Early predictors of epilepsy and subsequent relapse in children with acute disseminated encephalomyelitis (ADEM)

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Abstract

Objective: To identify predictors of epilepsy and clinical relapses in children presenting with ADEM
Methods: Children presenting with ADEM between 2005 and 2017 and tested clinically for MOG-Ab, were identified from three tertiary paediatric neurology centres in the UK. Patients were followed-up for a median of 6years (range 1-16 years).
Results: 74 children were studied (38 females; median age at first presentation: 4.5 years (range: 1.4–16). MOG-Ab was positive in 50/74(67.6%) of cases, and 27(54%) of MOG-Ab positive children presented with a neurological relapse over time. MOG-Ab was more frequently positive in the relapsing group than in the monophasic group (27/31 vs 23/43; odds ratio 5.9(95% CI 1.8-19.7); p=0.002). 16/74(22%) children had seizures during the acute presentation with ADEM and 12/74(16.2%) patients were diagnosed with post-ADEM epilepsy. The diagnosis of post-ADEM epilepsy was more frequently observed in children with relapsing disease than monophasic disease (10/31 vs 2/43; odds ratio 9.8 (95% CI: 2.0-48.7); p=0.003), positive intrathecal oligoclonal bands than those with negative bands (4/7 vs 4/30; odds ratio 8.7(95% CI: 1.4-54.0); p=0.027) and positive MOG-Ab than negative MOG-Ab cases (11/12 vs 39/62; odds ratio 6.5(95% CI:0.8-53.6); p=0.051).
Conclusion: A higher relapse rate and a greater risk of post-ADEM epilepsy in children with MOG-Ab-associated disease may indicate a chronic disease with immune-mediate seizures in these children.

Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated demyelinating CNS disorder most frequently presenting in younger children[1]. Patients present with polyfocal neurological deficits associated with encephalopathy, often accompanied by fever and a systemic illness. MRI typically demonstrates reversible, ill-defined white matter lesions of the brain and often also the spinal cord[1]. Although a favorable outcome is commonly reported, a proportion of affected children will present with clinical relapses over time. Predicting children who will have an isolated episode of demyelination and good recovery, or have subsequent relapses and neurological sequelae may help both in the counselling of parents, and potentially the tailoring of medical management to an inidividual's risk.

It has been long recognised that children with ADEM may relapse with more than one clinical syndrome. Based on multiple long-term surveillance study of children with acquired demyelinating syndromes (ADS), relapses following ADEM as defined by the International Paediatric Multiple Sclerosis Study Group (IPMSSG) revised criteria[2] may occur with patients having a (i) recurrence of neurological symptoms within 3 months, often as immunomodulatory treatment is being weaned, and now defined as the same ADEM episode; (ii) second episode of ADEM after 3 months defined as "multiphasic" where there is either re-emergence of previous neurologic symptoms or new and different signs and magnetic resonance imaging (MRI) findings; or (iii) second clinical event is not associated with encephalopathy, occurs three or more months after the incident neurologic event, and is associated with revised radiologic McDonald 2010 criteria for dissemination in space, thus meeting the criteria for multiple sclerosis (MS)[3]

The clinical phenotypes of children with MOG-Ab associated disease include monophasic ADEM[4], ADEM followed by recurrent optic neuritis (ON)[5], or AQP4-negative NMOSD[6]. MOG-Ab are present in more than 30% of children who present with an initial episode of demyelination[7], in more than 50% of those presenting with ADEM[8], and in almost all those with multiphasic ADEM (MDEM)[9]**.** Although initially thought to be associated with predominantly white matter disease, there are increasing reports of both adults[10, 11] and children[12] with MOG-Ab-associated disease presenting with grey matter disease and seizures. Recent report of isolated seizures (in the absence of ADEM) during the first episode of relapsing MOG-Ab associated demyelination in children, suggested that MOG-Ab may be a cause of an autoimmune epilepsy[13]

The objective of this study was to identify clinical features and investigations that predict clinical relapses and post-ADEM epilepsy. Furthermore, we examined the electro-encephalograms (EEG) of those children with post-ADEM epilepsy to obtain insights into the pathological processes that may contribute to the ongoing morbidity.

Methods

All children (under the age of 18yrs) were diagnosed with ADEM at first presentation with an acquired demyelinating syndrome between 2005-2017 and were tested for MOG-Ab during the course of their disease. This is a subgroup of a larger cohort of acquired demyelinating syndrome including patients from the Evelina Children's Hospital, Great Ormond Street Children's Hospital, and Birmingham Children's Hospital, previously described[8].

All patients were tested in Oxford for both MOG-Ab and AQP4-Ab (using live cell-based assays, as previously described)[7] as part of routine clinical care, but not always at the time of first presentation. We defined an incident cohort comprising those patients who developed symptoms after January 2014 (when MOG-Ab test was clinically available and tested during the acute presentation) and a retrospective cohort of children presenting before 2014 in whom the antibody testing was done retrospectively (either at time of relapse or from a sample previously sent for AQP4-Ab testing). All patients were managed according to their clinical diagnosis and the patients' antibody status did not impact treatment decisions.

Demographic information, clinical features at presentation, discharge and follow-up, and results of laboratory investigations, neuroimaging and EEG were compiled. EEGs were performed in accordance with national guidelines (30min for awake EEG and 60min for sleep).Demyelinating phenotype at onset was determined from the patient's clinical features, according to established criteria[14]. A relapse was defined as an acute or subacute episode of new or increasing neurological dysfunction followed by a full or partial recovery, in the absence of fever or infection.[15] Relapsing cases were assigned the following diagnostic categories: (1) ADEM, if the relapses only occurred within 3 months from symptoms onset (2) MDEM fulfilling the 2013 IPMSSG consensus criteria[2] (3)ADEM-ON defined as ADEM or recurrent ADEM proceeded with episodes of ON[5] (4)NMOSD, fulfilling the 2015 Wingerchuk criteria for antibody negative.[16] Further neurological events were defined as either a relapse, or the development of post-ADEM epilepsy, or both.

Post-ADEM epilepsy was defined as seizures requiring treatment with one or more anti-epileptic drugs (AEDs) for two or more years after the initial episode of ADEM, adopted from the definition of post-encephalitis epilepsy.[17] Drug resistant epilepsy was defined as failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom[18]. Children with a recognisable epilepsy syndrome were excluded from either a diagnosis of post-ADEM epilepsy or DRE. For those children who went on to develop post-ADEM epilepsy, all EEGs performed beyond the acute period (more than one month from presentation or relapse) were reviewed by an epileptologist.

Statistical analysis

Statistical analysis was performed using the commercially available software SPSS Version 24 (IBM, CA). Nonparametric statistical tests (Mann-Whitney tests) were used for continuous distributions, and χ^2 or Fisher exact tests were used for nominal data when comparing groups (relapsing versus monophasic; post-ADEM epilepsy versus no post-ADEM epilepsy and incident cohort versus retrospective cohort). Fisher exact test was used when any field had a value <5. Multivariate binary logistic regression utilising potential predictors at disease onset that achieved a univariate significance of <0.1 was used to calculate odds ratios and 95% confidence intervals for predictors of post-ADEM epilepsy and relapsing disease. Statistical significance was taken at 0.05.

Ethical approval

This study was approved by Great Ormond Street Hospital Research and Development Department (reference 16NC10)

Results

Seventy-four patients (38 females and 36 males; median age at first presentation: 4.5 years (range: 1.4– 16)) fulfilled the clinical criteria for ADEM at first presentation[14] and were included in this study. Brain MRI at onset was abnormal in all children and in keeping with a diagnosis of ADEM. Cerebro-spinal fluid (CSF) microscopy was available in 49 children, of whom 16 (21.6%) had raised white cell count (>5x10^6); CSF protein was elevated (>0.45g/dl) in 10/46 (13.5%) children, and oligoclonal bands were positive in 8/37 children (21.6%).

MOG-Ab was positive in 50/74 (67.6%) of ADEM cases. AQP4-Ab was negative in all patients.

16/74 (22%) children had seizures during the acute presentation of ADEM, and 12/74 (16.2%) patients were diagnosed with post-ADEM epilepsy. None of the patients were diagnosed with drug resistant epilepsy.

As we were concerned about introducing bias when comparing the clinical and paraclinical features of children in whom MOG-Ab testing was done during the first presentation (n=25) with those in whom it was performed retrospectively (n=49). We confirmed there were no differences in any of the clinical features at presentation (supplemental table 1). Despite the longer follow-up time in the retrospective cohort we did not detect a difference in the rate of relapse (p=0.084) and post-ADEM epilepsy (p=0.203)

Relapsing disease

Patients were followed-up for a median of 6 years (range 1-16); 43/74 (58.1%) had monophasic disease, while 31 (41.9%) went on to have a subsequent relapse. 27/31 were MOG-Ab positive. The final diagnosis was ADEM (n=46), MDEM (n=19), ADEM-ON (n=3) and NMOSD (n=6). None of the children were diagnosed with multiple sclerosis. Ten patients relapsed within three months of diseases onset, of which 3 children had only a single relapse. Of those three children one was MOG-Ab positive, and two MOG-Ab negative. Figure 1 shows the frequency of relapse events. One child who was MOG-Ab negative had 2 clinical relapses. All 11 children who had more than 2 relapses were MOG-Ab positive(Figure 1a). Survival without relapse is presented in Figure 1b, demonstrating a higher probability of relapse free survival in those who are MOG-Ab negative (Mantel-Cox p=0.04).

The presence of MOG-Ab gave an odds ratio of subsequent relapse of 5.9 (95% CI: 1.8-19.7)(p=0.002). Post-ADEM epilepsy was associated with an increased risk of subsequent relapse (odds ratio 9.8 (95% CI: 2.0-48.7)(p=0.003)(Table 1)

As potential early predictors of subsequent relapse, presence of MOG-Ab and seizures at presentation were entered into a multivariate binary regression mode. Only the presence of MOG-Ab remained a significant predictor of subsequent relapse (odds ratio 5.4 (95% CI:1.6-18.4); p=0.007).

Post-ADEM epilepsy

Twelve (16.2%) children (4 females and 8 males; median age at presentation: 5.5 years (range: 2.6 - 9.2); median duration of follow-up 8.5 years (range: 3-17 years)) developed post-ADEM epilepsy. Six of the 12 developed seizures at first presentation. The median time to onset of seizures was 3 months (range 0-61 months), with four children having seizures that continued from first presentation. MOG-Ab was positive in 11/12 (91.7%) children with post-ADEM epilepsy.

All patients with post-ADEM epilepsy were treated with at least one anti-epileptic drug two years after presentation. The decision to treat, duration of treatment and choise of AED were based on clinical and EEG findings (and not antibody positivity). One child had complete seizure control on two anti-epileptic drugs. All patients remained on AEDs two years from the acute presentation.

Ten (83.3%) children with post-ADEM epilepsy went on to have a relapsing disease course. The final diagnosis for children with post-ADEM epilepsy was MDEM (n=6), NMOSD (n=2), ADEM (n=2), and ADEM-ON (n=2).

The clinical characteristics of these children in comparison to children who did not develop epilepsy are presented in Table 2. Neuroimaging and EEG findings of the 12 children who went on to develop post-ADEM epilepsy were reviewed. EEG outside of the acute presentation in those children with a diagnosis of post-ADEM epilepsy showed focal or generalized slowing, and in one case an excess of fast activity (secondary to medication). The clinical history and characteristics are summarized in Table 3.

Children with seizures at first presentation were more likely to develop post-ADEM epilepsy. The odds ratio of developing post-ADEM epilepsy with seizures at first presentation was 5.2 (95% CI 1.4-19.4; p=0.009). There was a greater risk of post-ADEM epilepsy in children who relapsed than those who did not (odds ratio 9.8 (95% CI: 2.0-48.7); p=0.001), had positive oligoclonal bands than those who did not (odds ratio 8.7 (95% CI: 1.4-54.0); p=0.027), and a trend towards a greater risk in those who were MOG-Ab positive than those who were MOG-Ab negative (odds ratio 6.5 (95% CI: 0.8-53.6); p=0.051). (Table 2)

When seizures occurred at onset, MOG-Ab positivity and positive OCB were entered into a multivariate binary logistic regression model, both the presence of oligoclonal bands in the CSF (odds ratio 20.7 (95% CI: 1.5-286); p=0.023) and seizures at onset (odds ratio 13.5 (95%CI:1.1-171); p=0.044) remained significant predictors of post-ADEM epilepsy.

Discussion

In this study we have demonstrated that there is a greater risk of relapse in children presenting with ADEM who are MOG-Ab positive. While in our cohort relapse was seen in MOG-Ab negative patients, none went on to have more than two clinical relapses in contrast to several MOG-Ab positive patients who went on to have up to 20 relapses. This suggests that in the absence of MOG-Ab the risk of long term relapsing disease is relatively small, which may play a role in targeting immune modulation therapy.

Our results are in keeping with a previous finding of MOG-Ab identified in 19/33(57%) of children with ADEM.[4] In that study 4/19 (21%) children with MOG-Ab developed multiphasic disease compared to 0/14 of the MOG-Ab negative group. In our study we report multiphasic disease in 54% of children positive for MOG-Ab. The higher relapse rate in our cohort may reflect the longer duration of follow-up (median 6 years versus median 2 years) and indeed a longer duration of follow-up was associated with an increasing likelihood of further neurological morbidity. Although we did not detect a difference in the rate of relapse between the incident and retrospective cohort, there was a trend towards a higher rate of relapsing disease in the retrospective cohort which may have contributed to this. Twenty seven out of 31 children who relapsed had MOG-Ab; all 27 patients matched the typical phenotype thought to correspond with MOG-Ab positivity[19]. The other four children who were MOG-Ab negative and relapsed all had an MDEM phenotype. The only difference detected between the MOG-Ab positive vs MOG-Ab negative relapsing cases was the total number of relapses (Figure 2)

AQP4-Ab was negative in all patients. The patients who were diagnosed with NMOSD fulfilled the IPMD 2015 criteria[20] (which stratify patients into AQP4-Ab positive and negative). Nevertheless, although these patients fulfilled the criteria, the MOG-Ab positive children had a distinct phenotype to children reported with AQP4-Ab NMOSD[21]. In a large cohort of 197 adult patients with MOG-Ab[22] only 19% of patients fulfilled the IPND 2015 criteria for NMOSD. This emphasizes the complexity of classifying patients based on the clinical instead of biological phenotype

The second important observation of this study is that in the 12/74 that developed post ADEM-epilepsy, seizures at presentation and OCB positivity were early predictive risk factors. Seizures have been reported in other acquired demyelinating syndromes. The incidence of epilepsy is higher in adults with multiple sclerosis compared to the general population, with the increased risk resulting from a high risk in those with progressive disease.[23] The authors hypothesise that an increased grey matter lesion burden in progressive disease may account for the increased incidence of epilepsy. Although seizures are frequently reported during acute presentation with ADEM[1], in a single center Australian cohort of 34 children with ADEM there were no reports of post-ADEM seizures despite using the same diagnostic criteria.[17]

The association of intrathecal OCBs at presentation with the development of post-ADEM epilepsy may support the hypothesis that post-ADEM epilepsy may result from chronic inflammation. As the CSF analysis for oligoclonal bands were performed in only 37 patients, the small sample size and the lack of longitudinal assessment of CSF (which was not done clinically for children with ADEM) limits the clinical utility of these findings. In adults with NMDA-receptor encephalopathy mild clinical relapses with seizures may be related to subtle rises in CSF antibody titres not reflected in serum titres.[24] The relationship between MOG-Ab titres and clinical disease activity remains an area of active investigation, however the utility and applicability of this remains to be evaluated clinically in light of challenges of measuring antibody titres beyond a research setting. As the patients reported in this cohort were tested clinically, it was not possible to determine if deterioration in seizure control was associated with fluctuation in MOG-Ab titres.

There are strengths and limitations to this study. We have captured all children with a diagnosis of ADEM in whom MOG-Ab was tested from three tertiary paediatric neurology centres as previously described.[8] MOG-Ab testing was introduced clinically as of January 2014. Therefore this study includes both children whose serum was retrospectively tested, and those tested at presentation as part of clinical assessment. This introduces a potential for selection bias in that those children with a relapsing or more severe disease course may be more likely to be tested retrospectively. There may therefore be an over representation of children with relapsing disease who go on to be tested for MOG-Ab in the retrospective cohort. Furthermore, patients were recruited from specialised neuroimmunology centers and it is therefore possible that we have overrepresentation in our cohort of a more severe phenotype.

The proportion of children with a final diagnosis of ADEM was inevitably higher in the prospective cohort, in whom follow-up duration was shorter but interestingly there were no differences in the rate of relapse and the risk of post ADEM epilepsy. MRI analysis in those under 6 years of age typically requires general anaesthesia, and thus one of the obvious limitations of this study is the lack of standardised imaging, at regular follow-up times or at time of seizures to assess for evidence of disease accrual. Furthermore, imaging analysis focusing on grey matter involvement may help distinguish chronic inflammation from gliotic scaring as the cause of post-ADEM epilepsy.

To examine the relative significance of predictors of relapse or post-ADEM epilepsy we have undertaken multivariable logistic regression. This is limited by the small numbers in both the relapsing group, and the post-ADEM epilepsy group, which increases the risk of clinically significant predictors not achieving statistical significance. Furthermore, data was acquired clinically and not all parameters (for example oligoclonal band results) were available for all patients. Similarly, as all EEG were performed clinically, differences exist across different centres. Often, in accommodating the less compliant child, a shorter and imcomplete recording epoch is inevitable. These results must therefore be interpreted with the greatest caution.

This study is the first to identify an association between MOG-Ab associated disease and post-ADEM epilepsy in children. Although post-ADEM epilepsy could result from synaptic reorganisation or perturbation resulting from inflammation, the finding on EEG in those with post-ADEM epilepsy of focal or generalized slowing often discordant to epileptiform discharges, suggest that the possibility of a persisting low grade brain dysfunction mediated by inflammation cannot be discounted

In conclusion, in this study we demonstrate a higher relapse rate in children with MOG-Ab-associated ADEM, and a trend towards a greater risk of post-ADEM epilepsy. We hypothesise that this may be a result of ongoing subclinical inflammation resulting in recurring seizures supported by the higher rate of intrathecal oligoclonal bands detected in these patients. MOG-Ab-associated disease may therefore reflect a true antibody-mediated epilepsy, and treatment of seizures in these children, particularly in those without epileptic discharges on EEG or focal scarring on MRI, may be best directed towards management of an ongoing inflammatory process.

Contributors
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Figure 1: Number of relapse events according to MOG-Ab status

Figure 2: Kaplan-Meier plot showing relapse free survival according to MOG-Ab status. Diamonds (MOG-Ab negative) and lines (MOG-Ab positive) show the point at which relapse free patients were censored (last point of follow-up)

Table 1: clinical and paraclinical features of monophasic and relapsing patients. (CSF – cerebrospinal fluid; WCC – white cell count; OCB – oligoclonal bands)

	Relapse (n=31)	Monophasic disease (n=43)	Odds ratio (95%CI)	p-value
Sex (F:M)	18:13	20:23	0.7 (0.3-1.7)	0.355
Age at presentation (months)	47 (20-157)	67 (17-178)		0.191
Prodrome present	17/26	28/34	0.4 (0.1-1.3)	0.148
Raised CSF WCC	8/22	8/27	1.4 (0.4-4.5)	0.761
Raised CSF protein	7/22	3/24	3.3 (0.7-14.7)	0.159
CSF OCB	6/21	2/16	2.8 (0.5-16.2)	0.423
MOG-Ab	27/31	23/43	5.9 (1.8-19.7)	0.002
Seizures at presentation	10/31	6/43	2.9 (0.9-9.2)	0.086
Seizures post-ADEM	10/31	2/43	9.8 (2.0-48.7)	0.003
Duration of follow-up from first presentation (years)	7 (1-16)	5 (2-7)		0.001

Table 2: Clinical characteristics according to development of post-ADEM epilepsy

	Post-ADEM seizures (n=12)	No post-ADEM seizures (n=62)	Odds ratio (95% CI)	p-value
Sex (F:M)	4:8	34:28	2.4 (0.7-8.9)	0.172
Age at presentation (months)	66 (31-110)	53 (17-178)		0.558
Prodrome present	7/11	38/49	0.5 (0.1-2.0)	0.335
Raised CSF WCC	4/8	12/41	2.4 (0.5-11.3)	0.411
Raised CSF protein	3/7	7/39	3.4 (0.6-18.9)	0.163
CSF OCB	4/7	4/30	8.7 (1.4-54.0)	0.027
MOG-Ab	11/12	39/62	6.5 (0.8-53.6)	0.051
Seizures at presentation	6/12	10/62	5.2 (1.4-19.4)	0.009

Relapse	10/12	20/62	9.8 (2.0-48.7)	0.001
Final diagnosis				
ADEM	2/12	44/62		<0.001
MDEM	6/12	13/62		0.035
NMOSD	2/12	4/62		0.249
ADEM-ON	2/12	1/62		0.067
Duration of follow-up from first presentation (years)	8 (3-17)	5 (1-12)		<0.001

Table 3: Clinical history and characteristics of the 12 children who developed post-ADEM epilepsy

	Demographics	Diagnosis at last follow-up	Clinical presentation	MOG-Ab status	Subsequent neurologic events	Seizure semiology	Time to onset of seizures (Months)	Initial and/or latest interictal EEG	MRI pattern	AED	Maintenance Immunotherapy	Outcome and comorbidities
1	9yr M Mixed	ADEM	Encephalopathy, behavioural change and focal neurological signs	Negative	Nil	Focal seizures onset from one year following ADEM	11	Occasional bursts of sharp and slow activity and spike and wave discharges against a normal background. During sleep left sided discharges appear more frequent. Compatible with an increased liability to focal seizures.	Multifocal, hazy/poorly marginated lesions involving both the grey matter and white matter	Topiramate	Nil	Good seizure control for 2 years; Left hemiplegia; Normal Cognition
2	14yr M Mixed	ADEM-ON	Vomiting, severe headache and confusion and optic neuritis.	Positive	Relapse with optic neuritis five years after first presentation	Aura of nausea followed by twitching of arms or legs on either side lasting up to 2 minutes.	60	Asymetrical background. Loss of posterior rhythms and improving slowing over left hemisphere. No epileptiform discharges seen.	Multifocal, hazy/poorly marginated lesions involving both the grey matter and white matter	Carbamazepine	Nil	No further seizures; Normal neurology; Normal cognition
3	4yr F White British	MDEM	Behavioural change, ataxia and bilateral 6th nerve palsy following a febrile illness	Positive	Multiple relapses at 9-12 month intervals characterised by altered behaviour, loss of balance, weakness (left more than right), and slurred speech over 10years	Left sided motor seizures	4	Normal background rhythms. Persistent slow activity over the right hemisphere in keeping with a focal lesion. No epileptiform activity seen.	Leukodystrophy-like	Levetiracetam	On Azathioprine for three years which was then discontinued. Continues to relapse yearly.	On-going seizures, motor, cognitive and behavioural difficulties
4	6yr M White British	ADEM-ON	Encephalopathy with seizures. Intubated and ventilated for 7 days	Positive	Three episodes of ON (8, 9 and 10 years from ADEM)	Episodes of brief behavioural arrests. Developed soon after the initial presentation and PICU admission. Persisted for 9 months, subsequently controlled with Sodium Valproate	0	At presentation: Diffuse slowing. No periodic or epileptiform activity seen 6 months follow-up: Focal slowing with no epileptiform discharge	Cortical encephalitis	Previously Sodium Valproate	Nil	Seizure free off treatment; Normal neurology; Moderate learning difficulties; Significant anxiety disorder.
5	3yr M Indian	MDEM	Encephalopathy, ataxia and ON	Positive	Multiple relapses at 6-12month intervals characterised by altered behaviour, loss of balance, weakness (left more than right), and slurred speech over 10years	Eye deviation to the left, with right sided facial twitching and impaired consciousness.	48	Excess fast activity with 1-2Hz slow waves in left posterior region. Definite assymetry. Focal encephalopathy. Sharpened morphology left parietal left temporal, right sided sharp over P3, C4. Non-specific sharp waves, scatted sharps.	Leukodystrophy-like	Levetiracetam	Managed with Beta-interferon with no change in relapse frequency.	Seizure breakthrough with intercurrent illness; Normal neurology; Cognitive and behaviour difficulties
6	3yr F Black African	NMOSD	Encephalopathy, slurred speech and ataxia. Persistent left-sided squint.	Positive	One relapse at 6yr with simultaneous left ON+LETM	Prolonged focal dyscognitive seizure.	8	First EEG- Widespread high amplitude slowing. Few focal spikes. 9 month EEG - generalised 3Hz spike and wave. 7/11 intermittent slow waves, intermittent sharp transients. 12/2012 disorganised cerebral activity. Nothing epileptiform.	Leukodystrophy-like	Levetiracetam	Nil	Yearly breakthrough seizure; Normal neurology; No cognitive problems
7	2yr M Kuwait	MDEM	Encephalopathy, seizures, pyrexia, lower limb weakness, vomiting and lethargy.	Positive	At 1year, encephalopathy, seizures and cerebellar signs	Episodes of eye flickering, lip smacking and right sided tonic-clonic seizures.	0	Normal	Cortical encephalitis	Oxcarbazepine	Nil	2-3 seizures monthly; Normal neurology; Cognitive and behavioural difficulties
8	4yr F Caucasian	MDEM	Encephalopathy, lethargy and an unsteady gait.	Positive	Recurrent relapses with lethargy, ataxia, slurred speech and rigidity associated with increased seizure frequency.	Prolonged generalised tonic clonic seizure (1.5 years after first demyelination). Ongoing focal seizures	18	Abnormal excess of slow activity, more prominent slowing over left hemisphere. No discharges	Multifocal, hazy/poorly marginated lesions involving both the grey matter and white matter	Lamotrigine	Managed with Beta-interferon with no change in relapse frequency.	Yearly left sided focal seizures; Subtle cerebellar signs; Mild learning difficulties.
9	8yr M White British	MDEM	Encephalopathy, seizures and headaches. Intubated and ventilated for 3days	Positive	A further ADEM like presentation 7 years after initial presentation with encephalopathy and seizures.	Generalised tonic-clonic seizures from presentation.	0	1-2Hz - slow waves more in right frontal and left temporal region. Encephalopathic. PLEDS right frontotemporal and left centrotemporal on left	Cortical encephalitis	Sodium Valproate	Nil	GTCS twice a year; Normal neurology; Behavioural problems
10	8yr M White other	NMOSD	Encephalopathy, neck stiffness, headache, optic	Positive	Multiple relapses with encephalopathy, seizures, ataxia and optic neuritis	From presentation he developed right focal motor seizures	0	Slowing right frontotemporal and posteriorly. No discharges.	Multifocal, hazy/poorly marginated lesions involving both the grey matter and white matter	Lamotrigine, oxcarbazepine	Continued to relapse on Interferon, Rituximab and Natalizumab.	On-going seizures often accompanying intercurrent illness; Dysarthria, dysmetria,

			neuritis and urinary incontinence.			with secondary generalisation.					Relapse free on monthly IVIG	impaired right eye vision; Mild cognitive difficulties
11	6yr M White British	ADEM	Encephalopathy, ataxia and 6th nerve palsy.	Positive	N/A	Focal seizure from 3 months after presentation. Well controlled on Topiramate. Last seizure 2 years after presentation	3	Assymetrical background with reduction of amplitude of posterior rhythms over the left hemisphere. No epileptiform discharges	Multifocal, hazy/poorly marginated lesions involving both the grey matter and white matter	Topiramate	Nil	No seizures; Normal neurology Normal cognition and behaviour
12	5yr F White British	MDEM	Encephalopathy, ataxia and right focal seizures	Positive	Nine months after initial presentation developed encephalopathy with seizure and ataxia with new changes on imaging. Also developed optic neuritis. Nine or ten relapses over a six year period with longest inter-attack period of two years.	Right -sided focal motor seizure.	0	Background abnormality with excess of slow activity. Not focal, no epileptiform features	Leukodystrophy-like	Keppra Carbamazepine	Continued to relapse on Azathioprine and interferone. Stable on Natulizimab	2 seizures a month; Normal neurology; Cognitive and attention difficulties.