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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)

3

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3

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 data
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 9 content; Major role in the acquisition of data; Study concept or design.

- 11 Christina Benetou, Helga Hickson, Micheal Taylor: Major role in the acquisition of data
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Yael Hacohen, Evangeline Wassmer: Drafting/revision of the manuscript for content, including
 medical writing for content; Major role in the acquisition of data; Study concept or design; Analysis

- 21 or interpretation of data
- 22

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27

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6 7 8 9 10 11	Data availability statement Data are available upon reasonable request. The deidentified participant data are available from the corresponding author <u>ewassmer@nhs.net</u> . Both centre and department have to give the permission to reuse the database.
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1 Abstract

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

5

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.

9

10 **Results:** 24/125 (19.2%) children, identified in the original study, were diagnosed with multiple

11 sclerosis (MS, incidence of 2.04/million children/year); 23/24 fulfilled 2017 McDonald criteria at

- 12 onset. AQP4-Ab neuromyelitis optica spectrum disorders were diagnosed in 3/125 (1.6%,
- 13 0.26/million children/year), and relapsing MOG-Ab associated disease in 5/125 (4%, 0.43/million

14 children/year). 3/125 seronegative non-MS patients relapsed and 85/125 (68%) remained

15 monophasic over 10 years. 5/125 (4%) originally diagnosed with ADS were reclassified during follow-

16 up: three children diagnosed initially with acute disseminated encephalomyelitis were subsequently

17 diagnosed with acute necrotising encephalopathy (RANBP2 mutation), primary hemophagocytic

18 Iymphohistiocytosis (Munc 13-4 gene inversion) and anti-NMDA-R encephalitis. One child initially

19 diagnosed with optic neuritis was later diagnosed with vitamin B12 deficiency, and one presenting

20 with transverse myelitis was subsequently diagnosed with Sjögren's syndrome.

21

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.

25

26 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

1 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 images¹. ADS may occur as a monophasic
illness, such as optic neuritis (ON), transverse myelitis (TM), acute disseminated encephalomyelitis
(ADEM), with overall good prognosis² or as a chronic and relapsing condition, such as multiple
sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD), resulting in progressive
disabilities³.

10 Diagnosis of multiple sclerosis, the most common relapsing form of ADS in both children and adults, 11 requires evidence of inflammatory activity in more than 1 CNS location (dissemination in space, DIS) 12 in addition to recurrent disease over time (dissemination in time, DIT). The revised 2017 McDonald 13 criteria allowed for intrathecal oligoclonal bands to substitute for DIT, the inclusion of symptomatic 14 lesions as evidence of DIS/DIT and the inclusion of cortical grey matter lesions in DIS⁴. These criteria 15 also highlighted the importance of excluding alternative diagnoses, and have a high specificity and 16 sensitivity in the paediatric population, including children younger than 12 years not presenting with 17 ADEM^{5, 6}.

18

19 Many patients with NMOSD also have frequent relapses. Aquaporin-4 (AQP4) antibodies (Ab) have 20 been identified in NMOSD, which has led to more rapid initiation of treatment⁷. In approximately 21 40% of children with ADS, myelin oligodendrocyte glycoprotein antibodies (MOG-Ab) have been 22 reported⁸. Although largely associated with monophasic illness, MOG-Ab have also been associated 23 with relapses and detected in patients with multiphasic disseminated encephalomyelitis (MDEM)⁹, recurrent idiopathic optic neuritis¹⁰ and ADEM-ON (acute disseminated encephalomyelitis (ADEM), 24 25 which can be followed by recurrent or monophasic ON)¹¹. Identification and distinction of the 26 different subtypes of ADS, especially at first presentation, has important implications on treatment 27 and prognosis¹², with accurate diagnosis and management of inflammation being key to improving 28 patient outcomes⁴. 29

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 year¹³. Here, we conducted 10-year follow-up evaluations of the same cohort to
 ascertain the incidence of multiple sclerosis and other relapsing demyelinating syndromes.

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1 Methods

2 As detailed previously¹³, children under the age of 16 years, with a first episode of ADS evaluated 3 with MRI (brain and/or spine) were ascertained from a prospective national UK surveillance study 4 (2009-2010) using two well-established surveillance units; the British Paediatric Surveillance Unit 5 (BPSU) and the British Ophthalmological Surveillance Unit (BOSU). Serum Myelin Oligodendrocyte 6 Glycoprotein (MOG) and Aquaporin-4 (AQP4) antibodies (Ab) were not routinely tested. Serum 7 AQP4-Ab was only requested when NMOSD was suspected clinically and MOG-Ab testing was 8 additionally performed on these samples as previously reported $(n=49)^8$. Acute samples were taken 9 within 3 months of clinical presentation⁸ and samples were kept stored at -80°C. Additional MOG-Ab 10 testing was requested once the test became clinically available in 2014 (n=27). 11 12 Demyelinating phenotypes were classified by an expert review panel (EW, ML, SW, YH), at onset¹³ 13 and on final follow up on the basis of the International Paediatric Multiple Sclerosis Study Group 14 criteria¹⁴, the revised 2017 McDonald criteria for the diagnosis of Multiple Sclerosis¹⁵ and the 15 International Consensus Diagnostic Criteria for NMOSD¹⁶. Clinical, paraclinical data and final 16 diagnosis at 10 years were retrieved from the patient's medical records via the patient's primary 17 paediatric or adult neurologist using a questionnaire.

18

19Descriptive statistics were used to summarise the key components of the dataset. Non-parametric20statistical tests (Kruskal–Wallis tests) were used for continuous distributions as appropriate given21lack of normality, and χ^2 or Fisher's exact test were used for nominal data. Estimates of national22incidence with confidence intervals (Byar's approximation of the exact Poisson¹⁷) for the 13-month23study were annualised using mid-2010 UK and 2010 Republic of Ireland population estimates¹⁸.24Analyses were performed using GraphPad Prism 8 (GraphPad Software).

25

26 Ethical approval for the surveillance study was from the UK Multicentre Research Ethics Committee27 (09/H1202/92).

28

29 Results

30 A total of 125 children were included in the original cohort; follow-up data on diagnosis at 10 years

31 were collected. Paediatric and adult neurologists responded with completed questionnaires for

- 32 113/125 patients (90%). Of the 12 patients who did not have 10 year follow-up data (ON *n*=6, TM
- 33 *n*=3, ADEM *n*=3), all had remained monophasic at 3 years. Eighty-five (68%) of the 125 children
- 34 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).
- 3

4 Thirty-five children (28%) had relapsing demyelinating syndromes (RDS). Twenty-four children 5 (19.2%) had a final diagnosis of MS, including 23 with relapsing remitting MS (RRMS), and one had a 6 primary progressive phenotype. Therefore, the incidence of MS under the age of 16 years in the UK 7 and ROI was calculated as 2.04 per million children per year (95% confidence interval [CI] 1.31,3.04). 8 Of these 4/24 (16.7%) presented under the age of 12 years, with a UK incidence of 0.34 per million 9 children per year (95% CI 0.09,0.87). When retrospectively applied, the revised 2017 McDonald's 10 diagnostic criteria diagnosis of MS could be made at presentation in 23/24 (95.8%). The remaining 11 patient met the dissemination in space (DIS) criterion at presentation (did not have a contrasted 12 scan or a lumbar puncture) and had a clinical relapse within 1 year of disease onset. 13 14 Only 76/125 (60.8%) had MOG-Ab and AQP4-Ab tested of which 20/76 (26.3%) were positive for 15 MOG-Ab and 2/76 (2.6%) for AQP4-Ab. All 24 patients with a diagnosis of MS, including the four 16 patients with disease onset under the age of 12 years were negative for both autoantibodies. 17 Antibodies were tested in 41/85 patients with monophasic disease compared to 35/35 patients with 18 relapsing disease. Of the 41 patients with a monophasic disease who had antibody testing, 37/41 19 (90.2%) were tested at onset, and a further 4 were tested at follow up. Only 14/43 (32.6%) patients 20 presenting with ADEM had antibody testing at onset, and a further three at follow up. 19/35 (54.3%)

21 of the patients with a relapsing disease course who had antibody testing, were tested at onset and a

22 further 16 were tested at follow up. 5/20 (25%) of the MOG-Ab positive patients had a relapsing

23 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

25 NMOSD as 0.26 per million children per year (95% Cl 0.05,0.7).

26

27 Five patients originally diagnosed with an ADS had alternative diagnoses at 10-year follow-up. Three 28 patients originally diagnosed as ADEM were found to have the following three final diagnoses; acute 29 necrotising encephalopathy (ANEC) with a confirmed mutation in RANBP2, primary hemophagocytic 30 lymphohistiocytosis (HLH) with an inversion of the Munc 13-4 gene, and Anti-NMDA-R encephalitis 31 (with white matter involvement on neuroimaging) (Figure 2). One patient initially diagnosed with ON 32 did not respond to immunotherapy and was diagnosed with vitamin B12 deficiency (with a 33 concurrent mitochondrial ND5 variant). Finally, one patient who presented with transverse myelitis 34 was subsequently diagnosed with Sjögren's syndrome.

1					
2	Table 1 includes clinical and paraclinical information for this cohort. Children with monophasic ADS				
3	group were younger than the MS cohort (median age 8.7 yrs vs 13.9 yrs, <i>p</i> <0.0001) and were more				
4	likely to present with ADEM; none of the children presenting with ADEM were subsequently				
5	diagnosed with MS. Abnormalities in brain MRI at presentation were seen in 23/24 (95.8%) of MS				
6	patients compared to 50/83 (60.2%) of patients in the monophasic group ($p=0.0007$). Intrathecal				
7	oligoclonal bands were reported in 24/24 (100%) of the MS group compared to only 4/53 (7.5%) of				
8	the monophasic ADS group (p<0.0001).				
9					
10	Three children (2.4%) died during follow up; one patient during acute presentation of ADEM from				
11	acute fulminant inflammation inducing cerebral oedema, one with AQP4-Ab NMOSD 10 years after				
12	initial presentation during relapse following a hyperkalaemic cardiac arrest; and the patient with				
13	primary HLH died following an unsuccessful bone marrow transplant with further CNS relapses.				
14					
15	Discussion				
16	In this up to 10-year follow up of a UK population active surveillance study of children with ADS, we				
17	have shown that the majority of the children had a monophasic course. The key observation is that				
18	almost all children with multiple sclerosis (95.8%) met the 2017 revised McDonald criteria at				
19	presentation. Of note, oligoclonal band analysis and contrasted scans were not performed for the				
20	one patient who did not fulfil criteria at onset. At the time of the initial study, 2006 McDonald				
21	criteria were being used for MS diagnosis, which have subsequently been superseded by both 2010				
22	and 2017 McDonald criteria, with improved sensitivities in both adults ¹⁹ and children ^{20, 21} . In fact,				
23	10/24 (42%) of cases fulfilled 2010 McDonald criteria at the time of the study. The annual incidence				
24	of MS in children <16 years (2.04/million children) in our cohort is similar to that reported in a				
25	number of other studies internationally, ranging from 0.13 to 2.85 per 100,000 children per year ²²⁻²⁴ .				
26					
27	Since the initial surveillance period in 2009-2010 there has been a paradigm shift in the diagnosis				
28	and management of relapsing demyelinating syndromes (RDS) of childhood given the discovery of				
29	CNS autoantibodies with both AQP4-Ab associated disease and MOGAD being increasingly				
30	recognised ¹² . The low incidence of MOG-Ab positivity and proportion of relapsing MOGAD in this				
31	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 phenotypes²⁵, only 32
- 33 17/43 (39.5%) children presenting with ADEM had MOG-Ab tested, which is likely to explain the low
- 34 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 seronegative²⁶. Recent data suggests that up to one
third of children with ADS have MOG-Ab positivity²⁷ 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}

6

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.

14

15 Of note, five children who were initially reported in the ADS cohort were found to have alternative 16 inflammatory aetiologies with important treatment implications. Although traditionally, patients 17 with monogenetic disorders have been thought to be younger, to have underlying developmental 18 delay, symmetrical MRI and lack of response to immunosuppression; we now recognise an 19 increasing number of conditions mimicking ADS. Of note, the patient with primary HLH had a 20 relapsing disease course, good response to steroids and fulfilled both diagnostic criteria for MS and 21 NMOSD. In a study of 322 patients with ADS from the Canadian Pediatric Demyelinating Disease 22 Network, 20 children (6%) were ultimately diagnosed with alternative diagnoses³². In contrast to our 23 report, the most commonly reported diagnosis in 11/20 of those patients were vascular disorders 24 (primary or secondary central nervous system vasculitis, vasculopathy, stroke, or migraine). 25 Malignant brain tumours are also an important, if rare, differential to bare in mind³⁰

26

27 The study is limited by the potential under-reporting of cases as with other epidemiological studies; 28 this was largely addressed by using clear consensus case definitions and multiple sources of case 29 ascertainment. As seen in our study, loss of follow up can be an issue with epidemiological studies 30 due to patient migration; however the UK national healthcare system has allowed us to identify the 31 majority of patients (90% from clinician responses). In addition, it is unlikely that patients labelled 32 initially as monophasic ADS would have had further relapses and not been referred to clinicians 33 within the NHS England Highly Specialised Service for Paediatric Multiple Sclerosis. This service 34 includes children with MS and other recurrent demyelinating syndromes. Furthermore, there was a

1	lack of systematic antibody testing at onset and long-term follow-up data on disability e.g. using the						
2	Expanded Disability Status Scale (EDSS), and other parameters. Nevertheless, our study clearly						
3	demonstrates that (i) the majority of ADS presentations in children are monophasic; and (ii) the						
4	diagnosis of MS can be made at onset in the majority of cases when CSF and/or contrasted scans are						
5	available. This is relevant when counselling young people and their families at presentation.						
6	Understanding the actual 'real-world' burden of individual demyelinating conditions by geographic						
7	location, age, sex and ethnicity will facilitate more accurate diagnostics, effective treatment and						
8	advice, resource allocation and service development. Given the implications for treatment						
9	strategies, extensive investigations are also warranted to make sure both MS and CNS autoantibody						
10	mimics are excluded during the diagnostic journey.						
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Table 1: Clinical and paraclinical features of monophasic ADS, MS and all patients

	All patients (<i>n</i> =125)	Monophasic ADS (<i>n</i> =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:		71:14 (5.1:1)	16:8 (2:1)	0.06
Other)	102:23 (4.4:1)			
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	83/121 (68.6)	50/83 (60.2)	23/24 (95.8)	0.0007
MRI at onset (%)				
Abnormal spine	29/58 (50)	26/41 (63.4)	8/11 (72.7)	0.63
MRI at onset (%)				

3

Abbreviations: ADS; acquired demyelinating syndromes, MS; multiple sclerosis, IQR; inter-quartile

range, ADEM; acute disseminated encephalomyelitis, TM; transverse myelitis ON; optic neuritis, CIS;

7 8 9 clinically isolated syndrome, CSF; cerebrospinal fluid, OCB; oligoclonal bands

1

2 **Figure legends**

- 3 4 Figure 1: A total of 125 children were included in the original cohort; initial presentations were 5 ADEM in 43 (34.4%), ON in 31 (24.8%), TM in 25 (20%), and other CIS presentations in 26 patients 6 (20.1%). At 10 years follow-up 85 (68%) of the 125 children included had a monophasic ADS. Thirty-7 five children (28%) had relapsing demyelinating syndromes (RDS); 24 had a final diagnosis of MS, 4 8 had relapsing MOGAD, 3 had AQP4-Ab positive NMOSD and 3 had seronegative relapsing 9 demyelinating syndromes. Incidence was calculated for MS, relapsing MOG-AD and AQP4-4 NMOSD 10 and is shown below the relevant diagnoses. 11 12 Figure 2: Five cases with alternative diagnoses at 10-year follow-up: 13 14 a) Female patient presented at 16 months of age with encephalopathy, generalised seizures, 15 abnormal eye movements and hypotonia. Her sister also presented previously with ADEM at a 16 similar age. Axial T2-weighted FLAIR MRI brain imaging showed abnormal hyperintensity of the left 17 cerebellar grey matter and fairly symmetrical hyperintensity of the cerebral white matter, including 18 the external capsules. Genetic screening confirmed RANBP2 mutation in both siblings. 19 20 b) Female patient presented at 2 years of age with severe encephalopathy, seizures and a complex 21 movement disorder. She was noted to have a right sided hemiplegia on clinical examination. She 22 was positive for serum Anti-NMDA-R antibodies, and negative for MOG-antibodies. Axial T2-23 weighted FLAIR MRI brain imaging showed an asymmetric distribution of multiple hyperintense grey 24 and white matter lesions, with a notable grey matter predominance. 25 26 c) Female patient presented at 14 years of age with encephalopathy, bilateral weakness, sensory 27 loss with CSF protein elevation (2.6g/L) and positive oligoclonal bands. Axial T2-weighted MRI brain 28 imaging showed extensive bilateral asymmetrical patchy parenchymal signal abnormality involving 29 the deep white matter, brainstem, internal capsules and cerebellar peduncles. She also had 30 longitudinally extensive transverse myelitis (LETM) from C1-T4 (not shown here). She went on to 31 have two further relapses with a similar presentation within the first year.
- 32

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.

4

5 e) Male patient presented at 8 years of age with left convergent squint, ataxia, seizures in addition 6 to lung infiltrates, cycling cytopenia and hepatosplenomegaly. Coronal T2-weighted FLAIR and 7 contrast enhanced T1-weighted brain MRI imaging at presentation showed a heterogeneously 8 enhancing lesion in the right cerebellar hemisphere bearing some localised oedema and 9 leptomeningeal enhancement. Follow-up imaging on relapse showed symmetrical hyperintense 10 lesions on T2-weighted images in the cerebellum and dorsal pons, symmetrical lesions in the 11 cerebral hemispheres as well as an LETM. He underwent bone marrow transplant with an 12 unsuccessful CNS response with clinical and neurological evidence of progression that led to his 13 demise. 14

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