“Leukodystrophy-like” phenotype in young children with myelin oligodendrocyte glycoprotein (MOG) antibodies-associated disease

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<td>acquired demyelination syndromes, acute disseminated encephalomyelitis (ADEM), leukodystrophy, MOG antibodies, white matter disorders</td>
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</table>
Leukodystrophy-like phenotype in children with myelin oligodendrocyte glycoprotein antibody-associated disease

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ABBRÉVIATIONS
ADEM  Acute disseminated encephalomyelitis
ADS  Acquired demyelinating syndromes
EDSS  Expanded Disability Status Scale
MOG  Myelin oligodendrocyte glycoprotein

[Abstract]
AIM To review the demographics and clinical and paraclinical parameters of children with myelin oligodendrocyte glycoprotein (MOG) antibody-associated relapsing disease.

METHOD In this UK-based, multicentre study, 31 children with MOG antibody-associated relapsing disease were studied retrospectively.

RESULTS Of the 31 children studied, 14 presented with acute disseminated encephalomyelitis (ADEM); they were younger (mean 4.1 years) than the remainder (mean 8.5 years) who presented with optic neuritis and/or transverse myelitis ($p<0.001$). Similarly, children who had an abnormal brain magnetic resonance imaging (MRI) at onset ($n=20$) were younger than patients with normal MRI at onset ($p=0.001$) or at follow-up ($p<0.001$). ‘Leukodystrophy-like’ MRI patterns of confluent largely symmetrical lesions was seen during the course of the disease in 7 out of 14 children with a diagnosis of ADEM, and was only seen in children younger than 7 years of age. Their disability after a 3-year follow-up was mild to moderate, and most patients continued to relapse, despite disease-modifying treatments.

INTERPRETATION MOG antibody should be tested in children presenting with relapsing neurological disorders associated with confluent, bilateral white matter changes, and distinct enhancement pattern. Children with MOG antibody-associated disease present with age-related differences in phenotypes, with a severe leukoencephalopathy phenotype in the very young and normal intracranial MRI in the older children. This finding suggests a susceptibility of the very young and myelinating brain to MOG antibody-mediated mechanisms of damage.

[First page footer]
What this paper adds

- Myelin oligodendrocyte glycoprotein (MOG) antibody-associated demyelination manifest with an age-related phenotype.
- Children with MOG antibody and leukodystrophy-like imaging patterns tend to have poor response to second line immunotherapy.

There is growing evidence that a diagnosis of myelin oligodendrocyte glycoprotein (MOG) antibody-associated disease can be made in children with relapsing acquired demyelinating syndromes (ADS) whose sera are positive for MOG antibody.\(^1,2\)

Previous studies have detected MOG antibody both at first presentation and at time of a relapse in children with ADS.\(^3-6\) In a recent, multicentre study, we detected MOG antibody in 83% of children with the phenotype of aquaporin-4 antibody-negative neuromyelitis optica spectrum disorder and 100% of patients originally diagnosed with multiphasic disseminated encephalomyelitis.\(^1\) Children with MOG antibody-associated disease were, overall, young (median age 6y), mainly female, and mainly presented with either optic neuritis with visual disturbance or acute disseminated encephalomyelitis (ADEM) with encephalopathy, motor deficits, seizures, and cerebellar symptoms.\(^1\)

Clinical and imaging patterns of ADS may share features with some inherited conditions such as mitochondrial disorders, X-linked Charcot–Marie–Tooth, mucopolysaccharidoses, galactosaemia, and L-2-hydroxyglutaric aciduria.\(^7\) These differential diagnoses are most frequently suspected in children presenting with ADEM,\(^8\) and more so when the disease becomes more chronic with recurrent relapses.
and progressive disabilities. Magnetic resonance imaging (MRI) is felt to distinguish between the leukodystrophies and the acquired leukoencephalopathies. In very young children with leukodystrophies, brain MRI typically shows confluent and bilateral, essentially symmetric, white matter abnormalities. Although contrast enhancement may support an acquired condition this can also be found in genetically defined white matter disorders. Conversely, children with ADEM usually show multifocal and asymmetric white matter abnormalities on MRI. In our previous study, we found that patients with MOG antibody-associated disease can share clinical and MRI similarities with leukodystrophies.

The aim of this study was to examine whether there were age-related differences in MOG antibody-associated disease phenotypes, with an emphasis on the leukodystrophy-like pattern.

METHOD

In this retrospective study, we collected data from 31 participants attending three centres of the UK and Ireland Childhood CNS Inflammatory Demyelination Working Group: Great Ormond Street Hospital (London), Evelina London Children Hospital, and Birmingham Children Hospital; 26 cases have been included in a previous study and an additional five cases were studied. All children had (1) a diagnosis of ADS, defined as two or more episodes of acquired central nervous system demyelinating events characterized by deficits persisting for at least 24 hours and involving the optic nerve, brain, or spinal cord, and associated with focal T2 abnormalities on brain and/or spinal cord MRI; (2) presence of MOG antibody detected either at onset or at the time of a clinical relapse, using live cell-based assays; (3) at onset were younger than 18 years of age.

Demographic characteristics and clinical information on type of presentation, disability at onset (as measured by the Expanded Disability Status Scale [EDSS]), disease-modifying treatments, and number of relapses over time were collected. Outcomes at last follow-up were retrieved from the patients’ medical records to represent the most contemporary assessment of disability (stratified to cognitive, motor, visual defects, and seizures). If unavailable, the information was obtained directly from the patient’s primary treating physician. EDSS results were documented at point of disease stability at least 3 months from acute or relapsing events.
The brain and spinal cord MRI scans of the 31 children were reviewed (FB) and the following three patterns (in order of frequency) were identified, as previously described\(^1\): (1) multifocal, hazy/poorly marginated lesions involving both the grey and white matter; (2) spinal cord and/or optic nerve involvement with normal intracranial appearance or non-specific white matter lesions; (3) extensive and confluent white matter abnormalities, with a largely symmetric distribution, resembling a ‘leukodystrophy-like’ MRI pattern.

Statistical analysis was performed using commercially available software GraphPad Prism 6 (GraphPad, La Jolla, CA, USA). The differences in age between MOG antibody-positive children presenting with ADEM and those presenting with optic neuritis and/or transverse myelitis, and between children with abnormal MRI and those with normal MRI were tested using the Mann–Whitney \(U\) test. The difference in age between the three imaging patterns, was investigated using the Kruskal–Wallis test. The differences in clinical and MRI characteristics between children with ‘leukodystrophy-like’ phenotype and the remaining cases were explored using Fisher’s exact test.

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

**RESULTS**

The clinical and radiological characteristics of patients with MOG antibody-associated disease, followed-up for a median of 4 years, are shown in Table I.

Fourteen children presented with ADEM; they were younger than the remainder, who presented with optic neuritis and/or transverse myelitis (mean 4.1[1.9]y vs 8.5[3.3]y; \(p<0.001\)). Similarly, children who had an abnormal brain MRI were younger than patients with normal brain MRI at onset (\(n=20\); mean age 4.6[2.8]y vs 8.5[3.0]y; \(p=0.001\)) and at follow-up (mean age 4.8[2.6]y vs 9.5[2.7]y; \(p<0.001\)) (Fig. S1, online supporting information). The most common MRI pattern at onset was that of multifocal, hazy/poorly margined lesions involving both grey and white matter, and the least common pattern at onset was the ‘leukodystrophy-like’ MRI pattern (Table I). Over the course of the disease, seven children developed a ‘leukodystrophy-like’ pattern on MRI.

All patients showed a moderately active disease with a median annual relapse rate of 1, despite treatment with disease-modifying drugs in 12 children. All patients
with abnormal MRI at onset showed a significant (although not complete) resolution of lesions at follow-up. Nevertheless, despite low disability levels (measured by the EDSS) at follow-up (Table I), one-third (n=10) had ongoing cognitive problems.

**Age-related differences in phenotypes**

When the association between age and imaging patterns was examined, a ‘leukodystrophy-like’ pattern was seen more frequently in the youngest patients (mean age at onset 3.7[1.3]y, range 1.8–6y), whereas an MRI pattern of multifocal, hazy/poorly marginated lesions, involving both grey and white matter was seen in the middle age group (5.2[1.9]y). Isolated spinal cord and/or optic nerve involvement (with normal and/or non-specific white matter lesions on MRI) was seen in the oldest group (9.8[2.8]y; p=0.001) (Fig. 1).

**‘Leukodystrophy-like’ phenotype**

Examples of the clinical and radiological patterns of leukodystrophy-like lesions in MOG antibody-positive children are shown in Figure 2 and Table II. A summary of the cases can be found in Appendix S1 (online supporting information) together with serial imaging of all patients (Fig. S2, online supporting information).

All children with the ‘leukodystrophy-like’ lesions were given a diagnosis of ADEM at presentation. The patients presented with encephalopathy (n=7), ataxia (n=7), optic neuritis (n=5), and/or seizures (n=3) at presentation or relapse. The final diagnosis was ADEM for cases 1 to 6, and negative neuromyelitis optica spectrum disorder for case 7. All patients showed clinical improvement after acute treatment with steroids, but, overall, the outcome was poor. Four patients continued to relapse despite treatment with disease-modifying drugs.

When we compared the clinical characteristics of the patients with ‘leukodystrophy-like’ MRI pattern with the remainder of the patients with MOG antibody, we found that patients with this phenotype showed a worse overall outcome at follow-up than the other patients (median EDSS 3[range 1–5] vs median EDSS 0; p=0.001). However, there was no difference in the total number of relapses between the ‘leukodystrophy-like’ phenotype and the rest of the group.

**DISCUSSION**
MOG antibody disease is increasingly recognized, but the full range of clinical phenotypes is not yet clear. In this study we describe an unexpected phenotype, not easily distinguished from that of genetic or metabolic leukodystrophies, in seven paediatric patients under the age of 7 years. The children presented with relapsing neurological syndromes associated with a ‘leukodystrophy-like’ imaging pattern that emerged over time. These children showed a good response to treatment with steroids, but four continued to relapse on conventional multiple sclerosis treatments, and only showed a partial response to second-line immunotherapy with azathioprine and mycophenolate mofetil. Persistent cognitive and behavioural problems were seen in four and ongoing seizures in three of these children. In these patients, MRI findings of predominantly confluent, bilateral white matter changes raised the differential diagnosis of a leukodystrophy. Interestingly, the MRI abnormalities did not always correlate with the clinical state of the child. Furthermore, the highly contrast-enhancing lesions and the dramatic resolution on follow-up scans, early in the course of the disease, supported a diagnosis of a neuroinflammatory leukoencephalopathy.

This study demonstrates that clinical and radiological heterogeneity in MOG antibody-associated phenotypes is age dependent, with the youngest children presenting preferentially with extensive brain involvement and older children (and adults) predominantly with optic neuritis and normal intracranial imaging. This is consistent with the evidence for more profound and severe white matter abnormalities in the early-onset and severely affected patients with leukodystrophies, such as DARS2, than patients with late-onset and mild leukodystrophies.

The finding of a ‘leukodystrophy-like’ phenotype in young children may reflect susceptibility of the myelinating brain to MOG antibody-mediated disease. In rat studies, expression of MOG occurred after the initiation of myelination, from postnatal day 1 onwards. MOG was detected primarily at the extracellular surface of myelin sheaths and oligodendrocytes, and only at low levels in the lamellae of compacted myelin and the myelin/axon border zone. Whether expression of MOG on the lamella surface persists into adult life is unclear. It is plausible that the expression decreases as myelination proceeds and is much lower in the older children. In addition, the myelinating brain may be more susceptible to MOG antibody disease caused by MOG expression on uncompacted myelin, with resulting immune-mediated damage and axonal loss. Such factors may contribute to qualitative and quantitative differences in the imaging findings in younger children.
with demyelination and the poorer outcome seen in this group. The reduced susceptibility in the fully myelinated adult brain is consistent with the overall benign phenotype in adult cases of MOG antibody-negative neuromyelitis optica spectrum disorder.\textsuperscript{17–19} In a cohort of 56 adults with MOG antibody, the clinical course was favourable, with good clinical outcomes and minimal residual disability.\textsuperscript{20}

Although only 2 out of 7 patients with ‘leukodystrophy-like’ phenotype demonstrated these radiological features at onset it is possible that the MRI was not performed at nadir or that there is a lag between clinical and radiological features. Alternatively, progressive loss of tissue integrity over time, leading to increasing neuroaxonal injury, may explain the diffuse acquired white matter injury, the poor cognitive outcome seen in this group, and the reduced response to immunotherapy over time. As seen in patients with genetic white matter disorders, MOG antibody-positive patients with a ‘leukodystrophy-like’ MRI pattern showed a worse outcome at follow-up than older patients. The EDSS, which is used to assess disabilities in demyelinating conditions, is more heavily weighted towards motor disabilities than cognitive disabilities; this may explain the overall low scores seen in the cohort with MOG antibody-associated disease in general. Cognitive problems were seen in half of the children with abnormal MRI and were not reported in children with normal brain MRI. This finding is in keeping with recent studies observing perturbation of white matter trajectories and reduced age-expected brain growth (driven via reduced white matter growth) in children after a single episode of ADS with brain lesions.\textsuperscript{21,22}

Taken together, the physiological processes occurring during brain maturation (including increased axonal size with more efficient axonal transport, and myelin maturation and compaction) might explain the heterogeneity of MOG antibody phenotype, with a more severe leukoencephalopathy phenotype in the very young. Further studies into the exact pathobiological disease processes may result in better treatments and improved outcome in this distinct group of patients.

\textbf{ACKNOWLEDGEMENTS}

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the NIHR Great Ormond Street Hospital Biomedical Research Centre (YH, CH). YH, TR, KM, WKC have no disclosures. EW receives research grants from Action Medical Research and the MS Society; has received travel grants from UCB, Shire, and Biogen Idec, educational grants to organize meetings from Merck Serono, Novartis, Bayer, and Biogen Idec, speaker’s fees from Merck Serono, and consultancy fees from Genzyme. ML 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; has received travel grants from Merck Serono; and has been awarded educational grants to organize meetings by Novartis, Biogen Idec, Merck Serono, and Bayer. CH has received educational and travel grants from Merck Serono, Bayer, and Biogen. FB serves as a scientific consultant to Bayer Schering Pharma, Sanofi-Aventis, Biogen Idec, Teva Pharmaceutical Industries, Merck Serono, Novartis, Roche, Synthon BV, Janssen, Genzyme, and Toshiba Medical Systems, and has served on speakers’ bureaus for Serono Symposia Foundation and MedScape. OC serves as a consultant for GE, Biogen Idec, and Novartis, and all the payments are made to the institution (Queen Square MS Centre, UCL Institute of Neurology, London, UK).

Supporting information

The following additional material may be found online:

- **Figure S1**: Box plots showing the median and interquartile range.
- **Figure S2**: Serial imaging at follow-up of the seven index cases using axial T2-weighted sequences.
- **Appendix S1**: Leukodystrophy-like phenotype – case summaries.

REFERENCES


**Table I:** Characteristics of patients with myelin oligodendrocyte glycoprotein antibody-associated disease (n=31)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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<tr>
<td>Mean(SD) age at presentation (y:mo)</td>
<td>6:6(3:5.3)</td>
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<tr>
<td>Female:male ratio</td>
<td>1:1.6</td>
</tr>
<tr>
<td>Median(IQR) length of follow-up (from first clinical presentation) (y)</td>
<td>4(3–7)</td>
</tr>
<tr>
<td>Median(IQR) time to first relapse (mo)</td>
<td>4.5(3.1–8.1)</td>
</tr>
<tr>
<td>Median(range) EDSS at last visit</td>
<td>1(0–5)</td>
</tr>
<tr>
<td>Original RDS diagnoses</td>
<td></td>
</tr>
<tr>
<td>NMOSD without AQP4 antibody</td>
<td>16(52)</td>
</tr>
<tr>
<td>Multiphasic disseminated encephalomyelitis</td>
<td>9(29)</td>
</tr>
<tr>
<td>Recurrent optic neuritis</td>
<td>4(13)</td>
</tr>
<tr>
<td>ADEM-ON</td>
<td>2(6)</td>
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<tr>
<td>MRI patterns at onset</td>
<td></td>
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<td>MRI abnormalities in the optic nerve and/or spinal cord</td>
<td>17(55)</td>
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<td>Multifocal, poorly marginated lesions involving both grey and white matter</td>
<td>12(39)</td>
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<td>Leukodystrophy-like MRI</td>
<td>2(6)</td>
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<td>MRI pattern during the disease course</td>
<td></td>
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<tr>
<td>MRI abnormalities in the optic nerve and/or spinal cord</td>
<td>11(35)</td>
</tr>
<tr>
<td>Multifocal, poorly marginated lesions involving both grey and white matter</td>
<td>13(42)</td>
</tr>
<tr>
<td>Leukodystrophy-like MRI</td>
<td>7(23)</td>
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</tbody>
</table>

Data are n(%) unless otherwise indicated. IQR, interquartile range; EDSS, Expanded Disability Status Scale; RDS, relapsing demyelinating syndrome; NMOSD, neuromyelitis optica spectrum disorder; AQP4, aquaporin-4; ADEM-ON, acute disseminated encephalomyelitis followed by optic neuritis; MRI, magnetic resonance imaging.
Table II: Clinical, radiological, serological, and cerebrospinal fluid results; treatment; and clinical outcome of seven children with myelin oligodendrocyte glycoprotein antibody and ‘leukodystrophy-like’ phenotype
<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age(y)</th>
<th>Ethnicity</th>
<th>Diagnosis</th>
<th>Clinical presentation</th>
<th>TT</th>
<th>OCB</th>
<th>EBV</th>
<th>Subsequent neurological events</th>
<th>Treatment</th>
<th>Outcome</th>
<th>EDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>6</td>
<td>White</td>
<td>MDE M</td>
<td>Subacute onset encephalopathy with ataxia and motor regression</td>
<td>3</td>
<td>Negati ve</td>
<td>Negati ve</td>
<td>Multiple relapses with ataxia and cognitive regression evolving pyramidal signs lower limbs and bulbar dysfunction (3/y) over 8y</td>
<td>No response to IFN-β (1y); clinically stable on AZA</td>
<td>Cognitive, behaviour, motor difficulties</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>4</td>
<td>White</td>
<td>MDE M</td>
<td>Behavioural change, ataxia, and bilateral sixth nerve palsy after a febrile illness</td>
<td>4</td>
<td>Negati ve</td>
<td>NT</td>
<td>Multiple relapses at 9–12mo intervals characterized by altered behaviour, loss of balance, weakness (left more than right), and slurred speech over 10y</td>
<td>On AZA for 3y, which was then discontinued; continues to relapse yearly.</td>
<td>Cognitive seizures, behaviour, motor difficulties</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>1.7</td>
<td>White</td>
<td>MDE M</td>
<td>Encephalopathy with fluctuating sleepiness and irritability, intermittent squint,</td>
<td>4</td>
<td>Negati ve</td>
<td>Negati ve</td>
<td>Encephalopathy with ataxia and right-sided hemiplegia</td>
<td>Not on treatment</td>
<td>Clinical recovery but still early</td>
<td>1.5</td>
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<tr>
<td>No</td>
<td>Sex</td>
<td>Age</td>
<td>Race</td>
<td>MAR/Ataxia</td>
<td>Onset</td>
<td>Duration</td>
<td>Symptomatology</td>
<td>Treatment</td>
<td>Course</td>
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<tr>
<td>4</td>
<td>F</td>
<td>5</td>
<td>White</td>
<td>MDE M</td>
<td>Encephalopathy, ataxia, and right focal seizures</td>
<td>7</td>
<td>Negative</td>
<td>Relapses with encephalopathy with seizure and ataxia and optic neuritis; 9–10 relapses with similar symptomatology over a 6y period with longest interattack period of 2y</td>
<td>No response to IFN-β and AZA; commenced on natalizumab at 10y with no further relapses</td>
<td>Mild learning difficulties, visually impaired, and seizures (controlled on AED)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>2</td>
<td>White</td>
<td>MDE M</td>
<td>Encephalopathy with pyrexia and irritability</td>
<td>16</td>
<td>Negative</td>
<td>5 clinical relapses with similar symptomatology</td>
<td>Reduction of ARR on MMF from 3 to 1</td>
<td>Cognitive, behaviour, motor difficulties</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>5</td>
<td>Black</td>
<td>MDE M</td>
<td>Subacute onset encephalopathy with intermittent fever and headaches and lower-limb weakness</td>
<td>60</td>
<td>Negative</td>
<td>Two relapses with similar symptomatology 5 and 7y after initial presentation with encephalopathy and cerebellar signs; during the second episode developed optic neuritis</td>
<td>MMF after first relapse</td>
<td>Cognitive, behaviour, motor vision difficulties</td>
<td></td>
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<tr>
<td>Patient</td>
<td>Sex</td>
<td>Age</td>
<td>Race</td>
<td>Disease</td>
<td>Presentation</td>
<td>Diagnosis</td>
<td>Treatment</td>
<td>Outcome</td>
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<tr>
<td>7</td>
<td>F</td>
<td>3</td>
<td>Afro-Caribbean</td>
<td>NMO SD</td>
<td>Encephalopathy, slurred speech and ataxia; persistent left-sided squint; several months later developed focal seizures</td>
<td>72 Positive NT</td>
<td>Left optic neuritis and longitudinally extending transverse myelitis</td>
<td>Treated with steroids acutely both at onset and relapse</td>
<td>Clinical and radiological recovery (not complete); seizures (controlled on AED)</td>
<td></td>
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</table>

Patients 1 and 5 presented with leukodystrophy-like imaging characteristics at first presentation. TTFR, time to first relapse; OCB, oligoclonal bands; EBV, Epstein–Barr virus; EDSS, Expanded Disability Status Scale; M, male; MDEM, multiphasic disseminated encephalomyelitis; IFN, interferon; AZA, azathioprine; F, female; NT, not tested; AED, antiepileptic drugs; ARR, annual relapse rate; MMF, mycophenolate mofetil; NMOSD, neuromyelitis optica spectrum disorder.
Figure 1: Association between age at onset and magnetic resonance imaging patterns in myelin oligodendrocyte glycoprotein antibody-associated disease. The box-plot (showing median and interquartile range) demonstrates the relationship between the predominant imaging pattern and the age group. The leukodystrophy-like pattern was predominantly seen in (a) younger children; (b) confluent, hazy/poorly marginated lesions involving both grey and white matter were seen in the middle-age group; (c) the spinal cord/optic nerve (ON) involvement with normal or non-specific brain imaging was seen in the older group. TM, transverse myelitis.

Figure 2: Examples of patients with myelin oligodendrocyte glycoprotein (MOG) antibody with a leukodystrophy-like magnetic resonance imaging (MRI) pattern. (a) Radiological progression in patient 1 (top row). Age 2y at first presentation with encephalopathy, the MRI changes were predominantly in the grey matter of the basal ganglia and thalami. At clinical relapse 16mo later, there was similar symptomatology with near complete resolution of the previously signal abnormalities. Follow-up imaging when clinically improving 2mo later (18mo from onset) demonstrated confluent bilateral predominantly subcortical diffuse white matter changes, more posteriorly, with extensive nodular enhancement. There was significant resolution on follow-up scans 3mo later. (b) Radiological progression in patient 2 (second row). Age 20mo, at first presentation, there were confluent white matter lesions in the thalami and pons. Repeat imaging during the acute presentation (day 14), when still symptomatic, demonstrated expansion of the lesions with new cerebellar peduncle lesions and optic track involvement (not shown). Imaging at the time of clinical relapse 4mo later, demonstrated confluent bilateral predominantly subcortical diffuse white matter changes with extensive nodular enhancement. (c) MRI patterns observed in MOG antibody-positive patients with inflammatory leukoencephalopathy.

Comment [JM9]: TYPESETTER: Please fix the typo in Figure 1, y-axis to (years).
Figure 1

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Figure 2

529x705mm (72 x 72 DPI)
Supplemental figure 1

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Leukodystrophy-like phenotype – case summaries

Case 1: A 6 year-old boy presented with recurrent episodes of ataxia and progressive deterioration in gait over 8 months. MRI revealed subcortical white matter changes in the left temporal lobe, pons and cerebellar. He was treated with IV steroids and prolonged oral prednisolone course followed by interferon (1 year) but continued to deteriorate with worsening ataxia, evolving pyramidal signs in the lower limbs, and bulbar dysfunction. He has been clinically stable on Azathioprine and has not suffer any further deterioration he remains severely disable.

Case 2: A 4-years old girl presented with behavioural change, ataxia and a 6th nerve palsy following a febrile illness. MRI revealed confluent bilateral white matter changes. She relapsed 4 months later with a similar encephalopathy. Subsequent episodes occurred at 9 to 12 month intervals, characterised by altered behaviour, loss of balance, weakness (left more than right), and slurred speech. She was commenced on Azathioprine but continued to relapse. Azathioprine was therefore stopped after 3 years and she is currently on no treatment.. She has a left hemiparesis and mild learning difficulties.

Case 3: A 20-months old girl presented with encephalopathy, fluctuating drowsiness and irritability, intermittent squint, ataxia and tremor. MRI revealed predominantly grey matter involvement in the thalami and she was treated for viral encephalitis with no clinical improvement. Repeat scan at day 14, while still symptomatic, revealed some resolution of the thalamic lesions but new lesions in the pons and the middle cerebellar peduncle. She had a good response to steroids but relapsed at 4 months with similar symptoms to the initial presentation. She received a prolonged steroid weaning course and remained relapse free at follow-up one year after her second episode.

Case 4: A 5-year-old girl presented with a right-sided focal seizure while overseas. She was treated for encephalitis, and recovered. Three weeks later she developed fevers, joint pains and had a second seizure. MRI revealed cortical white matter changes and she was treated with steroids. She had a further relapse with ataxia and encephalopathy requiring steroids. She went on to have ten relapses over the next six years, with recurrent optic neuritis, dysarthric speech and further seizures. She was subsequently treated with further courses of steroids, azathioprine and interferon, and is currently on Natalizumab.

Case 5: A 2 year-old girl presented with subacute encephalopathy with irritability and intermittent temperatures. MRI revealed bilateral basal ganglia changes. She was treated with steroids and IVIG with a good response. She suffered a further clinical relapse 15 months later with similar symptomatology. MRI revealed extensive, bilateral diffuse white matter signal change. She was treated with IVIG and mycophenolate mofetil (MMF) but continued to relapse.

Case 6: A 5-year-old boy, with mild global delay and autistic spectrum disorder, presented with subacute onset
encephalopathy with intermittent fevers, headaches and lower limb weakness associated with falls. MRI revealed extensive signal changes involving cortical and subcortical white matter and thalamic changes bilaterally. CSF was negative with no OCB and he was diagnosed with ADEM but received no treatment. He recovered from his acute episode but remains developmentally delayed. He suffered a similar clinical and radiological relapse with additional optic neuritis 6 years later and was treated with 3 days of intravenous methyl prednisolone followed by oral prednisolone.

**Case 7:** A 2 years and 10 month-old girl presented with fever, slurred speech and unsteady gait. MRI revealed extensive white matter changes, with confluent diffuse areas of abnormal signal in the cerebral white matter, cerebellar white matter and brain stem. She made a gradual recovery but the left divergent squint persisted. A few months later she developed focal seizures. At 8 years of age her squint became more apparent, her vision deteriorated and she developed a right-sided foot drop. She went on to develop left leg weakness and urinary incontinence. She was treated with steroids with good response.

**Supplementary Figure legends**

**Figure S1:** Box plots showing the median and interquartile range. (a) Patients presenting with acute disseminated encephalomyelitis were younger than children presenting with optic neuritis or transverse myelitis \( (n=17; \ p<0.001) \). Children with a normal brain magnetic resonance imaging at (b) presentation and (c) throughout the disease course were older than those with abnormal intracranial magnetic resonance imaging \( (p=0.001 \) and \( p<0.001 \), respectively).

**Figure S2:** Serial imaging at follow-up of the seven index cases using axial T2-weighted sequences shows brain parenchymal changes in the supratentorial and infratentorial compartments. Case 1: the initial changes were in the internal and external capsular areas with involvement of the basal ganglia, thalami, and pons. On follow-up, bilateral confluent deep and subcortical white matter changes were noted in both cerebral hemispheres. Over time, these changes showed partial resolution accompanied by brain parenchymal volume loss, and the hind brain changes became more limited to the cerebello-pontine regions. Case 2: extensive bilateral cerebral white matter signal abnormality was noted with incomplete resolution on later scans. The initial changes in the cerebello-pontine angles resolved over time. Case 3: the initial changes in the thalami and brainstem evolved into a leukodystrophy-like pattern within 4 months. Case 4: the pattern of white matter involvement is diffuse but asymmetric, changing predominantly to the contralateral side over time with ensuing brain atrophy. Case 5: There was initial involvement of the basal ganglia and thalami but more symmetric white matter changes in both cerebral hemispheres on follow-up imaging. Case 6: extensive, rather symmetric white matter signal abnormality in both cerebral hemispheres and cerebello-pontine angles was followed by partial resolution of the cerebral changes over time. Case 7: early scans showed extensive subcortical white matter involvement and patchy hind brain changes, again localized to the cerebello-pontine regions, with gradual partial resolution over time.