Pearls & Oy-sters: 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 arsylsulfatase 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.

Oy-sters

- 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.
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 titer 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, nonenhancing, bilaterally confluent, and symmetric “tigroid” pattern involving the periventricular and deep white matter. The “tigroid pattern” is due to stripes of more normal signal (dark) within the abnormal white matter (hypertense T2) and is a result of sparing of the perivascular areas. 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. 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 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, and although the spatial pattern of affected brain structures is similar to the late infantile form, the variability between patients is higher. In addition, in the early juvenile and adult forms the white matter changes usually show a frontal predominance that is considered typical for MLD. The diagnosis is made through genetic analysis and biochemical findings including low ARSA enzymatic activity in leukocytes or cultured bone marrow mononuclear leukocytes.  

Therapeutic approaches to MLD such as genetic therapy or bone marrow transplantation are only possible in asymptomatic cases.
patients or at a very mild initial clinical stage, as once progressive neurologic symptoms occur, they are irreversible.\(^2,7\) Therefore, the identification of patients with incipient lesions in the corpus callosum at very early or presymptomatic stages is essential for improving outcome.\(^8\) 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.\(^9-11\) 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.\(^9\) 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,\(^12\) 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.\(^13\) There are 4 previously described cases of patients with ADEM-like episodes preceding the onset of progressive symptoms typical of MLD.\(^9-11\) All had early juvenile MLD, and only one patient was tested for MOG antibodies and was negative,\(^9\) although the sensitivity of MOG testing can be variable.\(^14\) 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,\(^15\) 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).\(^8\) 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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Appendix

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References