Incidence of paediatric multiple sclerosis and other acquired demyelinating syndromes

UK Childhood Inflammatory Demyelination Network

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Incidence of Paediatric Multiple Sclerosis and other relapsing demyelination conditions: 10-year follow-up UK surveillance of Paediatric Acquired Demyelinating Syndromes (ADS)

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Abstract

Aim: To describe 10-year follow-up of children <16 years with acquired demyelinating syndromes (ADS) from a UK-wide prospective surveillance study.

Methods: Diagnoses were retrieved from the patients' records via the patients' paediatric or adult neurologist using a questionnaire. Demyelinating phenotypes, at follow-up, were classified by expert review panel.

Results: 24/125 (19.2%) children, identified in the original study, were diagnosed with multiple sclerosis (MS, incidence of 2.04/million children/year); 23/24 fulfilled 2017 McDonald criteria at onset. AQP4-Ab neuromyelitis optica spectrum disorders were diagnosed in 3/125 (1.6%, 0.26/million children/year), and relapsing MOG-Ab associated disease in 5/125 (4%, 0.43/million children/year). 3/125 seronegative non-MS patients relapsed and 85/125 (68%) remained monophasic over 10 years. 5/125 (4%) originally diagnosed with ADS were reclassified during follow-up: three children diagnosed initially with acute disseminated encephalomyelitis were subsequently diagnosed with acute necrotising encephalopathy (RANBP2 mutation), primary hemophagocytic lymphohistiocytosis (Munc 13-4 gene inversion) and anti-NMDA-R encephalitis. One child initially diagnosed with optic neuritis was later diagnosed with vitamin B12 deficiency, and one presenting with transverse myelitis was subsequently diagnosed with Sjögren's syndrome.

Interpretations: The majority of ADS presentations in children are monophasic even at 10-year follow-up. Given the implications for treatment strategies, MS and CNS autoantibody mimics warrant extensive investigations.

What this paper adds:

- Majority of paediatric ADS presentations are monophasic even at 10-year follow-up
- UK paediatric multiple sclerosis incidence is 2.04 per million children per year
- MOG-Ab associated disease and AQP4-Ab NMOSD incidence was similar to previous cohorts
- Almost all MS patients (95.8%) met 2017 McDonald criteria at presentation
- Five children initially reported in the ADS cohort had alternative inflammatory aetiologies

Introduction

Acquired demyelinating syndromes (ADS) represent acute neurological illnesses characterised by deficits persisting for at least 24 hours and involving the optic nerve, brain, or spinal cord, associated with regional areas of increased signal on T2-weighted images[1]. ADS may occur as a monophasic illness, such as optic neuritis (ON), transverse myelitis (TM), acute disseminated encephalomyelitis (ADEM), with overall good prognosis[2] or as a chronic and relapsing condition, such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), resulting in progressive disabilities[3].

Diagnosis of multiple sclerosis, the most common relapsing form of ADS in both children and adults, requires evidence of inflammatory activity in more than 1 CNS location (dissemination in space, DIS) in addition to recurrent disease over time (dissemination in time, DIT). The revised 2017 McDonald criteria allowed for intrathecal oligoclonal bands to substitute for DIT, the inclusion of symptomatic lesions as evidence of DIS/DIT and the inclusion of cortical grey matter lesions in DIS[4]. These criteria also highlighted the importance of excluding alternative diagnoses, and have a high specificity and sensitivity in the paediatric population, including children younger than 12 years not presenting with ADEM[5, 6].

Many patients with NMOSD also have frequent relapses. Aquaporin-4 (AQP4) antibodies (Ab) have been identified in NMOSD, which has led to more rapid initiation of treatment[7]. In approximately 40% of children with ADS, myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) have been reported[8]. Although largely associated with monophasic illness, MOG-Ab have also been associated with relapses and detected in patients with multiphasic disseminated encephalomyelitis (MDEM)[9], recurrent idiopathic optic neuritis[10] and ADEM-ON (acute disseminated encephalomyelitis (ADEM), which can be followed by recurrent or monophasic ON)[11]. Identification and distinction of the different subtypes of ADS, especially at first presentation, has important implications on treatment and prognosis[12], with accurate diagnosis and management of inflammation being key to improving patient outcomes[4].

In a UK-wide prospective surveillance study of children under the age of 16 years (September 2009–September 2010) , the incidence of childhood CNS inflammatory demyelination was calculated as 9.83 per million per year[13]. Here, we conducted 10-year follow-up evaluations of the same cohort to ascertain the incidence of multiple sclerosis and other relapsing demyelinating syndromes.

Methods

As detailed previously[13], children under the age of 16 years, with a first episode of ADS evaluated with MRI (brain and/or spine) were ascertained from a prospective national UK surveillance study (2009-2010) using two well-established surveillance units; the British Paediatric Surveillance Unit (BPSU) and the British Ophthalmological Surveillance Unit (BOSU). Serum Myelin Oligodendrocyte Glycoprotein (MOG) and Aquaporin-4 (AQP4) antibodies (Ab) were not routinely tested. Serum AQP4-Ab was only requested when NMOSD was suspected clinically and MOG-Ab testing was additionally performed on these samples as previously reported (*n*=49)[8]. Acute samples were taken within 3 months of clinical presentation[8] and samples were kept stored at -80°C. Additional MOG-Ab testing was requested once the test became clinically available in 2014 (*n*=27).

Demyelinating phenotypes were classified by an expert review panel (EW, ML, SW, YH), at onset[13] and on final follow up on the basis of the International Paediatric Multiple Sclerosis Study Group criteria[14], the revised 2017 McDonald criteria for the diagnosis of Multiple Sclerosis[15] and the International Consensus Diagnostic Criteria for NMOSD[16]. Clinical, paraclinical data and final diagnosis at 10 years were retrieved from the patient's medical records via the patient's primary paediatric or adult neurologist using a questionnaire.

Descriptive statistics were used to summarise the key components of the dataset. Non-parametric statistical tests (Kruskal–Wallis tests) were used for continuous distributions as appropriate given lack of normality, and χ^2 or Fisher's exact test were used for nominal data. Estimates of national incidence with confidence intervals (Byar's approximation of the exact Poisson[17]) for the 13-month study were annualised using mid-2010 UK and 2010 Republic of Ireland population estimates[18]. Analyses were performed using GraphPad Prism 8 (GraphPad Software).

Ethical approval for the surveillance study was from the UK Multicentre Research Ethics Committee (09/H1202/92).

Results

A total of 125 children were included in the original cohort; follow-up data on diagnosis at 10 years were collected. Paediatric and adult neurologists responded with completed questionnaires for 113/125 patients (90%). Of the 12 patients who did not have 10 year follow-up data (ON *n*=6, TM *n*=3, ADEM *n*=3), all had remained monophasic at 3 years. Eighty-five (68%) of the 125 children included had a monophasic ADS of which 39/85 (45.8%) presented with ADEM, 23/85 (27.1%) with

ON, 18/85 (21.2%) with TM (4 with short TM and 14 with longitudinally extensive TM) and 5/85 (5.9%) with other clinically isolated syndrome (CIS) presentations (Figure 1).

Thirty-five children (28%) had relapsing demyelinating syndromes (RDS). Twenty-four children (19.2%) had a final diagnosis of MS, including 23 with relapsing remitting MS (RRMS), and one had a primary progressive phenotype. Therefore, the incidence of MS under the age of 16 years in the UK and ROI was calculated as 2.04 per million children per year (95% confidence interval [CI] 1.31,3.04). Of these 4/24 (16.7%) presented under the age of 12 years, with a UK incidence of 0.34 per million children per year (95% CI 0.09,0.87). When retrospectively applied, the revised 2017 McDonald's diagnostic criteria diagnosis of MS could be made at presentation in 23/24 (95.8%). The remaining patient met the dissemination in space (DIS) criterion at presentation (did not have a contrasted scan or a lumbar puncture) and had a clinical relapse within 1 year of disease onset.

Only 76/125 (60.8%) had MOG-Ab and AQP4-Ab tested of which 20/76 (26.3%) were positive for MOG-Ab and 2/76 (2.6%) for AQP4-Ab. All 24 patients with a diagnosis of MS, including the four patients with disease onset under the age of 12 years were negative for both autoantibodies. Antibodies were tested in 41/85 patients with monophasic disease compared to 35/35 patients with relapsing disease. Of the 41 patients with a monophasic disease who had antibody testing, 37/41 (90.2%) were tested at onset, and a further 4 were tested at follow up. Only 14/43 (32.6%) patients presenting with ADEM had antibody testing at onset, and a further three at follow up. 19/35 (54.3%) of the patients with a relapsing disease course who had antibody testing, were tested at onset and a further 16 were tested at follow up. 5/20 (25%) of the MOG-Ab positive patients had a relapsing disease course. Therefore, the incidence of relapsing MOG-Ab Associated Disease (MOGAD) in children was calculated as 0.43 per million children per year (95% CI 0.14,0.99) and that of AQP4-Ab NMOSD as 0.26 per million children per year (95% CI 0.05,0.7).

Five patients originally diagnosed with an ADS had alternative diagnoses at 10-year follow-up. Three patients originally diagnosed as ADEM were found to have the following three final diagnoses; acute necrotising encephalopathy (ANEC) with a confirmed mutation in RANBP2, primary hemophagocytic lymphohistiocytosis (HLH) with an inversion of the Munc 13-4 gene, and Anti-NMDA-R encephalitis (with white matter involvement on neuroimaging) (Figure 2). One patient initially diagnosed with ON did not respond to immunotherapy and was diagnosed with vitamin B12 deficiency (with a concurrent mitochondrial ND5 variant). Finally, one patient who presented with transverse myelitis was subsequently diagnosed with Sjögren's syndrome.

Table 1 includes clinical and paraclinical information for this cohort. Children with monophasic ADS group were younger than the MS cohort (median age 8.7 yrs vs 13.9 yrs, $p<0.0001$) and were more likely to present with ADEM; none of the children presenting with ADEM were subsequently diagnosed with MS. Abnormalities in brain MRI at presentation were seen in 23/24 (95.8%) of MS patients compared to 50/83 (60.2%) of patients in the monophasic group ($p=0.0007$). Intrathecal oligoclonal bands were reported in 24/24 (100%) of the MS group compared to only 4/53 (7.5%) of the monophasic ADS group ($p<0.0001$).

Three children (2.4%) died during follow up; one patient during acute presentation of ADEM from acute fulminant inflammation inducing cerebral oedema, one with AQP4-Ab NMOSD 10 years after initial presentation during relapse following a hyperkalaemic cardiac arrest; and the patient with primary HLH died following an unsuccessful bone marrow transplant with further CNS relapses.

Discussion

In this up to 10-year follow up of a UK population active surveillance study of children with ADS, we have shown that the majority of the children had a monophasic course. The key observation is that almost all children with multiple sclerosis (95.8%) met the 2017 revised McDonald criteria at presentation. Of note, oligoclonal band analysis and contrasted scans were not performed for the one patient who did not fulfil criteria at onset. At the time of the initial study, 2006 McDonald criteria were being used for MS diagnosis, which have subsequently been superseded by both 2010 and 2017 McDonald criteria, with improved sensitivities in both adults[19] and children[20, 21]. In fact, 10/24 (42%) of cases fulfilled 2010 McDonald criteria at the time of the study. The annual incidence of MS in children <16 years (2.04/million children) in our cohort is similar to that reported in a number of other studies internationally, ranging from 0.13 to 2.85 per 100,000 children per year[22-24].

Since the initial surveillance period in 2009-2010 there has been a paradigm shift in the diagnosis and management of relapsing demyelinating syndromes (RDS) of childhood given the discovery of CNS autoantibodies with both AQP4-Ab associated disease and MOGAD being increasingly recognised[12]. The low incidence of MOG-Ab positivity and proportion of relapsing MOGAD in this cohort is likely due to the fact MOG-Ab testing only becoming clinically available from 2014. In fact, despite the prevalence of MOG-Ab positivity being reported highest across ADS phenotypes[25], only 17/43 (39.5%) children presenting with ADEM had MOG-Ab tested, which is likely to explain the low MOG-Ab positivity reported here. Furthermore, patients who had antibodies tested in 2009-2010

were more likely to have relapsing disease and within the monophasic group it is possible that by the time of testing they had already become seronegative[26]. Recent data suggests that up to one third of children with ADS have MOG-Ab positivity[27] and the proportion of MOG-Ab positive patients with a relapsing disease course in this cohort is similar to that reported in other prospective cohorts[26, 28]

Our reported paediatric incidence of AQP4-Ab NMOSD (0.26 per million children per year) is similar to that reported in paediatric studies worldwide (ranging from 0.01 to 0.06 per 100,000/year)[29]; however data remains scarce in this group. NMOSD has global variations in both prevalence and incidence among different geographic areas and ethnicities. In two UK studies in small areas of England and Wales[30, 31], the prevalence of NMO/NMOSD was calculated as 19.6 per million (95% CI: 1.22,2.97), with 21% of the reported prevalent cases under age 20 years, resulting in a higher prevalence in the age group from 0 to 19 years.

Of note, five children who were initially reported in the ADS cohort were found to have alternative inflammatory aetiologies with important treatment implications. Although traditionally, patients with monogenetic disorders have been thought to be younger, to have underlying developmental delay, symmetrical MRI and lack of response to immunosuppression; we now recognise an increasing number of conditions mimicking ADS. Of note, the patient with primary HLH had a relapsing disease course, good response to steroids and fulfilled both diagnostic criteria for MS and NMOSD. In a study of 322 patients with ADS from the Canadian Pediatric Demyelinating Disease Network, 20 children (6%) were ultimately diagnosed with alternative diagnoses[32]. In contrast to our report, the most commonly reported diagnosis in 11/20 of those patients were vascular disorders (primary or secondary central nervous system vasculitis, vasculopathy, stroke, or migraine). Malignant brain tumours are also an important, if rare, differential to bare in mind[30]

The study is limited by the potential under-reporting of cases as with other epidemiological studies; this was largely addressed by using clear consensus case definitions and multiple sources of case ascertainment. As seen in our study, loss of follow up can be an issue with epidemiological studies due to patient migration; however the UK national healthcare system has allowed us to identify the majority of patients (90% from clinician responses). In addition, it is unlikely that patients labelled initially as monophasic ADS would have had further relapses and not been referred to clinicians within the NHS England Highly Specialised Service for Paediatric Multiple Sclerosis. This service includes children with MS and other recurrent demyelinating syndromes. Furthermore, there was a

lack of systematic antibody testing at onset and long-term follow-up data on disability e.g. using the Expanded Disability Status Scale (EDSS), and other parameters. Nevertheless, our study clearly demonstrates that (i) the majority of ADS presentations in children are monophasic; and (ii) the diagnosis of MS can be made at onset in the majority of cases when CSF and/or contrasted scans are available. This is relevant when counselling young people and their families at presentation. Understanding the actual 'real-world' burden of individual demyelinating conditions by geographic location, age, sex and ethnicity will facilitate more accurate diagnostics, effective treatment and advice, resource allocation and service development. Given the implications for treatment strategies, extensive investigations are also warranted to make sure both MS and CNS autoantibody mimics are excluded during the diagnostic journey.

Table 1: Clinical and paraclinical features of monophasic ADS, MS and all patients

	All patients (*n*=125)	**Monophasic ADS (*n*=85)**	**Multiple Sclerosis (*n*=24)**	**p value (Monophasic ADS vs MS)**
Age at presentation; median (IQR)	10.3 (6.4, 13.9)	8.7 (5.9, 12.2)	13.9 (12.8, 14.7)	<0.0001
Sex (Male:Female)	64:61 (1.05:1)	43:42 (1.02:1)	9:15 (1:1.7)	0.35
Ethnicity (White: Other)	102:23 (4.4:1)	71:14 (5.1:1)	16:8 (2:1)	0.06
Presentation				
ADEM (%)	43 (34.4)	39 (45.9)	0 (0)	<0.0001
TM (%)	25 (20)	18 (21.2)	4 (16.7)	0.57
ON (%)	31 (24.8)	23 (27.1)	7 (29.2)	0.93
CIS – Other (%)	26 (20.1)	5 (5.9)	13 (54.2)	<0.0001
CSF OCB (%)	24/80 (30)	4/53 (7.5)	17/17 (100)	<0.0001
Abnormal brain MRI at onset (%)	83/121 (68.6)	50/83 (60.2)	23/24 (95.8)	0.0007
Abnormal spine MRI at onset (%)	29/58 (50)	26/41 (63.4)	8/11 (72.7)	0.63

Abbreviations: ADS; acquired demyelinating syndromes, MS; multiple sclerosis, IQR; inter-quartile range, ADEM; acute disseminated encephalomyelitis, TM; transverse myelitis ON; optic neuritis, CIS; clinically isolated syndrome, CSF; cerebrospinal fluid, OCB; oligoclonal bands

Figure legends

Figure 1: A total of 125 children were included in the original cohort; initial presentations were ADEM in 43 (34.4%), ON in 31 (24.8%), TM in 25 (20%), and other CIS presentations in 26 patients (20.1%). At 10 years follow-up 85 (68%) of the 125 children included had a monophasic ADS. Thirty-five children (28%) had relapsing demyelinating syndromes (RDS); 24 had a final diagnosis of MS, 4 had relapsing MOGAD, 3 had AQP4-Ab positive NMOSD and 3 had seronegative relapsing demyelinating syndromes. Incidence was calculated for MS, relapsing MOG-AD and AQP4-4 NMOSD and is shown below the relevant diagnoses.

Figure 2: Five cases with alternative diagnoses at 10-year follow-up:

a) Female patient presented at 16 months of age with encephalopathy, generalised seizures, abnormal eye movements and hypotonia. Her sister also presented previously with ADEM at a similar age. Axial T2-weighted FLAIR MRI brain imaging showed abnormal hyperintensity of the left cerebellar grey matter and fairly symmetrical hyperintensity of the cerebral white matter, including the external capsules. Genetic screening confirmed RANBP2 mutation in both siblings.

b) Female patient presented at 2 years of age with severe encephalopathy, seizures and a complex movement disorder. She was noted to have a right sided hemiplegia on clinical examination. She was positive for serum Anti-NMDA-R antibodies, and negative for MOG-antibodies. Axial T2-weighted FLAIR MRI brain imaging showed an asymmetric distribution of multiple hyperintense grey and white matter lesions, with a notable grey matter predominance.

c) Female patient presented at 14 years of age with encephalopathy, bilateral weakness, sensory loss with CSF protein elevation (2.6g/L) and positive oligoclonal bands. Axial T2-weighted MRI brain imaging showed extensive bilateral asymmetrical patchy parenchymal signal abnormality involving the deep white matter, brainstem, internal capsules and cerebellar peduncles. She also had longitudinally extensive transverse myelitis (LETM) from C1-T4 (not shown here). She went on to have two further relapses with a similar presentation within the first year.

d) Female patient presented at 12 years of age with bilateral weakness of upper and lower limbs in addition to sphincter dysfunction. Sagittal T2-weighted MRI imaging of the spinal cord showed a lesion in the conus medullaris.

e) Male patient presented at 8 years of age with left convergent squint, ataxia, seizures in addition to lung infiltrates, cycling cytopenia and hepatosplenomegaly. Coronal T2-weighted FLAIR and contrast enhanced T1-weighted brain MRI imaging at presentation showed a heterogeneously enhancing lesion in the right cerebellar hemisphere bearing some localised oedema and leptomeningeal enhancement. Follow-up imaging on relapse showed symmetrical hyperintense lesions on T2-weighted images in the cerebellum and dorsal pons, symmetrical lesions in the cerebral hemispheres as well as an LETM. He underwent bone marrow transplant with an unsuccessful CNS response with clinical and neurological evidence of progression that led to his demise.

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