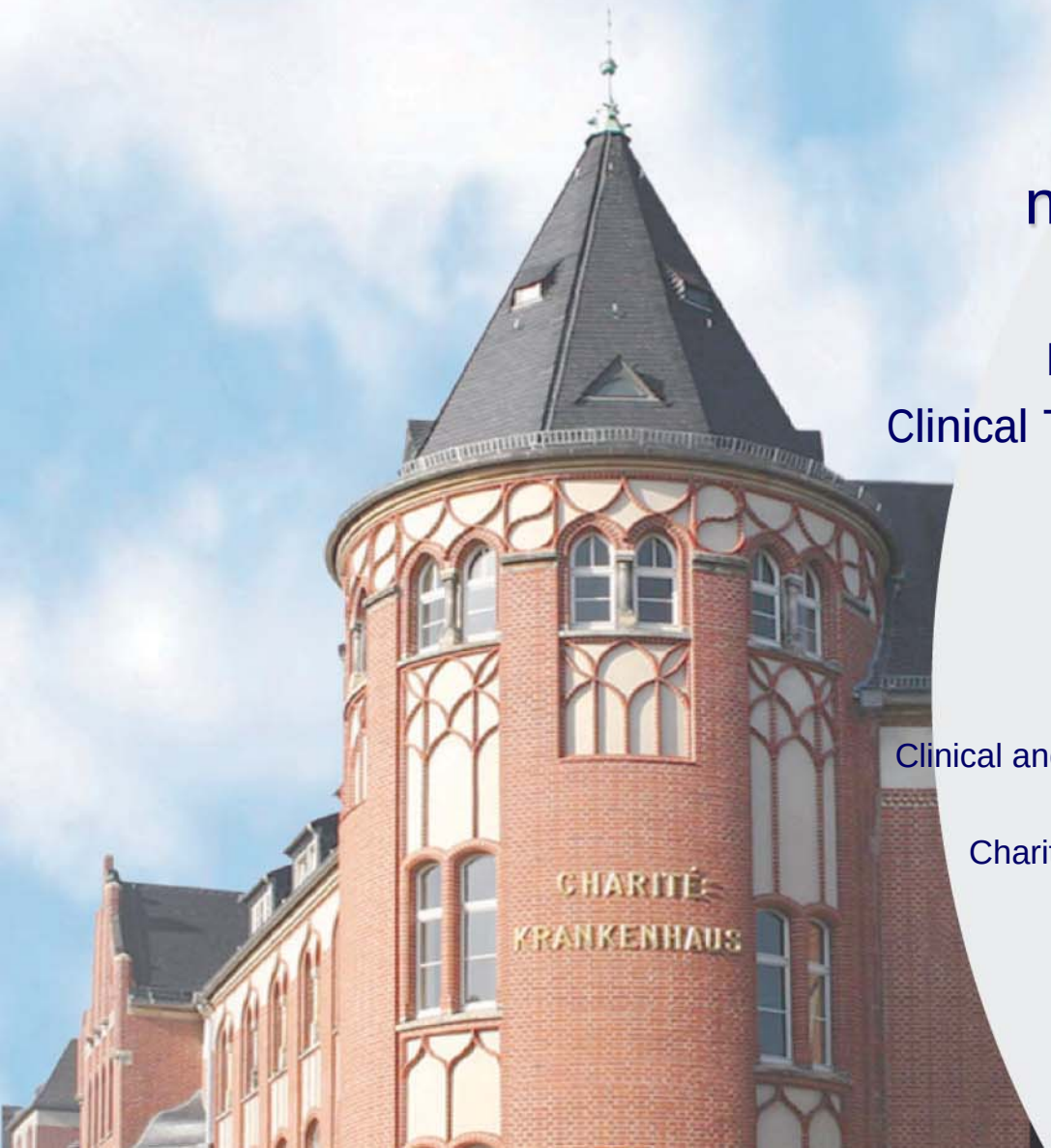

Natural history of neuromyelitis optica

EMA Regulatory Workshop on
Clinical Trials Designs in Neuromyelitis Optica and Spectrum Disorders
London, 10 October 2014

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Previous data on NMO cohorts (selection)

Country	N	Reference
UK	12	O'Riordan et al. J Neurol Neurosurg Psychiatry 1996
USA	71/80	Wingerchuk et al. Neurology 1999; Wingerchuk and Weinshenker Neurology 2003
USA	96	Wingerchuk et al. Neurology 2006
Italy	46	Ghezzi et al. J Neurol 2004
France	13	De Seze et al. J Neurol Sci 2002
France	125	Collongues et al. Neurology 2010
Japan	35	Takahashi et al. Brain 2007
Mexico	34	Rivera et al. J Neurol 2008
Germany	175	Jarius et al. J Neuroinflammation 2012
UK	106	Kitley et al. Brain 2012

Differences in ethnicity

Table 2 Demographic and disease-related characteristics of 125 patients with neuromyelitis optica (NMO)

	NMO
Gender, n (%)	
Female	94 (75.2)
Male	31 (24.8)
Ethnicity, n (%)	
White	74 (87)
Nonwhite	11 (13)

Collongues et al. Neurology 2010

NEMOS cohort
Caucasian 175/175 (100%)
Non-Caucasian 0/175 (0%)

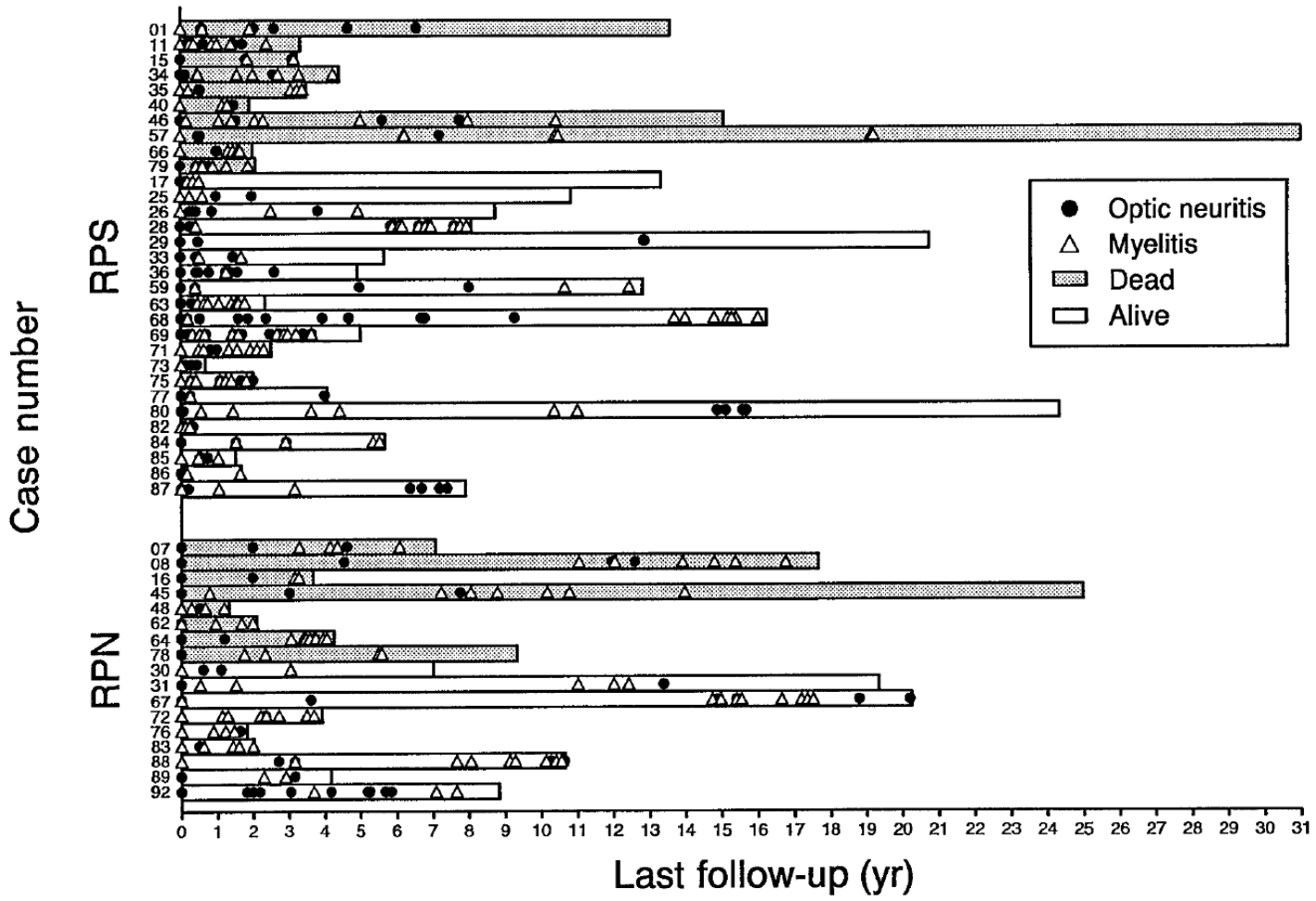
Characteristic	Valid n	NMO
N (total)	129	96
Female, n (%)	127	80/94 (85.1)
Non-caucasian, n (%)	119	35/91 (38.5)
Mean age of onset, y (SD)	123	37.8 (18.1)

Wingerchuk et al. Neurology 2006

The clinical course of neuromyelitis optica (Devic's syndrome)

Dean M. Wingerchuk, MD, FRCP(C); William F. Hogancamp, MD; Peter C. O'Brien, PhD; and Brian G. Weinshenker, MD, FRCP(C)

Neurology 1999



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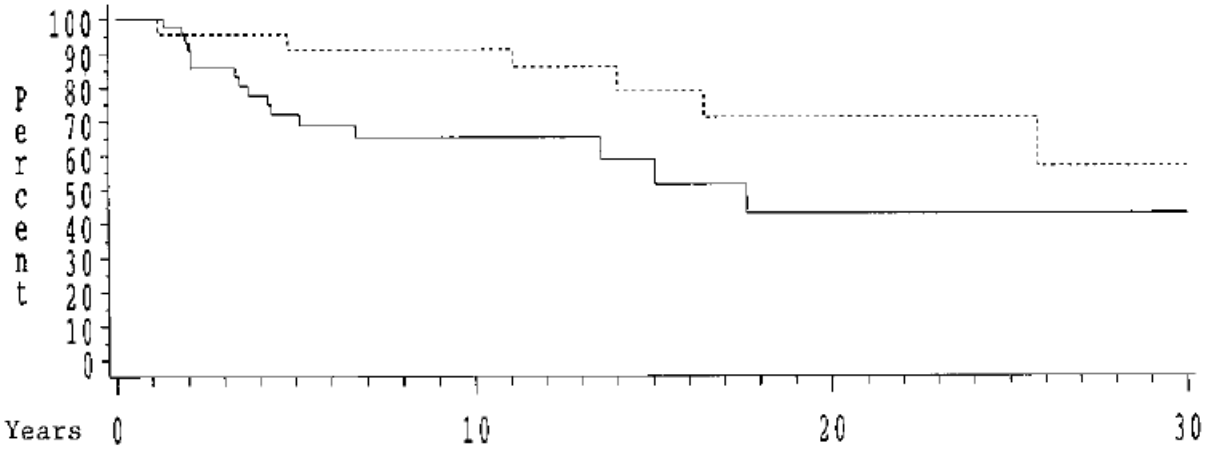


Figure 3. Survival analysis of patients with a monophasic (dashed line) and relapsing (solid line) course.

- 60 % of relapsing patients were functionally blind in at least one eye
- 52% of relapsing patients had permanent monoplegia or paraplegia

Conclusions: Clinical, laboratory, and imaging features generally distinguish neuromyelitis optica from MS. Patients with relapsing optic neuritis and myelitis may have neuromyelitis optica rather than MS. Patients with a relapsing course of neuromyelitis optica have a poor prognosis and frequently develop respiratory failure during attacks of cervical myelitis.

Neuromyelitis optica

Clinical predictors of a relapsing course and survival

Dean M. Wingerchuk, MD, FRCP(C); and Brian G. Weinshenker, MD, FRCP(C)

Table 4 *Multivariable predictive model of relapsing NMO*

Predictor	Odds ratio	95% CI		*p* Value
		Lower	Upper	
Age at onset, y	1.08	1.01	1.16	0.017
Sex	0.10	0.02	0.95	0.048
Nadir: motor	0.48	0.27	0.85	0.011
Time event 1 to 2 mo	2.16	1.23	3.79	0.007

Overall log likelihood = −17.937; $p < 0.001$.

Table 6 *Multivariable predictive model of survival time in relapsing NMO*

Predictor	Rate ratio	95% CI		*p* Value
		Lower	Upper	
History of autoimmune disease	4.15	1.49	11.56	0.0065
Recovery: motor	1.84	1.20	2.82	0.0049
Attack frequency: first 2 years	1.21	1.03	1.42	0.0065

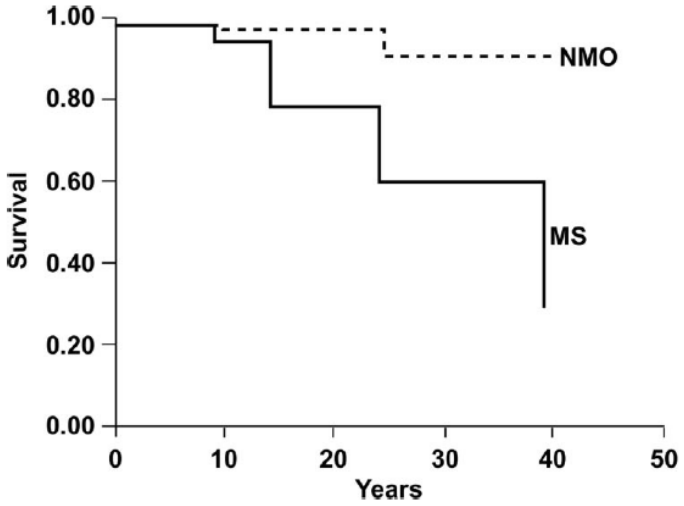
Model overall *p* value = 0.0005.

Neurology 2003

A secondary progressive clinical course is uncommon in neuromyelitis optica

D.M. Wingerchuk, MD, FRCP(C); S.J. Pittock, MD; C.F. Lucchinetti, MD; V.A. Lennon, MD, PhD; and B.G. Weinshenker, MD, FRCP(C)

Abstract—We compared the clinical course of 96 patients with neuromyelitis optica (NMO) to multiple sclerosis (MS) natural history data. Based on the distribution of follow-up data (median 6.1 year), we estimated that 21 NMO patients would convert to a secondary progressive course, but we observed only two conversions ($p = 0.00002$; relative risk = 0.08). The disparate natural histories of MS and NMO suggest dissociation between relapses and clinical progression in CNS demyelinating diseases.



Neurology 2007

Table 2 *Characteristics of NMO patients with a secondary progressive course*

Demographic features			Pre-SP course		SP course onset			Last follow-up	
Sex	Race	Onset age	Relapse no.	Treatments	Disease duration	EDSS	SP features	Disease duration	EDSS
M	African American	38 y	1	Corticosteroids, azathioprine	3 y	3.0	Cervical myelopathy; motor and sensory	8 y	6.5
F	White	30 y	10	Corticosteroids, interferon-β, azathioprine, plasmapheresis	12 y	6.5	Cervical myelopathy; sensory > motor	14 y	8.5

Caveats when assessing natural history in NMO

- Retrospective cohorts
- New diagnostic criteria (Wingerchuk et al. 2006, IPND 2014/2015)
- Increased awareness for the disease owing to broad availability of AQP4 testing
- Subsequently, lower number of misdiagnoses?
- NEMOS cohort: in 43% initial diagnosis of MS (54% before 2005, 20% after 2005)
- Assumption: patients are diagnosed earlier and thus treated earlier
- Increased awareness for detrimental of uneffective MS therapies in NMO (IFN-beta, NAT, FTY)
- How does treatment influence disease course?
- Benign NMO?

Revised diagnostic criteria for neuromyelitis optica

D.M. Wingerchuk, MD, FRCP(C); V.A. Lennon, MD, PhD; S.J. Pittock, MD; C.F. Lucchinetti, MD; and B.G. Weinshenker, MD, FRCP(C)

Table 2 *Diagnostic accuracy for NMO diagnosis of models combining clinical criteria and NMO-IgG status**

Model	Evaluable n (%)	NMO	MS	Sensitivity	Specificity	LR(+)	LR(–)
Model 1							
Cord lesion ≥3 segments AND onset MRI brain nondiagnostic	111/129 (86.1)	79/84 (94.1)	1/27 (3.7)	94 (89–99)	96 (89–100)	25.4 (3.71–174)	0.06 (0.03–0.15)
Model 2	117/129 (90.7)	61/84 (72.6)	2/33 (6.1)	73 (63–82)	94 (85–100)	12.0 (3.11–46.2)	0.57 (0.44–0.71)
NMO-IgG positive AND onset MRI brain nondiagnostic							
Model 3							
Cord lesion ≥3 segments OR NMO-IgG positive	129 (100)	96/96	7/33 (21.2)	100	79 (65–93)	4.71 (2.45–9.10)	0
Model 4							
≥3 segments AND NMO-IgG positive	114/129 (88.4)	63/86 (73.3)	0/28	73 (64–83)	100	∞	0.27 (0.19–0.38)
Model 5							
2 of 3 criteria	121/129 (93.8)	89/90 (98.9)	3/31 (9.7)	99 (97–100)	90 (80–100)	10.2 (3.49–30.0)	0.01 (0.002–0.09)
Cord lesion ≥3 segments							
Onset MRI brain nondiagnostic							
NMO-IgG positive							

* Not all evaluated models are shown.

Parentheses denote percent for proportion or 95% CI for point estimates of sensitivity, specificity, and likelihood ratios (LR).

NMO = neuromyelitis optica; MS = multiple sclerosis.

Neurology 2006

Revised diagnostic criteria for neuromyelitis optica

D.M. Wingerchuk, MD, FRCP(C); V.A. Lennon, MD, PhD; S.J. Pittock, MD; C.F. Lucchinetti, MD; and B.G. Weinshenker, MD, FRCP(C)

Table 3 *Proposed diagnostic criteria for neuromyelitis optica (NMO)*

Definite NMO

- Optic neuritis
- Acute myelitis
- At least two of three supportive criteria
  1. Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
  2. Brain MRI not meeting diagnostic criteria for multiple sclerosis
  3. NMO-IgG seropositive status

Relapsing neuromyelitis optica: long term history and clinical predictors of death

P Cabre,[1] A González-Quevedo,[2] M Bonnan,[1] A Saiz,[3] S Olindo,[1] F Graus,[3] D Smadja,[1] H Merle,[4] L Thomas,[5] J A Cabrera-Gomez[6]

JNNP 2009

- 96 patients from Cuba and French West Indies
- 70% with severe visual loss in one eye, 48% in both
- Median times to DSS 3, 6 and 8 in RNMO were 1, 8 and 22 years
- 25% died after a disease duration of 11 years

Table 2 Multivariate regression analysis of clinical predictors of death in RNMO

Predictor	Hazard ratio	95% CI	p Value
Age at onset: after 30 years	1.01	0.42 to 2.4	0.99
Sex: female	1.62	0.20 to 13.1	0.65
Race: black	0.92	0.27 to 3.09	0.89
Area of residence: Cuba	1.44	0.45 to 4.64	0.54
Autoimmunity	1.18	0.23 to 6.11	0.85
Blindness at onset	**3.04**	**1.05 to 8.82**	**0.040**
Motor signs at onset	1.21	0.25 to 5.89	0.81
Sensory signs at onset	0.20	0.04 to 1.09	0.20
Sphincter signs at onset	**8.86**	**1.35 to 58.18**	**0.023**
First inter-attack interval <1 year	**6.86**	**1.97 to 23.91**	**0.003**
Lack of recovery of first attack	**3.36**	**1.35 to 8.39**	**0.009**

Neuromyelitis optica in France

A multicenter study of 125 patients

N. Collongues, MD
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ABSTRACT

Background: There have been few epidemiologic studies on neuromyelitis optica (NMO) and none used the recent 2006 diagnostic criteria. Here we describe the clinical, laboratory, MRI, and disability course of NMO in a French cohort of 125 patients.

Methods: We performed an observational, retrospective, multicenter study. Data were collected from September 2007 through August 2008, corresponding to the endpoint of the study. We identified 125 patients fulfilling the 2006 NMO criteria. Selection was made using hospital files and a specific clinical questionnaire for NMO.

Results: Mean age at onset was 34.5 years (range 4–66) with a mean disease duration of 10 ± 7.8 years at the endpoint. The patients were mainly (87%) Caucasian, with a female:male ratio of 3:1. In 90% of cases, the association of optic neuritis, longitudinal extensive myelitis, and a Paty-negative initial brain MRI was sufficient to fulfill the supportive criteria. Eighty-eight percent of patients were treated with immunosuppressive therapies. Median delay from onset to Expanded Disability Status Scale (EDSS) score 4 was 7 years; score 6, 10 years; and score 7, 21 years. The first episode of myelitis was immediately followed by an EDSS score ≥4 in 37.3% of cases, and a severe residual visual loss was observed in 22% of patients after the first episode of optic neuritis. Multivariate analysis did not reveal any predictors of a poor evolution other than a high number of MRI brain lesions at diagnosis, which were predictive of a residual visual acuity ≤1/10.

Conclusions: Our demographic data provide new data on disability in patients with neuromyelitis optica, most of whom were receiving treatment. ***Neurology*® 2010;74:736–742**

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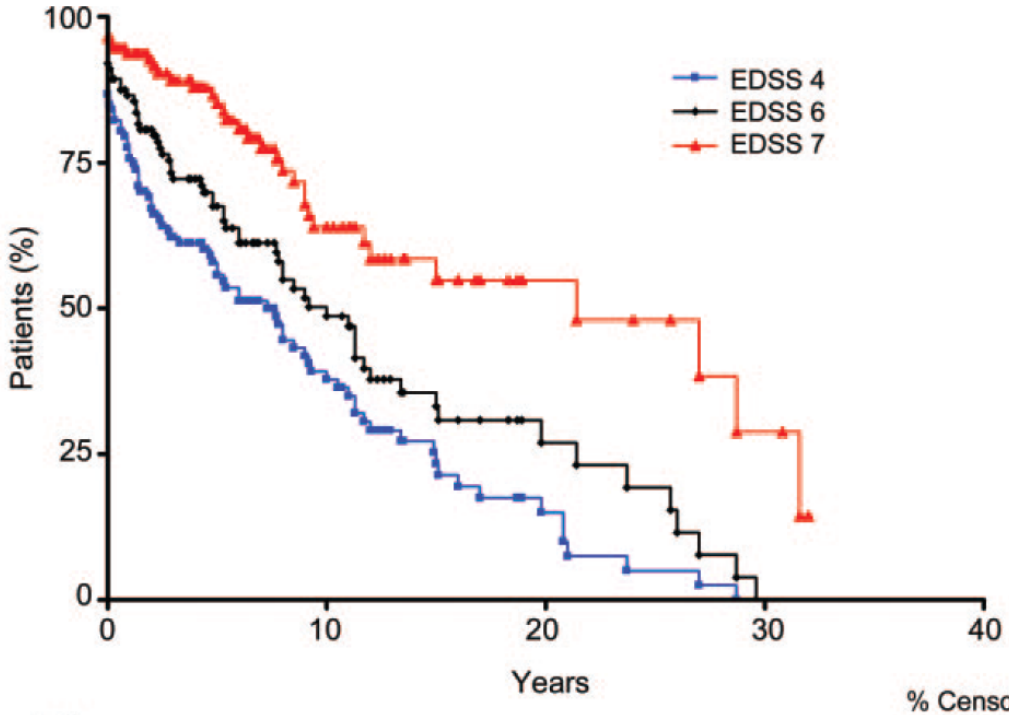
Figure Actuarial survival analysis of patients with neuromyelitis optica (NMO)



Number at risk					% Censored subjects*
EDSS 4	113	29	7	1	29%
EDSS 6	113	32	8	1	44%
EDSS 7	113	33	9	4	70%

Kaplan-Meier estimates of the age of the patients with NMO at the time of assignment of the scores of Expanded Disability Status Scale (EDSS) 4, 6, and 7, according to the initial course of NMO. Among 113 patients, the median time from the onset of NMO to the assignment of EDSS scores 4, 6, and 7 was as follows: score 4, 7 years; score 6, 10 years; score 7, 21 years. *Data on patients who had not reached an endpoint were censored at the time of the last clinical evaluation.

NEUROCURE Exzellenzcluster

Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: A multicentre study of 175 patients

Jarius et al. J Neuroinflammation 2012

Table 1 Comparison of demographic features according to the patients' AQP4-Ab serostatus.

	Seropositive	Seronegative	p-level
Sex ratio (male:female)			
All patients	1:10.4; N = 137	1:1.9; N = 38	$p < 0.0003^{‡}$
Patients meeting Wingerchuk's 2006 criteria	1:9.2; N = 92	1:2; N = 27	$p < 0.006^{‡}$
Age at onset (median, range; N)			
All patients	40 (10-81; N = 137)	38.5 (14-67; N = 38)	n.s.[§]
Patients meeting Wingerchuk's 2006 criteria	36 (10-79; N = 92)	37 (14-63; N = 27)	n.s.[§]
Cases of death, attack-related	5/137 (3.6%)°	0/38 (0%)	n.s.[‡]

Table 3 Comparison of clinical features according the patients' AQP4-Ab serostatus.

	Seropositive	Seronegative	p-level
Relapsing course			
Total cohort	127/137 (92.7%)	29/38 (76.3%)	$p < 0.008^{‡}$
Patients meeting Wingerchuk's 2006 criteria	92/92 (100%)	22/27 (81.5%)	$p < 0.0005^{‡}$
Relapse ratio, ON/MY*	0.85; N = 86	1; N = 25	n.s.[§]
Signs of-existing autoimmunity			
Total cohort	76/130 (58.5%)	3/35 (8.6%)	$p < 0.00001^{‡}$
Patients meeting Wingerchuk's 2006 Criteria	48/86 (55.8%)	3/25 (12%)	$P < 0.00009^{‡}$
Co-existing autoimmune disorders[†]	31/130 (23.8%)	2/35 (5.7%)	$p < 0.017^{‡}$
Co-existing auto-antibodies only[††]	45/97(46.4%)	1/30 (3.3%)	$p < 0.00001^{‡}$
CSF-restricted OCB at first LP			
All patients	30/110 (27.9%)	12/34 (35.3%)	n.s.[‡]
Patients meeting Wingerchuk's 2006 criteria	19/74 (25.7%)	10/26 (38.5%)	n.s.[‡]
Median CSF white cell count at first LP			
All patients	7 (0-750; N = 106)	7.5 (0-220; N = 30)	n.s.[§]
Patients meeting Wingerchuk's 2006 Criteria	7.5 (0-750; N = 68)	9 (1-220; N = 23)	n.s.[§]
Preceding infections at least once[#]	27/92 (29.3%)	5/28 (17.9%)	n.s.[‡]
Time to diagnosis of NMO (months)		11 (0-255; N = 29)	$p < 0.029^{§}$

Jarius et al. J Neuroinflammation 2012

Table 6 Optic neuritis, comparison of clinical features according to the patient's AQP4-Ab serostatus.

	Seropositive	Seronegative	p-level
Annualized ON relapse rate[†]			
All patients with a history of ON	0.38 (0.04-2.25; N = 83)	0.36 (0.08-3; N = 21)	n.s.[§]
Patients meeting Wingerchuk's 2006 criteria	0.37 (0.04-2.25; N = 80)	0.25 (0.08-3; N = 19)	n.s.[§]
Bilateral ON ever			
All patients with a history of ON	25/92 (27.2%)	15/29 (51.7%)	$p < 0.023$[‡]
Patients meeting Wingerchuk's 2006 criteria	23/87 (26.4%)	14/27 (51.9%)	$p < 0.019$[‡]
Bilateral ON at first ON attack*			
All patients with a history of ON	12/85 (14.1%)	11/28 (39.3%)	$p < 0.007$[‡]
Patients meeting Wingerchuk's 2006 criteria	12/81 (14.8%)	10/26 (38.5%)	$p < 0.023$[‡]
ON attacks with VA ≤ 0.1			
All patients with a history of ON	83/123 (67.5%)	13/35 (37.1%)	$p < 0.002$[‡]
Patients meeting Wingerchuk's 2006 Criteria	74/112 (66.1%)	12/33 (36.4%)	$p < 0.005$[‡]
Attacks with complete recovery			
All patients with a history of ON	68/205 (33.2%)	15/51 (29.4%)	n.s.[‡]
Patients meeting Wingerchuk's 2006 Criteria	64/190 (33.7%)	13/42 (31%)	n.s.[‡]

[†]Only patients with a disease duration > = 12 months were considered. *Irrespective of whether at disease onset or not. [‡]Fisher's exact test (2-tailed). [§]Mann Whitney U test. ON = optic neuritis; N = number of patients (not all data were available from all patients); n.s. = not significant; VA = visual acuity.

Jarius et al. J Neuroinflammation 2012

Table 7 Myelitis, comparison of clinical features according to the patients' AQP4-Ab serostatus.

	Seropositive	Seronegative	p-level
Annualized myelitis attack rate†			
All patients with a history of myelitis	0.6 (0.03-3.21; N = 108)	0.47 (0.04-2.88; N = 27)	n.s.§
Patients meeting Wingerchuk's 2006 Criteria	0.51 (0.03-2.73; N = 81)	0.39 (0.09-2.88; N = 20)	n.s.§
Motor symptoms, first myelitis§			
All patients with a history of myelitis	78/120 (65%)	22/35 (62.9%)	n.s.‡
Patients meeting Wingerchuk's 2006 Criteria	53/81 (65.4%)	17/27 (63%)	n.s.‡
Motor symptoms, all attacks§			
All patients with a history of myelitis	293/409 (71.6%)	54/91 (59.3%)	$p < 0.024$‡
Patients meeting Wingerchuk's 2006 Criteria	226/304 (74.3%)	42/74 (56.8%)	$p < 0.005$‡
MRC grade during motor attack*			
All patients with a history of myelitis	2 (0-5; N = 82)	3 (0-5; N = 24)	$p < 0.013$§
Patients meeting Wingerchuk's 2006 Criteria	2 (0-4.5; N = 55)	3.5 (0-5; N = 18)	$p < 0.006$§
Motor attacks with MRC ≤ 2			
All patients with a history of myelitis	88/159 (55.3%)	16/48 (33.3%)	$p < 0.009$‡
Patients meeting Wingerchuk's 2006 Criteria	71/119 (59.7%)	11/33 (33.3%)	$p < 0.01$‡
Attacks with complete recovery			
All patients with a history of myelitis	55/298 (18.5%)	7/61 (11.5%)	n.s.‡
Patients meeting Wingerchuk's 2006 Criteria	36/223 (16.1%)	6/49 (12.2%)	n.s.‡

Jarius et al. J Neuroinflammation 2012

Table 9 Myelitis, comparison of spinal cord MRI features according to the patients' AQP4-Ab serostatus.

	Seropositive	Seronegative	p-level
Median lesion length†, first MRI	6 (1-21; N = 104)	4.5 (2-12; N = 26)	n.s.§
Median lesion length†, all MRIs	5 (1-21; N = 264)	4 (1-16; N = 47)	$p < 0.01$§
SC lesions ≥ 3 vertebral segments, 1st MRI	134/142 (94.4%)	38/40 (95%)#	n.s.‡
SC lesions ≥ 3 vertebral segments, all MRIs	240/274 (87.6%)	46/51 (90.2%)#	n.s.‡
SC lesions ≥ 6 vertebral segments, 1st MRI	63/115 (54.8%)	10/28 (35.7%)	n.s.‡
SC lesions ≥ 6 vertebral segments, all MRIs	131/264 (49.6%)	12/47 (25.5%)	$p < 0.003$‡
Patients with entire SC involvement at least once	15/132 (11.4%)	0/36 (0%)	$p < 0.043$‡
MRIs with more than one lesion	59/274 (21.5%)	9/51 (17.6%)	n.s.‡
Total lesion load*, first MRI	6.5 (1-21; 104)	5 (2-12; 26)	$p < 0.022$§
Total lesion load*, all MRIs	6 (1-21; 264)	5 (1-16; 47)	$p < 0.006$§
Total lesion load > 6 segments*, first MRI	65/104 (62.5%)	11/26 (42.3%)	n.s.‡
Total lesion load > 6 segments*, all MRIs	153/264 (58%)	17/47 (36.2%)	$p < 0.007$‡

Jarius et al. J Neuroinflammation 2012

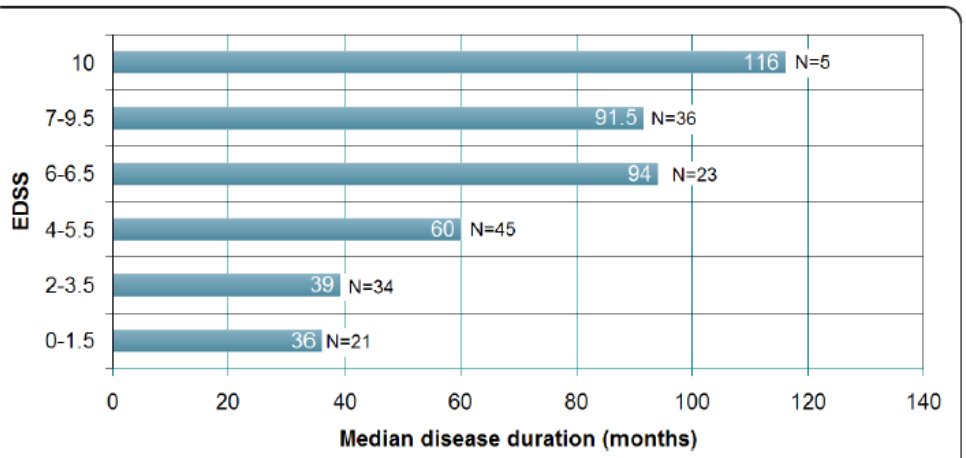


Figure 1 EDSS and disease duration at last follow-up grouped according to EDSS landmarks. EDSS < 2: No disability; EDSS 2-3.5: Disability but unrestricted walking range; EDSS 4-5.5: Restricted walking range but no walking aid required; EDSS 6-6.5: Walking aid required; 7-9.5: Essentially restricted to wheelchair or bed. In five cases the cause of death was directly related to attack-related neurological deterioration (EDSS 10). In those 4 cases in which the cause of death was not directly caused by neurological deterioration, the EDSS score obtained at the last examination prior to death was used for analysis.

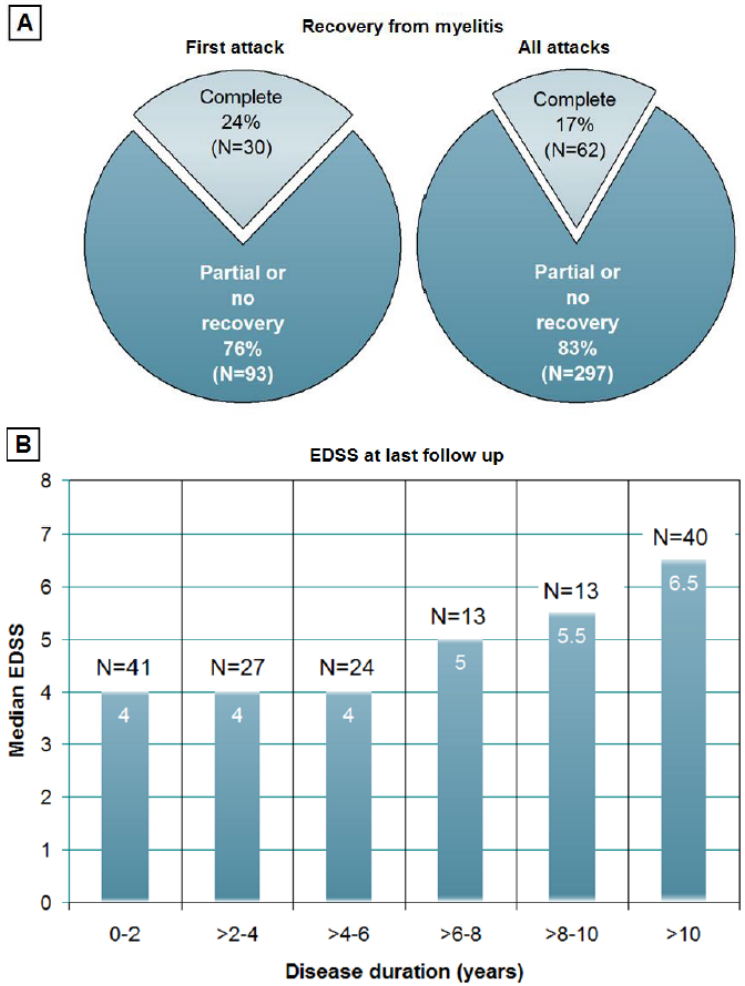


Figure 2 Recovery from myelitis and median EDSS scores in patients with NMO according to Wingerchuk et al. (2006) [36] **or LETM grouped for disease duration**. In line with the low rate of complete recovery from myelitis (A), a median EDSS of 4, indicating a restricted walking range, was notable already early in the disease course (B).

- 4 disease related deaths after disease duration of 6, 116, 158, 284 months
- median time to EDSS 6-6.5 appr. 5 years

Prognostic factors and disease course in aquaporin-4 antibody-positive patients with neuromyelitis optica spectrum disorder from the United Kingdom and Japan

NeuroCure Exzellenzcluster

Brain 2012

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Neuromyelitis optica and neuromyelitis optica spectrum disorders have been recently associated with the disease-specific autoantibody aquaporin-4, thought to be pathogenic. Identifying this antibody has allowed the clinical phenotype to be broadened. It is clear that some patients with similar clinical features do not have this antibody and may have a different condition with different outcomes and prognosis. Previous clinical neuromyelitis optica and neuromyelitis optica spectrum disorder studies have included such patients. We investigated clinical outcomes and prognostic characteristics of 106 aquaporin-4 antibody-seropositive patients from the UK and Japan. We looked at predictors of disability outcomes, namely visual disability (permanent bilateral visual loss with visual acuity of $<6/36$ in the best eye), motor disability (permanent inability to walk further than 100 m unaided), wheelchair dependence and mortality. Data were collected largely retrospectively through review of case records. After median disease duration of 75 months, 18% had developed permanent bilateral visual disability, 34% permanent motor disability, 23% had become wheelchair dependent and 9% had died. Age at disease onset appeared to be an important predictor of disability type. Young-onset patients in the UK, but not the Japanese cohort, commonly presenting with optic neuritis, had a high risk of visual disability while older patients in both cohorts had a high risk of motor disability, regardless of their onset symptom. Genetic factors also appeared important. The UK cohort seemed to have more severe disease than the Japanese cohort, with more severe onset attacks, a higher relapse frequency and greater disability at follow-up, despite earlier immunosuppression. Moreover, within the UK cohort, there were important differences between ethnic groups, with Afro-Caribbean patients having a younger age at disease onset, more brain and multifocal attacks and higher likelihood of visual disability than Caucasian patients. Thus, age at disease onset and genetic factors are both likely to be important in determining clinical outcomes in aquaporin-4 disease. This has important implications for interpreting clinical neuromyelitis optica and

Table 1 Comparison of demographic and clinical features between UK and Japanese cohorts

	Total	UK			Japanese
		Total	Caucasian	Afro-Caribbean	
No. of patients	106	59	45	12	47
Mean age at onset (range)	40.5 (2.7–76.7)	40.6 (2.8–76.8)	44.9 (7.2–76.8)	28.0 (2.8–48.5)	40.1 (13–73)
Female (%)	87	81	82	75	98
Median disease duration (range) (months)	75 (3–417)	60 (3–417)	60 (3–417)	46 (23–174)	115 (7–392)
Onset attack (%)					
LETM	43	49	53	33	36
Optic neuritis	41	37	38	33	45
Optic neuritis and LETM	4	5	5	8	2
Brain/brainstem	5	2	2	0	9
Mixed e.g. optic neuritis and brain	7	7	0	25	9
Disease course (%)					
Relapsing	86	86	82	100	85
Monophasic	14	14	18	0	15
Phenotype					
NMO[a]	53	53	44	75	53
Relapsing LETM	17	20	25	8	13
Relapsing optic neuritis	7	8	11	0	6
Monophasic optic neuritis	4	2	2	0	6
Monophasic LETM	9	12	16	0	6
Monophasic brain/brainstem	1	0	0	0	2
Other e.g. brain and optic neuritis	8	5	2	17	13
Median time to first relapse (months)	14	12	12	12	15
Mean annualized relapse rate	0.82	0.97	0.98	0.97	0.63
Reaching visual endpoint (%)	18	22	16	42	12
Reaching motor disability endpoint (%)	34	46	49	33	18
Reaching wheelchair endpoint (%)	23	29	31	25	15
Patients who died (%)	9	14	16	8	4

Table 3 Predictors of disability in AQP4 positive NMO/NMO spectrum disorder

	Visual disability (best eye worse than 6/36)	Motor disability (unable to walk >100 m unaided)	Wheelchair dependence	Death
Gender	Males more likely than females ($P = 0.003$; HR 4.9)	No difference ($P = 0.844$)	No difference ($P = 0.551$)	No difference ($P = 0.944$)
Ethnicity	Higher probability in Afro-Caribbeans than in Caucasians ($P = 0.046$; HR 1.83) or Asians ($P = 0.03$; HR 3.69)	Caucasians more likely than Asians ($P = 0.001$; HR 3.85)	Caucasians more likely than Asians ($P = 0.026$; HR 2.819)	Asians less likely than Caucasians ($P = 0.032$; HR 0.177)
Onset age	Lower risk with increasing age ($P = 0.007$; HR 0.62 for each decade). Due to UK cohort effect (no difference in Japanese group)	Higher risk with increasing age ($P < 0.001$; HR 1.82 for each decade). More profound effect in Japanese cohort	Higher risk with increasing age ($P < 0.001$; HR 1.92 for each decade). More profound effect in Japanese cohort	Higher risk with increasing age ($P = 0.003$; HR 2.12 for each decade). Effect seen in both cohorts
Onset relapse type	Optic neuritis more likely than LETM ($P = 0.023$; HR 4.31)	LETM more likely than optic neuritis ($P = 0.004$; HR 3.00). Due to effect in UK cohort only	No difference ($P = 0.188$)	No difference ($P = 0.137$)
Onset relapse severity	Severe onset relapse more likely ($P = 0.003$; HR 4.6)	No difference ($P = 0.132$)	No difference ($P = 0.256$)	No difference ($P = 0.591$)

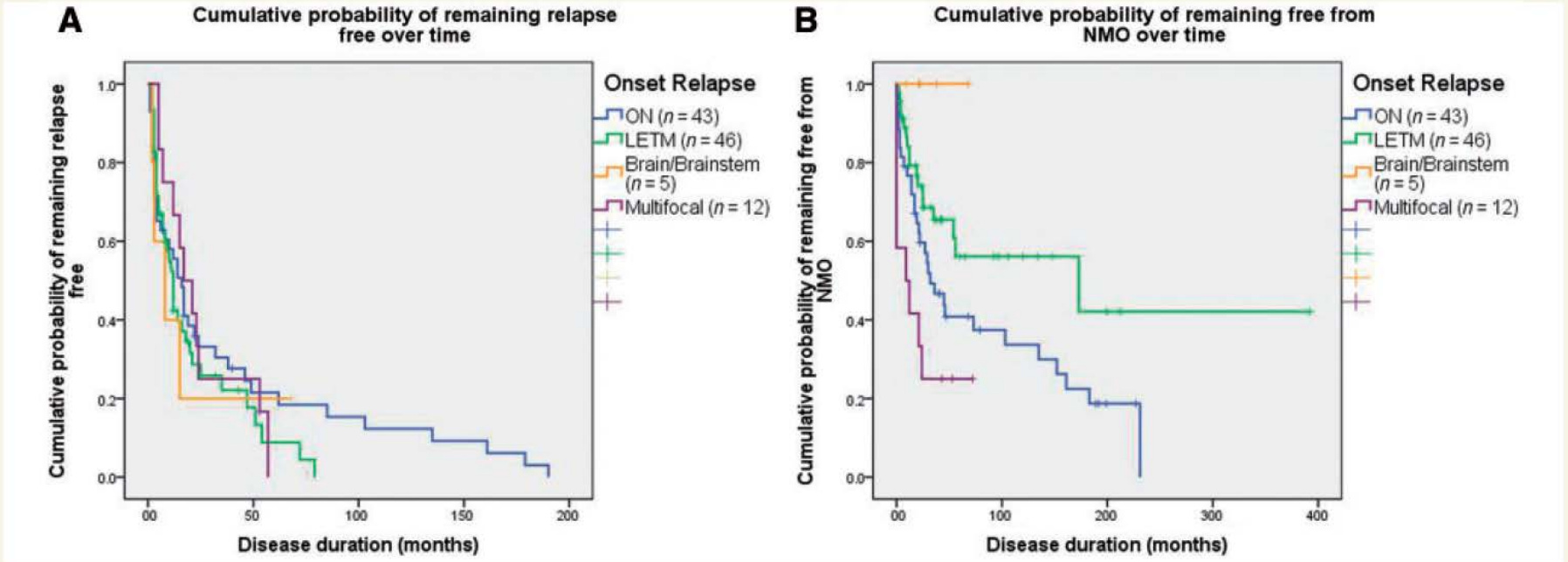
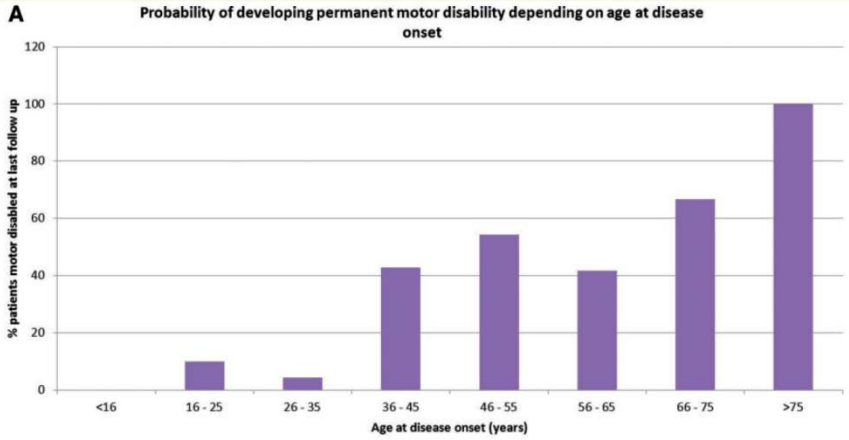
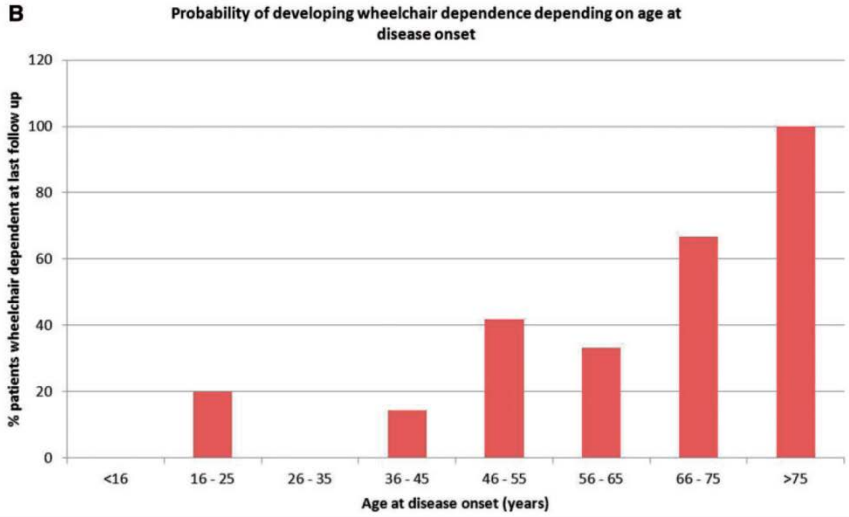


Figure 1 Kaplan–Meier curve showing cumulative probability over time of (**A**) developing relapsing disease and (**B**) developing NMO (defined as at least one attack of optic neuritis and one of LETM) depending on onset relapse type. (**A**) Time to first relapse was not influenced by type of onset attack. There was a trend towards LETM-onset patients relapsing sooner than optic neuritis-onset patients (median 12 versus 16 months). (**B**) Patients presenting with LETM were significantly less likely to develop NMO over time than patients presenting with optic neuritis (37% versus 72%; HR 0.539; 95% CI 0.298–0.977; $P = 0.042$). No patients presenting with brain disease progressed to NMO.





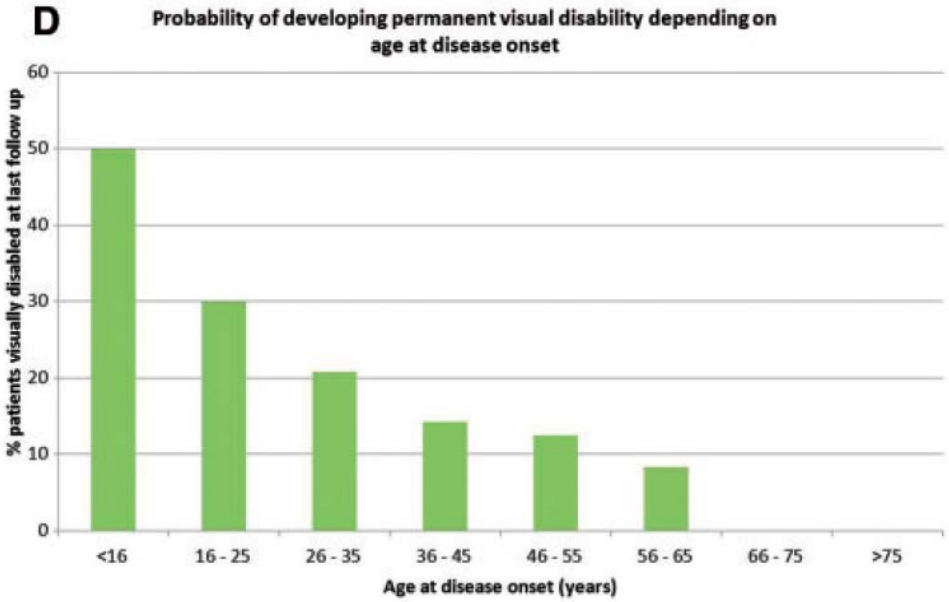


Figure 3 Bar charts showing that the probability of developing (**A**) permanent motor disability (defined as inability to walk >100 m unaided) and (**B**) wheelchair dependence increased with increasing age at disease onset. Older age at disease onset was significantly associated with likelihood of developing permanent motor disability (HR 1.82 for each decade of increasing age; 95% CI 1.45–2.28; $P < 0.001$) and wheelchair dependence (HR 1.92 for each decade of increasing age; 95% CI 1.34–2.74; $P < 0.001$). This effect was more profound in the Japanese group than in the UK group (for walk <100 m unaided, HR 2.37 for each increasing decade; 95% CI 1.48–3.81 versus HR 1.6; 95% CI 1.27–2.04; $P < 0.001$; for wheelchair dependence, HR 3.33; 95% CI 1.72–6.40 versus HR 1.92; 95% CI 1.34–2.74; $P < 0.001$).

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Factors Associated With the Time to Next Attack in Neuromyelitis Optica: Accelerated Failure Time Models With Random Effects

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Abstract

Background and Objective: Neuromyelitis optica (NMO) is an inflammatory demyelinating disorder of the central nervous system with a relapsing and remitting course. We aimed to identify factors associated with the time to next attack, including the effect of the natural disease course and the diverse treatment regimens, by applying a longitudinal statistical analysis to the individual attacks of each patient.

Methods: In total, 184 acute attacks among 58 patients with either NMO or NMO spectrum disorder with anti-aquaporin-4 antibody were assessed retrospectively. Patient demographics, clinical characteristics at each attack, and type of treatment during inter-attack periods were assessed. The dependent variable was defined as the time from each attack to the next attack (inter-attack interval). An exponential accelerated failure time model with shared gamma frailty was adapted for statistical analysis.

Results: A multivariable analysis revealed that the time from each attack to the next attack in NMO increased independently by 1.31 times (95% confidence interval (CI), 1.02–1.67; $p = 0.035$) with each additional cumulative attack experienced, by 5.34 times (95% CI, 1.57–18.13; $p = 0.007$) with combined azathioprine treatment and continued oral prednisolone, and by 4.26 times (95% CI, 1.09–16.61; $p = 0.037$) with rituximab treatment.

Conclusion: The time to next attack in NMO can increase naturally in the later stages of the disease as the number of cumulative attacks increases. Nevertheless, both combined azathioprine treatment with continued oral prednisolone and rituximab treatment were also associated with a longer time to next attack, independently of the natural disease course of NMO.

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Screening

74 patients with NMO or NMOSD with AQP4-Ab

Exclusion

11 with incomplete medical records
2 with negative AQP4-Ab test results
3 with a follow up period of less than 6 months

Inclusion

58 patients with NMO or NMOSD with AQP4-Ab

Analysis

184 acute attacks

Independent variables		Adjusted time ratio (95% CI)	*p*-value
Cumulative number of attacks		***1.31 (1.02-1.67)***	***0.035***
Disease duration		1.00 (0.99-1.00)	0.443
Age at the most recent attack		0.99 (0.97-1.01)	0.277
Recent attack at the optic nerve		0.64 (0.39-1.04)	0.073
AZA and Pd, combined Tx	AZA with <6 Mo Pd	0.73 (0.23-2.3)	0.590
	AZA with ≥6 Mo Pd [a]	5.70 (0.69-46.77)	0.105
	AZA with continued Pd	***5.34 (1.57-18.13)***	***0.007***
Rituximab		***4.26 (1.09-16.61)***	***0.037***
Interferon beta		0.69 (0.35-1.35)	0.281

Abbreviations: AFT, accelerated failure time; AZA, azathioprine; CI, confidence interval; Mo, month; Tx, treatment

[a] Oral prednisolone was discontinued before the next attack

A Benign Form of Neuromyelitis Optica

Does It Exist?

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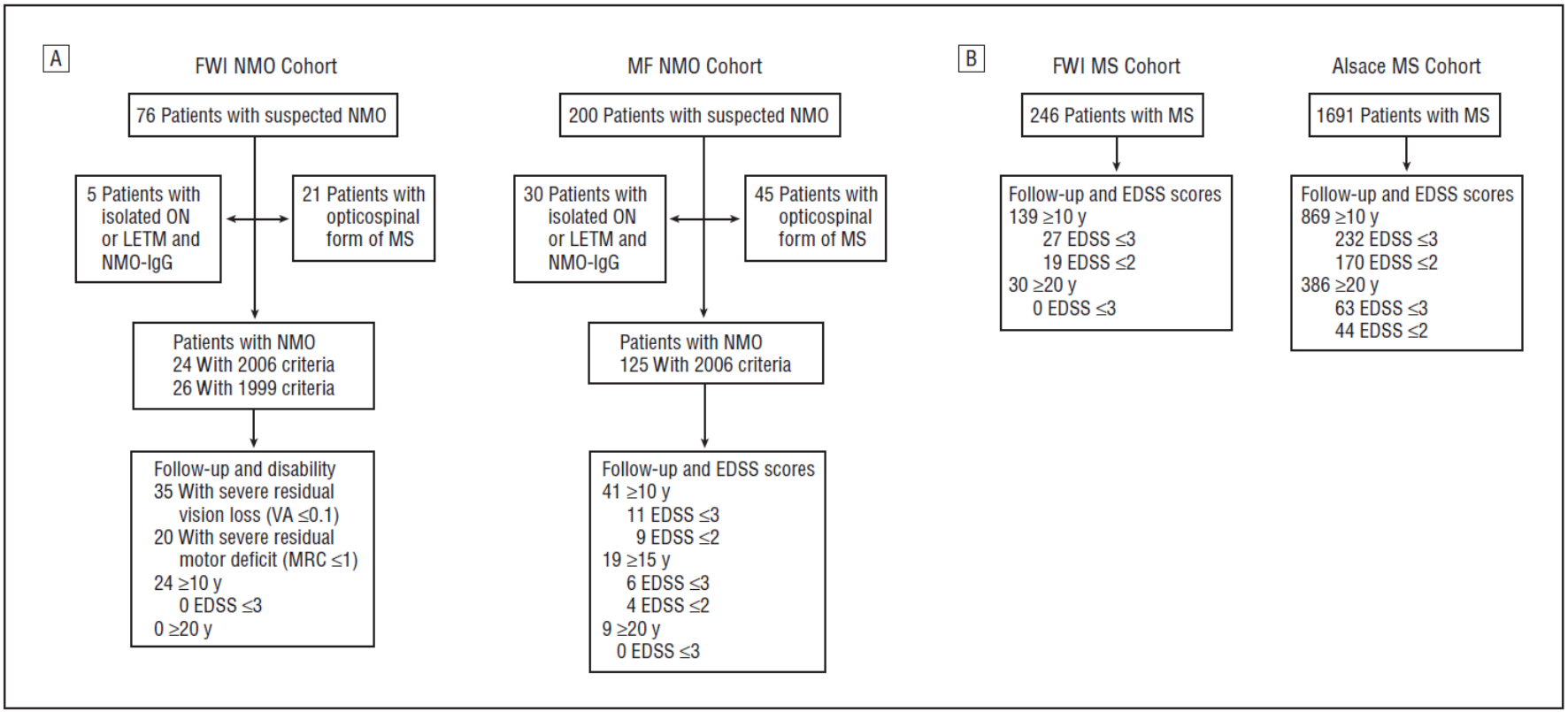
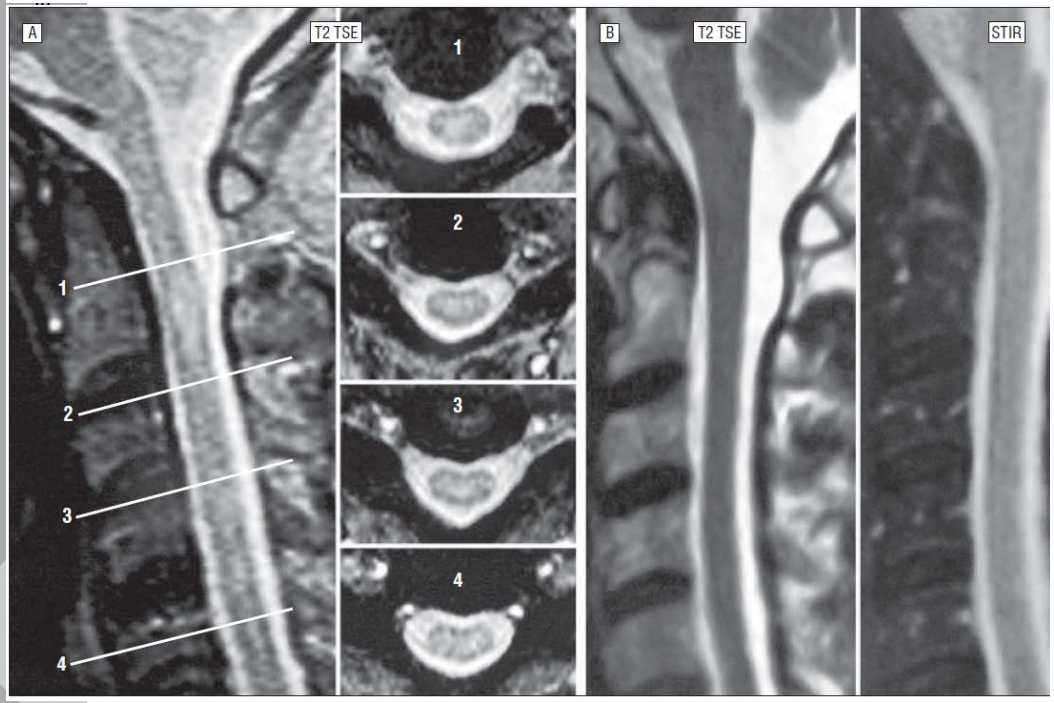


Arch Neurol 2011

Table 1. Demographic and Clinical Characteristics of Patients Having Neuromyelitis Optica (NMO) With a Good Outcome

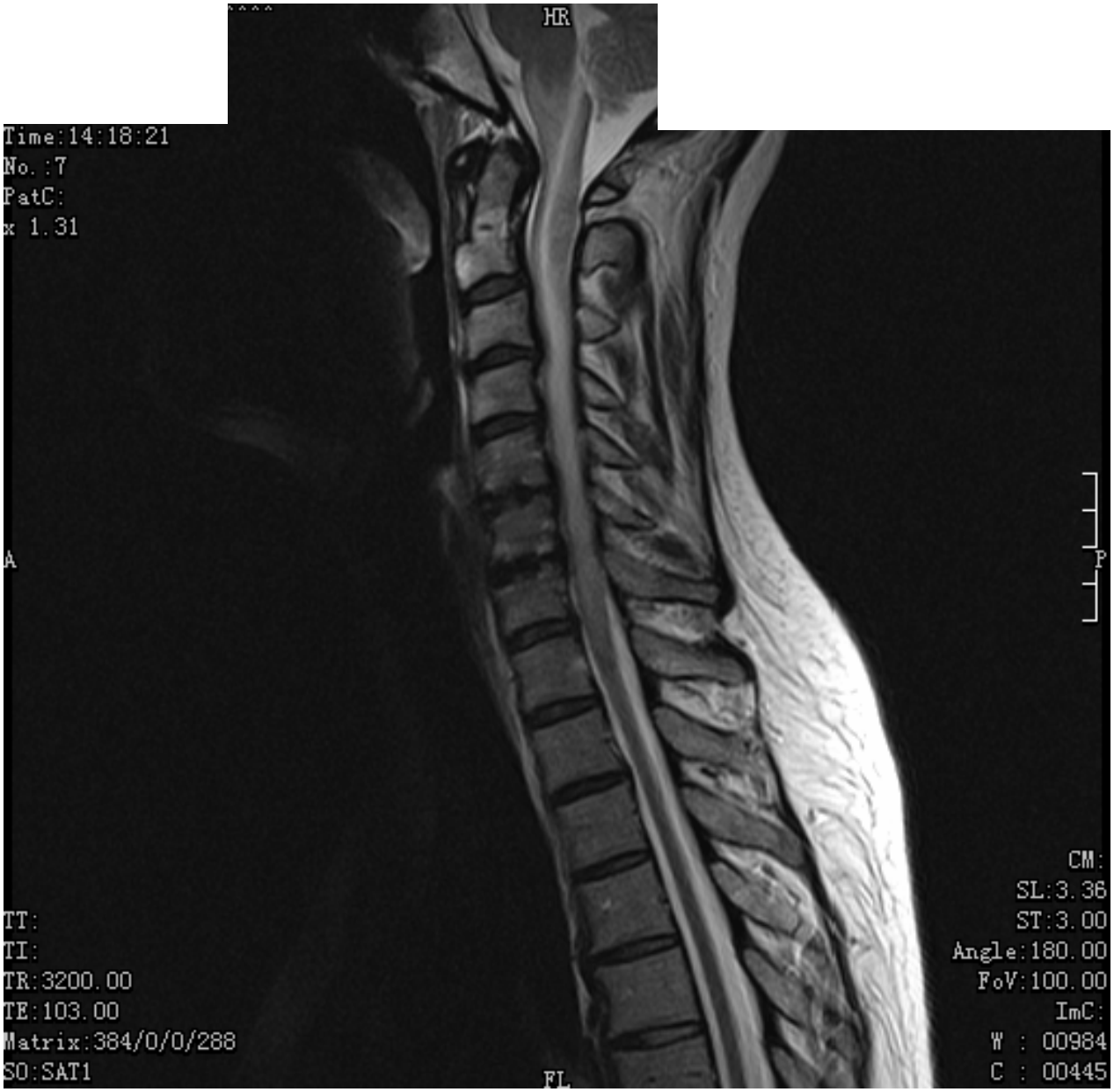
Patient No./Sex/ Race/Ethnicity/ Age at Onset, y/ Follow-up, y	Topography of First Attack	Opticospinal Interval, mo	First Interattack Interval, mo	Annualized Relapse Rate, Mean	NMO-IgG	Cerebrospinal Fluid, OCB/WBC Count, Cells/mm^3	Abnormal Spinal MR Imaging, No. of Lesions/ Location of LETM	First Brain MR Imaging, No. of Lesions[a]	Treatment
1/F/W/17.0/15.2	ON	22	22	0.7	+	+/0	1/CT	0	Interferon
2/M/W/51.2/14.3	SC	4	4	0.4	–	–/29	1/CT	1	Azathioprine
3/M/W/27.4/16.4	SC	108	108	0.2	–	+/0	2/C	0	. . .
4/M/W/37.8/19.2	ON	48	36	0.4	–	–/5	1/C	0	Interferon, glatiramer acetate
5/F/W/20.2/15.3	ON	96	24	0.3	–	–/3	3/C, T	1	. . .
6/F/W/24.8/25.4	ON	120	60	0.3	+	–/0	2/C, T	0	Interferon, cyclophosphamide
7/M/A/14.7/18.2	ON	75	75	0.3	+	–/128	1/CT	0	Cyclophosphamide
8/F/W/29.8/11.4	SC	119	119	0.2	+	+/16	1/. . .	0	. . .
9/F/B/35.5/14.3	ON	48	12	0.5	+	+/4	1/C	0	Interferon, mycophenolate mofetil
10/F/W/52.3/13.7	ON	3	3	0.2	–	–/5	1/C	0	Azathioprine
11/F/W/36.7/16.3	ON	48	48	0.4	+	–/12	1/T	0	Cyclophosphamide

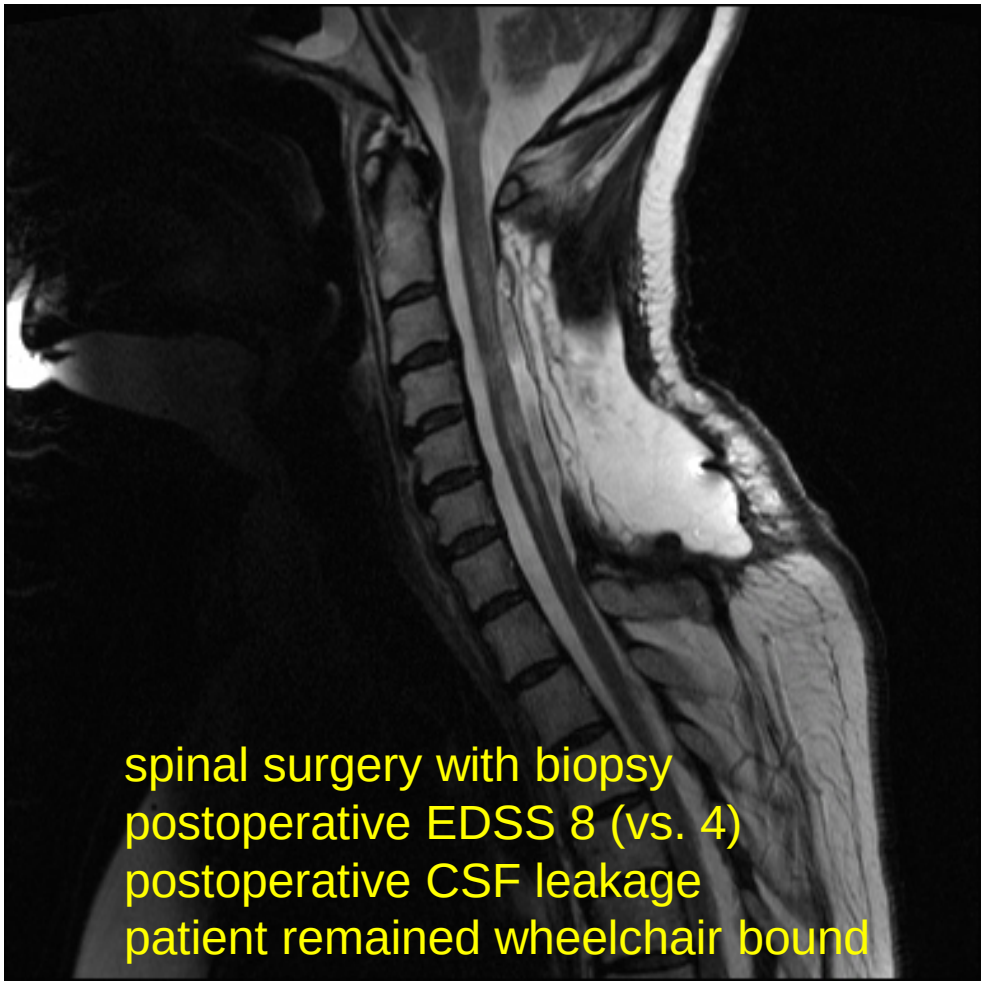


Results: In MF, go-NMO was observed in 11 patients, including 3 untreated patients. In the FWI, NMO was severe because of disability related to optic neuritis. Compared with standard NMO, go-NMO was associated with a lower annualized relapse rate (0.3 vs 1.0, $P<.01$), and 8 of 11 patients with go-NMO showed complete regression of myelitis on magnetic resonance imaging during the disease course. Three patients experienced a disabling attack of NMO after 15 years of follow-up. A good outcome occurred less frequently among patients with NMO than among patients with multiple sclerosis (12.0% vs 22.4%, $P=.03$).

Conclusions: Among patients in MF, go-NMO occurs rarely. However, because a disabling attack may occur after a long follow-up period, a benign form of NMO cannot be defined.

„Natural history“?????




spinal surgery with biopsy
postoperative EDSS 8 (vs. 4)
postoperative CSF leakage
patient remained wheelchair bound

Contribution of spinal cord biopsy to diagnosis of aquaporin-4 antibody positive neuromyelitis optica spectrum disorder

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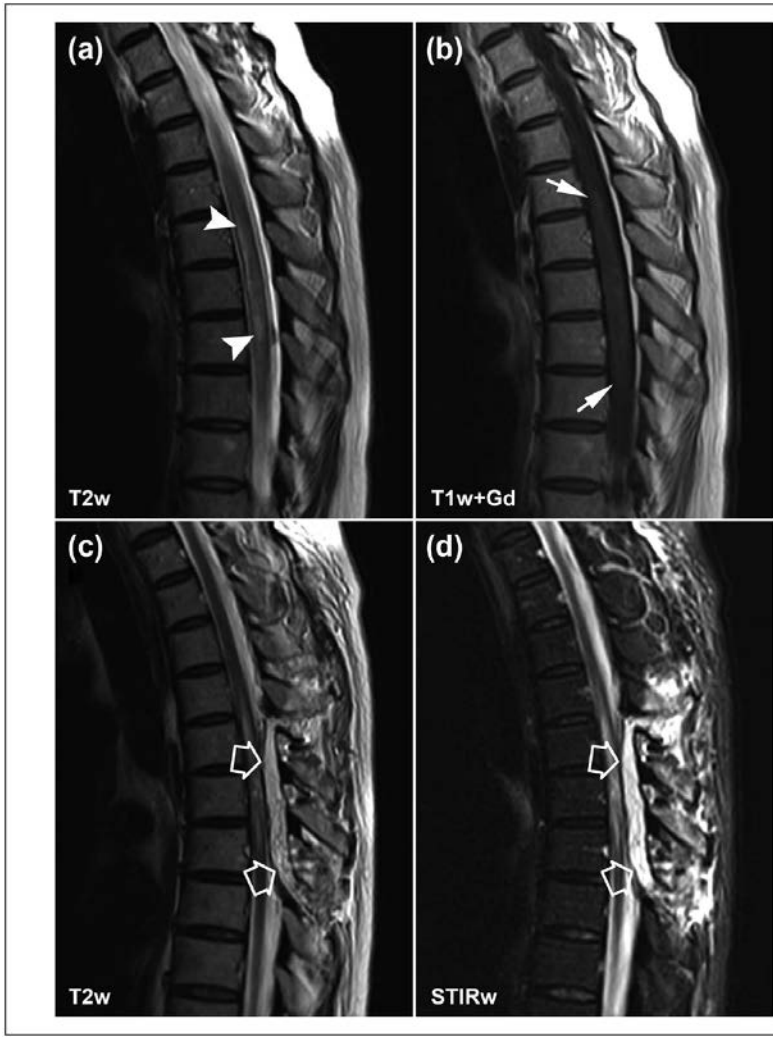
MSJ 2013



Abstract

Longitudinally extensive transverse myelitis is characteristic but not pathognomonic for neuromyelitis optica spectrum disorders (NMOSDs) and may mimic local tumors. In this retrospective study based on a cohort of 175 NMOSD patients we identified seven patients who initially presented with a longitudinally extensive spinal cord lesion and underwent spinal cord biopsy due to magnetic resonance imaging (MRI)-suspected malignancies. Remarkably, routine neuropathology was inconclusive and did not guide the diagnostic process to anti-aquaporin-4 (AQP4)-seropositive NMOSD. Serious postoperative complications occurred in 5/7 patients and persisted during follow-up in 2/7 patients (29%). Considering these sequelae, AQP4-antibody testing should be mandatory in patients with inconclusive longitudinally extensive spinal cord lesions prior to biopsy.

Summary

- Most studies are consistent regarding the devastating disease course in many patients
- Accrual of irreversible neurological disability ist almost exclusively attack-related, a progressive course is rare
- Mortality seems to have decreased, presumably related to earlier diagnosis and treatment
- Effective immunosuppression is likely to positively modify disease course
- Although a subset of patients may have mild disease, the concept of „benign NMO“ remains elusive and should not lead to therapeutic nihilism
- Prevention of further attacks should be the major goal of long-term treatment and in clinical trials

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