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Early predictors of disability of paediatric-onset AQP4-IgG seropositive neuromyelitis optica spectrum disorders

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Abstract

Objective:
To describe onset clinical features predicting time to first relapse and time to long-term visual, motor, and cognitive disabilities in paediatric-onset aquaporin-4-antibody (AQP4-IgG) neuromyelitis optica spectrum disorders (NMOSD).

Methods:
In this retrospective UK multicenter cohort study, we recorded clinical data of paediatric-onset AQP4-IgG NMOSD. Univariate and exploratory multivariable Cox proportional hazard models were used to identify long-term predictors of permanent visual disability, EDSS 4 and cognitive impairment.

Results:
We included 49 paediatric-onset AQP4-IgG patients (38.8% White, 34.7% Black, 20.4% Asians and 6.1% Mixed), mean onset age of 12 ± 4.1 years, and 87.7% were females. Multifocal onset presentation occurred in 26.5% of patients and optic nerve (47%), area postrema/brainstem (48.9%) and encephalon (28.6%) were the most involved areas. Overall, 52.3% of children had their first relapse within one year from disease onset. Children with onset age < 12 years were more likely to have an earlier first relapse (p=0.030), despite showed no difference in time to immunosuppression compared to those aged 12-18 years at onset. At the cohort median disease duration of 79 months, 34.3% had developed permanent visual disability, 20.7% EDSS 4 and 25.8% cognitive impairment. Visual disability was associated with White race (p=0.032) and optic neuritis presentations (p=0.002). Cognitive impairment was predicted by cerebral syndrome presentations (p=0.048), particularly if resistant to steroids (p=0.034).

Conclusions:
Age at onset, race, onset symptoms and resistance to acute therapy at onset attack predict first relapse and long-term disabilities. The recognition of these predictors may help to power future paediatric clinical trials and to direct early therapeutic decisions in AQP4-NMOSD.

INTRODUCTION

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory demyelinating disease of the central nervous system (CNS) affecting predominantly the optic nerves and spinal cord[1]. Approximately 60-80% have disease-specific aquaporin-4 antibodies (AQP4-IgG) in the serum which, due to the astrocytic location of the AQP4 water channels, lead to a primary autoimmune astrocytopathy[2,3,4] with a characteristic relapsing course. Only about 5% of AQP4-IgG positive NMOSD have a paediatric-onset[4,5]. Data on long-term clinical outcomes of AQP4-IgG positive paediatric patients are sparse due to the rarity of the disease[6,7,8,9] and further evidence is needed particularly because of the new therapies coming through[5]. This is a long-term outcome study of a relatively large single country paediatric-onset AQP4-IgG NMOSD cohort recruited from several UK neurology centers."

METHODS

We retrospectively analysed data prospectively collected from databases and clinical notes (recorded from 1980 to July 2020) of patients with paediatric-onset (defined as <18 years) AQP4-IgG seropositive NMOSD (diagnosed according to the 2015 diagnostic criteria[1]) from six tertiary UK NMO centres: (i) John Radcliffe Hospital, Oxford, UK (adult and paediatric); (ii) Great Ormond Street Hospital, London, UK (paediatric); (iii) Walton Centre, Liverpool, UK (adult and paediatric); (iv) Evelina London Children's Hospital, UK (paediatric); (v) Birmingham Children's Hospital, Birmingham, UK (paediatric); and (vi) Royal London Hospital, London, UK (adult). The presence of AQP4-IgGs was identified in the Autoimmune Neurology Laboratory using a cell-based assay as described by Waters et al[10].

All data was collected as standard clinical care at the respective centres (6 monthly neurological and ophthalmological follow-up in remission, serum AQP4-IgG testing, diagnostic MRIs and CSFs where diagnostically useful) and subsequently shared according to local trust policy with the coordinating centre in Oxford (Oxford Research Ethics Committee C Ref:10/H0606/56). Information was collected on sex, age at onset, race, onset attack type and severity at nadir, relapses, acute and maintenance immunosuppressive therapy, time to first relapse, time to long-term visual disability (best eye worse than 6/36 for longer than six months), motor disability (walk ≤ 500 m unaided for longer than six months-Expanded Disability Status Scale 4 [EDSS 4]), and cognitive impairment (defined by neuropsychological assessments or documented learning disability requiring extra support at school). Neurocognitive testing was performed using a varied battery of age appropriate standard tests (Supplementary Table 1) of cognition dictated by clinical need as outlined[11] by clinical psychologist/neuropsychologist working with tertiary adult and/or paediatric neuroscience centres. These tests typically include a measure of episodic memory, language, attention, and executive functioning. Cognition was considered impaired if any test within these domains fell below the 5th percentile. In patients where formal cognitive assessment was not performed, cognitive impairment was pragmatically defined as documented learning disability requiring extra support at school was defined as requiring a minimum of a special educational needs coordinator. Table 1 details the variables collected for each patient and definitions of the clinical phenotypes, severity scoring and visual, motor and cognitive disability outcomes.

Table 1: List of the collected clinical variables and definitions

- Sex: Male and Female
- Age at onset (continuous variable), Age at onset subgroups :< 12 years and 12-18 years
- Race: White, Asian, Black and Mixed
- Disease duration (months)
- Onset syndromes:
  - ◊ monolateral or bilateral optic neuritis (ON);
  - ◊ transverse myelitis (TM);
  - ◊ area postrema syndrome and/or brainstem syndrome (BS);
  - ◊ cerebral syndrome (acute disseminated encephalomyelitis syndrome [ADEM], diencephalic syndromes, or encephalopathies without typical MRI features of ADEM) (CS);
  - ◊ multifocal syndromes
- Severity of the onset attack, defined as:
  - ◊ inability to walk unaided at TM attacks nadir;
  - ◊ visual acuity 6/60 or worse in affected eye at ON attacks nadir;
  - ◊ documented reduction of consciousness or vomiting for more than 7 days with weight loss at CS and BS attacks nadir
- Age (years) and time (months) from onset to aquaporin-4 antibodies (AQP4-IgG) detection
- Acute therapy of the onset attack: intravenous methylprednisolone (IVMP), intravenous immunoglobulins (IVIG), plasma exchange (PLEX), no therapy
- Relapsing or monophasic course
- Time to first relapse (months)
- Annualized relapse rate (ARR) before and after the immunosuppressive therapy initiation
- Time from onset to immunosuppressive therapy initiation (months)
- First and current long-term immunosuppressive therapy: azathioprine (AZA), mycophenolate mofetil (MMF) and rituximab (RTX), methotrexate, cyclophosphamide
- Discontinuation of long-term immunosuppressive therapy due to relapse or intolerance
- Development of permanent visual disability after the onset attack or during the disease course*, defined as visual acuity in best eye worse than 6/36 on Snellen chart
- Time to permanent visual disability (months)
- Development of permanent motor disability after the onset attack or during the disease course*, defined as a persisting Expanded Disability Status Scale (EDSS) score 4 or EDSS 6 or EDSS 8
- Time to permanent motor disability (EDSS 4) (months)
- Development of cognitive impairment after the onset attack or during the disease course*, defined by neuropsychological assessments and/or documented learning disability requiring extra support at school
- Time to cognitive impairment (months)
- Death after the onset attack or during the disease course
- Time to death (months)

* recorded at 6 months from onset attack or confirmed at 6 months after the last relapse

Statistical analysis

Descriptive and groups comparison analysis were conducted considering the low number of observations. Categorical variables were presented as absolute frequencies and percentages and continuous variables as mean ± standard deviation (SD) or median and range. Mean and median differences between two groups were analysed using unpaired t-test or Mann-Whitney U-test, respectively. ANOVA and Kruskal Wallis tests were used to compare means and medians of more than two groups. Fisher's exact test was applied to compare proportions among groups. We used Kaplan-Meier curves to depict time to first relapse, to visual disability, to EDSS 4 and to cognitive impairment (dependent variables) among groups and groups differences were compared with log-rank test. Univariate cox proportional hazard model was performed to calculate survival rates of the aforementioned dependent variables. Independent continuous and categorical variables included sex, age at disease onset, onset clinical presentations, onset attack severity, acute therapy, second line acute therapy and time to immunosuppression. An exploratory multivariable cox proportional hazard model was performed using those predictors resulting with p-value < 0.10 in the univariate model. We evaluated the possible violation of the proportional hazard assumption with Schoenfeld residuals. Statistical analysis was performed using STATA 14.0 software.

RESULTS

Study population

We collected data on 49 patients with paediatric-onset AQP4-IgG seropositive disease with a median disease duration of 79 months (range 2-401). Female to male ratio was 7:1 and median current age was 21 years (range 6-53). In our cohort, 38.8% (n=19) of

patients were White, 34.7% (n=17) were Black, 20.4% (n=10) were Asian and 6.1% (n=3) were Mixed. Mean age at disease onset was 12 ± 4.1 years.

Twelve patients were previously included in a retrospective international multicenter analysis but additional 'time to' data, cognitive outcomes, acute attack treatment was obtained for this analysis[9].

Table 2 shows the demographic and clinical descriptive features and groups comparison. Patients with mixed Black ancestry were included in the Black ancestry group as they showed similarities in demographic and clinical features.

Table 2: Demographic, onset and disease course clinical features among groups in AQP4-IgG NMOSD with paediatric-onset

	Total cohort	Sex			Age at onset			Race			
	N=49	Female N=43	Male N=6	p-value	<12 years N=19	12-18 years N=30	p-value	Black* N=20	Asian N=10	White N=19	p-value
Demography:											
Female n (%)	43 (87.7)	-	-	-	16 (84.2)	27 (90%)	ns	15 (75)	9 (90)	17 (89.5)	ns
F:M	7:1	-	-	-	5:1	9:1	-	7.5:1	9:1	8.5:1	-
Mean onset age years ± SD	12.0 ± 4.1	12 ± 4	11 ± 5.5	ns	-	-	-	13.5 ± 3.74	12.7 ± 3.74	9.8 ± 4.11	0.014
Median age at AQP4-IgG diagnosis years (range)	14 (3-45)	14 (3-45)	15.5 (3-31)	ns	-	-	ns	13 (3-34)	19 (9-45)	12 (3-32)	ns
Median time from onset to AQP4-IgG detection years (range)	1 (0-32)	1 (0-32)	1 (0-17)	ns	0 (0-22)	1 (0-32)	ns	0 (0-17)	7 (0-32)	0 (0-22)	0.022
Median disease duration months (range)	79 (2-401)	78 (2-401)	100 (2-219)	ns	90 (6-367)	72 (2-401)	ns	51 (5-273)	155 (2-401)	79 (2-367)	ns
Median current age years (range)	21 (7-54)	21 (7-54)	22 (15-33)	ns	19 (7-43)	24 (16-54)	ns	18 (16-43)	28 (16-54)	21 (7-43)	ns
Race n (%):								-	-	-	-
Black	17 (34.7)	15 (34.9)	2 (33.3)	ns	3 (15.8)	14 (46.7)	0.025				
Asian	10 (20.4)	9 (21)	1 (16.7)	ns	3 (15.8)	7 (23.3)	ns				
White	19 (38.8)	17 (39.5)	2 (33.3)	ns	12 (63.1)	7 (23.3)	0.008				
Mixed	3 (6.1)	2 (4.6)	1 (16.7)	ns	1 (5.3)	2 (6.7)	ns				
Co-exisistent autoimmune diseases n (%)	7 (14)	4 (9.3)	3 (50)	0.019	4 (21)	3 (10)	ns	3 (15)	1 (10)	3 (15.8)	ns
Prodromal symptoms n (%)	14 (28.6)	13 (30.2)	1 (16.7)	ns	7 (36.8)	7 (23.2)	ns	8 (40)	1 (10)	5 (26.2)	ns
Onset syndromes n (%):											ns
ON	23 (47)	19 (44.2)	4 (66.7)	ns	10 (52.6)	13 (43.3)	ns	8 (40)	6 (60)	9 (47.4)	ns
BS	24 (48.9)	23 (53.5)	1 (16.7)	ns	6 (31.6)	18 (54)	ns	10 (50)	5 (50)	9 (47.4)	ns
TM	12 (24.5)	12 (28)	0	ns	5 (26.3)	7 (23.3)	ns	6 (30)	2 (20)	4 (21)	ns
CS	14 (28.6)	12 (28)	2 (33.3)	ns	5 (26.3)	9 (30)	ns	6 (30)	2 (20)	6 (31.6)	ns
ON+TM	4 (8.2)	4 (9.3)	0	ns	1 (5.3)	3 (10)	ns	2 (10)	2 (20)	0	
											ns
Monofocal	36 (73.5)	31 (72)	5 (83.3)	ns	14 (73.7)	22 (73.3)	ns	15 (75)	7 (70)	14 (73.8)	ns
Multifocal	13 (26.5)	12 (28)	1 (16.7)	ns	5 (26.3)	8 (26.7)	ns	5 (25)	3 (30)	5 (26.2)	

Onset syndromes n (%):											
ON	23 (47)	20 (46.5)	4 (66.7)	ns	10 (52.6)	14 (46.7)	ns	9 (45)	6 (60)	9 (47.4)	ns
BS	24 (48.9)	22 (51.2)	1 (16.7)	ns	6 (31.6)	17 (56.7)	ns	9 (45)	5 (50)	9 (47.4)	ns
TM	12 (24.5)	12 (28)	0	ns	5 (26.3)	7 (23.3)	ns	6 (30)	2 (20)	4 (21)	ns
CS	14 (28.6)	11 (25.6)	2 (33.3)	ns	5 (26.3)	8 (26.7)	ns	5 (25)	2 (20)	6 (31.6)	ns
ON+TM	4 (8.2)	3 (7.0)	0	ns	1 (5.3)	2 (6.7)	ns	2 (10)	1 (10)	0	ns
Monofocal	36 (73.5)	34 (79.1)	5 (83.3)	ns	15 (79)	24 (80)	ns	15 (75)	7 (70)	14 (73.8)	ns
Multifocal	13 (26.5)	9 (21)	1 (16.7)	ns	4 (21)	6 (20)	ns	5 (25)	3 (30)	5 (26.2)	ns
Severe onset attack n (%)	37 (75.5)	33 (76.7)	4 (66.7)	ns	13 (68.4)	24 (80)	ns	17 (85)	8 (80)	12 (63.1)	ns
Onset acute therapy n (%):											
IVMP	22 (45)	20 (46.5)	2 (33.3)	ns	9 (47.4)	13 (43.3)	ns	5 (25)	7 (70)	10 (52.6)	ns
IVMP+PLEX+IVIG	10 (20.4)	9 (20.9)	1 (16.7)	ns	2 (10.5)	8 (26.7)	ns	8 (40)	1 (10)	1 (5.3)	0.018
Unknown	1 (4.1)	1 (2.3)	0	-	1 (5.3)	0	-	1 (5.3)	0	0	-
No therapy	16 (30.6)	13 (30.2)	3 (50)	ns	8 (42.1)	8 (26.7)	ns	6 (30)	2 (20)	8 (42.1)	ns
Clinical course n (%):											
Monophasic (MON)	8 (16.3)	7 (16.3)	1 (16.7)	ns	2 (10.5)	6 (20)	ns	5(25)	1 (10)	2 (10.5)	ns
Relapsing (R)	41 (83.7)	36 (83.7)	5 (83.3)	ns	17 (89.5)	24 (80)	ns	15 (75)	9 (90)	17 (89.5)	ns
Median disease duration MON months (range)	8 (2-79)	9 (2-79)	NA	-	43 (6-79)	8 (2-48)	ns	9 (6-48)	NA	41 (2-79)	-
Median time to IS MON months (range)	4.5 (0-20)	4.5 (0-20)	NA	-	NA	2 (0-20)	-	4.5 (1-20)	NA	NA	-
Median disease duration R years (range)	96 (21-401)	96 (21-401)	138 (45-219)	ns	96 (33-367)	97 (21-401)	ns	71 (21-273)	200 (38-401)	78 (21-367)	ns
Median time to IS R months (range)	11(0-400)	11 (0-400)	21 (2-209)	ns	10 (3-216)	19 (0-400)	ns	6 (0-209)	48 (2-400)	10 (0-216)	ns
Mean annualized relapse rate (ARR)	0.80 ± 0.47	0.87 ± 0.44	0.88 ± 0.7	ns	1.03 ± 0.33	0.75 ± 0.49	ns	0.80 ± 0.54	0.75 ± 0.30	0.97 ± 0.60	ns

First long-term immunosuppressant therapy n (%):											
Azathioprine	30 (61.2)	28 (65.1)	2 (33.3)	ns	14 (73.6)	16 (53.3)	ns	9 (45)	9 (90)	12 (63.2)	ns
Mycophenolate Mofetil	7 (14.3)	5 (11.6)	2 (33.3)	ns	3 (15.8)	4 (13.3)	ns	3 (15)	1 (10)	3 (15.8)	ns
Rituximab	6 (12.2)	5 (11.6)	1 (16.7)	ns	1 (5.3)	5 (16.7)	ns	4 (20)	0	2 (10.5)	ns
Methotrexate	2 (4.1)	1 (2.3)	1 (16.7)	ns	0	2 (6.7)	-	2 (10)	0	0	-
Cyclophosphamide	2 (4.1)	2 (4.7)	0	ns	1 (5.3)	1 (3.3)	ns	1(5)	0	1 (5.3)	ns
Other[a]	2 (4.1)	2 (4.7)	0	ns	0	2 (6.7)	-	1 (5)	0	1 (5.3)	ns
Failure of first line therapy n (%)											
Azathioprine	13 (43.3)	11 (39.2)	2 (100)	ns	8 (57.1)	5 (31.2)	ns	4 (44.4)	1 (11.1)	8 (66.7)	ns
Mycophenolate Mofetil	6 (85.7)	4 (80)	2 (100)	ns	3 (100)	3 (75)	ns	2 (66.7)	1 (100)	3 (75)	ns
Rituximab	1 (16.7)	1 (20)	0	ns	0	1 (20)	ns	1 (25)	-	0	-
Methotrexate	1 (50)	1 (50)	-	-	-	1 (50)	-	1 (50)	-	-	-
Cyclophosphamide	2 (100)	2 (100)	-	-	1 (100)	1 (100)	ns	1(100)	-	1 (100)	-
Median time to therapy (months)	10.5 (4-46)	10 (4-38)	6.5 (4.2-9)	ns	10 (5-20)	11 (2-60)	ns	6 (2-20)	41 (18-201)	10 (5-27)	0.030
Mean number of relapses before therapy ±SD	2.93 ± 2.28	2.9 ± 2.22	3.4 ± 1.81	ns	3.11 ± 1.45	2.82 ± 2.55	ns	2.33 ± 1.81	4.2 ± 3.29	2.83 ± 1.46	0.036
ARR before starting long-term therapy ±SD	1.39 ± 0.75	1.31 ± 1.20	1.91 ± 2.68	ns	1.94 ±1.81	1.18±1.23	ns	0.85 ± 0.50	1.33 ± 1.39	1.94 ± 1.890	ns
ARR during long-term therapy ±SD	0.31 ± 0.05	0.31 ± 0.34	0.3 ± 0.41	ns	0.32 ± 0.41	0.29 ± 0.29	ns	0.35 ± 0.32	0.21 ± 0.21	0 .32 ± 0.41	ns
Disability after onset attack n (%):											
Visual disability	6 (12.2)	5 (11.6)	1 (16.7)	ns	4 (21.1)	2 (6.7)	ns	0	1 (10)	5 (26.3)	0.033
Cognitive impairment	2 (4.1)	1 (2.3)	1 (16.7)	ns	1 (5.3)	1 (3.3)	ns	1 (5)	0	1 (5.3)	ns
EDSS 4	1 (2)	1 (2.3)	0	ns	0	1 (3.3)	ns	0	0	1(5.3)	ns
EDSS 6	2 (4.1)	2 (4.7)	0	ns	0	2 (6.7)	ns	1 (5)	0	1 (5.3)	ns
EDSS 8	1 (2)	1 (2.3)	0	ns	0	1 (3.3)	ns	1 (5)	0	0	ns
Dead	0	0	0	-	0	0	-	0	0	0	-

P-value is estimated using Fisher's exact test for proportions comparisons; t-test (sex and age at onset) and ANOVA (race) for means comparisons; Mann-Whitney U-test (sex and age at onset) and Kruskal Wallis tests (race) for medians comparisons.a) Multiple sclerosis disease modifying drugs. ON= monolater and bilateral optic neuritis, BS= brainstem syndromes including area postrema syndrome or other brainstem syndromes; TM= transverse myelitis, CS= cerebral syndrome (including acute disseminated encephalomyelitis and diencephalic syndromes); ON+TM= neuromyelitis optica; IVMP= intravenous methylprednisolone; intravenous immunoglobulins; PLEX= plasma exchange; SD= standard deviation; EDSS= Expanded Disability Status Scale, ns=not significant. *Patients with mixed Black ancestry were included in the Black ancestry group as they showed similarities in demographic and clinical features.

Demographic and onset clinical findings

White children had significant younger age at onset compared to the other races (p=0.008) while Black children were older than other races (p=0.025) (Table 2). Children frequently presented with area postrema and/or brainstem syndrome (BS) (48.9%; n=24), unilateral or bilateral optic neuritis (ON) (47%; n=23, 12 had bilateral ON and 11 unilateral ON), cerebral syndromes (CS) (28.6%; n=14), and transverse myelitis (TM) (24.5%; n=12, 9 had longitudinally extensive transverse myelitis and 3 patients had unknown spinal cord lesion length as MRI was not available at the time of their onset). Multifocal presentation, defined as two or more of the aforementioned CNS syndromes, was seen in 26.5% (n=13) of patients. No difference in onset presentation was noted when analysing patients according to sex, age at onset or race. A severe onset attack was seen in overall 75.5% (n=37) of patients. Onset TM events were severe (unable to walk unaided at nadir) in 9 out of 12 patients (75%) and 2 patients (16.7%) were left with EDSS 6 (unable to walk >100 m unaided) after the onset event. Onset ON events were severe (visual acuity 6/60 or worse in affected eye) in 18 out of 23 patients (78.3%) and 6 patients (26%) were left with visual disability (visual acuity in best eye worse than 6/36 on Snellen chart) after the onset event.

Disease course

A relapsing course was observed in 83.7% (n=41) of children with a median time to first relapse of 12 months (IQR=4-26). Overall, 52.3% patients with a minimum disease duration of one year had a relapse within one year from onset, and 66.7% of patients with a minimum disease duration of two years had a relapse within two years from onset. Median time to first relapse was 26 months (IQR=17-37) in those starting the immunosuppressive therapy around the onset attack (n=14) while those who were not immunosuppressed at their first relapse (n=32) had a median time to first relapse

of 5 months (IQR=3-16) (p=0.039). It is noteworthy that those with monophasic disease had a significantly shorter follow-up time compared to those with relapsing disease (Table 2) but they also had a non-significant shorter time to immunosuppressive treatment (median time 4.5 months versus 11 months, p=0.065). Age at onset between 12-18 years was associated with approximately half the risk of relapse over time compared to those less than 12 years at onset (Figure 1 A and Table 3), despite no difference in time to immunosuppression between those aged <12 years and those aged 12-18 years at onset was observed (Table 2). No patients had progression of disability outside of relapses, and of the 8 who did not relapse none developed progressive disability.

Table 3: Survival and univariate analysis for early predictors of time to first relapse and time to long-term disability outcomes

	Time to first relapse (months)				Time to visual disability (months)				Time to EDSS 4 (months)				Time to cognitive impairment (months)			
	Median Survival time (IQR) [a]	**P value (log-rank)**	**HR (95%CI)**	**P value**	**Median Survival time (IQR) [a]**	**P value (log-rank)**	**HR (95%CI)**	**P value**	**Median Survival time (IQR) [a]**	**P value (log-rank)**	**HR (95%CI)**	**P value**	**Median Survival time (IQR) [a]**	**P value (log-rank)**	**HR (95%CI)**	**P value**
Sex																
Male	16 (5-17)		1 (reference)		176 (6-NR)		1 (reference)		NR (54-NR)		1 (reference)		NR (38- NR)		1 (reference)	
Female	11 (4-26)	ns	1.34 (0.47-3.87)	ns	171 (79-367)	ns	0.70 (0.19-2.48)	ns	NR (199-NR)	ns	1.05 (0.12-8.57)	ns	NR (127- NR)	ns	0.65 (0.14-2.99)	ns
Age at disease onset																
<12 years	5 (2-16)		1 (reference)		176 (6-367)		1 (reference)		253 (115-NR)		1 (reference)		240 (240- NR)		1 (reference)	
12-18 years	17 (9-34)	0.023	0.49 (0.25-0.93)	0.030	NR (120- NR)	0.076	0.44 (0.17-1.14)	0.093	NR (NR-NR)	ns	0.53 (0.14-1.99)	ns	NR (89- NR)	ns	1.28 (0.38-4.26)	ns
Race																
Black	17 (5-37)		1 (reference)		NR (171-NR)		1 (reference)		NR (199-NR)		1(reference)		NR (150- NR)		1 (reference)	
Asian	14 (4-26)		1.45 (0.62-3.37)	ns	176 (120-NR)		1.90 (0.42-8.82)	ns	NR (NR-NR)		NA	-	NR (89- NR)		0.39 (0.07-2.22)	ns
White	6 (3-16)	ns	1.78 (0.87-3.63)	ns	79 (6-367)	0.036	4.10 (1.13-14.8)	0.032	253 (115-NR)	0.054	1.07 (0.28-4.06)	ns	240 (127- NR)	ns	0.72 (0.20-2.58)	ns
Coexistent autoimmune diseases																
Absent	13 (4-34)		1 (reference)		367 (86-NR)		1 (reference)		NR (199-NR)		1 (reference)		240 (127-NR)		1 (reference)	
Present	4 (2-17)	ns	2.44 (0.91-6.54)	ns	176 (38-176)	ns	1.99 (0.56-7.13)	ns	NR (8-NR)	ns	2.33 (0.46-11.8)	ns	NR (9-NR)	ns	1.29 (0.28-5.92)	ns
Prodromal symptoms																
Absent	11 (3-24)		1 (reference)		176 (38-NR)		1 (reference)		NR (199-NR)		1 (reference)		1 (reference)		1 (reference)	
Present	13 (5-36)	ns	0.80 (0.39-1.66)	ns	171 (171-367)	ns	0.80 (0.28-2.28)	ns	253 (115-NR)	ns	1.20 (0.30-4.81)	ns	150 (41-240)	ns	2.73 (0.87-8.50)	ns
Onset symptoms																
ON																
Absent	11 (4-26)		1 (reference)		367 (367-NR)		1 (reference)		NR (199-NR)		1 (reference)		NR (150- NR)		1 (reference)	
Present	13 (5-24)	ns	0.88 (0.47-1.64)	ns	86 (6-171)	0.0002	7.80 (2.2-27.7)	0.002	NR (NR-NR)	ns	0.69 (0.16-2.97)	ns	NR (89- NR)	ns	1.43 (0.43-4.79)	ns
TM																
Absent	12 (4-24)		1 (reference)		171 (79-367)		1 (reference)		253 (199- NR)		1 (reference)		240 (127- NR)		1 (reference)	
Present	7 (4-34)	ns	0.99 (0.49-2.00)	ns	NR (38-NR)	ns	0.90 (0.29-2.82)	ns	NR (8- NR)	ns	1.58 (0.39-6.43)	ns	NR (72- NR)	ns	0.98 (0.26-3.70)	ns

BS *Absent* *Present*	10 (5-29) 12 (3-26)	ns	1 (reference) 0.90 (0.47-1.70)	ns	120 (15-176) NR (171- NR)	0.067	1 (reference) 0.39 (0.13-1.11)	0.078	253 (253-NR) NR (199-NR)	ns	1 (reference) 1.25 (0.33-4.73)	ns	240 (89- NR) NR (127- NR)	ns	1 (reference) 0.70 (0.22-2.22)	ns
CS *Absent* *Present*	9 (4-24) 17 (4-36)	ns	1 (reference) 0.80 (0.39-1.65)	ns	120 (36-NR) 367 (171-367)	0.072	1 (reference) 0.34 (0.10-1.20)	0.095	NR (199- NR) 253 (253- NR)	ns	1 (reference) 1.63 (0.40-6.55)	ns	NR (NR - NR) 150 (72-240)	0.035	1 (reference) 3.22 (1.02-10.2)	0.046
Multifocal *Absent* *Present*	8 (1-204) 13 (2-127)	ns	1 (reference) 0.83 (0.37-1.81)	ns	176 (79-367) 86 (6-171)	ns	1 (reference) 1.70 (0.63-4.63)	ns	NR (253- NR) NR (115- NR)	ns	1 (reference) 1-35 (0.33-5.45)	ns	NR (240- NR) 127 (72-150)	ns	1 (reference) 2.07 (0.65-6.57)	ns
Onset severity *Mild* *Severe*	11 (4-24) 17 (6-37)	ns	1 (reference) 1.86 (0.77-4.45)	ns	NR (NR-NR) 171 (15-367)	0.032	1 (reference) 6.77 (0.90-51.3)	0.064	NR (NR - NR) 253 (199- NR)	ns	1 (reference) 1.90 (0.24-15.2)	ns	NR (NR- NR) 240 (89-NR)	no	1 (reference) 3.88 (0.50-30.3)	ns
Onset AT *No* *Yes*	9 (4-36) 13 (4-26)	ns	1 (reference) 1.15 (0.59-2.24)	ns	171 (120-367) 171 (36-NR)	ns	1 (reference) 2.19 (0.71-6-81)	ns	NR (253- NR) NR (199- NR)	ns	1 (reference) 1.53 (0.35-6.70)	ns	240 (89- NR) NR (127- NR)	ns	1 (reference) 0.91 (0.26-3.17)	ns
II line AT *Not required* *Required*	9 (4-24) 24 (13-37)	ns	1 (reference) 0.64 (0.29-1.40)	ns	176 (36-367) 171 (86-171)	ns	1 (reference) 0.65 (0.14-2.88)	ns	NA (199- NA) NA (NA - NA)	ns	1 (reference) 2.20 (0.41-11.7)	ns	NR (240-NR) 127 (17-127)	0.035	1 (reference) 3.99 (1.11-14.4)	0.034
Time to IS (months)	-	-	0.99 (0.99-1.00)	ns	-	-	0.98 (0.97-0.99)	0.031	-	-	0.99 (0.98-1.00)	ns	-	-	0.99 (0.98-1.0)	ns

Log-rank test of Kaplan Meier curves and Univariate Cox proportional hazard model analysis of predictors of time to first relapse, to visual disability, to EDSS 4, to cognitive impairment.
a)Estimated from Kaplan Meier curves. NR= not reached; ns= not significant; EDSS= Expanded Disability Status Scale; HR= hazard ratio; IQR= interquartile range between 25° and 75° percentile; ON= optic neuritis at onset; TM= transverse myelitis at onset; BS= brainstem syndrome at onset; CS= cerebral syndrome at onset; AT= acute onset attack therapy; II line AT= plasma exchange and/or intravenous immunoglobulins; IS= immunosuppression. - = empty space when the statistical test was not applicable.

Acute and maintenance therapy

At first clinical presentation, 65.3% (n=32) of patients were treated with intravenous methylprednisolone (IVMP) and 20.4% (n=10) required a second line acute therapy (plasma exchange [PLEX] and/or intravenous immunoglobulins [IVIG]). Children who required treatment beyond IVMP were most likely to be Black (p=0.018) and to present with multifocal involvement of CNS (p=0.004). At first clinical presentation, 30.6% (n=16) of patients did not receive acute therapy: mild sensory symptoms or an under-recognized area postrema syndrome (n=10), unilateral ON (n=5) and one patient presenting with a encephalitic illness. Excluding the initial prednisolone cover, the first non-steroid maintenance immunosuppressive therapy was initiated after a median time of 10.5 months (range 2-400). Asian children received non-steroid maintenance therapy after a significant longer median time from onset (p=0.030) and had a higher mean number of relapses (p=0.036) as compared to the White and Black groups (Table 2). In order of frequency, the most used immunosuppressants were azathioprine (AZA, 2-2.5 mg/kg/day) (61.2%), mycophenolate mofetil (MMF, 10-20 mg/kg twice daily up to a maximum of 1.5 g twice daily if adult weight) (14.3%) and rituximab (RTX, repeated 6 monthly or when CD19 count rises, <50 kg 375mg/m2, weekly for 4 doses; >50kg 1 g 2 doses two weeks apart) (12.2%) (Table 2). At last review, 16.7% (n=1) of patients had discontinued first line RTX due to neutropenia (median disease duration 55 months, range 2-140). Discontinuations with AZA and MMF were 43.3% (n=13) (median disease duration 94 months, range 2-401) and 85.7% (n=6) (median disease duration 45 months, range 21-283) respectively. The percentage of discontinuation due to relapses was 53.8% (n=7) for AZA and 66.7% (n=4) for MMF. The percentage of discontinuation due to a lack of tolerability was 46.2% (n=6) for AZA and 33.3% (n=2) for MMF. There were no differences in medication use according to sex, age at disease onset and race (Table 2). A shorter

median time to initiating immunosuppressive therapy occurred in children presenting with TM (median 4 months, range 0-400) compared to those presenting with non-TM symptoms (median 11 months, range 0-216) (p=0.049).

Disability outcomes

The onset attack left 10 patients (20.4%) with at least one residual disability: 6 with visual disability (all bilateral ON related), 4 with EDSS 4 (3 TM related and one BS related) and 2 with cognitive impairment (both CS), with 2 patients having more than one disability. In this cohort with a median disease duration of 79 months (range 2-401), 36.7% (n=18) of patients had visual disability, 18.4% (n=9) reached EDSS 4.0, 10.2% (n=5) reached EDSS 6 and 2% (n=1) reached EDSS 8. Of patients presenting with ON, 26.1% (n=6) were left with visual disability from onset. Of patients presenting with TM 25% (n=3) were left with at least EDSS 4 due to the onset attack. Cognitive impairment was present in 24.5% (n=12) at follow-up and all cases were related to attacks involving the brain: 2 from the onset attack and 10 during later relapses (of whom 5 had CS at onset). Five required educational support and 7 of the 12 had in addition a formal neuropsychometric assessment. Although the protocols varied, the commonest findings were impairment of processing speed, executive and attention functions. Of patients presenting with cerebral syndromes attacks, 14.3% (n=2) were left with cognitive impairment. During follow-up, two patients (4%) died. Neither died from a relapse, one died due to a choking event one year after discharge having been left with bulbar problems from onset attack and was diagnosed post-mortem. The second had cardio-respiratory arrest during the COVID-pandemic (covid-19 PCR negative) after discharge at home. By the cohort median disease duration of 79 months, 34.3% (12/35) reached visual disability, 20.7% (6/29) reached EDSS 4, 14.8% (4/27) reached EDSS 6, 4.2% (1/24) reached EDSS 8, 25.8% (8/31) reached cognitive impairment, and 4.2% (1/24) died.

Early predictors of long-term disability

Table 3 summarizes log-rank and univariate hazard ratios (HR) relative to early predictors of the first relapse, visual disability, EDSS 4 and cognitive impairment. Figure 1 shows Kaplan Meier curves estimating the cumulative probability of remaining free from the aforementioned outcomes in relation to the most significant early clinical-demographical features. Multivariate cox proportional hazard model results for each outcome are provided in Table 4.

Table 4: Multivariable Cox hazard model for early predictors of time to visual and cognitive disability

	HR (95%CI)	P-value
Time to visual disability (months)		
Age at disease onset		
<12 years	1 (reference)	ns
12-18 years	2.43 (0.56-10.50)	
Race		
Black	1 (reference)	
Asian	2.14 (0.39-11.64)	ns
White	12.10 (1.91-76.61)	0.008
ON at onset	6.70 (1.43-31.37)	0.016
BS at onset	1.40 (0.37-5.84)	ns
CS at onset	0.14 (0.02-1.12)	0.064
Severity of onset attack	2.86 (0.30-27.10)	ns
Time to IS	0.99 (0.98-1.00)	ns
Schoenfeld residuals		0.850
Time to cognitive impairment (months)		
CS at onset	2.21 (0.59-8.32)	ns
Second line acute therapy	2.71 (0.65-11.3)	ns
Schoenfeld residuals		0.584

Mutivariable Cox hazard model for predictors of visual disability and cognitive impairment. HR= hazard ratio; CI= confidence interval; ON= optic neuritis; BS= brainstem syndrome; CS= cerebral syndrome; IS= immunosuppression; Second line acute therapy = IVMP+ IVIG/PLEX

Visual disability

ON phenotype was strongly associated with permanent visual disability (HR=7.8, p=0.002, 95%CI=2.2-27.7l), even when excluded the onset attack (HR=4.34, p=0.041, 95%CI=1.06-17.8) (Figure 1B). None of the 5 patients who received second line acute therapy in addition to IVMP for onset ON (Black=3, White=1, Asian=1) developed permanent visual disability versus 46.2% (6/13) of those ON treated with IVMP only (White=5, Asian=1, Black=0).

White children were approximately four times more likely to develop permanent visual disability compared to Black children (HR=4.1, p=0.032, 95%CI=1.13-14.8) (Figure 1 C). Older children (12-18 years) at onset tended to have a non-significant longer time to visual disability than younger children (<12 years) (HR=0.44, p=0.093, 95%CI=0.17-0.15) (Table 3). Longer time to immunosuppression was associated with a lower risk of developing visual disability (HR=0.98, p=0.026, 95%CI=0.97-0.99). However, this association was lost if patients who develop visual disability from onset attack were excluded (HR=0.98, p=0.067, 95%CI=0.98-1.00), possibly due to earlier introduction of immunosuppression.

Finally, from the exploratory multivariable cox hazard model, White race and an onset which includes ON were both associated with an increased risk of visual disability (White race: HR=12.10, p=0.022, 95%CI=1.91-76.61) (ON: HR=6.70, p=0.016, 95%CI=1.43-31.34) (Table 4).

EDSS 4

There was a trend toward non-Asians reaching an EDSS score of 4 considerably earlier than Asians (p=0.054) (Figure 1D). Those with an TM onset attack did not reach EDSS 4 earlier than other primary attacks sites (Table 3).

Cognitive impairment

CS presentations were associated with a greater risk of cognitive impairment than other presentations (HR=3.22, p=0.048, 95%CI=1.02-10.2) (Figure 1 E) and this association remained after exclusion of the CS onset attacks (HR=5.52, p=0.017, 95%CI=1.36-22.5). Patients resistant to IVMP and treated with second line acute therapy were more likely to develop early cognitive impairment (HR=3.99, p=0.034, 95%CI=1.11-14.4) (Figure 1 F). However, when these two factors were included in an exploratory multivariate hazard model the significance was lost (Table 4).

DISCUSSION

Key results and interpretation

This study reports the longest follow-up of paediatric-onset AQP4-IgG seropositive NMOSDs to date (79 months, range 2-401) and represents patients within a single country with similar environmental and treatment protocols. Some patients were diagnosed clinically at onset and confirmed when the AQP4-IgG result became available, the longest after 32 years. Children presenting under 12 years relapsed earlier than those aged 12-18 years. The non-White predominance, that has been reported in adults, was also observed in this study (2011 England and Wales census for 18-24 years old[12]) and predominance of Black race was greater in those aged 12-18 years as compared to those under 12 years of age. Black children were also more likely to be refractory to IVMP and require treatment with acute second line therapies. Prognostic differences were also seen: earlier time to a) motor disability in non-Asians, b) visual disability in Whites, c) cognitive impairment with IVMP resistant onset CS. Children with ON onset attacks and those with ON who did not escalate to second line acute therapies also reached visual disability earlier.

Existing studies on long-term outcomes of paediatric-onset NMOSD were limited to mixed cohorts of seropositive and seronegative patients[8], had shorter disease duration[7,9], or had more heterogeneity across different countries and health care systems[8]. However, we noted comparable demographic onset features (median age at onset, female to male ratio and Black predominance) in a single country (USA) one year of disease duration study on paediatric-onset AQP4-IgG disease[7]. We reported an elevated incidence of area postrema syndrome as onset presentation compared to other paediatric AQP4-IgG NMOSD studies[7,9]. This may relate to 'hindsight' diagnoses and improved awareness of the area postrema clinical presentation. RTX was superior to AZA and MMF as a first line therapy, with less discontinuations (none of the 6 patients followed for a median 4.5 years had relapses). This is in keeping with a recent multi-center study that reported no relapses in children treated with first line RTX followed for a median time of 2 years[9]. Despite methodological differences, similar studies found a higher probability of developing visual disability than motor disability in patients with paediatric-onset AQP4-IgG[4,7,8,9]. The only study investigating predictors of disability in children found a similar percentage of patients with cognitive impairment (25.4%) although with a shorter median disease duration of 4 years, and a similar relationship between long-term visual disability development and ON presentations to our study[9].

The use of survival analysis adjusts for varied disease durations amongst the different subgroups categorized by age, sex, race, onset presentations and therapy and permitted to report the risk of outcome at different timelines. To our knowledge this method has not been used before to look at early predictors of disability in children and allowed us to compare our findings to a three-center study on predominantly adult-onset patients (Oxford and Liverpool, United Kingdom and Sendai, Japan)[13] which used the same disability outcomes definitions.

Compared to Kitley et al[13], Black race predominance was greater in our paediatric-onset cohort (34.7% in children versus 20.3% in predominantly adults). We noted this was particularly marked in those with onset 12-18 years. Although racial differences in age of puberty are reported with earlier age in Black than White children, this seems unlikely to explain the rate of predominance of white children in younger ages and black children in older ages[14,15,16]. Unfortunately, the date of the pubertal age was not available in our cohort. The proportion of patients presenting with CS, BS and multifocal syndromes was greater in children than adults, while the proportion of those presenting with TM or with ON was respectively lower and similar in our paediatric-onset cohorts than in predominantly adult-onset cohort. Children receiving second line acute therapy due to IVMP resistance were mostly Black and with multifocal presentations. As a consequence of such severity, clinicians administered immunosuppressive therapy earlier and after lower annualized relapse rates to Black than to the other races, possibly resulting in a lower disability burden than Whites. Despite good diagnostic assays, children still had early relapses, especially in the younger age group (median time to first relapse 5 months) often before immunosuppressive therapy was started (median time 10.5 months). Time to first relapse in the older children group (17 months) was similar to the predominantly adult-onset cohort[13] (14 months), however that older study noted longer delay to immunosuppression than in our older children and therefore even the12-18-year-old may have more active disease than adults.

The survival analysis on long-term disabilities outcomes confirmed the age effect on visual and motor disability[8,13]. Despite similar median disease duration, children had double the risk of visual disability compared to the predominant adults cohort (36.7% of children versus 18% of predominantly adults) but were three times less likely to reach EDSS 6 (10.2% of children versus 34% of predominantly adults) and were ten

times less likely to reach EDSS 8 (2% of children versus 23% of predominantly adults). Four per cent of children versus 9% of predominantly adults died over the similar disease durations.

We found that, as in adults and in another paediatric study[9,13], ON onset predicted long-term visual disability and we found interesting that its acute treatment was a determinant factor. Paediatric patients with ON at onset had an higher proportion of severe onset attacks at nadir and had a greater residual visual disability rate after onset attack than predominantly adult-onset patients[13]. Our paediatric patients with TM at onset had an higher proportion of severe onset attacks but, interestingly, a lower proportion was left with residual motor disability compared to the adult-onset cohort[13]. This effect may highlight a possible increased susceptibility of the optic nerve and a reduced susceptibility of the spinal cord to AQP4-IgG related inflammation in children compared to adults[17]. Moreover, while ON presentation was predictive of shorter time visual disability, even excluding the onset attack influence, TM presentation did not predict long-term motor disability. However, the early use of immunosuppressive therapy in transverse myelitis patients over those with non-TM may have contributed. Patients with ON onset refractory to IVMP who were not treated with second line acute therapy were more likely to develop early visual disability. Several studies have demonstrated the safety and efficacy of treating refractory ON with PLEX, even in children[18,19,20]. Hence, we recommend the use of second line acute therapy in any case that is refractory to IVMP to prevent residual blindness and, although the number was too small to study the time interval, it is likely the sooner acute therapy is given the better the outcome[21].

We found that White race was predictive of long-term visual disability. Although in the prevalent adult study[13] Black race was more likely to develop visual disability, in our paediatric onset cohort White race had the highest risk, especially at onset attack

and even adjusting for age at onset. This may reflect the inclusion of very young patients (<12 years) in our study. We found race to be predictive also of motor disability (EDSS 4), as Asian children reached EDSS 4 later than the other ethnic groups, despite having longer disease duration time, higher number of relapses and longer time to immunosuppression. This data is consistent with findings on a racial influence on motor disability[13].

We found that cognitive impairment developed in around a quarter of children and it was particularly frequent in CS presentations refractory to IVMP, even when the influence of the onset attack was removed. However, these predictors lost their significance in the multivariable Cox Hazard model analysis, possibly because these predictors were interdependent. A larger prospective study may be able to establish whether these or other predictors are present. The proportion of cognitive impairment in AQP4-IgG NMOSD adults was estimated 29-57%[22], however, routine cognitive testing in AQP4-IgG seropositive patients is not consistently done and is difficult to perform in very young children, thus a direct comparison is not possible. The prolonged effect of AQP4-IgG related brain inflammation might cause irreparable damage on the cortex and its connections[23] possibly altering or delaying the development of the cognitive abilities in children. Cognition should be actively assessed in children and help offered from an early stage during rehabilitation and, because the risk of cognitive damage related to future attacks is greater in this group, more aggressive immunosuppression may be indicated.

Limitations

This study was limited by the low number of observations due to the rarity of the disease and results were not corrected for multiple comparisons. A prospective study analyzing a bigger sample of children with this disease might be useful to perform a multivariate analysis with multiple comparison correction. Noting similar

observations across different studies adds weight to our findings and new findings require validation in future studies. Although 12 patients were included in a previous report[9], our study had several additional features: it was a single country study, which removes heterogeneity of management regimes, with a longer disease duration (median 79 months versus 48 months), time to event were used instead of outcome at the end of follow-up, detailed cognitive outcomes, details of the onset attack severity and its treatment were included. Due to the long follow-up, patients presenting long ago might have been treated differently to those presenting currently. Future paediatric predictive studies should include genetic, environmental factors (i.e. passive smoking, vitamin D/sun exposure, dietary habits) serum, immunological and CSF biomarkers including NFL, GFAP[24,25].

CONCLUSIONS

Paediatric-onset AQP4-IgG NMOSD is a disabling disease affecting predominantly Black followed by Asian and then White children in the UK. Children have a more severe onset and shorter time to first relapse than adults and show a good response to first-line RTX compared to AZA and MMF. AQP4-IgG seropositive children appear more susceptible to optic nerve damage and less to spinal cord damage than older population studies which may reflect structural differences affecting capacity to repair. Second line acute therapy may reduce visual disability in ON attacks. White race and ON presentation predict future visual disability. Non-Asian ethnicities are more likely to develop EDSS 4 and TM at onset is not predictive of motor disability as this often occurred during subsequent TM attacks. A steroid-refractory onset attack involving cerebral hemispheres predisposes to long-term cognitive impairment development. With improved predictive data in paediatric AQP4-IgG NMOSD, clinical trial powering can be more accurately calculated, and individualized

monitoring, support and treatment regimens can be offered with the aim of improving outcomes in children.

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VC, SiM, StM, ML, CH, SH, SR, JP: conception and design of the work
VC, SiM, KTE, JSI, RM, YH, RD, EW, MIL, SR: acquisition and analysis of data for the work
VC, SiM, KTE, JSI, RM, YH, RD, EW, StM, ML, CH, SH, MIL, SR, JP: drafting the work or revising it critically for important intellectual content and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Competing of Interests

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Ethics approval: The study procedure was approved by the Oxford Research Ethics Committee C Ref:10/H0606/56. All patients signed the informed consent.

Data Sharing: The data collected for the present study will be available from the corresponding author upon request to qualified researchers (i.e. affialiated with universities or research institutions/Hospital trusts).

Dr. Valentina Camera and Prof. Jacqueline Palace had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis

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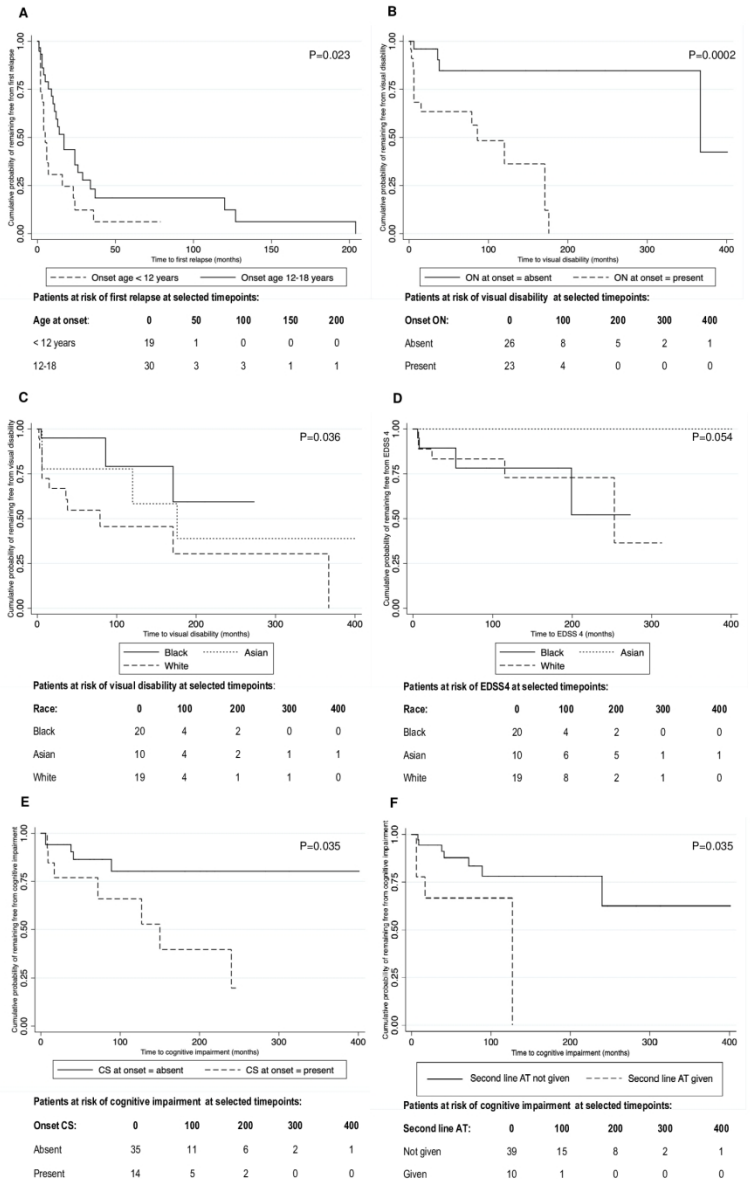
Figure 1: Most significant Kaplan Meier curves illustrating early predictors affecting the probability of remaining free from first relapse, visual disability, EDSS 4, and cognitive impairment

A. Time to first relapse was significantly shorter in children aged < 12 years at onset than those aged 12-18 years.
B. Time to permanent visual disability was shorter in those who had optic neuritis (ON) at onset than those who did not.
C. Time to permanent visual disability was shorter in the White than Black and Asian, and this difference was mainly due to the onset attack outcomes.
D. Time to EDSS 4 was significantly longer in Asian than Black and White.
E. Time to cognitive impairment was significantly shorter in those who presented a cerebral syndrome at onset (CS) than those who did not.
F. Time to cognitive impairment was significantly shorter in those who were treated with second-line acute therapy (IVIG or PLEX) than those who did not receive second-line acute therapy (no therapy or IVMP).

Supplementary Table 1:

Neuropsychological tests list
Assessment of Comprehension and Expression (ACE)
Babcock story recall test
The Brain Injury Rehabilitation Trust Memory and Information Processing Battery (BMIPB)
Boston naming test
Brixton spatial anticipation test
Category fluency
California Verbal Learning Test Children's (CVLT-C)
CVTL-C-II-long delay
Delayed recall test
Digit span test
Divergent naming
Hayling Sentence Completion test
Logical Memory tests
Measure of Cognitive Linguistic Abilities (MCLA)
Procedural narrative
Phonemic verbal fluency
Symbol-Digit Modalities Test (SDMT)
Unconnected completion test
Wechsler Adult Intelligence Scale -IV (WAIS-IV)
Wechsler Memory Scale -IV (WMS-IV)
Wide Range Achievement Test 4 (WRAT-IV)



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