelinating NMOSD attack [41]. One of the theories suggested to explain this finding is that dyslipidemic patients may have used hypolipidemic drugs as a long term treatment, such as statins, that have pleotropic anti-inflammatory effects and, therefore, a possible beneficial effect on disease control [42]. A second possible explanation is that the inflammatory activity is associated with reduction in LDL levels, as observed in other inflammatory diseases, such as rheumatoid arthritis, and in acute stress conditions, such as sepsis [43]. Thus, this could disguise the diagnosis of dyslipidemia in patients with greater inflammatory activity.

Conclusions

This is the first article to evaluate clinical, epidemiological and prognostic factors in the Brazilian northeast region, in which we assume concentrate an elevated prevalence of NMOSD, due to its ethnical singularities. Area postrema involvement and age at onset were independently associated with greater disability and optic neuritis at fist syndrome and dyslipidemia with less disease progression. Nevertheless, the prognostic aspects here reported need to be confirmed by prospective studies.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-022-02621-5.

Additional file 1: Supplementary Table 1. Comparison of demographic, clinical and radiological characteristics between patients with NMOSD with positive and negative aquaporin status 4.

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Authors' contributions
Thiago Gonçalves Fukuda: Conceptualization; Methodology; Writing—Original Draft; Project administration. Ivã Taiuan Fialho Silva: Formal analysis; Investigation; Writing—Original Draft. Tayla Samanta Silva dos Santos: Formal analysis; Investigation; Writing—Original Draft. Marcos Baruch Portela Filho: Formal analysis; Investigation; Writing—Original Draft. Fernanda Ferreira de Abreu: Formal analysis; Investigation; Writing—Original Draft. Jamary Oliveira-Filho: Conceptualization; Methodology; Writing—Review & Editing; Supervision. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request. Please contact TGF at thiagofukuda@gmail.com if this information is of interest.

Declarations

Ethics approval and consent to participate
This study was approved by Federal University of Bahia Hospital Research Ethics Committee based on Resolution No. 466/2012 of the National Health Council of Brazil, which regulates research with humans in Brazil. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication
Not applicable.

Competing interests
The authors declare no conflicts of interest.

Author details
[1]Post-Graduate Program in Health Sciences, Federal University of Bahia (UFBA), Salvador, Bahia, Brazil. [2]Neurology Service, Professor Edgar Santos University Hospital, Federal University of Bahia (UFBA), Salvador, Bahia, Brazil. [3]State University of Bahia (UNEB), Salvador, Bahia, Brazil.

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Supplementary Information

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Additional file 1: Supplementary Table 1. Comparison of demographic, clinical and radiological characteristics between patients with NMOSD with positive and negative aquaporin status 4.

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Authors' contributions
Thiago Gonçalves Fukuda: Conceptualization; Methodology; Writing—Original Draft; Project administration. Ivã Taiuan Fialho Silva: Formal analysis; Investigation; Writing—Original Draft. Tayla Samanta Silva dos Santos: Formal analysis; Investigation; Writing—Original Draft. Marcos Baruch Portela Filho: Formal analysis; Investigation; Writing—Original Draft. Fernanda Ferreira de Abreu: Formal analysis; Investigation; Writing—Original Draft. Jamary Oliveira-Filho: Conceptualization; Methodology; Writing—Review & Editing; Supervision. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request. Please contact TGF at thiagofukuda@gmail.com if this information is of interest.

Declarations

Ethics approval and consent to participate
This study was approved by Federal University of Bahia Hospital Research Ethics Committee based on Resolution No. 466/2012 of the National Health Council of Brazil, which regulates research with humans in Brazil. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all subjects and/or their legal guardian(s).

Consent for publication
Not applicable.

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The authors declare no conflicts of interest.

Author details
[1]Post-Graduate Program in Health Sciences, Federal University of Bahia (UFBA), Salvador, Bahia, Brazil. [2]Neurology Service, Professor Edgar Santos University Hospital, Federal University of Bahia (UFBA), Salvador, Bahia, Brazil. [3]State University of Bahia (UNEB), Salvador, Bahia, Brazil.

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VII. Resultados gerais

Descrição geral da amostra

Foram incluídos noventa e um pacientes no estudo, 72 (79,1%) eram do sexo feminino e 67 (73,6%) afrodescendentes. A média de idade na entrevista foi de 45 (± 14) anos, enquanto a média de idade de início da doença foi de 36 (± 14) anos. Os demais dados sócios demográficos podem ser encontrados na Tabela 1.

Tabela 1: Características gerais de 91 pacientes com transtornos do espectro da neuromielite óptica.

Características	**Total**
Idade de início (anos), média ± DP	36,3 ±13,6
Feminino, n (%)	72 (79,1)
Afrodescendente, n (%)	67 (73,6)
Primeira síndrome, n (%)	
Neurite óptica	19 (22,4)
Mielite Transversal	28 (32,9)
Síndrome da área postrema	5 (5,9)
ON + TM	18 (21,2)

ON + TM + APS	5 (5,9)
ON + APS	3 (3,5)
TM + APS	7 (8,2)
EDSS, mediana, (interquartil)	4 (2-6,2)
AQP4-IgG+, n (%)	55 (73,3) *
Doença autoimune associada n (%)	16 (17,5)
Recorrência, n (%)	71 (83,5)
Número de ataques, média ± DP	4,0 ±3,6
Tempo de doença (anos), média ± DP	7,8 ±6,9
Taxa de recidiva, média ± DP	1,3 ± 1,6
Índice de progressão, média ± DP	2,3 ±4,1
Lesões por RM cerebral, n (%)	57 (75,0)
Lesões por RM medular, n (%)	68 (90,7)
Número de corpos vertebrais afetados, mediana, (interquartil)	5 (3,0-7,0)
Lesão longitudinalmente extensa, n (%)	51 (78,5)
Topografia da lesão medular, n (%)	

Cervical	25 (38,5)
Torácico	10 (15,4)
Cervical e torácica	18 (27,7)
Torácica e lombar	2 (2,9)
Lombar e sacral	1 (1,5)
Sem acometimento	9 (13,8)
Tipo de tratamento, n (%)	
Azatioprina e glicocorticoide	37 (50,7)
Azatioprina	30 (41,1)
Rituximabe	6 (8,2)

ON = Neurite Óptica; MT = Mielite Transversal; SAP = Síndrome da área postrema

- Tivemos 55/75 (73,3% dos testados) pacientes positivos para AQP4, 20/75 (26,6% dos testados) pacientes com NMOSD Aquaporina-4 negativos e 16 preencheram os critérios diagnósticos, mas tinham status de aquaporina desconhecido (não testado ou resultados ainda não disponíveis).

Dentre as síndromes clínicas apresentadas no primeiro evento, a mielite transversa isolada (32,9%) e a neurite óptica isolada (22,4%) foram as mais frequentes, seguidas pela ON e MT simultaneamente (21,2%) e

síndrome da área póstrema (5,9%). Nos 75 pacientes com informações sobre o status do anticorpo anti-aquaporina-4 (AQP4), 73,3% foram positivos. Dos pacientes negativos para aquaporina-4 testamos apenas 7 pacientes foi testado para anticorpo Anti-MOG IgG, dois pacientes adicionais com soropositividade apenas para Anti-MOG foram excluídos da análise. Nenhum paciente positivo para aquaporina-4 foi testado. A mediana do EDSS na primeira entrevista foi EDSS de 4,0 [intervalo interquartil (IQR): 2-6]. O curso recorrente foi mais frequente (83,5%), e o número médio de ataques foi de 4,0 (± 3,6). A taxa média anualizada de recidiva foi de 1,3 (± 1,6) e o índice médio de progressão foi de 2,3 (± 4,1) pontos/ano.

A comorbidade mais frequente foi hipertensão arterial sistêmica (29,8%), seguida de depressão (24,4%), dislipidemia (22,0%), diabetes mellitus (15,7%) e tabagismo (10,8%).

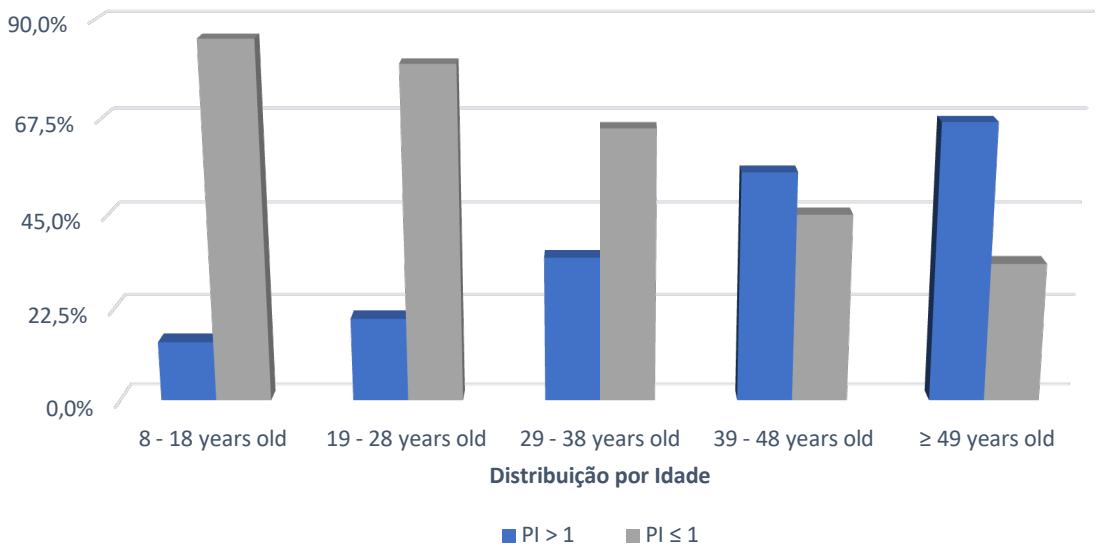
Lesões cerebrais foram encontradas em 52/73 (71,2%) pacientes submetidos à ressonância magnética (RM) cerebral. A maioria das lesões foi periventricular (17,8%), seguida de área postrema (16,4%) e cerebelo (13,7%). Em 65 pacientes submetidos à RM da coluna vertebral, 51 (78,5%) apresentaram lesão longitudinalmente extensa. A topografia mais acometida foi cervical (38,5%), seguida de acometimento cervical e torácico (27,7%) e apenas torácica (15,4%). A mediana do número de corpos vertebrais afetados foi de 5,0 (IQR: 3,0-7,0).

Associação de idade de início dos sintomas e pior taxa de progressão

[Gráfico 1]

Ao comparar os pacientes em termos de índice de progressão, a idade mais avançada no início da doença foi observada no índice de progressão rápida (>1 por ano) vs lenta (≤1 por ano) (43,0 ±13,8 vs 33,3 ±11,5 anos de idade, respectivamente). Da mesma forma, três outros achados foram mais frequentes entre os pacientes com índice de progressão rápida versus lenta: mielite transversa como apresentação inicial da doença (50,0% vs 21,7%), diagnóstico de doença autoimune (22,6% vs 4,3%) e lesões da área postrema (33,3% vs 2,7%).

Gráfico 1. Distribuição percentual do índice de progressão por idade de início dos sintomas.



Preditores univariáveis de pior progressão da incapacidade ao longo do tempo

A idade avançada no início da doença foi associada a uma pior progressão da incapacidade [RR = 1,07; IC 95% (1,01–1,12); p = 0,020]. Pacientes com dislipidemia tiveram uma progressão mais leve [RR = 0,09; IC 95% (0,18–0,51); p = 0,006].

Em relação à síndrome clínica do primeiro ataque, os pacientes que foram afetados apenas neurite óptica tiveram uma progressão de incapacidade mais lenta quando comparados àqueles que tiveram apenas mielite transversal [RR = 0,06; IC 95% (0,01–0,44); p = 0,006]. Da mesma forma, aqueles que apresentaram mielite transversa e neurite óptica simultaneamente no primeiro ataque tiveram progressão mais lenta [RR = 0,10; IC 95% (0,01–0,66); p = 0,017] quando comparados àqueles que tiveram apenas mielite transversa. O atraso até o diagnóstico foi associado a pior prognóstico [RR = 12,53; IC 95% (3,12-50,26); p <0,001].

Não houve diferença na progressão em relação à positividade do anticorpo AQP4-IgG [RR = 1,26; IC 95% (0,24–6,59); p = 0,781]. Pacientes com lesões na área postrema tenderam a pior progressão da incapacidade [RR = 6,55; IC 95% (0,98–43,58); p = 0,052].

Tabela 2: Fatores clínicos preditivos univariáveis para progressão precoce da NMOSD (regressão binomial negativa).

Variável	Risco relativo	Intervalo de confiança de 95%	Valor de p
Sexo			
Masculino	1.61	0.30 – 8.63	0.578
Feminino	Referência	–	–
Cor da pele			
Preto	0.757	0.16 – 3.58	0.726
Outros	Referência	–	–
Idade de início (anos)	1.07	1.01 – 1.12	**0.020**
Comorbidades			
Doença autoimune	3.37	0.45 – 25.50	0.239
Hipertensão	0.90	0.20 – 4.16	0.896

Diabetes mellitus	0.40	0.05 – 3.16	0.383
Dislipidemia	0.09	0.18 – 0.51	**0.006**
Depressão	0.20	0.04 – 1.12	0.067
Tabagismo	0.56	0.06 – 4.90	0.597
Primeira síndrome			
Neurite óptica	0.06	0.01 – 0.44	**0.006**
Área postrema	0.38	0.02 – 6.28	0.497
Neurite óptica + mielite transversa	0.10	0.01 – 0.66	**0.017**
Outros	0.94	0.30 – 2.92	0.917
Mielite transversal	Referência	–	–
AQP4-IgG +	1.26	0.24-6.59	0.781
Número de lesões cerebrais na ressonância magnética	1.13	0.66-1.92	0.657
Topografia de lesões cerebrais na RM			
Mesencéfalo	1.07	0.00-5.97	0.276

Pons	2.10	0.24-18.08	0.500
Medula oblonga	2.45	0.37-16.04	0.349
Medula espinhal cervical alta	2.94	0.39-22.35	0.298
Cerebelo	0.82	0.10-6.69	0.852
Periventricular	4.35	0.69-27.66	0.119
Área Postrema	6.55	0.98-43.58	**0.052**
Lesões de RNM do nervo óptico	0.13	0.00-8.71	0.346
Atraso até o diagnóstico (>12m)	12.53	3.12-50.26	**<0,001**

Análise multivariada

Na análise multivariada, neurite óptica [RR = 0,49; IC 95% (0,29 – 0,84); p = 0,009] e dislipidemia [RR = 0,50; IC 95% (0,26 – 0,96); p = 0,038] foram associados à progressão mais lenta da incapacidade. A lesão da área postrema [RR = 6,59; IC 95% (3,56 – 12,21); p < 0,001] e a idade de início [RR = 1,01; IC 95% (1,00 – 1,03); p = 0,047] foram associados à pior progressão da doença. (**Tabela 3)**

Tabela 3: Preditores multivariáveis de progressão precoce na Neuromielite óptica (regressão binomial negativa).

Variável	Risco relativo	Intervalo de confiança de 95%	Valor de p
Neurite óptica na primeira síndrome	0.49	0.29 – 0.84	**0.009**
Envolvimento da área postrema	6.59	3.56 – 12.21	**<0,001**
Dislipidemia	0.50	0.26 – 0.96	**0.038**
Depressão	1.30	0.69 – 2.43	0.408
Idade de início (anos)	1.01	1.00 – 1.03	**0.047**
Atraso até o diagnóstico (>12m)	4.82	0.54 – 43.02	0.158

Características clínicas, radiológicas e demográficas de pacientes aquaporina-4 positivos

Excluindo-se os pacientes com status de anticorpo indeterminado, foi realizada comparação das características demográficas, clínicas e radiológicas entre pacientes com DENMO com status positivo e negativo de

aquaporina-4 e não foi encontrada diferença estatisticamente significativa, conforme demostrada na **Tabela 4.**

Tabela 4. Comparação das características demográficas, clínicas e radiológicas entre pacientes com DENMO com status de aquaporina positivo e negativo 4.

Características	**Aqp4- (n=20)**	**Aqp4+ (n=55)**	***p***
Idade de início (anos), *média ± DP*	38,3±13.4	36,0±14,0	0.518
Feminino, *n (%)*	16 (80,0)	46 (83,6)	0.737
Afrodescendentes, *n (%)*	16 (80,0)	39 (70,9)	0.560
Primeira síndrome, *n (%)*			
Neurite óptica	6 (30,0)	10 (18,9)	
Mielite Transversal	4 (20,0)	17 (32,1)	
Área postrema síndrome	4 (20,0)	1 (1,90)	
NO + TM	4 (20,0)	14 (26,4)	0.058
NO + TM + AP	0 (0,0)	5 (9,4)	
NO + AP	0 (0,0)	3 (5,7)	
MT + SAF	2 (10,0)	3 (5,7)	
EDSS, *mediana, (interquartil)*	3 (1,5-4,5)	4(2,7-6,7)	0.150
Doença autoimune associada *n (%)*	4 (18)	12 (21,8)	1.000
Recidiva, *n (%)*	16 (84,2)	46 (83,6)	1.000

Número de ataques, *média ± SD*	3,4±3,1	4,6 ±3,9	0.230
Tempo de doença (anos), *média ± DP*	6,4 ±5,6	8,4 ±7,0	0.251
Taxa de surtos, *média ± DP*	1,5 ±1.7	1,3 ±1,5	0.697
Índice de progressão, *média ± DP*	2,2 ±4,7	2,2 ±3,9	0.975
Lesões de RM de encéfalo, *n (%)*	11 (68,8)	35 (74,5)	0.747
Lesões da RM da medula espinhal, *n (%)*	17 (94,4)	41 (87,2)	0.663
Número de corpos vertebrais afetados, *mediana, (interquartil)*	3 (2-5)	5 (3-7)	0.109
Lesão longitudinalmente extensa, *n (%)*	11 (68,8)	31 (79,5)	0.279
Topografia da lesão medular, *n (%)*			
Cervical	9 (60,0)	14 (35,0)	0.666
Torácico	2 (13,3)	8 (20,0)	
Cervicais e torácicas	2 (13,3)	9 (22,5)	
Torácica e lombar	0 (0,0)	1 (2,5)	
Lombar e sacral	0 (0,0)	1 (2,5)	
Sem lesão	2 (13,3)	7 (17,5)	
Tipo de tratamento, *n (%)*			
Azatioprina e glicocorticoide	10 (52,6)	28 (56,0)	0.729
Azatioprina	8 (42,1)	17 (34,0)	
Rituximabe	1 (5,3)	5 (10,0)	

Frequência de doenças autoimunes associadas

Dezesseis (17,5%) pacientes tinham o diagnóstico de alguma doença autoimune concomitante. A doença autoimune mais frequentemente associada à DENMO foi a Tireoidite de Hashimoto, presente em 6 (6,5%) dos pacientes. Lúpus eritematoso sistêmico foi diagnosticado em 4 (4,3%) dos pacientes. Apenas 1 (1,0%) paciente teve diagnóstico de Síndrome de Sjögren. Outras cinco condições imunomediadas estiveram presentes em pacientes distintos (vitiligo, artrite reumatoide, hepatite autoimune, artropatia de Jaccoud e miastenia gravis), correspondendo em conjunto a 5,0% da amostra. (**Tabela 5)**

Tabela 5: Frequência de doenças autoimunes associadas

Variável	**DENMO**
Doença autoimune, n (%)	16 (17,5)
Tireoidite de Hashimoto	6 (6,5)
Lúpus eritematoso sistêmico	4 (4,3)
Síndrome de Sjögren	1 (1,0)
Miastenia gravis	1 (1,0)
Vitiligo	1 (1,0)
Hepatite autoimune	1 (1,0)
Artrite Reumatoide.	1 (1,0)
Artropatia de Jaccoud	1 (1,0)

Frequência de biomarcadores

O anticorpo anti-AQP4 IgG foi identificado em 55 (70,4%) dos pacientes. O fator antinuclear foi reagente em 23 (52,3%) pacientes. Nove (25%) pacientes tiveram resultado positivo para o anticorpo anti-SSa, enquanto apenas 2 (6,1%) positivaram para o anticorpo anti-SSb. Apenas um paciente (4,2%) testou positivo para o anticorpo anti-TPO, enquanto o anti-Tg não foi identificado em nenhum dos pacientes testados. Fator reumatoide foi identificado em apenas um paciente (3,3%). (**Tabela 6)**

Tabela 6: Frequência de biomarcadores de autoimunidade.

Variável	**DENMO**	
	n=91	
Biomarcadores, n (%)	Reagente	Não reagente
Anti-AQP4 IgG	55/75 (73,3)	20/75 (26,6)
FAN	23/44 (52,3)	21/44 (47,7)
Anti-SSa/Ro	9/36 (25)	27/36 (75)
Anti-SSb/La	2/33 (6,1)	31/33 (93,9)
Anti-TPO	1/24 (4,2)	23/24 (95,8)
Anti-Tg	0/22 (0)	22/22 (100)
FR	1/30 (3,3)	29/30 (96,7)

FAN: fator antinuclear. Anti-TPO: anti-tireoperoxidase. AAT: anticorpos anti-tireoglobulina.

Padrão morfológico do FAN

Dentre os pacientes FAN positivo, 19 (82,6%) possuíam o registro do padrão morfológico. Os padrões mais frequentemente observados foram o

nuclear pontilhado fino e o nuclear pontilhado fino denso, ambos em 6 (31,6%) pacientes. Dois pacientes apresentaram FAN com padrão nucleolar (10,5%). Os padrões nucleares pontilhado grosso, homogêneo, citoplasmático fibrilar, citoplasmático pontilhado e aparelho mitótico tipo ponte intercelular foram observados em um (5,3%) paciente cada.**(Tabela 7)**

Tabela 7: Padrão morfológico do FAN

Padrão morfológico, n (%)	**FAN reagente n=19**
Nuclear pontilhado fino	6 (31,6)
Nuclear pontilhado fino denso	6 (31,6)
Nuclear pontilhado grosso	1 (5,3)
Nucleolar	2 (10,5)
Homogêneo	1 (5,3)
Citoplasmático fibrilar	1 (5,3)
Citoplasmático pontilhado	1 (5,3)
Aparelho mitótico (ponte intercelular)	1 (5,3)

Comparação outros estudos clínico demográficos no Brasil

Até a presente data foram encontrados onze estudos clínico epidemiológicos proveniente de população exclusivamente brasileira. Dentre os estudo oito foram provenientes do Sudeste, dois do Centro-oeste e apenas o nosso publicado com pacientes do nordeste do Brasil. Não foram encontrados estudos da região Sul ou Norte. Na tabela 7. Há uma sumarização dos principais achados demográficos dos estudos na **Tabela 8.**

Tabela 8. Comparação das características e demográficas com outros estudos em literatura.

Autor/ Ano	Cidade / Região	N	Idade sintomas	(%) Afrodescendentes	Homens: Mulheres	(%) Anti-AQP4+
Alvarenga et al. 2002	Rio de Janeiro Sudeste	24	32,8	58%	1:5	NR*
Alves-Leon el al. 2008	Rio de Janeiro Sudeste	28	26	50%	1:3	NR*
Bichuetti et al. 2009	São Paulo/ Sudeste	41	32,6	NR*	1:2,4	41%
Adoni et al 2010	São Paulo / Sudeste	28	26	NR*	1:8	64,3%
Pereira et al. 2015	Volta-Redonda Sudeste	1	NR*	0%	0:1	100%
Del Negro et al. 2017	Brasília / Centro-Oeste	34	34,6	44%	1:7,5	73,53%
Alvarenga et al. 2020	Rio de Janeiro Sudeste	122	31,3	70%	1:8,3	70%
Lana-Peixoto et al. 2021	Belo Horizonte/ Sudeste	69	39	24,6%	1:6,6	67,2%
Alves et al. 2021	Goiânia Centro-Oeste	48	36,7	31,3%	1:4	35,4%
Fukuda et al. 2022	**Salvador Nordeste**	**91**	**36,3%**	**73,6%**	**1:3,8**	**73,3%**
Silva et al. 2023	São Paulo / Sudeste	133	NR	NR*	NR	100%

*NR-Não relatado

VIII. Discussão:

Este estudo é o primeiro a avaliar as características clínicas e demográficas na região nordeste do Brasil. Embora nosso estudo não seja de base populacional, acreditamos que conseguimos investigar uma proporção significativa de pacientes com NMOSD no estado da Bahia, uma vez que nosso centro de estudo é o único centro de referência no estado.

Apesar das diferenças metodológicas e disparidades na definição de NMOSD ao longo dos anos, temos uma média de idade de início semelhante à maioria dos estudos, bem como a maior prevalência em mulheres, com proporções femininas: masculinas > 3:1(10,12,49–53). Nossa amostra apresenta maior percentual de pacientes afrodescendentes (73,6%) em comparação com outros estudos internacionais e até mesmo em comparação com outros estudos no Brasil. (10,12,49–53). Isso pode ser devido ao perfil populacional do local de estudo, a cidade de Salvador, estado da Bahia, que concentra a maior proporção de negros fora da África (54). A maior prevalência de NMOSD entre populações afrodescendentes explica o tamanho da amostra deste estudo, que é comparável a estudos multicêntricos anteriores que avaliaram aspectos epidemiológicos de países inteiros (53,55).

Apesar dessa peculiaridade, não encontramos associação significativa entre a raça dos pacientes e os piores desfechos clínicos. Essa associação

mostra uma grande divergência na literatura. Estudo prévio demonstrou que a raça não é um fator independente de pior prognóstico motor ou visual (21). Outro autor demonstra que há associação entre a raça branca e piores desfechos visuais e maiores escores de EDSS (56). Além disso, alguns trabalhos encontraram pior prognóstico em pacientes afro-caribenhos (57,58). Devido à ampla miscigenação da população é difícil definir raça no Brasil e de modo que a estratificação racial analisada neste estudo foi baseada no fenótipo de cor de pele dos pacientes pode não representar a raça dos participantes de maneira 100% fidedigna.

A diretriz da Academia Brasileira de Neurologia, que é a principal entidade representativa dos neurologistas no Brasil, sobre o NMOSD está em andamento. Existe um manual publicado por esta entidade em 2016 que orienta como primeira linha - primeira opção (rituximabe, azatioprina ou azatioprina mais corticoides), primeira linha - segunda opção (micofenolato) e segunda linha (metotrexato e ciclosporina). (59) Todos os nossos pacientes estavam usando medicamentos de primeira linha, como primeira opção de tratamento. No período de avaliação dos pacientes ainda não havia medicações aprovadas pela ANVISA. Atualmente temos 3 terapias monoclonais de alto custo aprovados pela ANVISA (Ravulizumabe, Inebilizumabe e o Satralizumabe) nenhum deles é distribuído pelo SUS nem incorporado no Rol da Agência Nacional de Saúde Suplementar.

A soropositividade para AQP4-IgG foi observada em 73,3% dos pacientes, estando de acordo com estudos prévios (10,12,50,51). Outros autores encontraram menor frequência de soropositividade para AQP4-IgG (49,55). Essa divergência pode ser atribuída à metodologia utilizada e ao momento do teste de anticorpos. Embora em alguns estudos a soropositividade do anticorpo AQP4-IgG tenha sido associada a um comprometimento mais grave (60–62). Outros, semelhantes aos nossos resultados, não mostraram associação (51,55).

De acordo com muitos estudos, a mielite transversal foi a síndrome de ataque inicial mais prevalente, dado também encontrado no presente estudo alcançando aproximadamente 1/3 dos pacientes (32,9%) (12,53,63). A apresentação clássica de ON e MT simultâneas foi observada em 21,2% dos pacientes, percentual que está de acordo com outras amostras. (12,49,51). No entanto, foi menor do que o percentual observado em outras coortes (50,53). Outra característica importante de nossa amostra é que 5,9% dos pacientes apresentaram ON, MT e SAP simultaneamente na apresentação inicial. Esse dado pode ser explicado por outro estudo que demonstrou que as síndromes clínicas iniciais combinadas são mais frequentes em populações afro-americanas e afro-europeias (21).

Com relação às doenças autoimunes associadas, a frequência em nossa amostra é semelhante (17,5%) ao demonstrado em alguns estudos anteriores

(49,50). Quando comparado a outros estudos, no entanto, onde até um terço dos pacientes apresentou esse tipo de comorbidade, nosso percentual foi menor (51,53,55). Em nosso estudo, observamos que a tireoidite de Hashimoto foi a doença autoimune mais frequente, seguida dos lúpus eritematoso sistêmico, comorbidades previamente associadas à NMOSD (64). Além disso, o percentual de doenças autoimunes associadas teve uma tendência de ser maior nos pacientes com progressão da doença, mas essa associação não foi estatisticamente significativa na análise multivariada. Estudo prévio descreveu associação entre concomitância de outras doenças autoimunes e maior incapacidade (32).

A taxa de recidiva anualizada, bem como a frequência de fenótipo remitente redicivante entre os pacientes foram semelhantes aos descritos na literatura. No entanto, encontramos um índice de progressão de 2,3 (±4,1) pontos/ano, índice superior ao relatado em estudo anterior do sudeste brasileiro (49). Fatores raciais ou menor acesso a terapias e reabilitação podem estar associados também devido diferenças regionais encontradas em relação a estrutura étnica e índice de desenvolvimento Humano (IDH). Em relação às opções de tratamento, o tipo de terapia de manutenção mais utilizado foi a combinação de azatioprina e glicocorticoide, o que está de acordo com outros estudos do mesmo período ou períodos anteriores (49,51,55). Atualmente com os surgimentos de novas terapias e maior

disponibilidade de terapias de mais alta eficácia como o Rituximabe, os panoramas regionais de tratamento tem uma tendência de mudança dos perfis de drogas modificadoras de doença.

Em relação aos fatores prognósticos, uma maior idade na apresentação sintomática inicial associou-se ao pior desfecho clínico, conforme relatado anteriormente (66,67). Nossos achados também sugerem que os pacientes que apresentaram lesões área postrema poderiam ter os piores desfechos da doença. Estudos prévios indicam que a medula oblonga é uma estrutura do SNC altamente frequente envolvida na NMOSD (prevalência variando entre 12,8% e 91,3%), com lesões ocorrendo geralmente em sua parte dorsal (65–70). Um estudo demonstrou que pacientes com lesões medulares eram mais propensos a ter um maior número de lesões cerebrais, bem como doença com atividade clínica elevada e progressão rápida, relatando maiores escores de EDSS e taxa de recidiva anualizada (71). Para explicar esse comportamento mais grave entre os pacientes com lesões da área postrema, especulamos que: 1) os sinais e sintomas decorrentes das lesões nessa topografia podem aumentar mais gravemente a EDSS; 2) esses pacientes são mais frequentemente acometidos por um maior número de lesões cerebrais e extensas da medula espinhal, o que poderia ter um impacto na gravidade da doença.

Embora não esteja claro se o tipo de síndrome clínica inicial tem influência no prognóstico, nosso estudo descobriu que a neurite óptica como primeira apresentação estava associada à progressão lenta da doença. Um estudo retrospectivo recente demonstrou que a neurite óptica como apresentação inicial da NMOSD correlacionou-se com o pior desfecho visual, sem diferenças em relação à EDSS (55). Um estudo mostrou que pacientes com neurite óptica como sintoma inicial de esclerose múltipla levaram mais anos para atingir EDSS 4,0, 6,0 e 7,0 quando comparados a pacientes sem neurite (72). Da mesma forma, outro estudo relatou que pacientes que tinham neurite óptica como ataque inicial (síndrome clinicamente isolada) apresentaram menor taxa de conversão para esclerose múltipla, quando comparados a outros tipos de apresentação da primeira doença (73). No entanto, esse tipo de neurite óptica difere da neurite óptica atípica, como geralmente visto na NMOSD e mais estudos prospectivos são necessários para investigar a real influência da síndrome inicial no prognóstico dos pacientes. Uma das limitações apresentadas pelo estudo foi o baixo percentual de pacientes testados para anti-MOG e uma possível associação de pacientes com fenótipo tipo ADEM e/ou neurite concomitante e mielite não estar associada a um pior prognóstico.

Um dos aspectos mais inesperados do presente estudo foi o achado de dislipidemia como fator associado a um melhor prognóstico, característica

que não foi analisada na maioria das coortes epidemiológicas anteriores. Este resultado é contrário a uma observação anterior de que a hipertrigliceridemia pode estar relacionada a uma pior recuperação do primeiro ataque desmielinizante de NMOSD (74). Uma das teorias sugeridas para explicar esse achado é que pacientes dislipidêmicos podem ter utilizado drogas hipolipidêmicas como tratamento a longo prazo, como as estatinas, que apresentam efeitos anti-inflamatórios pleotrópicos e, portanto, um possível efeito benéfico no controle da doença (75).Uma segunda explicação possível é que a atividade inflamatória está associada à redução dos níveis de LDL, como observado em outras doenças inflamatórias, como a artrite reumatoide, e em condições de estresse agudo, como a sepse (76). Assim, isso poderia disfarçar o diagnóstico de dislipidemia em pacientes com maior atividade inflamatória.

IX. Conclusões:

. 1- A maior parte dos pacientes acometidos em nossa população era composta por afrodescendentes e mulheres, destacando um perfil epidemiológico específico em nossa amostra.

2. A presença de anticorpos anti-aquaporina-4 (AQP4) não foi associada a diferenças clínicas significativas nem ao prognóstico dos pacientes em nossa casuística.

3. Dentre a alta frequência de comorbidades autoimunes, a tireoidite de Hashimoto foi a comorbidade mais frequentemente observada entre os pacientes.

4. Durante o período de nosso estudo, as terapias off-label e de menor eficácia prevaleceram no manejo clínico dos pacientes, evidenciando uma lacuna no acesso a tratamentos mais específicos.

5. O envolvimento da área postrema e a idade de início da doença foram independentemente associados com maior incapacidade. Em contrapartida, a neurite óptica como síndrome inicial e a presença de dislipidemia foram associadas a uma progressão mais lenta da doença.

X. Summary

Introduction: Neuromyelitis optica spectrum disorders (NMOSD) is a rare inflammatory and demyelinating disease of the central nervous system (CNS) more frequent in women and Afro-descendants. No previous epidemiological or prognostic study has been conducted in the region of the state of Bahia, Brazilian Northeast. **Objective:** To identify factors associated with greater disease progression in patients with ENMO in the State of Bahia. Material and Methods: A single-center retrospective study was conducted with consecutive patients diagnosed with NMOSD. Clinical and epidemiological characteristics were described. The degree of disability was

expressed by the Expanded Disability Status Scale (EDSS). The main outcome of the study was the progression rate, defined as the ratio between the EDSS and the duration of the disease in months. Predictors of disease progression were identified using negative binomial regression adjusted for disease duration. **Results:** Ninety-one patients were included, 72 (79.1%) female and 67 (73.6%) afro descendants. Mean age at onset was 36 (± 14) years and 73.3% were anti-aquaporin-4 antibody positive. Isolated transverse myelitis (32.9%) and isolated optic neuritis (22.4%) were the most frequent initial clinical syndromes. After multivariate analysis, optic neuritis (RR = 0.49; 95% CI=0.29 – 0.84; p = 0.009) and dyslipidemia (RR = 0.50; 95% CI=0.26 – 0.96; p= 0.038) were associated with slower disease progression. Area postrema involvement (RR = 6.59; 95% CI=3.56 – 12.21; p < 0.001) and age at onset (RR = 1.01; 95% CI=1.00 – 1.03; p = 0.047) were associated with faster disease progression. **Conclusions:** In the first clinical and prognostic study in northeastern Brazil, we identified involvement of the area postrema and older age at onset as factors associated with disease progression and optic neuritis as the initial syndrome and dyslipidemia as the main protective factors.

Keywords: Neuromyelitis optica spectrum disorders; Prognostic factors; Brazilian Northeast; Aquaporin-4.

XI. Considerações finais:

Este é o primeiro artigo a avaliar fatores clínicos, epidemiológicos e prognósticos na região nordeste do Brasil, no qual se supõe concentrar uma elevada prevalência de DENMO, devido às suas singularidades étnicas e com determinantes sociais diversas as regiões onde se concentram o maior número de dados no Brasil.

Este trabalho reflete não apenas a continuidade de uma das linhas de pesquisa em andamento no pós-graduação de ciências da saúde, mas a publicação dos primeiros dados do início de uma nova linha de pesquisa na Universidade Federal da Bahia em doença do Espectro Neuromielite Óptica, uma doença muito rara, mas que tem uma maior prevalência em pacientes afrodescendentes e de classe social menos favorecida. Durante pandemia do COVID-19, apesar de ter atendimento presencial suspenso, dados de nossa coorte com acompanhamento telefônico possibilitaram a contribuição em estudo multicêntrico nacional (**Anexo 6**). Neste momento já temos mais 2 pós-graduandos seguindo a linha de pesquisa, Daniel San-Martin avaliando preditores de falha terapêutica a azatioprina (Doutorado) e Thiago Nascimento (Mestrado) avaliando manifestações cognitivas da doença.

XII. Proposta de Estudo

No presente estudo, conseguimos descrever as características clínicas dos pacientes com a DENMO em um centro de referência no nordeste brasileiro e foram vistas, nesta população, associações prognósticas negativas como a idade de início dos sintomas, acometimento de área postrema e associado a melhor prognóstico o a presença de dislipidemia como comorbidade e a neurite óptica como primeira síndrome clínica. Os dados de associação vistos neste estudo precisam ser avaliados em um seguimento prospectivo e outros marcadores biológicos devem ser analisados também.

Portando o objetivo do estudo será a avaliação de biomarcadores e marcadores clínicos para prognósticos de pacientes com DENMO. Será um estudo de coorte prospectiva com a população de pacientes dos ambulatórios de neuroimunologia do Hospital Universitário professor Edgar Santos. Serão colhidos dados clínicos, epidemiológicos e biomarcadores séricos (citocinas e quimiocinas) através de técnica de Luminex que serão analisados em conjunto com o Laboratório de Pesquisas Clínicas da Fiocruz Bahia. Os pacientes serão acompanhados a cada 3 meses por 2 anos prospectivamente sendo analisados a taxa anualizada de surtos e a progressão do EDSS neste período. O projeto já apresenta aprovação do Comitê de ética em pesquisa CAAE: 19280819.3.0000.0049. (**Anexo 5**)

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XIV.Anexos

Anexo 1- Ficha de Coleta

FICHA DE COLETA – "DENMO"
DADOS PESSOAIS
Nome: _____ Idade: _____ Nº de ID:_____ Prontuário: _____ Telefone: (__) _____ Responsável: _____ Ocupação: _____ Gênero: M [1] F [2] Outro [3]:_____ Cor/Etnia: Branco [1] Negro [2] Pardo [3] Indígena [4] Data de nascimento: __/__/_____ Estado Civil: Casado [1] Solteiro [2] Viúvo [3] Separado [4] Natural de:_____ Procedente de:_____
DADOS CLÍNICOS Queixa Principal: _____ Peso: Altura: Data do diagnóstico: _____Data do inicio dos sintomas _____ Início do quadro: Neurite Óptica [1] Mielite transversa [2] Síndrome da área postrema [3] Síndrome cortical [4] Narcolepsia Sintomática [5] Sindrome de TE [6] Síndrome encefálica [7] Realizou o teste Anticorpo Anti-AQP4-IgG: Sim [1] Não [2] N° dosagens_____ Se sim, qual foi o resultado: Positivo [1] Negativo [2] Títulação_____/ Método_____ Surtos após manifestação inicial: Sim [1] Não [2] Nº_____ Data____/_____/____ Sintomas:_____ Data____/_____/____ Sintomas:_____ Data____/_____/____ Sintomas:_____ Data____/_____/____ Sintomas:_____ Realizou Ressonância Magnética do Encéfalo: Sim [1] Não [2
Se sim, houve alteração? Sim [1] Não [2]

Realizou Ressonância Magnética da órbita: Sim [1] Não [2]

Se sim, houve alteração? Sim [1] Não [2]

Quais? _____

Realizou Ressonância Magnética da medula (cervical/ torácica)? Sim [1] Não [2]

Se sim, houve alteração? Sim [1] Não [2]

Quais? _____

Presença de outras doenças autoimunes: Sim [1] Não [2]

Se sim, qual? LES [1] SS [2] Tireoidite de Hashimoto [3] Artrite Reumatóide [4]

Doença de Graves [5] Outra [6]: _____

Presença de outras comorbidades: HAS [1] DM [2] Dislipidemia [3] Depressão [4]

Tabagismo [5] Outro [6]: _____

EDSS:_____

Tempo de tratamento [meses]: _____

Já realizou o tratamento agudo? Sim [1] Não [2] Nº de vezes_____

Se sim, com o que? Pulsoterapia [ ] Plasmaférese [ ] Outro [ ]:_____

Está em Tratamento de Indução/Manutenção? Sim [1] Não [2]

Se sim, com o quê? [ ] Corticoterapia (dose)_____[ ] Azatioprina (dose)_____

[ ]Micofenolato(dose)_____ [ ]Metrotexato (dose)_____ [ ]Rituximab_____

[ ]Outro:_____

DADOS SOCIOECONÔMICOS

Renda familiar média [em salários mínimos]:_____

Nº de indivíduos dependentes:_____

Nº de habitantes na residência: _____ Nº de cômodos na residência:_____

Meio de transporte: Carro próprio [1] Táxi [2] Ônibus [3] Outro [4]:_____

Escolaridade: Analfabeto[1] Fundamental Incompleto [2] Fundamental Completo [3] Ensino médio Incompleto [4] Ensino Médio Completo [5] Ensino Superior Incompleto [6] Superior Completo [7]
POSSÍVEIS PREDITORES SOCIOECONÔMICOS DE ATRASO NO DIAGNÓSTICO
Município de residência no início dos sintomas:
Possui Hospital no Município onde mora? [1]Sim [2]Não
Possui Hospital no Bairro onde mora? [1]Sim [2]Não
Diagnóstico errôneo de EM:[1]Sim [2]Não
Tratado para EM:[1]Sim [2]Não
Tipo de local procurado pela primeira vez: [1] UBS/Posto [2]Hospital [3]Clínica/Médico Particular [4] Farmácia [5]Outros Especificar: _____
Situação de emprego no quadro agudo inicial (permitido marcar mais de um): [1]Emprego carteira assinada [2] Autônomo [3]Estudante [4] Estagiário [5]Desempregado [6]Aposentado [7] Beneficiário de outro programa (INSS/Bolsa Família, Defeso...) Qual Programa?_____
Carga horária semanal de trabalho e/ou estudo pré-diagnóstico_____
Possui Seguro de Saúde privado? [1]Sim [2]Não
Refere acesso a neurologista no início do quadro (até 1 mês do início dos sintomas)? [1]Sim [2]Não
Diagnóstico foi fechado neste ambulatório de Neuroimunologia?
Distância, em Km, do atual município/bairro para Ambulatório (Calcular posteriormente):_____

Refere dificuldade de acesso à rede pública de saúde? [1]Sim [2]Não

Qual(is):_____

_____

_____

Anexo 2. (Aprovaçãoo CEP)

UFBA - HOSPITAL UNIVERSITÁRIO PROF. EDGARD SANTOS DA

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: PERFIL CLÍNICO-EPIDEMIOLÓGICO DE PACIENTES COM DOENÇAS DO ESPECTRO NEUROMIELITE ÓPTICA ATENDIDOS EM AMBULATÓRIO DE REFERÊNCIA EM HOSPITAL TERCIÁRIO DE SALVADOR, BA

Pesquisador: thiago gonçalves fukuda

Área Temática:

Versão: 5

CAAE: 90834918.7.0000.0049

Instituição Proponente: Hospital Universitário Prof. Edgard Santos-UFBA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.349.221

Apresentação do Projeto:

Resposta de pendência a parecer anterior.

Objetivo da Pesquisa:

Resposta de pendência a parecer anterior.

Avaliação dos Riscos e Benefícios:

Resposta de pendência a parecer anterior.

Comentários e Considerações sobre a Pesquisa:

Resposta de pendência a parecer anterior.

Considerações sobre os Termos de apresentação obrigatória:

Resposta de pendência a parecer anterior.

Recomendações:

Resposta de pendência a parecer anterior.

Conclusões ou Pendências e Lista de Inadequações:

Em relação ao parecer anterior, solicitou-se anexar o documento "Termo de Compromisso do Pesquisador sem vínculo com o HUPES" para os novos pesquisadores. Pendência Atendida.

Considerações Finais a critério do CEP:

O participante da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu

Endereço: Rua Augusto Viana, s/nº - 1º Andar
Bairro: Canela **CEP:** 40.110-060
UF: BA **Município:** SALVADOR
Telefone: (71)3283-8043 **Fax:** (71)3283-8140 **E-mail:** cep.hupes@gmail.com

consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 466/12) e deve receber uma via do Termo de Consentimento Livre e Esclarecido, na íntegra, completamente assinado.

O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou, aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa que requeiram ação imediata.

O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo. É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas.

Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em _____/_____/_____ e ao término do estudo.

Situação: Emenda Aprovada.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1310732_E1.pdf	17/05/2019 09:15:54		Aceito
Outros	Termo_Responsabilidade.pdf	17/05/2019 09:15:16	thiago gonçalves fukuda	Aceito
Outros	equipe.pdf	05/04/2019 11:49:04	thiago gonçalves fukuda	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Emenda.pdf	05/04/2019 11:40:13	thiago gonçalves fukuda	Aceito

Endereço: Rua Augusto Viana, s/nº - 1º Andar
Bairro: Canela **CEP:** 40.110-060
UF: BA **Município:** SALVADOR
Telefone: (71)3283-8043 **Fax:** (71)3283-8140 **E-mail:** cep.hupes@gmail.com

Outros	Emenda.pdf	05/04/2019 11:39:30	thiago gonçalves fukuda	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Detalhado_Perfil_Clinico_Epidemiologico_NMOSD_HUPES_adendo.docx	22/03/2019 11:27:53	thiago gonçalves fukuda	Aceito
Cronograma	CRONOGRAMA.pdf	09/08/2018 09:36:57	thiago gonçalves fukuda	Aceito
Outros	FICHA_CADASTRO_PESQUISA_GEP_HUPES.docx	09/08/2018 09:36:45	thiago gonçalves fukuda	Aceito
Outros	Termo_de_Compromisso_Pesquisador_Responsavel.pdf	05/06/2018 09:34:36	thiago gonçalves fukuda	Aceito
Outros	Declaracao_Pesquisadores.jpg	05/06/2018 09:32:07	thiago gonçalves fukuda	Aceito
Outros	Carta_de_Apresentacao.pdf	05/06/2018 09:30:26	thiago gonçalves fukuda	Aceito
Outros	Carta_de_Anuencia.pdf	05/06/2018 09:28:47	thiago gonçalves fukuda	Aceito
Orçamento	Orcamento.docx	05/06/2018 09:01:09	thiago gonçalves fukuda	Aceito
Folha de Rosto	Folha_de_Rosto.pdf	04/06/2018 16:45:17	thiago gonçalves fukuda	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SALVADOR, 27 de Maio de 2019

Assinado por:
Pablo de Moura Santos
(Coordenador(a))

Anexo 3. (TCLE)

Termo de Consentimento Livre e Esclarecido

Título do Estudo: "PERFIL CLÍNICO -EPIDEMIOLÓGICO DE PACIENTES COM DOENÇAS DO ESPECTRO NEUROMIELITE ÓPTICA ANTENDIDOS EM AMBULATÓRIO DE REFERÊNCIA EM DOENÇAS DESMIELINIZANTES EM HOSPITAL TERCIÁRIO DE SALVADOR, BA"

Pesquisador Responsável: Thiago Gonçalves Fukuda.

O (A) Senhor (a) está sendo convidado (a) a participar de uma pesquisa. Por favor, leia este documento com bastante atenção antes de assiná-lo. Caso haja alguma palavra ou frase
que o (a) senhor (a) não consiga entender, converse com o pesquisador responsável pelo estudo ou com um membro da equipe desta pesquisa para esclarecê-los.
A proposta deste termo de consentimento livre e esclarecido (TCLE) é explicar tudo sobre o estudo e solicitar a sua permissão para participar do mesmo.
Esse termo é elaborado em 2 (duas) vias, rubricadas em todas as suas páginas e assinadas,
ao seu término, pelo convidado a participar da pesquisa, ou por seu representante legal, assim como pelo pesquisador responsável.

OBSERVAÇÃO: Caso o paciente não tenha condições de ler e/ou compreender este TCLE ou seja não tenho 18 anos completos, o mesmo poderá ser assinado e datado por um membro da família ou responsável legal pelo paciente.

Objetivo do Estudo

OBJETIVO PRIMÁRIO

- Avaliar o perfil dos sinais, sintomas e características epidemiológicas (idade, cor sexo, naturalidade, procedência, renda) dos pacientes com o diagnóstico de Doença do Espectro Neuromielite Óptica atendidos neste consultório referência do Ambulatório Magalhães Neto - Hospital Universitário Prof. Edgard Santos da Universidade Federal da Bahia, em Salvador - BA.

OBJETIVOS SECUNDÁRIOS

- Avaliar a presença de outras doenças coexistentes em pacientes com Doenças do Espectro Neuromielite Óptica;
- Analisar fatores associados a um maior tempo entre os sintomas iniciais e o diagnóstico de pacientes essa doença;

- Analisar as diferenças de apresentação de sintomas e sinais da pessoa e de seus exames complementares quanto ao resultado (reagente ou não reagente) do exame de Anti-aquaporina-4, que é o anticorpo presente no sangue que indica a presença da doença.

Duração do Estudo

A duração total do estudo é de **72 (setenta e dois)** meses. A sua participação no estudo será de aproximadamente doze meses. Descrição do Estudo Participarão do estudo aproximadamente **200** indivíduos. Este estudo será realizado no Ambulatório de Doenças Neuroimunológicas do Ambulatório Magalhães Neto, parte do Complexo do Hospital Universitário Professor Edgard Santos.

O (a) Senhor (a) foi escolhido (a) a participar do estudo porque:

Possui diagnóstico ou suspeita de Doenças do Espectro Neuromielite Óptica e está sendo avaliada neste ambulatório para tratamento ou diagnóstico da doença;
O Termo de consentimento livre e esclarecido foi preenchido pelo paciente ou familiar.

O (a) Senhor (a) não poderá participar do estudo se:

Não aceitar participar da pesquisa; Procedimento do Estudo Após entender e concordar em participar, será realizado um questionário para avaliar o perfil clínico e epidemiológico dos pacientes com Doenças do Espectro Neuromielite Óptica.

Riscos Potenciais, Efeitos Colaterais e Desconforto

Considera-se que toda pesquisa envolvendo seres humanos envolve risco em tipos e gradações variados, logo, os riscos encontrados no estudo estão no processo de coleta do estudo, em que pode haver constrangimento por alguma pergunta, cansaço e estresse pelo tempo extra para realização do questionário. Um meio de minimizar tais risco é buscar um ambiente adequado e confortável para a entrevista, fomentando uma empatia para diminuir constrangimentos e experiências negativas durante a coleta de dados. Além disso, há o risco de quebra do sigilo dos dados colhidos no estudo. Todos os cuidados serão tomados para que em nenhum momento nomes e dados pessoais sejam diretamente mencionados ou relacionados, não sendo possível identificar especificamente a quem pertence as informações.

O estudo busca a mínima possibilidade de danos de dimensão física, psíquica, moral, intelectual, social, cultural ou espiritual ao ser humano, em qualquer fase da pesquisa e dela decorrente.

Benefícios para o participante

Não há benefício direto para o participante desse estudo. Trata-se de estudo transversal que avaliará a hipótese de que há uma prevalência importante de Doenças do Espectro Neuromielite Óptica na população baiana. Somente no final do estudo poderemos concluir a presença de algum benefício. Porém, os resultados obtidos com este estudo poderão ajudar a esclarecer as características dos pacientes acometidos com Doenças do Espectro Neuromielite Óptica na população baiana.

Compensação

Você não receberá nenhuma compensação para participar desta pesquisa e também não terá nenhuma despesa adicional. Participação Voluntária/Desistência do Estudo Sua participação neste estudo é totalmente voluntária, ou seja, você somente participa se quiser. A não participação no estudo não implicará em nenhuma alteração no seu acompanhamento médico tão pouco alterará a relação da equipe médica com o mesmo. Após assinar o consentimento, você terá total liberdade de retirá-lo a qualquer momento e deixar de participar do estudo se assim o desejar, sem quaisquer prejuízos à continuidade do tratamento e acompanhamento na instituição.

Novas Informações

Quaisquer novas informações que possam afetar a sua segurança ou influenciar na sua decisão de continuar a participação no estudo serão fornecidas a você por escrito. Se você decidir continuar neste estudo, terá que assinar um novo (revisado) Termo de Consentimento informado para documentar seu conhecimento sobre novas informações.

Em Caso de Danos Relacionados à Pesquisa

Em caso de dano pessoal, diretamente causado pelos procedimentos ou tratamentos propostos neste estudo (nexo causal comprovado), o participante tem direito a tratamento médico na Instituição, bem como às indenizações legalmente estabelecidas.

Utilização de Registros Médicos e Confidencialidade

Todas as informações colhidas e os resultados dos testes serão analisados em caráter estritamente científico, mantendo-se a confidencialidade (segredo) do paciente a todo o momento, ou seja, em nenhum momento os dados que o identifique serão divulgados, a menos que seja exigido por lei.

Os registros médicos que trazem a sua identificação e esse termo de consentimento assinado poderão ser inspecionados por agências reguladoras e pelo CEP. Os resultados desta pesquisa poderão ser apresentados em reuniões ou publicações, contudo, sua identidade não será revelada nessas apresentações.

Quem Devo Entrar em Contato em Caso de Dúvida

Em qualquer etapa do estudo você terá acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. O responsável pelo estudo nesta instituição é Thiago Gonçalves Fukuda e que poderá ser encontrado no endereço: Rua Augusto Viana, Canela, do Hospital Universitário Professor Edgard Santos (HUPES) ou no respectivo telefone: (71) 98875-8494. Em caso de dúvidas com respeito aos aspectos éticos deste estudo, você poderá consultar:

PESQUISADOR(A) RESPONSÁVEL: THIGO GONÇALVES FUKUDA

ENDEREÇO: AMBULATÓRIO DE NEUROIMUNOLOGIA DO AMBULATÓRIO MAGALHÃES NETO, PARTE DO COMPLEXO DO HOSPITAL UNIVERSITÁRIO PROFESSOR EDGARD SANTOS, LOCALIZADO NA RUA AUGUSTO VIANA, CANELA. SALA: 3 ANDAR: 1º ANDAR

HORÁRIOS DE ATENDIMENTO: 13 ÀS 17 HORAS SALVADOR (BA) - CEP: 40110-060 FONE: (71) 98875-8494 / E-MAIL: THIAGOGFUKUDA@GMAIL.COM

CEP/HUPES - COMITÊ DE ÉTICA EM PESQUISA Endereço: Parte do HOSPITAL UNIVERSITÁRIO PROF. EDGARD SANTOS – UFBA, localizado na Rua Augusto Viana, s/n.º, 1º andar. Bairro: Canela | Município: Salvador | UF: Bahia CEP: 40.110-060

Horário de funcionamento: de segunda a sexta, das 8h às 12h30

Contatos: - FONE: (71) 3283-8043 - FAX: (71) 3283-8141 - Email: cep.hupes@gmail.com

Declaração de Consentimento

Concordo em participar do estudo intitulado "PERFIL CLÍNICO-EPIDEMIOLÓGICO DE PACIENTES COM DOENÇAS DO ESPECTRO NEUROMIELITE ÓPTICA ANTENDIDOS EM AMBULATÓRIO DE REFERÊNCIA EM DOENÇAS DESMIELINIZANTES EM HOSPITAL TERCIÁRIO DE SALVADOR, BA". Entendo que ao assinar esse documento, não estou abdicando de nenhum de meus direitos legais. Eu autorizo a utilização dos meus registros médicos (prontuário médico) pelo pesquisador, autoridades regulatórias e pelo Comitê de Ética e Pesquisa (CEP) da instituição.

Nome do Participante da Pesquisa

_____ _____

Assinatura do Participante da Pesquisa Data:

_____

Nome do Representante Legal do Participante da Pesquisa

_____ _____

Assinatura do Representante Legal do Participante da Pesquisa Data:

_____

Nome da pessoa obtendo o Consentimento

_____ _____

Assinatura pessoa obtendo o Consentimento Data:

_____

Nome do Pesquisador Principal

_____ _____

Assinatura Pesquisador Principal Data:

Anexo 4. EDSS

GOVERNO DO ESTADO DA BAHIA
Secretaria da Saúde do Estado da Bahia - SESAB
Superintendência de Assistência Farmacêutica, Ciência e Tecnologias em Saúde - SAFTEC
Diretoria de Assistência Farmacêutica - DASF
Coordenação de Assistência Farmacêutica na Atenção Especializada - COAFE

ESCALA DE EDSS- SISTEMAS FUNCIONAIS (SF) PARA A ESCALA EDSS

NOME:_____

FUNÇÕES PIRAMIDAIS	
Normal	0
Sinais Anormais sem incapacidade	1
Incapacidade mínima	2
Discreta ou moderada paraparesia ou hemiparesia; monoparesia grave	3
Paraparesia ou hemiparesia acentuada; quadriparesia moderada ou monoplegia	4
Paraplegia, hemiplegia ou acentuada quadriparesia	5
Quadriplegia	6
Desconhecido	(*)
FUNÇÕES CEREBELARES	
Normal	0
Sinais anormais sem incapacidade	1
Ataxia discreta em qualquer membro	2
Ataxia moderada de tronco ou de membros	3
Incapaz de realizar movimentos coordenados devido à ataxia	4
Desconhecido	(*)
FUNÇÕES DO TRONCO CEREBRAL	
Normal	0
Somente sinais anormais	1
Nistagmo moderado ou outra incapacidade leve	2
Nistagmo grave, acentuada paresia extraocular ou incapacidade moderada de outros cranianos	3
Disartria acentuada ou outra incapacidade acentuada	4
Incapacidade de deglutir ou falar	5
Desconhecido	(*)
FUNÇÕES SENSITIVAS	
Normal	0
Diminuição de sensibilidade ou estereognosia em 1-2 membros	1
Diminuição discreta de tato ou dor ou da sensibilidade posicional e/ou diminuição moderada da vibratória ou estereognosia em 1-2 membros; ou diminuição somente da vibratória em 3-4 membros	2
Diminuição moderada de tato ou dor, ou posicional e/ou perda da vibratória em 1-2 membros; ou diminuição discreta de tato ou dor e/ou diminuição moderada de toda propriocepção em 3-4 membros	3
Diminuição acentuada de tato ou dor, ou perda da propriocepção em 1-2 membros; ou diminuição moderada de tato ou dor e/ou diminuição acentuada da propriocepção em mais de 2 membros.	4
Perda da sensibilidade de 1-2 membros; ou moderada diminuição de tato ou dor e/ou perda da propriocepção na maior parte do corpo abaixo da cabeça.	5
Anestesia da cabeça para baixo	6
Desconhecido	(*)

FUNÇÕES VESICAIS	
Normal	0
Sintomas urinários sem incontinência	1
Incontinência < ou igual uma vez por semana	2
Incontinência > ou igual uma vez por semana	3
Incontinência diária ou mais que 1 vez por dia	4
Caracterização contínua	5
Grau 5 para bexiga e grau 5 para disfunção retal	6
Desconhecido	(*)
FUNÇÕES INTESTINAIS	
Normal	0
Obstipação menos que diária sem incontinência	1
Obstipação diária sem incontinência	2
Incontinência < uma vez semana	3
Incontinência > uma vez semana	4
Sem controle de esfíncter retal	5
Grau 5 para bexiga e grau 5 para disfunção retal	6
Desconhecido	(*)
FUNÇÕES VISUAIS	
Normal	0
Escotoma com acuidade visual (AV) igual ou melhor que 20/30	1
Pior olho com escotoma e AV de 20/30 a 20/59	2
Pior olho com grande escotoma, ou diminuição moderada dos campos, mas com AV de 20/60 a 20/99	3
Pior olho com diminuição acentuada dos campos a AV de 20/100 a 20/200; ou grau 3 com AV do melhor olho igual ou menor que 20/60	4
Pior olho com AV menor que 20/200; ou grau 4 com AV do melhor olho igual ou menor que 20/60	5
Grau 5 com AV do melhor olho igual ou menor que 20/60	6
Desconhecido	(*)
FUNÇÕES MENTAIS	
Normal	0
Alteração apenas do humor	1
Diminuição discreta da mentação	2
Diminuição normal da mentação	3
Diminuição acentuada da mentação (moderada síndrome cerebelar crônica)	4
Demência ou grave síndrome cerebral crônica	5
Desconhecido	(*)
OUTRAS FUNÇÕES	
Nenhuma	0
Qualquer outro achado devido à EM	1
Desconhecido	(*)

_____ _____/_____/20_____

Assinatura e carimbo do(a) médico(a) **Data**

Anexo 5. Aprovação Projeto Biomarcadores

UFBA - HOSPITAL UNIVERSITÁRIO PROF. EDGARD SANTOS DA UNIVERSIDADE FEDERAL DA BAHIA ¿ HUPES/UFBA

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Investigação de biomarcadores para prognóstico de pacientes com Doença do Espectro Neuromielite Óptica (DENMO)

Pesquisador: Jamary Oliveira-Filho

Área Temática:

Versão: 2

CAAE: 19280819.3.0000.0049

Instituição Proponente: Hospital Universitário Prof. Edgard Santos-UFBA

Patrocinador Principal: Financiamento Próprio
NIH/DMID/NIAI

DADOS DO PARECER

Número do Parecer: 3.653.165

Apresentação do Projeto:

Vide Parecer nº 3.591.671.

Objetivo da Pesquisa:

2.1 – Objetivo Primário

Investigar a presença de biomarcadores para exacerbações agudas em pacientes com NMOSD.

2.2 - Objetivos Secundários

- Determinar os níveis de citocinas e quimiocinas no soro de indivíduos com NMOSD através da técnica de luminex.

- Correlacionar os níveis de citocinas e quimiocinas no soro de indivíduos com NMOSD com o grau de incapacidade dos pacientes.

- Avaliar a associação entre acometimento visual grave e as concentrações de citocinas e quimiocinas em pacientes com neurite óptica aguda.

- Correlacionar a extensão de lesão medular e as concentrações séricas de citocinas e quimiocinas em pacientes com mielite aguda.

- Investigar o fenótipo de leucócitos em pacientes com NMOSD.

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Bairro: Canela **CEP:** 40.110-060
UF: BA **Município:** SALVADOR
Telefone: (71)3283-8043 **Fax:** (71)3283-8140 **E-mail:** cep.hupes@gmail.com

Avaliação dos Riscos e Benefícios:

Foram declarados pelos pesquisadores do estudo:

Riscos Potenciais, Efeitos Colaterais e Desconforto

Os riscos encontrados no estudo estão no processo de coleta do estudo, em que pode haver constrangimento por alguma pergunta, cansaço e estresse pelo tempo extra para realização do questionário. Um meio de minimizar tais risco e buscar um ambiente adequado e confortável para a entrevista, fomentando uma empatia para diminuir constrangimentos e experiências negativas durante a coleta de dados. Durante a realização da coleta de sangue pode haver algum desconforto, tais como dor ou vermelhidão, que logo passará e caso ocorram você será orientado por profissionais experientes em relação ao que fazer nestes casos.

Além disso, ha o risco de quebra do sigilo dos dados colhidos no estudo. Todos os cuidados serão tomados para que em nenhum momento nomes e dados pessoais sejam diretamente mencionados ou relacionados, não sendo possível identificar especificamente a quem pertence as informações. O estudo busca a mínima possibilidade de danos de dimensão física, psíquica, moral, intelectual, social, cultural ou espiritual ao ser humano, em qualquer fase da pesquisa e dela decorrente.

Benefícios para o participante Não ha benefício direto para o participante desse estudo. Trata-se de estudo que avaliara marcadores características dos indivíduos da nossa população e marcadores de risco para doença de maior atividade.

Somente no final do estudo poderemos concluir a presença de algum benefício. Porém, os resultados obtidos com este estudo poderão ajudar a esclarecer as características dos pacientes acometidos com Doenças do Espectro Neuromielite Óptica na população baiana e fatores de maior risco para pioras agudas.

Comentários e Considerações sobre a Pesquisa:

A pesquisa apresenta relevância clínica e científica pois pretende investigar biomarcadores para exacerbações agudas em pacientes com NMOSD, condição clínica rara.

Os pesquisadores pretendem acompanhar os participantes da pesquisa através de uma coorte retrospectiva e prospectiva para avaliar a taxa "anualizada" que será calculada baseada no tempo de acompanhamento e número de surtos que apresentou no período.

Considerações sobre os Termos de apresentação obrigatória:

Vide conclusões ou pendências.

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Telefone: (71)3283-8043 **Fax:** (71)3283-8140 **E-mail:** cep.hupes@gmail.com

Recomendações:

Vide conclusões ou pendências.

Conclusões ou Pendências e Lista de Inadequações:

Após avaliação do projeto de pesquisa e dos seus respectivos termos de apresentação obrigatória, faz-se necessária algumas adequações com vistas a atender à Resolução do CNS nº 466/2012.

1. O cronograma da pesquisa necessita ser adequado, visto que prevê início da coleta de dados em data anterior a aprovação pelo CEP. SOLICITAÇÃO ATENDIDA.

2. Faz-se necessário informar se o material biológico bem como os dados obtidos na pesquisa serão utilizados exclusivamente para a finalidade prevista no seu protocolo, ou conforme o consentimento do participante ou se haverá armazenamento de material biológico. Caso haja armazenamento, solicita-se adequação à legislação vigente;

3. Solicita-se informar se haverá armazenamento de material biológico (amostras de sangue); SOLICITAÇÃO ATENDIDA.

4. Não está claro nos critérios de inclusão, a idade dos participantes da pesquisa. Solicita-se informar a faixa etária dos participantes da pesquisa. Em caso de inclusão de participantes menores de 18 anos, solicita-se apresentação do termo de assentimento; SOLICITAÇÃO ATENDIDA.

5. Assegurar que todas as vias do TCLE estejam rubricadas em todas as suas páginas e assinadas pelo convidado a participar da pesquisa, ou por seu representante legal, assim como pelo pesquisador responsável, ou pela (s) pessoa (s) por ele delegada (s), devendo as páginas de assinaturas estar na mesma folha.. SOLICITAÇÃO ATENDIDA.

Considerações Finais a critério do CEP:

O participante da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 466/12) e deve receber uma via do Termo de Consentimento Livre e Esclarecido, na íntegra, completamente assinado.

O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP que o aprovou, aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da

pesquisa que requeiram ação imediata.

O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo. É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas.

Relatórios parciais e final devem ser apresentados ao CEP, inicialmente em _____/_____/_____ e ao término do estudo.

Situação: Projeto Aprovado.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1374364.pdf	03/10/2019 08:54:13		Aceito
Projeto Detalhado / Brochura Investigador	Projeto_DENMO3.docx	03/10/2019 08:53:08	thiago gonçalves fukuda	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE3_DENMO.docx	03/10/2019 07:53:45	thiago gonçalves fukuda	Aceito
Cronograma	Cronograma_DENMO.docx	24/09/2019 14:18:24	thiago gonçalves fukuda	Aceito
Outros	Carta_Anuencia2.pdf	19/08/2019 09:36:37	thiago gonçalves fukuda	Aceito
Outros	Thiago_Fukuda.pdf	19/08/2019 09:32:09	thiago gonçalves fukuda	Aceito
Outros	Iva_fialho.pdf	19/08/2019 09:12:35	thiago gonçalves fukuda	Aceito
Outros	Jamary_Oliveira.pdf	19/08/2019 09:12:04	thiago gonçalves fukuda	Aceito

Outros	Lucas_Pedreira.pdf	19/08/2019 09:11:16	thiago gonçalves fukuda	Aceito
Outros	Encaminhamento_CEP.pdf	14/08/2019 12:45:36	thiago gonçalves fukuda	Aceito
Outros	Equipe.pdf	14/08/2019 12:44:24	thiago gonçalves fukuda	Aceito
Outros	Termo_dados_prontuario.pdf	14/08/2019 12:43:33	thiago gonçalves fukuda	Aceito
Outros	Termo_compromisso.pdf	14/08/2019 12:40:57	thiago gonçalves fukuda	Aceito
Outros	Carta_de_anuencia_HUPES.pdf	14/08/2019 12:30:24	thiago gonçalves fukuda	Aceito
Folha de Rosto	Folha_de_Rostro.pdf	14/08/2019 12:23:11	thiago gonçalves fukuda	Aceito
Orçamento	Orcamento_DENMO.docx	25/07/2019 12:50:10	thiago gonçalves fukuda	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

SALVADOR, 21 de Outubro de 2019

Assinado por:
Pablo de Moura Santos
(Coordenador(a))

Endereço: Rua Augusto Viana, s/nº - 1º Andar
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Telefone: (71)3283-8043 **Fax:** (71)3283-8140 **E-mail:** cep.hupes@gmail.com

Anexo 6. Outras publicações cientificas no período do Curso de doutorado (2020-2024).

ARTICLE OPEN ACCESS

Clinical Features of COVID-19 on Patients With Neuromyelitis Optica Spectrum Disorders

Samira Luisa Apostolos-Pereira, MD, PhD,* Lis Campos Ferreira, MD,* Mateus Boaventura, MD,* Nise Alessandra de Carvalho Sousa, MD, Gabriela Joca Martins, MD, José Arthur d'Almeida, MD, PhD, Milena Pitombeira, MD, Lucas Silvestre Mendes, MD, Thiago Fukuda, MD, Hideraldo Luíz Souza Cabeça, MD, PhD, Luciano Chaves Rocha, MD, Bianca Santos de Oliveira, MD, Carla Renata Vieira Stella, MD, Enedina Maria Lobato de Oliveira, MD, PhD, Leizian de Souza Amorim, MD, Andréa Ferrari de Castro, MD, Antonio Pereira Gomes Neto, MD, Guilherme Diogo Silva, MD, Lucas Bueno, MD, Maria de Morais Machado, MD, Rafael Castello Dias-Carneiro, MD, MS, Ronaldo Maciel Dias, MD, Alvaro Porto Moreira, MD, Ana Piccolo, MD, Anderson Kuntz Grzesiuk, MD, Andre Muniz, MD, Caio Diniz Disserol, MD, Claudia Ferreira Vasconcelos, MD, PhD, Damacio Kaimen-Maciel, MD, Denise Sisterolli Diniz, MD, PhD, Elizabeth Comini-Frota, MD, PhD, Fernando Coronetti Rocha, MD, PhD, Gutemberg Augusto Cruz dos Santos, MD, Yara Dadalti Fragoso, MD, PhD, Guilherme Sciascia do Olival, MD, Heloisa Helena Ruocco, MD, PhD, Heloise Helena Siqueira, MD, Henry Koity Sato, MD, José Alexandre Figueiredo, Jr., MD, Leandro Cortoni Calia, MD, Mario Emilio Teixeira Dourado, Jr., MD, Letícia Scolari, MD, Herval Ribeiro Soares Neto, MD, Luiz Melges, MD, Marcus Vinicius Magno Gonçalves, MD, PhD, Maria Lucia Vellutini Pimentel, MD, PhD, Marlise de Castro Ribeiro, MD, Omar Gurrola Arambula, MD, Paulo Diniz da Gama, MD, PhD, Renata Leite Menon, MD, Rodrigo Barbosa Thomaz, MD, Rogério de Rizo Morales, MD, PhD, Silvana Sobreira, MD, Suzana Nunes Machado, MD, PhD, Taysa Gonsalves Jubé Ribeiro, MD, Valéria Coelho Santa Rita Pereira, MD, Vanessa Maia Costa, MD, Adaucto Wanderley da Nóbrega Junior, MD, Soniza Vieira Alves-Leon, MD, PhD, Marilia Mamprim de Morais Perin, MD, Eduardo Donadi, PhD, Tarso Adoni, MD, PhD, FAAN, Sidney Gomes, MD, Maria Brito Ferreira, MD, PhD, Dagoberto Callegaro, MD, PhD, Maria Fernanda Mendes, MD, PhD, Doralina Brum, MD, PhD, and Felipe von Glehn, MD, PhD, FAAN, and the Neuroimmunology Brazilian Study Group

Correspondence
Dr. von Glehn
felipeglehn@gmail.com

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Abstract

Background and Objectives

To describe the clinical features and disease outcomes of coronavirus disease 2019 (COVID-19) in patients with neuromyelitis optica spectrum disorder (NMOSD).

Methods

The Neuroimmunology Brazilian Study Group has set up the report of severe acute respiratory syndrome (SARS-CoV2) cases in patients with NMOSD (pwNMOSD) using a designed web-based case report form. All neuroimmunology outpatient centers and individual neurologists were invited to register their patients across the country. Data collected between March 19 and July 25, 2020, were uploaded at the REDONE.br platform. Inclusion criteria were as follows:

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*These authors contributed equally to this work.

From the Hospital das Clínicas (S.L.A., M.B., G.D.S., L.B., C.C.D.D., D.C.), FM-USP, São Paulo; Universidade Federal de Sergipe and Univ. Tiradentes (L.C.F.), Aracaju; Hospital Univ. Getúlio Vargas (N.A.d.C.S.), Manaus; Hospital Geral de Fortaleza (G.J.M., J.A.d.A., M.S.P., L.S.M.); Universidade Federal da Bahia/Ebserh (T.F.), Salvador; Hospital Ophir Loyola (H.L.S., L.C.R.), Belém; FUNAD (B.E.S.), João Pessoa; UNICAMP (C.R.A.), Campinas; Universidade Federal de São Paulo (E.M.L., L.d.S.A.), UNIFESP; Universidade Metropolitana de Santos (A.A.F.d.C., Y.D.F.); Santa Casa (A.P.G.), Belo Horizonte; Hospital da Restauração (M.I.d.M., A.J.P.), Recife; Santa Casa (R.P.C., M.F.M.), São Paulo; Hospital de Base do Distrito Federal (R.M.D.), Brasília; Hospital Santa Marcelina (A.C.P.), São Paulo; Private Service (A.K.), Cuiabá; Clínica AMO (A.M.), Salvador; Hospital Universitário Gaffree e Guinle (C.C.F.V.), Rio de Janeiro; Santa Casa (D.R.K.M.), Londrina; Universidade Federal de Goiás (D.S.D.), Goiânia; Private Service (E.R.C.-F.), Belo Horizonte; Faculdade de Medicina de Botucatu (F.C.G.D.R. D.G.B.), UNESP; Santa Casa and ABEM-Assoc. Brasileira de Esclerose Múltipla (G.S.d.O.), São Paulo; Universidade Estácio de Sá and Universidade Federal Fluminenses (G.A.C.), Rio de Janeiro; Universidade Federal Fluminense (H.H.R.), Campinas; Universidade Federal do Mato Grosso (H.H.S., J.A.F., L.S.), Cuiabá; Private Service (H.K.S.), Curitiba; IAMSPE (H.R.S.N.), São Paulo; Private Service (L.C.C.), São Paulo; Faculdade de Medicina de Marília (L.D.M.); Univ. da Região de Joinville (Univille) (M.V.M.G.); Santa Casa (M.L.V.P.), Rio de Janeiro; Univ. Federal R G Norte (M.E.T.D.), Natal; Univ. Federal Ciências da Saúde de Porto Alegre (M.d.C.R.); PUC (P.D.d.G.), Sorocaba; Hospital Israelita Albert Einstein (R.B.T.), São Paulo; Univ. Federal de Uberlândia (R.d.R.M.); Hospital Beneficência Portuguesa (S.G.), São Paulo; Hospital Memorial São José (S.S.), rede D'OR, Recife; Univ. Federal do Rio de Janeiro (S.N.M., V.C.S.R.P.); Private Service (S.N.M.), Florianópolis; Univ. Federal de Goiás (T.A.G.J.R.), Goiânia; Hospital Neurológico de Goiânia (V.M.C.); Pontifícia Universidade Católica de Campinas (M.M.d.M.P.); Hospital Universitário da Universidade Federal de Santa Catarina (A.W.d.N.J.), Florianópolis; Faculdade de Medicina de Ribeirão Preto (E.A.D.), USP; Hospital Sírio-Libanês (T.A.), São Paulo; and Faculty of Medicine (F.v.G.), University of Brasília, Brazil.

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Glossary

AQP4 = aquaporin 4; **CBA** = cell-based assay; **CI** = confidence interval; **COVID-19** = coronavirus disease 2019; **DMT** = disease-modifying therapy; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorders; **OR** = odds ratio; **pwNMOSD** = patients with NMOSD; **RT-PCR** = reverse transcription-polymerase chain reaction; **SARS** = severe acute respiratory syndrome.

(1) NMOSD diagnosis according to the 2015 International Panel Criteria and (2) confirmed SARS-CoV2 infection (reverse transcription-polymerase chain reaction or serology) or clinical suspicion of COVID-19, diagnosed according to Center for Disease Control / Council of State and Territorial Epidemiologists (CDC/CSTE) case definition. Demographic and NMOSD-related clinical data, comorbidities, disease-modifying therapy (DMT), COVID-19 clinical features, and severity were described.

Results

Among the 2,061 pwNMOSD followed up by Brazilian neurologists involved on the registry of COVID-19 in pwNMOSD at the REDONE.br platform, 34 patients (29 women) aged 37 years (range 8–77), with disease onset at 31 years (range 4–69) and disease duration of 6 years (range 0.2–20.5), developed COVID-19 (18 confirmed and 16 probable cases). Most patients exhibited mild disease, being treated at home (77%); 4 patients required admission at intensive care units (severe cases); and 1 patient died. Five of 34 (15%) presented neurologic manifestations (relapse or pseudoexacerbation) during or after SARS-CoV2 infection.

Discussion

Most NMOSD patients with COVID-19 presented mild disease forms. However, pwNMOSD had much higher odds of hospitalization and intensive care unit admission comparing with the general Brazilian population. The frequency of death was not clearly different. NMOSD disability, DMT type, and comorbidities were not associated with COVID-19 outcome. SARS-CoV2 infection was demonstrated as a risk factor for NMOSD relapses. Collaborative studies using shared NMOSD data are needed to suitably define factors related to COVID-19 severity and neurologic manifestations.

Coronavirus disease 2019 (COVID-19), as an unprecedented challenge to global public health, requires international data collection to address the effect of the disease in groups at potential increased risk.[1] Brazil, one of the main epicenters of the COVID-19 pandemic, reached the unfortunate milestone of more than 2 million severe acute respiratory syndrome (SARS-CoV2) infection cases and more than 100k deaths (accessed on August 8, Johns Hopkins COVID19 resource center). The international community has rapidly launched several patient registries to ascertain the overall effect of the COVID-19 in neuroimmunologic diseases, particularly multiple sclerosis (MS).[2] Notwithstanding, some series of MS patients have been recently reported.[3–6] Scarce data are available about the effect of SARS-CoV2 infection on patients with neuromyelitis optica spectrum disorders (NMOSD), a severe CNS autoimmune astrocytopathy treated with immunosuppressant therapy.[7,8]

Compared with MS, patients with NMOSD (pwNMOSD) are older at disease onset and present higher disability, higher rate of hospitalization, and early-age risk of mortality.[8] Because NMOSD prognosis is relapse-related, it is mandatory to start disease-modifying therapy (DMT) soon after the index clinical event.[9] Many of the commonly used DMTs for NMOSD are cell-depleting immunosuppressants, which may potentially increase the risk of viral and bacterial infections.[10] The effect of SARS-CoV2 infection on pwNMOSD is a gap of knowledge. The purpose of this study was to describe the frequency and clinical features of COVID-19 in a cohort of patients with NMOSD.

Methods

Study Design and Participants

This was a prospective observational cohort study developed by the Brazilian Academy of Neurology using the REDONE.br (Brazilian Registry of Neurological Diseases) platform, starting on March 19, 2020, and punctually closed on July 25, 2020, to be resumed afterward. REDONE.br invited 51 neuroimmunology university and private centers distributed across all 27 Brazilian states. Forty-seven of 51 centers (92%) from 19 states (70%) participated in this study. Each referral center received a link to register all flu-like symptoms among pwNMOSD using a web-based case report form. Neurologists have continuously updated the REDONE.br database reporting the longitudinal follow-up of patients during the SARS-CoV-2 pandemic. Inclusion criteria: (1) patients diagnosed according to the 2015 International Panel for NMOSD criteria[10] and (2) flu-like illness presenting a SARS-CoV2 positive test classified as a confirmed case (reverse transcription-polymerase chain reaction [RT-PCR] and/or IgA/IgM or IgG seropositivity), or clinical suspicion of COVID-19 diagnosed according to CDC/CSTE case definition,[9] classified as a possible case. The cell-based assay (CBA) test to detect antibodies against aquaporin 4 (AQP4-IgG) was performed in most

patients. Exclusion criteria for this study included confirmed infections by H1N1, H3N2, or influenza B and myelin oligodendrocyte protein (MOG)-IgG seropositivity. The anti-MOG IgG was detected using an in-house CBA in live human embryonic kidney (HEK)-293 cells as described elsewhere.[11]

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the Ethics Committee of the "Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (Unesp)" under the internal review board number CAAE 31021220.2.0000.5411. All participants signed a written informed consent form before enrollment. This study was conducted according to the latest Declaration of Helsinki.

NMOSD Characteristics

Data collection was related to specific variables such as sex, comorbidities, age at disease onset, disease duration, disability at the last follow-up evaluated by Expanded Disability Status Scale (EDSS), previous use of DMT, maintenance or not during the pandemic, and relapse after infection.

COVID-19 Features

Data regarding COVID-19 included diagnostic criteria (confirmed or probable) and clinical presentation. Chest CT data were recorded when available.

Clinical Outcome

Clinical outcome and disease severity of COVID-19 were evaluated in the pwNMOSD considering the variables: treatment at home (mild cases) or at hospital (moderate cases) and the development of critical conditions (severe cases), such as sepsis, septic shock, acute respiratory syndrome, and need of ventilatory support. In addition, demographic and clinical features of COVID-19 in pwNMOSD were compared with those reported for the general Brazilian population, using similar features as observed for patients with NMOSD (home treatment, hospital admission, intensive care unit [ICU] admission, death, sex, age range [15–59 years], and comorbidity). Data from the Brazilian population were obtained at official national sources at antigo.saude.gov.br/images/pdf/2020/July/30/Boletim-epidemiologico-COVID-24.pdf and opendatasus.saude.gov.br/dataset/bd-srag-2020.[12] Data collection from both groups started from the beginning of the pandemics in Brazil till the closure date of this study (July 25, 2020). For both groups, we considered patients who exhibited positive results for SARS-CoV2 by RT-PCR or serology (as defined by the Brazilian Ministry of Health) from the beginning of the pandemics in Brazil till the closure date of this study (July 25, 2020).

Statistical Analysis

Demographic data, NMOSD clinical and disability profile, COVID-19 clinical features, and outcome were descriptively reported. The comparison of means between groups' home treatment and hospital admission was made using the Student *t* test. The comparison of the proportions between groups for the categorized variables was performed by the test of difference of proportions, analogous to the χ^2 test. The odds ratio (OR) and the 95% confidence interval (95% CI) were obtained through the contingency table of the association between groups and the categorized variables of interest. In addition, the clinical outcome of COVID-19 in patients with NMOSD was compared with the Brazilian general population, using the 2-tailed Fisher's exact test, estimating the OR and the 95% CI. Considering the exploratory nature of the study, no adjustment for multiple comparison was made, and p values ≤ 0.05 were significant. All analyzes were performed using the SAS for the Windows v9.4 program.

Data Availability

Anonymized patient data are available on request.

Results

A total of 34 cases of SARS-CoV2 infection, classified as confirmed (n = 18) or probable (n = 16), were identified in a cohort of 2,061 pwNMOSD, distributed among all 5 Brazilian regions (north = 82 patients, northeast = 643, midwest = 140, southeast = 1,119, and south = 77). Most COVID-19 probable or confirmed cases were from the southeast region (n = 15; 44%), followed by northeast (n = 13; 38%) and north (n = 6; 18%) regions.

Demographic, clinical, and laboratory features of NMOSD patients exhibiting COVID-19 are summarized in Table 1. The women:men ratio was of 6:1. The mean age was 37 years old (range 8–77), and only 3 of 34 patients were older than 50. The mean age at NMOSD diagnosis was 31 years (range 4–69), and disease duration was 6 years (range 0.2–20.5). The median EDSS was 3.5, ranging from 0 to 8.5. Fifteen of 27 patients (56%) exhibited AQP4-IgG, 12 patients did not exhibit anti-AQP4 IgG, and 7 patients were not tested; however, all patients fulfilled the 2015 International Panel Criteria.

More than half of patients (56%) had no comorbidity, whereas 24% of patients exhibited more than 1 comorbidity. Hypertension (21%), obesity (24%), diabetes (15%), and dyslipidemia (15%) were the most common comorbidities. Nine patients presented lymphopenia, which was severe in 2 patients (364 and 600/mm^3), and none of these patients needed to be hospitalized for COVID-19 treatment.

General COVID-19 characteristics in pwNMOSD are listed in Table 2. Main symptoms included fever or chill (79%), dry cough (56%), myalgia (65%), fatigue (53%), coryza (47%), and dyspnea (38%). Gastrointestinal symptoms that occurred in 7 of 34 patients are diarrhea (7; 21%) and abdominal pain (3; 9%). Neurologic symptoms included headache (62%), anosmia (50%), ageusia (24%), and delirium (3%). Most patients (77%) exhibited mild COVID-19 forms being treated at home, and 8 patients (23%) needed to be hospitalized (moderate and severe cases). No differences were observed

Table 1 Demographic, Clinical, and Treatment Features of Patients With Neuromyelitis Optica Spectrum Disorders Who Developed COVID-19

	Total (n = 34)	Home treatment (n = 26)	Hospital admission (n = 8)	*p* Value or (95% CI)
Age (mean, range)	37 (8–77)	42 (8–56)	36 (16–77)	0.72
Age of NMOSD onset (mean, range)	31 (4–69)	35 (4–54)	31 (14–69)	0.89
Disease duration–y (mean, range)	6 (0.2–20.5)	6 (0.2–20.5)	5 (2–8.5)	0.41
EDSS (median, range)	3.5 (0–8.5)	3 (0–8.5)	4 (1–8.5)	0.25
Sex (n, %)				
Female	29 (85)	22 (85)	7 (87.5)	0.84; 0.8 (0.1–8.2)
Male	5 (15)	4 (15)	1 (12.5)	
Color (n, %)				
White	9 (27)	6 (23)	3 (37)	0.73; 0.5 (0.1–2.7)
African descent	23 (67)	19 (73)	4 (50)	0.43; 2.7 (0.5–13.9)
Asian descent	1 (3)	1 (4)	0	1.00
Not informed	1 (3)	0	1 (13)	1.00
No. of comorbidities (n, %)				
No comorbidities	19 (56)	15 (58)	4 (50)	1.00; 1.4 (0.3–6.7)
1 comorbidity	7 (21)	5 (19)	2 (25)	1.00; 0.71 (0.1–4.7)
>1 comorbidity	8 (23)	6 (23)	2 (25)	1.00; 0.9 (0.1–5.7)
Comorbidities (n, %)				
Obesity	8 (24)	6 (23)	2 (25)	1.00; 0.9 (0.1–5.7)
Hypertension	7 (21)	5 (19)	2 (25)	1.00; 0.7 (0.1–4.7)
Diabetes	5 (15)	3 (12)	2 (25)	0.71; 0.4 (0.1–2.9)
Dyslipidemia	5 (15)	2 (8)	3 (38)	0.13; 0.1 (0.02–1.1)
Cardiomyopathy	1 (3)	0	1 (13)	1.00
Neoplasm	1 (3)	1 (4)	0	1.00
Other autoimmune disease	3 (9)	3 (12)	0	0.77
Smoking	1 (3)	1 (4)	0	1.00
Treatment (n, %)				
No treatment	2 (6)	1 (4)	1 (13)	0.96; 0.3 (0.02–5.1)
AZT	10 (30)	9 (35)	1 (13)	0.45; 3.7 (0.3–35)
MTX	1 (3)	1 (4)	0	1.00
MMF + PD	1 (3)	0	1 (13)	1.00
RTX	12 (35)	9 (35)	3 (38)	1.00; 0.9 (0.2–4.6)
AZT + RTX	1 (3)	0	1 (13)	1.00
AZT + PD	5 (15)	4 (15)	1 (13)	1.00; 0.9 (0.1–10)
RTX + PD	2 (6)	2 (8)	0	1.00

Abbreviations: AD = autoimmune disease; AZT = azathioprine; CI = confidence interval; MTX = methotrexate; MMF = mycophenolate mofetil; NMOSD = neuromyelitis optica spectrum disorders; PD = prednisone; RTX = rituximab.

Table 2 Clinical and Neurologic Features, and Outcome of COVID-19 in Patients With Neuromyelitis Optica Spectrum Disorders (NMOSD), Encompassing Confirmed (n = 18) and Probable (n = 16) Cases

	Total (n = 34)
COVID-19 laboratory diagnosis	
Real-time reverse transcription-polymerase chain reaction severe acute respiratory syndrome-CoV2	18 (53%)
General symptoms (n, %)	
Fever	23 (68)
Chill	14 (41)
Dry cough	19 (56)
Myalgia	22 (65)
Fatigue	18 (53)
Arthralgia	5 (15)
Coryza	16 (47)
Sore throat	10 (29)
Diarrhea	7 (21)
Abdominal pain	3 (9)
Nausea	3 (9)
Dyspnea	13 (38)
Neurologic symptoms (n, %)	
Headache	21 (62)
Anosmia	17 (50)
Ageusia	8 (24)
Delirium	1 (3)
Severity (n, %)	
Hospitalization	8 (24)
Intensive care unit (ICU)	4 (12)
Death	1 (3)

Only the frequency of ageusia was different in these groups, being more frequent in confirmed cases (44% vs 6%, $p = 0.02$).

regarding demographic and clinical features comparing confirmed and probable COVID-19 cases, except for ageusia, which was more frequent in confirmed cases (44% vs 6%, $p = 0.02$).

Considering the hospitalized patients, 6 of 8 patients exhibited ground glass opacity, and 4 of 8 patients presented 1 or more comorbidities and used immunosuppressive drugs. Among the 8 hospitalized patients, (1) 4 patients required intensive care support (severe cases); (2) 2 women without comorbidities (16 years old, EDSS 3.5, rituximab and 32 years old, EDSS 4.0, azathioprine) and 1 patient with dyslipidemia (46 years old, EDSS 7.0, azathioprine and prednisone) needed mechanical ventilation; (3) 1 patient needed ICU but no mechanical ventilation, and although patient was treated with rituximab, she was also an elderly patient (77 years old) exhibiting multiple comorbidities, including hypertension, diabetes, dyslipidemia, and cardiomyopathy; and (4) a 46-year-old patient with EDSS 7.0 using azathioprine plus prednisone and presenting dyslipidemia died after evolving SARS, sepsis, and shock septic. Clinical characteristics of hospitalized and critical patients are summarized in eTable 1, links.lww.com/NXI/A540.

NMOSD treatment was suspended in 1 patient during the pandemic and in another during the active COVID-19. Fifteen patients (44%) used rituximab either as a monotreatment (12; 35%) or combined with other oral immunosuppressive drugs (3; 9%). Sixteen of 34 patients (56%) used azathioprine as monotherapy (10; 29%) or combined with prednisone (5; 15%) or rituximab (1; 3%). Four of 8 hospitalized patients and 11 of 26 patients treated at home were in use of rituximab. Among the hospitalized patients, 2 patients used prednisone (with mycophenolate or azathioprine) and 1 used only azathioprine. One patient did not use any immunosuppressive drugs.

Five of 34 patients (15%) with NMOSD presented neurologic manifestations (relapse or pseudoexacerbation) during or after SARS-CoV2 infection. A 48-year-old patient, EDSS 3.0, using rituximab, presented a new right optic neuritis 7 days after the viral infection onset, being treated with oral corticosteroids, with complete recovery (patient 1). A 25-year-old patient, EDSS 5.0, who had a previous optic neuritis, evolved with flu-like syndrome and visual acuity worsening, being treated with IV methylprednisolone with good recovery (patient 2). A 16-year-old patient, EDSS 3.5, also had optic neuritis and presented total recovery after therapy with corticosteroids (patient 3). A 22-year-old patient had myelitis, being treated with IV methylprednisolone with poor recovery (EDSS 8.5) (patient 4). A 32-year-old patient exhibited a 1-point increase in EDSS (EDSS 4.0 to 5.0), even after 50 days after being discharged from the intensive care unit (patient 5). These patients who presented neurologic manifestations requiring hospital admission are given in eTable 1, links.lww.com/NXI/A540.

No associations were observed regarding EDSS (≤4.0 or >4.0) and the duration (≤17 or >17 days) of COVID-19 and its outcomes (home treatment, hospital admissions, ICU, cure, and death) in pwNMOSD. Similarly, no associations were observed between DMT type (azathioprine or rituximab) and comorbidities (without or at least 1 comorbidity) with COVID-19 outcomes (home treatment, hospital admission, ICU, cure, or death) (all p values > 0.05, data not shown).

Demographics and clinical features of COVID-19 in pwNMOSD were compared with those reported for the general Brazilian

Table 3 Demographic and Clinical Features of COVID-19 in 18 PCR-Confirmed Patients With NMOSD Compared With Those Reported for the General Brazilian Population

	NMOSD	General Brazilian population	*p* Value	OR (CI)
Severe acute respiratory syndrome-CoV2 infection by PCR testing or serology (confirmed COVID-19)	n = 18	n = 2,394,513	—	—
Home treatment	12 (67%)	2,157,661 (90%)[a]	—	—
Hospital treatment	6 (33%)	236,852 (11%)	0.01	4.6 (1.6–12.0)
Hospital-ICU	4 (22%)	71,826 (3%)[a]	0.002	9.2 (2.6–26.8)
Death	1 (6%)	86,449 (4%)	0.62	1.6 (0.1–8.7)
Hospitalized patients				
Men	0	134,468 (57%)	—	—
Women	6 (100%)	102,317 (43%)	0.01	2.0-undefined
Age <60 y (15–59)	5 (83%)	101,707 (43%)[a]	0.06	0.9–158.1
At least 1 comorbidity	2 (33%)	138,499 (58%)[a]	0.25	0.05–2.0

Abbreviations: CI = confidence interval; ICU = intensive care unit; NMOSD = neuromyelitis optica spectrum disorders; OR = odds ratio; PCR = polymerase chain reaction.
[a] antigo.saude.gov.br/images/pdf/2020/July/30/Boletim-epidemiologico-COVID-24.pdf and opendatasus.saude.gov.br/dataset/bd-srag-2020

population (Table 3). pwNMOSD presented with a higher frequency of hospital treatment (33% vs 11% OR 4.6 [95% CI 1.6–12.0] $p = 0.01$) and a higher frequency of ICU treatment (22% vs 3% OR 9.2 [95% CI 2.6–26.8] $p = 0.002$). An increased risk of death was not seen.

Discussion

To date, this study included the greatest number of probable and confirmed cases of COVID-19 among pwNMOSD. The estimated prevalence of NMOSD in Latin America is 5 of 100,000 inhabitants.[13] Taking account that the Brazilian population is estimated to have 210,147,125 inhabitants by July 25, 2020, the total number of Brazilian patients with NMOSD may be roughly estimated to 10,590. Therefore, the coverage of the REDONE.br registry was approximately 20% of national cases, a number that can be considered a representative sample. The distribution of COVID-19 in patients with NMOSD was heterogeneous among the 5 major Brazilian regions, agreeing with the more populated areas exhibiting higher COVID-19 incidence rates in the general population.[14]

The preponderance of women and African descents in pwNMOSD with COVID-19 is in accordance with the known demographic profile of the disease.[13] Although male sex and older age have been associated with severity of COVID-19,[1] it is possible that the female preponderance and low median age (only 1 of 34 patient was aged >60 years) as observed in this cohort may be responsible for the predominance of mild COVID-19 cases in pwNMOSD.

Chronic diseases such as hypertension, diabetes mellitus, heart disease, asthma, and obesity are already known to increase COVID-19 severity.[15] The prevalence of known risk factors associated with severe COVID-19, such as hypertension and obesity, is also high in patients with MS and NMOSD.[16,17] Although obesity, hypertension, dyslipidemia, and diabetes were observed in this series, more than half (56%) of pwNMOSD did not present comorbidities. Although comorbidities play an important role in COVID-19 outcome, this scenario is multifaceted and cannot be resolved by this case series.[18]

Besides underlying disorders, patients with NMOSD have an additional morbidity factor associated with DMT and disability related to NMOSD (EDSS). Scarce and inconclusive theoretical efforts based on the use of immunosuppressive drugs in autoimmune disorders during the pandemic or during the SARS-CoV2 infection have challenged neurologists on the decision to maintain or suspend the NMOSD treatment.[19] In this series, 97% (33/34) of patients maintained immunosuppressive drugs during the pandemic and even 97% (32/33) during the infection. Almost half of the patients were treated with rituximab and the other half with azathioprine in mono or combined treatment.

To understand the effect of COVID-19 on pwNMOSD, we compared the NMOSD demographic and clinical features with those reported for the general Brazilian population exhibiting COVID-19, using data available at the Brazilian Ministry of Health Databank. As given in Table 3, pwNMOSD presented a higher rate of hospitalization and of ICU admission than the general population. By contrast, the frequency of death was not

clearly higher between pwNMOSD (n = 1; 6%) and the general Brazilian population (n = 86,449; 4%). On the search for factors that could contribute to higher severity of COVID-19 in pwNMOSD, we analyzed variables such as sex, adjusted age range (15–59 years), and comorbidities between the 2 groups. A difference was observed regarding women having a higher frequency of hospital admission, which could be explained by known disease-associated incidence in women and a low number of cases included in this study. Further studies are needed to confirm this result (Table 3).

Because of the low prevalence of NMOSD,[13] it is understandable that only case report[8] and small sample size[7] have been reported. Considering that there are expectations about the potential risk of interrupt treatment on patients with NMOSD[20] and pondering the conflicting data regarding the use of anti-CD20,[7,8,21] collaborative studies with sharing data are needed to clarify the effect of immunosuppressive drugs on COVID-19 severity and clinical outcome in these patients.[22]

Neurologic symptoms reported in this series included headache, anosmia, ageusia, and delirium, which were already described as neurologic manifestations in recently published articles.[23] Another important issue refers to the effect of SARS-CoV2 infection on NMOSD features. Among the patients who exhibited neurologic manifestations during COVID-19, 2 patients presented new neurologic manifestations and increased EDSS and poorly responded to methylprednisolone treatment. An additional patient exhibited a new episode of optic neuritis 7 days after COVID-19 recovery. These patients may be classified as NMOSD relapses. The other 2 patients exhibited exacerbation of their previous neurologic manifestations and presented a good response to methylprednisolone therapy. Whether these 2 patients exhibited relapse or pseudoexacerbation during COVID-19 is challenging because imaging procedures were not performed. Despite the small number of patients, the coincidence between SARS-CoV2 infection and NMOSD neurologic manifestations (e.g., relapse and pseudoexacerbation) deserves further investigation to ascertain whether the virus itself or the host inflammation associated with COVID-19 may contribute to impair previous or promote new neurologic findings.[24]

Major methodological limitations of this study included the following: (1) the low number of tests for COVID-19 diagnosis at the time of the study and (2) the electronic communication between patients and their neurologists. Despite these limitations, this is the first data collection on patients with NMOSD in the context of the superimposed COVID-19 infection in a severely affected country.

In conclusion, most NMOSD patients with COVID-19 presented mild disease forms, particularly among women. However, pwNMOSD had much higher odds of hospitalization and ICU admission comparing with the general Brazilian population. The frequency of death was not clearly different. NMOSD disability, DMT type, and comorbidities were not associated with COVID-19 outcome. SARS-CoV2 infection was demonstrated as a risk factor for NMOSD relapses. Collaborative studies using shared NMOSD data are needed to suitably define factors related to COVID-19 severity and neurologic manifestations.

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Disclosure

S.L. Apostolos-Pereira, L. C. Ferreira, M. Boaventura, and F. von Glehn report no disclosures relevant to the manuscript. S.N. Machado is deceased; disclosures are not included for this author. In general, the authors from the Neuroimmunology Brazilian Study Group report no disclosures relevant to the manuscript. Go to Neurology.org/NN for full disclosures.

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Appendix Authors

Name	Location	Contribution
Samira Luisa Apóstolos Pereira, MD, PhD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Design and conceptualized study, analyzed the data, and drafted the article for intellectual content
Lis Campos Ferreira, MD	Universidade Federal de Sergipe and Univ. Tiradentes, Aracaju, Brazil.	Drafted the article for intellectual content and analyzed and interpreted the data
Mateus Boaventura, MD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Drafted the article for intellectual content and analyzed and interpreted the data
Nise Alessandra de Carvalho Sousa, MD	Hospital Univ. Getúlio Vargas, Manaus, Brazil	Design and conceptualized study, revised the article for intellectual content, and major role in the acquisition of data
Gabriela Joca Martins, MD	Hospital Geral de Fortaleza, Fortaleza, Brazil	Major role in the acquisition of data
José Arthur d'Almeida, PhD	Hospital Geral de Fortaleza, Fortaleza, Brazil	Major role in the acquisition of data
Milena S. Pitombeira, MD	Hospital Geral de Fortaleza, Fortaleza, Brazil	Major role in the acquisition of data

Continued

Appendix *(continued)*

Name	Location	Contribution
Lucas Silvestre Mendes, MD	Hospital Geral de Fortaleza, Fortaleza, Brazil	Major role in the acquisition of data
Thiago Fukuda, MD	Universidade Federal da Bahia/Ebserh, Salvador, Brazil	Major role in the acquisition of data
Hideraldo Luís Souza Cabeça, PhD	Hospital Ophir Loyola, Belém, Brazil	Major role in the acquisition of data
Luciano Chaves Rocha, MD	Hospital Ophir Loyola, Belém, Brazil	Major role in the acquisition of data
Bianca Etelvina Santos de Oliveira, MD	FUNAD, João Pessoa, Brazil	Major role in the acquisition of data
Carla Renata Aparecida Vieira Stella, MD	UNICAMP, Campinas, Brazil	Major role in the acquisition of data
Enedina Maria Lobato de Oliveira, PhD	Universidade Federal de São Paulo, UNIFESP, São Paulo, Brazil	Design and conceptualized study and major role in the acquisition of data
Leizian de Souza Amorim, MD	Universidade Federal de São Paulo, UNIFESP, São Paulo, Brazil	Major role in the acquisition of data
Andréa Anacleto Ferrari de Castro, MD	Universidade Metropolitana de Santos, Santos, Brazil	Major role in the acquisition of data
Antonio Pereira Gomes Neto, MD	Santa Casa, Belo Horizonte, Brazil	Major role in the acquisition of data
Guilherme Diogo Silva, MD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Major role in the acquisition of data
Lucas Bueno, MD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Major role in the acquisition of data
Maria Íris de Morais Machado, MD	Hospital da Restauração, Recife, Brazil	Major role in the acquisition of data
Rafael Paternò Castello Dias-Carneiro, MD	Santa Casa, São Paulo, Brazil	Major role in the acquisition of data
Ronaldo Maciel Dias, MD	Hospital de Base do Distrito Federal, Brasília, Brazil	Major role in the acquisition of data
Alvaro Jose Porto Moreira, MD	Hospital da Restauração, Recife, Brazil	Major role in the acquisition of data
Ana Claudia Piccolo, MD	Hospital Santa Marcelina, São Paulo, Brazil	Major role in the acquisition of data
Anderson Kuntz Grzesiuk, MD	Private Service, Cuiabá, Brazil	Major role in the acquisition of data
Andre Muniz, MD	Clínica AMO, Salvador, Brazil	Major role in the acquisition of data
Caio César Diniz Disserol, MD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Major role in the acquisition of data
Claudia Cristina Ferreira Vasconcelos, MD, PhD	Hospital Universitário Gaffree e Guinle, Rio de Janeiro, Brazil	Major role in the acquisition of data

Appendix *(continued)*

Name	Location	Contribution
Damacio R Kaimen-Maciel, PhD	Santa Casa, Londrina, Brazil	Major role in the acquisition of data
Denise Sisterolli Diniz, PhD	Universidade Federal de Goiás, Goiânia, Brazil	Major role in the acquisition of data
Elizabeth R Comini-Frota, PhD	Private service, Belo Horizonte, Brazil	Major role in the acquisition of data
Fernando Coronetti G Da Rocha, PhD	Faculdade de Medicina de Botucatu, UNESP, Botucatu, Brazil	Major role in the acquisition of data
Gutemberg Augusto Cruz dos Santos, MD	Universidade Estácio de Sá and Universidade Federal Fluminenses, Rio de Janeiro, Brazil	Major role in the acquisition of data
Yara Dadalti Fragoso, PhD	Universidade Metropolitana de Santos, Santos, Brazil	Major role in the acquisition of data
Guilherme Sciascia do Olival, MD	Santa Casa and ABEM-Assoc. Brasileira de Esclerose Múltipla, São Paulo, Brazil	Major role in the acquisition of data
Heloisa Helena Ruocco, PhD	Universidade Federal Fluminense, Campinas, Brazil	Major role in the acquisition of data
Heloise Helena Siqueira, PhD	Universidade Federal do Mato Grosso, Cuiabá, Brazil	Major role in the acquisition of data
H Koity Sato, PhD	Private Service, Curitiba, Brazil	Major role in the acquisition of data
Herval Ribeiro Soares Neto, PhD	IAMSPE, São Paulo, Brazil	Major role in the acquisition of data
José Alexandre Figueiredo, PhD, Jr	Universidade Federal do Mato Grosso, Cuiabá, Brazil	Major role in the acquisition of data
Leandro Cortoni Calia, PhD	Private Service, São Paulo, Brazil	Major role in the acquisition of data
Mario Emilio Teixeira Dourado Jr, MD	Univ. Federal R G Norte, Natal, Brazil	Major role in the acquisition of data
Letícia Scolari, MD	Universidade Federal do Mato Grosso, Cuiabá, Brazil	Major role in the acquisition of data
Herval Ribeiro Soares Neto, PhD	IAMSPE, São Paulo, Brazil	Major role in the acquisition of data
Luiz D Melges, MD	Faculdade de Medicina de Marília, Marília, Brazil	Major role in the acquisition of data
Marcus Vinicius Magno Gonçalves, MD	Univ. da Região de Joinville (Univille), Joinville, Brazil	Major role in the acquisition of data
Maria Lucia Vellutini Pimentel, MD	Santa Casa, Rio de Janeiro, Brazil	Major role in the acquisition of data
Marlise de Castro Ribeiro, MD	Univ. Federal Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil	Major role in the acquisition of data

Appendix *(continued)*

Name	Location	Contribution
Omar Gurrola Arambula, MD	Faculdade de Medicina de Botucatu, UNESP, Botucatu, Brazil	Major role in the acquisition of data
Paulo Diniz da Gama, PhD	PUC, Sorocaba, Brazil	Major role in the acquisition of data
Renata Leite Menon, MD	Santa Casa, Londrina, Brazil	Major role in the acquisition of data
Rodrigo Barbosa Thomaz, MD	Hospital Israelita Albert Einstein, São Paulo, Brazil	Major role in the acquisition of data
Rogério de Rizo Morales, PhD	Univ. Federal de Uberlândia, Uberlândia, Brazil	Major role in the acquisition of data
Silvana Sobreira, MD	Hospital Memorial São José, rede D'OR, Recife, Brazil	Major role in the acquisition of data
Suzana Nunes Machado, MD (In memoriam)	Private Service, Florianópolis, Brazil	Major role in the acquisition of data
Taysa A Gonsalves Jubé Ribeiro, MD	Univ. Federal de Goiás, Goiânia, Brazil	Major role in the acquisition of data
Valéria Coelho Santa Rita Pereira, MD	Univ. Federal do Rio de Janeiro, Rio de Janeiro, Brazil	Major role in the acquisition of data
Vanessa Maia Costa, MD	Hospital Neurológico de Goiânia, Goiânia, Brazil	Major role in the acquisition of data
Adaucto Wanderley da Nóbrega Junior, MD	Hospital Universitário da Universidade Federal de Santa Catarina, Florianópolis, Brazil	Major role in the acquisition of data
Marilia Mamprim de Morais Perin, MD	Pontifícia Universidade Católica de Campinas, Campinas, Brazil	Major role in the acquisition of data
Soniza Vieira Alves-Leon, PhD	Univ. Federal do Rio de Janeiro, Rio de Janeiro, Brazil	Major role in the acquisition of data
Eduardo Antonio Donadi, PhD	Faculdade de Medicina de Ribeirão Preto, USP, Ribeirão Preto, Brazil	Revised the article for intellectual content
Tarso Adoni, PhD	Hospital Sírio-Libanês, São Paulo, Brazil	Revised the article for intellectual content
Sidney Gomes, MD	Hospital Beneficência Portuguesa, São Paulo, Brazil	Major role in the acquisition of data
Maria Lucia Brito Ferreira, MD	Hospital da Restauração, Recife, Brazil	Major role in the acquisition of data
Dagoberto Callegaro, PhD	Hospital das clínicas, FM-USP, São Paulo, Brazil	Major role in the acquisition of data
Maria Fernanda Mendes, PhD	Santa Casa, São Paulo, Brazil	Design and conceptualized study and revised the article for intellectual content
Doralina G. Brum MD, PhD	Faculdade de Medicina de Botucatu, UNESP, Botucatu, Brazil	Design and conceptualized study, drafted the article for intellectual content and analyzed and interpreted the data
Felipe von Glehn MD, PhD, FAAN	Faculty of Medicine, University of Brasília, Brasília, Brazil	Design and conceptualized study, interpreted the data, and revised the article for intellectual content

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Clinical Features of COVID-19 on Patients With Neuromyelitis Optica Spectrum Disorders

Samira Luisa Apostolos-Pereira, Lis Campos Ferreira, Mateus Boaventura, et al.

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Original article

Predictors of azathioprine and mycophenolate mofetil response in patients with neuromyelitis optica spectrum disorder: A cohort study

Daniel Lordelo San Martin [a,*], Thiago Gonçalves Fukuda [a], Thiago Santos Nascimento [a], Mariana Brito Silva [a], Marcos Baruch Portela Filho [b], Mirasol Forcadela [c], Chiara Rocchi [c], Emily Gibbons [c], Shahd Hamid [c], Saif Huda [c,#], Jamary Oliveira-Filho [a,#]

[a] Postgraduate Program in Health Sciences, Federal University of Bahia, Salvador, Brazil 40026-010
[b] State University of Bahia. Salvador, Brazil 41.150-000
[c] NMOSD National Service, Walton Centre Foundation Trust Liverpool, United Kingdom L9 7LI

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ABSTRACT

Background: Relapse rates of 47 % have been reported in patients with neuromyelitis optica (NMOSD) using Azathioprine (AZA) and mycophenolate mofetil (MMF). Prediction of non-responders could help determine which patients are most likely to benefit from newer monoclonal antibody treatments from the outset.
Objectives: To identify predictors of AZA and MMF treatment response in NMOSD.
Methods: Multicenter cohort study of NMOSD patients from Brazil and the United Kingdom, treated with AZA and MMF. An unsatisfactory response was defined as one severe or two non-severe attacks in a year. Cox regression was used to identify predictive factors of unsatisfactory response to AZA and MMF.
Results: 103 NMOSD patients, mean age 38 years, 83% female, and 65% of Black ethnic group were included. An unsatisfactory IS response was observed in 42% of patients over 2.5 years (IQR 1.0–8.8) years. A severe preceding attack was more common in non-responders (31.1% x 76.7%, $p = <0.001$). In multivariable analysis, severe attack (RR 3.13; 95 % CI 1.37-7.18, $p = 0.007$) or higher annualized relapse rate (RR 4.84; 95 % CI 2.01-11.65, $p = < 0.001$) predicted an unsatisfactory response. Interestingly, Black NMOSD patients had a lower risk of poor response (RR 0.39, 95 % CI 0.17-0.85, $p = 0.019$).
Conclusion: Severe attack and a higher annualized relapse rate before AZA or MMF initiation were associated with an unsatisfactory IS response. In patients with these characteristics, treatment with higher-efficacy drugs should be considered from the outset.

1. Introduction

Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune inflammatory disease of the central nervous system, resulting in astrocytopathy and secondary demyelination (Wingerchuk et al., 2015; Contentti and Correale, 2021). This condition is often mediated by aquaporin-4 IgG antibodies (AQ4-IgG), however approximately 20% are seronegative patients (Wingerchuk et al., 2015). The worldwide prevalence is around 0.5–1/1000 people and NMOSD is more frequent in females and Black or Asian populations (Papp et al., 2021).

The effectiveness of Azathioprine (AZA) and mycophenolate mofetil (MMF) has been reported in observational studies: 55.9% of patients with AZA and 50–73% with MMF were free from relapse, during 15.5 to 19.5 months of follow-up (Zhang et al., 2022; Huang et al., 2018), and 69% of patients presented no disability accumulation along 4.6 years of follow-up with AZA (Bichuetti et al., 2019). However, in a randomized clinical trial from Iran of 68 patients, the patients in the rituximab group presented with fewer relapses compared to AZA (21.2% and 45.7%,

Abbreviations: NMOSD, Neuromyelitis optica spectrum disorder; AQP4-IgG, aquaporin-4 IgG antibodies; AZA, azathioprine; MMF, mycophenolate mofetil; IS, immunosuppressant; RR, relative risk; EDSS, Expanded disability status scale; MRI, Magnetic resonance imaging; IQR, interquartile range; ARR, annualized relapse rate.

* Corresponding author at: Praça Ramos de Queirós, s/n - Largo do Terreiro de Jesus Salvador, Bahia, Brazil 40026-010.
E-mail addresses: daniel_lordelo@hotmail.com (D.L. San Martin), mirasol.forcadela@nhs.net (M. Forcadela), chiara.rocchi@nhs.net (C. Rocchi), emily.gibbons@nhs.net (E. Gibbons), shahd.hamid1@nhs.net (S. Hamid), shuda@nhs.net (S. Huda), jamary@mail.harvard.edu (J. Oliveira-Filho).
# Jamary Oliveira-Filho and Saif Huda contributed equally to this study.

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respectively) (Nikoo et al., 2017). Another randomized clinical trial, from China, demonstrated greater efficacy of tocilizumab over AZA in patients with frequent relapses (Zhang et al., 2020).

In studies from South Korea and China, patients who had severe pre-treatment relapses were more likely to have an unsatisfactory response to traditional immunosuppressants (AZA and MMF) (Zhang et al., 2022; Kim et al., 2017). It is unclear if these findings apply to other populations. For instance, this finding was not reproduced in a German study in which no relapse predictors were identified (Stellmann et al., 2017).

The optimal starting therapy for NMOSD remains unclear. AZA and MMF continue to be widely used in resource-limited countries and are effective in a proportion of patients (Zhang et al., 2022; Huang et al., 2018; Bichuetti et al., 2019). A priori knowledge of a patient's likelihood to respond favorably or unfavorably to AZA or MMF could help personalize and rationalize high-cost treatments. This study aimed to establish predictors of AZA or MMF response and identify patients in whom high-efficacy drugs should be required from the outset.

2. Materials and methods

This was an ambispective observational cohort. NMOSD patients ≥18 years old fulfilling INPD 2015 diagnostic criteria and treated with AZA or MMF for at least 6 months from the neuroimmunology reference centers at Professor Edgard Santos University Hospital, Salvador, Brazil, and from Walton Centre Foundation Trust, Liverpool, England between July 1, 2010, to July 1, 2023, were included. Other immunosuppressant was not accepted (except steroids). We excluded patients with insufficient treatment data or poor drug compliance. No patients included were positive for serum myelin oligodendrocyte glycoprotein-immunoglobulin antibodies. Based on a previous study, we estimated a 30% difference in the frequency of severe attacks between responders and non-responders (Kim et al., 2017). A prevalence of 80% of severe attack before AZA/MMF commencement in non-responders was used. Using an α of 0.05 and 80% power, a minimum sample size of 86 patients, 43 responders, and 43 non-responders was required. We increased this to 103 patients (1.2x) to account for the loss of follow-up and missing data. To address the latter, when possible, we attempted to contact patients by telephone or e-mail.

In the Brazilian cohort, we screened the whole cohort and included patients fulfilling the criteria exposed above. In the UK cohort, considering its larger number, we selected 60 patients using a random number generator and consecutively included only patients who satisfied the criteria.

From case records, we extracted the following information- age at onset, sex, ethnicity, educational level, relapses, annualized relapse rate, Expanded Disability Status Scale (EDSS), co-existent autoimmune disease, AQP4-IgG status, magnetic resonance imaging (MRI) and treatment history. AQP4-IgG was tested by live cell-based assay.

The maintenance dose of AZA was 2–3 mg/kg/day based on leukocyte counts and AZA metabolites. The MMF dose was 2–3 g/day based on lymphocyte counts. Chronic steroid use was considered if it was used for at least one year during the follow-up period.

A relapse was defined as new neurological symptoms or signs for more than 24 h (with or without new MRI lesions) not accounted for by infection and more than 30 days after the last relapse. Based on a previous study, an unsatisfactory response to AZA or MMF was defined as a severe relapse (visual acuity <20/200 at nadir or bilateral eye involvement or EDSS≥ 6 at nadir or an increase of ≥0.5 points if baseline EDSS ≥6) or two or more relapses in one year after at least 4 months of treatment (Kim et al., 2017).

For normally distributed continuous variables, means and standard deviation were used otherwise median and interquartile range (IQR) are given. Categorical and continuous variables were compared using Chi-squared or Fisher's test and T-tests and Mann-Whitney tests respectively. Due to numerical differences in follow-up duration, we performed stepwise univariable Cox regression with an unsatisfactory AZA/MMF response as the dependent variable. Predictors with a p-value <0.1 were included in the multivariable model. Results were adjusted for the confounding variables of age at onset, sex, and ethnicity. Two-sided p-values <0.05 were considered significant. Kaplan-Meier time-to-event analysis was also performed. Statistical analysis was performed using STATA version 14.1 (StataCorp, CollegeStation, TX).

This study was approved by Hospital Professor Edgar Santos University ethics committee on October 21, 2019 (number 3,653,165) and Research Ethics Service, NRES Committee London- Hampstead, Ref. no. 15/LO/1433. All patients provided written informed consent. Guidelines from Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were followed (von Elm et al., 2007).

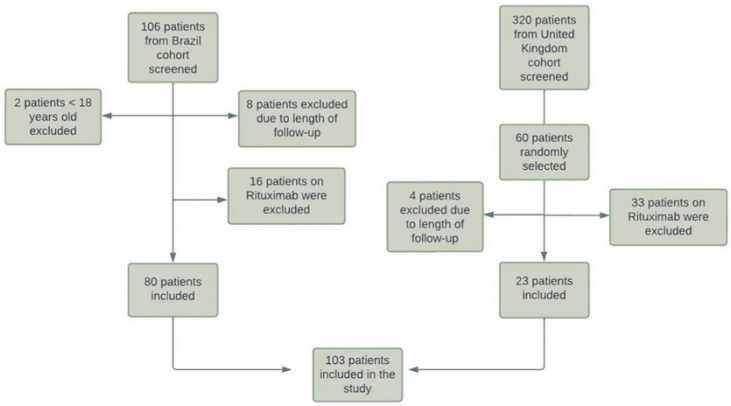
Table 1
Clinical and demographic characteristics of the whole cohort.

Characteristics	Total	AQP4-IgG positive status	AQP-4 negative patients
Age at onset, mean (SD)	38 (12.9)	37 (13.0)	39 (12.9)
Female, n (%)	86 (83.5)	69 (90.7)	17 (62.9)
Ethnicity, n (%)			
Black	67 (65.0)	44 (57.8)	23 (85.1)
White	33 (31.9)	29 (38.7)	4 (14.8)
Asian	3 (2.9)	3 (3.9)	0
Time since diagnosis until end of follow up in years, median (IQR)	2.5 (1.0–8.8)	2.6 (1.0–9.1)	2.27 (1.0–8.1)
First syndrome, n (%)			
Optic neuritis	25 (24.2)	17 (22.3)	8 (29.6)
Transverse myelitis	35 (33.9)	29 (38.1)	6 (22.2)
Area postrema syndrome	6 (5.8)	4 (5.2)	2 (7.4)
Optic neuritis and transverse myelitis	21 (20.3)	14 (18.4)	7 (25.9)
Others	16 (15.5)	11 (14.4)	5 (18.5)
EDSS before AZA or MMF, mean (SD)	4.9 (2.0)	5.2 (1.9)	4.0 (2.0)
AQP4-IgG positive, n (%)	76 (73.7)	76 (100)	27 (0)
Autoimmune disease, n (%)	18 (17.4)	14 (18.4)	4 (14.8)
Annualized relapse rate, median (IQ)	1.0 (0.6–2.0)	1.0 (0.5–2.0)	0.6 (1.0–2.0)
Spinal cord lesions on MRI, n (%)	79 (76.6)	55 (72.3)	24 (88.9)
Brain lesions on MRI, n (%)	55 (53.3)	38 (50.0)	17 (62.9)
Type of treatment, n (%)			
Azathioprine	34 (33.0)	23 (30.2)	11 (40.7)
Azathioprine + steroids	53 (51.4)	38 (50.0)	15 (55.6)
Mycophenolate	2 (1.9)	2 (2.6)	0
Mycophenolate + steroids	14 (13.5)	13 (17.1)	1 (3.7)
Death, n (%)	3 (2.9)	2 (2.6)	1 (1.3)

EDSS: Expanded Disability Scale Score; AZA: azathioprine, MMF: mycophenolate mofetil; AQP4 IgG: aquaporin 4 immunoglobulin G; MRI: magnetic resonance image.

3. Results

We screened 106 patients from the Brazilian cohort and randomly selected 320 patients from the United Kingdom cohort, as shown in the Flowchart below. We included 103 NMOSD (74% AQP4-IgG positive and 26% AQP4-IgG negative) patients of which 83% were female with a mean age of 38 (SD 12.9). The median disease duration was 5.4 years (IQR 2.0–12.5 years) with a median follow-up interval of 2.5 years (IQR 1.0–8.8 years, range 6 months to 13 years). Most patients were Black (65%) and transverse myelitis was the most common index clinical event (33%). Table 1 summarizes the demographic, clinical, and treatment data for the cohort.



Flow chart. Screening process with inclusion and exclusion criteria applied, with 103 participants included to the final analysis.

During the follow-up period, 44% of patients were relapse-free in the MMF group and 45% in the AZA group, and, overall, 55% of patients had at least one relapse after a minimum of 4 months of AZA or MMF treatment, and 42% of patients were classed as having an unsatisfactory response, at a rate of 9.3 events per 100 patient-years. Of these 65% were due to a severe attack and 35% were due to 2 or more relapses in a single year (Table 2). A higher proportion of non-responders had a severe first attack (77% vs 31%, $p<0.0001$) with a trend towards younger age of onset (35 vs 40 years, $p = 0.076$); (Table 2). Although the follow-up duration between responders and non-responders was not statistically different (2.1 vs 3.1 years), numerically there was a difference of 12 months.

Accordingly, we used univariable Cox regression analysis and found that a severe attack and ARR $\geq$1 preceding MMF or AZA initiation were associated with non-responder status (Table 3). This association was maintained in the multivariable analysis; severe attack (RR 3.13, 95 % CI 1.37–7.18, $p = 0.007$) and ARR $\geq$1 (RR 4.84, 95 % CI 2.01-11.65, $p = < 0.001$). Interestingly, Black NMOSD patients were more likely to respond to AZA or MMF in the multivariable analysis (RR 0.39, 95 % CI 0.17–0.85, $p = 0.019$).

Table 2
Demographic and clinical comparisons between satisfactory and unsatisfactory response to AZA or MMF.

Characteristics	Satisfactory response	Unsatisfactory response	P value
Age at onset, mean (SD)	40.1 (13.2)	35.3 (12.1)	0.076
Female, n (%)	50 (83.3)	36 (83.7)	1.000
Black ethnicity, n (%)	43 (71.6)	24 (55.8)	0.142
First syndrome, n (%)			0.335
Optic neuritis	11 (18.3)	14 (32.5)	
Transverse myelitis	21 (35.0)	14 (32.5)	
Area postrema syndrome	3 (5.0)	3 (6.9)	
Optic neuritis and transverse myelitis	15 (25.0)	6 (13.8)	
Others	11 (18.3)	6 (13.8)	
Time since diagnosis until end of follow up in years, median (IQR)	3.1 (0.6–8.7)	2.1 (1.0–8.9)	0.709
Time since symptoms onset until AZA or MMF start, years, median (IQR)	0.50 (0.20–1.40)	0.95 (0.20–3.10)	0.231
Severe attack before AZA or MMF, n (%)	19 (31.1)	33 (76.7)	<0.001
EDSS before AZA or MMF, mean (SD)	4.6 (2.0)	5.2 (1.8)	0.158
ARR before AZA or MMF, median (IQR)	1.0 (0.5–2.0)	1.0 (0.6–2.0)	0.674
AQP4-IgG positive, n (%)	41 (68.3)	35 (81.3)	0.160
AQP4-IgG negative, n (%)	19 (31.6)	8 (18.6)	0.162
Autoimmune disease, n (%)	10 (16.6)	8 (18.6)	0.793
Brain lesion on MRI, n (%)	30 (49.1)	17 (39.5)	0.327
Spinal cord lesion on MRI, n (%)	44 (72.1)	31 (72.0)	0.371
Chronic steroid use, n (%)	43 (71.6)	35 (81.3)	0.352

ARR: annualized relapse rate; EDSS: Expanded Disability Scale Score; AZA: azathioprine, MMF: mycophenolate mofetil; AQP4 IgG: aquaporin 4 immunoglobulin G. MRI: magnetic resonance image.

Table 3
Univariable and multivariable Cox regression analysis of NMOSD patients to predict unsatisfactory response to AZA or MMF.

Variables	Univariable analysis RR (95 % IC)	P-value	RR (95 % IC)	Multivariable analysis P-value
Age at onset	0.99 (0.97–1.02)	0.939	0.99 (0.95–1.02)	0.599
Sex	1.25 (0.48–3.25)	0.642	0.82 (0.27–2.46)	0.730
Black ethnicity	0.58 (0.28–1.19)	0.141	0.39 (0.17–0.85)	0.019
Severe attack before AZA or MMF	2.44 (1.16–5.11)	0.018	3.13 (1.37–7.18)	0.007
EDSS before AZA or MMF	1.00 (0.84–1.19)	0.954		
ARR before AZA or MMF $\geq$ 1	2.28 (1.14–4.54)	0.018	4.84 (2.01–11.65)	<0.001
AQP4-IgG positive status	0.98 (0.42–2.26)	0.964		
AQP4-IgG negative status	0.91 (0.39–2.09)	0.830		
Autoimmune disease	1.04 (0.47–2.27)	0.915		
Brain lesion on MRI	0.78 (0.42–1.47)	0.447		
Spinal cord lesion on MRI	0.60 (0.26–1.39)	0.241		
Time symptoms onset until AZA or MMF start	0.91 (0.82–1.01)	0.107		

EDSS: Expanded Disability Scale Score; AZA: azathioprine, MMF: mycophenolate mofetil; ARR: annualized relapse rate; AQP4 IgG: aquaporin 4 immunoglobulin G. MRI: magnetic resonance image.

Table 4
Univariable and multivariable Cox regression analysis of AQP4-IgG positive NMOSD patients to predict unsatisfactory response to AZA or MMF.

Variables	Univariable analysis RR (95 % IC)	P-value	Multivariable analysis RR (95 % IC)	P-value
Age at onset	1.00 (0.97–1.03)	0.880	1.00 (0.97–1.04)	0.645
Sex	1.42 (0.42–4.76)	0.563	1.01 (0.28–3.61)	0.982
Black ethnicity	0.49 (0.25–0.97)	0.041	0.42 (0.18–1.01)	0.053
Severe attack before AZA or MMF	1.79 (0.80–3.98)	0.150		
EDSS before AZA or MMF	0.93 (0.76–1.15)	0.545		
ARR before AZA or MMF ≥ 1	2.76 (1.28–5.97)	0.010	4.90 (1.88–12.73)	0.001
Autoimmune disease	1.15 (0.47–2.83)	0.747		
Brain lesion on MRI	0.55 (0.26–1.15)	0.117		
Spinal cord lesion on MRI	0.47 (0.20–1.10)	0.084		
Time symptoms onset until AZA or MMF start	0.94 (0.86–1.04)	0.274		

EDSS: Expanded Disability Scale Score; AZA: azathioprine, MMF: mycophenolate mofetil; ARR: annualized relapse rate. MRI: magnetic resonance image.

As differences exist in treatment response between AQP4-IgG and seronegative NMOSD, we did a subgroup analysis of AQP4-IgG positive NMOSD patients. An ARR ≥ 1 before MMF or AZA commencement was associated with non-responder status (Table 4). This association was maintained in the multivariable analysis (RR 4.90, 95% CI 1.88–12.73, $p = 0.001$). Black NMOSD patients were more likely to respond to AZA or MMF in univariable analysis but this association was not maintained in the multivariable analysis albeit a trend was observed (RR 0.42, 95% CI 0.18–1.01, $p = 0.053$).

The survival curves are presented in Figs. 1 and 2. Fig. 1 demonstrates the difference between patients with and without severe attack before AZA or MMF commencement until an unsatisfactory response happens (log-rank $p = 0.035$) and Fig. 2 shows the divergence in patients with or without ≥ 1 ARR before starting these drugs until an unsatisfactory response occurs (log-rank $p = 0.003$).

4. Discussion

The monoclonal antibodies treatment for NMOSD (Nikoo et al., 2017; Zhang et al., 2020; Yamamura et al., 2019; Pittock et al., 2023; Pittock et al., 2019) are raising a necessity: acknowledge the patients that would benefit the most with higher efficacy drugs since first clinical manifestation. Considering health resources, pregnancy plans, preference for oral medications, and adequate response in some patients (55% of our participants never had a new relapse), AZA or MMF are widely used, especially in public health systems or low-income countries (Zhang et al., 2022; Huang et al., 2018; Bichuetti et al., 2019). Our study aimed to detect predictors of an unsatisfactory response in NMOSD before starting first-line drugs. A history of severe attack or ARR ≥ 1 before the commencement of AZA or MMF were associated with an unsatisfactory response. Accordingly, patients with these characteristics may benefit most from high efficacy monoclonal antibodies from the outset.

Our general clinical and demographic characteristics were similar to previous studies, regarding age at onset, higher female prevalence, high rates of Black ethnic group (Asian patients were not well represented for geographical reasons), optic neuritis, transverse myelitis, or both syndromes at the same time as the most common clinical presentation. Other autoimmune disease were also prevalent (Papp et al., 2021; Tisavipat et al., 2022). Death occurred in a minority (mortality rate 2.9%), lower than already reported previously (7%) (Mealy et al., 2018). AZA use was higher than MMF in our study, likely explained by the Brazilian public health system's preference for the former. In the United Kingdom, MMF and AZA are widely used as the first option. These countries currently consider rituximab as a second treatment line if a failure or unsatisfactory response occurs with AZA or MMF.

In this cohort, 42% of patients had unsatisfactory responses, higher than a similar Chinese article (34%), perhaps due to the choice of AZA or MMF for less severe patients and the acceptance of 2006 diagnostic criteria (Wingerchuk et al., 2006) in their study, which could favor the inclusion of patients with other diagnosis (Kim et al., 2017). 45% of patients had at least one relapse in our study while using these first-line drugs. In a systematic review, 53% of patients had at least one relapse while on the use of azathioprine (Luo et al., 2020), while MMF failed in 50% in one cohort (Zhang et al., 2022). There are data showing better results with monoclonal antibodies. In a randomized clinical trial,

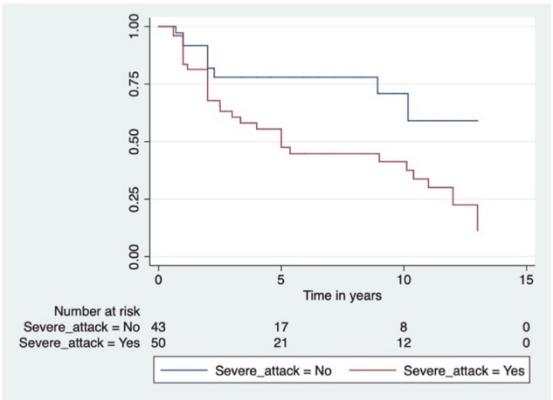


Fig. 1. Kaplan-Meyer curve comparing patients with or without severe attack prior to commencement of AZA or MMF until an unsatisfactory response is reached.

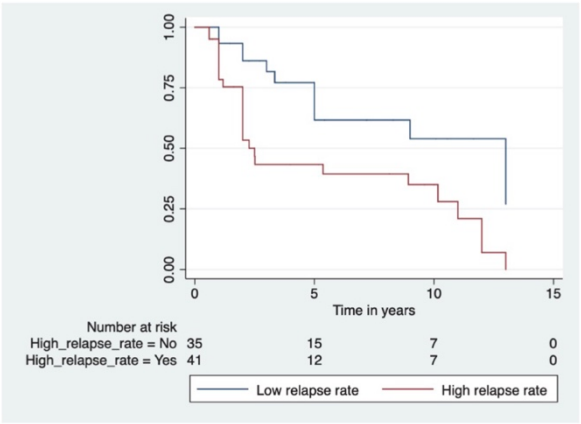


Fig. 2. Kaplan-Meyer curve comparing patients with high annualized relapse rate (≥ 1) and low attack rate (<1) before commencement of AZA or MMF until an unsatisfactory response is reached.

rituximab reduced ARR compared to AZA in 68 patients. Furthermore, a small placebo-controlled trial (38 patients) with rituximab found no relapse during a 72-week follow-up (Tahara et al., 2020). Regarding tocilizumab and AZA, a randomized clinical trial presented relapse in 14% and 47% of the patients for 60 weeks minimum of follow-up, respectively (Zhang et al., 2020). These data confirm the idea that AZA and MMF efficacy is not the best available, and wise selection of patients is mandatory.

The absolute difference in severe attack at the outset between unsatisfactory and satisfactory response groups was 45.6%, reassuring findings on the Kaplan-Meyer and Cox analysis. In agreement with these findings, in two studies from China and South Korea, severe attack was also a predictor for relapse or unsatisfactory response (Zhang et al., 2022; Kim et al., 2017). However, in the Chinese study, it was found a higher magnitude of effect with a broader confidence interval (OR 10.54, CI 95% 3.42–32.55, p <0.001) (Kim et al., 2017), likely due to methodological disparities. In our study, Cox regression analysis and Kaplan-Meyer curve showed ARR as an important variable to predict an unsatisfactory response. Nevertheless, other studies did not have the same results. This difference can be explained by smaller sample sizes, differences between 2006 and 2015 NMOSD criteria, or intrinsic variations between ethnicities (Zhang et al., 2022; Kim et al., 2017; Stellmann et al., 2017).

Regarding younger age at onset, we found a higher frequency in patients with unsatisfactory responses. However, it was not a predictor of this outcome, and similar results were described previously (Zhang et al., 2022). Interestingly, there was one article that found younger age at onset as a predictor factor (Kim et al., 2017). Larger multicenter observational studies could clarify this topic.

Black ethnicity was the most common in our population, and it was homogeneously distributed between groups. Interestingly, in multivariable analysis, black ethnicity was a protective factor. Opposed to this finding, former studies found that this race is more likely to develop NMOSD or has a higher mortality rate (Mealy et al., 2018; Amezcua et al., 2021). Nevertheless, ethnicity was not reported as associated with the effectiveness or prediction of response to immunosuppressants in previous studies (Zhang et al., 2022; Bichuetti et al., 2019; Kim et al., 2017; Stellmann et al., 2017). Likewise, one article showed that the risk of worse outcomes at the last follow-up was not different for blacks and other ethnicities (Kim et al., 2018). Considering these results, black ethnicity may be a protective factor before starting an immunosuppressant.

In a multicenter cohort involving 442 patients, cerebral or brainstem onset attacks were associated with a higher relapse risk (Palace et al., 2019). In a Chinese study, brain attack at onset was more common in patients with poor response to AZA or MMF, however, it was not associated with poor response prediction (Kim et al., 2017). We presented that brain lesions occurred in 53.3% of the patients, similarly distributed between groups, and it was not a prediction of unsatisfactory response, likely because of the infrequent occurrence of brain and brainstem lesions in our sample.

It was described previously that AQP4-IgG positive NMOSD patients have a more aggressive clinical course (Jarius et al., 2012). These seropositive participants were most of our population. In a subgroup analysis considering these patients, a higher ARR was associated with unsatisfactory prediction, however, severe attack showed only a trend to this outcome. Conversely, Black ethnicity may be a protective factor. It is important to state that there was no sample size calculation for these results and they must be taken cautiously. Former studies did not approach this topic. A larger multicenter study may explain this issue with a higher level of certainty.

Our study has limitations expected in observational studies, for example, non-randomized group selection. There was missing data that we attempted to correct in our sample size calculation. Also, management of azathioprine varied through the centers (2–3 mg/kg or according to AZA's metabolites). Considering that there is no data showing the superiority of each approach in NMOSD, it should not impact our results. Due to a lack of data, it was not possible to attain systematic information on steroid dosage in every patient during follow-up, however, the rate of steroid use for a long period between satisfactory and unsatisfactory groups was similar. Finally, our participants represent more black and white races (96.9%), and other ethnicities are not appropriately represented.

5. Conclusion

In patients with NMOSD, almost half had unsatisfactory responses to AZA or MMF during a long follow-up. Severe initial attack and $a \geq 1$ ARR before starting these drugs were associated with this poor outcome. These findings suggest that these characteristics could guide the prescription of higher efficacy drugs.

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CRediT authorship contribution statement

Daniel Lordelo San Martin: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Thiago Gonçalves Fukuda:** Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision. **Thiago Santos Nascimento:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration. **Mariana Brito Silva:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration. **Marcos Baruch Portela Filho:** Conceptualization, Data curation, Investigation, Methodology. **Mirasol Forcadela:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources. **Chiara Rocchi:** Conceptualization, Data curation, Investigation, Methodology, Resources, Software. **Emily Gibbons:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources. **Shahd Hamid:** Conceptualization, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft. **Saif Huda:** Conceptualization, Formal analysis, Investigation, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jamary Oliveira-Filho:** Conceptualization, Formal analysis, Methodology, Project administration, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

Acknowledgments

None.

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MULTIPLE SCLEROSIS JOURNAL | MSJ

Short Report

Incidence and clinical outcome of Coronavirus disease 2019 in a cohort of 11,560 Brazilian patients with multiple sclerosis

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REDONE.br – Neuroimmunology Brazilian Study Group Focused on COVID-19 and MS*

Correspondence to:
DG Brum
Faculdade de Medicina Campus de Botucatu, Universidade Estadual Paulista Julio de Mesquita Filho, Av. Prof. Montenegro, s/n—Distrito de, Botucatu—SP 18618-687, Brazil.
doralinagbrum@gmail.com

*See supplementary document for full membership of the study group.

Abstract

Background: Little information is available regarding the incidence and clinical outcome of the SARS-CoV2 infection in patients with multiple sclerosis (pwMS).

Objective: To determine the incidence, clinical outcome, and impact of COVID-19 on pwMS.

Methods: This observational study was prospectively performed on a cohort of pwMS ($N = 11{,}560$) followed up by 47 out of 51 Brazilian MS referral centers that registered pwMS with COVID-19 at the REDONE platform from 13 March to 4 June 2020.

Results: The incidence of COVID-19 for pwMS patients was 27.7/10,000 patients and for the general population was 29.2/10,000 inhabitants. A total of 94 (77 women) pwMS patients, aged 40 ± 10.25 years, presenting 9.9 ± 8.6 years of MS disease duration, developed the COVID-19, most of them (87%) exhibited the mild form of the disease. Eighty (96%) patients maintained the use of MS disease-modifying treatment (DMT) during COVID-19 pandemic and 14 patients were not in use of DMTs.

Conclusion: Incidence of COVID-19 in Brazilian pwMS was not different from those observed for the general Brazilian population. Most pwMS exhibited mild COVID-19, despite the maintenance of the underlying MS treatment.

Keywords: Multiple sclerosis, COVID-19, virus infection SARS-CoV2

Date received: 21 July 2020; revised: 21 October 2020; accepted: 23 October 2020.

Background

On 21 July 2020, 5 months after the first COVID-19 report,[1] 2,159,654 cases were registered in Brazil, causing 81,487 fatalities. Brazil is only below the United States in the number of deaths from SARS-CoV2 infection, and nowadays is the second in terms of incidence (1027.7/100,000 inhabitants) and mortality rate (38.8/100,000 inhabitants).[2] Little information is available regarding the SARS-CoV2 infection in patients with multiple sclerosis (pwMS).[3] It is not known whether the incidence of COVID-19 in pwMS is different from the general population.

Objective

To determine the incidence and clinical outcome of COVID-19 among pwMS and the impact of COVID-19 on MS features.

Methods

This observational study was prospectively performed on a cohort of 11,560 Brazilian pwMS followed up by 47 MS referral centers, which registered at the REDONE platform patients exhibiting flu-like symptoms, starting from 13 March and partially closed on 4 June 2020. REDONE invited 51 MS referral centers from all the 27 Brazilian States, receiving adherence of 47 (response rate 92%) centers from 19 States (response rate 70%), encompassing a group of more than 70 neurologists. Each referral center received a link to access to a questionnaire to be filled at the REDONE COVID-19 MS web platform. All pwMS were diagnosed according to revised McDonald criteria.[4] Patient data were evaluated by the REDONE coordinators who diagnosed COVID-19 using the CDC/CSTE criteria, classifying patients as confirmed (reverse transcription polymerase chain reaction,

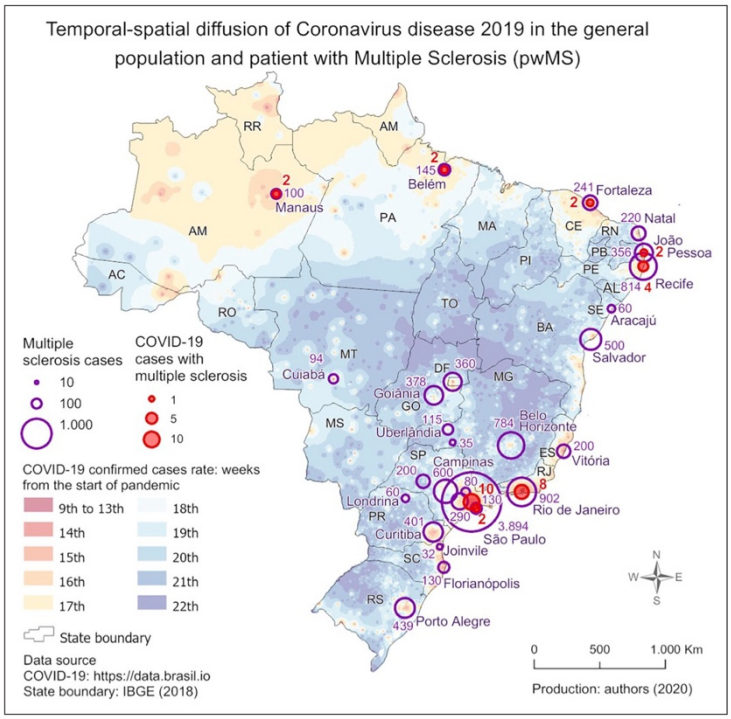

Figure 1. Mapping of COVID-19 in the general Brazilian population and in Brazilian patients with multiple sclerosis (pwMS). To understand the COVID-19 risk exposure of Brazilian patients with multiple sclerosis, we performed a temporal-spatial analysis. The data regarding pwMS were interpolated with a space-time surface for SARS-CoV2 exposure, in terms of epidemiological weeks (shades of red to yellow: old exposition from 9th to 17th weeks; shades of blue: recent exposition from 18th to 22nd weeks after the beginning of the COVID-19 pandemics). We can observe that COVID-19 has spread from State capitals to inland Brazil (as far as the number of epidemiological weeks increases) both for the general population and for pwMS. Regions registering higher number of pwMS coincided with areas exhibiting higher temporal exposure to COVID-19 (epidemiological weeks COVID-19). Lilac circles represent the pwMS sample distributed in Brazilian Regions and red circles represent the pwMS with COVID-19 infection. We can observe that the number of COVID-19 cases in pwMS followed proportionally the number of epidemiological weeks in major cities (São Paulo (n = 10 cases pwMS/COVID-19); Rio de Janeiro (n = 8); Recife (n = 4)).

background of the Brazilian pwMS)[10] is close to MS French[3] and Italian[11] cohorts.

Fourteen out the 94 pwMS were not using DMT, and among the 80 patients on DMT, 77 (96%) were maintained on same therapy during COVID-19. Whether or not DMT influences COVID-19 outcome is a question that deserves further studies, since the small sample size of this study and the size samples of the Italian[11] and French[3] studies do not allow conclusive analyses. Future studies with global sharing data evaluating large samples and using standardized clinical, image, and DMT are needed to define COVID-19 outcome in pwMS.

Conclusion and relevance

Although the incidence of COVID-19 in pwMS varied on a regional basis, the overall incidence did not differ from that observed for the general Brazilian population. Most patients developed mild

Table 1. Demographic and clinical characteristics of all patients with multiple sclerosis (pwMS) presenting Coronavirus Disease 2019, as informed at REDONE-COVID19 Brazilian Registry.

Incidence on 4 June 2020	27.7/10,000
COVID-19/pwMS	32
MS Cohort	11,560
Total number	$N = 94$ (%)
Age (mean ± SD)	40.59 (± 10.25)
Age ⩽ 50	77 (83%)
Age > 50	15 (16%)
Missing	2 (1%)
Gender	
Women	73 (78%)
Men	21 (22%)
MS onset age (mean ± SD years)	31.81 (± 8.40)
MS disease duration (mean ± SD years)	9.93 (± 8.61)
Skin color	
White	58 (62%)
Non-White	31 (33%)
Severity	
Mild	82 (87%)
Moderate	10 (11%)
Severe	2 (2%)
Symptoms	
Fever	68 (72%)
Cough	55 (58%)
Myalgia	55 (58%)
Coryza	39 (41%)
Asthenia/fatigue	43 (46%)
Dyspnea	36 (38%)
Odynophagia	41 (44%)
Chills	21 (22%)
Diarrhea	17 (18%)
Headache	51 (54%)
Hyposmia or dysgeusia	43 (46%)
Comorbidity	
No comorbidity	75 (80%)
Hypertension	8 (8%)
Diabetes	1 (1%)
Dyslipidemia	6 (6%)
Cardiac disease	1 (1%)
Lung disease	1 (1%)
Asthma	2 (2%)
Obesity	2 (2%)
Thyroid disease	2 (2%)
Neoplasm	2 (2%)
Smoker	9 (10%)
Disease-modifying therapy (DMT)	
No therapy	13 (14%)
Interferon beta	9 (10%)
Glatiramer acetate	5 (5%)
Natalizumab	20 (21%)
Teriflunomide	5 (5%)
Fumarate dimethyl	17 (18%)
Fingolimod	16 (16%)
Ocrelizumab	5 (5%)
Rituximab	2 (2%)
Alemtuzumab	1 (1%)

MS: multiple sclerosis; SD: standard deviation; RT-PCR: reverse transcription polymerase chain reaction.
The incidence of COVID-19 in the general Brazilian population and in pwMS was calculated using the same criterion considering SARS-CoV2 infection by RT-PCR or serology.

COVID-19 disease, despite the maintenance of DMT. Further and larger studies are needed to define the role of MS per se and of DMTs on COVID-19 outcome.

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Declaration of Conflicting Interests

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Supplemental material

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SUPPLEMENTARY FILE

AUTHOR

NAME, TITLE, AFFILIATION – ROLE PERFORMED IN THE STUDY

Neuroimmunology Brazilian Study Group Focused on COVID-19 and MS:

Lis Campos Ferreira, MD	Univ. Federal de Sergipe (UFS) and Univ. Tiradentes (UNIT), Aracaju, Brazil.	Drafted the manuscript for intellectual content; analyzed and interpreted the data; major role in the acquisition of data.
Nise Alessandra de Carvalho Sousa, MD	Hospital Univ. Getúlio Vargas, Manaus, Brazil	Design and conceptualized study; revised the manuscript for intellectual content; major role in the acquisition of data.
Maria Lucia Brito Ferreira, MD	Hospital da Restauração, Recife, Brazil	Drafted the manuscript for intellectual content; major role in the acquisition of data.
Rafael Paternò Castello Dias-Carneiro, MD	Santa Casa, São Paulo, Brazil	Drafted the manuscript for intellectual content; major role in the acquisition of data.
Maria Fernanda Mendes, PhD	Santa Casa, São Paulo, Brazil	Design and conceptualized study; revised the manuscript for intellectual content; major role in the acquisition of data.
Ana Claudia Piccolo, MD	Hospital Santa Marcelina, São Paulo, Brazil	Design and conceptualized study; revised the manuscript for intellectual content; major role in the acquisition of data.
Rodrigo Barbosa Thomaz, MD	Hospital Israelita Albert Einstein, São Paulo, Brazil	Design and conceptualized study; major role in the acquisition of data.
Claudia Cristina Ferreira Vasconcelos, PhD	Hospital Univ. Gaffree e Guinle, Rio de Janeiro, Brazil	Revised the manuscript for intellectual content; major role in the acquisition of data.
Soniza Vieira Alves-Leon, PhD	Univ. Federal do Rio de Janeiro, Rio de Janeiro, Brazil	Revised the manuscript for intellectual content; major role in the acquisition of data.
Gutemberg Augusto Cruz dos Santos, PhD	Univ. Estacio de Sá and Universidade Federal Fluminense, Rio de Janeiro, Brazil	Major role in the acquisition of data
Valéria Coelho Santa Rita Pereira, MD	Univ. Federal do Rio de Janeiro, Rio de Janeiro, Brazil	Major role in the acquisition of data
Enedina Maria Lobato de Oliveira, PhD	Univ. Federal de São Paulo, UNIFESP, São Paulo, Brazil	Design and conceptualized study; major role in the acquisition of data.
Samira Luisa Apóstolos Pereira, MD, PhD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Design and conceptualized study; major role in the acquisition of data.
Mateus Boaventura, MD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Major role in the acquisition of data
Caio César Diniz Disserol, MD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Major role in the acquisition of data
Herval Ribeiro Soares Neto, PhD	IAMSPE, São Paulo, Brazil	Major role in the acquisition of data
Gabriela Joca Martins, MD	Hospital Geral de Fortaleza, Fortaleza, Brazil	Major role in the acquisition of data
José Arthur d´Almeida, PhD	Hospital Geral de Fortaleza, Fortaleza, Brazil	Major role in the acquisition of data
Milena S. Pitombeira, MD	Hospital Geral de Fortaleza, Fortaleza, Brazil	Major role in the acquisition of data
Lucas Silvestre Mendes, MD	Hospital Geral de Fortaleza, Fortaleza, Brazil	Major role in the acquisition of data
Mario Emilio Teixeira Dourado Jr, MD	Univ. Federal R G Norte, Natal, Brazil	Major role in the acquisition of data
Bianca Etelvina Santos de Oliveira, MD	FUNAD, João Pessoa, Brazil	Major role in the acquisition of data
Davi Veloso Guerra, MD	FUNAD, João Pessoa, Paraiba, Brazil	acquisition of data
Maria Íris de Morais Machado, MD	Hospital da Restauração, Recife, Brazil	Major role in the acquisition of data
Alvaro Jose Porto Moreira, MD	Hospital da Restauração, Recife, Brazil	Major role in the acquisiton of data
Thiago Fukuda, MD	Universidade Federal da Bahia/Ebserh, Salvador, Brazil	Major role in the acquisition of data
Hideraldo Luís Souza Cabeça, PhD	Hospital Ophir Loyola, Belém, Brazil	Major role in the acquisition of data
Luciano Chaves Rocha, MD	Hospital Ophir Loyola, Belém, Brazil	Major role in the acquisition of data
Maria Cecilia Aragon de Vecino	Hospital Moinhos de Vento, Porto Alegre, Brazil	Major role in the acquisition of data

Camila Batista Oliveira Silva, PhD	Neurology Clinic Vecino	Major role in the acquisition of data
Leizian de Souza Amorim, MD	Univ. Federal de São Paulo, UNIFESP, São Paulo, Brazil	Major role in the acquisition of data
Andréa Anacleto Ferrari de Castro, MD	Universidade Metropolitana de Santos, Santos, Brazil	Major role in the acquisition of data
Antonio Pereira Gomes Neto, MD	Santa Casa, Belo Horizonte, Brazil	Major role in the acquisition of data
Fernando Coronetti G Da Rocha, PhD	Universidade Estadual Paulista (Unesp), Faculdade de Medicina de Botucatu, Botucatu, Brazil	Major role in the acquisition of data
Sidney Gomes, MD	Hospital Beneficiência Portuguesa, São Paulo, Brazil	Major role in the acquisition of data
Heloisa Helena Ruocco, PhD	Universidade Federal Fluminense, Campinas, Brazil	Major role in the acquisition of data
Yara Dadalti Fragoso, PhD	Universidade Metropolitana de Santos, Santos, Brazil	Major role in the acquisition of data
Marcus vinicius Magno Gonçalves, MD, PhD	Univ. da Região de Joinville (Univille), Joinville, Brazil	Major role in the acquisition of data
Maria Lucia Vellutini Pimentel, MD, PhD	Santa Casa, Rio de Janeiro, Brazil	Major role in the acquisition of data
Suzana Nunes Machado, MD (*In memorian*)	Private Service, Florianópolis, Brazil	Major role in the acquisition of data
Omar Gurrola Arambula, MD	Universidade Estadual Paulista (Unesp), Faculdade de Medicina de Botucatu, Botucatu, Brazil	Major role in the acquisition of data
Anderson Kuntz Grzesiuk , MD	Private Service, Cuiabá, Brazil	acquisition of data
Damacio R Kaimen-Maciel, PhD	Santa Casa, Londrina, Brazil	acquisition of data
Denise Sisterolli Diniz, PhD	Universidade Federal de Goiás, Goiânia, Brazil	acquisition of data
Elizabeth R Comini-Frota, PhD	Private service, Belo Horizonte, Brazil	acquisition of data
Guilherme Sciascia do Olival, PhD	Santa Casa and ABEM- Assoc. Brasileira de Esclerose Múltipla, São Paulo, Brazil	acquisition of data
Ronaldo Maciel Dias, MD	Hospital de Base do Distrito Federal, Brasília, Brazil	acquisition of data
Luiz D Melges, MD	Faculdade de Medicina de Marília, Marília, Brazil	acquisition of data
Paulo Diniz da Gama, PhD	Faculdade de Ciências Médicas, PUC-SP, Sorocaba, Brazil	acquisition of data
Marlise de Castro Ribeiro, MD, PhD	Univ. Federal Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil	acquisition of data
Rogério de Rizo Morales, PhD	Univ. Federal de Uberlândia, Uberlândia, Brazil	acquisition of data
Ana Carolina Amaral de Andrade	Hospital Santa Marcelina, São Paulo, Brazil	acquisition of data
Heloise Helena Siqueira, PhD	Universidade Federal do Mato Grosso, Cuiabá, Brazil	acquisition of data
Monica Koncke Fiuza Parolin	Private Service, Curitiba, Brazil	acquisition of data
Henry Koity Sato, PhD	Private Service, Curitiba, Brazil	acquisition of data
José Alexandre Figueiredo Jr., PhD	Universidade Federal do Mato Grosso, Cuiabá, Brazil	acquisition of data
Leandro Cortoni Calia, PhD	Private Service, São Paulo, Brazil	acquisition of data
Letícia Scolari, MD	Universidade Federal do Mato Grosso, Cuiabá, Brazil	acquisition of data
Carlos Alberto Magirius Peixoto	Universidade Federal do Espírito Santo, Vitória, Brazil	acquisition of data
Vera Lúcia Ferreira Vieira	Universidade Federal do Espírito Santo, Vitória, Brazil	acquisition of data
Renata Leite Menon, MD	Santa Casa, Londrina, Brazil	acquisition of data
Marlos Aureliano Dias de Sousa	Universidade Federal do Triângulo Mineiro, Uberaba, Brazil	acquisition of data
Silvana Sobreira, MD	Hospital Memorial São José, rede D'OR, Recife, Brazil	acquisition of data
Taysa A Gonsalves Jubé Ribeiro, MD	Univ. Federal de Goiás, Goiânia, Brazil	acquisition of data
Vanessa Maia Costa, MD	Hospital Neurológico de Goiânia, Goiânia, Brazil	acquisition of data
Carla Renata Aparecida Vieira Stella, MD	UNICAMP, Campinas, Brazil	acquisition of data
Fernando Elias Borges, MD	Hospital alberto Rassi, Goiânia, Brazil	acquisition of data
Adaucto Wanderley da Nóbrega Junior, MD	Hospital Universitário da Universidade Federal de Santa Catarina, Florianópolis, Brazil	acquisition of data
Dagoberto Callegaro, PhD	Hospital das Clínicas, FM-USP, São Paulo, Brazil	Major role in the acquisition of data
Eduardo Antonio Donadi, PhD	Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto, Ribeirão Preto, Brazil	Revised the manuscript for intellectual content.

Tarso Adoni, PhD	Hospital Sírio-Libanês, São Paulo, Brazil	Revised the manuscript for intellectual content; major role in the acquisition of data.
Rafael de Castro Catão	Universidade Federal do Espírito Santo, Vitória, Brazil	Graphic design - Cartography
Carlos Magno Castelo Branco Fortaleza	Universidade Estadual Paulista (Unesp), Faculdade de Medicina de Botucatu, Botucatu, Brazil	Drafted the manuscript for intellectual content
Helio Amant Miot, PhD	Universidade Estadual Paulista (Unesp), Faculdade de Medicina de Botucatu, Botucatu, Brazil	Analyzed and interpreted the data
Edmur Pugliesi	Universidade Estadual Paulista (Unesp), Faculdade de Ciências e Tecnologia, Presidente Prudente, Brazil	Graphic Design - Cartography
Raul Borges Guimarães	Universidade Estadual Paulista (Unesp), Faculdade de Ciências e Tecnologia, Presidente Prudente, Brazil	Drafted the manuscript for intellectual content
Felipe von Glehn, MD, PhD, FAAN	Faculty of Medicine, University of Brasilia, Brasilia, Brazil	Design and conceptualized study; analyzed and interpreted the data; revised the manuscript for intellectual content.
Doralina G. Brum, PhD	Universidade Estadual Paulista (Unesp), Faculdade de Medicina de Botucatu, Botucatu, Brazil	Design and conceptualized study; drafted the manuscript for intellectual content; analyzed and interpreted the data.

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Recommendations by the Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology (DCNI/ABN) and the Brazilian Committee for Treatment and Research in Multiple Sclerosis and Neuroimmunological Diseases (BCTRIMS) on vaccination in general and specifically against SARS-CoV-2 for patients with demyelinating diseases of the central nervous system

Recomendações do Departamento Científico de Neuroimunologia da Academia Brasileira de Neurologia (DCNI/ABN) e do Comitê Brasileiro de Tratamento e Pesquisa em Esclerose Múltipla e Doenças Neuroimunológicas (BCTRIMS) sobre vacinação em geral e contra a SARS-CoV-2 para pacientes com doenças desmielinizantes do sistema nervoso central

Jefferson BECKER[1], Lis CAMPOS FERREIRA[2,3], Alfredo DAMASCENO[4], Denis Bernardi BICHUETTI[5], Paulo Pereira CHRISTO[6], Dagoberto CALLEGARO[7], Marco Aurélio LANA PEIXOTO[6], Nise Alessandra de CARVALHO SOUSA[8], Sérgio Monteiro DE ALMEIDA[9], Tarso ADONI[10], Juliana SANTIAGO-AMARAL[6], Thiago JUNQUEIRA[11], Samira Luisa APÓSTOLOS PEREIRA[7], Ana Beatriz Ayroza Galvão RIBEIRO GOMES[7], Milena PITOMBEIRA[12], Renata Barbosa PAOLILO[7], Anderson KUNTZ GRZESIUK[13], Ana Claudia PICCOLO[14], José Arthur Costa D´ALMEIDA[12], Antonio Pereira GOMES NETO[15], Augusto Cesar PENALVA DE OLIVEIRA[16], Bianca Santos de OLIVEIRA[17], Carlos Bernardo TAUIL[18], Claudia FERREIRA VASCONCELOS[19], Damacio KAIMEN-MACIEL[20], Daniel VARELA[21], Denise SISTEROLLI DINIZ[22], Enedina Maria LOBATO DE OLIVEIRA[5], Fabiola RACHID MALFETANO[23], Fernando ELIAS BORGES[24], Fernando Faria ANDRADE FIGUEIRA[25], Francisco de Assis AQUINO GONDIM[26], Giordani Rodrigues dos PASSOS[1], Guilherme DIOGO SILVA[7], Guilherme SCIASCIA DO OLIVAL[27,28], Gutemberg Augusto CRUZ DOS SANTOS[23,29], Heloisa Helena RUOCCO[29,30], Henry Koiti SATO[31], Herval Ribeiro SOARES NETO[32], Leandro CORTONI CALIA[33], Marcus Vinícius MAGNO GONÇALVES[34], Maria Cecilia ARAGÓN DE VECINO[35], Maria Lucia VELLUTINI PIMENTEL[36], Marlise de CASTRO RIBEIRO[37], Mateus BOAVENTURA[7], Mônica Koncke FIUZA PAROLIN[38], Renata Brant de SOUZA MELO[15], Robson LÁZARO[39], Rodrigo Barbosa THOMAZ[40], Rodrigo KLEINPAUL[6], Ronaldo MACIEL DIAS[41], Sidney GOMES[42], Simone Abrante LUCATTO[43], Soniza Vieira ALVES-LEON[44], Thiago FUKUDA[45], Taysa Alexandrino Gonsalves JUBÉ RIBEIRO[22], Thereza Cristina D'ÁVILA WINCKLER[38], Yara Dadalti FRAGOSO[46], Osvaldo José Moreira do NASCIMENTO[23,29], Maria Lucia BRITO FERREIRA[47], Maria Fernanda MENDES[28], Doralina Guimarães BRUM[48], Felipe VON GLEHN[4,49], and the NEUROIMMUNOLOGY BRAZILIAN STUDY GROUP

[1]Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre RS, Brazil.
[2]Universidade Federal de Sergipe, Aracaju SE, Brazil.
[3]Universidade Tiradentes, Aracaju SE, Brazil.
[4]Universidade de Campinas, Faculdade de Ciências Médicas, Campinas SP, Brazil.
[5]Universidade Federal de São Paulo, Escola Paulista de Medicina, São Paulo SP, Brazil.
[6]Universidade Federal de Minas Gerais, Belo Horizonte MG, Brazil.
[7]Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas, São Paulo SP, Brazil.
[8]Universidade Federal do Amazonas, Manaus AM, Brazil.

[9]Universidade Federal do Paraná, Curitiba PR, Brazil.
[10]Hospital Sírio Libanês, São Paulo SP, Brazil.
[11]Escola Bahiana de Medicina e Saúde Pública, Salvador BA, Brazil.
[12]Hospital Geral de Fortaleza, Fortaleza CE, Brazil.
[13]Clínica Nossa Senhora das Graças, Cuiabá MS, Brazil.
[14]Hospital Santa Marcelina, São Paulo SP, Brazil.
[15]Santa Casa, Belo Horizonte MG, Brazil.
[16]Instituto de Infectologia Emílio Ribas, São Paulo SP, Brazil.
[17]Fundação Centro Integrado de Apoio ao Portador de Deficiência, João Pessoa PB, Brazil.
[18]Secretaria de Estado da Saúde, Brasília DF, Brazil.
[19]Universidade Federal do Rio de Janeiro, Rio de Janeiro RJ, Brazil.
[20]Santa Casa, Londrina PR, Brazil.
[21]Hospital de Clínicas de Passo Fundo, Passo Fundo RS, Brazil.
[22]Universidade Federal de Goiás, Goiânia GO, Brazil.
[23]Universidade Estácio de Sá, Rio de Janeiro RJ, Brazil.
[24]Private Service, Goiânia GO, Brazil.
[25]Hospital São Francisco na Providência de Deus, Rio de Janeiro RJ, Brazil.
[26]Universidade Federal do Ceará, Fortaleza CE, Brazil.
[27]Associação Brasileira de Esclerose Múltipla, São Paulo SP, Brazil.
[28]Santa Casa, São Paulo SP, Brazil.
[29]Universidade Federal Fluminense, Niterói RJ, Brazil.
[30]Pontifícia Universidade Católica, Campina SP, Brazil.
[31]Instituto de Neurologia de Curitiba, Curitiba PR, Brazil.
[32]IAMSPE, São Paulo SP, Brazil.
[33]Private Service, São Paulo SP, Brazil.
[34]Universidade da Região de Joinville, Joinville SC, Brazil.
[35]Hospital Moinhos de Vento, Porto Alegre RS, Brazil.
[36]Santa Casa, Rio de Janeiro RJ, Brazil.
[37]Universidade Federal Ciências da Saúde de Porto Alegre, Porto Alegre RS, Brazil.
[38]Private Service, Curitiba PR, Brazil.
[39]Faculdade de Medicina de Jundiaí, Jundiaí SP, Brazil.
[40]Hospital Israelita Albert Einstein, São Paulo SP, Brazil.
[41]Hospital de Base do Distrito Federal, Brasília DF, Brazil.
[42]Hospital Beneficiência Portuguesa, São Paulo SP, Brazil.
[43]Hospital Regional de Vilhena, Vilhena RO, Brazil.
[44]Universidade Federal do Estado do Rio de Janeiro, Rio de Janeiro RJ, Brazil.
[45]Hospital Universitário Prof. Edgar Santos, Salvador BA, Brazil.
[46]Universidade Metropolitana de Santos, Santos SP, Brazil.
[47]Hospital da Restauração, Recife PE, Brazil.
[48]Universidade Estadual Paulista, Faculdade de Medicina de Botucatu, Botucatu SP, Brazil.
[49]Universidade de Brasília, Faculdade de Medicina, Brasília DF, Brazil.

JB https://orcid.org/0000-0002-9981-3620; LCF https://orcid.org/0000-0002-4456-2684; AD https://orcid.org/0000-0002-7919-3989; DBB https://orcid.org/0000-0002-4011-3734; PPC https://orcid.org/0000-0003-1224-5243; DC https://orcid.org/0000-0003-0077-173X; MALP https://orcid.org/0000-0003-2454-681X; NACS https://orcid.org/0000-0003-3185-2903; SMA https://orcid.org/0000-0001-5690-105X; TA https://orcid.org/0000-0002-5008-2783; JSA https://orcid.org/0000-0003-1615-8008; TJ https://orcid.org/0000-0002-5679-1759; SLAP https://orcid.org/0000-0003-3493-1199; ABAGRG https://orcid.org/0000-0003-1657-6891; MP https://orcid.org/0000-0002-3298-0264; RP https://orcid.org/0000-0003-3548-8467; AKG https://orcid.org/0000-0002-7480-6782; ACP https://orcid.org/0000-0003-0834-1056; JADA https://orcid.org/0000-0002-6627-6515; APGN https://orcid.org/0000-0002-0755-9478; ACPO https://orcid.org/0000-0002-4084-7973; BSO https://orcid.org/0000-0001-7484-3586; CBT https://orcid.org/0000-0003-1137-2398; CFV https://orcid.org/0000-0003-0833-4024; DKM https://orcid.org/0000-0002-8699-0636; DV https://orcid.org/0000-0002-3043-1640; DSD https://orcid.org/0000-0002-3078-6804; EMLO https://orcid.org/0000-0002-4939-7200; FRM https://orcid.org/0000-0002-8275-3801; FEB https://orcid.org/0000-0001-7668-0434; FFAF https://orcid.org/0000-0003-3242-9007; FAAG https://orcid.org/0000-0002-8957-5796; GRP https://orcid.org/0000-0002-8949-6115; GDS https://orcid.org/0000-0001-9764-3763; GSO https://orcid.org/0000-0002-2717-7522; GACS https://orcid.org/0000-0002-7333-1420; HHR https://orcid.org/0000-0001-5394-648X; HKS https://orcid.org/0000-0002-5582-1792; HRSN https://orcid.org/0000-0002-1694-0457; LCC https://orcid.org/0000-0002-5758-5789; MVMG https://orcid.org/0000-0002-9127-7886; MCAV https://orcid.org/0000-0001-9393-6999; MLVP https://orcid.org/0000-0003-3515-4061; MCR https://orcid.org/0000-0002-4402-099X; MB https://orcid.org/0000-0002-5914-8099; MKFP https://orcid.org/0000-0003-2171-8241; RBSM https://orcid.org/0000-0002-6267-2940; RL https://orcid.org/0000-0001-7537-5729; RBT https://orcid.org/0000-0002-9287-6864; RK https://orcid.org/0000-0001-5750-6828; RMD https://orcid.org/0000-0003-3987-9596; SG https://orcid.org/0000-0002-9744-5916; SAL https://orcid.org/0000-0002-8856-0007; SVAL https://orcid.org/0000-0002-1538-6730; TF https://orcid.org/0000-0002-7718-4288; TAGJR https://orcid.org/0000-0001-8202-8856; TCDAW https://orcid.org/0000-0003-1438-2583; YDF https://orcid.org/0000-0001-8726-089X; OJMN https://orcid.org/0000-0003-3516-485X; MLBF https://orcid.org/0000-0002-6136-4612; MFM https://orcid.org/0000-0003-3983-6019; DGB https://orcid.org/0000-0002-9050-3319; FVG https://orcid.org/0000-0002-1004-7641

Correspondence: Felipe von Glehn; Email: felipeglehn@gmail.com.

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ABSTRACT

The Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology (DCNI/ABN) and Brazilian Committee for Treatment and Research in Multiple Sclerosis and Neuroimmunological Diseases (BCTRIMS) provide recommendations in this document for vaccination of the population with demyelinating diseases of the central nervous system (CNS) against infections in general and against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. We emphasize the seriousness of the current situation in view of the spread of COVID-19 in our country. Therefore, reference guides on vaccination for clinicians, patients, and public health authorities are particularly important to prevent some infectious diseases. The DCNI/ABN and BCTRIMS recommend that patients with CNS demyelinating diseases (e.g., MS and NMOSD) be continually monitored for updates to their vaccination schedule, especially at the beginning or before a change in treatment with a disease modifying drug (DMD). It is also important to note that vaccines are safe, and physicians should encourage their use in all patients. Clearly, special care should be taken when live attenuated viruses are involved. Finally, it is important for physicians to verify which DMD the patient is receiving and when the last dose was taken, as each drug may affect the induction of immune response differently.

Keywords: Demyelinating Autoimmune Diseases, CNS; Multiple Sclerosis; Neuromyelitis Optica; Vaccination; COVID-19; SARS-CoV-2.

RESUMO

O DC de Neuroimunologia da ABN e o BCTRIMS trazem, nesse documento, as recomendações sobre vacinação da população com doenças desmielinizantes do sistema nervoso central (SNC) contra infecções em geral e contra o coronavírus da síndrome respiratória aguda grave 2 (SARS-CoV-2), causador da COVID-19. Destaca-se a gravidade do atual momento frente ao avanço da COVID-19 em nosso País, o que torna mais evidente e importante a criação de guia de referência para orientação aos médicos, pacientes e autoridades de saúde pública quanto à vacinação, meio efetivo e seguro no controle de determinadas doenças infecciosa. O DCNI/ABN e o BCTRIMS recomendam que os pacientes com doenças desmielinizantes do SNC (ex., EM e NMOSD) sejam constantemente monitorados, quanto a atualização do seu calendário vacinal, especialmente, no início ou antes da mudança do tratamento com uma droga modificadora de doença (DMD). É importante também salientar que as vacinas são seguras e os médicos devem estimular o seu uso em todos os pacientes. Evidentemente, deve ser dada especial atenção às vacinas com vírus vivos atenuados. Por fim, é importante que os médicos verifiquem qual DMD o paciente está em uso e quando foi feita a sua última dose, pois cada fármaco pode interagir de forma diferente com a indução da resposta imune.

Palavras-chave: Doenças Autoimunes Desmielinizantes do Sistema Nervoso Central; Esclerose Múltipla; Neuromielite Óptica; Vacinação; COVID-19; SARS-CoV-2.

INTRODUCTION

The Scientific Department of Neuroimmunology of the Brazilian Academy of Neurology (DCNI/ABN) and Brazilian Committee for Treatment and Research in Multiple Sclerosis and Neuroimmunological Diseases (BCTRIMS) provide recommendations in this document for vaccination of the population with demyelinating diseases against infections in general and against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. These are not absolute recommendations, as there is yet no published evidence on the safety and efficacy of vaccines, particularly against SARS-CoV-2 and its variants in this population, but it may serve as a guide to vaccination. The text is based on the limited scientific evidence available, mainly centered on other autoimmune diseases and on expert opinion. However, for some specific vaccines, there are already more robust clinical trials related to the use of some disease-modifying drugs (DMDs), which are discussed in more detail below.

We emphasize the seriousness of the current moment in view of the progression of COVID-19 in our country, and refer to new variants of SARS-CoV-2, especially the P1 variant identified throughout the country, with the possibility of coinfection events occurring[1]. The participation of the entire medical and health community is essential to raise awareness of the importance of non-pharmacological measures associated with vaccination.

The history of vaccination in humans began in 1796 in the United Kingdom with the development of the smallpox vaccine[2]. It is clear, therefore, that the experience and knowledge of the effects and safety of immunizations, especially in public health, are already scientifically consolidated[3]. Immunization should be understood as a way of exposing the immune system beforehand to a particular pathogen through its antigens, so that immune memory is developed and the body can respond more quickly in the case of infection, reducing the morbidity and mortality associated with the disease. Traditional forms of vaccination use live attenuated viruses, dead viruses or recombinant proteins, with or without polysaccharides[4]. Most of the existing vaccines available in the Brazilian National Immunization Program (NIP)[5] and in several other countries use these techniques[6]. Unvaccinated individuals are at increased risk of morbidity and mortality by a given infectious disease and of spreading the infection.

An ideal vaccine should contain antigens targeted by the immune system, produce effective immunity (antibodies and T cells) and protective immunity, provide a good level of protection, preferably without the need for booster doses, cause few or no side effects, not cause illness or death, and be inexpensive, easy to administer and biologically stable[4,7]. During the current COVID-19 pandemic, other types of vaccines have been introduced, such as those with a non-replicating viral vector and with DNA or RNA of the pathogen (Table 1). Due to

Table 1. Characteristics of the main vaccine types.

Type of vaccine	Live attenuated	Inactivated virus	Subunit	Toxoid	Nucleic acid	Recombinant vector
Mechanism	Made with whole pathogen, weakened under laboratory conditions	Uses the whole pathogen that has been inactivated in the laboratory	Uses the most immunogenic components of the pathogen	Uses inactivated bacterial toxins	Acts by encoding the RNA or DNA of the target antigen in order to produce antibodies	Employs an inactivated viral vector to introduce the pathogen's genetic material
Advantages	Provides strong humoral and cellular responses, conferring long-term immunity with one or two doses	Safe and stable as it contains no active virus	Safe and stable, as it contains no active pathogen	Safe and stable, as it contains no active pathogen	Stable and low-cost. Safe in principle, as it contains no active virus	More specific delivery of genes to target cells. Safe, in principle, as it contains no active virus
Disadvantages	Contraindicated in people with compromised immune systems, as it can induce reactivation of the pathogen and cause the disease	Provides a weaker immune response, which is why additional adjuvant or booster doses may be required	Increased cost, as the combination of antigens that will generate an effective response needs to be determined	Aims to protect against a specific toxin only. Does not provide collective protection and requires multiple doses to maintain protection	Induces limited response to antigen protein, thereby not being highly immunogenic	Can induce the formation of neutralizing antibodies that can reduce its effectiveness

the great current importance of this subject, issues related to SARS-CoV-2 infection will be discussed later as a separate topic.

Whenever the use of vaccines is addressed in the context of immune-mediated diseases, we must take into consideration two main issues. First, we must assess whether vaccines are safe in this population[8]. It is important to remember that after more than 200 years of use, there is no evidence that vaccination causes serious adverse events or deaths. Although there are reports of adverse effects, no causal link has been definitively established, and as such, the scientific community worldwide considers that the benefits of vaccination far outweigh the possible risks[9]. The second aspect concerns the individual's ability to generate or not generate an adequate protective immune response while using therapies that act on the immune system[10,11]. It is important to note that this response can be affected in a totally different way, depending on the treatment used and the time interval since the last dose was received. In Brazil, it is recommended that the vaccination of individuals with Central Nervous System (CNS) immunological diseases not only comply with the recommendations of the NIP according to age groups, but also include coverage for some pathogens that can infect patients using immunosuppressive drugs, such as varicella zoster virus and encapsulated bacteria (i.e., pneumococci and meningococci)[12]. It is important that the attending physician review the patient's vaccination record at the initial consultation and at any planed DMDs change. The vaccination history should specifically include seasonal influenza, pneumococcus, hepatitis A and B, tetanus/diphtheria, varicella (chickenpox) and measles vaccination. Pre-vaccination serology testing for hepatitis A, hepatitis B, measles, rubella, and varicella zoster may also be necessary. Another important aspect is to assess the vaccination status of household contacts and close contacts of patients, especially those who use immunosuppressants and vaccinate contacts if necessary.

Several medical specialty societies and the American agency Center for Disease Control (CDC, USA) consider immunocompromised patients to be at high risk for the development of serious infectious diseases compared to immunocompetent individuals, whether they present permanent or reversible immune dysfunction[6]. The risks of developing serious forms of infectious diseases are related to conditions such as cancer, bone marrow transplant, solid organ transplant, genetic immunological deficiencies, human immunodeficiency virus (HIV), chronic use of intravenous or oral corticosteroids, and use of immunosuppressive medications, among others. The effectiveness of vaccination depends on the person's intact immune response, especially concerning antigen function, activation of T and B lymphocytes, formation of plasma cells and antibodies production. Therefore, immunization may be less effective in immunocompromised patients compared to the general population[4]. Table 2 shows the main medications used for the treatment of demyelinating diseases of the CNS.

Regarding safety, vaccines containing inactivated virus, subunits, toxoid, nucleic acid and recombinant virus do not pose a risk in immunosuppressed patients, since they inoculate the inactivated pathogen or fragments of it. In transplant patients or patients with autoimmune diseases, there are no data indicating risk of transplant rejection or increased activity of the

Table 2. List of the main therapies available or in the process of approval in Brazil for the treatment of CNS autoimmune demyelinating diseases.

Oral immunosuppressants	immunomodulators	Immunobiological/ venous immunosuppressants	Others
Azathioprine	Glatiramer acetate	Alemtuzumab	Gene therapies
Cladribine	Beta interferons	Cyclophosphamide	Autologous stem cell transplant
Corticosteroids		Eculizumab	
Fingolimod		Human immunoglobulin	
Dimethyl fumarate		(intravenous)	
Methotrexate		Inebilizumab	
Mycophenolate mofetil		Mitoxantrone	
Siponimod		Natalizumab	
Teriflunomide		Ocrelizumab	
		Ofatumumab	
		Rituximab	
		Satralizumab	

underlying autoimmune disease associated with vaccination[6]. Additionally, data on vaccination for other diseases do not indicate increased risks. In the specific case of Multiple Sclerosis (MS), Neuromyelitis Optica Spectrum Disorders (NMOSD), and other CNS demyelinating diseases, there is no causal association between any type of vaccine and risk of developing these autoimmune inflammatory conditions[10,11,13]. Most studies on vaccination and MS have been conducted with a seasonal influenza vaccine, including randomized placebo-controlled clinical trials that found no evidence of increased risk of MS after vaccine administration[14,15].

Regarding vaccines with live attenuated viruses, there are reports of induced relapses in isolated cases, such as the yellow fever vaccine in patients with MS[10,13,15]. For this reason, the recommendation of this type of vaccine is made after assessing the benefits against the risk of inducing an exacerbation of the disease. It is important to emphasize that there is no causal association and, in most cases, the benefits outweigh the risks. Table 3 shows all available vaccines, including those accessible through the NIP and recommendations for use in patients with CNS demyelinating diseases.

CONSIDERATIONS ON THE EFFICACY OF VACCINES DURING TREATMENT WITH IMMUNOMODULATORY/ IMMUNOSUPPRESSIVE DRUGS

An effective immune response that provides long-term immune memory is generated primarily by the adaptive immune system, including B lymphocytes (humoral or antibody-mediated response) and T lymphocytes (cellular response). The humoral response is usually measured using serum IgG antibody levels against a specific antigen. The cellular response, on the other hand, is less studied, more complex, and methods for its evaluation vary in the literature[4].

The immunomodulatory and immunosuppressive effects of different DMDs make assessment of vaccine efficacy more complex. The impact of these therapies on the adaptive immune system can decrease the response to vaccination by modifying the development of long-term immune memory[8,10,11,13]. Few studies have specifically addressed this issue and scientifically based recommendations do not yet exist for most existing therapies (Table 4).

In general, the use of interferons beta and glatiramer acetate probably do not imply a reduction in seroprotection in response to influenza, tetanus, and diphtheria vaccines. On the other hand, the use of anti-CD20 monoclonal antibodies or fingolimod, for example, may result in decreased seroprotection in response to the influenza vaccine[8]. Given the lack of knowledge regarding the real impact of different DMDs on the effectiveness of particular vaccines, it may be appropriate to evaluate the seroprotection after vaccine administration for those patients under treatment and to consider the administration of booster doses, if necessary, after case-by-case evaluation. Whenever possible, evaluation of the vaccine-induced immune memory should be performed four weeks after application of the last recommended dose (expert opinion, level VII evidence).

VACCINATION FOR SARS-COV-2

Since January 2020, the world has been facing one of the worst pandemics. The SARS-CoV-2 virus has already infected millions of people globally and caused more than 2.5 million deaths. The only measures that can contain the spread of the virus are social distancing and isolation, frequent hand washing, and the correct use of masks[39]. This new infectious disease caused by the coronavirus (COVID-19), which causes severe acute coronavirus 2 respiratory syndrome (SARS-CoV-2), is a complex clinical syndrome that most often produces systemic manifestations and represents an ongoing challenge for neurologists who care for people with MS or NMOSD[40]. According to the World Health Organization (www.who.int), on November 3, 2020, there were 47 vaccine candidates under clinical evaluation and 155 vaccine candidates under preclinical evaluation.

Table 3. Types of vaccines and recommendations for their use in patients with CNS demyelinating diseases.

Vaccine	Vaccine type	Timetable recommended by the Brazilian Immunization Society (SBIm)	Recommendation for patients with MS/NMOSD
Acellular triple bacterial vaccine for adults Diphtheria-Tetanus-Pertussis (DTaP or DTaP-IVP) Diphtheria-Tetanus (DT) for adults	Diphtheria and tetanus toxoids Inactivated components of the *Bordetella pertussis* capsule	Update the DTaP regardless of previous DT or TT intervals. With complete basic vaccination regimen: DTaP boost every 10 years. With incomplete basic vaccination regimen: one dose of DTaP at any time and complete the basic vaccination with DT (double adult vaccine) in a total of three doses of vaccine containing the tetanus component. Unvaccinated and/or unknown vaccination history: one dose of DTaP and two doses of DT in regimen of 0 - 2 - 4 to 8 months. For individuals who intend to travel to countries where poliomyelitis is endemic: DTaP vaccine combined with inactivated polio (DTaP-IVP) is recommended. The DTaP-IVP can replace the DTaP.	Considered safe
HPV	Recombinant vaccine Virus particles	For unvaccinated adolescents ≥ 15 years of age, the regimen is 3 doses (0, 1-2, 6 months.) Two vaccines are available in Brazil: quadrivalent HPV, licensed for women aged 9 to 45 years and men aged 9 to 26 years; and bivalent HPV, licensed for women from 9 years of age.	Probably safe
Triple viral MMR (measles, mumps, rubella)	Live attenuated virus	Two doses of vaccine above 1 year of age, with minimum interval of one month between the two. For fully vaccinated adults, there is no evidence to justify a routine third dose, which can be considered in situations of a mumps and/or measles outbreak and disease risk	Probably safe, consider immunosuppression used
Meningococcal ACWY	Inactivated vaccine	Administer 2 (two) doses, at 3 (three) and 5 (five) months of age, with interval of 60 days between doses, minimum 30 days. Adolescents aged 11 and 12 years, administer 1 (one) booster dose or a single dose, according to their vaccination status. For unvaccinated adults: one dose	Probably safe
Meningococcal B	Recombinant vaccine	3 and 5 months of age and between 12 and 15 months. For adolescents not previously vaccinated, 2 doses one month apart are recommended. For adults up to 50 years of age, when justified: two doses with an interval of one to two months. After 50 years: use is off-label. High-risk groups, such as people living with HIV, or anatomic or functional asplenia, who have a complement deficiency or are using eculizumab or other biological drugs that interfere with the complement pathway: booster dose given three years after completing the vaccination regime	Probably safe
10-valent pneumococcal conjugate vaccine (VPC10) 13-valent pneumococcal conjugate vaccine (VPC13)	Inactivated vaccine	Routine vaccination with VPC10 or VPC13 is recommended for children from 2 months to 6 years of age. For children over 6 years of age, adolescents and adults with certain chronic diseases, the VPC13 and VPP23 vaccines are recommended. For those aged over 50 years, and especially over 60 years, the VPC13 and VPP23 vaccines are recommended	Probably safe
23-valent pneumococcal polysaccharide	Polysaccharide vaccine	From the age of 60 years, administer 1 (one) single additional dose, respecting a 5-year minimum interval from the initial dose.	Insufficient data

Table 3. Cont.

Vaccine	Vaccine type	Timetable recommended by the Brazilian Immunization Society (SBIm)	Recommendation for patients with MS/NMOSD
Herpes zoster	Live attenuated virus	Vaccine is licensed for people aged 50 + years and is recommended as routine for those over 60 years of age. Generally contraindicated in immune suppressed individuals	Insufficient data, consider immunosuppression used
Hepatitis B	Recombinant vaccine	Administer 1 (one) dose at birth, as early as possible in the first 24 hours, preferably in the first 12 hours after birth, still in the maternity ward. This dose can be administered up to 30 days after birth. Children from 7 (seven) years of age: Without vaccination proof: administer 3 (three) doses of hepatitis B vaccine with an interval of 30 days between the first and second dose, and 6 (six) months between the first and third dose (0, 1 and 6 months). With incomplete vaccination regimen: do not restart vaccination schedule, simply complete it according to the situation encountered. For pregnant women, any age group and gestational age: administer 3 doses of hepatitis B vaccine, considering the previous vaccination history and recommended intervals between doses. If it is not possible to complete the vaccination schedule during pregnancy, it must be completed after delivery	Considered safe
Hepatitis A	Inactivated vaccine	One dose administered at 15 months of age. For those children up to 4 years, 11 months and 29 days, who missed vaccination, administer one dose of hepatitis A vaccine. Case-by-case evaluation should be made of children with immunosuppression and those susceptible who fall outside the age range recommended in the National Vaccination Calendar	Considered safe
Inactivated Polio	Inactivated vaccine	Administer 3 (three) doses, at 2 (two), 4 (four) and 6 (six) months of age, with an interval of 60 days between doses. The minimum interval is 30 days between doses. Individuals 5 years of age or older without proof of vaccination or with an incomplete vaccination schedule should receive the OPV as an exception if they are residing in Brazil and will travel to areas with a vaccine recommendation.	Considered safe
Haemophilus influenzae type B (Pentavalent vaccine)	Conjugate vaccine	Administer 3 (three) doses, at 2 (two), 4 (four) and 6 (six) months of age, with an interval of 60 days between doses, minimum of 30 days. The third dose should not be administered before 6 (six) months of age. The pentavalent vaccine is contraindicated for children from 7 (seven) years of age.	Insufficient data
Yellow Fever	Live attenuated virus	Children from 9 (nine) months and younger than 5 (five) years of age: Administer 1 (one) dose at age 9 (nine) months, and a booster dose at 4 (four) years. Individuals from 5 (five) years to 59 years of age: Administer 1 (one) single dose. Conduct a risk-benefit assessment from 60 years of age. Yellow fever vaccine is usually contraindicated in immune suppressed patients (rheumatological diseases, malignant neoplasms, solid organ transplant, hematopoietic stem cell transplant), but it may be considered in certain situations depending on the degree of immunosuppression and epidemiological risk, with careful medical evaluation being necessary in such cases.	Probably increases the risk of an outbreak; the immunosuppression drug used should be considered

Table 3. Cont.

Vaccine	Vaccine type	Timetable recommended by the Brazilian Immunization Society (SBIm)	Recommendation for patients with MS/NMOSD
Influenza	Inactivated vaccine	For individuals from 9 (nine) years of age: administer 1 (one) dose annually during campaigns. Where available, the quadrivalent influenza vaccine (4V) is preferable to the trivalent influenza vaccine (3V), as it provides greater coverage of circulating strains.	Considered safe
Varicella (component of tetraviral vaccine available in the public health system)	Live attenuated viruses	Routinely recommended for children from 12 months of age onwards (use from 9 months onwards in exceptional circumstances, for example in situations of outbreak). All susceptible children, adolescents and adults (who have not had chickenpox) should be vaccinated	Probably safe, consider immunosuppression used

Table 4. Effect of main disease-modifying drugs in response to vaccination.

Medicines	Comments
Interferons beta	No change in humoral response when compared to healthy individuals. Tested for influenza, meningococcal, pneumococcal and DT[8,11,16,17]. Level III evidence *American Academy of Neurology* (AAN); or 3 *Centre for Evidence-Based Medicine – University of Oxford* (CEBM)
Glatiramer	Possible slight reduction in seroprotection in response to influenza vaccinations, when compared to healthy individuals or those using beta-interferons[8,11,17]. Level III evidence (AAN); or 3 (CEBM)
Teriflunomide	Studies with small sample sizes have shown a slight reduction in immune response after vaccination against influenza and rabies[16,18]. Level III evidence (AAN); or 2 (CEBM) The AAN recommendation is to not use live attenuated virus during treatment, or immediately before and up to 6 months after stopping treatment. Screening for tuberculosis (TB) and Varicella. Vaccinate for varicella (immune susceptible).
Dimethyl fumarate	A small sample study showed no difference in humoral response to vaccination, when compared to individuals using beta-interferons (DT, meningococcal and pneumococcal)[19]. Level III evidence (AAN); or 3 (CEBM) Post-hoc analysis of a subgroup of patients showed no relationship between lymphocyte count and response to vaccination[19]. Level IV evidence (AAN); or 4 (CEBM)
Fingolimod	Reduced immune response against influenza (A and B) and tetanus vaccines, when compared to patients using beta-interferons or healthy individuals[17,20–22]. Level I/II evidence (AAN); or 2 (CEBM) Screening for hepatitis B. Vaccinate for varicella (immune susceptible). There may be a reduction in antibody titers produced by the vaccine after initiation of treatment with fingolimod[23]. Level III evidence (AAN); or 3 (CEBM).
Natalizumab	Some studies suggest a reduced immune response against influenza and tetanus vaccines in a percentage of patients using natalizumab, when compared to those using beta-interferons or healthy individuals[17,21,24,25]. Level III evidence (AAN); or 3 (CEBM)
Ocrelizumab	The VELOCE study showed a reduction in immune response and seroconversion rate in patients treated with ocrelizumab compared to patients using beta-interferons or without treatment (tetanus, pneumococcal, meningococcal and influenza vaccines were evaluated)[26]. Level II evidence (AAN); or 2 (CEBM). Vaccinate with live attenuated virus vaccine at least 4 weeks before starting treatment and 2 weeks before for other vaccines. If the patient is already using ocrelizumab, the vaccine should ideally be applied between the 3rd and 5th month after the last infusion, so that induction of immune memory is more effective. In the event that additional doses are required, it is recommended that both or at least one of them be performed in this time window (expert opinion). Level 5 evidence (CEBM). The AAN recommendation is not to use a live attenuated virus vaccine during treatment, or immediately before and up to 6 months after stopping treatment. Screening for hepatitis B.

Table 4. Cont.

Medicines	Comments
Corticosteroids	Live attenuated virus vaccines are contraindicated within 3 months after treatment discontinuation for adults using 20mg/day or children using 2mg/kg/day for more than 2 weeks. If the patient has used corticosteroids in high doses, there should be a gap of at least 15 days before carrying out the vaccination (expert opinion). Level 5 evidence (CEBM).
Eculizumab	Insufficient data. Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated. Patients need to receive vaccines for meningococcus at least 2 weeks before starting treatment. If medication needs to be started sooner than this, prophylactic treatment should be given for 2 weeks
Inebilizumab	Insufficient data. Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated. In the absence of specific studies for inebilizumab, the authors recommend observing the same recommendations made for ocrelizumab (expert opinion)
Satralizumab	Insufficient data. Consider immunization schedule for immunocompromised patients (expert opinion). Level 5 evidence (CEBM). Live attenuated virus vaccines generally contraindicated

Vaccines in development or already approved by regulatory agencies are formulated with nucleic acids (RNA or DNA), viral vector with adenovirus (non-replicating), inactivated virus or protein components of the virus – vaccine types that have no chance of viral replication – and consequently considered safe for use in immunosuppressed patients, without the need to suspend or modify the dosage of disease-modifying therapies cited below[8,41,42]. As previously discussed, the use of live attenuated virus-based vaccines is not recommended in patients taking immunosuppressive therapies, should vaccines of this type against SARS-CoV-2 be approved in the future by any regulatory agency.

The shorter than usual approval time for these new vaccines can be explained by a number of factors. First, research on RNA vaccines began years prior to the emergence of the COVID-19 pandemic and many resources have been allocated for this purpose in a short period of time. Second, in comparison with traditional clinical trials, the results obtained have been evaluated quickly by regulatory agencies. This evaluation was performed as the data was produced and not just after completion of the entire study, as usually occurs.

Some examples of vaccines against SARS-CoV-2 already released by different international regulatory agencies include:

mRNA-based vaccines (Moderna and Pfizer/BioNTech), which promote an immune response against viral spike proteins;

Vaccines based on non-replicating adenovirus vector (CanSino, Gamaleya, Johnson & Johnson, Oxford-AstraZeneca), which increase the immune response against the coronavirus through a genetically modified vector that produces the spike glycoprotein;

Protein-based vaccines (Vector, Novavax, others), which induce an immune response against various proteins present in the coronavirus;

Inactivated virus-based vaccines (Sinopharm-Beijing, Sinopharm-Wuhan, Sinovac), which induce response to the different components of the inactivated coronavirus.

If there is no contraindication, immunosuppressed patients should be vaccinated due to the potential risk of developing severe forms of COVID-19 when infected with SARS-CoV-2. It is important to highlight that as of the beginning of February 2021, no international or national epidemiological study, such as that of the Brazilian Academy of Neurology (ABN) Brazilian Register of Neurological diseases (REDONE), has demonstrated an increased risk of serious COVID-19 disease in patients with MS and NMOSD treated with different DMDs or increased susceptibility for relapsing or CNS demyelination progression[43].

There is currently no data on the effectiveness of the available vaccines in this group of individuals, as no clinical study with an adequate sample size of patients with these conditions has yet been conducted. Considering safety aspects, clinical studies of vaccines against SARS-CoV-2 do not indicate a relationship with the onset of CNS demyelinating inflammatory diseases in vaccinated individuals[44].

The main side effects that have been associated with approved vaccines for SARS-CoV-2 are low fever, myalgia, headache, nausea, fatigue, and pain/redness at the injection site. These effects are more frequent after the second dose (booster dose) of the vaccine and are self-limited[45,46]. Additional data will become available from time to time through existing vaccine monitoring programs in different countries. It is important to note that most vaccines have been tested on patients over 18 years of age, and none were tested on pregnant women.

Immunosuppressed patients vaccinated against COVID-19 should be advised about the potential for reduced effectiveness and, therefore, they should be advise to continue with protective measures, including social distancing, mask wearing, and hand washing and hygiene. People living with these patients should also be vaccinated to protect them.

Patients using DMDs who are known to have been infected with SARS-CoV-2, whether or not COVID-19 developed, should be vaccinated. Although some immune memory against the virus is to be expected, the immune response may be less efficient or even absent upon re-exposure to the virus.

Data on the efficacy of vaccination in patients with lymphopenia are limited, but there is evidence that it may reduce the effectiveness of the vaccine. Considering that the use of DMDs can lead to lymphopenia, physicians can make administration of the DMD more flexible, temporarily suspending or delaying the dose before beginning vaccination against COVID-19, resuming treatment after the vaccination schedule has been completed. Decisions must be made on individual basis, weighing the risks of suspending treatment against the underlying disease and the risk of severe COVID-19. Although there are no definitive recommendations for this group yet, and in the absence of a specific contraindication, vaccination should be considered rather than rejected, even in cases where the use of DMDs induces lymphopenia or more severe immunosuppression (less than 500 lymphocytes per ml of blood). Therefore, in the context of potential lymphopenia, it is recommended to request a complete blood count before immunization.

If there is no time to relax the administration of drugs, it is better to vaccinate and acquire a minimum degree of immunity against infection than otherwise. High vaccination rates in a community protect not only those who have been vaccinated, but also those who have not been vaccinated for some reason, whether or not they have developed immunity to the virus. This is the collective or 'herd' immunity that is so important in the fight against the SARS-CoV-2 pandemic.

In light of the above, the DCNI/ABN and BCTRIMS recommend that patients with MS or NMOSD be constantly monitored in terms of updating of their vaccination regimen, especially at the onset or before a change in DMD treatment. If the patient has vaccines pending, it is recommended that they be administered whenever possible before starting a DMD that may interfere with induction of immune memory. The safety of vaccines should be emphasized, and physicians should encourage their use in all patients. Clearly, special attention should be paid when live attenuated viruses are involved. Finally, it is important for physicians to verify which DMD the patient is taking and when the last dose was taken, as each drug may affect the induction of immune response differently.

SUPPLEMENTARY MATERIAL

Names in alphabetic order and afiliations.

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Central nervous system demyelination following isolated levamisole use: Case report and systematic review

Luan Côrtes[a,*], Silas Santana[a], Thiago Gonçalves Fukuda[b], Aroldo Bacellar[c]

[a] Hospital São Rafael, Fundação Monte Tabor Centro Ítalo-Brasileiro de Promoção Sanitária, Salvador, BA, Brazil
[b] Complexo Hospitalar Universitário Prof. Edgard Santos, Department of Neurology, Universidade Federal da Bahia, Salvador, BA, Brazil
[c] Hospital São Rafael, Department of Neurology, Instituto D'Or de Pesquisa e Educação, Salvador, BA, Brazil

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ABSTRACT

Background: In most reported cases of central nervous system (CNS) demyelination following levamisole use, patients were exposed to at least one more known neurotoxic drug (contaminated cocaine or colon cancer combination therapy with fluorouracil). No reviews of CNS demyelination following isolated levamisole use have been published to date. This study aimed to assess clinical, diagnostic, and therapeutic features of CNS demyelination following isolated levamisole use and report an original case.

Methods: A sensitive search strategy was used to search MEDLINE, EMBASE, and LILACS (inception to February 2021) databases for English, Spanish, and Portuguese articles. Publications reporting on cases of CNS demyelination following isolated levamisole use in patients without previously diagnosed demyelinating diseases were included. A standardized approach was employed to extract predefined data, including demographics, details on levamisole exposure, clinical features, diagnostic workup, treatment, and outcomes. Descriptive statistics was used to summarize data.

Results: Eleven articles reporting on 61 patients met inclusion criteria and were reviewed together with the present report for a total of 62 cases. Patient mean age was 45.1 ± 13.3 years, and two thirds of them were women. Patients were exposed to variable total doses of levamisole (50 to 13,500 mg) mainly for the treatment of recurrent aphthous ulcers and intestinal parasitic infections. One to 144 days after exposure, patients developed a subacute, progressive neurological syndrome characterized by encephalopathy, including cognitive impairment in 22 (40.7%) and an altered level of consciousness in 9 of them (16.7%), accompanied by focal neurological deficits, chiefly muscle weakness in 25 (46.3%), language disorder in 23 (42.6%), and ataxia in 18 cases (33.3%). In all patients, brain magnetic resonance imaging (MRI) showed multiple, hyperintense lesions on T2-weighted and fluid-attenuated inversion recovery images characteristic of demyelination in the white matter, most of them periventricular and subcortical; in 17 (31.5%) and 27 cases (50.9%), MRI showed infratentorial and basal ganglia involvement, respectively; and in 26 cases (72.2%), enhancing lesions were detected. Cerebrospinal fluid analysis showed pleocytosis (8 to 22 cells/mm^3), elevated protein levels (49 to 81 mg/dL), and oligoclonal bands in 11 (34.4%), 9 (28.1%), and 2 (11.1%) patients, respectively. Improvement was seen in 59 cases (96.7%) after levamisole discontinuation, and 60 patients (96.8%) received high-dose corticosteroids. Missing data for many included patients and language restrictions were the key limitations.

Conclusion: Neurologists should be aware of the clinical features of CNS demyelination following isolated levamisole use to avoid diagnostic errors.

1. Introduction

Levamisole is an imidazothiazole derivative used as an antiparasitic agent to treat ascariasis (Moens et al., 1978). Its incompletely understood immunostimulatory properties led to its application to several conditions in the past, including recurrent aphthous ulcers, chronic hepatitis, and some types of cancer, such as colon adenocarcinoma, as combination therapy with fluorouracil, and melanoma (Amery and Bruynseels, 1992; Stevenson et al., 1991; Sun et al., 1994). Because of the risk of fatal agranulocytosis associated with levamisole, it was withdrawn from the market in the USA (Krensky et al., 2015), but it is still available as an over-the-counter anthelminthic in many countries, including Brazil (Cloridrato de levamisol, 2019). Moreover, levamisole has been increasingly used as a cutting agent for cocaine since 2003

* Corresponding author.
E-mail address: cortesluan@gmail.com (L. Côrtes).

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(Chang et al., 2010; Larocque and Hoffman, 2012) and it was detected in about 80% of all cocaine samples analyzed in the USA in 2010 (US Department of Justice National Drug Intelligence Center 2011).

In addition to mild gastrointestinal adverse events (Moens et al., 1978) and bone marrow toxicity (Larocque and Hoffman, 2012; Buchanan et al., 2010), neurological signs and symptoms, including ataxia, changes in mental status, diplopia, and dysarthria, had been reported before in patients treated with levamisole, albeit initially without related neuroimaging data published (Hook et al., 1992; Parkinson et al., 1977).

In a canine neurotoxicity model, oral levamisole was reported to cause the appearance of disseminated mononuclear perivascular cuffing in the brain (especially in the white matter) and leptomeninges, sometimes associated with demyelination of adjacent nerve fibers (Vandevelde et al., 1978). Levamisole was also shown to worsen and hasten the process of central nervous system (CNS) demyelination in susceptible mice, but not to induce demyelination in normal mice, suggesting individual genetic susceptibility may play a role in the development of this type of neurotoxicity (Lucchinetti et al., 1997).

Since the first report of CNS demyelination following combination therapy with levamisole and fluorouracil for colon cancer in 1992, termed multifocal inflammatory leukoencephalopathy (MIL) (Hook et al., 1992), multiple case reports and series have been published describing a subacute-onset, progressive, monophasic neurological syndrome characterized chiefly by altered mental status, ataxia, impaired language, and muscle weakness, which improved in most cases after chemotherapy discontinuation and corticosteroid therapy (Critchley et al., 1994; Enterline et al., 1995; Fassas et al., 1994; Galassi et al., 1996; Hwang et al., 2003; Israel et al., 2000; Kim et al., 2014; Kimmel and Schutt, 1993; Luppi et al., 1996; Murray et al., 1997; Neu, 1993; Recht and Primavera, 1999; Savarese et al., 1996; Yeo et al., 1999). Similar cases, although occasionally with distinct neuroimaging findings and generally with a less favorable prognosis, have been rarely reported in patients taking cocaine presumably (Grasso et al., 2020; Pessini et al., 2020; Kocaman et al., 2018; Vosoughi and Schmidt, 2015) or definitely adulterated with levamisole (Vitt et al., 2017).

CNS toxicity of fluorouracil and its derivatives has been reported both in humans, including cases of leukoencephalopathy, some of which with histopathological evidence of demyelination in the absence of levamisole use (Kuzuhara et al., 1987), and dogs, in whose myelin sheaths large vacuoles were detected following chronic exposure (Okeda et al., 1984). Similarly, the toxic effects of cocaine on the CNS are widely known and may result from vascular (intracranial hemorrhage and ischemic stroke associated with vasoconstriction or cardioembolism) (Smollin and Hoffman, 2019) and metabolic mechanisms, including reports of leukoencephalopathy, even with no suspicion of contamination with levamisole (Vosoughi and Schmidt, 2015; Anbarasan et al., 2011).

Considering most previously reported cases of MIL induced by levamisole were associated with combination therapy with fluorouracil or contaminated cocaine use, both neurotoxic drugs also known to induce CNS demyelination, we conducted a systematic review of reported cases of CNS demyelination following isolated levamisole use in patients without a history of CNS demyelinating disorders and reported an original case in the present study to summarize existing evidence and better delineate this serious entity.

2. Methods

2.1. Data sources and searches

Studies were identified by searching electronic databases (MEDLINE, EMBASE, and LILACS), with no language restrictions, from inception to February 2021 based on the following Medical Subject Headings or equivalent terms: levamisole, demyelination, and leukoencephalopathy.

2.2. Study selection

Case reports and case series of CNS demyelination following isolated levamisole use in patients not previously diagnosed with CNS demyelinating disorders were selected. Review articles including no original case reports, reports of demyelination following exposure to levamisole in association with other drugs, reports without a description of exposure to levamisole, preclinical studies, studies comprising patients with multiple sclerosis (MS), reports without a description of CNS demyelination, and reports published in languages other than English, Spanish, or Portuguese were excluded. Eligibility assessment was carried out by two authors based on titles and abstracts initially, and then the full text of all selected publications was examined in detail to confirm eligibility.

2.3. Data extraction

One author performed data collection using a specifically developed data extraction tool including the following data items: first author, year of publication, number of cases, demographics, details on levamisole exposure, clinical features, diagnostic workup, treatment, and outcomes.

2.4. Data synthesis and analysis

Data were analyzed qualitatively and summarized quantitatively by means of descriptive statistics, with means, standard deviations, and medians for continuous variables, and frequencies and percentages for dichotomous variables. Microsoft Excel® 2019 and IBM SPSS Statistics®, version 21, were used for statistical analysis.

2.5. Case report

The patient's medical records dating back to 2016 from a neuroimmunology clinic were reviewed to obtain demographics and details on levamisole exposure, as well as clinical, diagnostic, treatment, and follow-up data. The patient provided written informed consent, and this study was approved by the local institutional review board under the protocol no. 44248921.5.0000.0049.

3. Case report

In February 2016, a previously healthy 26-year-old female presented with a severe headache 24 h after taking 150 mg of oral levamisole as self-medication for a suspected intestinal parasitic infection, improving spontaneously in the following 24 h. After a second levamisole dose 3 weeks later, she presented again with a more severe, migraine-like headache associated with nausea, malaise, and vomiting, persisting for the following days despite the use of simple analgesics. Ten days after the second levamisole dose, the patient started having difficulty walking because of progressive weakness in her right leg and, over the following five days, became unable to recognize some family members and developed disorientation, drowsiness, and worsening muscle weakness to the point of losing the ability to walk. She was then admitted to the hospital, in March 2016, with aphasia, right-sided hemiparesis, and weakness in her left leg on examination. As an inpatient, she further developed tetraparesis, ataxia, and urinary incontinence. She had no history of fever, exposure to other prescription or recreational drugs, recent vaccination, or evidence of recent infection. Her brain magnetic resonance imaging (MRI) scan showed multiple lesions, hyperintense on fluid-attenuated inversion recovery (FLAIR) and T2-weighted images, some of them hypointense on T1-weighted images, located in the white matter of the cerebral hemispheres, many of them confluent and with a periventricular predominance, in the nucleo-capsular regions, and, to a lesser degree, in the brainstem, notably in the left midbrain (Fig. 1). Most lesions were contrast-enhancing, and some of them exhibited sub-

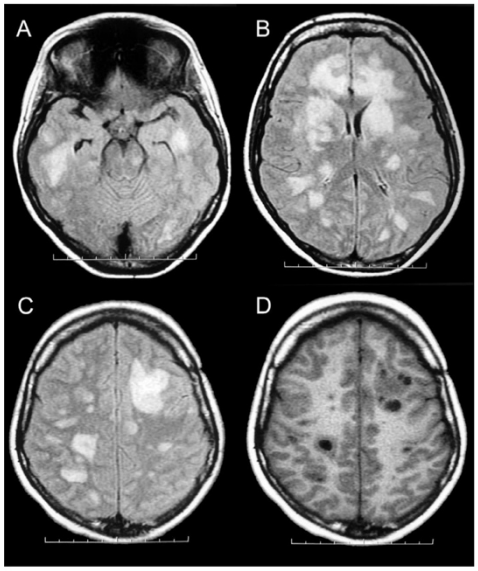

Fig. 1. Initial brain MRI: axial FLAIR images showing multiple hyperintense lesions (A, B, and C) and an axial T1-weighted image showing some matching hypointense focal areas (D).

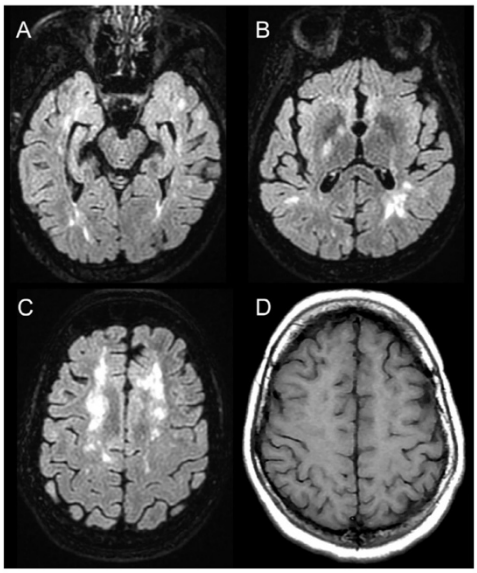

Fig. 2. Repeat brain MRI after 44 months: axial FLAIR images (reconstructed from three-dimensional volumetric acquisitions) showing improvement in the hyperintense lesions (A, B, and C) and an axial T1-weighted image now showing no hypointense areas (D).

tle foci of restricted diffusion. Oligoclonal bands were the only abnormality detected in her cerebrospinal fluid (CSF) analysis, with a normal cell count (1 lymphocyte/mm^3), normal glucose (67 mg/dL) and protein levels (12 mg/dL), and no evidence of infectious agents. Additional workup, including general laboratory testing, serology testing for sexually transmitted infections, and cervical and thoracic spine MRI scans, showed no abnormalities. The patient was treated with high-dose intravenous methylprednisolone, 1000 mg daily for 5 days, which was then switched to oral prednisone, 60 mg daily for the remainder of her hospital stay. She improved significantly until she was discharged home 14 days later, when she was fully oriented and managing to ambulate with a walking aid. Over the following 20 days as an outpatient, she went on to make a full recovery. Repeat MRI scans performed 2 and 44 months after hospital admission showed marked improvement in the appearance of her brain lesions, with no new signal abnormalities and no gadolinium enhancement (Fig. 2). At her last follow-up visit, in January 2021, the patient had no new complaints and a completely normal neurological examination.

4. Results

4.1. Study selection

A total of 108 unique publications were identified through database searching. After initial screening and exclusion of 3 reports in Russian and 2 in Chinese, 47 potentially eligible articles were selected for full-text examination, resulting in the exclusion of 34 reports of exposure to levamisole in association with other drugs (fluorouracil or cocaine) and 2 without a description of CNS demyelination. Eleven publications were then included in the present review (Fig. 3). No unpublished reports were identified.

4.2. Publication characteristics

All included studies were published in English and reported on a total of 61 cases from six countries, namely, China, with three articles and 32 cases, Taiwan, with four articles and 25 cases, and the USA, Argentina, Italy, and Iran, with one article and one case each (Table 1). Most publications reporting on more than one case included reasonable clinical data for each case separately. In some of them, however, a few variables were described in general or were not provided, thus limiting quantitative analysis. The original case reported in the present study was included in the universe of patients, totaling 62 cases.

4.3. Patient characteristics and levamisole exposure

Patient mean age was 45.1 years (standard deviation: 13.3 years), ranging from 7 to 82 years, and 42 were women (67.7%). Levamisole was administered to patients mainly for the treatment of recurrent aphthous ulcers (46.8%) (Liu et al., 2006; Wu et al., 2006; Lin et al., 2007; Xu et al., 2009; Aberastury et al., 2011) and intestinal parasitic infections (45.2%) (Xu et al., 2009; Yan et al., 2013; Long et al., 2015), but melanoma (Kimmel et al., 1995), hepatitis C (Lucia et al., 1996), pemphigus vulgaris (Wu et al., 2006), verrucae (Cheng and Po, 2011), and a case of accidental exposure (Sariaslani et al., 2012) were also reported. Patients were exposed to levamisole orally in a mean total dose of 1989.5 ± 2132.9 mg (median: 875 mg), ranging between 50 and 13,500 mg, for a mean duration of 11.8 ± 17.4 days (median: 1 day), going from 1 to 150 days. Mean total dose or individual dosing data were unavailable for 24 patients, with a range of 700 to 2250 mg being described in a study reporting on 9 patients (Liu et al., 2006) and another of 50 to 150 mg in a report comprising 15 cases (Yan et al., 2013). Similarly, exposure duration data were left out for 9 patients

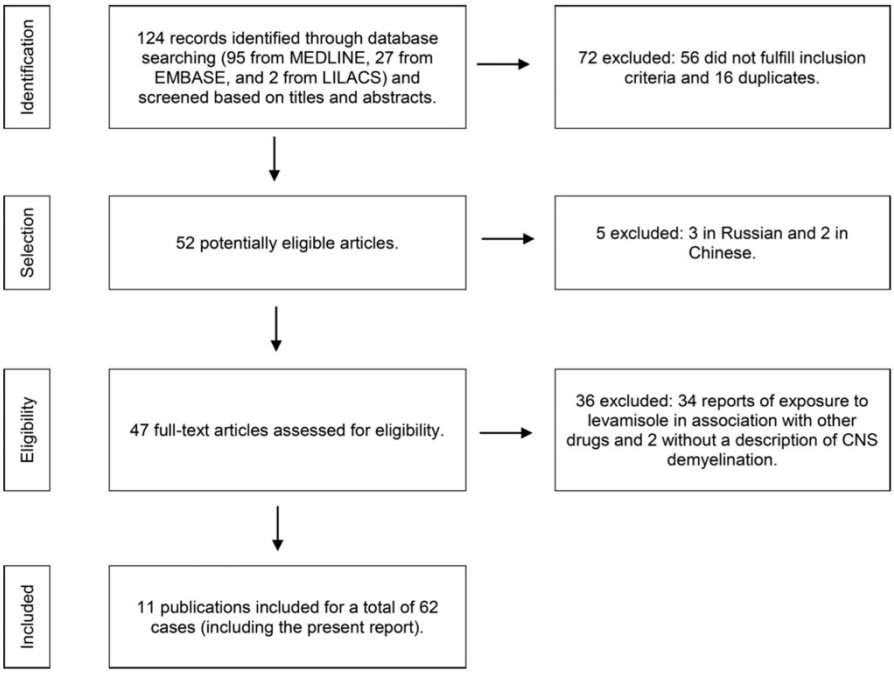

Fig. 3. Study selection flowchart.

Table 1
General characteristics of included publications reporting on cases of CNS demyelination following isolated levamisole use.

Author	Year	Country	n	Reporting quality
Kimmel et al. (Kimmel et al., 1995)	1995	USA	1	Good
Lucia et al. (Lucia et al., 1996)	1996	Italy	1	Intermediate
Liu et al. (Liu et al., 2006)	2006	Taiwan	9	Poor
Wu et al. (Wu et al., 2006)	2006	Taiwan	7	Good
Lin et al. (Lin et al., 2007)	2007	Taiwan	8	Poor
Xu et al. (Xu et al., 2009)	2009	China	16	Intermediate
Aberastury et al. (Aberastury et al., 2011)	2011	Argentina	1	Intermediate
Cheng and Po (Cheng and Po, 2011)	2011	Taiwan	1	Intermediate
Sariaslani et al. (Sariaslani et al., 2012)	2012	Iran	1	Intermediate
Yan et al. (Yan et al., 2013)	2013	China	15	Poor
Long et al. (Long et al., 2015)	2015	China	1	Poor

(Liu et al., 2006). The mean latency period between exposure to levamisole and the onset of neurological symptoms was 38.3 ± 29.2 days (median: 30 days), ranging from 1 to 144 days (Table 2). The latency period was not provided or was not reported individually or as a mean for 28 cases in 5 studies (Wu et al., 2006; Lin et al., 2007; Xu et al., 2009; Sariaslani et al., 2012; Yan et al., 2013), with a range of 2 to 8 weeks being described for 15 of them in one study (Yan et al., 2013).

4.4. Clinical manifestations

Clinical manifestations of levamisole-associated neurotoxicity are summarized in Table 3. The most common signs and symptoms were muscle weakness in 25 cases (46.3%) (especially hemiparesis and tetraparesis), language impairment in 23 (42.6%), cognitive dysfunction in 22 (40.7%), and ataxia in 18 cases (1/3), especially gait ataxia. Dizziness, an altered state of consciousness, facial palsy, sphincter disturbances (especially urinary incontinence), and systemic features such as malaise, nausea, vomiting, and fever were also reported, with fever being described in only 3 patients in one study (Yan et al., 2013). Seizures (Xu et al., 2009; Aberastury et al., 2011), diplopia (Wu et al., 2006; Xu et al., 2009), dysphagia, sensory disturbances (Cheng and Po, 2011), and the presence of primitive reflexes were rarely reported (Sariaslani et al., 2012). Individual descriptions of clinical presentation were unavailable for 8 patients in one study, but hemiparesis and an altered state of consciousness were generally referred to as the most common manifestations (Lin et al., 2007).

Table 2
Demographics and exposure data of the included cases of CNS demyelination following isolated levamisole use.

	n	
Age (years)	62	45.1 ± 13.3
Sex	62	
Female	42	67.7%
Male	20	32.3%
Clinical indication	62	
Recurrent aphthous ulcers	29	46.8%
Intestinal parasitic infections	28	45.2%
Others	5	8.0%
Total levamisole dose (mg)	38	
Mean ± standard deviation	–	1989.5 ± 2132.9
Median (range)	–	875 (50 to 13,500)
Duration of exposure (days)	53	
Mean ± standard deviation	–	11.8 ± 17.4
Median (range)	–	1 (1 to 150)
Latency period (days)	34	
Mean ± standard deviation	–	38.3 ± 29.2
Median (range)	–	30 (1 to 144)

Table 3
Signs and symptoms in 54 included cases of CNS demyelination following isolated levamisole use.

Clinical feature	*n* = 54	%
Muscle weakness	25	46.3
Language impairment	23	42.6
Cognitive dysfunction	22	40.7
Ataxia	18	33.3
Dizziness	10	18.5
Altered state of consciousness	9	16.7
Facial palsy	9	16.7
Sphincter disturbances	9	16.7
Systemic features	9	16.7
Pyramidal signs	8	14.8
Visual disturbances	8	14.8
Paresthesia	6	11.1
Dysarthria	4	7.4
Headache	4	7.4
Seizures	3	5.6
Diplopia	2	3.7
Others	4	7.4

4.5. Neuroimaging findings

Consistent brain MRI findings included multiple asymmetric lesions, hyperintense on FLAIR and T2-weighted images, occasionally hypointense on T1-weighted images and with some degree of restricted diffusion, in the white matter of the cerebral hemispheres, with a periventricular predominance, and also, less often, in the brainstem and cerebellum, with most lesions exhibiting contrast enhancement in 26 patients (72.2%). Supratentorial involvement was reported in all cases and was associated with infratentorial lesions in 17 cases (31.5%). Basal nuclei were also affected in 27 cases (50.9%) (Table 4). For 8 patients, no individual information on the location of brain lesions was available, but, on the whole, similar findings and a periventricular predominance were reported (Lin et al., 2007). In 3 studies, for a total of 26 patients, there were no data on the occurrence of contrast enhancement or the administration of gadolinium (Wu et al., 2006; Xu et al., 2009; Yan et al., 2013).

4.6. Cerebrospinal fluid analysis

CSF abnormalities included pleocytosis in 11 patients (34.4%), increased protein levels in 9 (28.1%), an elevated IgG index in 8 (42.1%), and oligoclonal bands in 2 cases (11.1%) (Table 4). For the patients with CSF abnormalities and reported data on cell count (Kimmel et al., 1995; Wu et al., 2006; Xu et al., 2009; Aberastury et al., 2011) and protein levels (Wu et al., 2006; Xu et al., 2009; Aberastury et al., 2011; Cheng and Po, 2011; Sariaslani et al., 2012), these variables ranged from 8 to 22 cells/mm^3 (9 patients), with a mononuclear predominance, and from 49 to 81 mg/dL (8 patients), respectively. Basic CSF data were unavailable or were not reported separately for 30 patients in 4 studies (Liu et al., 2006; Xu et al., 2009; Yan et al., 2013; Long et al., 2015), while there were no data on oligoclonal bands for 44 patients in 7 studies (Kimmel et al., 1995; Lucia et al., 1996; Liu et al., 2006; Xu et al., 2009; Cheng and Po, 2011; Yan et al., 2013; Long et al., 2015) and no information regarding IgG index for 43 cases in 8 studies (Lucia et al., 1996; Liu et al., 2006; Lin et al., 2007; Xu et al., 2009; Aberastury et al., 2011; Sariaslani et al., 2012; Yan et al., 2013; Long et al., 2015). In one report with incomplete CSF data, 9 out of 15 cases underwent lumbar puncture, and 4 of them were noted to have mild inflammatory changes (Yan et al., 2013).

Table 4
Brain MRI characteristics, CSF analysis, and brain biopsy of the included cases of CNS demyelination following isolated levamisole use.

	n	%
MRI lesions		
Supratentorial only	37/54	68.5
Supra and infratentorial	17/54	31.5
Basal nuclei involvement	27/53	50.9
Gadolinium enhancement	26/36	72.2
CSF analysis		
Pleocytosis	11/32	34.4
Increased protein levels	9/32	28.1
Oligoclonal bands	2/18	11.1
Elevated IgG index	8/19	42.1
Brain biopsy performed	4/62	6.5

Table 5
Treatment and outcome data of the included cases of CNS demyelination following isolated levamisole use.

	n	%
Treatment	62	
Corticosteroids	60	96.8
Plasma exchange therapy	8	12.9
Intravenous immune globulin	2	3.2
Supportive treatment only	1	1.6
Clinical outcome	61	
Favorable	59	96.7
Unfavorable	2	3.3

4.7. Histopathology

Only 4 out of 62 patients underwent brain biopsy, with findings compatible with active demyelination, consistent with an inflammatory leukoencephalopathy and overall similar to those seen in other demyelinating disorders such as MS (Liu et al., 2006; Wu et al., 2006; Xu et al., 2009).

4.8. Treatment and outcomes

Almost all patients (96.8%) received corticosteroid therapy, mostly as high-dose intravenous pulse therapy for 3 to 5 days, with or without a short prednisone taper (Table 5). Seven patients were additionally treated with plasma exchange, and one case received both plasma exchange and intravenous immune globulin, without corticosteroid therapy (Liu et al., 2006; Wu et al., 2006; Cheng and Po, 2011). Another patient received corticosteroids, plasma exchange, and lastly intravenous immune globulin (Liu et al., 2006). Only one patient received supportive

treatment alone, which consisted mainly of antiseizure drugs for epilepsia partialis continua (Aberastury et al., 2011). Most cases (96.7%) improved significantly or recovered completely (Table 5), including improvements in the brain lesions seen on MRI, after variable follow-up periods, usually of 3 months. In one report, a second exposure to levamisole a year after the initial event, which initially had a favorable outcome, resulted in a recurrence of neurological symptoms, with worse inflammatory findings on brain MRI, but there was no follow-up information after the second exposure (Liu et al., 2006). In one of the cases with an outcome deemed unfavorable, an older adult initially exposed to levamisole was eventually diagnosed with MS after a mean follow-up period of 36.9 months, although more details on this particular diagnostic process were not provided (Lin et al., 2007). The other patient with an unfavorable outcome was only diagnosed and therefore treated 8 months after the exposure to levamisole, with remaining ataxia and only a slight improvement in cognition being observed after 3 months (Sariaslani et al., 2012).

5. Discussion

The stimulatory effects of levamisole on cellular immunity, although not completely understood, have been observed both in vitro and in cancer patients (Stevenson et al., 1991; Spreafico et al., 1975), supporting the possibility of an immune-mediated mechanism of toxicity for the occurrence of CNS demyelination in genetically susceptible individuals. The evidence of levamisole neurotoxicity from animal models does not suggest direct toxicity to oligodendrocytes, but rather a potentially harmful immune response to an unknown antigen that is induced by the drug and culminates in demyelination in predisposed subjects (Lucchinetti et al., 1997). However, this susceptibility does not seem obvious, as levamisole did not lead to neurological worsening in patients with MS who were followed up for a mean period of 2 years in a clinical trial (Gonsette et al., 1982), despite one report of neurological deterioration in 5 out of 7 MS patients exposed to levamisole in an uncontrolled experimental study (Dau et al., 1976). The median latency period of 30 days (1 to 144 days) and the absence of a correlation between clinical severity and the wide levamisole dosing range to which the patients included in this review were exposed (50 to 13,500 mg) also favor the possibility of an immune-mediated pathogenic mechanism, rather than direct toxicity.

The clinical picture of subacute-onset neurological manifestations characterized by diffuse encephalopathy and focal deficits progressing over days, occasionally associated with nonspecific systemic features, seen in the included cases of CNS demyelination following levamisole use resembles that of acute disseminated encephalomyelitis (ADEM) (Koelman et al., 2016; Schwarz et al., 2001). However, despite the visual symptoms (blurred or otherwise impaired vision) reported in 8 cases (14.8%) and sphincter disturbances in 9 patients (16.7%), no involvement of the optic nerves, optic tracts, and spinal cord was recorded, and thus such manifestations likely resulted from brain lesions (Liu et al., 2006; Wu et al., 2006; Xu et al., 2009; Yan et al., 2013). In addition, systemic features and headache were reported less often, in 9 and 4 cases respectively, than would usually be expected in ADEM patients (Koelman et al., 2016; Schwarz et al., 2001), and there was no account of preceding infections or immunizations.

All 62 patients were reported to have multiple hyperintense lesions on FLAIR and T2-weighted images scattered throughout the supratentorial white matter, especially in the periventricular region, with contrast enhancement in 26 patients (72.2%) and additional deep gray matter and infratentorial involvement in 27 (50.9%) and 17 cases (31.5%), respectively. This neuroimaging pattern is therefore very similar to that seen in ADEM, which is also the case for CSF findings, consisting of usually mild inflammatory changes and occasionally oligoclonal bands (Koelman et al., 2016; Schwarz et al., 2001). Levamisole-associated MIL has indeed been classified by some authors as a type of ADEM (Xu et al., 2009), but this is disputable both clinically and pathophysiologically, as discussed.

Only 4 patients underwent brain biopsy, and the reported findings of active demyelination and perivascular mononuclear infiltrates were considered nearly identical to those seen in other CNS demyelinating disorders such as MS or ADEM in 3 cases (Liu et al., 2006; Wu et al., 2006); in the somewhat deviating case, demyelination was observed, but not the typically described inflammatory infiltrate (Xu et al., 2009).

Prognosis was predominantly favorable (96.7%), with most patients improving significantly or making a full recovery after levamisole discontinuation and corticosteroid therapy, which is consistent with the presumption of an immune-mediated pathogenic mechanism, even though the exact contribution of the administered treatments (corticosteroids, plasma exchange, and intravenous immune globulin) cannot be confidently established without evidence from controlled clinical trials. Moreover, only supportive treatment, which consisted mainly of antiseizure drugs, was provided to one female patient whose primary clinical manifestation was epilepsia partialis continua, and thus she achieved spontaneous remission, both clinically and on MRI (Aberastury et al., 2011). The importance of levamisole discontinuation and avoidance is underscored by one report of recurrence of symptoms and worsening MRI lesions after a drug re-exposure (Liu et al., 2006). In addition, failure to promptly diagnose CNS demyelination following levamisole use might lead to an unfavorable outcome, with long-term neurological sequelae (Sariaslani et al., 2012). In the absence of further exposure, levamisole-associated MIL has a typically monophasic course, although a single patient among all reviewed cases was reportedly diagnosed with MS over a 3-year follow-up period, yet the authors did not clarify whether the demyelinating event ascribed to levamisole use was considered the first MS attack and did not provide further details on the diagnostic process in this particular context (Lin et al., 2007), precluding an in-depth analysis of this case.

To our knowledge, this is the first systematic review of case reports and case series of CNS demyelination following isolated levamisole use. Key limitations of this review include the inconsistent reporting quality of included publications, missing data, and the exclusion of studies published in Chinese and Russian. Our findings are nevertheless useful in better characterizing CNS demyelination following isolated levamisole use, often termed MIL, which, albeit rare, should be considered in the differential diagnosis of CNS demyelinating affections in light of the high prevalence of intestinal parasitic infections in developing countries and the availability of levamisole as an over-the-counter antiparasitic agent.

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Data statement

Available upon reasonable request from the corresponding author.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Luan Côrtes: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Silas Santana:** Conceptualization, Investigation, Writing – review & editing. **Thiago Gonçalves Fukuda:** Writing – review & editing, Supervision. **Aroldo Bacellar:** Writing – review & editing, Supervision.

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Original Research

Timed Average Mean Maximum Velocity (TAMMV) of Cerebral Blood Flow of Children and Adolescents with Sickle cell Disease: correlation with clinical and hematological profiles in country

Bartholomew Chukwu[1], Lyra Menezes[2], Thiago Fukuda[3], Jamary Filho[3], Marilda Goncalves[4]

1. Department of Paediatrics, Faculty of Medical Sciences, University of Nigeria, Nsukka
2. Hospital Univesitario Professor Edgard Santos, Paediatric Haematology Service, Universidade Federal de Bahia, Brazil
3. Ambulatorio Pediatrico de doenca cerobrovascular, Universidade Federal da Bahia, Brazil
4. Departmento de Anelises Clinicas e Toxicalogicas, Facuidade da Farmacia, Universidade Federal da Bahia, Brazil

Correspondence: Bartholomew Chukwu (barth.chukwu@unn.edu.ng)

Abstract

Background

Detection of abnormal TAMMV with transcranial Doppler is fundamental in primary stroke prevention in children with sickle cell disease (SCD). The study aimed at evaluating TAMMV and correlating it with clinical and hematological profiles of children and adolescent with SCD.

Methods

Transcranial Doppler was performed on subjects aged 2-16 years, using a 2 MHz probe placed over the transtemporal windows. Pulse oximetry was used to determine the peripheral oxygen saturation while clinical and hematological profiles were retrieved from their medical records.

Results

One hundred and thirty five patients were recruited. The mean TAMMV was 125cm/s. Patients with HbSS had a significantly higher TAMMV (131cm/s) than those with HbSC (107cm/s). Only one (0.74%) patient had abnormal TAMMV. TAMMV correlated inversely with oxygen saturation, Hct and patient's age, and positively with white cell and platelet counts. Previous history of acute chest syndrome (ACS) and recurrent painful crises increased the risk of development of abnormal and conditional velocity.

Conclusion

Frequency of abnormal TAMMV in this study was low. Younger children and those with HbSS had higher TAMMV. Age, oxygen saturation and haematocrit correlated negatively while white cell and platelet counts correlated positively with TAMMV. Previous history of ACS and recurrent bone pain were associated with increased risk of having abnormal and conditional TAMMV.

Key words: sickle cell disease, TAMMV, Transcranial Doppler, children, adolescents, Salvador.

Introduction

Sickle cell disease (SCD) is the commonest genetic disorder worldwide. In Brazil, the frequency of sickle cell trait (SCT, HbAS) and prevalence of SCD range from 1.1% to 9.8% and 0.8 to 60 per 100,000 births respectively. It is estimated that about 700-1000 children are born annually in Brazil with SCD[1,2,3,4]. Salvador, Bahia, has the highest burden of both the trait and the disease, with frequency of SCT and prevalence of SCD being 9.8% and 0.17% respectively[5,6].

Cerebrovascular accident (CVA) or stroke is a devastating complication of SCD and up to 11% of children with HbSS genotype are at risk of developing stroke before the age of 20 years, with highest incidence occurring between 2-5 years[7]. The incidence of stroke among Brazilian children with SCD ranged from 17.2-27.3%[8]. Proliferative vasculopathy of large intracranial internal carotid arteries and their proximal branches is the pathophysiological basis for development of ischemic stroke in SCD, although micro-infarcts in the deep white matter and diffuse arteriolar thickening have been reported in some neuropathological studies with normal cerebral angiograms in cases of acute clinical stroke[9,10,11] Risk factors for occurrence of stroke in SCD include anemia, leukocytosis, thrombocytosis, previous stroke, silent cerebral infarction, and systemic hypertension with abnormal TAMMV as the most important risk factor[7,12]. Detection of abnormal TAMMV with transcranial Doppler (TCD) and prophylactic blood transfusion are fundamental to primary stroke prevention in SCD[13].

Apart from TCD, are there other parameters that may indicate an increased TAMMV in children with SCD? Previous studies on TCD in Brazilian children were mainly on relationship between TAMMV and haemoglobin concentration[14,15] and there is paucity of data on TAMMV and its relationship with other haematological parameters. The aim of the present study was to evaluate TAMMV of children and adolescents with SCD, detect those with conditional and abnormal TAMMV and correlate TAMMV with hematological (haematocrit, WBC, platelets) and clinical profiles of the patients.

Materials and Methods

This cross sectional study was conducted at the Pediatric Hematology outpatient clinic of Professor Edgard Santos University Hospital, Salvador, Brazil, between March 2016

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and Feb. 2017. Patients included in the study were aged 2-16 years, confirmed to have SCD, in a steady state while patients with past history of stroke or on prophylactic blood transfusion or had received blood transfusion for any other reason within the preceding 3 months were excluded. Patients in steady state were regarded as those that did not present with any acute illness necessitating emergency visit or hospital admission in the past four weeks and did not have recurrent infection or inflammation within the past four weeks before TCD evaluation[16]. All the patients who presented to the clinic over the study period and met the inclusion criteria were recruited consecutively for TCD evaluation. Clinical risk factors of stroke including past history of stroke, ACS or pneumonia, recurrent bone pain and priapism within the preceding twelve months were obtained from patients or caregivers and verified from the patients' medical records. Recurrent bone pain crisis was regarded as three or more painful episodes that required visit to the emergency room or hospital admission within the past 12 months. The steady state hematological parameters and use of hydroxyurea (HU) were also obtained from patients' medical records. The steady state hematological parameters were taken as values obtained within the preceding 3 months without blood transfusion; and included, hemoglobin concentration, hematocrit, reticulocyte, WBC, neutrophil, monocyte, and platelet counts. It was ensured that patients on HU had been on stable dose for at least six months before TCD evaluation.

The arterial oxygen saturation (SpO_2) was determined with pulse oximeter (Geratherm Medical, Germany) placed on the right index finger of the patient at the time of TCD. Conventional TCD screening as recommended by Stroke prevention trial in SCA (STOP) and the Brazilian guidelines for TCD in children and adolescents with SCD was performed, using a single non-imaging device Doppler probe (2MHZ) transducer (Sonatek, Viasys Healthcare and Cardinal Health, USA) on the trans-temporal windows.[17,18] The indications, procedures, advantages and risks of the examination were explained to the patients and/or caregivers before the examination.

The examination was done while patient was in supine position, awake, calm, and alert but not allowed to sleep because increase in CO_2 during sleep can increase TAMMV. It was also ensured that patient was not febrile, agitated or crying during examination as these may falsely increase TAMMV. While patient was lying supine and looking contra laterally, the examiner sat at the head of the bed with easy access to the instruments. The lubricated 2MHz frequency TCD probe was placed over the transtemporal window to insonate the basal cerebral arteries. The arteries were identified based on relative direction of the probe within the acoustic window, direction of blood flow relative to the probe, and depth of insonation. The distal internal carotid artery (ICA) or its bifurcation was identified at depths of 55 to 65mm with simultaneous flow away and towards the probe. The middle cerebral artery (MCA) was identified at depths of 35 to 55mm with blood flow towards the probe while the anterior cerebral artery (ACA) was viewed at depths of 60 to 70mm with blood flow away from the probe. Both audible and visual signals of the Doppler wave form were assessed with the aim of recognizing turbulence and other audible clues that suggest high velocities; and with the goal of obtaining the "cleanest," sharpest and highest velocity signal. The timed average mean maximum velocities (TAMMV) in the proximal MCA and distal ICA were recorded from both hemispheres according to the STOP protocol for SCD[17].

Written informed consent was obtained from caregivers and ascent from children of seven years and above. Ethical approval was obtained from the Institutional Review Board before commencing the study (IR 314.636).

The data were analyzed with statistical software (STATA 10, College Station, Tex: Stata Corp) and (SPSS 20.0, Armonk, NY: IBM Corp). Interval variables were presented as means and standard deviations for parametric variables or median and range for non-parametric variables. Categorical variables were presented in form of tables, proportions and percentages. Test of significance was assessed using Student's-T test for parametric interval variables and Mann Whitney test for non-parametric variables. Chi-square test or Fischer's exact test was used to test for significant difference between categorical variables. Correlations were assessed using Spearman's correlation coefficients. Eta coefficient was used to determine the strength of association between categorical independent variable (class of TAMMV) and interval dependent variables. Linear regression analysis was used to establish associations between dependent (TAMMV) and independent variables (age, SpO2, haematocrit, WBC, platelets, reticulocytes) after log transformation of the data. Odds of having abnormal or conditional TCD result were calculated for those that had history of clinical risk factors under study. Test of significance was set at $p < 0.05$.

Results

Patients' Characteristics

The subjects comprised 74 (54.8%) females and 61 (45.2%) males with median age of 8 years (2-16). Ninety three (68.9%) of them had HbSS genotype, 41 (30.4%) HbSC and one (0.7%), Sβ+ thalassemia genotype. Fifty one (37.8%) of the patients were taking HU as at the period of TCD screening for various indications, such as recurrent bone pain, past history of acute chest syndrome, or previous abnormal TCD report. The median weight, height and body mass index (BMI) of the patients were 23.6 (11-75.2) kg, 1.3 (0.8-1.8) M and 16.3 (10.7- 27.3) Kg/M^2 respectively.

Transcranial Doppler screening

The median of the TAMMV was 125 cm/s (74.4-202). One patient (0.74%) had abnormal result (≥200cm/s) while 18 (13.33%) had conditional TAMMV (170-199cm/s). None had low TCD result (< 70cm/s).

The females had a median TAMMV of 125.5 (74.7-199) cm/s in comparison with the males' 122 (74.4-202) cm/s, with no significant difference (Mann-Whitney test, $p = 0.5$). One (1.6%) of the males had abnormal result, 8 (13.1%) had conditional results while 10 (13.5%) of the females also had conditional results, with no significant difference (Fischer's exact, $p = 0.7$).

The age group, 6-9 years had the highest median TAMMV of 131cm/s while those aged 14-16 years had the lowest velocity of 111cm/s (Kruskal-Wallis test, $p = 0.01$) as shown in table 1. While the only abnormal TCD result was recorded in the age group 2-5 years, 88.9% (16/18) of the conditional results was in the under 10.

TAMMV did not differ significantly (Wilcoxon signed-rank test: $z= -0.9$, $p= 0.4$) between the right (118cm/s) and left (120cm/s) middle cerebral arteries, nor among patients on (128cm/s) or not on (121cm/s) HU therapy (Mann-Whitney

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Table 1: TCD results based on patients'age.

Age category (years)			TCD result		
	N (%)	Median (cm/s)	Normal (%)	Conditional (%)	Abnormal (%)
2-5	41 (30.4)	127.0	32 (23.7)	8 (5.9)	1(0.7)
6-9	43 (31.8)	131	35 (25.9)	8 (5.9)	0 (0)
10-13	36 (26.7)	121.5	26 (19.3)	(0.7)	0 (0)
14-16	15 (11.1)	111	23 (17.0)	1 (0.7)	0 (0)

P = 0.01

Table 2: Hematological variables and SpO_2 based on TCD result.

TCD	Hct (%)	Hb (g/dl)	SpO_2 (%)	WBC (/L)	ANC (/L)	AMC (/L)	Platelets (/L)	Retics (%)	HbF (%)
Normal	27.4	9.2	97	9200	5388	727	369,148	3.6	9.2
Conditional	23.2	7.8	94	14250	8216	1388	538,300	8.3	6.3
Abnormal	21	6.9	92	12300	6396	1250	529,000	4.4	3.2
P value	0.008	0.005	0.0002	0.01	0.004	0.0001	0.0003	0.1	0.05

Values indicated in the table were median values, except hemoglobin which was as mean value. Hct, Hematocrit; Hb, Hemoglobin; Retics, Reticulocyte count; HbF, Fetal hemoglobin; ANC, Absolute neutrophil count; AMC, Absolute monocyte count.

test: p= 0.4).

Comparing TAMMV among the two major genotypes, it was observed that patients with HbSS had higher median TAMMV (131cm/s) compared to those with HbSC (107cm/s), with a statistically significant difference (Mann-Whitney test, p<0.0001). Only the HbSS patients had abnormal or conditional velocity (OR = 10.8, 95% CI = 1.58-485.5, p = 0.005).

The study compared the hemoglobin oxygen saturation (SpO2) and hematological indices among the patients in relation to their TCD results (Table. 2). It was observed that patients with abnormal or conditional results had lower SpO2 (< 95%) compared to those with normal result with a statistically significant difference (Kruskal-Wallis test: p= 0.0002). Patients with abnormal or conditional TCD results also had lower mean hemoglobin concentration compared with those with normal results. One-way analysis of variance (ANOVA) indicated a statistically significant difference in the mean hemoglobin concentrations (ANOVA: F= 5.58, p= 0.005).

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Table 3: Median haematological variables compared between patients on hydroxyurea and those not taking the drug

Variables	Hydroxyurea	Median	P value
Total WBC(µl)	Yes	9600	
	No	9700	0.7
Hct (%)	Yes	27.3	
	No	27.0	0.9
ANC (µl)	Yes	4317	
	No	4816	0.5
AMC (µl)	Yes	689	
	No	765	0.5
Platelets (µl)	Yes	406000	
	No	389500	0.7
Retics (%)	Yes	4.7	
	No	4.5	0.9

ANC; absolute neutrophil count, AMC; absolute monocyte count, Retics; reticulocyte count

Table 4: Correlation between TAMMV and patients' hematological indices and SpO_2

Variable	N	Spearman ▯	P value
Age	135	-2.0	0.02
SpO_2	135	-0.35	0.0001
Hemoglobin	75	-0.50	0.0000
Hematocrit	75	-0.50	0.0000
Reticulocyte count	72	- 0.51	0.0000
HbF	72	0.03	0.8
Total WBC	75	0.34	0.003
Platelet count	75	0.34	0.003
ANC	75	0.30	0.01
AMC	75	0.53	0.0000

ANC, absolute neutrophil count; AMC, absolute monocyte count; HbF, fetal hemoglobin; TAMMV, Timed average mean maximum.

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Table 5: Association between class of TAMMV (normal, conditional, abnormal) and the independent variables

			Eta coefficient
Nominal by Interval	Eta	Class of TAMMV (normal, conditional, abnormal)	
		SpO2	0.415
		Age	0.175
		Haemoglobin	0.379
		Haematocrit	0.367
		Total WBC	0.263
		Absolute neutrophil count	0.310
		Absolute monocyte count	0.509
		Platelet count	0.449
		Reticulocyte count	0.147
		Fetal haemoglobin	0.256

0.2-0.39 indicate weak association, 0.4-0.69 indicates medium association, ≥0.7-1 indicates strong association

Table 6: Multiple linear regression analysis between TAMMV and its independent predictors.

Variables	Coef.	T	P value	95% CI.
Age	-0.0006	3.2	0.002	0.0009-0.0002
SpO_2	-0.0002	0.36	0.7	-0.007-001
Hb	-0.004	-1.8	0.08	-0.0005-0.0008
WBC	1.97	3.17	0.002	3.2-7.3
ANC	1.84	2.23	0.03	1.93-3.48
AMC	9.9	3.95	0.000	0.0002-4.9
Platelets	1.03	1.42	0.16	2.48-4.22
Retics	0.00035	1.54	0.13	0.0001-0.0008
HbF	-0.005	-2.79	0.007	0.0009-0.0001

TAMMV= Timed average mean maximum velocity, ANC= Absolute neutrophil count, AMC= Absolute monocyte count, Retics= Reticulocyte count, HbF= fetal hemoglobin.

Percentage of HbF was lower in patients with abnormal (3.3%) or conditional (6.3%) TCD results than those with normal (9.2%) results, but the difference was not significant (Kruskal-Wallis test: p= 0.05). Following a similar pattern, there was no significant difference (Kruskal-Wallis test: p= 0.1) in the reticulocyte count among patients with normal (4.4%), conditional (8.3%) or abnormal (3.6%) TCD results. It was observed that patients with conditional or abnormal TCD results had higher white cell and platelet counts than those with normal results. Test of significance (Kruskal-Wallis test) also indicated that the differences in WBC and platelet counts were statistically significant.

The haematological profiles of patients on hydroxyurea were comparable with those not taking the drug as shown in table 3. Most of the parameters were higher in children that were not on hydroxyurea, although the differences were not significant. The haematocrit was higher in children on hydroxyurea.

As shown in table 4, Spearman's correlation analysis indicated that patients' age, SpO2, and hematocrit negatively correlated with TAMMV. Total leukocyte, neutrophil, monocyte, platelet, and reticulocyte counts had positive correlation with TAMMV. These findings demonstrate that increased TAMMV is associated with younger age, low SpO2, low hematocrit/hemoglobin and elevated leukocyte, neutrophil, monocyte, platelet, and reticulocyte counts. There was no correlation between HbF concentration and TAMMV.

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The strength of association between the class of TAMMV (normal, conditional, abnormal) and the dependent variables is as in table 5. While the strength of association between class of TAMMV and oxygen saturation, absolute monocyte count and platelet count was medium, that with age, haematocrit, fetal haemoglobin was a weak association.

After log transformation of the non-parametric variables, a multiple linear regression model was used to assess for a linear relationship between TAMMV and the independent variables (age, SpO2, haematocrit, WBC, platelets, reticulocytes). This regression model showed that the independent variables statistically significantly predicted the dependent variable (TAMMV), F (10, 60) =8.87, p=0.0000), although responsible for only 60% of the variability of TAMMV (R2 = 0.5964). Young age and low HbF had negative association with TAMMV while total leukocyte, neutrophil, and monocyte counts independently had positive association with TAMMV, when other variables were held constant (p= 0.002, 0.002, 0.03, 0.000, and 0.007 respectively)-Table 6.

A risk analysis showed that patients who have had ACS in the preceding year were sixteen times at risk of having abnormal or conditional TCD result compared to those without the complication. Out of the 23 patients that suffered ACS, 12 had altered TAMMV (Odds ratio= 16.4; X2 =33.3, p= 0.000, 95% CI= 4.6-58.6). In the same vein, 17 of 66 that had recurrent painful crises had abnormal or conditional result (Odds ratio= 11.3, X2 = 14.1, p= 0.0002, 95% CI= 2.4535-103.5636). No case of priapism was recorded in the present study.

Discussion

Since the revelation from STOP clinical study with TCD in the late 1990s, the incidence of stroke in children with SCD has markedly reduced, compared to the pre-TCD era[13]. TCD identifies those at high risk of developing stroke and by instituting prophylactic blood transfusion program on them, stroke and other complications of SCD are minimized[13,19].

In this study, the prevalence of abnormal TCD result was comparable to 1.6% and 2.6 % reported by Hokazono et al and Melo et al., as well as that by Leite et al. in different parts of Brazil[14,20,21]. However, it was lower than that reported in Nigeria (8.4%) by Lagunju et al and in Iraq (13.33%) by Hasan et al.[22,23]. The difference in prevalence could have resulted from use of hydroxyurea in Brazilian children. Access and adherence rate of hydroxyurea among sickle cell patients is high in Brazil[24]. The differences in prevalence could also be due to differences in the number of patients screened or other factors including genetic. Genetic factors associated with increased risk of stroke in SCD include the haplotype, co-inheritance of alpha thalassemia, persistence of HbF production as well as inheritance of genes involved in inflammation, hypoxia, adherence molecules and coagulation[25].

There is tendency for conditional TCD to convert to abnormal result, which increases the risk of stroke. It is therefore imperative that measures be put in place to avert this conversion[26]. Apart from 3-6 monthly monitoring of TCD velocity in those with conditional results, no intervention measure is yet recommended, although some researchers have demonstrated the effectiveness of HU in preventing conversion of conditional to normal result, thereby reducing the risk of stroke in children with SCD[27].

Patients with SCA had higher TAMMV compared to other genotypes. This was in agreement with report by Hokazono et al.[14] In the present study, all the abnormal and conditional results were from patients with HbSS genotype. Vieira et al. observed also that patients with HbSS had significantly higher TAMMV compared to HbSC disease patients and suggested a lower cut-off point for the latter patients[15]. HbSS genotype confers is a more severe type of SCD compared to other genotypes[28]. Apart from higher prevalence of abnormal or conditional TAMMV and higher risk of CVA, patients with genotype HbSS have higher rates of hemolysis, lower hemoglobin, SpO2, and cardiac and other complications when compared with other genotypes[29]. In a comparative study of chronic kidney disease among SCD patients, it was observed that homozygous HbS patients were more severely affected than HbSC counterparts[30]. HbSS and HbSβ0 -thalassemia generally present most severe clinical and hematological symptoms while HbSC and HbSβ+ -present less severe disease.

This study also observed that the age group with the highest median of TAMMV was 6-9 years. Thereafter, TAMMV decreased with increasing age. This trend was in agreement with report by Lagunju et al and Makani et al. among patients with HbSS genotype and conformed to the general pattern of TAMMV in children without SCD.[22,31] According to Sch□ning et al., TAMMV increases markedly from 3 years of age and peaks at about the age of 6 years, and gradually decreasing until 15 years when it reaches a constant value[32]. Brass et al. also observed that cerebral blood flow reaches maximum at about the 6th year of life, with a direct relationship between it and blood flow velocity[33]. This study also established a significant inverse correlation between TAMMV and patient's age. This trend, in combination with other factors such as genetic and environmental factors could be the reason why vasculopathy in SCD, abnormal TCD, and stroke are commoner in younger children with SCD. Other complications of SCD commoner in the younger age group include ACS, splenic sequestration and parvovirus B19 infection with aplastic crisis. These complications have a common association with infection, either viral or bacterial[34,35,36]. Therefore, it may be conceivable to think that sickle cell vasculopathy is also related to infections among this age group. Further studies are required to prove or debunk this conception.

It may be surprising to note that there was no significant difference in TAMMV between those taking HU and their counterparts who were not taking the medication. It is known that HU can reverse abnormal TAMMV to conditional or normal and it may be possible that the patients on HU previously had conditional or abnormal TAMMV that reversed on taking the drug. However, we did not document the specific indications for use of HU among the individual patients.

A significant negative correlation was noted between TAMMV and SpO_2, hemoglobin and hematocrit. This finding concurred with previous studies[22,31,37]. Blood desaturation impairs oxygen delivery to the cerebral tissue and predisposes to CVA. Patients with SCD have chronic anemia arising from chronic hemolysis and recurrent infections. In anemia and desaturation, the circulatory system responds by lowering peripheral resistance, increasing cardiac output, which increases cerebral blood flow through increase in blood flow velocity[38]. Increased blood flow triggers turbulent flow, predisposing to vascular endothelial

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damage, inflammation, hyperplasia and hypertrophy of vascular smooth muscle, stenosis, cerebral ischemia, and increased risk stroke[39]. Maintaining a stable hemoglobin concentration at or close to 10g/dl by transfusions or drugs that increase the level of HbF and hemoglobin such as HU reduces the risk of abnormal TAMMV and stroke in children with SCD. Increased hemoglobin level improves oxygen transport and delivery to the brain, thereby reducing the risk of stroke. Chronic transfusion increases the normal hemoglobin level, reduces hypoxia and percentage of HbS (< 30%) and improves oxygen saturation and delivery to cerebral and other tissues.

The positive correlation between TAMMV and leukocyte, neutrophil and monocyte counts, platelet count and reticulocyte was also observed by Ismail et al in Kano, Nigeria[40], Adekunle et al[41] in Lagos, Nigeria also observed a significant correlation between TAMMV and leukocytosis and this could be ascribed to the fact that these cells are active participants in the chronic inflammatory process in SCD. Other studies have also shown higher counts and activation of these cells in patients with SCD, and more so in those with complications of the disease[21,42]. Reticulocyte count is an indirect marker of intravascular hemolysis, a major pathological process in SCD in which free hemoglobin and heme are released into the circulation, with consequent scavenging of nitric oxide, endothelial injury, elaboration of proinflammatory cytokines and cellular adhesion molecules. The WBC in the multiple linear regression model independently predicted cerebral blood flow velocity, a major risk factor in development of CVA in children with SCD. Study by Conran and colleagues observed that severity of SCD is associated with increased WBC count while a reduction ameliorates the severity of the disease[7,43]. The platelet count, absolute monocyte count and oxygen saturation had medium strength of association with the class of TAMMV as these are important risk factors for development of conditional or abnormal TAMMV and stroke in sickle cell disease.

In the multiple linear regression model, patient's age, total WBC, absolute neutrophil and monocyte counts, and HbF, were independently associated with cerebral blood flow velocity. Studies by Quinn et al observed inverse relationship between TAMMV and SpO_2 and hematocrit[37]. Also in the multivariate model by Makani et al, it was observed that low $SPO_2 \leq 95\%$, young age and a history of fever were associated with high cerebral blood flow velocity[31]. There is a dearth of information on a direct relationship between TAMMV and WBC, although Colombatti et al recently report an association between it and increased leukocyte count[44]. The final consequence of cerebral vasculopathy in SCD is vascular stenosis, which results from vascular smooth muscle remodeling, hyperplasia and hypertrophy. All these result from chronic inflammation, which is directly or indirectly triggered by hemolysis, adherence of sickle red cells and other cells to vascular endothelium, elaboration of proinflammatory cytokines and activation of proinflammatory cells[45].

Children who had suffered ACS/pneumonia or recurrent painful crises had higher probability of having an abnormal or conditional cerebral blood flow velocity. ACS is an acute illness characterized by fever, acute respiratory symptoms, new pulmonary infiltrates on chest X-ray and hypoxia. This complication may result from pulmonary infection (pneumonia) or fat embolism from necrotic bone infarction, resulting in fall in pulmonary oxygen tension, oxygen desaturation, sickle hemoglobin polymerization, red blood cell sickling leading to hemolysis and inflammation[35]. ACS is a known risk factor of stroke and other encephalopathies in patients with SCA[7,46]. Pulmonary hypoxia from ACS can predispose to reduction in delivery of oxygenated blood to cerebral tissues with resultant cerebral vascular endothelial injury, cerebral arterial smooth muscle modeling, stenosis with cerebral ischemia and stroke. Recurrent vaso-occlusion and pain with subsequent reperfusion injury, endothelial activation, inflammation and vascular smooth muscle hyperplasia and hypertrophy predisposes to cerebral vessel stenosis and increased risk of elevated TAMMV and ischemic stroke in sickle cell disease.

Conclusion

The frequency of abnormal TCD result was low in children with SCD in Salvador. Children with HbSS and those with past history of acute chest syndrome or recurrent vaso-occlusive episodes are more likely to have abnormal result while TAMMV correlated negatively with hematocrit, peripheral oxygen saturation and age, and positively with white cell and platelet counts. In facilities where universal TCD screening is not possible, priority may be given to those with HbSS, low oxygen saturation, past history of ACS, recurrent painful crisis or abnormally high leukocyte and platelet counts.

The study was limited by a few number of patients with abnormal or conditional TCD results, making it difficult to have a statistically reliable conclusion. The retrieval of haematological profile of the patients from the medical records was also a limitation as the values may not represent the true values as at time of TCD. There was also no documentation of the specific indications for use of HU among individual patients on the medication. Further studies with more patients and documentation of blood cellular values at time of TCD are required.

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Anexo 7. Folha de Aprovação

UNIVERSIDADE FEDERAL DA BAHIA
Faculdade de Medicina da Bahia
Programa de Pós-graduação em Ciências da Saúde
Largo do Terreiro de Jesus, s/n. Centro Histórico
40.026-010 Salvador, Bahia, Brasil.
Tel.: 55 71 3283.5582 | Fax: 55 71 3283.5567
www.possaude.ufba.br | pos.saude@ufba.br

THIAGO GONÇALVES FUKUDA

Aspectos Clínicos e Prognósticos de Pacientes com Diagnóstico de Doença do Espectro da Neuromielite Óptica.

Tese apresentada como requisito para obtenção do grau de Doutor em Ciências da Saúde do Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal da Bahia.

Aprovada em: 08/11/2024

Banca Examinadora

Prof. Dr Jamary Oliveira Filho
Doutor em Neurologia/USP
Professor Titular/UFBA (Presidente/ Orientador)

Prof. Dr. Pedro Antonio Pereira de Jesus
Doutor em Medicina e Saúde/ UFBA
Professor Adjunto/UFBA

Prof. Dr. Rafael Miranda Sousa
Doutor em Oftalmologia/USP
Professor Adjunto/UFBA

Prof. Dr. Eduardo Souza Cardoso
Doutor em Medicina e Saúde/ UFBA
Professor/UNEB

Profa. Dra. Samira Luisa Apóstolos Pereira
Doutora em Neurologia/FMUSP
Médica Hospital das Clínicas/USP.

Programa de Pós-Graduação em Ciências da Saúde – 08/11/2024