Autoimmunity Reviews 11 (2012) 231–248

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Transverse myelitis

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ARTICLE INFO

Available online 18 May 2011

Keywords:
Transverse myelitis
Autoimmunity
Anti-phospholipid antibodies
Infection
Immunization

ABSTRACT

Acute transverse myelitis (ATM) is an etiologically heterogeneous syndrome with acute or subacute onset, in which inflammation of the spinal cord results in neurologic deficits, manifesting as weakness, sensory loss and autonomic dysfunction. It is frequently associated with infectious or systemic autoimmune diseases, but its etiology remains unknown in a substantial portion of cases, which are classified as idiopathic. Unifying diagnostic criteria for idiopathic and disease-associated ATM were proposed in 2002. Although they have been applied to a few cohorts of patients, the limited information provided in the relevant publications has not yet yielded many new insights on the clinical characteristics, disease course, and outcome of adult patients with idiopathic ATM compared to older studies that did not always distinguish between the various etiologies of ATM. There is, however, some new epidemiological data indicating that the incidence of idiopathic ATM is considerably higher, and the female preponderance greater, than previously recognized. In addition, new data on children with ATM show that the prognosis in pediatric patients is not always as benign as previous studies had indicated. The combination of ATM and optic neuritis characterize Devic's syndrome or neuromyelitis optica (NMO). A seminal discovery was the identification of an antibody that is a specific marker not only for NMO, but also of some of its characteristic manifestations in isolation, including longitudinally extensive TM. This has resulted in the proposal that all of the disorders that are associated with NMO–IgG positivity constitute part of an NMO spectrum of disorders. This antibody recognizes aquaporin-4, which represents the most abundant water channel of the central nervous system. There is growing evidence that the antibodies targeting this channel protein have pathogenic potential, thereby providing insights into the possible pathogenetic mechanisms of at least one type of ATM.

Contents

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1568-9972/$ – see front matter © 2011 Published by Elsevier B.V.
doi:10.1016/j.autrev.2011.05.018

1. Introduction

1.1. Definitions and diagnostic criteria

Acute transverse myelitis (ATM) refers to the inflammatory subtype of transverse myelopathy, which is an acute or subacute clinical syndrome in which injury to the spinal cord results in neurologic deficits, manifesting as weakness, sensory loss and autonomic dysfunction. The etiologies of myelopathies are varied and can be subdivided into compressive and non-compressive causes. While compressive myelopathies stem from trauma and intra- or extra-spinal tumors, the etiologies of non-compressive myelopathies can be classified as delayed radiation effects, ischemic, paraneoplastic, infectious or parainfectious, or systemic autoimmune diseases. Among the latter, ATM can be associated with systemic lupus erythematosus (SLE), Sjögren's syndrome (SS), sarcoidosis, Behçet's disease, other connective tissue diseases, and the antiphospholipid syndrome (APS), either primary or secondary to SS. In addition, ATM can be the first manifestation of multiple sclerosis (MS) and of neuromyelitis optica (NMO), also called Devic's syndrome, which is defined as the combination of ATM with optic neuritis (ON). Despite extensive work-up, an etiology of ATM cannot be identified in a significant portion of cases, and these are classified as idiopathic. Previously proposed diagnostic criteria for acute transverse myelopathies generally excluded those resulting from spinal cord compression, but differed in their inclusion of disease-associated etiologies. In 2002, the Transverse Myelitis Consortium Working Group (TMCWG) proposed diagnostic criteria and nosology of ATM [1]. Mostly for prognostic reasons, it decided to classify ATM as either idiopathic or disease-associated (see Table 1). It is suggested that patients who fulfill the clinical criteria of idiopathic ATM, but lack evidence of inflammation, be classified as possible idiopathic ATM.

Table 1
TMCWG criteria for idiopathic ATM [1].

Inclusion criteria	Exclusion criteria
Development of sensory, motor, or autonomic dysfunction attributable to the spinal cord	History of previous radiation to the spine within the last 10 years
Bilateral signs and/or symptoms (though not necessarily symmetric)	Clear arterial distribution clinical deficit consistent with thrombosis of the anterior spinal artery
Clearly defined sensory level	Abnormal flow voids on the surface of the spinal cord c/w AVM
Exclusion of extra-axial compressive etiology by neuroimaging (MRI or myelography; CT of spine not adequate)	Serologic or clinical evidence of connective tissue disease (sarcoidosis, Behcet's disease, Sjögren's syndrome, SLE, mixed connective tissue disorder, etc.)*
Inflammation within the spinal cord demonstrated by CSF pleocytosis *or* elevated IgG index *or* gadolinium enhancement. If none of the inflammatory criteria is met at symptom onset, repeat MRI and lumbar puncture evaluation between 2 and 7 days following symptom onset meet criteria	CNS manifestations of syphilis, Lyme disease, HIV, HTLV-1, Mycoplasma, other viral infections (e.g., HSV-1, HSV-2, VZV, EBV, CMV, HHV-6, enteroviruses)*
Progression to nadir between 4 h and 21 day following the onset of symptoms (if patient awakens with symptoms, symptoms must become more pronounced from point of awakening)	Brain MRI abnormalities suggestive of MS*
	History of clinically apparent optic neuritis*

Abbreviations:
AVM = arteriovenous malformation; CMV = cytomegalovirus; EBV = Epstein-Barr virus; HHV = human herpes virus; HSV = herpes simplex virus; HTLV-1 human T-cell lymphotrophic virus-1; SLE = systemic lupus erythematosus; VZV varicella zoster virus
* Do not exclude disease-associated ATM.

By excluding patients with a history of clinically apparent ON from the diagnosis of idiopathic ATM, these criteria classify ATM in NMO as disease-associated. Note, however, that there is a major difference in the nature of the association between ATM and systemic autoimmune or infectious diseases on the one hand and its association with NMO on the other hand. NMO itself, like ATM, can occur in the context of various systemic autoimmune diseases. More importantly, ATM may or may not occur at any time in the course of autoimmune diseases and may or may not be a neurological manifestation of infectious diseases. In contrast, ATM is one of the defining features of the NMO, the other one being ON. This is not obvious in the currently most widely used diagnostic criteria, which only require “acute myelitis” [2], but is specifically stated in the NMO diagnostic criteria proposed by an international Task Force on Differential Diagnosis in MS [3] (see Table 2). Of note, the Task Force criteria specify that the TM in NMO can be clinically complete or incomplete. Clinically complete TM is characterized by moderate to severe bilateral neurologic dysfunction associated with a lesion located centrally and occupying most of the cross-sectional area of at least one spinal segment. Incomplete, or partial, TM manifests as milder and often markedly asymmetric neurological deficits usually in association with involvement of less than half of the cross-sectional area of the cord. The TMCWG criteria for ATM do not specifically address this issue but, by requiring bilateral signs or symptoms, are more likely to identify patients with complete TM.

Acute TM along with isolated ON and NMO are part of a spectrum of inflammatory demyelinating disorders, which also includes acute disseminated encephalomyelitis and MS. These disorders differ in their spatial distribution of inflammation and their recurrence rates, but the factors determining the spatial and temporal disease patterns remain unknown. Both idiopathic ATM and NMO were originally considered to be monophasic disorders. In Devic's syndrome this meant that the two index events (TM and ON) occurred simultaneously or in close temporal association. Recurrent forms were diagnosed as MS. However, it is now widely accepted that ATM can be recurrent in up to 25% of cases. It is also recognized that the two index events of NMO can occur months, years or even decades apart and that the disease takes a recurrent or relapsing/remitting course in >80% of patients. This makes NMO difficult to distinguish clinically from MS, but it is increasingly obvious that the immunological, pathological, laboratory and imaging characteristics of NMO are distinct.

Table 2
Comparison of the diagnostic criteria for NMO proposed by the Task Force on Differential Diagnosis in MS [3] and by Wingerchuk et al. [2].

	Task Force	Wingerchuk 2006
Major/absolute criteria	(All required by may be separated by unspecified interval)	
	Optic neuritis in one or more eyes	Optic neuritis
	Transverse myelitis, clinically complete or incomplete, but associated with radiological evidence of spinal cord lesion extending over ≥3 segments on T2-weighted MRI images and hypointensity on T1-weighted images when obtained during acute episode of myelitis	Acute myelitis
	No evidence of sarcoidosis, vasculitis, clinically manifest SLE or SS, or other explanation for the syndrome	
Minor/supportive criteria	(At least one must be satisfied)	(At least two of three must be satisfied)
		Contiguous spinal cord MRI lesion extending over ≥3 vertebral segments
	Most recent brain MRI scan must be normal or may show abnormalities not fulfilling Barkhof criteria used for McDonald diagnostic criteria[a]	Brain MRI not meeting diagnostic criteria for multiple sclerosis
	Positive test in serum or CSF for NMO–IgG/Aquaporin-4 antibodies	NMO–IgG seropositive status

[a] The nature of these lesions is characterized in considerable detail.

1.2. NMO–IgG/anti-Aquaporin antibodies

A milestone in establishing the distinctiveness of MS and NMO was the discovery that sera from >70% of patients with NMO contained an antibody that was detected in few (<10%) patients with MS [4]. This antibody, originally designated as NMO immunoglobulin G (NMO–IgG), was subsequently shown to recognize aquaporin-4 (AQP4) [5], which constitutes the most abundant water channel of the CNS. Several assay systems using human embryonic kidney cells transfected with recombinant human AQP4 have since been developed for the detection of anti-AQP4 antibodies (AQP4 Abs), and many have been shown to provide a higher sensitivity and similar specificity compared to the original method of indirect immunofluorescence on mouse brain tissues [6–9]. Unfortunately, the lack of standardization does not allow direct comparison of the results. Nonetheless, the demonstration of AQP4 Abs in 97% of sera from patients with NMO in one of the most recent investigations indicates that the available data on NMO–IgG seroprevalence as measured by indirect immunofluorescence may represent considerable underestimates of the true prevalence of seropositivity [10].

Table 3 summarizes the frequencies of NMO–IgG seropositivity in patients with NMO and other groups of patients with some of the characteristic features of NMO. Several findings are worth highlighting. Firstly, NMO–IgG has been detected in 50–70% of NMO patients from the US and Europe (see also Ref. [11]). Significantly lower seroprevalence rates have been reported for patients with NMO from Cuba and Martinique (33%) [12], Singapore (9%) [13], and India (12.5%) [14], although the analyses were performed by some of the same US and European laboratories [4,15,16]. Secondly, in contrast to the conventional form of MS, much higher NMO–IgG positivity rates (55–63%) have been reported in patients with the opticospinal form of MS (OSMS) [4,17], which is characterized by predominant involvement of the spinal cord and optic nerves. Based on the similar clinical characteristics and frequency of NMO–IgG positivity in NMO and OSMS patients, it has been postulated that the two disorders are actually the same entity [4]. However, another Japanese group obtained a positivity rate of only 18.5% [18]. The reported frequencies of AQP4 Abs show similar variability [19–22]. Consequently, the question of whether OSMS is identical to NMO remains a matter of considerable debate [18,20].

Thirdly, a characteristic feature of NMO is the presence of lesions on spinal MRI spanning 3 or more contiguous segments, referred to as longitudinally extensive TM (LETM). NMO–IgG has also been found in patients with LETM without clinical or subclinical ON, the seropositivity rate being 50% (70/139) in the combined data from 7 US and European studies [8,15,16,23–26] and 67% in Hong Kong Chinese [27]. Again, considerably lower rates have been reported from India [14]), Cuba and Martinique [12]), and Brazil [28]. Note that NMO–IgG is detected more frequently in patients with recurrent LETM compared to those who experienced a single episode [23], but even for this patient group the NMO–IgG seropositivity rates were only 14% and 17% in India and Cuba/Martinique, respectively [12,14]. Again, these samples were processed at the same laboratories that had analyzed some of the US or European sera [4,15,16]. Therefore, neither methodological differences nor disparities in the proportion of patients with recurrent vs. monophasic LETM account for this variation in seropositivity rates, suggesting that there may be true geographic differences. Fourthly, a subset of patients with bilateral or recurrent ON (13–27%) also exhibit NMO–IgG ([16,27] and Table 3), whereas patients with a single attack of ON are rarely positive [27]. Seropositivity for NMO–IgG was found to predict relapse or development of ON (i.e., NMO) in patients with LETM [26]. It also was associated with the development NMO in patients with recurrent ON, although the number of patients was small, precluding any firm conclusions as to the predictive value of NMO–IgG positivity [29].

In addition, Devic's syndrome, LETM or recurrent ON can occur in patients with SS or SLE, and there is limited evidence that the frequency of NMO–IgG in such patients is at least as high as that observed in NMO without associated autoimmune diseases [23,30–32]. In contrast, patients with SLE or SS without manifestations of NMO or related disorders never test positive for this antibody, even if they have other neurological involvement [23,30]. This suggests that NMO is not secondary to SLE or SS, but that these patients suffer from two independent, co-existing autoimmune diseases.

As a result of these discoveries, it has been proposed that all of the disorders that are associated with NMO–IgG constitute part of an NMO spectrum of disorders (NMOsd), including OSMS and limited forms of NMO such as recurrent LETM or recurrent ON, either alone or in association with systemic autoimmune diseases [33]. Unfortunately, it remains unclear whether the spectrum includes all cases or only those that test positive for NMO–IgG/AQP4 Abs.

2. Epidemiology of ATM and NMO

2.1. Incidence and prevalence of ATM and NMO

The earliest study on the frequency of transverse myelopathies yielded an annual incidence of 1.34/million in Israel for the period 1955–1975 [34]. The incidence of MS-associated, parainfectious, spinal cord ischemia and idiopathic myelitis was 4.6/million in the US for the years 1960–90 (Albuquerque, NM) [35]. Idiopathic myelitis constituted 21% of the total number of cases. In contrast, a recent analysis of medical records from a large health care organization in California produced an estimated TM incidence of 31/million (95% CI 26–36) in people aged 10–62 years during the period 1998–2004 based on a review of medical records of all cases with an ICD-9 code 323.9 (unspecified causes of encephalitis, myelitis, and encephalomyelitis) [36]. The first and to date only study of the annual incidence of definite or possible idiopathic ATM according to TMCWG criteria

Table 3
Seroprevalence of NMO–IgG in NMO, MS, other patient populations, and healthy controls.

Country	NMO	OSMS	MS	LETM (R indicates recurrent LETM)	TM	Bilateral or recurrent ON	Miscellaneous neurological and/or autoimmune disorders	Healthy controls	Reference
USA	33/45 (73%)		2/22 (9%)	9/27 (33%)[d]		1/8 (13%)			[4]
Japan		6/11 (55%)	0/5 0	1/1			0/5 0		"
USA				11/29 (38%)					[26]
Europe	22/36 (61%)		1/80 (1.2%)	4/5 (80%)			0/21 0	0/25 0	[24]
UK and Germany	14/24 (58%)		0/38 0	5/10 (50%)			1/26 (4%)		[8]
France	14/26 (54%)		5/52 (10%)	7/13 (54%)	0/8 0	4/21 (19%)	0/43 0		[16]
Spain	10/16 (62.5%)		0/127 0	2/4 R (50%)		1/7 (14%)			[15]
Turkey	8/14 (57%)		0/14 0					0/15 0	[166]
Cuba and Martinique[a]	16/48 (33%)		2/41 (4.8%)	2/14 R (14%)		2/12 (17%)	0/37		[12]
Brazil	18/28 (64%)		0/20 0	3/13 (23%)		3/11 (27%)			[28]
Korea		5/27 (18.5%)	2/25 (8%)						[18]
India[b]	1/8 (12.5%)	1/14 (7%)	1/16 (6%)	1/21[c] (5%)					[14]
Hong Kong	6/10 (60%)		1/30 (3%)	6/9 (67%)	0/20 0	2/9 (22%)	0/35 0	0/10 0	[27]
Singapore	1/11 (9%)	Comb w/NMO			0/5 0	0/5 0	1/10 (10%)	0/10 0	[13]

[a] Note that the Cuban samples were analyzed by the same laboratory as in the Spanish cohort [15], while the Martinique samples were analyzed by the same laboratory as in the French cohort [16], with both European cohorts showing significantly higher positivity rates.
[b] These samples were analyzed at the Mayo Clinic Laboratory that developed the original assay [4].
[c] This patient was one of 6 with recurrent LETM, 1/21 with LETM overall.
[d] In the "Materials and methods" section, the LETM patient group was defined as having "one or more attacks" of ATM with the lesion spanning ≥3 segments on spinal cord MRI, but the Table presenting the data designates them as "recurrent LETM" [4].

(ATM_{TMCWG}) yielded an estimate of 6.2/million (95% CI 2.9–9.6) for New Zealand in the years 2001–05 [37]. When cases of ATM with brain lesions detectable by MRI and cases of partial ATM with or without brain lesions were included, the total figure rose to 24.6/million (95% CI 18.2–31.1) [37]. An ATM incidence of 1.1/million was reported for Japanese children aged ≤15 years for the years 1998–2003 [38]. In Canadian children aged <18 years, the annual incidence of ATM_{TMCWG} was found to be 2/million (95% CI 1.5–3) [39]. It is estimated that 20%–30% of ATM cases occur in children (<18 years of age) [40].

In rare cases, ATM — with or without ON — can also be the first manifestation of SLE or SS or can occur at any time during the course of SLE [31,41–44]. The incidence of ATM is estimated to be 1–3% and <1% in SLE and SS, respectively [45–47]. In the first retrospective application of the TMCWG criteria to a multi-center cohort of 288 ATM patients, 15.6% of the cases were classified as idiopathic, 10.8% eventually developed MS, 19% were associated with spinal cord infarcts, 17.3% were classified as infectious or parainfectious, 17% of patients ultimately were diagnosed as NMO, and 20.5% of patients had associated systemic autoimmune diseases [48]. An association with SS was seen most frequently (28/288 or almost 10% of the whole ATM cohort), followed by sarcoidosis (5.9%), SLE (3.8%) and APS (1.4%). However, the frequency of the individual etiologies differed widely between the participating centers. For example, the proportion of idiopathic cases ranged from 6% to >60%, that of ATM associated with systemic diseases from 0 to 40%.

Far fewer data are available on the frequency of NMO. The figures provided in the study of Canadian pediatric cases suggest an incidence of TM plus ON (NMO) of ~0.3/million [39]. In a recent population-based study from Cuba, the annual incidence of NMO was estimated to be 0.53/million, while the prevalence was 5.2/million (95% CI 3.9–6.7) [49]. Data from similar studies in Japan and Martinique allow the calculation of prevalence rates of 3.2 and 31 per million respectively [49–51].

2.2. Gender and ethnicity

According to older case series, isolated transverse myelopathies affect men and women in approximately equal numbers [52–55], although females were affected twice as often as males in at least one cohort [56]. In patients with ATM_{TMCWG}, an equal proportion of males and females has also been reported in some studies, [57,58], but the majority of cohorts show a clear female predominance [37,48,59,60] (see also Table 4). Females also represented 71% of the 150 cases with TM aged between 18 and 62 years in the California health care provider incidence study (F:M 2.4:1) [36]. Divergent results in studies applying the same diagnostic criteria suggest that there are true geographic differences in the proportion of females affected by ATM, although it is possible that the fairly small number of subjects in most of the studies distorts the results. Male and female children are represented approximately equally among cases of pediatric ATM [39,61,62], although boys constituted a larger portion of patients in the <10 year-old age group in a recent study [39].

In NMO, females outnumber males by as much as 9:1 [11,12,28,63–65] (see also Table 5), and data from population-based studies also show significantly higher NMO prevalence rates in females than in males [49,50]. However, the female:male ratios vary widely between studies even from the same country. There are data suggesting that monophasic NMO affects males and females equally [63], but others found no statistically significant difference in the gender distribution between monophasic and recurrent diseases [11]. In contrast to MS, which is more common in people of European

Table 4
Demographic characteristics and some clinical and laboratory features of patients with ATM.

Characteristics and disease features	France [48] ATM_{TMCWG}	Spain [57] ATM_{TMCWG}	Pakistan [58] ATM_{TMCWG}	New Zealand [37] ATM_{TMCWG}	Saudi Arabia [81]	Denmark [55]	Massachusetts, USA [75]	Maryland, USA [53]	New York, USA [52]
n	45	45	20	15	31	30	52	34	67
Age at onset mean/median (range)	38.3	40.7/? (>18 years)	34/? (>18 years)	35.6/? (?)	30/? (18–51)	?/36 (12–74)	32/? (4–83)	(15–55)	(1.4–65)
Female:male	2.46	0.67	1	6.5	0.55	0.67	1.17	1.27	1
Prior infection (%)		38	30		81	43	33	44	25
Sensory level									
Cervical	–	–	20	0	–	17	11	12	22
Upper thoracic	–	–	65	80	–	20	39	50	30
Lower thoracic	–	–	〃	〃	–	50	39	35	37
Lumbosacral	–	–	15	20	–	13	11	3	11
Time to maximum deficit, median (range) in days		3 (1–21)				Median 3.5 (1 h–20 days)		<1 h–14 days	
CSF									
Normal	–				2	14 (47%)			
Pleocytosis	19 (42%)	13/24 (54%)[b]	65%	8/13 (62%)	26/31 (84%)	15 (50%)	18 (35%)[a]	50%	–
OCB	8 (18%)	–	–	2/13 (15%)	0	1/13 (8%)	–		–
IgG index	–	7/24 (29%)[b]	–	4/13 (31%)	–	6 (20%)	–		–
Elevated protein	9 (20%)	–	45%	7/13 (54%)	28/31 (90%)	10 (33%)	18 (35%)	33%	50%
Definition elevated protein				>0.4 g/L	>0.45 g/L	>0.6 g/L	>0.5 g/L		>0.5 g/L

[a] Pleocytosis was defined as ≥4 cells/mm^3, 6 patients had between 200 and 300 cells.
[b] The frequency is reported only for the 24 patients with definite ATM_{TMCWG}.

ancestry, NMO is relatively more frequent in non-European populations with a low incidence of MS, including people from Asia and sub-Saharan Africa and indigenous populations of the Americas [66–68]. The results of case series suggest that non-Europeans are overrepresented in NMO cohorts relative to their proportion in the general patient population [2,68,69]. Although that implies that non-Europeans have a higher incidence of NMO, this is not borne out by the results of a recent population-based study from Cuba, in which inhabitants of mainly European, mainly eastern African, or mixed descent showed similar incidence and prevalence rates [49].

Table 5
Characteristics of ATM in children.

Reference	[62]	[76]	[77]	[61]	[78]	[79]
Cohort	Baltimore, MD, USA	Melbourne, Australia	New Delhi, India	Paris, France	Melbourne, Australia	Boston, MA, USA
Observation period	2000–04	1997–2004	2003–07	1965–95	1966–83	1929–1952
n	47	22	15	24	21	25
Female:male	1:1.04		6:9	13:11	11:10	15:10
Age at onset	8.3 (0–17)	7.5 (0.3–15 years)	7.9 (3.5–14)	8 (1–14)	7 months–14 years	8.2 (6 months–15 years)
Preceding infectious disease, %	47	71	60	58	38	52
Preceding vaccination or allergy shots, %	28	9	0	8		8
Sensory level		[d]				
Cervical, %	25	8	0	12[a]	19	8
Thoracic, %	53	58	53	85[a]	71	48
Lumbar, %	5	33	0	0	5	16
Sacral, %	3	0	0	0		
Unclear	14	0	47	0[a]	5% without	28
Complete paraplegia at nadir, %	89	74	60	65	67	
Acute sphincter dysfunction, %	82	68	80	83	86	96
Chronic bladder dysfunction, %	50	14	50	33[c]	33	
Full recovery, %	[b]	50	43	43	38	33
Good outcome, %	[b]	32	21	24	24	29
Fair outcome, %	[b]	9	14	14	19	25
Poor outcome, %	≥ 43	9	21	19	19	13
Deaths	2	0	1	1	0	1
Recurrent TM	2	0	0	0	0	0
Abnormal CSF						
Pleocytosis, %	50	67	50	58	48	57
Oligoclonal bands	<5			0		
IgG index	<5					
Elevated protein	48	38	67	12	52	

[a] These percentages are taken from Table 2 of [61]; the text reports 88% thoracic and 12% cervical, Table 1 shows 7 (29%) patients without information as to their sensory level.
[b] This study measured functional performance of daily skills using the WeeFIM for children and FIM for those aged >18 years at the time of follow-up. See the text for more details on outcome in this cohort.
[c] This derives from a subgroup of 16 patients with a mean follow-up of 7.25 years, of whom 15 had sphincter dysfunction and 5 were left with severe sequelae (another 5 had mild sequelae).
[d] Present in only 57% at nadir.

Table 6
Demographic and clinical characteristics of patients with NMO.

Reference	[102]		[103]	[11]	[104]	[65]	[28]	[12]	[68]		[107]
Cohort	USA		Italy	France	Brazil	Brazil	Brazil	Cuba/ Martinique	Mexico		Iran
	Monophasic	Relapsing	Relapsing			Relapsing	Relapsing	Relapsing	Monophasic	Relapsing	
n	23	48	46	125	24	41	28	48	34		44
Criteria	Wingerchuk 1999		Own	Wingerchuk 2006	Own	Wingerchuk 2006	Wingerchuk 1999	Wingerchuk 1999	Wingerchuk 1999		Wingerchuk 2006
Age of onset in years, mean/median (range)	?/29 (1–54)	?/39 (6–72)	40.1/? (12–77)	34.5/34.7 (4–66)	32.8/? (14–55)	32.6/? (20–60)	25.4/26 (7–55)	31.3/? (?)	35	31	32/31 (10–56)
Gender F:M	0.9:1	5:1	4.1:1	3:1	5:1	2.4:1	8.3:1	8.6:1	2.8:1	1.75:1	3:1
Duration of follow-up in years			8.8 (1–26)	10/8.7/(0.1–39.5)	9.2/? (?)	4.3/?	7 (2–14)	9.7	5.9		4.7/4 (1–16)
Monophasic, %	32		Excluded	26	12	Excluded	Excluded	Excluded	68		0
Relapsing, %		68	100	74	88	100	100	100		32	100
Presenting attack											
Myelitis, %	22	42	39	45.6	38	42	39		35	36	31
ON, %	43	56	57	36.8	33	34	61		22	27	52
ON + myelitis, %	35	2	4	17.6	29	24	0		43	36	2[b]
Time to 2nd index event mean or median (range) in months	5 days	166 days		???/15 (0–264) months	20 days (1–45)	mean 21 (1–200) months		2.5 years	12.4/3.5 (0–101)		17.9/9 (0.5 month–12 years)
Time to first relapse (mean/median/range in months)			17/? (1–120)	30.8/15/1–204				20.3 (±25.1) months			
Relapse rate			1.3 (0.1–5.5)	0.99		1		0.9			1.1
Death secondary to respiratory failure, %		31	11	1.6	22	12	11				0
CSF analysis (no patients)	15	38	Variable		Variable	31		44			9
Pleocytosis[a], %	73	82	39		41 (≥4 cells)						
WBC >50, %	36	34	13% of samples		6%	13		7			
OCB, %	43	33	34	23.8	22%	0/10			0	0	22
NMO–IgG, %				54		41	64	33			30
ANA, %	0	48	11			34	46		0	0	18
Autoimmune diseases, %		31	11	10.4	8	2 (possibly SS)	25				3

[a] Generally defined as >5 cells/mm^3.
[b] 6 patients had "other" onset.

2.3. Age of onset

Acute transverse myelopathies can occur at any age, but age of onset in older studies showed a bimodal distribution, with peaks between the ages of 10–20 and 30–40 years [52,54,55]. The data provided on patients diagnosed according to the TMCWG criteria generally does not contain information on the age distribution, but the mean age of onset ranges between 35 and 40 years [37,48,57,60] (see also Table 4). There may be a third peak, as evidenced by the observation that 38% of the patients were under the age of three in a recent study of 47 pediatric (<18 years of age) patients with ATM_{TMCWG} [62]. Similarly, 42% of children with ATM_{TMCWG} were under the age of 10 years at disease onset in the Canadian incidence study [39].

Like ATM, NMO can affect people of all ages, but onset most frequently occurs between the ages of 20 and 50 ([63,70] and see Table 6). At the Mayo Clinic, the median age of onset was found to be significantly higher in patients with recurrent NMO compared to those with monophasic disease (41 compared to 29 years) [63]. A similar trend was obvious in a large French cohort (38 compared to 33 years), but the difference just failed to reach statistical significance ($p = 0.07$) [11]. In contrast to these US and European cohorts, the mean age of onset in patients from a variety of other countries is considerably younger, even though many of the cohorts consist exclusively of patients with relapsing disease (see Table 6). Somewhat paradoxically, the mean age at onset was 31.8 years, but was markedly lower in white compared to black patients (29.9 vs. 36.9 years) in a population-based study from Cuba [49].

3. Clinical characteristics of ATM

3.1. Diagnosing ATM

The first priority after taking the patient's history and performing a physical examination to confirm acute myelopathy is to rule out a compressive etiology by MRI or myelography. For this purpose, a gadolinium enhanced MRI of the spinal cord should be taken within 4 h of presentation. If no structural abnormalities or spinal mass are detected, the next priority is to establish whether there is inflammation of the spinal cord as evidenced either by gadolinium enhancement on MRI or the results of CSF analysis showing either pleocytosis or an elevated IgG index. The third priority is to determine whether demyelination extends beyond the spinal cord, i.e., also affects the brain and/or optic nerve or tract by obtaining a brain MRI and visual evoked potential. If confined to the spinal cord, a diagnosis of ATM is reached, and the final step then is an attempt to establish an etiology. It should be determined whether the patient or if the patient has clinical or serologic evidence of SS, SLE, APS, sarcoidosis, or other autoimmune diseases, or even fulfills the standard criteria for the suspected disorder. If there are indications of an inflammatory process, and particularly if the patient reports a preceding or concomitant infectious disease, the work-up should also encompass performing serology for a variety of antibodies (e.g., to HSV, VZV, HTLV-1, *B. burgdorferi*), serology for hepatitis A, B, C, *Mycoplasma*, and possibly parasites, and determining whether the CSF provides evidence of bacterial, viral, or parasitic infection. Of note, although case reports document the occurrence of true infectious transverse myelitis, the required proof of the presence of infectious organisms or the appropriate antibodies in CSF is often difficult [71]. In addition, ATM often develops after the infection has subsided. In such cases, the TM is classified as parainfectious or postinfectious. Unfortunately, there are no universally accepted criteria for classifying ATM as post- or parainfectious. Consequently the proportions of cases considered as parainfectious vary widely between studies [35,48,56,62]. If no association with systemic autoimmune diseases, viral, bacterial or parasitic infections, or NMO can be found, ATM is classified as idiopathic. This may have to be revised if the patient later develops ON, MS, or evidence of other systemic autoimmune diseases.

The differential diagnosis of ATM is complex and, in addition to the diseases defined by the exclusion criteria listed by the TMCWG (see Table 1), includes inflammatory diseases of the CNS not confined to the spinal cord, such as various forms of encephalomyelitis, and also some metabolic myelopathies. The most important among these are myelopathy due to acquired copper (Cu) deficiency and subacute combined degeneration (SCD), i.e., myelopathy caused by vitamin B12 (B12) deficiency. The well known hematological manifestations of Cu and B12 deficiency may or may not be present in affected patients.

The clinical and imaging features of Cu deficiency myelopathy and SCD are virtually indistinguishable and include ascending paresthesias, weakness, and gait disturbances arising from sensory ataxia most commonly due to posterior column dysfunction. In contrast to ATM, both are most commonly subacute and progressive syndromes, although progression to spastic paraparesis may occur within a few weeks in some patients. In accordance with these clinical findings, signal abnormalities on T2-weighted MRI images are seen predominantly in the posterior columns of the lower cervical and upper thoracic cord. This selective tract involvement distinguishes most metabolic myelopathies from ATM, where central or even holocord lesions are typical. However, more extensive signal abnormalities or lesions involving the central cord have been described in some patients with SCD or Cu deficiency myelopathy [72,73]. Even contrast enhancement of the lesion after gadolinium injection has been reported in some cases of SCD, though it has not been observed in Cu deficiency myelopathy [72,73].

The most important risk factor for Cu deficiency myelopathy is previous upper gastrointestinal surgery, with onset of symptoms of Cu deficiency myelopathy occurring on average 11 years after bariatric surgery and 22 years after non-bariatric surgery [72]. In addition, Cu deficiency may arise from zinc overload (in some cases due to the use of zinc-containing denture creams), and malabsorption syndromes. While malabsorption syndromes and previous gastrectomy also constitute risk factors for SCD, B12 deficiency is more likely to arise from pernicious anemia, but can also be caused by intrinsic factor defects and insufficient dietary intake (e.g., in strict vegetarians) [74]. In about 15% of cases SCD develops following exposure to nitrous oxide during general anesthesia or from chronic use as a recreational drug. Of note, Cu and B12 deficiencies may co-exist in the same patient.

Vitamin B12 or Cu therapy halts the progression of myelopathies due to the respective deficiency and results in some improvement in most patients. However, complete resolution is rare and mostly occurs in patients who are treated early in the course of their illness at a stage where their neurologic deficits are less severe. This underscores the importance of timely diagnosis and treatment. It is widely thought that Cu deficiency myelopathy is currently underrecognized, yet the prevalence of this syndrome is likely to increase due to the growing prevalence of gastric bypass surgery. Therefore, it is important for physicians to be aware that B12 and Cu deficiencies may underlie myelopathies that can mimic ATM.

3.2. Clinical course of ATM

Detailed information on the clinical course of ATM largely comes from studies of patients with acute transverse myelopathies, which used a variety of diagnostic criteria and included cases with a wide range of inflammatory and non-inflammatory etiologies. A substantial portion (25% to 44%) of patients report a variety of bacterial or viral infections preceding the onset of symptoms [52,55,75], the corresponding figures for patients with ATM_{TMCWG} are 7% to 38% [57,60]. The proportion is even higher in children, ranging between 38% and 71% [61,62,76–79]. It appears that much of the variability derives from the level of evidence required for establishing the occurrence of an

infectious disease and for deciding whether to classify ATM as parainfectious or idiopathic. There are few direct comparisons between parainfectious and idiopathic myelitis, and the numbers of patients are too small, the criteria too inconsistent, and the results too variable to allow firm conclusions about potential differences in disease expression. Particularly in pediatric cases, a considerable portion of patients also received vaccinations or allergy shots in the month preceding the onset of symptoms [61,62]. According to a recent review article, 43 cases of post-vaccination TM were reported between 1970 and 2007, 37 of them with sufficient data for further analysis [80]. Vaccination against hepatitis B virus (HBV) was most frequently implicated, followed by measles–mumps–rubella or rubella alone, diphtheria–tetanus–pertussis, rabies, polio, influenza, Japanese B encephalitis, and typhoid vaccines. In the pediatric age range, where multiple routine vaccinations are scheduled, an association between preceding immunization and the onset of TM may be spurious. However, at least one third of ATM cases subsequent to vaccination have been reported in adults, providing somewhat stronger support for a possible causal association with ATM [80]. Indeed, a causal relationship between the oral polio vaccine and TM is considered to be established; in other cases an association may appear plausible but causality has not been demonstrated.

A frequent presenting sign of ATM is fever in and is often, but not always, associated with infections [52,55,58,81]. Early symptoms generally consist of combinations of sensory dysfunction, paresthesias or pain in the back, abdomen or the extremities, and an often ascending pattern of numbness or weakness of the legs, whereas the upper extremities are less frequently and generally less severely affected. Loss of pain and temperature sensation is the most common sensory disturbance, position and vibration perception may be spared. Autonomic signs consisting of urinary retention, incontinence, constipation, fecal incontinence, and possibly sexual dysfunction may already be present at onset as well. These signs and symptoms progressively worsen over a period of hours or days, with a majority of patients reaching their maximum deficit within 7 days, although full evolution may take up to 21 days, the maximum allowed by the TMCWG criteria [52,53,55,75,82]. A recent analysis of patients with idiopathic ATM_{TMCWG} confirmed a median time to maximal deficit of 3 days with a range of 1–21 days [57]. A hyperacute onset, i.e., reaching nadir within less than 4 h, is an exclusion criterion because it is most commonly seen in vascular myelopathy [1]. However, the TMCWG acknowledged that some cases of true ATM with very rapid progression might be excluded by this criterion.

At the time the maximum deficit is reached, at least two thirds of patients are unable to walk because of severe paraparesis or paraplegia [34,52,53,55,58,75,81,82]. Spinal shock, i.e., flaccid paralysis with are flexia and loss of cord function below a discrete level is seen in up to one third of patients with ATM [53,55,75], and possibly is more frequent in parainfectious compared to idiopathic ATM [35]. Essentially all patients experience some degree of bladder dysfunction, which most commonly manifests as urinary retention and is severe enough to require catheterization in approximately half of all patients. In addition, a vast majority of patients exhibit various types of sensory dysfunction, including sensory loss, but also hyperesthesias, paresthesias, or bandlike dysesthesias. Pain persists in many patients.

There usually is a well-defined rostral border of clinical sensory loss, which is most frequently thoracic, i.e., in ~60–80% of patients in older studies [52–55,81], similar to what has been reported in patients with ATM_{TMCWG} [37,58,83] (see also Table 4). A cervical sensory level is observed in most of the remaining patients, while a lumbosacral level is relatively rare (3–20%). According to unpublished data from the Johns Hopkins Transverse Myelitis Center (JHTMC) on 170 patients with idiopathic ATM, the sensory levels were cervical in 22% of the patients, thoracic in 63%, lumbar in 9%, and sacral in 6% (the remaining 7% had no sensory level) [40]. The corresponding location of the T2 signal abnormality on spinal MRI was cervical in 44%, thoracic in 37%, and multifocal in 5%; in 6% of cases there was a hypointense lesions on T1-weighted images, indicating tissue loss and persistent axonal damage. In contrast, spinal MRI revealed cervical and thoracic lesions in 60% and 33%, respectively, in a cohort of French patients with ATM_{TMCWG}; no patient had a lumbar lesion, (the remaining 7% are unaccounted for) [48]. There are few systematic investigations of lesion length in idiopathic ATM. It is clear, however, that a considerable portion of patients manifest LETM on spinal MRI, with several studies reporting rates between 60% and >90% [14,15,60,82,84,85]. In contrast, in a recent study of patients with definite or possible ATM_{TMCWG}, the median number of segments involved on spinal MRI was 2 (range 0–8) [57]. And in another analysis of 20 patients with ATM_{TMCWG}, the mean length of signal abnormalities was 1.6 [86]. The results of CSF analysis of patients with ATM are summarized in Table 4.

3.3. Outcome of ATM

The outcome of ATM can range from spontaneous and full recovery to complete inability to walk and, in cases with involvement of the upper cervical cord reaching into the brain stem, to death from respiratory failure [53,60]. If any degree of recovery occurs, it usually starts within weeks after onset of symptoms and is most rapid during the first 3–6 months, although further improvement may be seen for up to 2 years, and some patients report subjective return of sensation for up to 4 years [53,55,75]. The results of older studies of non-compressive myelopathies indicate that complete recovery is seen in a minority (up to 15%) of adult patients [52,75,81]. Overall, approximately one third of patients has a good outcome (either complete recovery or left with normal gait, mild urinary symptoms, and normal or minimally abnormal neurological signs), one third has a fair outcome (functional and ambulatory, but with varying degrees of spasticity, urgency and/or constipation, and some sensory signs) and one third has a poor outcome, i.e. remains completely or largely unable to walk, has at best partial sphincter control, and is left with severe sensory deficits [52,55,75,81]. Unfortunately, information on the evolution of the disease and the eventual outcome is not available for cohorts of patients diagnosed with idiopathic ATM_{TMCWG}, except that 1/3 of such patients had a poor outcome in the French study that was the first to apply these criteria [48]. According to unpublished data, only 20% of patients experienced a good outcome in the JHTMC cohort, which may reflect the greater severity of cases seen at a tertiary referral center [40].

3.4. ATM in children

Compared to adults, TM in children is more frequently preceded by an infectious disease (between 38% and 71% of cases — see also Table 5) [61,62,76,78,79]. The disease course appears to be more severe, with at least 60% and as many as 90% of pediatric patients being unable to move their legs at the time of maximum deficit. Nonetheless, complete recovery occurred in 33–50% of patients, whereas a poor outcome was only seen in 10–20% of cases (Table 5) in most series reported to date [61,76,78,79]. This suggested that, despite its severe expression in pediatric patients, the disease had a much more favorable prognosis compared to adults. However, this contrasts with the results reported for a cohort of 47 children with ATM_{TMCWG} (including disease-associated cases) who were followed at the JHTMC [62]. After a median of >3 years of follow-up, 43% remained unable to walk at least 30 ft, 21% required a walker or other forms of support to walk more than 30 ft. In addition, permanent bladder dysfunction was severe enough to necessitate catheterization in 50% of patients. The reasons for these discrepant results are not immediately obvious. Disease-associated cases were also included in other studies, but the proportion of toddlers was

higher in the JHTMC cohort compared to all others (38% vs. 4%–25%), and onset under 3 years of age was associated with worse outcome in terms of independence in activities of daily living and continence [62]. Similarly, age <6 months at onset was associated with a poor prognosis in another series of children with ATM_{TMCWG}, but only 2 children were in this age group [76]. Of note, lesions on MRI of the spinal cord are longitudinally extensive in a majority of children (67–87%) [62,76,77,87]. While LETM is associated with recurrences and is generally considered to be characteristic of NMO in adults, children with idiopathic ATM rarely have relapses or progress to NMO [62,88] (see also Table 5).

3.5. Prognostic factors for poor outcome in ATM

A long list of factors has been associated with a poor outcome in ATM, including back pain [55,75], time to maximal deficit of <24 h [61,75], and the longitudinal extent of spinal cord involvement [62,82]. In children, requirement for respiratory support and young age at onset [62,76], a higher sensory and anatomical level of the spinal lesion [62], and complete paraplegia were identified as additional factors [61]. Presentation with spinal shock was found to be highly predictive of a poor outcome in ATM_{TMCWG} [48], confirming earlier findings in acute transverse myelopathies [53,55,75]. However, in the only existing multivariate analysis of data from patients with ATM_{TMCWG} available to date, only a higher disability (Rankin) score upon admission predicted poor outcome [57], as had also been noted in an earlier study [81]. The difficulty of predicting outcome even in homogeneous patient groups like those diagnosed according to TMCWG criteria has prompted researchers to search for serum or CSF markers that could predict a poor outcome [48]. One candidate is the 14-3-3 protein, an indicator of neuronal injury. It was associated with failure to recover in one study [89], but others found that it lacked sensitivity and specificity [90].

There are no randomized controlled trials of treatment modalities in idiopathic ATM, but small observational studies suggest that intravenous (i.v.) methylprednisolone may be helpful in the acute stage, particularly in children [40,61]. Some physicians follow up with oral prednisolone. Plasma exchange is offered when methylprednisolone is ineffective, and some patients are treated with i.v. cyclophosphamide or i.v. immunoglobulins. For prevention of relapses in the subgroup of patients with recurrent ATM, immunomodulators such as azathioprine, methotrexate, mycophenolate or oral cyclophosphamide may be helpful. Several studies did not reveal a significant association between treatment and outcome in adult patients [48,57,81], but oral steroids were associated with better mobility in children [62].

3.6. Conversion to MS

Acute myelitis can be a presenting feature of MS, but this is rare when ATM is defined according to the TMCWG criteria, occurring in 0 to 11% of adult patients [37,48,57,58,86] and 2% in children [62]. More commonly, patients who eventually are diagnosed with MS present with acute partial TM. This corresponds to one of the clinically isolated syndromes, defined as “a monophasic presentation with suspected underlying inflammatory demyelinating disease” [3], which may or may not be the first manifestation of MS. Like ATM, acute partial TM shows acute or subacute onset, but the sensory or motor dysfunction is mild and often unilateral, or bilateral and markedly asymmetrical.

When associated with cerebral MRI abnormalities typical for MS, acute partial TM converts to MS in 70% to 90% of patients in a few years, while the conversion rate in patients without such abnormalities ranges between 20% and 40% over a follow-up of 2 to 5 years [37,59,91–93]. In addition to abnormal brain MRI results, the presence of oligoclonal bands (OCBs) or an elevated IgG index in CSF is consistently associated with conversion to MS [37,59,92,93], which accords with the high frequency of OCBs in MS patients (at least those of European extraction) and their rather infrequent detection in patients with idiopathic complete ATM (0–18%) [37,48,81]. In addition, CSF pleocytosis, posterolateral lesions on spinal MRI [93], the presence of ≥2 spinal lesions [37], a family history of MS and higher disability scores at onset may have prognostic significance [92]. Note that >40% of patients with acute partial TM experience monophasic disease, while the frequency of relapses limited to the spinal cord has varied between 0% and 47% [37,59,91–93]. Much of this variability appears to depend on whether patients who experience a relapse at a different spinal level are classified as MS or recurrent TM. Because ATM and acute partial TM are closely related syndromes, but differ markedly in their prognosis, it has been proposed that acute partial TM should be included in the classification of idiopathic TM syndromes [91].

3.7. Recurrences in ATM

While recurrences of ATM had been known to occur in cases associated with infectious or systemic autoimmune diseases, idiopathic ATM was originally considered to be monophasic. Now, it is recognized that up to 25% of patients with ATM_{TMCWG} have recurrent disease [40,48,86]. Early descriptions of recurrent TM deal with patients in whom ATM relapsed at the same clinical site as the initial attack [94,95]. Some subsequent reports describe cases with similar sensory level as during the initial attack in conjunction with rostral and/or caudal expansion of the lesion in later episodes, though still overlapping the originally affected spinal segments [96,97], whereas other recent studies include cases with different sensory levels and involvement of different spinal segments in each of their attacks [86,98,99]. Of note, in many of these cases, the lesions are longitudinally extensive, although not all of the relapses in a single patient represent LETM [86], and some episodes of acute partial TM have been reported in patients who experienced LETM during another attack [98]. Among a cohort of 41 Brazilian patients with ATM_{TMWCG}, 61% experienced a recurrence [60]. Interestingly, in many of these patients the myelitis was both partial and longitudinally extensive. While the majority of patients with recurrent ATM described to date exhibit LETM, the frequency of LETM was higher in patients with a single attack compared to patients with recurrent disease (81% vs. 48%) in this Brazilian cohort.

Cord swelling is a common finding on spinal cord MRI in patients with recurrent ATM, and contrast enhancement of the lesion after gadolinium injection is generally seen [86,94,96,97,99,100]. Lymphocytic CSF pleocytosis is frequent, whereas oligoclonal bands are occasionally observed, but both features may only be present in some of the attacks. Of note, in one case with acellular CSF, a cervical biopsy revealed polymorphonuclear infiltration [99]. Such polymorph infiltration is typical of NMO; however, eosinophils and hyalinized vessels, which are other typical findings in NMO, were not detected in the biopsy. Visual evoked potentials were normal. Nonetheless, this and another patient described in the same report were later found to be positive for NMO–IgG [27]. Similarly, 4 of 17 Brazilian patients tested positive for AQP4 Abs, 3 of them with recurrent disease, 2 with LETM [60]. This again underscores the considerable overlap between recurrent TM, particularly LETM, and NMO. In contrast, marked male predominance (compared to the female preponderance in NMO) and a very low positivity rate for AQP4 Abs in Korean patients suggest that recurrent LETM does not represent a limited form of NMO in this population, but constitutes a separate entity [25,98].

The results of a small study suggest an association between recurrence and anti-Ro (SSA) antibodies in patients with ATM_{TMCWG} with or without optic neuritis [101]. This is not confirmed by another investigation, in which only 18% (8/44) patients with recurrent LETM tested positive for anti-SSA antibodies [23]. Unfortunately, whether

the patients with recurrent ATM_{TMCWG} manifested LETM was not reported [101].

4. Clinical characteristics of NMO

4.1. Clinical course of NMO

Relatively few studies address the frequency of infections preceding the onset of NMO, but these show rates between 15 and 25% [102–104]. The literature published between 1975 and 2009 was found to contain reports on only 25 cases of parainfectious NMO, 16 of them with sufficient data for further analysis [105]. Varicella-zoster virus and *Mycobacterium pneumonia* (3/5) were the most frequently identified viral and bacterial pathogens, respectively. As summarized in Table 6, the most common initial event in NMO is ON. At least one third of patients present with myelitis before developing ON, whereas a minority of patients manifest TM and ON simultaneously or in close temporal association. A relapsing remitting course is typical of NMO, seen in >80% of patients [11,12,28,63–65], the exception being a Mexican cohort in which 68% of patients experienced monophasic disease [68]. Relapses can consist of TM or ON, rarely both together, occurring in random sequence and at unpredictable intervals. There are some indications, that relapses are most frequent during the first two or three years after disease onset [11,102]. Generally, there is some improvement seen after each attack, although overall deterioration is cumulative with each new episode of either TM or ON [102]. A progressive course is rare (≤2%) [11,106]. The results of serum and CSF analyses are also summarized in Table 6.

According to the Task Force criteria for the diagnosis of NMO specify, the TM can be clinically complete or incomplete [3]. Partial TM was reported to constitute one of the index events in 7 of 24 Brazilian NMO patients and, with one exception, further episodes of myelitis were also characterized as partial in these patients [104]. Similar to recurrent ATM, a characteristic feature of NMO is the presence of LETM on spinal cord MRI [2,11,12,16,64,65,107]. Indeed, evidence of LETM is an absolute requirement for the diagnosis of NMO according to the criteria proposed by the international Task Force [3]. However, while LETM is observed in 87 to 100% of patients in at least one of their attacks, the lesions may not be longitudinally extensive during all episodes, including the initial one [2,11,12,16,64,65,107]. Therefore, requiring LETM as an absolute criterion may be overly restrictive and delay appropriate treatment. It would also exclude a substantial portion of patients with OSMS from the diagnosis of NMO since LETM is only seen in ~60% of this patient group [20,21]. In NMO patients, the spinal MRI abnormalities are cervical or cervico-thoracic in ~80% of patients [28,68,69,107]. In addition, brain MRI reveals abnormalities are present at onset or develop during the course of the disease in up to 60% of pediatric and adult patients [88,108]. Brain lesions used to be an exclusion criterion for NMO, but are now considered to be compatible with a diagnosis of NMO as long as they do not satisfy the diagnostic criteria for MS (see also Table 2). The brain MRI abnormalities in NMO patients are most frequently non-specific white matter lesions, but in some NMO patients they resemble those typically seen in MS, while approximately 10% of patients have distinctive lesions that are atypical of MS. These lesions mainly involve the hypothalamus, sometimes extending into the third and fourth ventricles. The corpus callosum or the brain stem can also be affected. Brain stem lesions can occur in isolation or as rostral extensions of cervical lesions. While clinically silent in most cases, this brain involvement can be symptomatic in some patients.

4.2. Outcome of NMO

The most detailed data on the outcome of myelitis in NMO derives from a study that analyzed data from 71 patients with NMO with a mean disease duration of 19.9 and 7.7 years in the monophasic and relapsing groups, respectively [102]. Approximately one third (31%) of the patients with monophasic disease and 52% of those with relapsing disease exhibited permanent monoplegia or paraplegia. Among the survivors, the proportion of patients who could walk with no or unilateral assistance was 65% and 53% in the monophasic and relapsing groups, respectively. Despite the shorter disease duration, motor strength, sensory function, and visual acuity were significantly more severely impaired in the relapsing compared to the monophasic group. This suggests that, compared to ATM, the outcome of TM NMO is worse because a relapsing/remitting disease course is more frequent, and relapses generally result in the stepwise accumulation of damage. In addition, damage is also accrued in the optic nerve, with 60% of the patients with a relapsing disease course manifesting severe residual visual loss (SRVL, defined as visual acuity of ≤20/200) in at least one eye, compared to 22% of the monophasic group [102].

In more recent studies, the outcome of TM in NMO is difficult to appreciate since it has become customary to report global expanded disability status scale (EDSS) scores, which reflect disability in a variety of functional systems, including pyramidal, sensory, bowel/bladder, and visual. An EDSS score of 6 features in several studies because it represents loss of autonomy due to disability reaching a grade that is severe enough to alter everyday activities. Unfortunately, the manner in which results are reported differs substantially between studies, making overall comparisons difficult. Median delay to EDSS 6 was 10 years in a recent large multicenter study involving 125 French NMO patients [11], and 7 years in an Italian cohort [103]. In a cohort of Brazilian patients with relapsing NMO, the median EDSS score was 5.5 after a median follow-up of 7 years, and 46% of patients had EDSS ≥6 [28]. Among another Brazilian cohort with recurrent NMO, 39% of patients reached EDSS 6 within an average of 37 months (range 5–89 months) [65]. Afro-Caribbean patients with NMO had reached a mean EDSS score of 7.1 after a mean disease duration of 6.9 years [50]. In contrast, only 13.6% of Iranian patients with relapsing NMO had an EDSS score ≥6 after a median disease duration of 4 years [107]. Median time from onset to severe residual visual loss (SRVL, ≤20/200) also varies widely [11,64,68,109]. The overall data and some direct comparisons suggest that patients of African descent experience more rapid and more severe overall disability and visual loss compared to patients of European extraction [28,64,104]. In contrast, others did not find significant differences in EDSS scores between Cuban NMO patients of predominantly European, African, or mixed descent [49]. Patients with NMO also face a significant risk of death from respiratory failure caused by acute myelitis with high cervical cord involvement extending into the brainstem. The rates of death secondary to respiratory failure range from 0 in an Iranian cohort [107] to 32% in a large US patient series [63] (see also Table 6). Mortality rates have been reported to be higher in patients of African descent [64,104].

4.3. NMO in children

There are few data available on NMO in pediatric patients, reflecting the rarity of the disorder in children. It would seem that the female predominance and the frequency of LETM are similar in children with NMO compared to their adult counterparts, but bilateral ON and brain involvement may be more common while a relapsing disease course seems to be somewhat less frequent [88,110,111]. In some series, the prognosis is relatively benign, with the vast majority of patients experiencing a good or complete recovery of motor function and a minority being left with severe visual impairment [88,110]. However, in a recent series of 8 children with NMO and 1 with LETM plus NMO–IgG positivity, only 2 experienced complete recovery, 4 were left with paraparesis or quadriparesis, and 4 experienced severe vision impairment [111]. Similarly poor outcomes have been reported in a cohort of children with NMOsd, including patients with definite NMO [112].

4.4. Predictors of a relapsing disease course and prognosis in NMO

Female sex, older age at onset, milder initial motor impairment, and longer time between the two index events were identified as predictors of a relapsing disease course in multivariate analysis [63,102]. A previous analysis of data from a subset of this cohort had indicated that the presence of systemic autoimmunity was also associated with a relapsing disease course [102], but this was not retained in the final model based on the analysis of the larger cohort [63]. In contrast, in the largest study to date, neither the gender nor the age distribution was significantly different between patients with monophasic vs. relapsing disease [11]. A review of case reports indicated that post-infectious NMO was frequently monophasic (88%), and complete recovery was seen only in patients with NMO following viral infections (4/11), whereas little recovery and one death occurred in patients with NMO after bacterial infections [105]. Note, however, that preceding viral illness was not associated with a monophasic vs. relapsing disease course or survival in a cohort of 80 patients from the Mayo clinic [63].

Later age at onset (>40 years), a short interval between the index events, and a high relapse frequency, particularly during the first year, have been identified as possible predictors of disability in NMO [11,103]. Interestingly, a residual EDSS ≥3 at onset correlated with less disability (probability of not reaching EDSS 6) in the long term [103]. In addition, "type of treatment" was reported to be associated with disability in univariate analysis, but neither the treatment modalities nor the direction of the association was specified [11]. Because of confounding factors, none of the variables associated with disability was significant in multivariate analysis, but a high number of lesions on brain MRI independently predicted a shorter time to the diagnosis of SRVL [11]. Possible association of disease severity and disability with seropositivity for NMO–IgG will be discussed later. Predictors of death consisted of history of other autoimmune disease, attack frequency during the first two years of the disease, and better motor recovery after the index myelitis event [63]. In another study, however, an association with autoimmune abnormalities was not detected [103].

5. Serologic or clinical evidence of autoimmunity in ATM and NMO

Serologically, idiopathic ATM and NMO are clearly different since up to 97% of patients with NMO are positive for NMO–IgG/AQP4 Ab [10], whereas this antibody generally is not detected in patients with monophasic ATM [13,15,27] and is also absent in at least 35% of patients with LETM [10] (see also Table 3). Little is known about the prevalence of autoantibodies in the absence of clinical disease in patients with idiopathic ATM because serologic evidence of autoimmune disease has long been considered sufficient to exclude these patients from the idiopathic category. A notable exception is the small study showing high frequencies of anti-Ro and ANA positivity in patients with recurrent ATM_{TMCWG} and in a lower, but still substantial, proportion of the control patients, who mostly had definite or possible monophasic ATM_{TMCWG} [101]. In addition, the prevalence of anti-GM1 ganglioside Abs was found to be 46% in children with ATM compared to 7% in controls [77]. Furthermore, it was recently reported that 26% of 27 children with ATM_{TMCWG} had a family history of autoimmune disease [87]. Approximately 20% of ATM_{TMCWG} cases were reportedly associated with systemic autoimmune diseases [48]. Unfortunately, it was not stated how patients were classified if they had non-organ-specific autoantibodies but did not fulfill official diagnostic criteria for SLE, SS and other autoimmune diseases.

Patients with NMO and NMOsd without clinical signs of other autoimmune diseases frequently manifest a variety of non-organ-specific autoantibodies, most commonly antinuclear antibodies (ANA), but also antibodies to dsDNA and extractable nuclear antigens ([2,70] and see Table 6). Even higher frequencies have been reported in children [111,112]. There are indications that such autoantibodies are significantly more common in patients who are positive for NMO–IgG/AQP4 Abs compared to seronegative patients [21,23], although this is not an entirely consistent finding [17]. The proportion of NMO patients with associated autoimmune diseases has ranged from zero in Mexico to 38% in a small cohort of French patients (see Table 6 and also [2,23,113]). Patients with NMOsd (LETM) show a similar frequency of coexisting autoimmune diseases as patients with definite NMO [23]. Compared to patients with ATM, the spectrum of autoimmune disorders associated with NMO and NMOsd is broader, encompassing not only systemic autoimmunity, but also organ-specific autoimmune diseases such as autoimmune thyroiditis, ulcerative colitis, myasthenia gravis, and various others [11,23,103]. A family history of autoimmune disease also appears to be quite frequent in patients with NMO [2], particularly in pediatric patients [111]. Even some cases of familial NMO have been described, but do not include any multigenerational pedigrees [114]. The frequency of familial aggregation has been estimated around 3% [114].

Of note, the Task Force NMO diagnostic criteria specifically exclude cases showing evidence for sarcoidosis, vasculitis, or clinically manifest SLE or SS from the diagnosis of NMO [3]. Although aware of the evidence strongly suggesting that patients with NMO in the context of SLE or SS are afflicted by two independent, co-existing autoimmune diseases [23,30,31], the Task Force chose this conservative approach pending further studies [3]. The mere presence of ANA or anti-SSA/SSB, however, is not an exclusion criterion.

6. Pathogenesis of idiopathic ATM and NMO

6.1. Infectious and inflammatory mechanisms in idiopathic ATM and NMO

Since infectious diseases frequently precede the onset of ATM, it has long been hypothesized that microbial agents may play an important role in the pathogenesis of this syndrome [40]. They could do so by causing neurological injury either directly, or indirectly by triggering an immune reaction that damages neural tissue as a bystander effect, or by infecting a remote site, thereby activating systemic immune responses. Although there are examples of ATM arising from a direct infectious process, most frequently a preceding infection has fully subsided before the onset of signs and symptoms of TM and an infectious agent cannot be demonstrated in the CNS. In addition, cases of TM subsequent to vaccination have been reported. Together, these findings suggest that TM results from the activation of autoimmune responses. Possible mechanisms include 1) acceleration of a pre-existing autoimmune process; 2) polyclonal activation of B cells or bystander activation of autoreactive T cells, resulting in humoral or cell-mediated derangements targeting the central nervous system, or 3) molecular mimicry, i.e., the ability of viral or bacterial antigens to induce cross-reactive immune responses against self antigens. While the wide variety of vaccines associated with TM suggests that a common denominator, possibly an adjuvant, may be responsible for triggering TM in these cases [80], there is at least one report implicating a vaccine not containing any adjuvant [115]. Furthermore, there are indications that molecular mimicry may play a role in cases of ATM subsequent to immunization or infection. For example, the HBV surface antigen (HBsAg) not only shares strong homology with myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG), but almost half of normal subjects who received a HBV vaccine exhibited anti-HBsAg antibodies that also recognized one or more MOG peptide(s), although none cross-reacted with MBP peptides [116]. Of note, cases of ATM have also been reported after HBV infection [117], and in a high-titer HBsAg carrier [118]. Immune complexes containing HBsAg were detectable in serum, but not CSF of this carrier. This indicated that immune complex deposition in CNS was unlikely to represent a relevant

mechanism and suggested that other mechanisms, possibly molecular mimicry, were involved.

Molecular mimicry has long been thought to play a primary role in triggering a variety of autoimmune diseases. However, evidence has remained elusive in most cases, with the possible exception of Guillain–Barré syndrome (GBS). Like ATM and NMO, GBS is a demyelinating disease, but it primarily affects the peripheral nervous system, although CNS pathology may also be present. There is substantial evidence implicating molecular mimicry between lipo-oligosaccharide (LOS) components of *Campylobacter jejuni* and human gangliosides in the pathogenesis of GBS in a subset of patients [119]. Gangliosides are sialic acid-containing glycosphingolipids present in the outer part of the plasma membrane that are expressed predominantly in the central and peripheral nervous systems. There have been a few case reports of ATM developing in close temporal association with *C. jejuni* infection [120,121], and in one case, the serum of the patient contained high titers of anti-GM1 ganglioside IgG and IgM, and the IgG antibodies were shown to cross-react with LOS from a *C. jejuni* strain that is known to contain a GM1 mimic [121]. (Unfortunately, the patient's own strain was not available for molecular mimicry studies.)

In a group of Indian children with ATM, 46% were positive for anti-GM1 IgG compared to 7% of control children, the corresponding figures for IgM being 33% vs. 7% [77]. Although 60% of the cases reported a preceding infectious disease (either upper respiratory tract infection or gastroenteritis), stool cultures were negative for *C. jejuni* in all children. Only one child each was positive for *C. jejuni*-specific IgM and IgA. Other infectious agents that have been associated with TM in conjunction with the production of anti-GM1 antibodies include *Enterobius vermicularis* (pinworm) [122] and *Brucella melitensis* [123,124].

There are also indication that molecular mimicry of *Mycoplasma pneumoniae* antigens and another class of nervous system glycosphingolipids, namely galactocerebrosides (GalC), may be of pathogenic relevance in demyelinating diseases of the central and peripheral nervous system [125,126]. Several cases of TM and acute disseminated encephalomyelitis with predominant spinal cord involvement subsequent to *M. pneumoniae* infection have been described [127]. The elaboration of anti-GalC antibodies in these patients has not been explored.

While there is limited data supporting autoimmune mechanisms in the pathogenesis of ATM, there is at least some histopathological evidence of inflammatory changes in the spinal cord tissue from TM patients [40]. According to unpublished data from the JHTMC, the affected segments invariably show perivascular infiltration by monocytes and lymphocytes in addition to astroglial and microglial activation, confirming earlier similar autopsy results [53]. Demyelination of white matter tracts and axonal injury are other prominent findings in both postinfectious and idiopathic ATM [40,128].

The CSF of patients with idiopathic ATM_{TMCWG} was found to contain dramatically higher (>260-fold) concentrations of the pro-inflammatory cytokine IL-6 compared to patients with non-inflammatory CNS diseases [128]. Serum levels of IL-6 were not significantly different between the groups, suggesting that IL-6 in ATM patients was synthesized within the CNS. IL-6 production during the acute phase of the disease correlated with disability (EDSS scores) at 6-month follow-up. It also correlated with CSF levels of 14-3-3 protein, which is thought to be a marker of neuronal injury. In addition, IL-6 was shown to be necessary and sufficient to cause demyelination and axonal damage in a nitric oxide-mediated and microglial cell-dependent manner in rat spinal cord organotypic cultures. Rats that received IL-6 infusions into the subarachnoid space also demonstrated demyelination and axonal degeneration similar to that seen in the autopsy material of a patient with a very high CSF concentration of IL-6. The effects of IL-6 were specific to the spinal cord and were not observed in hippocampal or cortical organotypic cultures or in rats infused into the cerebral ventricles. Astrocyte cytotoxicity was associated with increased nitric oxide production subsequent to activation of the JAK/STAT signal transduction pathway in spinal cord sections. This pathway was not activated by IL-6 in hippocampal or cortical tissue, suggesting that differential susceptibility to the cytotoxic effects of IL-6 underlies the selective targeting of the spinal cord in ATM.

The IL-6 concentrations in CSF samples from NMO patients were even higher than those of TM patients, although the difference did not reach statistical significance, with both groups showing significantly elevated levels compared to disease controls [129]. Anti-AQP4 positive NMO patients exhibited markedly higher levels of IL-6 in serum and particularly in CSF compared to AQP4 negative patients, and CSF IL-6 concentrations were significantly correlated with AQP4 FU values and EDSS scores [129]. Of note, patients with a limited form of NMO (AQP4 positive TM) showed significantly lower CSF concentrations of IL-6 at the nadir of attacks compared to patients with definite NMO (8/9 AQP4 Ab positive) [130]. Otherwise, however, the two groups did not differ significantly when compared during the first 5 years of their disease, except that EDSS scores at remission were higher in definite NMO. This suggests that IL-6 does not play an important role in the initial stages of NMO, but may contribute to exacerbating damage over time. A possible source of this IL-6 is suggested by the finding that NMO patients harbored significantly higher numbers of CSF mononuclear cells secreting IL-6 (and IL-5, but not IL-12) in response to stimulation with anti-MOG compared to patients with MS or healthy controls [131]. The NMO patients also had significantly higher numbers of cells secreting IgG and IgM after stimulation with MOG. IL-6 plays an important role in enhancing humoral immune responses, and this may represent another pathogenic mechanism in NMO, possibly in addition to its direct cytotoxicity for astrocytes at high concentrations [128].

Astrocytes themselves were identified as the major source of the markedly upregulated IL-6 concentrations in CSF of ATM patients [128]. IL-17 is known to induce cytokines that stimulate the production of IL-6 by astrocytes, but IL-17 was not detectable in CSF of TM patients, although T cells capable of producing IL-17 were demonstrable in CSF of some patients with TM (3/6) and MS (1/8) [132]. In contrast, the CSF concentrations of IL-17 and IL-8 were significantly higher in patients with OSMS compared to patients with conventional MS and control patients with non-inflammatory neurological disease [133]. This was not accompanied by enhanced CSF IL-6 levels, which contrasts with the markedly elevated concentrations of IL-6 reported in NMO patients [129]. Consistent with the role of IL-17 and IL-8 in neutrophil recruitment, neutrophils were detected in autopsy samples from 3 of 6 OSMS patients, and prominent neutrophilia was seen in 2 of 5 CSF samples [133]. Eosinophils, which are consistently found in autopsy material of NMO patients, were not detected in any of the OSMS samples, but this may have been due to methodological issues.

6.2. Humoral immunity in NMO

Even before the discovery of NMO–IgG as a specific marker of NMO and related disorders, there were several indications that humoral immunity plays an important role in the pathogenesis of Devic's syndrome. Patients with NMO frequently harbor non-organ-specific autoantibodies even in the absence of clinical signs and symptoms of autoimmune disease ([23] and see also Table 6). No treatment for NMO has been tested in randomized controlled trials, but the results of observational studies suggest that therapies targeting humoral effector mechanisms, such as plasmapheresis and depletion of B cells, are effective in reducing the relapse rate of NMO [134–136]. Most importantly, immunocytochemical studies of autopsy specimens from patients with NMO reveal spinal cord lesions characterized by extensive demyelination, cavitation, necrosis, and axonal loss in

association with inflammatory infiltrates consisting predominantly of macrophages/microglial cells and B lymphocytes with few $CD3^+$ and $CD8^+$ T lymphocytes [137,138]. In addition, eosinophils and granulocytes are prominent in the perivascular infiltrate of all early active demyelinating NMO lesions. These early active lesions further contain deposits of predominantly IgM and some IgG, which co-localize with products of complement activation in a typical "rim and rosette" pattern, surrounding thickened, hyalinized vessels. Of note, 3 of the 21 patients examined in these studies had a monophasic disease course, yet there is no indication that the immunopathology of these patients differs from that seen in a relapsing NMO [137,138]. In addition, a biopsy sample from a patient with limited NMO consisting of LETM with AQP4 seropositivity also showed the same characteristic pathologic findings [130].

6.2.1. Evidence of a potential role of AQP4 antibodies in the pathogenesis of NMO

6.2.1.1. Tissue and cellular distribution of AQP4. Aquaporin-4 is the most important water channel in the CNS and has vital roles in the formation of the blood brain barrier (BBB) and in cerebral water homeostasis. It is abundant not only in the spinal cord and optic nerve, but is highly expressed throughout much of the brain [139]. In addition, there is very strong expression of AQP4 in the basolateral membranes of collecting tubules of the kidney and of gastric parietal cells [5,139], high expression in the sarcolemma of skeletal muscle and in the lower respiratory airways and the alveoli in the lung, and moderate expression in the parotid salivary gland and in parts of the male reproductive system [139]. There are at least three isoforms of AQP4, the two major ones being M1 and M23, which arise from different start codons and differ in length by 23 amino acids. These two variants form heterotetramers, but only tetramers containing M23 can form larger structures known as orthogonal arrays of particles (OAPs) [140]. It currently is unknown whether the frequency and size distribution of OAPs differ in the various tissues with AQP4 expression. It also remains unclear whether AQP4 Abs preferentially recognize one or the other variant — or tetramers compared OAPs — since the available data are highly contradictory [6,10,140].

At the cellular level, AQP4 is expressed on astrocytes and ependymal cells in the CNS [139,141]. In normal human brain and spinal cord, strong AQP4 immunoreactivity is detected in astrocytic foot processes apposing microvessels and pia, particularly in the subpial and subependymal zones [141]. Within the brain stem, expression is most intense in the subependymal layers at the floor of the fourth ventricle. In brain stem and spinal cord white matter and in the optic nerve, strong AQP4 expression is detected in a perivascular rim and rosette pattern. Importantly, this normal distribution of AQP4 coincides with the deposition pattern of IgG, IgM, and products of complement activation described in active NMO lesions [137,138]. Also note that the typical brain MRI lesions of patients with NMO affecting the hypothalamus and brain stem, in particular the periventricular and subependymal regions, coincide with sites of high AQP4 expression [142].

6.2.1.2. Loss of AQP4 immunoreactivity from NMO lesions. Several studies have described complete loss of AQP4 expression in essentially all NMO lesions independent of their staging, particularly in perivascular areas with evidence of complement deposition, whereas AQP4 expression in MS lesions is stage-dependent, with increased levels being observed in most stages and decreased expression only occurring in inactive lesions [138,141]. Note that the NMO–IgG status is not known for any of these NMO patients. One of these studies observed that loss of AQP4 was accompanied by partial or complete loss of glial fibrillary acidic protein (GFAP), a marker of astrocytes, suggesting that astrocyte death is a major contributor to the loss of AQP4 immunoreactivity [138]. This is supported by the detection of extremely high concentrations of GFAP in CSF obtained from NMO patients during acute exacerbations [143]. In the other study, however, a certain type of lesion exhibited loss of AQP4 immunoreactivity despite the presence of GFAP-positive astrocytes [141]. This type of lesion was found in the medullary subependyma of three patients and was characterized by inflammatory infiltrates in the absence of demyelination. Others also found that the loss of GFAP was consistently smaller compared to the loss of AQP4 [130]. This argues for mechanisms other than astrocyte death contributing to the disappearance of AQP4 immunoreactivity in NMO lesions. Of note, myelin basic protein expression is preserved in acute inflammatory and active demyelinating NMO lesions, though lost in chronic lesions [138,141]. This indicates that inflammatory demyelination is not a primary pathogenetic mechanism in NMO — unlike in MS — but is secondary to astrocyte loss.

6.2.1.3. Association between NMO–IgG/AQP4 positivity and titers with clinical features of NMO. The preceding observations provide circumstantial evidence for an involvement of AQP4 antibodies in the pathogenesis of NMO. Further support comes from the observation of associations between NMO–IgG/AQP4 positivity or titers and clinical features of NMO. Positivity for NMO–IgG/AQP4 Ab is seen approximately twice as frequently in patients with recurrent LETM or recurrent ON compared to those with a single attack [23,27]. Reportedly, the frequency of NMO–IgG positivity in patients with recurrent NMO is 86% compared to 12% in patients with a monophasic disease course, and similar rates were found in children with NMO [4,88]. In addition, there are several reports that positive NMO–IgG/AQP4 Ab status correlated with a higher relapse frequency [12,20,21,27,66]. This suggests that different factors play a role in the initiation of the first attack and the development of relapses and that NMO–IgG may actually be more strongly associated with relapses. On the other hand, in a cohort of patients with recurrent ON, 6/12 NMO–IgG positive patients developed TM and fulfilled the diagnostic criteria for NMO, whereas only 1/15 seronegative patients experienced an attack of TM [29]. Similarly, in a study of patients with a first episode of LETM, only NMO–IgG positive patients ($n = 2$ of 11) subsequently developed ON and fulfilled NMO diagnostic criteria, 4 others had recurrent TM, whereas none of the 18 seronegative patients manifested either recurrent TM or ON [26]. The total number of patients in these studies is small, but the results nonetheless suggest that NMO–IgG is associated not only with recurrences but also strongly correlates with the development of the combination of TM and ON that characterizes definite NMO. This is further supported by the detection of NMO–IgG/AQP4 Ab in a considerably higher proportion of patients with definite NMO when compared directly to patients with limited forms such as recurrent LETM or recurrent ON (see Table 3).

In addition to a higher relapse frequency, positive NMO–IgG/AQP4 Ab status is associated with higher EDSS scores in patients with NMO and NMOsd, including OSMS [12,20,21,27,66], although these are not entirely consistent findings [9,16]. The incidence of complete blindness in at least one eye was also associated with NMO–IgG/AQP4 Ab seropositivity in patients with OSMS or CMS [17]. In addition, seropositivity correlated with the incidence of longitudinally extensive lesions on spinal MRI in various patient groups [17,20,27], but this was not observed in other cohorts of NMO patients [16,28].

The results of studies examining the association between NMO–IgG/AQP4 titers and clinical features of NMO and related disorders are more variable. For example, some studies found a positive association between titers and the longitudinal extent of spinal cord lesions, particularly at the nadir of exacerbation [9,20]. Others failed to detect such a correlation [8]. There are several reports that NMO–IgG/AQP4 titers are higher during relapse compared to remission in patients overall [8,144], although that is not seen consistently, either [21]. Clinical improvement or remission after treatment was accompanied

by a reduction in antibody titers or even their complete disappearance [9,136,144]. Increasing titers during clinical relapse after discontinuation or failure of therapy have also been reported [136,144]. However, in a longitudinal study of 8 patients, there were several instances where rising antiAQP4-Ab levels were not followed by clinical relapse, and in other cases relapses occurred in association with low titers [144]. Of note, there are isolated reports of NMO–IgG/AQP4 Ab positivity being detectable years (10 years in one patient, 3 years in another) before the onset of clinical symptoms [145,146]. Together, these findings suggest that AQP4 Abs alone are not sufficient to trigger or exacerbate NMO. It is worth underscoring, however, that the presence of these antibodies years before disease onset also indicates that they have the potential of participating in the pathogenesis of NMO and related disorders.

6.2.1.4. In vitro studies on the pathogenic potential of AQP4-specific antibodies. The results of in vitro studies suggest that, in the absence of complement, binding of AQP4-specific IgG to its target antigen triggers endocytosis of AQP4 and its subsequent targeting to the endolysosomal pathway for degradation [147]. This may represent a mechanism for the loss of AQP4 immunoreactivity in the absence of astrocyte death observed in some NMO lesions [130,141]. In the presence of complement, however, serum or isolated IgG from seropositive NMO patients can induce the death of human astroglioma cells, rat or mouse astrocytes, and other AQP4-expressing cells in a complement-dependent manner and via NK-cell mediated antibody-dependent cellular cytotoxicity [6,147–150]. This was also observed with a recombinant AQP4-specific Ab prepared from intrathecal clonally expanded NMO plasma cells [150]. Necrosis rather than apoptosis accounted for the death of astrocytes [148,149]. In partial contrast, others found that NMO–IgG positive serum plus complement was insufficient to kill human fetal astrocytes, though capable of inducing NK-cell mediated antibody-dependent cellular cytotoxicity of these cells [151]. The reasons for these discrepancies are not immediately obvious, but are unlikely to involve species-specific differences since human astroglioma cells were susceptible to complement-mediated lysis [6].

Aquaporin 4 is expressed on astrocytes, but not on oligodendrocytes, raising the question of how NMO–IgG/antiAQP4 Abs can induce demyelination. Only recently, it was shown that serum from NMO–IgG/AQP4 Ab positive patients did not directly injure oligodendrocytes, but resulted in oligodendrocyte death (apoptosis) in the presence of astrocytes [152]. A disruption in glutamate homeostasis in astrocytes was identified as a possible mechanism for this toxic bystander effect.

Another question concerns the source of AQP4 Abs in the CNS, since intrathecal production of AQP4-IgG can be demonstrated very rarely [6,153]. This is consistent with the relatively low frequency of oligoclonal bands or elevated IgG index in patients with NMO (see Table 6). The antibody is not detectable in CSF in 30–60% of seropositive patients, and if detectable, is found at titers that are quite consistently ~500-fold lower than in serum [9,66,153]. CSF AQP4 positivity was more frequently found during acute relapses, in patients with evidence of BBB dysfunction, and with serum titers >1:250. A very similar cut-off value was obtained in Japanese patients with NMO or NMO spectrum disorders, even though a different assay system was used for the detection of AQP4 Abs [9]. This suggests that the source of CSF AQP4 Abs is peripheral and that a certain threshold needs to be reached before AQP4 Abs become detectable in CSF. However, observations in experimental animals suggest that the low NMO–IgG/AQP4 Ab titers in CSF could be due to absorption of the antibodies by their cognate antigens [154]. In addition, analysis of the light and heavy chain repertoire of $CD138^+$ plasma cells in the CSF of a patient with NMO after her first clinical attack revealed numerous clonal populations that showed high intraclonal diversity and preferential usage of VH2 and VH4 [150]. This suggests an antigen-driven intrathecal humoral immune response. Six of 11 recombinant antibodies prepared from CSF plasma cells of this individual bound AQP4 with high affinity and induced complement-mediated lysis of AQP4-transfected cells. Calculation of the antibody synthesis index (2.0 and 2.2 in different assays) suggested that AQP4 was produced intrathecally in this patient [150]. Note, however, that a cut-off of 4 is recommended if titers rather than concentrations are used [153], as was the case in this study [150]. Several lines of evidence suggest that intrathecal production of AQP4 Abs may not be necessary. First, it has been demonstrated that that AQP4 itself can increase the permeability of an in vitro model of the human BBB [151]. Second, AQP4 is expressed in certain regions of the brain where the BBB is absent or intrinsically more permeable, as in the circumventricular organs and the optic nerve head, respectively. Note that the optic nerve head was found to show massive inflammation in experimentally induced NMO-like disease [154].

The model that emerges is that AQP4 Abs produced peripherally reach the spinal cord and optic nerves by increasing the permeability of the BBB and/or gaining access at sites where the BBB is lacking or intrinsically leaky. They then induce astrocyte death and/or disrupt the function of astrocytes that are vital for supporting oligodendrocytes. The resulting loss of oligodendrocytes leads to demyelination and eventually to axonal loss. However, several unresolved issues remain. For one, it currently remains unclear what triggers the peripheral production of AQP4 Abs and whether CNS or peripheral AQP4 pools are involved in the initial priming of AQP4-specific B and T cells. It also remains to be elucidated what mechanisms account for the specific involvement of spinal cord and optic nerve even though AQP4 is present throughout the CNS and is expressed at equal or higher levels in kidney and gastric mucosa. Furthermore, the Ig that is deposited along with products of complement activation in active NMO lesions consists primarily of IgM [137], and the loss of AQP4 in a specific type of inflammatory non-demyelinated brainstem lesion is most pronounced in regions of IgM deposition [141]. Yet, NMO–IgG and AQP4 Abs in serum and CSF are almost exclusively of the IgG1 subclass [8,21,147]. In addition, almost all $CD138^+$ plasma cells in the CSF of a patient with recent onset NMO produced IgG1 [150]. The presence of IgM antibodies to AQP4 has been reported in some NMO patients (10–27%), but the titers were much lower compared to AQP4-specific IgG antibodies [10,155]. These low titers together with other available evidence strongly suggest that the IgM deposited in NMO lesions is not AQP4-specific.

Patients with NMO frequently exhibit not only NMO–IgG/AQP4 Abs but also a variety of autoantibodies targeting neuronal antigens, such as glutamic acid decarboxylase-65, potassium and calcium channels, and ganglionic acetylcholine receptor [112]. In a detailed study of the brain-specific autoantibody response of 4 patients with NMO, all patients demonstrated serum IgG antibodies against myelin oligodendrocyte glycoprotein (MOG), 3 of them also had MOG-specific IgM [156]. Two patients also showed IgG responses to myelin basic protein and one to S100β. Similarly, serum and CSF of NMO patients contained considerably higher numbers of cells secreting IgM and IgG after stimulation with MOG compared to various control groups [131]. Importantly, the IgM-producing cells outnumbered the IgG-producing cells and the number of antibody secreting cells was significantly higher in CSF compared to peripheral blood (14-fold for IgG and 24-fold for IgM). Therefore MOG may represent one of the candidate antigens for the IgM deposited in NMO spinal cord and brain lesions.

6.2.1.5. Animal studies on the pathogenic role of AQP4-specific antibodies. Intravenous injection of Ig from NMO–IgG-positive serum was not sufficient to induce NMO-like disease in experimental animals even if young rats with leaky BBB were used [154]. However, such treatment could induce pathology reminiscent of human NMO in rats with experimental autoimmune encephalomyelitis (EAE)

[154,157,158]. Similar results were obtained with a human recombinant AQP4 antibody [150]. As suggested by the results of immunopathological studies of human autopsy material, astrocyte injury precedes demyelination in this model [158]. The inability of AQP4 containing IgG to induce NMO-like disease in the absence of T cell-induced inflammation suggests that antigen-specific encephalitogenic T cells are required for increasing the permeability of the BBB, thereby allowing the antibodies access to the CNS. Whether AQP4 itself can induce such cells has not been addressed yet. However, this may not be required. When administered together with human complement, but not mouse complement, intra-cerebral injection of IgG from AQP4 Ab positive patients could induce NMO-like lesions in mice in the absence of EAE [159]. Such lesions could also be induced by intraspinal injection of lipopolysaccharide, although the loss of AQP4 and the reduction in astrocyte numbers were less pronounced compared to cotransfer of AQP4 Ab-containing IgG [158]. Nonetheless, this indicates that non-specific inflammatory stimuli are able to reproduce some of the features of NMO. That may provide some insights into the pathogenesis of NMO in the subset of patients who are consistently negative for NMO–IgG, although this subset is shrinking rapidly [10]. Kinoshita et al. [160] recently reported that pre-treatment of rats with complete Freund's adjuvant was sufficient for intraperitoneally administered IgG from AQP4 Ab-positive patients to induce NMO-characteristic histopathological changes, such as astrocyte damage, Ig and complement deposition and granulocyte infiltration, although no clinical symptoms were observed. Interestingly, the astrocytes exhibited evidence of apoptosis, whereas the results of in vitro studies and of the EAE experimental model indicate that astrocyte death is due to necrosis [148,149,154]. There are as yet no investigations of whether astrocyte loss in non-necrotic human NMO lesions is due to necrosis or apoptosis. In any case, the results of Kinoshita et al. [160] suggest that non-specific inflammation allows AQP4 Abs to exert pathogenic effects, although other factors appear to be required for clinical disease to develop. This is consistent with human data suggesting that NMO–IgG/AQP4 Ab alone is not sufficient to trigger or exacerbate NMO [144–146]. The nature of the other factor(s) required for the development of clinical signs and symptoms remains to be elucidated. Recently, a case of LETM in association with positivity for AQP4 Abs was reported within 2 weeks after the diagnosis of herpes zoster [161]. The virus could not be detected in CSF and the VZV-specific antibody index was also normal, but the close temporal association suggests that the etiology of this limited form of NMO was post-infectious and that infection with VZV and possibly other infectious agents may represent triggering events that allow the development of symptomatic disease.

6.2.2. Pathology of NMO in SS and SLE

Pathological data indicate that myelopathies in patients with systemic autoimmune diseases, especially patients with SS or SLE, are often attributable to vasculitis or thrombosis [40,162]. Particularly in SLE, a strong association between myelitis and antiphospholipid antibodies was found in some studies, but this remains a matter of debate. Immune-mediate mechanisms involving autoreactive T cells and autoantibodies targeting a variety of brain components may also play a role in the development of myelitis in SS and SLE patients [162]. In the last decade, there has been a growing number of case reports and case series describing LETM as a frequent feature of both SS and SLE [31,41,42,163]. It is also becoming increasingly recognized that some of these patients are positive for NMO–IgG, suggesting that LETM represents a limited form of NMO; and definite NMO itself is also observed in patients with SS or SLE [31,163,164]. The somewhat limited data available to date suggest that the frequency of NMO–IgG in such patients is similar to that observed in NMO spectrum disorders without associated autoimmune diseases [23,30–32]. In contrast, patients with SLE or SS without manifestations of NMO or associated disorders never test positive for this antibody [23,30]. This suggests that NMO spectrum disorders are not secondary to SLE or SS, but that these patients manifest two independent, co-existing autoimmune diseases. On the other hand, it was recently reported that 9/12 patients with NMO and 7/8 patients with LETM exhibited severe labial salivary gland inflammation on biopsy, which is one of the defining features of SS [32]. Of note, inflammation of salivary glands is not sufficient to diagnose SS and can be found in a substantial portion of patients with other connective tissue diseases. Furthermore, only 25% of the patients with a positive salivary gland biopsy in this study also had anti-SSa/SSb antibodies [32]. It could be that NMO or LETM in these patients represented a first manifestation of SS, since neurological signs precede the diagnosis of SS in a substantial portion of patients and many SS patients are initially negative for anti-SSA/SSB, but turn positive later in their disease course [165]. It is also possible, however, that SS and NMO share some immunopathogenic mechanisms since AQP4 is not only expressed in the CNS but also in salivary glands [139]. It also has been hypothesized that NMO–IgG reacts with AQP5, which is strongly expressed in salivary glands and shares ~50% sequence identity with AQP4 [32].

Recent data also suggest that the relationship between SLE and NMO and its spectrum of disorders is more complex than suggested by the concept of co-existing, independent autoimmune diseases. Analysis of data from 22 patients indicates that ATM_{TMCWG} with or without ON in SLE may consist of two distinct syndromes that differ in their clinical patterns and pathogenetic mechanisms [164]. Eleven of the patients presented with flaccidity and hyporeflexia suggesting gray matter involvement, whereas the other 11 patients showed spasticity and hyperreflexia consistent with white matter dysfunction. Gray matter myelitis was more likely to occur in the context of active SLE, had a more acute onset and more severe symptoms at nadir, but lesions in patients with white matter myelitis more frequently showed post-gadolinium enhancement. Attacks of ON and fulfillment of NMO diagnostic criteria were exclusively observed in patients with white matter myelitis. In addition, white matter myelitis was associated with significantly higher frequencies of relapses and lupus anticoagulant positivity, and tended to be associated with a higher incidence of NMO–IgG, anti-ro/SSA, and anti-dsDNA positivity and APS. This suggests that an inflammatory process other than SLE itself triggers white matter myelitis. The authors conjectured that this could involve ischemia induced by antiphospholipid autoantibodies in cooperation with NMO–IgG or other autoantibodies. In contrast, the authors hypothesized that spinal cord swelling during active SLE may result in ischemia selectively compromising the blood flow to the gray matter tracts, which would suggest that gray matter myelitis is a consequence of SLE.

7. Conclusions

The proposal of unifying diagnostic criteria for idiopathic ATM has resulted in the identification of more homogeneous groups of patients with little risk of conversion to MS. However, the prognosis remains difficult to predict, and a more thorough understanding of the pathogenesis of this disorder would be highly desirable. An autoimmune mechanism has long been suspected but, aside from isolated case reports, the only evidence pointing in that direction is the recent report of an elevated frequency of anti-GM1 ganglioside antibodies in children [77] and a family history of autoimmune disease 26% of children with ATM_{TMCWG} [87]. If some form of autoimmunity were actually responsible for idiopathic ATM, the question then arises as to what mechanisms would allow re-establishment of tolerance since the majority of patients do not experience recurrent disease. Patients with a relapsing disease course frequently appear to have early or limited manifestations of NMO, since they often manifest LETM and have, in some cases, been shown to be positive for NMO–IgG/AQP4 Abs. It remains to be elucidated

whether patients without AQP4 Abs and recurrent LETM really belong into the spectrum of NMO-associated disorders. In order to compare patients with LETM with or without AQP4 Abs (as well as seropositive and seronegative patients with other NMOsd), it will be absolutely essential to develop a highly sensitive and standardized assay for the detection of AQP4 antibodies since it is becoming increasingly obvious that the indirect immunofluorescence assay that is the current standard yields too many false negative results.

Disclosure statement

The authors report no conflicts of interest.

Take-home messages

- Transverse myelitis is a serious neurologic disease that has catastrophic implications.
- Early identification and treatment is critical to reduce inflammation.
- There are multiple etiological triggers for transverse myelitis, including infection, immunizations and as a component of a systemic autoimmune disease.

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