Brain & Development 43 (2021) 626–636

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Prognostic factors for relapse and outcome in pediatric acute transverse myelitis

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Received 13 August 2020; received in revised form 4 December 2020; accepted 24 December 2020

Abstract

Objective: It may be difficult for clinicians to estimate the prognosis of pediatric acute transverse myelitis (ATM). The aim of this study was to define prognostic factors for relapsing disease and poor outcome in pediatric ATM.

Methods: This prospective cohort study included 49 children, 18 boys and 31 girls (median age 13.1 years, IQR 6.5–16.2) with a first episode of ATM. Factors associated with relapsing disease and poor outcome (Expanded Disability Status Scale (EDSS) ≥ 4) were assessed during a median follow-up of 37 months (IQR 18–75).

Results: In total, 14 patients (29%) experienced ≥ 1 relapse(s) and nine patients (18%) had a poor outcome. Factors at onset associated with relapsing disease included higher age (16.1 vs. 11.6 years, $p = 0.002$), longer time to maximum severity of symptoms (5.5 vs. 3 days, $p = 0.01$), lower maximum EDSS score (4.0 vs. 6.5, $p = 0.003$), short lesion on spinal MRI (64 vs. 21%, $p = 0.006$), abnormalities on brain MRI (93 vs. 44%, $p = 0.002$) and presence of oligoclonal bands in cerebrospinal fluid (67 vs. 14%, $p = 0.004$). The only factor associated with poor outcome was presence of a spinal cord lesion on MRI without cervical involvement (56 vs. 14%, $p = 0.02$).

Conclusion: Pediatric ATM patients presenting with clinical, radiological and laboratory features associated with multiple sclerosis (MS) are at risk for relapsing disease. In absence of these known MS risk factors at onset of disease these patients are at low risk for relapses. Only a minority of pediatric ATM patients in this cohort have a poor outcome.

Keywords: Acute transverse myelitis; Multiple sclerosis; Neuromyelitis optica spectrum disorders; Pediatric; Relapsing disease; Outcome

1. Introduction

Acute transverse myelitis (ATM) is an inflammatory syndrome of the spinal cord, affecting both children and adults. In children the estimated incidence is 1.7–2/million children/year [1–3]. ATM can occur as an isolated syndrome, known as idiopathic ATM. However, ATM can also be associated with other (multifocal

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https://doi.org/10.1016/j.braindev.2020.12.019
0387-7604/

and/or multiphasic) acquired demyelinating syndromes (ADS) of the central nervous system, including acute disseminated encephalomyelitis (ADEM), multiple sclerosis (MS) and neuromyelitis optica spectrum disorders (NMOSD).

The Transverse Myelitis Consortium Working Group (TMCWG) proposed diagnostic criteria for idiopathic ATM in 2002 [4]. Children with ATM fulfilling these criteria may subsequently be diagnosed with MS or NMOSD.

The risk of permanent disability with impairment in mobility and bladder function may influence the quality of life of children following ATM [5,6]. It can be challenging for clinicians to determine the course of the disease and the rate of recovery during the acute phase, while these are often the most important concerns of children with ATM and their families.

The aim of this prospective cohort study was to define factors predictive for relapsing disease and poor outcome in children with a first presentation of ATM, and to compare these to prognostic factors found with a systematic literature search.

2. Material and methods

2.1. Study participants

All included patients are participants of the Dutch nationwide multicenter prospective PROUD-kids study (Predicting the Outcome of a Demyelinating event in childhood). Patients younger than 18 years with a first episode of transverse myelitis between June 2006 and May 2018 were reviewed. They were included if they had a minimum follow-up of one year and fulfilled the clinical TMCWG criteria for idiopathic ATM [4]. These include (1) sensory, motor or autonomic dysfunction attributable to the spinal cord; (2) bilateral signs and/or symptoms, not necessarily symmetric; and (3) progression to nadir (maximum severity of symptoms) between 4 hours and 21 days following the onset of symptoms. A clearly defined sensory level was not taken into account due to the difficulty of a reliable assessment in young children. Furthermore, the inflammation TMCWG criteria, i.e. inflammation within the spinal cord demonstrated by cerebrospinal fluid (CSF) pleocytosis or elevated immunoglobulin G (IgG) index or gadolinium enhancement on MRI, were not applied, because a lumbar puncture and gadolinium administration for spinal MRI are not always carried out in pediatric patients. Patients with transverse myelitis due to a systemic inflammatory disease or present infection were excluded, including patients with acute flaccid myelitis associated with enterovirus D68. Moreover, patients with ADEM were excluded, because of the established differences in clinical characteristics and outcome between ATM associated with ADEM and ATM not associated with ADEM [7]. Patients that fulfilled Wingerchuk criteria for NMOSD or International Pediatric Multiple Sclerosis Study Group (IPMSSG) criteria for MS were not excluded, consistent with the aim of our study and in line with the TMCWG criteria to not exclude a disease-associated ATM [4,8,9].

2.2. Study parameters and definitions

In the PROUD-kids study, patients are assessed at baseline and reassessed prospectively, at least annually. Collected demographic, clinical, laboratory and radiological data at baseline and during follow-up were used for the current study. These data included date of birth, medical history, presenting symptoms, prodromal symptoms (reported infection or vaccination in the preceding four weeks), time to nadir (maximum severity of clinical symptoms), duration of hospitalization, treatment at onset, recovery measured by using the Expanded Disability Status Scale (EDSS), serum and CSF parameters at onset and initial brain and/or spinal MRI images. Location of spinal cord lesions was separated in two groups; the first group included every lesion with cervical involvement (cervical (C1-C7), cervico-thoracic (C1-Th12) or entire spinal cord (C1-conus)); the second group included every lesion without cervical involvement (thoracic (Th1-Th12) or thoraco-lumbar (Th1-conus)). A longitudinally extensive lesion on spinal MRI was defined as a lesion extending over three or more contiguous segments. Consequently, a short lesion on spinal MRI was defined as a lesion extending less than three contiguous segments.

Patients and caregivers were instructed to contact the hospital in case of new symptoms. A relapse was defined as acute worsening of existing symptoms, or new symptoms after 30 days of improvement or stable disease, and no evidence of alternative diagnosis. The symptoms should exist for at least 24 hours and should not be preceded by fever. Relapses were confirmed by neurological examination [10].

Final diagnosis at last follow-up was determined as (1) monophasic idiopathic ATM, (2) ATM as first presentation of MS (defined by the IPMSSG) [8] (3) ATM as first presentation of NMOSD (according to current diagnostic criteria) [9] (4) ATM as a first presentation of myelin oligodendrocyte glycoprotein (MOG)-antibody-associated disorders (MOGAD) [11] or (5) ATM as part of ADS with additional demyelinating features besides ATM, not fulfilling mentioned MS, NMOSD or MOGAD criteria. Furthermore, disability outcome was assessed at latest follow-up; poor outcome was defined as EDSS score of ≥ 4 (restricted walking distance or need for assistance to walk), while good outcome was defined as EDSS score of < 4 (unrestricted walking distance without aid).

2.3. Ethics approval / standard protocol approvals and patient consents

The PROUD-kids study protocol was approved by the Medical Ethical Committee of Erasmus MC Rotterdam and the other participating centers in the Netherlands. All patients and/or their families gave written informed consent.

2.4. Systematic literature search

Previous published literature was systematically searched in several databases including Embase, Medline Ovid, Cochrane, Web of Science and Google Scholar until June 2020. The details of the search strategy are provided in Appendix A. All results were reviewed by two independent reviewers (JH and AB) and discrepancies were discussed. Studies that reported prognostic factors for outcome of ATM in pediatric patients were included if they met the following criteria: (1) comprehensible English language, (2) conducted after 1990 and (3) including $\geq$ 10 patients $<$ 18 years old with ATM. Patients with ATM due to underlying diseases such as Behcet's disease, Lyme borreliosis, or sarcoidosis were excluded. Moreover, if data regarding adult and pediatric patients were not shown separately, studies were excluded. Observational studies including randomized controlled studies (RCTs) or cohort studies were eligible for inclusion. Letters, comments, conference abstracts and reviews were excluded.

2.5. Statistical analysis

For descriptive and statistical analysis we used SPSS, version 24.0 (SPSS Inc). Chi-square test and Fisher Exact test were used for categorical data. Student's *t*-test and Mann-Whitney *U* test were used for continuous data when appropriate. P-value $<$ 0.05 was considered significant. Correlation analyses between two continuous variables were done using Pearson or Spearman rho when appropriate.

3. Results

3.1. Characteristics

In total, 69 children with transverse myelitis were identified. Of these, four patients were excluded because of a time to nadir longer than 21 days, and 16 patients because of a final diagnosis of ADEM (Fig. 1). Forty-nine cases of ATM were further analyzed for factors associated with relapsing disease and poor outcome. In these 49 children median age at onset was 13.1 years (IQR 6.5–16.2, range 1.1–17.7), with a non-significant overrepresentation of female patients (63%) (Table 1). None of the patients had a medical condition that was considered relevant for diagnosis of ATM. Virology studies in CSF were performed in 34 patients (69%), all with negative results. Virology studies in other specimens were positive in five cases, showing enterovirus (not further subtyped) in feces in one patient with a clinical picture not consistent with acute flaccid myelitis. At onset, three patients fulfilled the IPMSSG criteria for MS and three patients fulfilled current Wingerchuk criteria for NMOSD. Serum antibodies against MOG and aquaporin-4 (AQP4) were found in respectively 7/31 (23%) and 2/35 (6%) patients. Median follow-up time was 37 months (IQR 18–75 months), with a minimum follow-up of 12 months.

3.2. Factors associated with relapsing disease

During follow-up, 35 patients remained monophasic. The remaining 14 children had a relapsing disease and were eventually diagnosed with MS (11/14, 79%), NMOSD (2/14, 14%) or MOGAD (1/14, 7%). Comparing patients with a relapsing and monophasic disease course (Table 1), clinical factors at baseline that were associated with relapsing disease were higher age (16.1 vs. 11.6 years, p = 0.002), longer time to nadir (5 vs. 3 days, p = 0.01) and lower maximum EDSS score at the point of nadir (4.0 vs. 6.5, p = 0.003). In contrast, presence of prodromal disease (57 vs. 14%, p = 0.007) and radicular pain (57 vs. 7%, p = 0.001) were significantly more often found in the monophasic group.

Almost all patients with relapsing disease showed white matter lesions on initial cerebral MRI (13/14, 93%), compared to 44% of patients (14/35) with a monophasic disease course (p = 0.002), fulfilling 2010 Revised McDonald criteria for dissemination in space and time in 31% and 25% of these patients, respectively (Table 1). All relapsing patients who fulfilled these criteria were diagnosed with MS. On the other hand, in all monophasic patients fulfilling these criteria, the white matter lesions were atypical for MS (i.e. large, not well circumscribed, involvement of basal ganglia and/or periaqueductal gray) and none of these patients were diagnosed with MS. This demonstrates that these criteria should only be applied in case of white matter lesions suggestive of MS. Short lesions on initial spinal MRI were significantly more often seen in the relapsing patient group (64 vs. 21%, p = 0.006) and longitudinally extensive lesions significantly more often in the monophasic patient group (79 vs. 36%, p = 0.006). Unique oligoclonal bands in CSF were more often identified in relapsing disease (67 vs. 14%, p = 0.004). In our cohort with only a small number of AQP4- (n = 2) and MOG-antibody (n = 7) positive patients, presence of these auto-antibodies was not associated with relapsing disease. After exclusion of AQP4- and MOG-antibody positive patients, all factors associated with relapsing disease remained significant. Additionally, in this sub

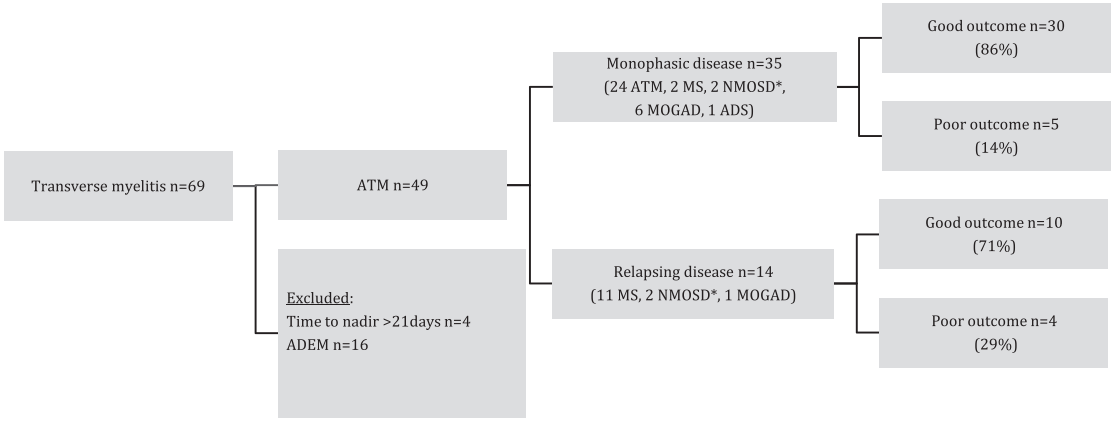

Fig. 1. Description of the selection process, based on clinical TMCWG-criteria [4] and the subdivision in monophasic or relapsing disease and good or poor outcome. ADEM: acute disseminated encephalomyelitis, ADS: acquired demyelinating syndrome, ATM: acute transverse myelitis, MOGAD: myelin oligodendrocyte glycoprotein-antibody-associated disorders, MS: multiple sclerosis, NMOSD: neuromyelitis optica spectrum disorders. * Including 1 AQP4-antibody positive patient.

analysis without antibody positive patients, elevated CSF IgG (>0.55) was more often found in the relapsing group (80 vs. 46%, p = 0.04).

At onset of disease, a total of 45 children (92%) received treatment with intravenous methylprednisolone (MPS). The remaining four did not receive any treatment. None of the children with relapsing disease were treated with intravenous immunoglobulins (IVIg) as add-on treatment, compared to a third of monophasic patients (p = 0.01). Follow-up time and eventual outcome did not differ significantly between the relapsing and monophasic group.

3.3. Factors associated with poor outcome

Nine out of 49 included pediatric ATM patients (18%) had a poor outcome at final follow-up; five with a monophasic disease (all ATM) and four with relapsing disease (one AQP4-antibody seronegative NMOSD patient and three MS patients). The NMOSD patient died during follow-up due to respiratory failure based on progressive brainstem involvement.

Patients with an MRI lesion without involvement of the cervical spinal cord significantly more often had a poor outcome (56 vs. 14%, p = 0.02), whereas patients with an MRI lesion with involvement of the cervical spinal cord more often had a good outcome (86 vs. 44%, p = 0.02) (Table 2). Headache occurred only in patients with a good outcome (33 vs. 0%, p = 0.046). Age at onset, sex, time to nadir, CSF leukocytosis, presence of serum antibodies, and duration of hospitalization during first event were not associated with outcome. Maximum EDSS score at onset did not differ significantly between the good and poor outcome group. However, a positive correlation between maximum EDSS score at onset and EDSS score at last follow-up was found (Spearman's rho 0.36, p = 0.013). Relapses, follow-up time and treatment type did not differ significantly between the good and poor outcome group.

In our cohort with a limited number of AQP4- and MOG-antibody positive patients, presence of autoantibodies was not associated with poor outcome. Exclusion of autoantibody positive patients did not change factors significantly associated with poor outcome.

3.4. Systematic review

A total of 1029 articles were found with the described search strategy (Appendix A). After screening based on title and abstract, 48 articles were selected for full text analysis. After reading the full text, 18 studies were included and summarized in Table 3 [1,2,5,7,11–23].

Most studies were retrospective cohort studies with less than 50 patients. The largest cohort was the study described by Deiva et al. on prognostic factors for relapsing disease and poor outcome in 95 children with ATM [5]. There was a large heterogeneity in inclusion criteria applied in included studies, with variation in (1) definition of ATM, (2) in- or exclusion of transverse myelitis associated with other diseases and (3) selected age group, impairing comparison between included studies.

A slight male preponderance was found in ten out of 16 cohorts (including the population based study by de Goede et al., which described a male:female ratio of 1:0.64) [2]. However, analyzing the included patients in the reported cohorts all together, males and females were almost equally divided (268 males vs. 259 females, ratio 1:0.97). Most studies described a mean age, varying between 5.3 and 11.2 years. Only three studies mentioned the examination of AQP4 antibodies, which were identified in five out of 48 examined patients (10%) [5,18,20]. None of the included studies reported on the presence of MOG antibodies.

Table 1
Clinical features and findings at onset of disease and at follow-up with a subdivision in monophasic and relapsing disease. For continuous values median and interquartile ranges (IQR) are shown. *comparison between patients with a monophasic and relapsing disease course, **consistent with 2010 Revised McDonald criteria. AQP4: aquaporin-4, CSF: cerebrospinal fluid, DIS: dissemination in space, DIT: dissemination in time, EDSS: Expanded Disability Status Scale, IgG: immunoglobulin G, IVIg: intravenous immunoglobulins, MOG: myelin oligodendrocyte glycoprotein, MPS: methylprednisone, MRI: magnetic resonance imaging, n.a.: not applicable, nadir: maximum severity of clinical symptoms, NS: not significant, OCB: oligoclonal bands.

ONSET OF DISEASE		**All patients**	**No.**	**%**	**Monophasic (35)**	**%**	**Relapsing (14)**	**%**	**P-value***
Demographics	Age at onset (year)	13.1 (6.5–16.2)	49	n.a.	11.6 (5.2–15.7)	n.a.	16.1 (13.6–17.0)	n.a.	0.002
	Male sex	18	49	37	14	40	4	29	NS
Clinical findings	Prodromal disease	22	49	45	20	57	2	14	0.007
	Time to nadir (days)	4.0 (3.0–5.5)	49	n.a.	3.0 (2.0–5.0)	n.a.	5.5 (3.8–9.0)	n.a.	0.01
	Motor involvement	40	49	82	31	89	9	64	NS
	Symmetry	14	40	35	12	39	2	22	NS
	Sensory involvement	41	49	84	30	86	11	79	NS
	Autonomic features	28	49	57	23	66	5	36	NS
	Radicular pain	21	49	43	20	57	1	7	0.001
	Optic neuritis	10 (3 bilateral)	49	20	8	23	2	14	NS
	EDSS max	6.0 (4.0–7.5)	49	n.a.	6.5 (4.5–8.0)	n.a.	4.0 (2.4–6.0)	n.a.	0.003
	Time in hospital	10 (5–17)	48	n.a.	11 (6–18)	n.a.	5 (3–19)	n.a.	0.048
MRI	>3 vertebral segments	31	47	66	26	79	5	36	0.006
	With cervical involvement	34	44	77	24	80	10	71	NS
	Without cervical involvement	10	44	23	6	20	4	29	NS
	Intracerebral white matter lesions	27	46	59	14	44	13	93	0.002
	- Fulfilling DIS and DIT**	− 7	− 25	− 28	− 3	− 25	− 4	− 31	NS
CSF	pleocytosis > 5	29	45	64	19	59	10	77	NS
	protein > 0.5	15	45	34	13	42	2	15	NS
	IgG > 0.55	24	39	62	14	52	10	83	NS
	OCB	11	33	33	3	14	8	67	0.004
Antibodies	MOG	7	31	23	6	25	1	14	NS
	AQP4	2	35	6	1	4	1	13	NS
Treatment	MPS	45	49	92	33	94	12	86	NS
	IVIg	11	49	22	11	31	0	0	0.01
	Plasmapheresis	4	49	8	4	11	0	0	NS
FOLLOW-UP									
Recovery	Follow-up time (months)	37 (18–75)	49	n.a.	31 (15–55)	n.a.	61 (30–81)	n.a.	NS
	EDSS	2.0 (1.0–3.0)	48	n.a.	1.5 (1.0–3.0)	n.a.	2.5 (1.5–4.0)	n.a	NS
	EDSS>=4	9	49	18	5	14	4	29	NS

Table 2
Prognostic factors for poor outcome at onset of disease and follow-up. For continuous values median and interquartile ranges (IQR) are shown. P-values are mentioned in the last column. AQP4: aquaporin-4, CSF: cerebrospinal fluid, EDSS: Expanded Disability Status Scale, IVIg: intravenous immunoglobulins, MOG: myelin oligodendrocyte glycoprotein, MRI: magnetic resonance imaging, n.a.: not applicable, nadir: maximum severity of clinical symptoms, NS: not significant.

ONSET OF DISEASE		Good outcome (40)	No.	%	Poor outcome (9)	No.	%	P-value
Demographics	Age at onset (year)	13.3 (7.6–16.1)	40	n.a.	12.2 (5.6–16.0)	9	n.a.	NS
	Male sex	16	40	40	2	9	22	NS
Clinical findings	Time to nadir (days)	4.0 (3.0–5.0)	40	n.a.	3.0 (1.5–13.5)	9	n.a.	NS
	Headache	13	40	33	0	9	0	0.046
	EDSS max	5.8 (4.0–7.5)	40	n.a.	7.0 (5.0–7.3)	9	n.a.	NS
	Time in hospital (days)	9 (5–17)	39	n.a.	14 (6–41)	9	n.a.	NS
MRI	with cervical involvement	30	35	86	4	9	44	0.02
	without cervical involvement	5	35	14	5	9	56	0.02
CSF	pleocytosis > 5	26	39	67	3	6	50	NS
Antibodies	MOG	7	28	25	0	3	0	NS
	AQP4	2	30	7	0	5	0	NS
Treatment	IVIg	7	40	18	4	9	44	NS
FOLLOW-UP	Follow-up time (months)	32 (17–61)	40	n.a.	64 (24–83)	9	n.a.	NS
	Relapses	10	40	25	4	9	44	NS

Poor outcome was defined by the inability to walk unassisted (EDSS $\geq$ 6) in most studies. Outcome was variable among included studies, with poor outcome reported in between 20 and 30% of patients. The occurrence of relapses was only reported in six studies, with relapses occurring in 0–17% of patients during a follow-up time ranging between 0.1 and 16.7 years.

Factors found to be associated with outcome and relapsing disease course are mentioned in Table 3. A shorter time to nadir and a greater severity of weakness at nadir were mentioned in respectively five [2,5,19,21,24] and six [1,5,7,18,19,24] different cohorts as a prognostic factor for poor prognosis. Presence of a short lesion on spinal MRI and abnormalities on brain MRI were associated with relapsing disease and final diagnosis of MS in several cohorts [5,15,18]. Early treatment with high dose steroids and plasmapheresis may improve outcome in pediatric ATM [14,17,23–25].

4. Discussion

In this study we confirmed known prognostic factors and found new prognostic factors for relapse and poor outcome in children with ATM. A longer time to nadir, presence of a lesion shorter than three contiguous segments on spinal MRI, abnormalities on brain MRI and presence of oligoclonal bands in CSF were predictors for relapsing disease which were described before [5,15,18,20]. In addition, our study found a higher age and a lower maximum EDSS score as new factors at onset associated with following relapsing disease.

Not surprisingly, these factors are largely consistent with features of MS and may point out that the profile of ATM associated with MS is different than that of monophasic ATM, as was previously suggested by Meyer et al. [15] Also in adults, both a partial ATM, as defined by less severe clinical deficits, and presence of cerebral lesions on brain MRI are prognostic for MS diagnosis [26,27].

The only factor associated with poor outcome in our cohort was presence of a spinal cord lesion without cervical involvement on MRI, while a lesion with involvement of the cervical spinal cord was associated with good outcome. This matches the finding by Deiva et al., that absence of cervical (lesion within C1 to C7) or cervico-thoracic (lesion within C1 to Th12) involvement on spinal MRI was associated with poor outcome [5]. This possibly represents a subgroup including MS patients, since spinal cord lesions in MS are more often found at the cervical level [28–30], and typically patients with MS associated ATM show less residual symptoms than other ATM patients [28].

The number of patients with a poor outcome in our cohort was slightly lower than in most other cohorts that described outcome in ATM in children [2,5,16,18,21], especially the cohorts described by Deiva et al. [5] and Pidcock et al. [16] An explanation could be the higher age of our population compared to most cohorts, since a younger age has been associated with poor outcome in previous studies [12]. Furthermore, older patients may be diagnosed earlier in the disease course due to better recognition of their symptoms, and thus may be treated sooner. Some studies have shown that a delay in start of treatment was associated with a worse outcome, although this could not be confirmed in our cohort [14,23].

A shorter time to nadir, worse maximal deficits and a delay in onset of recovery were mentioned to be predictive for a poor outcome in several previous cohorts (Table 3) [1,2,5,7,15,19,21,24]. In our study we could not confirm these or other factors mentioned in Table 3, although we did find a positive correlation between maximum EDSS score at nadir and final follow-up. An explanation may be found in the relatively low num-

Table 3
Systematic review. *2002 TMCWG criteria for ATM were used at least partially. #MRI of the brain was available in 27 of 39 patients. ADEM: acute disseminated encephalomyelitis, ATM: acute transverse myelitis, CI: confidence interval, CSF: cerebrospinal fluid, FU: follow-up, LETM: longitudinally extensive transverse myelitis, MRI: magnetic resonance imaging, MPS: methylprednisolone, MS: multiple sclerosis, NMOSD: neuromyelitis optica spectrum disorders, OCB: oligoclonal bands, USA: United States of America.

	Author	Inclusion period	Country	No pts	Sex male: female	Type of patients	Age (yrs); Mean (range)	FU (yrs); Mean (range)	Outcome	Good outcome	Poor outcome	Relapse risk
1	Adams et al. [19]	1960–1988	Canada	23		ATM (exclusion of MS)	9.4 (1.7–14)	5.8 (0.1–17)	5/22 poor outcome (23%)		1. Shorter time to nadir 2. Maximal severity of weakness 3. Delay in onset of recovery	
2	Alper et al. [20]	1985–2008	USA, Pittsburgh	27	1: 0.92	ATM* (exclusion of MS/NMO)	9.5 (0.5–16.9)	5.2 (0.04–13.1)	0/27 relapsing disease			Isolated MT (67% LETM) low risk of developing MS
3	Chen et al. [21]	1995–2008	China	39	1:0.77	ATM* (exclusion cerebral MRI abnormalities#)	7.1	8.6	8/39 poor outcome (21%); 2/39 relapsing disease (MS) (5%)		1. Shorter time to nadir 2. Longer time to start of treatment 3. Secondary infection 4. Delay in onset of recovery 5. High CSF protein	
4	DaJusta et al. [22]	1995–2004	USA, New Jersey	14	1:0.75	ATM	11.2 (0.7–18)	Unknown	4/14 poor outcome (29%)		1. Cervical clinical level associated with worse bladder recovery 2. Poor bladder recovery	
5	De Goede et al. [2]	2002–2004	UK	41	1:0.64	Acquired myelopathy (<16yrs)	10.2 (0.5–15.9)	0.5 (for all patients)	6/41 poor outcome (15%)	1. Preceding infection 2. Early onset of recovery 3. Age under 10yrs 4. Lumbosacral level.	1. Flaccid leg weakness 2. Sphincter involvement 3. Short time to nadir	
6	Defresne et al. [23]	1975–1999	Europe (incl France)	29	1: 0.81	ATM (severe)	8.6 (1–14)	3.9 (1–15)	9/12 (MPS) good outcome (75%); 4/17 (No MPS) good outcome (24%)	Treatment with high dose steroids		

7	Defresne et al. [24]	1965–1995	France	24 (16 FU data)	1: 1.18	ATM	8 (1–14)	7.3 (1–20)	14/16 good outcome (88%)	1. Plateau phase < 8 days 2. Supraspinal symptoms 3. Time to independent walking < 1 month 4. Steroid treatment	1. Complete paraplegia 2. Time to nadir < 24hrs	
8	Deiva et al. [5]	2004–2011	France/UK	95	1:0.82	ATM* (<16yrs)	Median 9 (0.7–16)	Median 1.4 (1–8)	28/95 poor outcome (29%); 16/95 relapsing disease (17%)		1. Gadolineum enhancement on MRI 2. Absence of cervical or cervico-thoracic lesion 3. Time to nadir < 24 h 4. Higher ASIA score (<D) 5. Sphincter involvement 6. Female sex 7. Pleocytosis > 10 Spinal cord atrophy on follow-up imaging	1. Abnormal brain MRI 2. Time to nadir > 24 h
9	Kim et al. [13]	1995–2009	Korea	20	1:1.50	ATM	5.3 (1–12)	Unknown	8/20 poor outcome (40%)			
10	Lahat et al. [14]	1990–1995	Israel	10	1:0.67	ATM (<16yrs)	10.8 (7–14)	2.5 (>2)	10/10 good outcome (100%); 8/10 complete recovery (80%)	Possibly steroid treatment		
11	Meyer et al. [15]	1994–2009	France	30	1:1.13	ATM* (<16yrs) (5/30 ADEM)	Median 11.0 (3–15)	5.1 (0.5–16.7)	24/30 good outcome (80%); 5/30 relapsing disease (MS) (16%)		1. > 1 month before ambulation 2. Complete paraplegia 3. Urinary catheterization	Acute partial myelitis and brain MRI abnormalities prognostic for MS diagnosis
12	Miyazawa et al. [12]	1987–2001	Japan	50	1:1.53	ATM	8.0 (1–15)	Unknown			1. Lower age 2. Low reflexes 3. Absence of Babinski sign	
13	Noland et al. [25]	2010–2016	USA, Dallas	19	1:0.72	ATM	9.4 (0.6–17)	2.1 (0–6)	12/15 good outcome (80%)	Possibly plasma exchange		
14	Pidcock et al. [16]	2000–2004	USA, Baltimore	47	1:1.04	ATM	8.3 (0–17)	8 (CI 4.5–11.9)	20/47 poor outcome (43%); 5/47 relapsing disease (11%)	1. Lower MRI rostral border 2. Lower number of segments on MRI 3. Diagnosis within 7 days	1. T1 hypo-intensity on MRI 2. Age < 3 years at onset 3. higher sensory level 4. Increased leukocytes in CSF	

15	Sebire et al. [17]; Included in 7	1975–1995	France	15	1:0.88	ATM (severe)	9.2 (MPS) 8.6 (no-MPS) (2–14)	Minimum 1	4/5 (MPS) good outcome (80%); 1/10 (No-MPS) good outcome (10%)	High dose steroids (Also faster recovery)		
16	Thomas et al. [18]	1999–2006	Canada	38	1: 1.92	ATM* (8/38 ADEM)	10.9 (0.5–17)	3.2 (0.1–7.3)	9/38 poor outcome (24%); 5/38 relapsing disease (MS (13%))		1. Complete cord syndrome (motor, sensory and bladder involvement) 2. Lower age associated with poor bladder recovery	1. Focal lesions associated with MS diagnosis 2. LETM associated with monophasic TM 3. OCB associated with MS
17	Suthar et al. [1]	2008–2014	India	36	1: 0.71	ATM* (<12yrs)	Median 7.5	Median 2.9 (IQR 0.9–4.8)	15/36 poor outcome (42%); 3/36 relapsing disease (NMOSD) (8%)		1. Severe weakness at onset 2. Spinal shock 3. Respiratory muscle weakness, mechanical ventilation 4. Greater mean time to diagnosis and treatment	
18	Yiu et al. [7]	1997–2004	Australia	34	1:0.62	ATM* (12/34 ADEM)	7.5 (0.3–15)	1.7 (3 weeks-8.5 years)	16/22 (ATM) good outcome (73%); 12/12 (ADEM) good outcome (100%)	Myelitis associated with ADEM	1. Flaccid paraparesis at presentation 2. Age < 6mnths 3. Respiratory failure, requiring ventilatory support	
19	Helfferich et al.	2006–2018	The Netherlands	49	1:1.72	ATM	11.7; Median 13.1 (1.1–17.7)	Median 3.1 (range 1–10.2) (IQR 1.5–6.3)	9/49 poor outcome (18%); 14/49 relapsing disease (29%)	1. Cervical spine involvement on MRI 2. Headache	1. No involvement cervical spinal cord on MRI	1. Higher age 2. Longer time to nadir 3. Lower maximal EDSS 4. MRI brain abnormalities 5. MRI spine lesion < 3 segments 6. Presence of OCB

ber of patients with a poor outcome in our cohort. Also, the differences in demographics between our and other cohorts could play a role, i.e. our study population contained a higher proportion of females and the median age was slightly higher compared to the other studies. These differences may also be the reason for the relatively high number of MS cases.

Previous studies on autoantibodies in pediatric ATM are scarcely available, with MOG-antibody positivity in 22–43% and AQP4-antibody positivity in 7–10% in small and selected cohorts [5,18,20,31,32]. Especially AQP4-antibody positivity has been associated with a relapsing disease course with a worse outcome as compared to pediatric MS patients [33]. Of the MOG-antibody positive pediatric patients, a small subgroup will have relapses during follow-up, in particular those with persisting MOG antibodies [11,34,35]. In our study, presence of MOG or AQP4 antibodies was not a predictor for relapsing disease or poor outcome. However, the limited number of MOG- or AQP4-antibody positive patients impairs proper investigation of this potentially important subgroup of patients with ATM.

Our study has several strengths, which include a long follow-up duration in most patients (median 37 months), with a minimum follow-up of one year in all patients. Furthermore, patients were assessed at least annually during the entire follow-up period. Finally, our data was collected as part of the PROUD-kids study, which is a prospective study, in contrast to most previously published retrospective cohorts.

A limitation of our study is the relatively small number of patients, precluding further statistical tests such as logistic regression. As described earlier, differences in demographic details hindered accurate comparison of studies identified by our literature search. Nevertheless, many of the predictors for relapsing disease and poor outcome did correspond with earlier studies. At last, by using an EDSS score of 4 or higher as a measurement for poor outcome, we focused on mobility for defining a poor outcome, while for example pain and bladder function may also influence quality of life in children with ATM [6].

5. Conclusion

In this prospective cohort study we found different factors associated with relapsing disease in pediatric ATM, corresponding with typical MS features. In absence of these factors at onset of disease, pediatric ATM patients are at low risk for relapses. Absence of a cervical lesion on spinal cord MRI was prognostic for a poor outcome in this study, while other features such as a shorter time to nadir, a longer time to recovery and severity of symptoms at nadir were found as predictors for a poor outcome in literature.

Further research should focus on the use of AQP4- and MOG-antibody serostatus and spinal MRI features, such as involvement of gray matter, as prognostic markers in pediatric ATM.

Acknowledgements

We would like to express our gratitude to the late prof. dr. Rogier Hintzen (former head of our MS Center ErasMS and Dutch National Pediatric MS center, Erasmus MC, Rotterdam) who unexpectedly passed away recently. He was one of the founders of our nationwide study on acquired demyelinating syndromes in children (PROUD-kids study) and his driven creative mind will still be inspiring for our following research. We also would like to thank Wichor Bramer (biomedical information specialist) for his help with the literature search.

Conflict of interest disclosures

Jelte Helfferich, Arlette L. Bruijstens, Yuyi M. Wong, E. Danielle van Pelt and Maartje Boon declare no competing interests. Rinze F. Neuteboom participates in trials by Sanofi and Novartis, and received honorarium from Novartis and Zogenix.

Funding

This study was supported by the Dutch MS research Foundation. This study was not industry sponsored.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2020.12.019.

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