NEUROMIELITE ÓPTICA

SENADO FEDERAL 06/12/2017

UNIFESP
UNIVERSIDADE FEDERAL DE SÃO PAULO
1933

ESCOLA PAULISTA MEDICINA
1933

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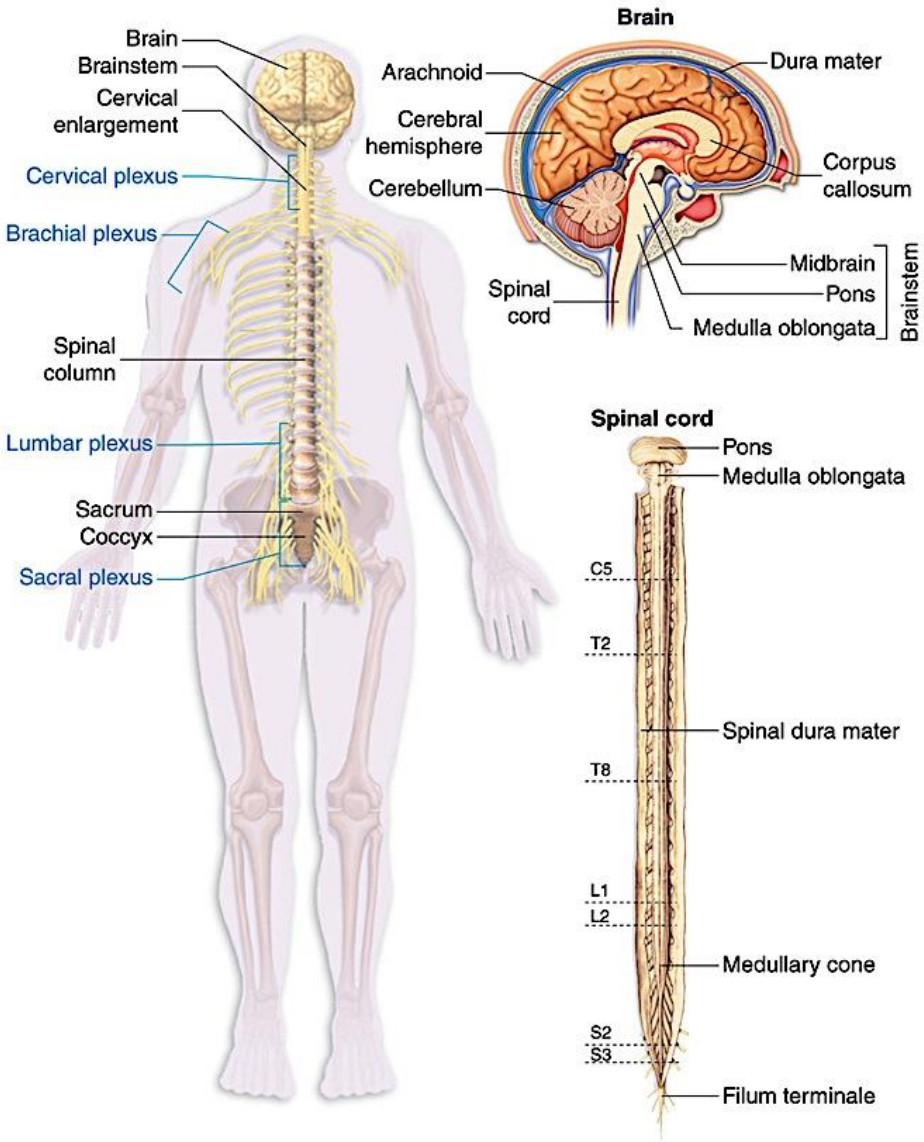
PROGRAMA

1. O que é neuromielite óptica
2. Situação atual no Brasil
3. Necessidades não atendidas

DEFINIÇÕES

- Doenças desmielinizantes do sistema nervoso central
  - Esclerose múltipla
  - Neuromielite óptica

General anatomy of the central nervous system

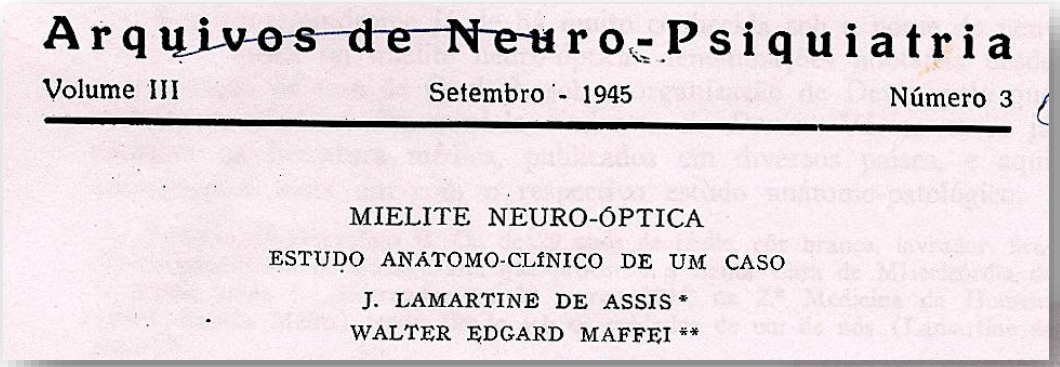


ESCLEROSE MÚLTIPLA

- 3,0 milhões de pessoas com EM
- A prevalência varia ao redor do mundo
- **30 a 40/100.000 no Brasil**
- **40.000 pessoas no Brasil**
- Frequência duas vezes mais alta em mulheres do que em homens
- Causada por uma interação complexa de fatores ambientais e genéticos
- Média de idade de início precoce: 20 a 40 anos de idade
- EUA: principal causa de incapacidade e aposentadoria em pessoas < 50 anos
- Escandinava: 50% pessoas com EM desempregados < 40 anos

HISTÓRICO – NMO

- Primeiros relatos brasileiros
  - Aluizio Marques (1943)
  - Assis e Maffei (1945)
  - Assis, Aidar e Lombardi (1951)



Arquivos de Neuro-Psiquiatria

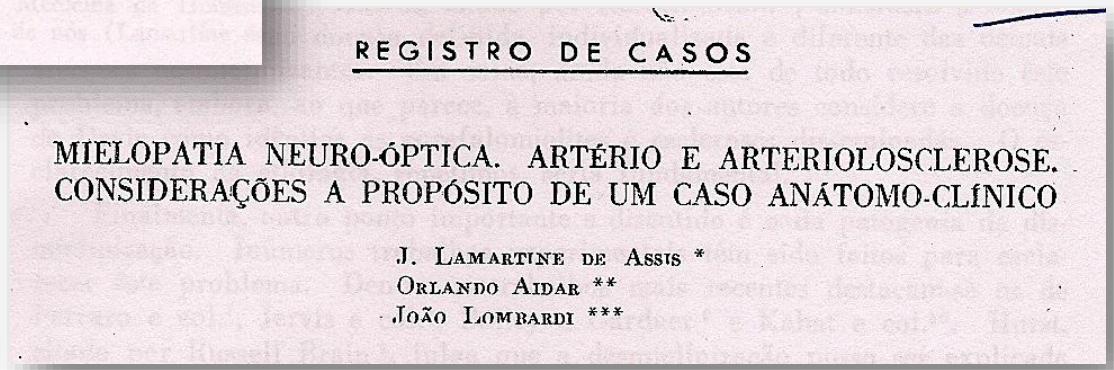
Volume III Setembro - 1945 Número 3

MIELITE NEURO-ÓPTICA

ESTUDO ANATOMO-CLÍNICO DE UM CASO

J. LAMARTINE DE ASSIS *

WALTER EDGARD MAFFEI **



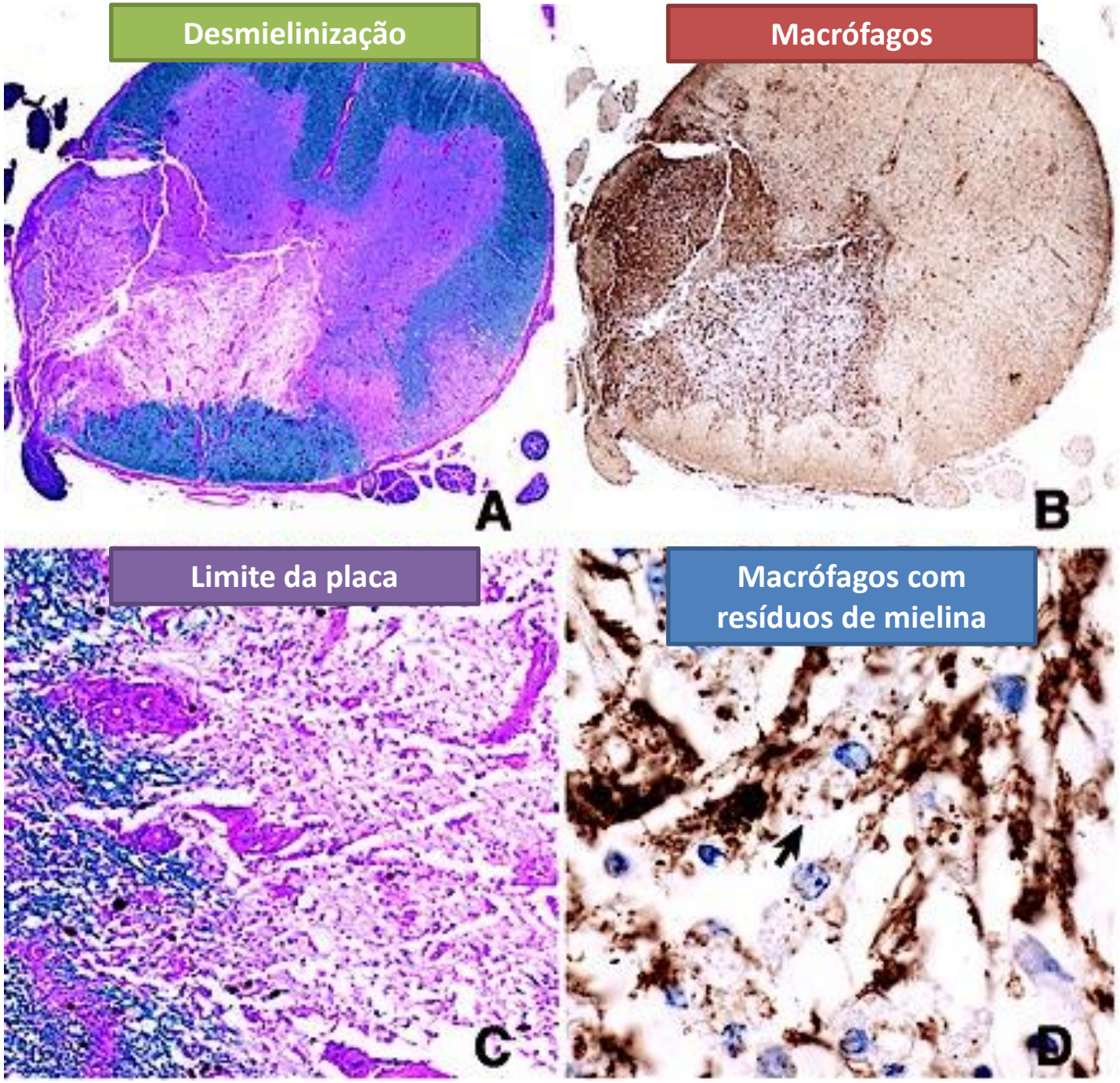
REGISTRO DE CASOS

MIELOPATIA NEURO-ÓPTICA. ARTÉRIO E ARTERIOLOSCLEROSE. CONSIDERAÇÕES A PROPÓSITO DE UM CASO ANÁTOMO-CLÍNICO

J. LAMARTINE DE ASSIS *

ORLANDO AIDAR **

JOÃO LOMBARDI ***

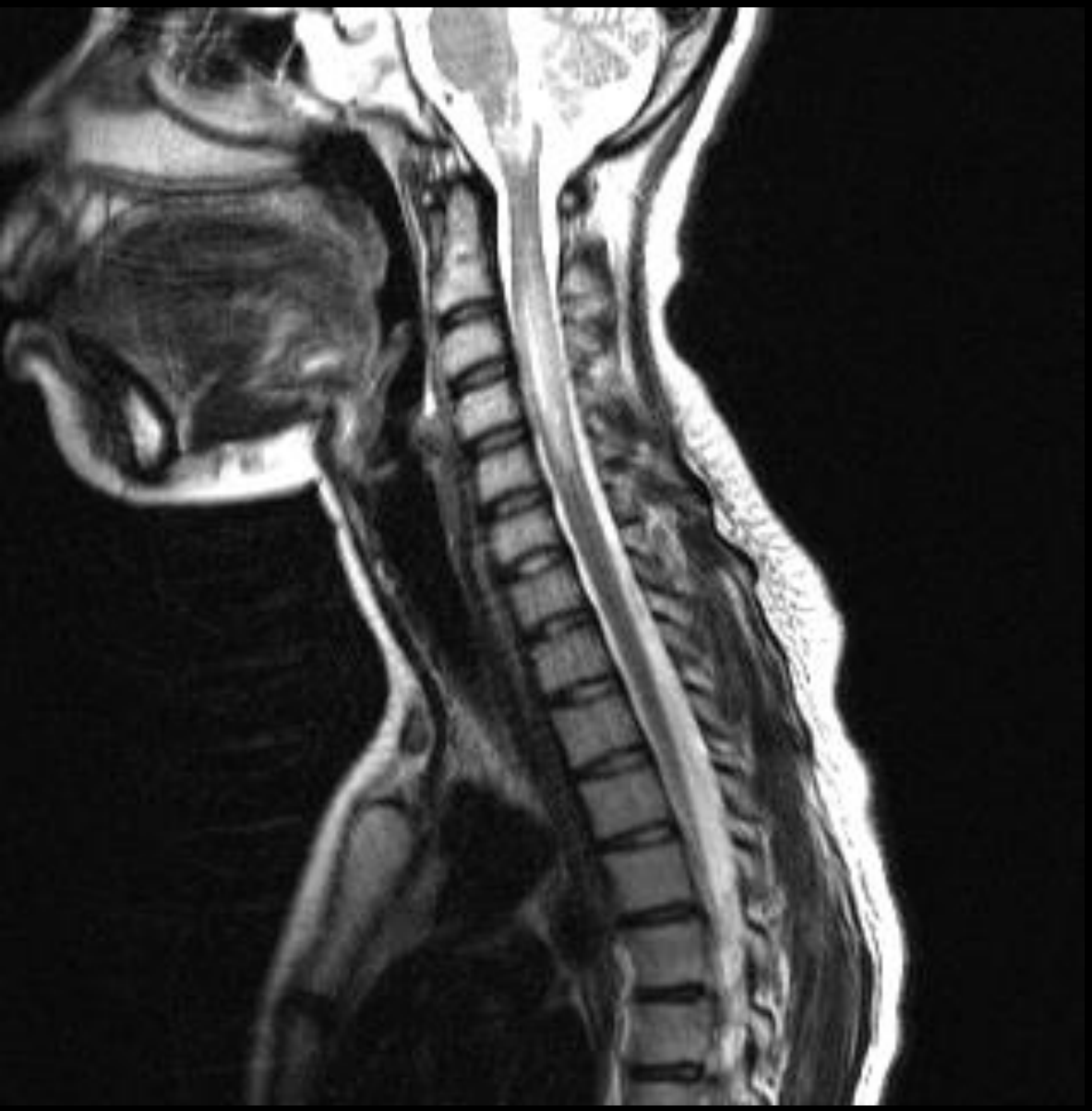


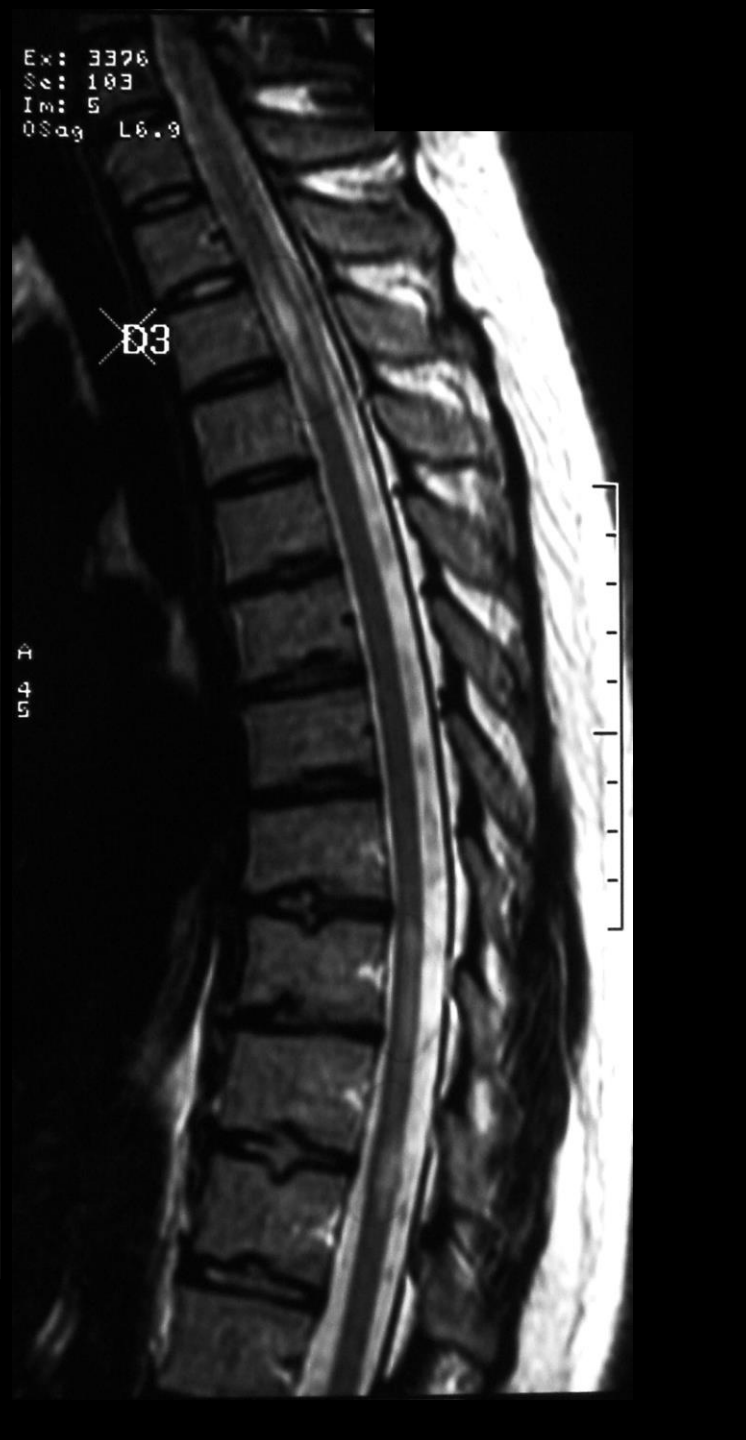
Brain 2002;125:1450

NEUROMIELITE: SINTOMAS

- Crises
  - Perda visual
  - Perda de força: paraplegia, tetraplegia, hemiplegia
  - Bexiga neurogênica (incontinência urinária)
- Sequelas permanentes
  - Cegueira
  - Perda de mobilidade ➔ bengala, andador e cadeira de rodas
  - Espasmos crônicos (caimbras)
  - Dor neuropática

Neuromyelitis Optica. Multiple Sclerosis and Demyelinating Diseases (2006); 98: 39
Weinchenker 2017. Mayo Clin Proc. 92(4):663-679

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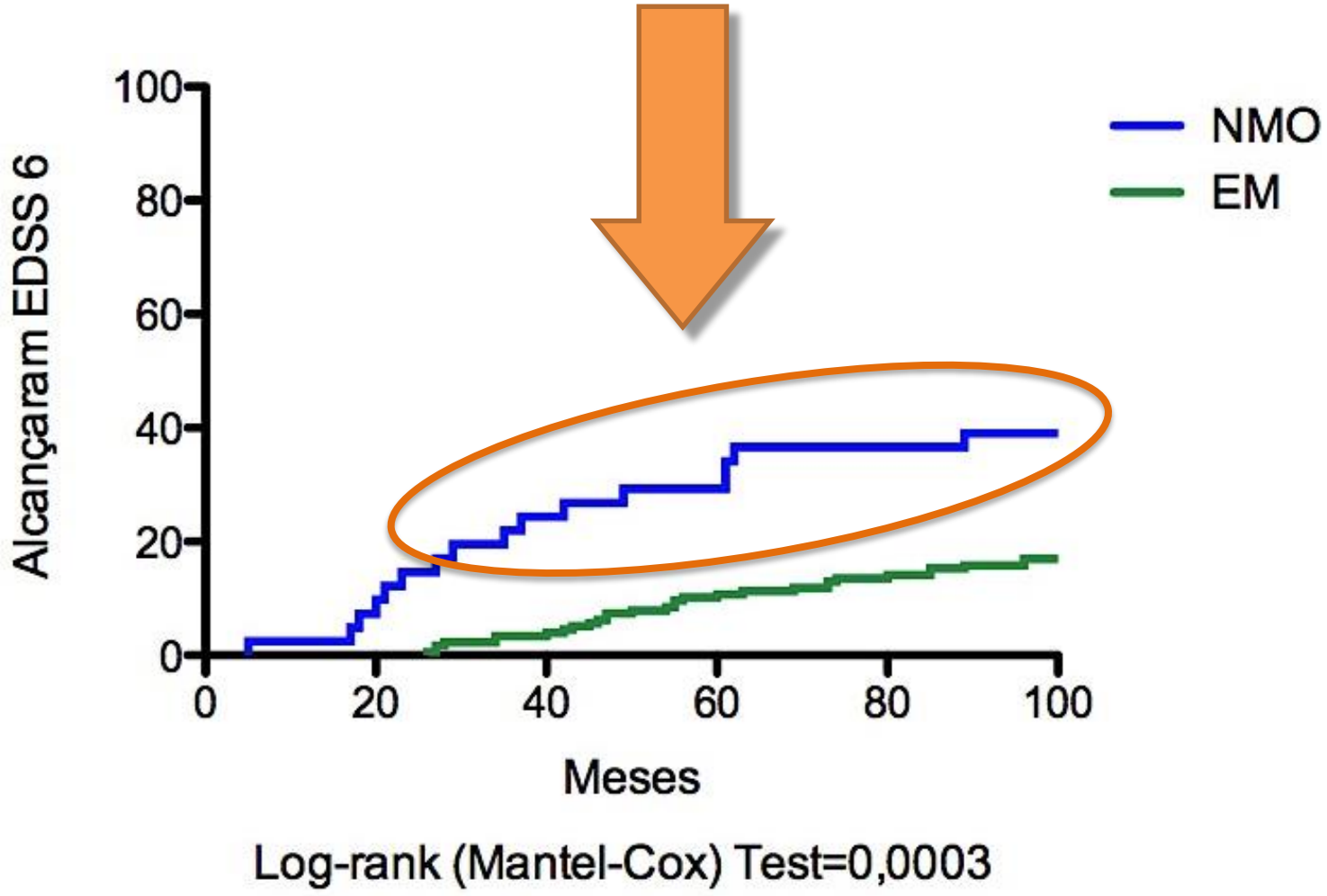
Pacientes com neuromielite óptica dependem de auxilio para andar muito antes de pacientes com esclerose múltipla



Bchuetti, Arquivos de Neuropsiquiatrtia 2013;71:275

NMO X EM

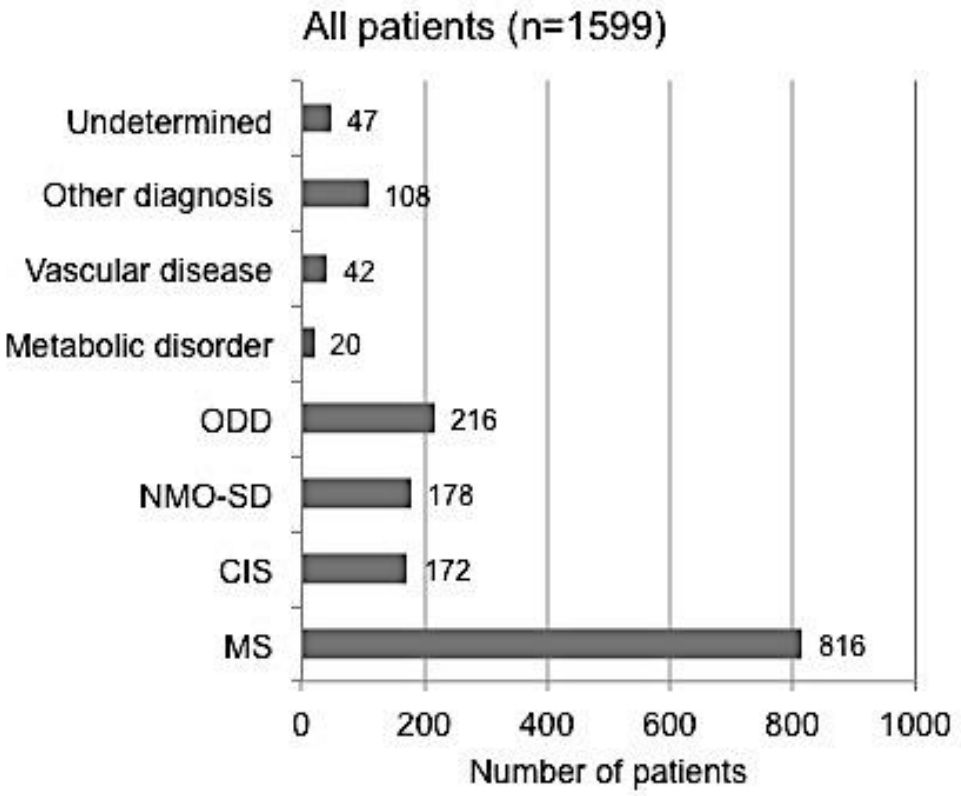
	NMO (n=41)	MS (n=177)	p-value
Age of onset (years)	32.6 (±11.5)	30.2 (±10.5)	0.2062
Sex (F:M)	2.4:1	3.8:1	0.3429
Ethnicity			<0.0001
Caucasian	18 (44%)	127 (72%)	
African	11 (24%)	5 (3%)	
Asian	2 (5%)	0 (0%)	
Mulatto	10 (24%)	45 (25%)	
Disease duration (years)	7.4 (±4.9)	10.3 (±7.6)	0.0239
Time to first evaluation (months)	37.2 (±47.4)	69.0 (±86.6)	0.0368
EDSS first evaluation	3.9 (±1.7)	2.4 (±2.0)	<0.0001
EDSS last evaluation	5.2 (±2.7)	3.6 (±2.7)	0.0013
Annualized relapse rate	1.0 (±0.8)	0.8 (±0.9)	0.0079
Progression index	0.9 (±0.7)	0.6 (±1.0)	<0.0001
Patients reaching EDSS 6, n (%)	16 (39%)	30 (17%)	0.0036
Patients deceased	5 (12%)	2 (1%)	0.0017

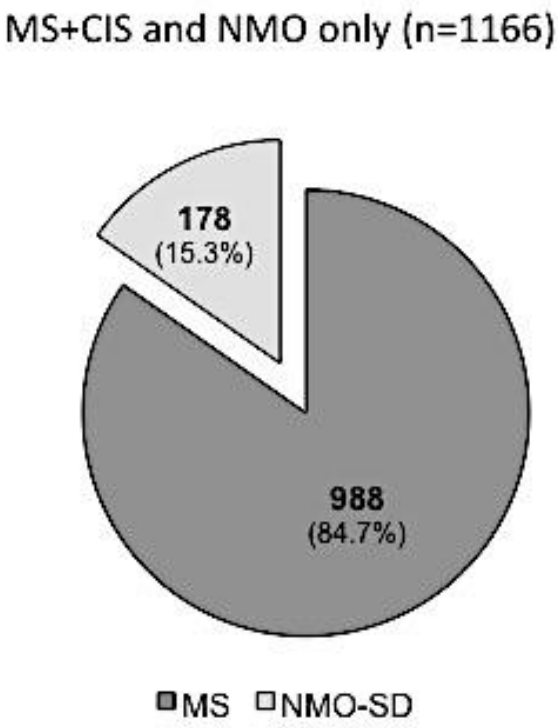
EDSS 6 = necessidade de bengala

12% de mortalidade em 8 anos

Bchuetti, Arquivos de Neuropsiquiatrtia 2013;71:275

EPIDEMIOLOGIA





- 15% dos pacientes com doença desmielinizante autoimune e primária do SNC em um centro especializado devem ter NMO-SD.
- Se EM = 40/100.000 ➔ **NMO = 4-6/100.000? (4.000 a 6.000 pacientes?)**
- 500.000 pacientes globalmente (?)

Bichuetti 2015. Arq Neuropsiquiatr;73(4):1

TRATAMENTO

- Poucos trabalhos publicados
- “Neuromyelitis optica / Devic treatment” ~ 100 referências (meio de 2014)
- Nenhum trabalho prospectivo duplo cego de longa duração e com número de alto de pacientes
- Poucos consensos escritos

Medication	Date	Lead author	Location	Population size
Azathioprine	1998	Mandler	United States	7
	2008	McKeon	United States	10
	2010	Bichuetti	Brazil	25
	2010	Sarhaian	Iran	28
	2011	Constanzi	United States	99
	2014	Elsone	United Kingdom	103
	2015	Qiu	China	77
Mycophenolate	2009	Jacob	United States	24
	2014	Mealy	United States	28
	2014	Huh	South Korea	59
Rituximab	2005	Cree	United States	8
	2008	McKeon	United States	8
	2008	Jacob	United States	25
	2011	Bedi	United States	23
	2011	Pellkofer	Germany	10
	2011	Kim	South Korea	30
	2013	Ip	China	7
	2013	Gredler	Austria	6
	2014	Mealy	United States	30
	2014	Dale	Australia	20
	2015	Fernandez-Megia	Spain	6
	2015	Kim	South Korea	100
	2015	Zephir	France	32
	2015	Radaelli	Italy	21
	2015	Collongues	France	11
Methotrexate	2000	Minagar	United States	8
	2013	Kitley	United Kingdom	14
Oral corticosteroids	2007	Watanabe	Japan	11
Mitoxantrone	2006	Weinstock-Guttman	United States	5
	2011	Kim	Korea	20
	2013	Cabre	French West Indies	51
Eculizumab	2013	Pittock	United States	14
Tocilizumab	2014	Araki	Japan	7
	2015	Ringelstein	Germany	8

Kessler 2016. Curr Treat Options Neurol; 18(1): 2

TRATAMENTO NMO

Crise / Surto	Prevenção
• Metilprednisolona 3-10g	• Prednisona 0-1mg/kg
• Plasmaferese	• Azatioprina 3mg/kg
• Imunoglobulina	• Metotrexato 15-25mg
• Leucoaferese	• Micofenolato 2-3g
	• Rituximabe
	• Tocilizumabe
	• Eculizumabe

- **SUS e Saúde Suplementar**
  - **Disponivel**
  - **Acesso restrito**
  - **Não disponível**

Weinchenker 2017. Mayo Clin Proc. 92(4):663-679
Kessler 2016. Curr Treat Options Neurol; 18(1): 2

CUSTO POR MEDICAMENTO (U$)

Drug	Dose	Daily use	Unitary Cost	Annual Doses	Annual Cost
Prednisone	5mg	2tb/day (10mg)	$0,58	730	**$424,31**
Azatioprine	50mg	3tb/day (150mg)	$2,11	1095	**$2.310,45**
Mycophenolate	500mg	2,5tb/day (2.500mg)	$7,93	1825	**$14.464,77**
Rituximab	500mg	2g every 6 months	$5.011,32	8	**$40.090,56**

Combos		Annual Cost	5year cost	10year cost
Pred + AZA		$2.734,76	$13.673,81	**$27.347,63**
Pred + MMF		$14.889,08	$74.445,40	**$148.890,80**
Rituximab		$40.090,56	$200.452,80	**$400.905,60**

UpToDate Drug information. April 2017

NEUROMYELITIS OPTICA

20-YEAR SINGLE CENTER OBSERVATIONAL DATA

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✉ email: **bichuetti@unifesp.br**

OBJECTIVES

- To present an update on our observational series, previously published in 2009 (Bichuetti. *Mult Scler* 2009; 15; 613)

METHODS

- Observational study, single center
- Prospective cohort with retrospective analysis
- Inclusion criteria
  - NMO as per 2006 or 2015 criteria (Wingerchuk 2006 and 2015)
- Exclusion criteria
  - Absence of retrievable information
  - Single appointment
- Clinical, demographic, radiological and treatment information obtained from medical records
- Treatment efficacy will be further evaluated, but the main goal will be EDSS stability, as retrieval information for all relapses are difficult to obtain
- Patients were divided in two groups: monophasic NMO (mNMO) and relapsing NMO (rNMO). The rNMO was further divided in "all patients", comprising all rNMO patients fulfilling inclusion criteria, and "2013+", intending to include all patients with clinical data available up to 2013, thus excluding those lost to follow-up into a more homogenous group
- Data is presented as median (1st – 3rd quartile) when non parametric and as mean (+/- standard deviation) when parametric, and analyzed according to these results.
- % data is presented on the known information (% of known data) except when disclosed in tables

RESULTS

- 1.748 medical records reviewed up to December 31st 2015
  - 216 possible NMO
  - 37 excluded due to irretrievable information
  - 21 excluded not fulfilling diagnostic criteria
  - 158 patients included
  - 8 monophasic NMO
  - 150 relapsing NMO (115 2013+)
- Each group's information is presented in the tables

Clinical data for the 158 patients

Feature Subjects	mNMO 8	rNMO 150	rNMO – 2013+ 115
Age of onset in years	33.6 (+/-13.3)	33.0 (24.0-43.3)	33.8 (+/-12.3)
Sex (F:M)	1:1	4.4:1	4.2:1
Ethnicity, n (%)			
Caucasian	3 (38%)	77 (51.3%)	52 (45.2%)
Afro descendant (mulatto + afro)	4 (50%)	71 (47.3%)	61 (53.0%)
Asian descendant	1 (13%)	2 (1.3%)	2 (1.7%)
America Indian	0	0	0
Years of follow-up	7.4 (1.5-11.2)		
Years of disease	8.3 (2.8-21.2)		
First relapse, n (%)			
Myelitis			
Optic Neuritis			
Brainstem			
Encephalitic			
Optic Neuritis + Myelitis	8 (100%)		
Optic Neuritis + Brainstem			
Myelitis + Brainstem			
ON + Brainstem + Myelitis			
Encephalitic + Brainstem + Myelitis			
Unregistered			
Months to index event	NA		
Months to 2nd relapse	NA		
Months from 1st relapse to evaluation	17.5 (1.9-51.8)		
EDSS on first appointment	3.0 (2.0-3.0)		
EDSS on last appointment	3.0 (2.0-3.0)		
Relapse Rate	NA		
Progression Index	NA		
Abnormal brain MRI not meeting criteria for MS, n (%)	2 (25.0%)		
Unknown/unavailable, n (%)	3 (37.5%)		
Patients reaching EDSS, n (%)			
3.0	5 (62.5%)		
4.0	1 (12.5%)		
6.0	1 (12.5%)	50 (33.3%)	38 (33.0%)
6.5	1 (12.5%)	44 (29.3%)	32 (27.8%)
7.0	1 (12.5%)	39 (26.0%)	29 (25.2%)
10	0 (0%)	6 (4.0%)	6 (5.2%)
CSF analysis (number of patients available)	5	105	81
WBC/mm³	5.0 (3.5-21.5)	7.0 (2.0-19.5)	5.0 (2.0-18.0)
> 50 WBC/mm³, n (%)	0 (100%)	15 (14.3% of 105)	13 (16.0% of 81)
OCB (analyzed/+)	1/0	32/5	26/4
NMO-IgG, tested/positive (%)	6/0 (0%)	126 (54.0%)	107 (52.3%)
Patients fulfilling 2015 NMOSD criteria			
Yes	NA	124 (82.7%)	97 (84.3%)
No		18 (12.0%)	16 (13.9%)
Incomplete information		8 (5.3%)	2 (1.7%)
NMOSD, n (%)			
rNMO	NA	112 (74.7%)	87 (75.7%)
rLETM		16 (10.7%)	13 (11.3%)
rON		22 (14.7%)	15 (13.0%)
Comorbid autoimmunity	1 (12.5%)	29 (19.3%)	25 (21.7%)

Brain MRI lesion sites (%)

	Medulla	Pons	Midbrain	Optic Chiasm	Diencephalon	Internal Capsule	Corpus Callosum	Cerebral White matter*
mNMO 8 (% from 5 exams)	20.0							20.0
rNMO 150 (% from 140 exams)	43.8	23.3	20.5	12.3	17.8	8.2	15.1	72.6
rNMO 115 – 2013+ (% from 108 exams)	45.6	21.1	19.3	12.3	22.8	7.0	14.0	71.9

Comparison between normal and abnormal brain MRI, 150 patients

	150			115 – 2013+		
	Normal MRI	Abnormal MRI	p value	Normal MRI	Abnormal MRI	p value
Age of onset in years [mean (+/- SD)]	32.6 (+/-12.5)	34.3 (+/-12.2)	0.4203	33.0 (+/- 11.9)	33.4 (+/-12.3)	0.8499
Disease duration in years [median(1st-3rd quartiles)]	7.0 (4.0-11.1)	7.7 (3.5-13.9)	0.9947	8.3 (4.7-11.6)	8.2 (4.0-14.1)	0.8899
EDSS on first appointment [median(1st-3rd quartiles)]	3.0 (2.8-4.0)	3.5 (3.0-4.0)	0.4051	3.0 (3.0-4.0)	3.5 (3.0-4.0)	0.1479
EDSS on last appointment [median(1st-3rd quartiles)]	4.0 (3.0-6.4)	4.0 (2.5-6.0)	0.9856	4.0 (3.0-4.0)	4.0 (3.0-6.0)	0.7256
Relapse Rate (RR) [median(1st-3rd quartiles)]	0.6 (0.4-1.0)	0.6 (0.3-0.9)	0.6712	0.6 (0.4-0.8)	0.5 (0.3-0.8)	0.8118
Progression index (PI) [median(1st-3rd quartiles)]	0.4 (0.3-1.0)	0.6 (0.3-1.3)	0.5434	0.4 (0.3-0.8)	0.4 (0.3-1.0)	0.8038

DISCUSSION / CONCLUSIONS

- This cohort has similar clinical ad demographic characteristics that previously presented
- Most patients fulfill 2015 NMO criteria, though 13% remain unclassified. Most of these are patients with relapsing optic neuritis or relapsing LETM negative for anti-AQP4. Anti-AQP4 methodology might be one cause for the negative results. Most Brazilian laboratories did not offer CBA until late 2016
- Nearly 90% of the patients are beyond EDSS 3.0 and 30% EDSS 6.0. This is a little less than our previous analysis (Bichuetti 2009) and might be influenced by better treatment protocols
- Patients with brain MRI abnormalities did not have a more severe disease
- Treatment and prognostic analysis are being performed and will be presented later this year

References: Bichuetti 2009. Neuromyelitis optica in Brazil: a study on clinical and prognostic factors. Mult Scler. 2009 May;15(5):613-9. Bichuetti 2010. Neuromyelitis optica treatment: analysis of 36 patients. Arch Neurol. 2010 Sep;67(9):1131-6. Pittock 2006. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. Arch Neurol. 2006 Jul;63(7):964-8.Sellner 2010. EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol. 2010 Aug;17(8):1019-32.Wingerchuk 2006. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006 May 23;66(10):1485-9.Wingerchuk 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul 14;85(2):177-89.

Disclosures: Bichuetti DB has received speaking honoraria from Bayer Health Care, Roche, TEVA and Merck Serono and travel expenses to scientific meetings from Bayer Health Care, Merck Serono, Novartis and TEVA. Souza NA received travel expenses to scientific meetings from Bayer Health Care, Merck Serono and TEVA. Oliveira EML has received compensations for participating in meetings sponsored by Bayer Health Care, Biogen Idec, Merck Serono, and Teva Pharmaceuticals.

Neuromyelitis Optica
20-year single center observational data

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70% sem piora clínica com tratamento de primeira linha = azatioprina

when parametric, and analyzed according to these results.
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RESULTS

- 1.748 medical … up to December 31st 2015
  - 216 pos…
  - 37 excluded … able information
  - 21 excluded … agnostic criteria
  - 158 patients i…
  - **8 monophas…**
  - **150 relapsin…**
- Each group's in… resented in the table
- All patients in th… p received at least one preventive treat… g disease modifying therapies for m… s (16), prednisone (101), azathioprine (1… nolate (4), cyclosporine (2), methotrexate (20), cyclophosphamide (16), rituximab (2) or IV immunoglobulin (8)
- **EDSS variation under treatment**
  - 0 - 0.5 70.0%
  - 1.0 - 1.5 12.7%
  - 2.0 - 2.5 6.0%
  - 3.0 - 3.5 4.7%
  - ≧ 4.0 6.7%
- **6 patients were deceased during follow-up**

Clinical data for the 158 patients

Feature Subjects	mNMO 8	rNMO 150
Age of onset in years	33.6 (+/-13.3)	33.0 (24.0-43.3)
Sex (F:M)	1:1	4.4:1
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Afro descendant (mulatto + afro)	4 (50%)	71 (47.3%)
Asian descendant	1 (13%)	2 (1.3%)
America Indian	0	0
	7.4 (1.5-11.2)	4.6 (2.1-8.7)
	8.3 (2.8-21.2)	7.0 (3.7-12.6)
		60 (40.0%)
		56 (37.3%)
		9 (6.0%)
		2 (1.3%)
+ Myelitis	8 (100%)	13 (8.7%)
+ Brainstem		2 (1.3%)
instem		5 (3.3%)
em + Myelitis		1 (0.7%)
+ Brainstem + Myelitis		1 (0.7%)
		1 (0.7%)
vent	NA	11.6 (2.0-36.1)
se	NA	11.3 (3.1-25.9)
ntment	3.0 (2.0-3.0)	3.0 (3.0-4.0)
EDSS on last appointment	3.0 (2.0-3.0)	4.0 (3.0-6.5)
Abnormal brain MRI not meeting criteria for MS, n (%)	2 (25.0%)	73 (48.7%)
Unknown/unavailable, n (%)	3 (37.5%)	10 (6.7%)
Patients reaching EDSS, n (%)		
3.0	5 (62.5%)	126 (84.0%)
4.0	1 (12.5%)	88 (58.7%)
6.0	1 (12.5%)	50 (33.3%)
6.5	1 (12.5%)	44 (29.3%)
7.0	1 (12.5%)	39 (26.0%)
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NMOSD, n (%)		
rNMO		112 (74.7%)
rLETM	NA	16 (10.7%)
rON		22 (14.7%)
Comorbid autoimmunity	1 (12.5%)	29 (19.3%)

DISCUSSION / CONCLUSIONS

- Most patients fulfill 2015 NMO criteria
- 13% did nod fulfill 2015 NMO criteria, most are relapsing optic neuritis or relapsing LETM anti-AQP4 negative
- 90% have EDSS ≦ 3.0 and 30% EDSS ≦ 6.0. This is less than our previous analysis and might be influenced by earlier interventions and better treatment protocols
- 82.7% of patients treated with immunosuppressants, most of them azathioprine and methotrexate +/- prednisone, remained stable or with minimal EDSS variation during the 8 years of follow-up
- Early diagnosis and treatment implementation might have contributed to this result, which is important for those practicing in countries with restricted access to monoclonal antibodies

References: Bichuetti 2009. Neuromyelitis optica in Brazil: a study on clinical and prognostic factors. Mult Scler. 2009 May;15(5):613-9. Bichuetti 2010. Neuromyelitis optica treatment: analysis of 36 patients. Arch Neurol. 2010 Sep;67(9):1131-6. Sellner 2010. EFNS guidelines on diagnosis and management of neuromyelitis optica. Eur J Neurol. 2010 Aug;17(8):1019-32.Wingerchuk 2006. Revised diagnostic criteria for neuromyelitis optica. Neurology. 2006 May 23;66(10):1485-9.Wingerchuk 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology. 2015 Jul 14;85(2):177-89.

INICIATIVAS

- Médicos e universidades brasileiras focados em pesquisa
  - Identificar pacientes
  - Selecionar terapias
  - Prevenir sequelas
- Associações de pacientes
  - ABEM
- Associações internacionais
  - Guthy Jackson Charitable Foundation

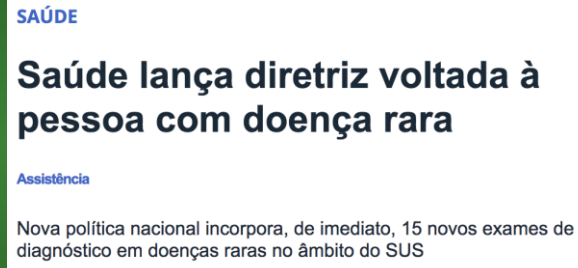
abem
Associação Brasileira de Esclerose Múltipla

GUTHY JACKSON
Charitable Foundation

UNIFESP
UNIVERSIDADE FEDERAL DE SÃO PAULO

PESQUISAS BRASILEIRAS

Governo do Brasil



SAÚDE

Saúde lança diretriz voltada à pessoa com doença rara

Assistência

Nova política nacional incorpora, de imediato, 15 novos exames de diagnóstico em doenças raras no âmbito do SUS

- Atualmente, o SUS conta com **25 tratamentos protocolados e oferta medicamentos para as seguintes doenças raras**: Angiodema Hereditário, Deficiência de Hormônio do Crescimento (Hipopituitarismo), Doença de Gaucher, Doença de Wilson, Fenilcetonúria, fibrose cística, hiperplasia adrenal congênita, ictioses hereditárias, síndrome de Turner, hipotiroidismo congênito, osteogêneses imperfeita. **E NMO?**
- O conceito de doença rara utilizado pelo Ministério da Saúde é o mesmo recomendado pela Organização Mundial de Saúde (OMS), ou seja, de doença que afeta até **65 pessoas em cada 100 mil indivíduos** (1,3 para cada duas mil pessoas). As doenças raras são caracterizadas por ampla diversidade de sinais e sintomas e variam não só de doença para doença, mas também de pessoa para pessoa. No Brasil, cerca de 6% a 8% da população (cerca de 15 milhões de brasileiros) pode ter algum tipo de doença rara. Estima-se que 80% das doenças raras têm causa genética e as demais têm causas ambientais, infecciosas, imunológicas, entre outras.
- A Política Nacional de Atenção Integral às Pessoas com Doenças Raras no SUS foi construída de forma participativa com a sociedade civil. Em 2012, foi instituído um **Grupo de Trabalho (GT), pelo Ministério da Saúde, que contou com a participação de representantes de Sociedades/Especialistas e Associações de Apoios às Pessoas com Doenças Raras**, para elaboração de dois documentos que subsidiaram a criação da Política. Esses documentos foram submetidos à consulta pública e diversas contribuições foram recebidas.

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http://www.brasil.gov.br/saude/2014/01/saude-lanca-diretriz-voltada-a-pessoa-com-doenca-rara

NECESSIDADES NÃO ATENDIDAS

- Reconhecimento do CID G 36 (Neuromielite óptica) como doença, deficiência e incapacidade
- Ministério da Saúde
  - Protocolos Clínicos e Diretrizes Terapêuticas (PCDT) ➔ **NÃO EXISTE**
- Exame diagnóstico: **anticorpo antiaquaporina 4**
- Terapias de tratamento de crise: Plasmaferese e imunoglobulina com acesso restrito em muitos lugares

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