

# Pearls & Oysters: Tumefactive Demyelinating Lesions With MOG Antibodies Preceding Late Infantile Metachromatic Leukodystrophy

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## Abstract

The development of acute neurologic dysfunction associated with tumefactive demyelinating lesions and mild diffuse involvement of the corpus callosum has been described in children as a sentinel event that may allow diagnosis of juvenile metachromatic leukodystrophy (MLD) at an early and potentially treatable stage. We report a child who developed this clinico-radiologic pattern associated with myelin oligodendrocyte glycoprotein antibodies several months before the onset of progressive symptoms of late infantile MLD.

## Pearls

- Metachromatic leukodystrophy (MLD) is an inherited rare lysosomal storage disorder that leads to progressive demyelination of the central and peripheral nervous system.
- It typically manifests with regression of motor skills, cognitive decline, vision impairment, peripheral neuropathy, and gallbladder disease, associated with progressive, bilaterally symmetric T2/fluid-attenuated inversion recovery hyperintensities in the periventricular and deep white matter.
- Some patients may develop acute disseminated encephalomyelitis (ADEM)-like acute steroid-responsive inflammatory demyelinating episodes preceding the onset of the progressive symptoms typical of MLD.
- Subtle involvement of the splenium of the corpus callosum in association with tumefactive demyelinating lesions (TDLs) with or without myelin oligodendrocyte glycoprotein (MOG) antibodies in a child may be a clue for early diagnosis of late infantile MLD.
- Suspicion of MLD should lead to an evaluation for arylsulfatase A (*ARSA*) gene sequence variations and biochemical testing in which low serum *ARSA* activity in leukocytes or cultured skin fibroblasts, and elevated urine sulfatides are the hallmark biomarkers.

## Oysters

- The presence of MOG antibodies should not dissuade from performing genetic and/or biochemical testing in a child with tumefactive demyelinating lesion and involvement of the splenium.
- The early radiologic signs of MLD in children with tumefactive demyelinating lesions may be subtle and missed if not specifically looked for.
- Delaying genetic and/or biochemical testing until the development of more typical MRI involvement (e.g., diffuse bilateral tigroid pattern) may result in it being too late for treatments to potentially be effective.

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## Glossary

**ADEM** = acute disseminated encephalomyelitis; **ARSA** = arylsulfatase A; **MLD** = metachromatic leukodystrophy; **MOG** = myelin oligodendrocyte glycoprotein; **MOGAD** = MOG associated disease; **TDL** = tumefactive demyelinating lesions.

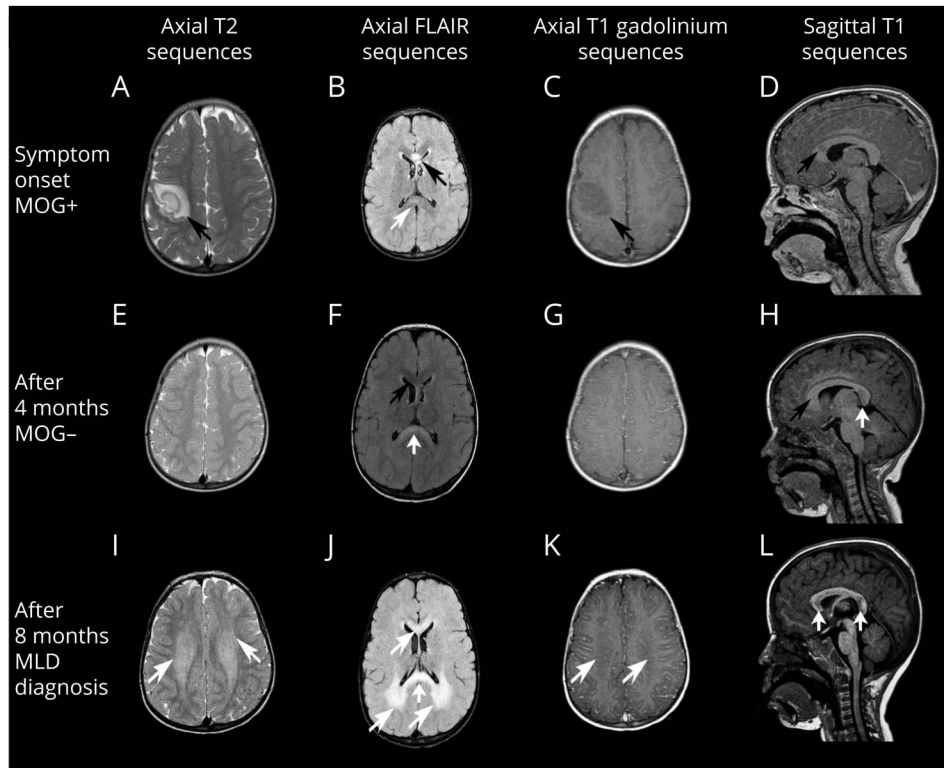
## Case Summary

A previously healthy 20-month-old boy presented with new onset dystonic posturing of the left arm, gait disturbance, paroxysmal convergent strabismus of the right eye, and somnolence. MRI of the brain showed a large frontoparietal tumefactive hyperintense T2 lesion, a hyperintense T2 lesion in the genu of the corpus callosum, and mild diffuse involvement of the splenium of the corpus callosum without contrast enhancement or restricted diffusion (Figure, A–D). Based on the suspicion of TDL in the context of an ADEM-like syndrome, extensive microbiological studies were performed and were negative. CSF analysis showed mild pleocytosis (25 white blood cells), normal protein and glucose levels, and no oligoclonal bands. Using live cell-based assays, blood and CSF samples showed high titers of MOG antibodies but were negative for aquaporin 4 antibodies. The child was started on intravenous steroids and had clinical and radiologic improvement. At the 4-month follow-up, he had residual mild gait disturbance and hyperreflexia and was now seronegative for MOG antibodies (CSF not studied). The MRI of the brain showed complete resolution of the tumefactive frontoparietal lesion and the lesion in the genu of the corpus callosum, but revealed progression of the diffuse involvement of the splenium (Figure, E–H). Four months later, he was readmitted for new onset ataxia and language impairment. On examination, hyperreflexia and spasticity in both legs were noted. MRI of the brain showed worsening of the splenium lesion that was now more diffuse and associated with restricted diffusion. There was also a bilaterally symmetric tigroid pattern in the deep white matter with a posterior predominance; the subcortical U fibers were relatively preserved (Figure, I–L). Evaluation showed decreased arylsulfatase A activity in blood (ARSA activity in leukocytes was 16% of normal controls) and an increase in urinary sulfatide excretion. The study of the ARSA gene identified a compound heterozygous sequence variation (c.[641C>T ( ) 881G>A]) inherited from the mother and father, respectively, confirming the diagnosis of late infantile MLD. He was started on enzyme replacement therapy in the context of a clinical trial. During follow-up, he developed progressive worsening of motor and cognitive impairment but no further acute demyelinating episodes were observed. At the last follow-up at age 5 years, he was nonambulatory because of global spasticity, dystonia, and loss of head and trunk control (Gross Motor Function Classification for MLD Level M6)<sup>1</sup> and was being treated with trihexyphenidyl, oral baclofen, and diazepam. He maintains visual and social interaction and understands simple commands but does not speak (Expressive Language Function Classification for MLD Level E4<sup>1</sup>).

## Discussion

MLD is an inherited lysosomal storage disorder caused by recessive mutations in the ARSA gene encoding the arylsulfatase A enzyme<sup>2</sup> and more rarely in the PSAP gene encoding the sphingolipid activator protein saposin B (SAP-B), which is responsible for the degradation of sulfatides by ARSA.<sup>2</sup> The accumulation of sulfatides in the central and peripheral nervous system leads to demyelination that results in progressive motor and cognitive decline.<sup>1</sup> MLD is one of the most common leukodystrophies and has a prevalence rate of 1 in 40,000–160,000 worldwide.<sup>3</sup> MLD is divided into 3 clinical subtypes based on the age at onset of first symptoms: late infantile (younger than 30 months), early juvenile (older than 30 months to 16 years), and adult (older than 16 years) forms.<sup>3</sup> The late infantile form is characterized by rapid psychomotor regression with ataxia and weakness with arreflexia.<sup>3</sup> Progressive peripheral neuropathy can be seen before the onset of CNS deterioration.<sup>3</sup> Extreme irritability and seizures are commonly seen.<sup>3</sup> Gallbladder disease can also be seen during evolution of the disease.<sup>4</sup> In contrast to the late infantile form, in the early juvenile and adult forms, behavior abnormalities and cognitive decline are the most frequent symptoms at onset.<sup>3</sup> Radiologic features are white matter abnormalities frequently first seen in the corpus callosum that may precede the development of progressive symptoms.<sup>5</sup> These features progress to a more diffuse, nonenhancing, bilaterally confluent, and symmetric “tigroid” pattern involving the periventricular and deep white matter.<sup>6</sup> The “tigroid pattern” is due to stripes of more normal signal (dark) within the abnormal white matter (hyperintense T2) and is a result of sparing of the perivascular areas.<sup>5,6</sup> Although this pattern may be seen in other diseases, MLD has a characteristic MRI spatial pattern and temporal evolution that varies according to the age at disease onset.<sup>6</sup> In the late infantile form, there is a high correlation between MRI involvement and disease progression and the white matter involvement starts at the parieto-occipital lobes and the splenium of the corpus callosum<sup>6</sup> as seen in our case. By contrast, in the early juvenile and adult forms, the MRI is usually clearly abnormal before or at onset of first neurologic symptoms,<sup>6</sup> and although the spatial pattern of affected brain structures is similar to the late infantile form, the variability between patients is higher.<sup>6</sup> In addition, in the early juvenile and adult forms the white matter changes usually show a frontal predominance that is considered typical for MLD.<sup>5,6</sup> The diagnosis is made through genetic analysis and biochemical findings including low ARSA enzymatic activity in leukocytes or cultured skin fibroblasts and high excretion of urine sulfatides.<sup>3</sup>

Therapeutic approaches to MLD such as genetic therapy or bone marrow transplantation are only possible in asymptomatic



At onset of symptoms associated with MOG antibody seropositivity, MRI of the brain showed 2 tumefactive demyelinating lesions (TDL) (A, frontoparietal and B, genu of the corpus callosum, black arrows). These lesions were hypointense in T1 (C, D, black arrows) but did not show contrast enhancement (C) or restricted diffusion (not shown). Both lesions completely resolved after 4 months at which time MOG antibodies were negative (E-H, black arrows). At this time, the diffuse involvement of the splenium of the corpus callosum observed at onset (B, white arrow) but attributed to the acute attack had progressed (F, white arrow) and was now hypointense in T1 (H, white arrow). Four months later when progressive neurologic symptoms occurred, the splenium lesion had continued to progress, involved the whole corpus callosum (J, L, white arrows), and was now associated with restricted diffusion (not shown). There was also a bilaterally symmetric tigroid pattern in the deep white matter with a posterior predominance (hyperintense in T2 [I] and T2-fluid-attenuated inversion recovery [J], white arrows, but hypointense in T1 [K, white arrows]; the U-shaped fibers were relatively preserved).

patients or at a very mild initial clinical stage, as once progressive neurologic symptoms occur, they are irreversible.<sup>2,7</sup> Therefore, the identification of patients with incipient lesions in the corpus callosum at very early or presymptomatic stages is essential for improving outcome.<sup>8</sup> Unfortunately, this is not very common but may occur in siblings of affected individuals who undergo screening MRI or as recently described, in children with ADEM-like presentations associated with tumefactive lesions preceding the development of progressive symptoms who may have incipient corpus callosum lesions.<sup>9-11</sup> An immune-mediated response triggered by myelin epitope exposure secondary to sulfatide accumulation and active myelin breakdown has been proposed to be the cause of acute ADEM-like events preceding some MLD cases.<sup>9</sup> Our patient demonstrates that these acute presentations may also occur in the presence of MOG antibodies and that the presence of these antibodies supports the autoimmune nature of these steroid-responsive attacks. Patients with acute acquired inflammatory MOG-associated disease (MOGAD) may also show inflammatory involvement of the corpus callosum,<sup>12</sup> but this typically resolves or improves with steroid therapy. In our patient, the more inflammatory-appearing lesion in the genu of the corpus callosum resolved with steroids, in contrast to the more diffuse splenium involvement typical of MLD that continued to evolve over time, despite the steroid therapy and the fact that MOG antibodies became negative. Although some patients with MOGAD may develop a relapsing form of disease, the absence of antibodies during follow-up, as in our patient, is associated

with lower risk of relapses in comparison with MOGAD patients who remain seropositive.<sup>13</sup> There are 4 previously described cases of patients with ADEM-like episodes preceding the onset of progressive symptoms typical of MLD.<sup>9-11</sup> All had early juvenile MLD, and only one patient was tested for MOG antibodies and was negative,<sup>9</sup> although the sensitivity of MOG testing can be variable.<sup>14</sup> In these cases, the subtle involvement of the corpus callosum in the initial MRI was not noticed or was attributed to the acute episode, as occurred with our patient. Because TDL are exceptional in children,<sup>15</sup> their presence even in association with MOG antibodies should put physicians on alert of a possible association with MLD and to carefully review the MRI for early presymptomatic radiologic involvement (e.g., diffuse splenium involvement typical of late infantile MLD).<sup>8</sup> Even when not detected at onset, if during follow-up, the TDL lesions improve or resolve but splenium involvement progresses; this should also raise an alert.

Genetic and/or biochemical testing for MLD should be performed urgently as waiting for the development of more typical, deep white matter involvement may result in it being too late for treatments to be effective.

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