Pediatric acquired CNS demyelinating syndromes
Features associated with multiple sclerosis

ABSTRACT
Approximately one-third of children with an acquired demyelinating syndrome (ADS) will be diagnosed with multiple sclerosis (MS), either at onset according to the 2010 McDonald criteria, or on the basis of clinical or MRI evidence of relapsing disease, in the majority of patients within 2–4 years. ADS in adolescents, female patients, and patients with polyfocal deficits is associated with the highest likelihood of MS, while children with acute disseminated encephalomyelitis, those with documented preceding infection, and ADS presentation in young children more commonly portends a monophasic outcome. While pediatric MS associates with similar genetic risk alleles as have been documented in adult-onset MS, such associations are not diagnostically valuable at the individual level. The presence of antibodies directed against aquaporin-4 strongly supports a diagnosis of neuromyelitis optica, and should be assayed in children manifesting with severe optic neuritis, longitudinally extensive myelitis, or brainstem/hypothalamic syndromes. Further research will determine whether other antibody signatures are indicative of relapsing demyelination distinct from MS.

GLOSSARY
ADEM = acute disseminated encephalomyelitis; ADS = acquired demyelinating syndromes; CI = confidence interval; CIS = clinically isolated syndrome; HLA = human leukocyte antigen; HR = hazard ratio; MOG = myelin oligodendrocyte glycoprotein; MS = multiple sclerosis; NMO = neuromyelitis optica; NPV = negative predictive value; OCB = oligoclonal band; ON = optic neuritis; OR = odds ratio; PPV = positive predictive value; SNP = single nucleotide polymorphism; TM = transverse myelitis.

We describe the clinical presentations of acquired CNS demyelinating syndromes (ADS) in the pediatric age group, with a special focus on the clinical, MRI, laboratory, and genetic factors that identify children for whom incident ADS represents the first attack of multiple sclerosis (MS).

CLINICAL MANIFESTATIONS OF ADS IN CHILDREN
Clinical presentations of acute-onset neurologic deficits associated with evidence of CNS demyelination are termed ADS. ADS phenotypes are currently classified based on clinical localization of symptoms and signs. Neuroimaging findings are supportive. The various ADS phenotypes may occur as monophasic illnesses or represent the sentinel clinical attack of a chronic demyelinating disease, such as MS. The term clinically isolated syndrome (CIS) is also often applied (and is used almost exclusively in adults presenting with an incident demyelinating attack) with specific ADS presentations such as optic neuritis (ON), transverse myelitis (TM), as well as other ADS presentations that localize to one (monofocal) or multiple (polyfocal) CNS locations; however, CIS generally does not include acute disseminated encephalomyelitis (ADEM), whereas ADS encompasses both CIS and ADEM.

ON is characterized by unilateral or bilateral visual loss of variable severity, pain with ocular movement, central scotoma or reduced visual fields, reduced perception of color, and on imaging often by increased signal, swelling, and occasionally by enhancement of the optic nerves. TM manifests with acute symptoms (worsening over 4 hours to 21 days) of spinal cord dysfunction, with acute infection, postradiation, and spinal cord compression having been excluded. Most children with TM have a partial myelitis with bilateral motor deficits, sensory level, and depending on localization impairment, in bowel and bladder control.

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Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
Other clinically monofocal ADS presentations include those with brainstem (i.e., internuclear ophthalmoplegia) or cerebellar localization (i.e., ataxia, dysmetria), or may manifest as focal motor/sensory deficits due to a single supratentorial CNS lesion.

ADEM, a presentation most commonly experienced by younger children, is defined by encephalopathy (impairment in consciousness or marked irritability not accounted for by fever, recent seizure, or systemic illness) and polyfocal neurologic deficits. The requirement of encephalopathy is critical, as this appears to best distinguish ADEM from other ADS phenotypes.

Polyfocal deficits (neurologic signs and symptoms that require more than one CNS site for localization) without encephalopathy may also occur, and are more likely to represent the first attack of MS.

**Clinical Parameters that Help Differentiate Monophasic ADS from MS**

A number of studies have tried to characterize clinical features that reliably identify those children for whom ADS represents the first attack of MS. The relative proportion of children with MS in various ADS cohorts differs across different world regions (table 1). These regional differences explain the broad range (15%–57%) of MS outcomes reported in various pediatric ADS cohorts. Combining results from the studies, and excluding ADS studies with the most discrepant MS outcome percentages, it appears that approximately 21%–35% of children will be diagnosed with MS in the first 2–4 years after ADS.

The following cohort studies describe the proportion of patients with a first episode of demyelination who have MS, and the clinical features that are suggestive of MS. Logistic regression is here described as hazard ratio (HR) plus confidence intervals (CIs).

If no logistic regression was performed, statistically significant differences between MS and non-MS are presented instead. However, it should be noted that many of these cohorts were analyzed before consensus definitions of pediatric MS were proposed and later revised. In addition, some cohorts were described before the testing of anti-aquaporin-4 antibody became available.

In a prospective cohort study of 302 Canadian children with a first episode of CNS demyelination, Banwell et al. found that 21% were confirmed to have MS after a median of 3.1 years follow-up. Using univariate analysis, polyfocal signs without encephalopathy (2.34, 1.39–3.95), female sex (1.87, 1.1–3.1), and older age (1.18, 1.1–1.27) were predictive of MS, whereas children manifesting with ADEM were unlikely to have MS (0.23, 0.08–0.65).

In a nationwide retrospective follow-up study of 296 French children with a first episode of CNS demyelination, Mikaeloff et al. found that after a mean follow-up of 2.9 years, 168/296 (57%) were confirmed to have MS. A diagnosis of ADEM was against a second attack using univariate analysis (HR 0.48, CI 0.32–0.7). Using multivariate analysis, age at onset >10 years (HR 1.67, 1.04–2.67) was predictive of MS, and myelitis at onset (HR 0.23, 0.1–0.56) and severe mental status change (HR 0.59, 0.33–1.07) were against a diagnosis of MS.

In a single-center retrospective follow-up cohort study of 118 US children with ADS, Peche et al. found that after a mean follow-up of 6.6 years, 25% had been diagnosed with MS. Although ADEM and younger age were against a diagnosis of MS using univariate analysis, multivariate analyses were not significant. Multivariate analysis found that brainstem and hemispheric dysfunction (as a CIS) (HR 24.6, 3.0–196) and female sex (HR 12.4, 1.03–149) were predictive of an MS diagnosis. Radiologic features were more predictive than clinical features.

In a nationwide retrospective multicenter cohort of 117 Dutch children with ADS, Neuteboom et al. found that after a mean follow-up of 4.5 years, 32% had been diagnosed with MS. Older age was predictive of MS, whereas encephalopathy, headache, fever, seizures, and preceding infection were against a diagnosis of MS.

In a retrospective follow-up cohort of 88 Australian children from a single center who were followed for a minimum of 1 year (mean 5.2 years), Tantis et al. found that only 15% of patients had MS. Using univariate analysis, cerebellar signs were associated with MS (4.3, CI 1.35–13.74), and preceding infection was against a diagnosis of MS (0.23, CI 0.07–0.75). However, when applying multivariate analysis, only preceding infection remained significant (HR 0.16, 0.03–0.86), whereas the other predictive features of MS were radiologic.

**Acute disseminated encephalomyelitis.** While ADEM is typically a monophasic illness, an ADEM-like first attack can rarely represent the first attack of MS. The largest dedicated study regarding the risk of relapse after an episode of ADEM was from the French KIDSEP cohort, and described 132 children followed for a mean of 5.4 years. This study found that 24/132 (18%) patients had a second attack, and 11/132 (8%) had a third attack during the follow-up period. Using the 2012 consensus definitions for MS, 22/132 (17%) had an ADEM event followed by one or more non-ADEM events. However, it is not clear how many of these children had dissemination in space on MRI, which is a requirement to fulfill the criteria for MS.

In the prospective nationwide Canadian study, 77 children fulfilled criteria for ADEM, and only 4/77
### Table 1

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Country</th>
<th>No.</th>
<th>Follow-up, y</th>
<th>MS, n (%)</th>
<th>Features for MS/relapsing disease</th>
<th>Features against MS/relapsing disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>First episode of CNS demyelination (any)</td>
<td>Canada</td>
<td>302</td>
<td>3.1 (median)</td>
<td>63/302 (21)</td>
<td>Polyfocal signs; female sex; older age</td>
<td>Encephalopathy (ADEM)</td>
<td>Banwell et al.⁴</td>
</tr>
<tr>
<td></td>
<td>France</td>
<td>296</td>
<td>2.9 (mean)</td>
<td>168/296 (57)</td>
<td>Older age</td>
<td>Myelitis; encephalopathy</td>
<td>Mikaeloff et al.²</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>118</td>
<td>6.6 (mean)</td>
<td>30/118 (25)</td>
<td>Brainstem or hemispheric dysfunction; female sex</td>
<td>—</td>
<td>Peche et al.⁹</td>
</tr>
<tr>
<td></td>
<td>Netherlands</td>
<td>117</td>
<td>4.5 (mean)</td>
<td>37/117 (32)</td>
<td>Older age</td>
<td>Encephalopathy; headache, fever, seizures, preceding infection</td>
<td>Neuteboom et al.³</td>
</tr>
<tr>
<td></td>
<td>Australia</td>
<td>88</td>
<td>5.2 (mean)</td>
<td>13/88 (15)</td>
<td>Cerebellar signs</td>
<td>Preceding infection</td>
<td>Tantsis et al.¹</td>
</tr>
<tr>
<td>First episode ADEM</td>
<td>France</td>
<td>132</td>
<td>5.4 (mean)</td>
<td>22/132 (17)</td>
<td>Familial history of inflammatory demyelination; ON; no sequelae after first event</td>
<td>—</td>
<td>Mikaeloff et al.¹⁰</td>
</tr>
<tr>
<td></td>
<td>Argentina</td>
<td>84</td>
<td>6.6 (mean)</td>
<td>0/84 (0)</td>
<td>—</td>
<td>—</td>
<td>Tenembaum et al.¹¹</td>
</tr>
<tr>
<td></td>
<td>Canada⁵</td>
<td>77</td>
<td>2.82 (mean)</td>
<td>4/77 (5)</td>
<td>—</td>
<td>Young age (≤:11.85 y)</td>
<td>Banwell et al.⁶</td>
</tr>
<tr>
<td>First episode TM</td>
<td>France, United Kingdom⁷</td>
<td>95</td>
<td>1.4 (median)</td>
<td>13/95 (14)</td>
<td>Female sex</td>
<td>Time to nadir ≤24 h</td>
<td>Deiva et al.¹²</td>
</tr>
<tr>
<td>First episode ON</td>
<td>United States</td>
<td>79⁶</td>
<td>19.4 (median)</td>
<td>15/79 (19)</td>
<td>Bilateral sequential or recurrent ON</td>
<td>Infection 2 wk before ON</td>
<td>Luccinetti et al.¹³</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>36</td>
<td>2.4 (mean)</td>
<td>13/36 (36)</td>
<td>Bilateral vs unilateral ON; presence of other neurologic features</td>
<td>—</td>
<td>Wilejto et al.¹⁴</td>
</tr>
<tr>
<td></td>
<td>United Kingdom</td>
<td>44</td>
<td>1.8 (mean)</td>
<td>11/44 (25)</td>
<td>—</td>
<td>—</td>
<td>Absoud et al.¹⁵</td>
</tr>
<tr>
<td></td>
<td>Germany, Switzerland, Austria</td>
<td>357</td>
<td>4.0 (median)</td>
<td>145/357 (41)</td>
<td>Older age</td>
<td>—</td>
<td>Heussinger et al.¹⁶</td>
</tr>
</tbody>
</table>

Only features with statistical significance using statistical paired tests or logistic regression are presented in this table. Features are listed in descending frequency of statistical significance (where possible).

³A total of 123 in cohort, 118 with available follow-up.

⁴Part of a first episode of acute demyelination cohort rather than a specific ADEM cohort.

⁵Logistic regression odds ratio was for relapsing disease, and included neuromyelitis optica (n = 3) as well as MS (n = 13).

⁶Ninety-five in cohort, but 79 with adequate follow-up.
years. In a study of 44 British children with ON, children were diagnosed with MS after a mean of 2.4 years (range 3–16), these 8 patients had no further clinical relapses and no new MRI lesions. This cohort reminds the clinician that not all relapses after ADEM represent MS.

**Transverse myelitis.** The likelihood of children manifesting with TM as the first attack of MS has been examined in several cohorts. The cohorts, ranging in size from 14 to 95 cases, generally describe a low proportion of patients who have MS (0%–14%), although the mean follow-up of these studies ranges from 0.5 to 8 years. The largest cohort (French and UK collaborative) describing 95 pediatric patients with TM found that 14% relapsed with a diagnosis of MS and 3% with neuromyelitis optica (NMO), with a median follow-up time of 1.4 years (range 1–8 years) (table 1). Female sex was the strongest clinical predictor of relapsing disease (odds ratio [OR] 3.2), although notably an abnormal cerebral MRI had a significantly higher predictive value (OR 14). It should be noted that this study grouped the relapsing diseases (NMO and MS) together for the logistic regression. A short time to nadir of symptoms (<24 hours) was against a relapsing course, and more typically seen in monophasic TM.

**Optic neuritis.** Lucchinetti et al. performed a long follow-up of childhood ON from a single US center, and found that 19% of 79 patients had been diagnosed with MS after 20 years of follow-up. Of note, MRI scans were not routinely performed and testing for anti-aquaporin-4 was not yet available. At least 4 patients in the cohort had NMO by clinical criteria. A study of 36 Canadian children with ON (unilateral in 58%, bilateral in 42%) (table 1) found that 36% of children were diagnosed with MS after a mean of 2.4 years. In a study of 44 British children with ON followed for a mean of 1.8 years, 25% were diagnosed with MS, but no clinical parameters were predictive of MS at first episode. In an important recent German-speaking retrospective multicenter cohort of 357 children with ON followed for a median of 4.0 years, the strongest predictors were the presence of CSF oligoclonal bands and abnormal cranial MRI, whereas features such as sex or laterality (unilateral vs bilateral) were not predictive of MS.

Table 1 demonstrates features that are predictive of MS (older age, female sex, polyfocal signs). In children with ADS, those presenting with ADEM and longitudinally extensive myelitis and patients younger than 12 years are less likely to be manifesting with the first attack of MS and are more likely to have a monophasic illness.

**MRI ABNORMALITIES ASSOCIATED WITH MS** The MRI features incorporated into the diagnostic criteria for MS and NMO are discussed in detail in “MRI in the evaluation of pediatric multiple sclerosis” (p. S88). MRI features that assist in distinguishing children presenting with the first attack of MS from those children likely to experience a monophasic demyelinating course have been evaluated in several pediatric ADS cohorts (table 2). The French KIDMUS study showed that the presence of lesions perpendicular to the long axis of the corpus callosum and the sole presence of well-defined lesions had a sensitivity of 21%, specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value (NPV) of 61% for identification of MS. The Callen et al. demonstrated that the presence of 2 out of 3 of (1) absence of diffuse bilateral lesion pattern, (2) presence of black holes, or (3) presence of 2 or more lesions with periventricular lesions yielded a sensitivity of 81%, specificity of 95%, PPV of 95%, and NPV of 79% of identifying a child as having MS rather than ADEM. Verhey et al. demonstrated that the presence of ≥1 periventricular T2 bright lesion and ≥1 T1-hypointense lesion had a sensitivity of 84%, specificity of 93%, PPV of 76%, and NPV of 96% of identifying children with MS as compared to children with monophasic ADS.

When evaluating MRI features associated with monophasic ON, as compared to those features indicative of MS or NMO, the presence of ≥1 brain T2 hyperintense lesion was a strong predictor for development of MS, while the coexistence (or subsequent development) of longitudinally extensive myelitis or diencephalic lesions should prompt reconsideration of NMO. A normal brain MRI at the time of ON conveys a very low likelihood of MS, at least as evidenced by studies with up to 7 years observation. A normal brain MRI at the time of presentation with TM also conveys a low likelihood of MS.

**LABORATORY PARAMETERS ASSOCIATED WITH MS** CSF analysis is an important tool in the diagnostic workup of childhood ADS. Although specific CSF findings are not obligatory for MS diagnosis, CSF is informative on MS likelihood and can play a key role in prompting evaluation of other etiologies. The CSF cell count and composition should first be evaluated. In pediatric MS, CSF pleocytosis (predominantly monocytic) has been described in 52%–66% of patients. A cell count above 60 cells/µL is rare in pediatric MS. CSF neutrophils...
The presence of oligoclonal bands (OCBs) in CSF that are absent in serum is strongly supportive of an MS diagnosis and can be detected in up to 90% of patients using isoelectric focusing technique in an experienced laboratory.3,4,21-23 Two studies have investigated the presence of CSF OCBs in children with MS aged under and above 11 years; CSF OCBs were detected in 43%-60% of the younger group and 63%-73% in the children older than 11.22,23 Detection of CSF OCBs increases when analyzed CSF is obtained serially.23 The presence in CSF of OCBs is not pathognomonic for MS, as OCBs are detected in 8%-15% of children with ADS who have not been subsequently diagnosed with MS.5,23 CSF OCBs have recently been shown to have useful predictive potential: in a cohort of 357 children with ON, intrathecal OCBs were strongly predictive of MS (HR 3.69, 95% CI 2.32–5.86, p < 0.001).16

**SERUM ANTIBODIES TO MYELIN OLIGODENDROCYTE GLYCOPROTEIN (MOG)** Patients with ON, myelitis, and brainstem syndromes should have testing for AQP4 antibodies. MOG antibodies may also have a role in disease classifications, although this has not been incorporated into consensus definitions to date. There are emerging data to suggest that MOG antibodies define a non-MS subgroup of CNS demyelination, and are found frequently in patients with ADEM, ON, and myelitis (see “Immunopathophysiology of pediatric CNS inflammatory demyelinating disease,” p. S12).

Several studies have focused on the antibody response to MOG in pediatric ADS cohorts.24-26 The percentage of anti-MOG antibody–positive patients within these ADS groups ranges between 12% and 35%. Children with antibodies to MOG are typically younger than children without antibodies to MOG. A Dutch nationwide cohort study on 117 children with ADS showed that patients with ADS with antibodies to MOG more frequently present with a polyfocal disease onset with or without encephalopathy, next to TM (recurrent), ON, or NMO negative for antibodies to aquaporin-4.24 Children with multiphasic ADS not fulfilling MS diagnostic criteria were likely to be positive (8/11) for anti-MOG antibodies. These children with a multiphasic disease course often have ADEM followed by one or more ON.24,26 Similar results have been documented by other groups,25 indicating that the presence of anti-MOG positivity tested with cell-based assays statistically suggests against a diagnosis of MS. Still, other studies using cell-based assays have found anti-MOG antibodies particularly in children diagnosed with MS younger than 10 years,27 suggesting an age-dependent presence of MOG antibodies in pediatric MS.

**GENETIC BACKGROUND ASSOCIATED WITH MS** Although there are now at least 159 genes involved in genetic vulnerability (Phil de Jager, personal communication on behalf of the International MS Genetics Consortium and abstract ECTRIMS, 2014), the presence of any one of these genetic variations is not predictive of MS, nor does the absence of these genetic variations exclude MS. Therefore, there is no reason to perform genetic testing to support a diagnosis of MS in an individual patient.

Genetic factors, however, do influence MS risk, and recent studies have indicated that the genes overrepresented in MS are not similarly overrepresented in monophasic ADS. The main genetic locus associated worldwide with adult MS is within the major histocompatibility complex, and in particular risk associates with the human leukocyte antigen (HLA)–DRB1*15 allele.28 In a Canadian study of pediatric ADS, the presence of 1 or 2 HLA-DRB1*15 alleles conferred an OR of 2.7 for MS outcome.29 Children with positive MOG antibodies have similar rates of HLA-DRB1*15 allele to the general population (3/18), whereas children with negative MOG antibodies have higher rates of HLA-DRB1*15 allele

<table>
<thead>
<tr>
<th>Criteria</th>
<th>KIDMUS15</th>
<th>Callen et al.16 MS vs ADEM</th>
<th>Verhey et al.19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesions perpendicular to the long axis of the corpus callosum; the sole presence of well-defined lesions</td>
<td>21</td>
<td>81</td>
<td>84</td>
</tr>
<tr>
<td>Two out of three of (1) absence of diffuse bilateral lesion pattern; (2) presence of black holes; (3) presence of 2 or more lesions with periventricular lesions</td>
<td>61</td>
<td>79</td>
<td>96</td>
</tr>
</tbody>
</table>

Abbreviations: ADEM = acute disseminated encephalomyelitis; NPV = negative predictive value; PPV = positive predictive value.
(7/22), further strengthening the case that MOG antibody supports a non-MS diagnosis, although larger cohorts are required to further test this association.30

Another study evaluated the frequencies of 57 of the newly identified non-HLA MS risk single nucleotide polymorphisms (SNPs) in 188 children with ADS, of whom 53 individuals had a subsequent diagnosis of MS.31 In order to control the effect of genetic variation due to ancestry, only patients with European ancestry were included. Control groups were 456 patients with adult MS and 2,046 healthy adults. A weighted genetic risk score of this set of SNPs discriminated between children with MS vs those with monophasic ADS. The association with MS further increased with the addition of (female) sex and HLA-DRB1*15. Interestingly, the combined effect of the 57 SNPs exceeded the effect of the HLA-DRB1*15 alone.

DISCUSSION

The prompt diagnosis of MS in children and adolescents is aided by recognition of the various clinical manifestations, by specific lesion patterns on baseline and serial MRI, and by the presence of intrathecal OCBs. No pattern of serum antibodies or immune cell signatures has yet been identified that reliably identifies children with MS, but antibodies against aquaporin-4 and myelin oligodendroglial protein serve to identify children who are likely to have diseases distinct from MS.

AUTHOR CONTRIBUTIONS


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R. Hintzen received honoraria for serving on advisory boards from Biogen Idec, Roche, and Sanofi. He participated in trials with Biogen Idec, Merck-Serono, Roche, Genzyme, and Novartis. He is on the editorial board of Multiple Sclerosis and Related Disorders. R. Dale has received honoraria from Biogen Idec and Bristol-Myers-Squibb. R. Neuteboom is a member of the LAREB Scientific Advisory Board. S. Mar reports no disclosures relevant to the manuscript. B. Banwell serves as a central MRI reviewer for Novartis. Dr. Banwell provides advice on clinical trial design to Novartis, Biogen Idec, Sanofi, and Teva Neuroscience. She is not remunerated for this work. Dr. Banwell is a senior editor for Multiple Sclerosis and Related Disorders. Go to Neurology.org for full disclosures.

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