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Eric N. Faerber
Joseph J. Melvin
Eleanor M. Smergel

MRI appearances of metachromatic leukodystrophy

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E. N. Faerber (✉) · J. Melvin · E. Smergel
Department of Radiology,
St. Christopher's Hospital for Children,
MCP. Hahnemann School of Medicine,
Erie Avenue and Front Street,
Philadelphia, PA 19134-1095, USA

Abstract *Background.* The leukodystrophies constitute a wide spectrum of cerebral disorders of varying etiology. The imaging appearances on CT and MRI are recognizable as abnormalities of white matter; however, it may be impossible to arrive at the correct diagnosis based on imaging studies alone.
Patients and methods. Three patients of varying age and clinical symptomatology diagnosed with metachromatic leukodystrophy (MLD) had remarkably similar MRI appearances. A "tigroid" or "leopard-skin" appearance was demonstrated within deep white matter in each case.
Results. All of the patients had biochemical confirmation of MLD.
Conclusion. Although the "tigroid" pattern previously was considered to be pathognomonic of Pelizaeus-Merzbacher disease, the diagnosis of MLD must now be considered when these MRI appearances are encountered.

Introduction

Metachromatic leukodystrophy (MLD) is an autosomal recessive degenerative disorder of myelin metabolism. We report three cases of children diagnosed with MLD within a 15-month period. A 2-year-old girl, a 5-year-old boy, and an 11-year-old girl were diagnosed with MLD based on history, physical, examination, electrophysiology studies, biochemical analysis, and imaging studies. In spite of their varied ages and clinical presentations, the salient features of the MRI studies were remarkably similar.

Previous reports of MRI studies in patients with MLD have described symmetric diffuse high signal on proton density and T2-weighted images throughout the white matter [1–3]. The MRI studies of the three patients described in this report exhibit these abnormalities. In addition, the MRI studies revealed a distinct inhomogeneous pattern of diffusely abnormal white-matter signal in the centrum semiovale. Linear and punctate areas of normal white-matter signal were interspersed with demyelinated areas producing a "tigroid" pattern. Although there is a recent report of a similar pattern noted in late infantile MLD [4], this "tigroid" pattern has previously been thought to be characteristic of Pelizaeus-Merzbacher disease [5–7].

Patients and methods

The patients were two girls and one boy ages 2 years, 11 years, and 5 years, respectively, at the time of presentation. Magnetic resonance imaging of the brain with gadolinium was performed in all three patients at the time of presentation. The characteristics of the signal abnormalities are described in detail and compared with each other.

Case reports

Patient 1

J. M. is a 2-year-old girl who presented with progressive ataxia and lower extremity weakness. The past medical history was significant for a left esotropia that was surgically repaired at age 11 months. The developmental history is notable for delay in gross motor skills without a concomitant delay in cognition or language.

The neurologic examination was remarkable for deficits in cognition, language, and motor development. She exhibited mild bilat-

eral lower extremity distal weakness, and demonstrated significant ataxia and dysmetria. She was unable to walk without falling because of her ataxia.

Serum lysosomal enzyme studies disclosed a gross deficiency of arylsulfatase A activity in peripheral leukocytes. An MRI of the brain documented diffuse and symmetric high signal on proton density and T2-weighted images throughout the white matter, consistent with demyelination. A radiating "tigroid" and punctate "leopard-skin" appearance was noted within the centrum semiovale on T2-weighted MR images (Fig. 1).

Patient 2

M.L. is a 5-year-old boy who presented with a history of clumsiness, behavior difficulties, increasing difficulty with ambulation, and occasional enuresis during the month prior to his neurologic examination. His past medical history was significant for an unspecified "problem with his eyes" at age 2 years that resolved with the use of glasses by age 3. He was otherwise healthy and never hospitalized. His developmental history was significant for a mild cognitive delay and overall difficulty with coordination. His neurologic examination revealed a right-handed child who became irritable and restless if required to perform tasks requiring concentration. An assessment of motor strength revealed a marked decrease in tone with normal muscle bulk. He exhibited distal weakness of the upper and lower extremities bilaterally, especially in dorsiflexion. His gait was wide-based and unsteady with foot dragging bilaterally. The physical examination was also significant for a right-sided plantar extensor response.

Serum lysosomal enzyme studies reported grossly deficient arylsulfatase A activity in peripheral leukocytes. Urine studies established the presence of sulfatides. An MRI of the brain demonstrated diffuse abnormal signal intensities throughout the white matter best demonstrated on T2-weighted images. The abnormalities involved the periventricular white matter of the posterior horns of the lateral ventricles more than the anterior horns. T2-weighted MR images demonstrated the tigroid and leopard-skin appearances of spared perivascular white matter within the diffuse demyelination in the centrum semiovale (Fig. 2).

Patient 3

E.S. is an 11-year-old female who presented with a history of a gait abnormality first noted with difficulty ascending stairs. The gait problems had worsened over the preceding year. She also had a significant deterioration in the quality of her school work over the preceding year as well as several episodes of fecal and urinary incontinence without alteration in consciousness. Her past medical history was unremarkable.

Her neurologic examination was significant for spasticity with increased reflexes more marked in the lower than upper extremities and a bilateral flexor plantar response. Her gait was characterized by instability with a wide base. A dysmetria was noted on finger-to-nose testing.

Lysosomal enzyme studies revealed a very low arylsulfatase A activity in peripheral leukocytes. Cerebral MRI demonstrated diffusely symmetric increased signal intensity on T2-weighted images without enhancement, caused by demyelination. A punctate tigroid pattern was present within the demyelinated centrum semiovale (Fig. 3).

Discussion

Metachromatic leukodystrophy is one of several inherited disorders of myelin in which a metabolic abnormality has been identified [8, 9].

Biochemically, MLD is characterized by accumulation of galactosyl sulfatide in the white matter of the central and peripheral nervous system, as well as other organs (kidney, liver, gallbladder, etc). Galactosyl sulfatide is normally metabolized through the combined action of the lysosomal enzyme arylsulfatase A and a protein activator. In MLD, the accumulation of galactosyl sulfatide results from a deficiency of the activity of arylsulfatase A [8].

The clinical forms of the disease have been distinguished by age of onset. The late infantile form is usually manifest by the ages of 1.5–2 years. The children develop a gait abnormality with hypotonic diplegia, ataxia, progressive weakness, and cognitive abnormalities. There is rapid progression over the next 1–2 years with progressive hypotonia, weakness, and intellectual deterioration. The late stages of the late infantile form are characterized by loss of speech, spasticity, decerebrate posturing, and death usually by 5 years of age.

The juvenile form of MLD manifests between 4 and 12 years of age. A previously well child develops a spastic gait, ataxia, and intellectual deterioration. Patients develop increasing spasticity and dementia with episodes of decerebrate posturing and generalized tonic-clonic seizures. The disease progressives more slowly than the late infantile MLD [8–11].

The adult form of MLD may begin at any age beyond puberty, but usually presents between the third and fourth decades of life. A change in personality or poor job or school performance may herald the onset of the disease. Defective visual-spatial discrimination, poor memory, disorganized thinking, and decreased mental alertness are observed. In addition to the intellectual and emotional changes, general slowness and clumsiness are also presenting features of the illness. A 5- to 10-year survival is common.

The MRI characteristics of the different forms and stages of MLD have not been completely elucidated. We present three patients with MLD confirmed by biochemical analysis. All demonstrate strikingly similar MRI features in spite of diverse presentations with regard to age, sex, and symptoms.

Published reports of the MRI features of MLD describe diffuse high signal abnormalities of the white matter on proton density and T2-weighted images [1–3]. The descriptions have varied from focal and asymmetric abnormalities occurring more often in the anterior areas to symmetric and diffuse changes in white matter with little evidence of cortical atrophy. There is sparing of the subcortical white matter with later involvement of the subcortical arcuate U fibers.

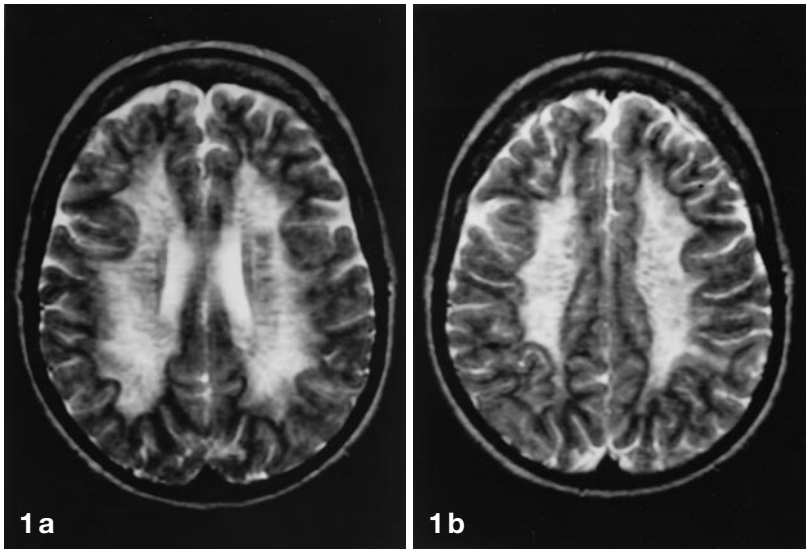

Fig. 1 2-year-old girl with MLD. T2-weighted axial MR images demonstrate **a** Linear tubular structures of low signal intensity within the centrum semiovale. There is a radiating pattern ("tigroid" appearance) indicative of spared perivascular white matter. **b** There is a punctate appearance to the linear structures ("leopard-skin" appearance) within the demyelinated centrum semiovale at a level superior to the previous illustration

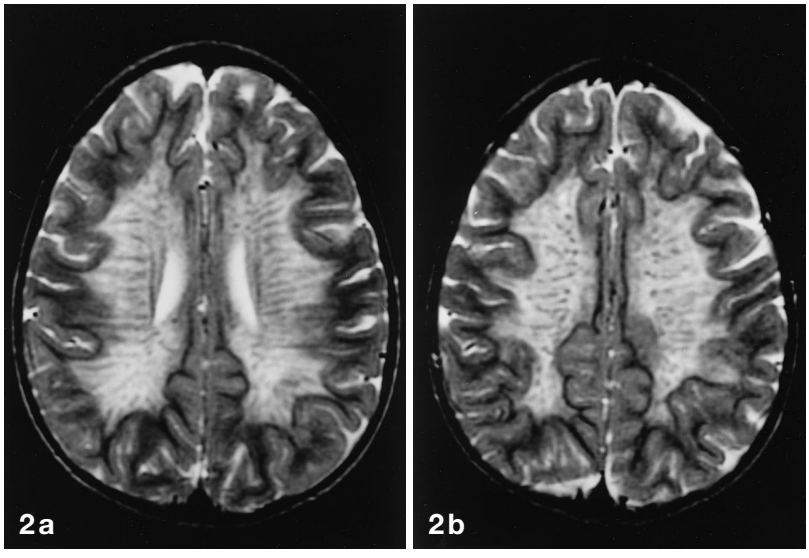

Fig. 2 5-year-old boy with MLD T2-weighted axial MR images demonstrate **a** Radiating tigroid appearance in the demyelinated centrum semiovale. **b** Radiating ("tigroid") and punctate ("leopard-skin") appearance in demyelinated centrum semiovale

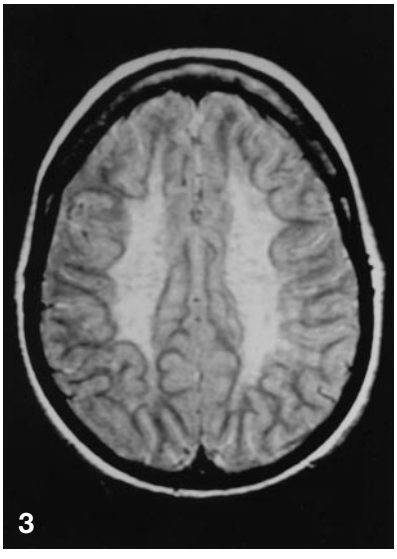

Fig. 3 11-year-old girl with MLD T2-weighted axial MR image demonstrates the punctate ("leopard-skin") appearance in the demyelinated centrum semiovale

The MRI features of our patients consist of diffuse and symmetric high signal abnormalities within the white matter on both proton density and T2-weighted images consistent with demyelination. In addition, there are hypointense signal abnormalities in the white matter of the centrum semiovale. There are two distinct appearances: a radiating pattern ("tigroid" appearance) of linear tubular structures of horizontal linear hypodense indicative of spared perivascular white matter and areas of relatively normal-appearing white matter ("leopard-skin" appearance) (Figs. 1–3).

The characteristics of a tigroid pattern have previously been described in conjunction with the MRI features of Pelizaeus-Merzbacher disease [5–7]. Pelizaeus-Merzbacher disease is a form of sudanophilic leukodystrophy. It is characterized by an x-linked recessive demyelinating disease with variable age of onset, usually

within the neonatal period or early infancy. The pathophysiology of the "tigroid" pattern is purported to be residual isles of normal myelin within the demyelinated areas. Recently, a "tigroid" pattern has been reported in cases of late-infantile MLD [4].

We describe three cases where a "tigroid" pattern was noted before a biochemical analysis confirmed the diagnosis of MLD. One of our patients would be classified as late-infantile while the other two would be juvenile MLD based on age of presentation. The diagnosis of MLD should be considered whenever a "tigroid" appearance of the white matter is present on the MRI images. The "tigroid" pattern may be seen in both late-infantile and juvenile MLD regardless of the age or presenting symptoms. A pathophysiology of scattered areas of normal white matter within zones of demyelination similar to that found in Pelizaeus-Merzbacher disease may be also be responsible for producing the "tigroid" appearance in MLD.

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