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Original article

Long term outcome in non-multiple sclerosis paediatric acquired demyelinating syndromes

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ABSTRACT

Objectives: We aimed to study the risks of relapse and long term disability in children with non-MS acquired demyelinating syndromes (ADS).
Methods: In this prospective, multi-centre study, from the 14 UK pediatric neurology centres, children (<16 years) experiencing a first episode of ADS were recruited from 2010 to 2014. Case report forms were collected prospectively.
Results: A total of 269 children were recruited and followed up for a median of 7.2 years. Median age at onset was 9y (IQR 9.5–14.5, 126 females). At last follow-up, 46 (18 %) had MS, 4 AQP4-Ab NMOSD and 206 (80 %) had other ADS, of which 27 (13 %) relapsed. Relapsing MOGAD was the diagnosis in 12/27, 6 were seronegative and 9 did not have antibodies tested. Frequency of relapse differed according to first presentation in non-MS ADS, being least likely in transverse myelitis ($p = 0.025$). In the non-MS group, MOG-Ab was predictive of relapse (HR = 8.42; $p < 0.001$) occurring 8 times as often decreasing over time. Long-term difficulties did not differ between children with monophasic vs relapsing diseases.

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Conclusion: The risk of relapse in non-MS ADS depends on initial diagnosis, and MOG-Ab positivity. Long-term difficulties are observed regardless of relapses and are determined by presenting phenotype.

1. Introduction

Acquired demyelinating syndromes (ADS) represent acute neurological illnesses characterised by deficits persisting for at least 24 h and involving the optic nerve, brain or spinal cord, associated with regional areas of increased T2 signal on conventional MRI [1]. If monophasic, these conditions are classified as benign, requiring only short-term anti-inflammatory treatments, but if these patients relapse, they were previously considered to have probable multiple sclerosis (MS). It is now well recognised that not all demyelinating diseases are the same, and specifically ADS in children may have a different aetiology to that in adults. Some patients who were previously labelled as "opticospinal MS" are now known to have a different disease mediated by Aquaporin-4 antibodies (AQP4-Ab), called neuromyelitis optica spectrum disorder (NMOSD) [2].

Over the last 10 years, a further sub-group of patients with myelin oligodendrocyte glycoprotein antibody disease (MOGAD) has been recognised with both monophasic and relapsing forms [3]. Younger children who relapse following ADEM were previously labelled as paediatric MS, but are now known to have MOGAD, and in older children with NMOSD, MOG-Ab is three times more common than AQP4-Ab [4,5]. This condition, like AQP4-Ab NMOSD, is phenotypically distinct from MS [6]: patients with MOGAD do not respond to MS disease modifying therapies [7] and when treated with B-cell depleting therapies are more likely to relapse than patients with AQP4-Ab NMOSD [8,9]. Another important distinction is that the majority of children with MOG-Ab will have a monophasic disease course and relapse prevention treatment is not required after the first event [5].

Natural history studies of paediatric ADS identified parameters which distinguish monophasic ADS from MS. These include the age of the patient (prepubertal versus post pubertal), the presence of encephalopathy, intrathecal oligoclonal bands (OCBs), MOG and AQP4 antibody status, EBV IgG status, and findings on brain and spinal cord imaging [10,11]. The diagnosis of MS requires evidence of inflammatory activity in more than one central nervous system (CNS) location (dissemination in space) in addition to recurrent disease over time (dissemination in time). The revised 2017 McDonald criteria allowed for OCBs to substitute for dissemination in time [12]. As MS can be diagnosed at the first clinical attack, many of the patients are now being treated with disease modifying therapies after a single attack with the aim of preventing relapses [13]. Simillarly, the presence of AQP4-Ab in patients with the characteristic clinical presentation [14] is associated with a very high risk of relapse and consequently leads to blindness and paralysis if the condition remains untreated [15]. Natural history studies infer an attack related stepwise accumulation of disabilities, therefore attack prevention strategies are used as maintenance treatment after the first event. The current advice is for lifelong treatment [16,17].

The decision on when to commence relapse preventative treatment for MOGAD is more challenging, particularly in paediatrics, as most patients will have a monophasic disease course. To date there are no early predictors of relapse [3]. This study aims to explore predictors for relapse in children with ADS with non-MS and non-AQP4-Ab NMOSD. Prospective research looking at their disease course and long-term difficulties in comparison to paediatric-onset MS has been lacking.

2. Methods

This project was a multi-institutional, prosepective study run within the UK Childhood Neuroinflammatory Diseases Network and included patients from Birmingham Children's Hospital, Great Ormond Street Hospital (London), Evelina Children's Hospital (London), Alder Hey Children's Hospital (Liverpool), Royal Manchester Children's Hospital, University Hospital Southampton, Royal Preston Hospital, Leicester Royal Infirmary, University Hospital Bristol NHS Foundation Trust, Leeds Teaching Hospitals, Bradford Teaching Hospital NHS Foundation Trust, Sheffield Children's Hospital, Nottingham University Hospitals, and John Radcliffe Hospital (Oxford). Children younger than 16 years experiencing a first episode of inflammatory CNS demyelination were recruited over a 4 year and 6 months study period (2010–2014). All patients (whether tested retrospectively for antibodies or at the time of disease onset) fulfilled their respective MOGAD [18], AQP4-Ab NMOSD [14] or MS diagnostic criteria [12]. MOG and AQP4 antibodies were tested as part of the patients clinical care and were not systematically tested in all patients.

Case report forms were collected prospectively and included demographics, clinical findings, neuroimaging reports, laboratory results, first and subsequent relapse characteristics. Relapses were defined as "new neurological symptom" or "clear acute worsening of previous neurological deficit" with objective clinical signs, lasting for at least 24 h and attributed to an inflammatory CNS event, and occurring after a period of clinical remission of >1 month, as defined by the International MOGAD Panel proposed criteria [17], confirmed by the treating physician.

The outcomes, as measured by the range of difficulties the patients were experiencing (education, motor abilities, bowels, bladder, and vision), were reported as yes (the difficulty is present) or no (no difficulty) by the patient's primary paediatric neurologist. Disease severity was assessed using the *Multiple Sclerosis Impact Scale* (MSIS-29 version 2) and the Expanded Disability Status Scale (EDSS). Fatigue and Quality of Life were measured using the Pediatric Quality of Life Inventory (PedsQL TM 3.0), using the Total Generic Core Scale score and the Total General Fatigue Score (from the Multidimensional Fatigue Scale) respectively [19]. The Health Related Quality of life questionnaire consists of 23 items across 5 domains, including physical health, psychological functioning, social functioning, school functioning, and overall health-related quality of life [20]. Both parents and self-reports of the MSIS-29 and PedsQL were included in analyses according to availability.

2.1. Statistics

Descriptive statistics were performed on the demographic and clinical variables. Mean, median, SD, and interquartile range (IQR) were reported as appropriate. To compare the demographic, clinical, and paraclinical characteristics of the different disease group and monophasic and relapsing patients, parametric or non-parametric statistical tests (Mann-Whitney-U and Kruskal-Wallis tests) were used for continuous distributions as appropriate given normality, and Pearson's chi squared test with Yates' continuity correction or Fisher exact tests were used for nominal data. Results associated with a value of $p < 0.05$ were considered statistically significant.

Multivariable logistic regression was used to calculate odds ratios (ORs) and 95 % confidence intervals for potential confounders between the different groups (including sex, age at presentation, cerebrospinal fluid analysis and acute immunotherapies). Cox regression and Kaplan-Meier survival analyses were used to estimate the cumulative risk of clinical relapses. Statistical analyses were computed using SPSS v26 (IBM Corp., 2019).

3. Standard protocol approvals, registrations, and patient consents

Informed consent and assent were obtained from all children and their parent or carer. Case Report Forms were completed by the clinician annually as well as patient-reported and proxy outcome questionnaires. The study was ethically approved by the South Birmingham Research Ethics Committee (09/H1207/160) in the UK.

4. Results

269 children were recruited and followed up for a median of 7.2 years. Of the 269 patients the diagnosis at presentation was ADEM (n = 110, 40.9 %), ON (N = 59, 22 %), TM (N = 54, 20 %) and CIS-other (n = 46, 17.1 %). MRI brain was abnormal in 231/269 (86 %) and MRI spine was abnormal in 97/186 (52 %). MOG-Ab were positive in 32/109 and AQP4-Ab positive in 4/174 tested. Intrathecal oligoclonal bands (type 2 and 3) were present in 51/182 with additional 14 patients with matched oligoclonal bands (type 4). Five children died during the study period, two with monophasic ADEM and severe disability (EDSS 8), one with antibody negative NMOSD, one with Multiple Sclerosis and severe depression and one who had a final diagnosis of genetically confirmed Haemophagocytic lymphohistiocytosis (HLH).

Table 1 describes the characteristics of the cohort stratified to demyelinating phenotype at presentation. Age at onset significantly differed with diagnostic group (one-way ANOVA, $p < 0.001$ and a Tukey's HSD post hoc test showed the ADEM group was younger than the other diagnostic groups ($p < 00.001$, 95 % CI -5.8, −2.34). MOG-Ab were more frequent in ADEM($p < 0.001$) and intrathecal oligoclonal bands were seen more frequently in patients presenting with CIS ($p < 00.001$). CIS was associated with a relapsing disease course i.e. MS ($p < 00.001$).

At last follow-up 256 children has an acquired demyelinating syndrome. Thirteen children although presenting initially with a demyelinating -like event, were diagnosed with an alternative diagnosis; cerebellitis (n = 3), Autoimmune encephalitis (n = 3, 2 seronegative, 1 NMDAR-Ab), genetic hemophagocytic lymphohistiocytosis (n = 2), acute necrotising encephalitis with mutation in RANBP2, mitochondrial disorder, neurosarcoidosis, parainfectious myeloradiculopathy and cortical dysplasia. Multiple sclerosis was the final diagnosis in 46/256 (18 %) children, 4 had AQP4-Ab NMOSD and 206 (80 %) had other demyelinating syndromes, of which 27 (13.1 %) relapsed (Fig. 1).

Table 1
Patient demographics and clinical and paraclinical features stratified to presenting phenotype.

	Total (N = 269)	TM (n = 54)	ON (n = 59)	CIS (n = 46)	ADEM (n = 110)	P Value
Sex(F:M)	143:126	23:30	37:23	29:17	54:56	
Age of onset (mean ±SD)	9 ± 4.8	9.8 ± 4.8	11.3 ± 3.8	12.8 ± 4	5.8 ± 3.7[a]	*<0.001*
MOG-Ab	32/109	4/17	6/28	2/26	20/38[a]	*<0.001*
AQP4-Ab	4/174	0/41	1/50	2/30	1/51	
Intrathecal OCB	51/182	5/38	12/39	27/36[a]	7/62	*<0.001*
F/u duration in years Median (IQR)	7.2 (5.4, 8.8)	7 (4.9, 8.8)	7 (4.7, 8.9)	7.5 (5.9, 8.7)	7.4 (5.6, 8.8)	
Relapsing disease	79/269	5/54	18/59	39/46	17/110	*<0.001*

Abbreviations: TM = transverse myelitis; ON = optic neuritis; CIS = clinically isolated syndrome; ADEM = acute disseminated encephalomyelitis; MOG = Myelin oligodendrocyte glycoprotein; AQP4 = Aquaporin-4, OCB = oligoclonal bands.

[a] Significantly different at p. <0.001.

In total 77 children had a relapsing demyelinating disease course. The final diagnosis in these relapsing children was: RRMS (N = 46), relapsing MOGAD (N = 12), AQP4-Ab NMOSD (N = 4) and seronegative/not tested RDS (N = 15). Table 2 and Table 3 summarise key demographics and clinical and paraclinical features for each relapsing diagnosis.

In the 77 demyelinating relapsing children the median time between onset and first relapse was 6 months (IQR 3, 13) This was longer for relapsing MOGAD (median 12 months, IQR 7, 27 months) and shorter for seronegative RDS (median 3 months, IQR 2, 9 months, p = 0.004). A presentation of TM had the lowest relapse risk. ON, ADEM and CIS at initial presentation did not significantly differ in terms of relapse risk. Of the 206 with non-MS, non-AQP4-Ab NMOSD only 27/206 (13.1 %) relapsed (Fig. 1).

Median EDSS at last follow-up was 1 (IQR 1,2) (Table 5). Difficulties at the last follow-up in all domains did not differ in frequency between children with (i) non-MS ADS and MS (Supplemental Table 1), (ii) monophasic non-MS ADS vs relapsing non-MS ADS (Supplemental Table 2). In terms of specific diagnoses, patients with TM were found to have the highest frequency of motor (43 %), bladder (32 %) and bowel (19 %) difficulties. Children presenting with ADEM had the highest rate of school difficulties (20 %). Long-term visual impairment was seen in 15 % of patients with ON.

We also used patient questionnaires focused on their experiences of fatigue, QoL, physical and psychological impact to determine the long-term outcomes in ADS. No significant differences were found in outcome between children diagnosed with a monophasic syndrome and children with a multiphasic diagnosis at follow-up (Supplemental Table 3).

We then further investigated which biomarkers could predict relapse in non-MS non-AQP4-Ab NMOSD ADS at initial presentation. The Cox regression analysis was used for the 58 non-MS patients where all parameters were available (age, sex, OCB and antibody status), including 17 patients that developed relapsing disease and 41 who did not (Table 4). MOG-Ab positivity was the only predictor of relapse. The analysis suggested that MOG-Ab positivity at onset, made relapsing to occur 8 times as often. The negative time interaction term suggested that the effect of MOG-Ab positivity on probability of relapse decreases over time (Fig. 2). Age of onset, sex and OCBs did not predict risk of relapse. When comparing MOG-Ab positive monophasic patients (n = 20) and relapsing (n = 12) no significant differences were detected.

5. Discussion

This was a large prospective longitudinal study to establish clinical features and biomarkers predictive of disease course and outcome in non-MS ADS. We were able to demonstrate that the presence of MOG-Ab in non-MS ADS predicts the risk of relapse, and patients with MOG-Ab positivity are 8 times more likely to relapse in the first year, although he risk of relapse reduces with time. As the risk of relapse was still low in the MOGAD group, our results highlight that children with ADS who do not fulfil criteria for MS and are MOG and AQP4 antibody negative have a very low risk of relapse overall.

Similar to previous studies comparing monophasic ADS and MS [10] we also identified that age of onset is younger in the monophasic ADS and OCBsds are seen less frequently. Importantly, in contrast to adult-onset disease, CIS converting to RRMS is rarely seen and children with MS fulfil the diagnostic criteria at onset as we have previously demonstrated [21].

Studies reporting outcomes for children with ADS often focus on specific disease groups of patients, e.g. MS or ADEM [22]. We found that, overall, the long-term outcomes in our cohort did not differ between MS and non-MS patients with 10–30 % reporting long term difficulties with school/cognition, motor, vision or bladder. Severity of the symptoms at initial presentation, involvement of the spine or optic nerve and relapses are likely to be more important for long-term outcome

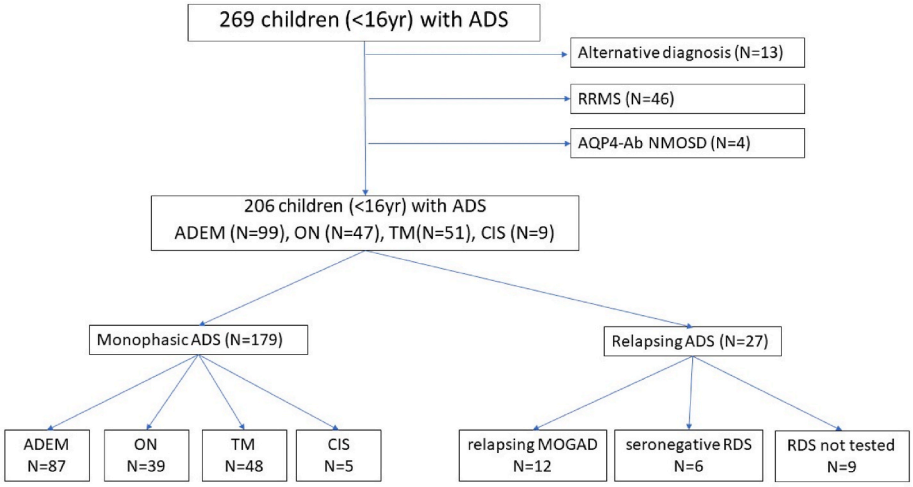

Fig. 1. Participant characteristics
269 children with a diagnosis of acquired demyelinated syndrome, studied prospectively from symptom onset with a baseline MRI and clinical assessment. At last follow-up 256 children has an acquired demyelinating syndrome. Thirteen children although presenting initially with a demyelinating -like event, were diagnosed with an alternative diagnosis; cerebellitis (n = 3), Autoimmune encephalitis (n = 3, 2 seronegative, 1 NMDAR-Ab), genetic hemophagocytic lymphohistiocytosis (n = 2), acuete necrotising encephalitis with mutation in RANBP2, mitochondrial disorder, neurosarcoidosis, parainfectious myeloradiculopathy and cortical dysplasia. We excluded patients with MS (N = 46) and AQP4-Ab NMOSD (N = 4). Of all non-MS and non-AQP4-Ab NMOSD ADS (n = 206), 99 (48.1 %) presented with ADEM, 47 (22.8 %) with optic neuritis (ON), 51 (24.8 %) with transverse myelitis (TM) and 9 (4.4 %) with non-TM, non-ON clinically isolated syndrome (CIS-other). At final follow-up, 27 relapsed and the rest remained monophasic.

Table 2
Clinical and paraclinical features stratified to final diagnosis.

Factors	Final multiphasic diagnosis					
	MS (n = 46)	AQP4-Ab NMOSD (n = 4)	Relapsing MOGAD (n = 12)	Seronegative RDS (n = 6)	RDS Ab not tested (n = 9)	Total (n = 77)
Age of onset years, mean (± std dev)	13.6 (±3.1)	12.2 (±5)	9.2 (±4.1)	11.2 (±3.7)	4.7 (±2.4)	11.6 (±4.4)
Sex(F:M)	28:18	3:1	8:4	3:3	4:5	46:30
Abnormal brain MRI at onset	45/46 (97.8 %)	4/4 (100 %)	10/12 (83.3 %)	2/6 (33.3 %)	9/9 (100 %)	70/77 (90.9 %)
Abnormal spine MRI at onset	24/33 (73 %)	2/4 (50 %)	4/8 (50 %)	2/4 (50 %)	1/2 (50 %)	33/51 (64.7 %)
Intrathecal OCB	36/38 (94.7 %)	1/3 (33.3 %)	1/11 (9.1 %)	0/4	2/6 (33.3 %)	39/62 (62.9 %)
Time to first relapse months, median, (IQR)	6 (3–16)	3 (1–5)	12(7–27)	3 (2–9)	6 (5–16)	6 (3–13)
DMT started within 2 years	41/46 (89.1 %)	2/3 (66.7 %)	4/12 (33.3 %)	4/6 (66.7 %)	2/9 (22.2 %)	53/77 (68.8 %)

Abbreviations: AQP4 Aquaporin-4, DMT Disease Modifying Treatment, MOG Myelin oligodendrocyte glycoprotein, MS multiple sclerosis, OCB oligoclonal bands, RDS relapsing demyelinating syndrome.

rather than specific diagnosis. Regarding spinal involvement for example, up to 40 % of children with TM in our study had a poor motor or bladder outcome despite a monophasic disease course, as seen in other studies [23]. Visual recovery following optic neuritis was good, with 85 % making a full recovery in monophasic optic neuritis (33/39) while a third relapsed. Although our study was not designed to capture treatment effect with no data available on Disease Modifying Treatment (DMT) choice or compliance, most patients with MS (41/46) were started on DMTwithin 2 years of first presentation and this may have impacted the outcome [24].

Natural history studies show that patients who have onset of MS before the age of 18 years (paediatric onset) take longer to reach sustained neurologic disability with motor impairment than those with adult-onset disease [25,26]. However cognitive impairment in children with MS has been reported in up to one-third of patients [27,28]. Interestingly, there has been a mismatch between the reported difficulties across multiple domains in the paediatric MS group, including walking and coordination difficulties, as the EDSS and the disease impact scale did not capture the severity. These scales used in adults with MS focus on walking ability and underestimate the impact in children of mood, fatigue and frequent hospital admissions on motor and cognitive function. With new diagnostic criteria allowing earlier diagnosis of MS and the availability of higher efficacy treatment (which were not available during the study recruitment period) it is likely that children diagnosed with MS today will have a better functional outcome than reported here.

Although patient reported outcomes including quality of life are important, not many children opted to participate in this part of the study. Our study did not find a significant difference in fatigue and quality of life scores between monophasic and relapsing diseases. Interestingly, the scores were lower when compared to healthy children (in healthy children the mean total score for the Multidimensional Fatigue Scale is 82.6 for the same age and sex, and 75.8 for the overall Health QOL score).

The main limitation of our study is that as patients were recruited between 2010 and 2014, MOG-Ab was not routinely performed in all patients. This introduces bias towards patients who were more likely to be tested at that time. Our study has a number of additional limitations:

Table 3
Features of children with relapsing demyelination, who are antibody negative (AQP4 and MOG) or have not been tested.

Case	Age at onset (YR)	Sex	Initial Diagnosis given	MRI	OCBs	AB testing	Relapse phenotype (time to relapse)	Number of relapses	Final diagnosis given
1	10	F	ON	Abnormal brain and spine	neg	neg	TM (1month)	1	NMOSD
2	15	f	ON	Normal brain and spine	–	neg	ON (3months)	9	CRION
3	14	m	ON	Normal brain and spine	neg	neg	ON (3months)	2	CRION
4	14	m	ON	Normal brain	neg	neg	ON (3months)	4	CRION
5	5	m	TM	Abnormal brain and spine	neg	neg	ADEM (5months) ON (12months)	2	MDEM
6	10	f	ON	Normal brain	–	neg	ON (19 months)	2	CRION
7	4	m	ADEM	Abnormal brain	Pos	_	ADEM (6 months)	1	MDEM
8	6	f	ADEM	Abnormal brain	neg	–	ADEM (3 months)	1	MDEM
9	6	m	ADEM	Abnormal brain	neg	–	ADEM (41 months)	1	MDEM
10	8	m	ADEM	Abnormal brain	Pos	–	ADEM (6 months)	1	MDEM
11	4	f	ADEM	Abnormal brain	neg	–	ADEM (3months)	1	MDEM
12	2	F	ADEM	Abnormal brain	–	–	ADEM (6 monhts)	3	MDEM
13	5	M	ADEM	Abnormal brain	–	–	ADEM (6 months)	1	MDEM
14	9	M	ON	Normal brain and spine	–	–	ON (24 months)	2	CRION
15	1	f	ADEM	Abnormal brain and normal spine	neg	–	ADEM (7 months)	2	MDEM

Abbreviations: ON = optic neuritis; ADEM = acute disseminated encephalomyelitis.
OCB oligoclonal bands, AB Antibodies (MOG and AQP4), NMOSD Neuromyelitis Optica Spectrum Disorder, CRION Chronic Relapsing Inflammatory Optic Neuropathy, MDEM Multiphasic ADEM.

Table 4
Factors predicting non-MS relapse in a Cox survival regression model.

Predictors	Statistics						
	B (SE)	SE	Wald's χ^2	Hazard ratio	*p* value	95 % CI for OR	
						Lower	Upper
Age of onset	0.07	0.06	1.433	1.076	0.231	0.954	1.214
OCB	−1.15	1.07	1.149	0.317	0.284	0.039	2.587
MOG	2.13	0.58	13.593	8.422	<0.001[a]	2.713	26.146
sex	−0.15	0.52	0.084	0.860	0.771	0.311	2.378
MOG × Log(time)	−1.29	0.39	11.246	0.273	<0.001[a]	0.128	0.583

Note. OR = Odds ratio; CI = confidence interval; OCB = Oligoclonal bands; MOG = Myelin oligodendrocyte glycoprotein.
[a] Significant at $p \leq 0.001$.

Table 5
Long term difficulties at final follow-up according to final diagnosis.

	ADEM (N = 87)	TM (N = 48)	ON (N = 39)	CIS (N = 5)	Seronegative RDS (N = 6)	RDS not tested (N = 9)	Relapsing MOGAD (N = 12)	AQP4-Ab NMOSD (N = 4) AQP4	MS (N = 46)
EDSS median (IQR)	1 (1,2)	2 (1,4.5)	1 (1,1)	1 (1,1.5)	1 (1,2.3)	1 (1.1.5)	1 (1, 2)	1 (1,0)	1 (1,3)
School difficulties 45/269 (17 %)	15/87 (17 %)	8/48 (17 %)	2/39 (5 %)	0/5 (0 %)	1/6 (17 %)	3/9 (33 %)	4/12 (33 %)	0/4 (0 %)	7/46 (15 %)
Motor impairment 60/269 (22 %)	17/87 (20 %)	20/48 (42 %)	2/39 (5 %)	1/5 (20 %)	1/6 (17 %)	1/9 (11 %)	2/12 (17 %)	0/4 (0 %)	14/46 (30 %)
Bowel disorder 18/269 (7 %)	3/87 (3 %)	9/48 (19 %)	1/39 (3 %)	0/5 (0 %)	1/6 (17 %)	1/9 (11 %)	1/12 (8 %)	0/4 (0 %)	1/46 (2 %)
Bladder disorder 37/269 (14 %)	12/87 (14 %)	16/48 (33 %)	0/39 (0 %)	0/5 (0 %)	1/6 (17 %)	1/9 (11 %)	1/12 (8 %)	0/4 (0 %)	4/46 (9 %)
Visual impairment* 37/269 (14 %)	11/87 (12 %)	0/48 (0 %)	6/39 (15 %)	0/5 (0 %)	1/6 (16 %)	2/9 (22 %)	4/12 (33 %)	3/4 (75 %)	10/46 (22 %)

Abbreviations: TM = transverse myelitis; ON = optic neuritis; CIS = clinically isolated syndrome; ADEM = acute disseminated encephalomyelitis; MOG = Myelin oligodendrocyte glycoprotein; AQP4 = Aquaporin-4; OCB = oligoclonal bands; EDSS = extended disability status scale.
* Visual impairment defined as a visual Functional Systems Score >1 scotoma with visual acuity > 20/30 in worse eye.

many of these are related to the study design and the long term outcome. We did not analyse the impact of acute treatement used and time to initiation of treatment, which is likely to have influenced outcome, as has been shown for optic neuritis [29,30]. The data set was incomplete especially with regards to patient reported outcome measures; this was a long-term study and it was challenging to keep patients engaged over

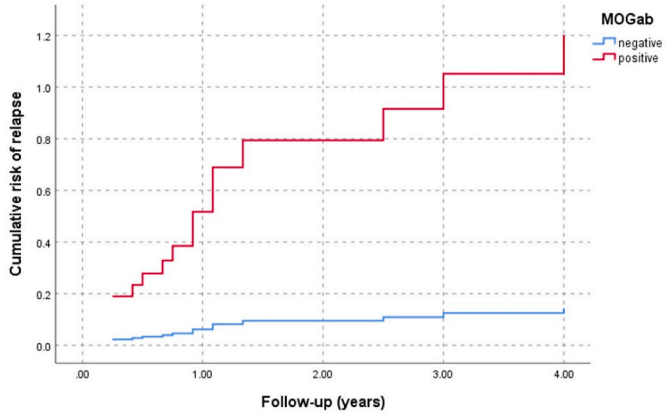

Fig. 2. risk of relapse in patients with non-MS, AQP4-Ab negative ADS. Stratified to MOG-Ab serostatus.

several years. The outcome (education, motor abilities, bowels, bladder, and vision), reported by the patient primary paediatric neurologist was binary, which may have caused a ceiling and may explain why no differences were found betweenthe several disease entities. Fatigue assessment differs depending on whether it is self-reported or parental reported: Florea and colleagues found that children tended to report their social problems less than parents [31]. This may have affected the study, which included both forms of reports. Parents also tended to report more elevated scores of psychosocial functioning and fatigue in monophasic syndromes [31].

Despite these limitations, this study highlights some key results that are useful in clinical practice: (1) the relapse risk in paediatric ADS is low and in non-MS, antibody negative patients, relapse is rare; (2) the risk of long term disability is related to the presenting phenotype and not necessary the disease course; and (3) outcome measures used clinically and as part of clinical trials do not capture the impact of the disease on patients' subjective difficulties, which are likely to be multifactorial. While some factors that predict outcome in ADS have been identified here, there is still a need for more research to identify additional predictors that could help guide treatment and management decisions and improve outcomes.

Declaration of competing interest

There are no conflicts of interest.

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CH has consulted for Novartis, Biogen, Roche, UCB and VielaBio and on Clinical Trials Advisory Boards for Biogen and Roche.

SR has received speaker fees from Roche and Novartis, and served on advisory boards for Novartis, Roche, Sarepta and Argenx.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2024.07.002.

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