Imaging Manifestations of the Leukodystrophies, Inherited Disorders of White Matter

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KEYWORDS

• Leukodystrophy • Inborn error of metabolism • Dysmyelination • Demyelination • Spectroscopy • White matter

KEY POINTS

- Recognition of leukodystrophies requires a solid understanding of normal myelination.
- When a leukodystrophy is encountered, a pattern-based approach is useful for developing a reasonably sized differential diagnosis. The patterns stressed in this review include globally delayed myelination, subcortical white matter predominant, central white matter predominant, and combined gray/white matter patterns.
- Special emphasis should be placed on recognizing unusual combinations of findings that suggest a specific diagnosis.

INTRODUCTION

In contrast to most other white matter diseases discussed in this issue, leukodystrophies are inherited disorders that result from mutations in a specific gene product or biological pathway. Various working definitions of leukodystrophy have been proposed that further restrict the meaning of this term to inborn errors of metabolism (ie, a specific type of gene product) or demyelination (ie, a specific pathogenic mechanism).[1–3] Matters become more complicated still because some investigators define demyelination as any process leading to myelin loss, whereas some would restrict the meaning of this term to inflammatory disorders such as multiple sclerosis, leaving disorders of myelin synthesis/maintenance under the grouping of 'dysmyelination.'

Because there is considerable overlap in the appearance of inherited white matter diseases regardless of type of gene product or pathogenesis of the signal abnormality seen on imaging, this review uses a pragmatic definition of leukodystrophy, namely any disorder of white matter signal secondary to a defective or absent gene product. Although this definition is fairly broad, it excludes disorders that exclusively affect gray matter structures or at least lack discrete white matter signal abnormality. Therefore, this article excludes some well-known metabolic disorders such as pantothenate kinase deficiency, creatine deficiency syndromes, and many of the organic acidemias (eg, 3-methylgluconic and methylmalonic acidemia). Diffuse white matter disease seen in association with congenital muscular dystrophies has a distinctive clinical presentation,[4–6] and imaging of disorders of peroxisomal biogenesis have been recently reviewed elsewhere[7]; both are also omitted from this review.

As a category, the leukodystrophies usually present a challenge to radiologists because specific disease entities are rarely encountered and there are numerous diseases with overlapping imaging appearance. In this review, a practical approach

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to recognizing and categorizing the leukodystrophies is described, focusing on 4 common patterns of signal abnormality in the brain parenchyma (**Box 1**). Special emphasis is given to unusual imaging features or combinations of features that suggest a specific diagnosis. For the interested reader, additional resources are provided, including reference works dedicated to the topic.[8–10]

IMAGE ACQUISITION

As with other white matter disorders, leukodystrophies are best appreciated on magnetic resonance (MR) imaging.[11] Standard MR imaging protocols should include high-resolution T1-weighted and T2-weighted imaging in at least 2 planes to provide an accurate evaluation of the maturity and integrity of brain myelination. Diffusion-weighted imaging is

Box 1
Simplified pattern-based approach to leukodystrophies

Globally Arrested/Absent Myelination

Pelizaeus-Merzbacher disease
18q-deletion syndrome
Free sialic acid storage disorders (Salla)
Trichothiodystrophy
Cockayne syndrome*
Fucosidosis
Hypomyelination with hypodontia and hypogonadotropic hypogonadism (4H syndrome)
Hypomyelination with atrophy of the basal ganglia and cerebellum*
Hypomyelination with congenital cataracts
Nonketotic hyperglycinemia

Subcortical Predominant White Matter Signal Abnormality

Galactosemia
Megalencephalic leukoencephalopathy with subcortical cysts*
Aicardi-Goutières syndrome*

Central White Matter Predominant Signal Abnormality, With or Without Brainstem Involvement

X-linked adrenoleukodystrophy, acyl-coenzyme A oxidase deficiency*
Metachromatic leukodystrophy
Mucopolysaccharidosis
Lowe syndrome*
X-linked Charcot-Marie-Tooth*
Cockayne syndrome+
Vanishing white matter disease (childhood ataxia with central nervous system hypomyelination)
Neuronal ceroid lipofuscinosis+
Leukoencephalopathy with brainstem and spinal cord evolvement and increased lactate*
Phenylketonuria
Sjögren-Larsson syndrome
Nonketotic hyperglycinemia
Hyperhomocysteinemia
Biotinidase (multiple carboxylase) deficiency

Combination of Gray and White Matter Signal Abnormality

Canavan disease*
GM1/GM2 gangliosidoses (Tay-Sachs, Sandhoff syndromes)*
Alexander disease*
Krabbe disease*
Maple syrup urine disease*
Leigh disease and other mitochondrial disorders
Urea cycle disorders*
L-2-hydroxyglutaric aciduria*
Glutaric aciduria type I and II

* indicates a disease with highly characteristic imaging findings.
+ indicates a minority manifestation.
Data from Barkovich AJ, Patay Z. Metabolic, toxic, and inflammatory brain disorders. In: Barkovich AJ, editor. Pediatric neuroimaging. Philadelphia: Lippincott Williams & Wilkins; 2012. p. 81–239.