Early predictors of long-term disability of paediatric-onset acquaporin-4 antibody-positive neuromyelitis optica spectrum disorders

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Key Points

Questions: Which are the early predictors of long-term disability in aquaporin-4 antibody-positive (AQP-IgG) neuromyelitis optica spectrum disorders (NMOSD) with paediatric-onset?

Findings: In this UK retrospective observational study, by a median time of 79 months, 34.3% of paediatric-onset AQP4-IgG NMOSDs reached visual disability, 25.8% cognitive impairment, 20.7% motor disability and 4% patients died due to the disease. Ethnicity, age at onset and onset phenotypes and onset acute therapy influenced long-term visual, motor and cognitive outcomes.

Meaning: Paediatric-onset AQP-IgG NMOSD is associated with high morbidity. The recognition of predictors of poor outcome can help direct the early management of the disease.

Words=99/100

Abstract

Importance: The identification of prognostic factors during the early stages of paediatric-onset aquaporin-4 antibody-positive (AQP4-IgG) neuromyelitis optica spectrum disorders (NMOSD) might help clinicians to individualise treatment regimes with the hope of improving outcomes.

Objective: To describe and characterize onset clinical features predicting long-term visual, motor and cognitive disability in patients with paediatric-onset AQP4-IgG disorders.

Design, Setting, Participants: In this UK multi-center retrospective study, clinical and demographical features of patients with paediatric-onset AQP4-IgG NMOSD followed at five British tertiary neurologic centres were recorded. Predictors of permanent visual disability (bilateral visual loss with visual acuity of <6/36 in the best eye), EDSS 4 (inability to walk further than 500 m), cognitive impairment (documented intellectual disability requiring extra support at school) were analysed.

Main Outcome(s) and Measure(s): The effects of sex, onset age, race/ethnicity, onset symptomes, onset severity (definition?) and therapy on time to first relapse, long-term visual, motor and cognitive disability.

Results: Forty-nine paediatric-onset AQP4-IgG patients (38.8% Caucasians/White, 34.7% Afro-Caribbeans/Black, 20.4% Asians and 6.1% Mixed) were included. Mean age at disease onset was 12 ± 4.1 years, 87.7% were females. Multifocal presentation was reported in 26.5% of patients and the three most common involved anatomical sites were optic nerve (47%), area postrema/ brainstem (48.9%) and brain (28.6%). Severe disease onset was seen in 75.5% of children. Children aged < 12 years at onset were likely to have early first relapse (p=0.030). By the 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 predicted by younger age at onset (p=0.016), Caucasian race/White ethnicity (p=0.032) and optic neuritis presentations (p=0.002). EDSS 4 was predicted by non-Asian races/ethnicity (p=0.054), while cognitive impairment by cerebral syndrome presentations (p=0.048), especially if resistent to intravenous steroids (p=0.034).

Conclusions and Relevance: Children with AQP4-IgG disease have more severe onset, and, at follow up, have higher visual, similar cognitive and lower motor disability compared to that reported in adults. Age at disease onset, race/ethnicity, onset symptoms/event and resistence to acute therapy at onset attack predict long-term outcomes and should be taken in consideration when deciding on the management regimes.

(words 351 /= < 350)

Introduction

Neuromyelitis optica spectrum disorders (NMOSD) are inflammatory demyelinating diseases of the central nervous system (CNS) affecting predominantly optic nerves and spinal cord[1]. Approximately 60-80% have disease-specific acquaporin-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] with a characteristic relapsing course. Only about 5% of AQP4-IgG positive NMOSD have a paediatric-onset[4]. Data on long-term clinical outcomes of AQP4-IgG positive paediatric patients are sparse[5,6]. This is a longer term outcome study of a relatively large single country paediatric-onset AQP-IgG NMOSD cohort collected from several UK neurology centres.[7].

Methods

We obtained data from prospectively collected databases and clinical notes of AQP4-IgG seropositive patients with paediatric-onset (defined as <18 years) from five tertiary UK NMO centres: (i) the John Radcliffe Hospital, Oxford, UK (adult and paediatric); (ii) Great Ormond Street Hospital, London (paediatric); (iii) The Walton Centre, Liverpool, UK (adult and paediatric); (iv) Evelina London Childrens Hospital (paediatric); (v) Royal London Hospital, London, UK (adult). The presence of AQP4-IgGs were identified in the Autoimmune Neurology Laboratory using a cell-based assay as described by Waters et al[8].

Informed consent was obtained according to local Ethics/ All data was collected as standard clinical care at all respective centres and subsequently shared with coordinating centre Oxford (add your rec no here). Information was collected on age at disease onset, race/ethnicity, onset attack types and severity at nadir, relapses, acute and immunosuppressive therapy, time to first relapse, long-term visual impairment (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 time to cognitive impairment (defined by neuropsychological assessments or documented intellectual disability requiring extra support at school). The full list of collected anonymised data is available on supplementary table 1/ Supplementary table 1 details the variables collected anonymously for each patient .

Statistical analysis

Normal distribution of continuous variables was assessed by Shapiro-Wilk normality test. Descriptive and groups comparison analysis were conducted considering the low number of observations. 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 (LR). 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 phenotypes, onset attack severity, acute therapy, second line acute therapy and time to immunosuppression. Multivariate cox proportional hazard model was performed using sex, age at disease onset, race/ethnicity, those factors significant/ with p-value < 0.10 in the univariate model, and adding in time to immunosuppression because the early use of such treatment may be biased towards more severe attacks and thus not significant in univariate modelling. We evaluated the possible violation of the proportional hazard assumption with Shoenfeld residuals.

Results

Disease presentation, clinical course and therapy

We collected data on 49 patients with paediatric-onset AQP4-IgG seropositive disease with a median disease duration of 79 (range 6-401) months, female to male ratio was

7:1 and median current age was 2 (range 6-53) years. The most predominant race/ethnic group in our cohort was Caucasian/White (38.8%) followed by Afro-Caribbean/Black (34.7%), Asian (20.4%) and mixed (6.1%). However, the 2011 census reported that in England and Wales Caucasians/White were the 81.5%, Afro-Caribbeans/Black the 3.7%, Asian the 10.3%, Mixed the 3.2% and other ethnicities 1.3% of the population aged between 18 and 24 years, demonstrating the increased frequency of non-Caucasians in our cohort. Table 1 shows their demographic and clinical descriptive features and groups comparison. Patients with mixed Black ancestrory/Mixed Afro-Caribbean patients were included in the Black ancestory group/Afro-Caribbean group because they showed similarities in demographical and clinical features.

Demographical findings

Mean age at disease onset was 12 ± 4 years. Caucasian/White children had significant younger age at onset compared to the other races/ethnicities (p=0.008, Fisher's exact test) while Black children were older (p=0.025, Fisher's exact test) than other ethnic groups/races (table 1).

Clinical findings

Children frequently presented with area postrema and/or brainstem syndrome (BS=48.9%), unilateral or bilateral optic neuritis (ON=47%), cerebral syndromes, (namely, acute disseminated encephalomyelitis-like syndrome -ADEM-like-, diencephalic syndromes and aspecific encephalopathies) (CS=28.6%), and transverse myelitis (LETM=24.5%) (all had active longitudinally extensive transverse myelitis). Multifocal presentation was seen in 26.5% (13/49) of patients. No difference in onset/index presentation was noted when analysing patients according to sex, age at onset and races/ethnicity (table 1). A severe onset attack (defined as inability to walk at nadir for spinal attacks; visual acuity 6/60 or worse in affected eye at nadir of the optic neuritis attacks; alteration of consciousness, vomiting for more than 7 days with weight

loss for area postrema syndromes and brainstem attacks) was seen in 75.5% of patients and overall 20.4% of patients reached any of the disability milestones at first presentation (two patients reached two disabilities milestones).

A relapsing course was observed in 83.7% of children with a median time to first relapse of 9 (range 2-204) months (table 1). Children aged less than 12 years at onset were less likely to have monophasic disease and of those with relapsing disease the time to first relapse was shorter as compared to children 12-18 years old at onset (median 4 vs 13 months; p=0.040, Mann-Whitney U test). However, monophasic patients were followed for a signicantly shorter time than relapsing patients (p=0.0005; Mann-Whitney U test) (table 1).

Acute and maintenance therapy

At first clinical presentation, 65.3% of patients were treated with intravenous methylprednisolone (IVMP) and 20.4% required second line acute therapy (plasma exchange (PLEX) and/or intravenous immunoglobulins (IVIG)) (table 1). Children refractory to IVMP were most likely to Black/Afro-Caribbean (p=0.018, Fisher's exact test), presented with multifocal involvement of CNS (p=0.004, Fisher's exact test).

At first clinical presentation, 30.6% (n=16) of patients did not receive acute therapy due to mild sensory symptoms or/, an under-recognized area postrema syndrome (n=10), isolated severe unilateral ON (n=5) and onset in 1988 with encephalopathic symptoms (n=1).

Exluding prednisolone tapers, the first maintenance immunosuppressive therapy was initiated after a median time of 10.5 (2-400) months. Asians children received therapy after a significant longer time from onset (p=0.030, Mann-Whitney U test) and higher mean number of relapses (p=0.036, ANOVA) as compared to White and Black groupd/ than the other two races/ethnic groups (table 1). In order of frequency, the most used immunosuppressants were azathioprine (AZA=61.2%), mycophenolate mofetil

(MMF=14.3%) and rituximab (RTX=12.2%). At last review, no patients had discontinued RTX as a first immunosuppressant (median follow-up time 55 months_IQR-). Discontinuations with AZA and MMF were 43.3% (median follow-up time 94 months -IQR-) and 85.7% (median follow-up time 45 months -IQR-) respectively (table 1). There was no differences in medications use according to sex, age at disease onset and race/ethnicity (table 1). A shorter median time to immunosuppression initiation was seen in children presenting with LETM (median 4 months, IQR=0.5-26) compared to those presenting with non-LETM symptoms (median 11 months, IQR=5-60) (p=0.049, Mann-Whitney U test).

Disability outcomes

After /In this cohort with/ a median follow up of 79 months (range/IQR), 18/49 (36.7%) patients had visual disability at follow-up and 7/18 reached the end point from the onset attacks, which, as expected, were all ON attacks. Of patients presenting with ON, 30.4% were left with visual disability from onset.

Of 49 patients, 9 (18.4%) reached motor disability EDSS 4.0, 5 (10.2%) reached EDSS 6 and one (2%) reached EDSS 8. EDSS 4 was reached from onset attack in 4/9 (LETM=3 and BS=1). Thus, 25% of LETM onset patients were left with EDSS 4 due to the onset attack.

Cognitive dysfuncton was present in 12/49 (24.5%) at follow-up, of which two reached this endpoint from onset attacks and both, as expected, related to CS presentation at onset/2 of these were from the onset attack and, as expected, both related to CS attacks/. Thus, of those with CS onset 14.3% had cognitive impairment from onset.

During the follow up, two patients (4%) died due to life-threatening brainstem relapses impairing the respiratory capability.

Visual impairment after onset attack was observed in 7/49 (14.3%; Caucasian/White=5, Asian=1, Mixed=1). Of these patients, 6 were treated with IVMP only and one was not

treated. Contrastingly, none of the 5 patients who received second line acute therapy for onset ON (n=23) developed permanent visual impairment versus 39% (7/18) of those not treated with second line acute therapy. No significant differences in motor or cognitive disability outcomes after onset attack were found according to sex, age at disease onset and race/ethnicity.

By the 79 month timepoint and excluding those with shorter disease durations, 34.3% reached visual disability, 20.7% reached EDSS 4, 14.8% reached EDSS 6, 4.2% reached EDSS 8, 25.8% reached cognitive disability, and 4.2% died.

Early predictors of long-term disability

Table 2 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 aforemention outcomes in relation to the most significant early clinical-demographical features. Multivariate cox proportional hazard model results for each outcome are provided in table 3.

First relapse

Children aged between 12-18 years experienced a first relapse at half the rate as children aged <12 years at onset (HR=0.49, p=0.030, 95%CI=0.25-0.93) (figure 1 A and table 2). However, this difference was not significant after adjusting for sex, race/ethnicity and time to immunosuppression (table 3).

Visual disability

Caucasian/White children were approximatrly/over four times more likely to develop early permanent visual disability than children with Black ethnicity (HR=4.1, p=0.032, 95%CI=1.13-14.8) (figure 1 C). This difference was lost but the hazard ratio increased when those who reached this endpoint from onset attack were excluded (HR=5.2, p=0.130, 95%CI=0.61-44). Using age at onset as continuous variable (years), older

children (12-18 years) at onset had longer latency to visual disability than younger children (<12 years) (HR=0.86, p=0.016, 95%CI=0.76-0.97). This effect is lost if those who reached this endpoint at onset attack were excluded (HR=0.87, p=0.149, 95%CI=0.73-1.05).

ON onset phenotype was strongly associated with permanent visual disability (HR=7.8, p=0.002, 95%CI=2.2-27.7) (figure 1B), and this observation/association was only slightly reduced when excluding those who reached this endpoint from at onset attack (HR=4.34, p=0.041, 95%CI=1.06-17.8).

Longer time to immunosuppression was associated with lower risk of developing visual disability (HR=0.98, p=0.026, 95%CI=0.97-0.99). However, this effect was lost if patients who develop visual disability from onset attack were excluded (HR=0.98, p=0.067, 95%=0.98-1.00), possibly due to earlier introduction of immunosuppression.

Finally, from the multivariate cox hazard model emerged that Caucasians/White showed a marked rise of hazard ratio (HR=12.2, p=0.024, 95%CI=1.39-107), patients presenting with ON showed a slight hazard ratio decrease (HR=7.6, p=0.020, 95%CI=1.38-41.9), while time to immunosuppression lost its significance (HR=0.99, p=0.302, 95%CI=0.97-1.00) (table 3).

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 index LETM/LETM presentation did not reach EDSS 4 earlier than other primary attacks sites, including following adjustment for sex, age at disease onset, race/ethnicity and time to immunosuppression (table 3).

Cognitive impairment

CS presentations were associated with a greater risk of cognitive impairment earlier than other presentations (HR=3.22, p=0.048, 95%CI=1.02-10.2) (figure 1 E) and this

effect remained after exlusion of CS index attacks/ even when the onset attack effect was removed/ (HR=5.52, p=0.017, 95%CI=1.36-22.5). Patients resistent 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, with the multivariate hazard model, both these effects were lost adjusting for sex, age at onset, race, CS presentation, need of second line acute therapy and time to immunosuppression (table 3).

Discussion

Key results and interpretation

This study reports the longest country wide follow-up of paediatric-onset AQP4-IgG seropositive NMOSDs to date and represents patients within a single country with similar environmental and treatment protocols. Children presenting under 12 years relapsed earlier than those aged 12-18 years. The non-caucasian/White predominance that has been reported in adults was also observd and predominance of Black ethnicity 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 treatemtn with acute second line therapies. Prognostic differences were also seen; earlier time to a) motor disability in non-Asians, b) visual disability in Caucasians, c) cognitive impairment with IVMP resistant onset CS. Younger children, those with index ON attacks, and those with ON who did not escalate to second line acute therapies also reached visual disability earlier .

Existing studies/Current knowledge about long-term outcomes of paediatric-onset NMOSD is is limited by studies that combined seropositive and seronegative patients all together[6,9] or had shorter follow-up times[5,10], or more heterogeneity across different countries and health care systems[10]. However, we noted comparable demographic

onset features (median age at onset, female to male ratio and BlacK predominance) in another single country study on paediatric-onset AQP4-IgG disease[5]. In addition, we reported an elevated incidence of area postrema syndrome as onset presentation compared to other paeditric AQP4-IgG NMOSD studies [5,10]. This may relate to hindsight retrospective diagnoses and improved awareness of the area postrema clinical presentation. RTX was superior to AZA and MMF as a 1st line therapy, both in terms of annualised relapse rate and tolerability . This is in keeping with a recent multi-center study that reported no relapses in children treated with first line RTX[10]. Despite methodological differences, many studies, similarly to ours, found an higher probability of developing visual disability than motor disability in patients with paediatric-onset AQP4-IgG[5,6,9,10]. The only study investigating predictors of long-term disability in children found a similar percentage of patients with cognitive impairment (25.4% and 24.5%) and a similar relationship between long-term visual disability development and ON presentations to our study[10].

The present study, uniquely, reported a survival analysis adjusted for varied follow-up times among the different subgroups to be compared. This method allowed us to look at early predictors of long-term disability independently from disease duration and to compare our findings to a three centre based study on predominantly adult patients[7] which used the same disability outcomes definitions.

Compared to Kitley et al/a predominant adult study on AQP4-IgG seropositive patients with a median follow-up time of 75 months[7], Afro-Caribbean predominance was greater in the our paediatric-onset cohort (34.7% in children versus 20.3% in predominantly/mostly adults). The younger age of onset in the Afro-Cariebbean /Black predominantly adult patients[7] may have been because the majority of patients were in the 16-30 year at onset group. The proportion of patients presenting with CS, BS and multifocal syndromes were greater in children than adults, while the proportion of those

presenting with LETM and with ON were respectively greater and similar in children cohort than predominantly adults cohort. Severe disease onset was more frequent in paediatric-onset than predominantly adults onset patients (75.5% versus 42.5%), although both showed similar residual disability as result of their onset attack (20.4% in children and 19% in predominantly adults)[7]. Patients receiving second line acute therapy due to resistance to IVMP were mostly Afro-Caribbean/Black and with multifocal presentions. As consequence of such severity, clinicians had administered immunosuppressive therapy earlier and after a lower annualized relapse rates to Afro-Caribbean/Black than to the other races, possibly resulting in a lower disability burden than Caucasians/White. Despite good diagnostic assays, children still had early relapses, especially in the younger age group (median time to first relapse 4 months) often before immunosuppressive therapy was started (median time 10 months). Time to first relapse in the older children group (13 months) was similar to the predominantly adults cohort[7] (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[6,7]. Despite similar median disease duration, children had double to risk of visual disability compared to the predominant adults cohort (36.7% of children versus 18% of predominantly adults) but reached EDSS 6 three times less frequently (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 follow up time. We found that Caucasian/White race/ethnicity, younger age at onset, and ON at presentation were predictive of long-term visual disability. Although in the prevalent adult study Afro-Caribbeans/Black were more likely to develop visual disability, in our

paeditric onset cohort Caucasian/White patients 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 that, as in adults and in another paediatric study[7,10], ON onset predicted long-term visual disability and we found interesting that its acute treatment was a determinant factor. Patients with ON refractory to IVMP who were not treated with second line acute therapy were more likely to develop earlier visual disability. Several studies demonstared safety and efficacy of treating refractory ON with PLEX, even in children[11,12,13]. Hence, we suggest to use a second line acute therapy in any case of IVMP lack of efficacy to prevent blindness development. Moreover, while ON presentation was predictive of shorter time visual disability, LETM presentation did not predict long-term motor disability even adjusting for covariates. This highlights a possible increased susceptibility of the optic nerve and a reduced susceptibility of the spinal cord in children compared to adults[14]. However, the early use of immunosuppressive therapy in transverse myelitis patients over those with ON may also have contributed.

We found ethnicity to be predictive of motor disability (EDSS 4) with Asian children reached EDSS 4 later than the other ethnic groups, despite had longer follow-up, higher number of relapses and longer time to immunosuppression. This data is consistent with findings of Japanese patients having less EDSS disability than UK Caucasian and Afro-Caribbean/Black patients[7]. Exclusively, we found that cognitive impairment was developed in around a quarter of children and it was particularly frequent in CS presentations refractory to IVMP, even when the effect of onset attack was removed. The proportion of cognitive impairment in AQP4-IgG NMOSD adults was estimated 29-57%[15], however, adults have the possibility of being assessed by sensitive neuropsycological tests capable of detecting subtle cognitive deficits while children might have been reffered to neuropsychological evaluation when presenting a decrease

of school performances. The prolonged effect of AQP4-IgG related brain inflammation might cause irreparable damage on the cortex and its connections[16] 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 in the future 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. Moreover, due to the retrospective nature of the study, patients presenting during the past decades might have been treated differently according to that time current practices however we included patients diagnosed since the AQP4-IgG seropositive assay was available in the UK (since 2007).

Conclusions

Peaditaric onset AQP4-IgG NMOSD is a disabling disease affecting predominantly Afro-Caribbean/Black followed by Asian and Caucasian/White children in UK. Children have a more severe onset and shorter time to first relapse than adults and show a good response to RTX when used first line compared to AZA and MMF. AQP4-IgG seropositive children are more likely to develop visual disability than motor disability compared to AQP4-IgG seropositive adults and have a notable risk of developing cognitive impairment. Caucasian ethnicity, younger age at onset and ON presentation predict future visual disability. Second line acute therapy is strongly adviced when ON is resistent to IVMP in order to avoid untimely blindness in children. Non-Asian ethnicities are more likely to develop EDSS 4 and LETM at onset is not predictive of motor disability, highlighting the greater capability of spinal cord to recover compared to optic nerve in this phase of life. A steroid-refractory onset attack involving cerebral

hemispheres predisposes to long-term cognitive impairment development. With increasing recognition of the predictors of AQP4-IgG NMOSD disability, individualized monitoring and treatment regimes can be offered to improve outcomes in children (figure 2).

Other information

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Figure 1: Most significant Kaplan Meier curves illustrating early predictors affecting probability of remaining free from first relapse, visual disability, motor disability

(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 who had optic neuritis (ON) than who did not especially during the first year after onset.

(C) Time to permanent visual disability was shorter in Caucasian group than Afro-Caribbean and Asian ethnic groups, and this difference was mainly due to the onset attack outcomes.

(D) Time to motor disability, defined as EDSS 4, was significantly longer in Asian than Afro-Caribbean and Caucasian ethnic groups.

(E) Time to cognitive impairment was significantly shorter in who presented a cerebral syndrome at onset (CS at onset =present) than who did not (CS at onset=absent).

(F) Time to cognitive impairment was significantly shorter in who was treated with second line acute therapy (IVIG or PLEX) than those who did not received second line acute therapy (no therapy or IVMP).

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Table 1: Demographical, clinical features among groups in AQP4-IgG NMOSD with paediatric onset

	Total cohort	SEX			AGE AT ONSET			ETHNICITY			
	N=49	**Female N=43**	**Male N=6**	**p-value**	**<12 years N=19**	**12-18 years N=30**	**p-value**	**Afro-Caribbean N=20**	**Asian N=10**	**Caucasian N=19**	**p-value**
Demography:											
Female n (%)	43 (87.7%)	-	-	-	16 (84.2%)	27 (90%)	ns	15 (75%)	9 (90%)	17 (9.5%)	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 disease duration months (IQR)	79 (38-182)	78 (37-181)	100 (49-191)	ns	90 (42-140)	72 (32-192)	ns	51 (29-106)	155 (82-256)	79 (42-181)	ns
Median current age years (IQR)	21 (17-29)	20 (15-29)	21 (17-30)	ns	19 (15-22)	23 (17-32)	ns	18 (16-26)	28 (22-39)	21 (17-28)	ns
Ethnicity n (%):								-	-	-	-
Afro-Caribbean	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				
Caucasian	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				
Onset syndromes n (%):											
ON (monolater and bilateral)	23 (47%)	20 (46.5%)	4 (66.7%)	ns	10 (52.6%)	14 (46.7%)	ns	9 (45%)	6 (60%)	9 (47.4%)	ns
APS and/or brainstem encephalitis	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
LETM	12 (24.5%)	12 (28%)	0	ns	5 (26.3%)	7 (23.3%)	ns	6 (30%)	2 (20%)	4 (21%)	ns
ADEM-like/diencephalic syndrome	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+LETM	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%)	0.278	**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	5/20	1/10	2/19	ns
Relapsing (R)	41 (83.7%)	36 (83.7%)	5 (83.3%)	ns	17 (89.5%)	24 (80%)	ns	15/20	9/10	17/19	ns
Median disease duration MON months (IQR)	8 (6-41)	9 (6-41)	NA	-	43 (6-79)	8 (6-48)	ns	9 (6-33)	NA	41 (3-79)	-
Median disease duration R years (IQR)	96 (44-182)	96 (43-182)	138 (62-209)	ns	96 (62-140)	97 (44-201)	ns	71 (43-182)	200 (98-247)	78 (42-181)	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 (%):	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
Azathioprine	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
Mycophenolate Mofetil	6 (12.2%)	5 (11.6%)	1 (16.7%)	ns	1 (5.3%)	5 (16.7%)	ns	4 (20%)	0	2 (10.5%)	ns
Rituximab	2 (4.1%)	1 (2.3%)	1 (16.7%)	ns	0	2 (6.7%)	-	2 (10%)	0	0	-
Methotrexate	2 (4.1%)	2 (4.7%)	0	ns	1 (5.3%)	1 (3.3%)	ns	1(5%)	0	1 (5.3%)	ns
Cyclophosphamide	2 (4.1%)	2 (4.7%)	0	ns	0	2 (6.7%)	-	1 (5%)	0	1 (5.3.%)	ns
Other***											
Failure of first line therapy n (%)	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
Azathioprine	6 (85.7%)	4 (80%)	2 (100%)	ns	3 (100%)	3 (75%)	ns	2 (66.7%)	1 (100%)	3 (75%)	ns
Mycophenolate Mofetil	0	0	0	-	0	0	-	0	-	0	-
Rituximab	1 (50%)	1 (50%)	-	-	-	1 (50%)	-	1 (50%)	-	-	-
Methotrexate	2 (100%)	2 (100%)	-	-	1 (100%)	1 (100%)	ns	1(100%)	-	1 (100%)	-
Cyclophosphamide											
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 ±1.811	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 impairment	7 (14.3%)	5 (11.6%)	2 (33.3%)	ns	5 (26.3%)	2 (6.7%)	0.093	1 (5%)	1 (10%)	5 (26.3%)	0.093
Cognitive impairment	2 (4%)	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%)	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	-

ON=optic neuritis, APS= area postrema syndrome; LETM= longitudinally extensive transverse myelitis, ADEM= acute disseminated encephalomyelitis; ON+TM= neuromyelitis optica; IVMP= intravenous methylprednisolone; intravenous immunoglobulins; PLEX= plasma exchange; SD= standard deviation; IQR= interquartile range; EDSS= Expanded Disability Status Scale. Where is *** in legend here

Table 2: Survival 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) *	**P value (Log-rank)**	**HR (95%CI)**	**P value**	**Median Survival time (IQR) ***	**P value (Log-Rank)**	**HR (95%CI)**	**P value**	**Median Survival time (IQR) ***	**P value (Log-Rank)**	**HR (95%CI)**	**P value**	**Median Survival time (IQR) ***	**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)	0.572	1.34 (0.47-3.87)	0.377	171 (79-367)	0.583	0.70 (0.19-2.48)	0.584	NR (199-NR)	0.965	1.05 (0.12-8.57)	0.377	NR (127- NR)	0.572	0.65 (0.14-2.99)	0.576
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)	0.095	NR (NR-NR)	0.339	0.53 (0.14-1.99)	0.348	NR (89- NR)	0.687	1.28 (0.38-4.26)	0.688
Race																
Afro-Caribbean	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)	0.385	176 (120-NR)		1.9 (0.42-8.82)	0.391	NR (NR-NR)		NA	-	NR (89- NR)		0.39 (0.07-2.22)	0.294
Caucasian	6 (3-16)	0.254	1.78 (0.87-3.63)	0.112	79 (6-367)	0.036	4.1 (1.13-14.8)	0.032	253 (115-NR)	0.054	1.07 (0.28-4.06)	0.921	240 (127- NR)	0.561	0.72 (0.20-2.58)	0.622
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)	0.824	0.88 (0.47-1.64)	0.691	86 (6-171)	0.0002	7.8 (2.2-27.7)	0.002	NR (NR-NR)	0.665	0.69 (0.16-2.97)	0.621	NR (89- NR)	0.554	1.43 (0.43-4.79)	0.556
LETM																
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)	0.894	0.99 (0.49-2.00)	0.986	NR (38-NR)	0.824	0.90 (0.29-2.82)	0.867	NR (8- NR)	0.538	1.58 (0.39-6.43)	0.522	NR (72- NR)	0.987	0.98 (0.26-3.70)	0.987
BS																
Absent	10 (5-29)		1 (reference)		120 (15-176)		1 (reference)		253 (253-NR)		1 (reference)		240 (89- NR)		1 (reference)	
Present	12 (3-26)	0.804	0.90 (0.47-1.70)	0.748	NR (171- NR)	0.067	0.39 (0.13-1.11)	0.078	NR (199-NR)	0.792	1.25 (0.33-4.73)	0.734	NR (127- NR)	0.544	0.70 (0.22-2.22)	0.547
CS																
Absent	9 (4-24)		1 (reference)		120 (36-NR)		1 (reference)		NR (199- NR)		1 (reference)		NR (NR - NR)		1 (reference)	
Present	17 (4-36)	0.495	0.80 (0.39-1.65)	0.552	367 (171-367)	0.072	0.34 (0.10-1.20)	0.095	253 (253- NR)	0.781	1.63 (0.40-6.55)	0.487	150 (72-240)	0.035	3.22 (1.02-10.2)	0.046
Multifocal																
Absent	8 (1-204)		1 (reference)		176 (79-367)		1 (reference)		NR (253- NR)		1 (reference)		NR (240- NR)		1 (reference)	
Present	13 (2-127)	0.505	0.83 (0.37-1.81)	0.641	86 (6-171)	0.274	1.70 (0.63-4.63)	0.297	NR (115- NR)	0.671	1-35 (0.33-5.45)	0.674	127 (72-150)	0.207	2.07 (0.65-6.57)	0.218

Onset severity *Mild* *Severe*	11 (4-24) 17 (6-37)	0.273	1 (reference) 1.86 (0.77-4.45)	0.163	NR (NR-NR) 171 (15-367)	0.032	1 (reference) 6.77 (0.90-51.3)	0.064	NR (NR - NR) 253 (199- NR)	0.305	1 (reference) 1.90 (0.24-15.2)	0.545	NR (NR- NR) 240 (89-NR)	0.163	1 (reference) 3.88 (0.50-30.3)	0.196
Onset AT *No* *Yes*	9 (4-36) 13 (4-26)	0.982	1 (reference) 1.15 (0.59-2.24)	0.682	171 (120-367) 171 (36-NR)	0.521	1 (reference) 2.19 (0.71-6-81)	0.172	NR (253- NR) NR (199- NR)	0.694	1 (reference) 1.53 (0.35-6.70)	0.565	240 (89- NR) NR (127- NR)	0.649	1 (reference) 0.91 (0.26-3.17)	0.879
II line AT *Not required* *Required*	9 (4-24) 24 (13-37)	0.250	1 (reference) 0.64 (0.29-1.40)	0.265	176 (36-367) 171 (86-171)	0.513	1 (reference) 0.65 (0.14-2.88)	0.572	NA (199- NA) NA (NA - NA)	0.488	1 (reference) 2.20 (0.41-11.7)	0.351	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)	0.139	--	-	0.98 (0.97-0.99)	0.031	-	-	0.99 (0.98-1.00)	0.164	-	-	0.99 (0.98-1.0)	0.161

*Estimated from Kaplan Meier curves

NR= not reached; EDSS= Expanded Disability Status Scale; HR= hazard ratio; IQR= interquartile range; ON= optic neuritis at onset; LETM= longitudinally extensive 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.

Table 3: Multivariate Cox regression analysis for early predictors of time to first relapse and time to long-term disability

	HR (95%CI)	P-value
Time to first relapse (months)		
Sex		
Male	1 (reference)	
Female	1.12 (0.36-3.43	0.849
Age at disease onset		
<12 years	1 (reference)	
12-18 years	0.55 (0.24-1.28)	0.164
Race		
Afro-Caribbean	1 (reference)	
Asian	1.48 (0.57-3.83)	0.418
Caucasian	1.26 (0.49-3.23	0.624
Time to IS	0.99 (0.99-1.00)	0.138
Schoenfeld residuals		0.830
Time to visual disability (months)		
Sex		
Male	1 (reference)	
Female	1.04 (0.21-5.2)	0.955
Age at disease onset ©	1.11 (0.93-1.34)	0.239
Race		
Afro-Caribbean	1 (reference)	
Asian	2.13 (0.32-14.08)	0.432
Caucasian	12.2 (1.39-107)	0.024
ON at onset	7.6 (1.38-41.9)	0.020
BS at onset	1.60 (0.38-6.58)	0.515
CS at onset	0.15 (0.39-6.58)	0.086
Severity of onset attack	3.72 (0.42-32.70)	0.235
Time to IS	0.99 (0.97-1.00)	0.302
Shoenfeld residuals		0.863
Time to EDSS 4 (months)		
Sex		
Male	1 (reference)	
Female	1.11 (0.12-10.5)	0.928
Age at disease onset		
<12 years	1 (reference)	
12-18 years	0.76 (0.13-4.50)	0.767
Race		
Afro-Caribbean	1 (reference)	
Asian	NA	NA
Caucasian	0.59 (0.09-3.62)	0.572
LETM	1.11 (0.20-6.05)	0.901

Time to IS	0.99 (0.98-1.00)	0.432
Shoenfeld residuals		0.365
Time to cognitive impairment (months)		
Sex		
Male	1 (reference)	
Female	1.05 (0.12-9.10)	0.964
Age at disease onset		
<12 years	1 (reference)	
12-18 years	1.04 (0.26-4.24)	0.952
Race		
Afro-Caribbean	1 (reference)	
Asian	1.58 (0.11-21.9)	0.731
Caucasian	1.07 (0.13-9.10)	0.945
CS at onset	2.44 (0.53-11.30)	0.252
Second line acute therapy	3.12 (0.36-27)	0.301
Time to IS	0.99 (0.97-1.00)	0.149
Shoenfeld residuals		0.618

HR= hazard ratio; CI= confidence interval; ON= optic neuritis; BS= brainstem syndrome; CS= cerebral syndrome; LETM= longitudinally extensive transverse myelitis; IS= immunosuppression; II line AT=Second line acute therapy (IVMP+ IVIG/PLEX); ©=continuous variable