Paediatric ADEM followed by optic neuritis: disease course, treatment response and outcome

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Word count: 2621

Abstract: 195

References: 15

Tables: 1

Figures: 1

Running title: children with ADEM followed by optic neuritis

Key words: acute disseminated encephalomyelitis, optic neuritis, anti-MOG antibodies, paediatric, treatment response

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ABSTRACT

Background: Acute disseminated encephalomyelitis, followed by optic neuritis (ADEM-ON) is a rare demyelinating syndrome different than MS and neuromyelitis optica spectrum disorder. We aim to describe the disease course, treatment response and outcome of these children.

Methods: children <18 years were identified from 6 countries of the EU Paediatric Demyelinating Disease Consortium. Patients fulfilled the diagnostic criteria for ADEM, followed by at least one ON. Anti-MOG antibodies (MOG-Ab) were tested in all patients.

Results: in this study of 17 patients (9 boys) with ADEM-ON, MOG-ab were identified in 16/17. Age at onset was 6.1 years (IQR 5.1-9.2). Twelve patients received oral prednisolone and 10 received maintenance immunosuppression (e.g. azathioprine, intravenous immunoglobulins, Rituximab). During a follow-up of 5.3 years (IQR 1.8-10.2), 54 relapses occurred with a median 3 relapses/patient (range 1-9). Patients relapsed on all treatments but no relapses occurred on a prednisolone dose>10mg/day. Visual and cognitive residual deficits were common in this group.

Conclusion: ADEM-ON is a MOG-Ab associated relapsing disorder and can have a heterogeneous disease course. Patients were refractory for maintenance immunosuppression and appeared to be corticosteroid-dependent. Further international collaborations are now required to unify guidelines in this difficult to manage group of patients.

INTRODUCTION

Acute disseminated encephalomyelitis (ADEM) is a well-recognized acquired demyelinating syndrome (ADS) characterized by a polyfocal onset and encephalopathy. It is most commonly seen in young children.[1] Although predominantly monophasic, some children relapse and may fulfill the diagnostic criteria of multiple sclerosis (MS) or neuromyelitis optica spectrum disorders (NMOSD).[1] More recently, a distinct clinical phenotype has been recognized, different than MS and NMOSD, with patients relapsing with single or recurrent episode of ON following ADEM.[2] The majority of these children have myelin oligodendrocyte glycoprotein antibodies (MOG-Ab). [3-5] In a Dutch paediatric cohort of acquired demyelinating syndrome (ADS) only 1.2% of children were diagnosed with ADEM-ON.[6] Despite the rarity of ADEM-ON in ADS, ADEM-ON has been the final diagnosis in about 40% of MOG-ab positive relapsing patients who initially presented with ADEM.[7]

As no treatment guidelines are currently available for patients with ADEM-ON the aim of this European collaboration study was to escribe the disease course, treatment response and outcome of ADEM-ON patients in a multinational approach.

PATIENTS AND METHODS

Data collection

We collected demographic, clinical, radiological and serological data of 17 patients under age 18 from 6 countries of the EU Paediatric Demyelinating Disease Consortium (The Netherlands n=7, United Kingdom n=6, Germany n=1, France n=1, Spain n=1, Belgium n=1). This consortium was initiated as a component of the ERN-RITA (European Reference Network for Rare Immunodeficiency, Autoinflammatory

and Autoimmune Disease). Patients were identified by reviewing local or national paediatric demyelination registries and included after fulfilling the following criteria: i) presenting with ADEM as a first demyelinating event in accordance with the IPMSSG criteria ii) experiencing ≥1 subsequent attack of optic neuritis (ON) without encephalopathy ≥3 months after ADEM onset, with or without additional episodes of ADEM in between (MDEM-ON).[1]

A unified case reporting form was distributed to all participating sites to collect de-identified patient data. Assessments of visual function were carried out by ophthalmology departments at the respective centres, including high contrast visual acuity measured by the logarithm of the minimum angle of resolution (logMAR) and colour vision measured by Ishihara plates.

All patients were tested locally in the respective reference laboratories of the referring countries for serum MOG and AQP4 antibodies, using live cell-based assays, as part of standard clinical care while clinically symptomatic.[3, 4, 8-10]
Institutional review board and/or national research ethics approval was obtained at individual centers or national programs respectively.

STATISTICAL ANALYSIS

Chi square and Mann-Whitney U test were used for group comparison. Time to first ON-relapse (TTFR) was calculated by subtracting the date of ON-relapse from the onset date of the last ADEM attack. ARR after the first ON was analyzed with a negative binomial regression, with the natural logarithm of follow-up years after the first ON as offset. This offset was used to correct for the different follow-up durations between patients. Statistical significance was set at p-value of 0.05.

RESULTS

Seventeen ADEM-ON patients were included in this study. Clinical, paraclinical features, treatment response and outcome are summarised in **Table 1** and **Figure 1.** MOG-Ab were identified in 16/17 (94%). This seronegative patient had a typical ADEM-ON disease course and serum was tested in the acute phase at onset and re-tested during relapses. MOG-ab were persistently positive in all patients who were retested at follow-up (n=8) irrespective of the presence of disease activity. All patients were AQP4-Ab negative. Brain MRI at follow-up showed improvement or complete resolution of ADEM brain lesions in all patients.

A total of 54 relapses were reported in the cohort (median 3 relapses per patient, range 1-9), during a median follow-up of 5.3 years (IQR 1.8-10.2). Of which 51/54(94.4%) were ON (10/51 bilateral) and 3/54(5.6%) ADEM-relapses (Figure 1). Nadir visual acuity (VA) at relapses (n=32) was median 0.08 (IQR <1/300 – 0.38). No differences in nadir VA or residual deficits was observed between treated and untreated patients. Oral prednisolone taper was used in 12/17 (70.6%) patients starting dose 1-2 mg/kg/day). Twenty-seven of the 54 relapses occurred when oral corticosteroids were tapered off to a low dose (median 8.5 mg, range 1-10 mg) or in the four weeks following discontinuation (median 1.1 weeks; range 0.5-5 weeks). Oral corticosteroid was re-introduced using a higher dose when relapse occurred (median 20 mg, range 10-60 mg), resulting in prolonged corticosteroid exposure (median 6 months, IQR 1.7-14.8 months). No relapses occurred while using a dose>10mg.

Maintenance immunotherapy was commenced in 10/17(59%); Azathioprine 2-3 mg/kg/day (n=6), Mycophenolate 1200 mg/m^2/day (n=1), regular IVIG 0.4-1.0

g/kg/dosis (n=2) and Cyclophosphamide 750 mg/m^2/month for 6 months (n=1). Median time from acute treatment to initiating maintenance therapy was 3 days (range 0-42 days). Treatment response was evaluated at least 6 months after initiation (time of treatment range 6-61 months). Six patients relapsed on maintenance treatment (total 13 relapses) and were switched to another therapy or another agent was added to the treatment regime, including Rituximab (500 mg/m^2/dosis, 2 dosis per cycle; every 6 months) and IviG (Figure 1). Of these 6/13 relapses occurred when the oral corticosteroids were tapered off to a low dose (≤10 mg/day) despite ≥6 months of treatment with maintenance therapy. Seven relapses occurred in patients on maintenance treatment only. The disease course differed between patients in the annual relapse rate and interattack duration (median 5.7 months, range 3-247 months), in both treated and untreated patients (Figure 1).

A shorter TTFR was associated with more relapses after the first ON during follow-up (spearman rho -0.531,p=0.028). The median TTFR was 7months(IQR 4-85). There was a trend to have higher ARR in patients who relapsed within 7months (mean ARR 1.24 vs 0.35,p=0.061).

At last follow-up, residual deficits were reported in 12/17(71%) patients and included visual impairments (n=8), cognitive impairments (n=8), seizures (n=2), behavioural problems (n=3), weakness in extremities (n=1) and bladder/bowel dysfunction (n=1) were less common. The median EDSS score at last follow-up was 1.0 (IQR 0-3.0).

Residual deficits did not correlate with number of relapses or TTFR.

DISCUSSION

Here we report the disease course, treatment and outcome of ADEM-ON patients identified from six European countries. MOG-Ab were identified in 16/17. This rare group of patients was characterized by large heterogeneity in disease course and applied treatment regimens. By contrast to the reported literature in adults with MOG-Ab associated disease, residual deficits such as visual and cognitive impairments were common.[10-14]

Despite heterogeneity in treatment we observed that relapses occurred on all treatments even under more potent therapies such as Rituximab and/or IVIG. Oral prednisone, on the contrary, was effective if given in doses >10mg daily. This indicates a certain degree of corticosteroid dependence in these children, although the worrisome side effects and unpredictable disease course of ADEM-ON patients warrant against long-term use of high doses (>10mg) prednisone. Corticosteroid dependence may be typical for relapsing MOG-Ab relapsing ON.[15]

We observed a prolonged interattack intervals (>5 years) which is not typically seen in children with RRMS and may result in potential overtreatment and exposure to long-term immunosuppression. This stresses the importance of identifying early predictors for future disease course. TTFR may be good marker, as children with a short TTFR tended to have a higher ARR. Monitoring of MOG-Ab during the course of disease may aid in predicting the future disease course and guiding treatment.[16]

Although this study was the result of a multinational EU collaboration, the sample size remained relatively small due to the extreme rarity of ADEM-ON. Some patients with solely one ON-relapse within the first three months of ADEM were excluded as we followed the IPMSSG 2012 criteria[1]. However this three months duration merits

further study as it is arbitrary. International collaborations are now required to unify treatment guidelines to inform on early prognostic markers and treatment effect in this rare demyelinating syndrome.

ACKNOWLEDGMENTS

We are thankful for the support of the reference laboratories who have provided MOG-Ab and AQP4-ab testing for patients in this study: Dr Dörte Hamann (Department of Immunopathology and Blood Coagulation, Sanquin, Diagnostic Services, Amsterdam); Prof. Markus Reindl (Clinical Department of Neurology, Medical University of Innsbruck, Innsbruck, Austria); Dr Philippe Horellou (Inserm, U 1184, Centre for Immunology of Viral Infections and Autoimmune Diseases, Paris, France); Dr Anne Ruiz (Lyon Neuroscience Research Centre, INSERM U1028/CNRS 5292, France); Drs Paddy Water and Dr Mark Woodhall (Nuffield Department of Clinical Neurosciences, Oxford, United Kingdom); Dr Albert Saiz, Neuroimmunology Program, IDIBAPS-Hospital Clinic, University of Barcelona, Spain.

We are grateful to the co-investigators from the participating countries for their inclusions and referrals, including physicians from the Dutch paediatric MS and ADEM study group and the UK childhood inflammatory Disorders (UK-CID) study group.

STUDY FUNDING

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

CONFLICT of INTEREST

Evangeline Wassmer – receives research grants from Action Medical Research and MS Society and has received travel grants from UCB, Shire, and Biogen Idec; educational grants to organize meetings from Merck Sereno, Novartis, Bayer, and Biogen Idec; speaker's fees from Merck Sereno; and consultancy fees from Genzyme.

Cheryl Hemingway - received educational and travel grants from Merck Serono, Bayer, and Biogen.

Rogier Hintzen - Received honoraria for serving on advisory boards for Biogen Idec, Roche, Sanofi. He participated in trials with BiogenIdec, Merck-Serono, Roche, Genzyme and Novartis

Kumaran Deiva - He participates in clinical trials for Novartis, Biogen and Sanofi.

Ming Lim - receives research grants from Action Medical Research, DES society, GOSH charity, NIHR, MS Society, SPARKS charity and; receives research support grants from the London Clinical Research Network and Evelina Appeal; has received consultation fees from CSL Behring; received travel grants from Merck Serono; and awarded educational grants to organize meetings by Novartis, Biogen Idec, Merck Serono and Bayer

Rinze Neuteboom- participates in trials with Sanofi Genzyme and Novartis.

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Table 1 – Patient characteristics

Clinical parameters	**Patients n=17**
Male, n (%)	9 (56)
Age of onset, years (IQR)	6.1 (5.1-9.2)
Caucasian, n (%)	13 (81)
Autoimmune disease, n (%)	0
Admission to ICU, n (%)	7 (41)
Preceding event <4 weeks before onset, n (%) - Vaccination - Infection/fever	 - 5 (29) - 11 (65)
CSF oligoclonal bands, n (%)	0/14
MOG-Ab	16/17
MRI brain at baseline*	
ADEM-like[a]	15
Unspecific lesions[b]	1
Unavailable[c]	1
MRI Spine at baseline	12/15 (80%)
Presenting symptoms	
Seizures, n (%)	7 (41)
Vision disturbances, n (%)	6 (35)
Autonomic features, n (%)	7 (41)
Cranial nerves, n (%)	3 (18)
Bulbar dysfunction, n (%)	1 (6)
Sensory, n (%)	3/15 (20)

Motor dysfunction, n (%)	9 (53)
Cerebellar symptoms, n (%)	9 (53)
Headache, n (%)	10 (59)
Acute treatment, n (%) - IvMP 3-5 days - Dexamethasone - IvIG 5 days - Additional treatment o 2nd IvMP 3-5 days o 2nd IvIG 5 days	13 (77) - 10/13 (77) - 2/13 (15) - 1/13 (8) - 7/13 (54) o 4/7 o 3/7
Outcome, n (%) - Residual deficits - Visual impairment - Visual acuity impairment - Visual field impairment - Colour vision - Cognitive impairment - Seizures	 12 (71) 8 (47) 7 (41) 7 (41) 4 (24) 8 (47) 2 (12)

Definitions. IQR: interquartile range. ICU: intensive care unit. CSF: cerebral spinal fluid. ADEM: acute disseminated encephalomyelitis. IvMP: intravenous methylprednisolone. IvIG: intravenous immunoglobulins. MOG-Ab: myelin oligodendrocyte glycoprotein antibodies (IgG subtype).

***** Baseline MRI brain performed within 3 months after onset of symptoms. **[a]** ADEM-like MRI: predominantly confluent, hazy and poorly demarcated involving both grey and white matter.**[b]**Unspecific lesions: non-specific white

matter lesions not fulfilling MAGNIMS criteria for MS specific lesions.

[c]Unavailable: patient was retrospectively identified. MRI was not assessable. However, the patient had encephalopathy at presentation and patient charts mentioned lesions fitting the diagnosis of ADEM.

Figure Caption and legend

Figure 1 – ADEM-ON disease course and treatment. The disease course and given treatments per patient are shown in this figure. MRI images are displayed from patient 12. Onset MRI: bilateral multiple large and hazy lesions on FLAIR sequence. Relapse 1: MRI shows resolution of white matter lesions on FLAIR, and a thickened left optic nerve on T1 sequence without gadolinium enhancement. Relapse 3: relapse of ON without new T2 lesions.

Abbreviations. ADEM: acute disseminated encephalomyelitis. ON: optic neuritis. P: oral prednisone. AZA: azathioprine. MMF: mycophenolate mofetil. CYC: cyclophosphamide. RTX: Rituximab. IvIG: intravenous immunoglobulins