Adult Leukodystrophies: A Step-by-Step Diagnostic Approach

Leukodystrophies usually affect children, but in the last several decades, many instances of adult leukodystrophies have been reported in the medical literature. Because the clinical manifestation of these diseases can be nonspecific, MRI can help with establishing a diagnosis. A step-by-step approach to assist in the diagnosis of adult leukodystrophies is proposed in this article. The first step is to identify symmetric white matter involvement, which is more commonly observed in these patients. The next step is to fit the symmetric white matter involvement into one of the proposed patterns. However, a patient may present with more than one pattern of white matter involvement. Thus, the third step is to evaluate for five distinct characteristics—including enhancement, lesions with signal intensity similar to that of cerebrospinal fluid, susceptibility-weighted MRI signal intensity abnormalities, abnormal peaks at MR spectroscopy, and spinal cord involvement—to further narrow the differential diagnosis.

Introduction

Leukodystrophies currently are defined as genetically determined disorders that primarily affect the white matter of the central nervous system, regardless of the structural white matter component, molecular process, patient age group, and disease course involved. Genetic testing is of paramount importance (1).

Although these disorders primarily manifest in early infancy and childhood, they may also affect adults, who occasionally present with clinical and imaging findings that are distinct from those observed in children (2,3). There is growing recognition that leukodystrophies may manifest initially during adulthood (4).

Adult leukodystrophies usually are progressive diseases. Patients may present with movement disturbance, vision problems, hearing impairment, imbalance, memory loss, behavioral changes, and attention deficits (5–8).

Because the clinical manifestation of leukodystrophy can be nonspecific, MRI has been used as a powerful paraclinical tool; it sometimes can be the key to narrowing the diagnosis, even at the early stages of the disease in presymptomatic patients and carriers (5,7). Symmetric involvement in the white matter at MRI is an essential finding in patients with adult leukodystrophies, because it commonly is associated with inherited disorders. However, the imaging pattern of adult leukodystrophy can vary according to the disease and its time course (9,10).

In addition to symmetry, many other MRI features can help in reaching a final diagnosis in patients who are presumed to have adult leukodystrophy or at least in narrowing the list of diagnoses for which to evaluate as part of the differential diagnosis. An algorithm that allows evaluation of all of these characteristics has been developed to help differentiate among white matter diseases overall (11).
The purpose of this review is to adapt this algorithm for adult leukodystrophies and to demonstrate the imaging features of some of the most prevalent forms of this disease. The approach we propose here must be used mainly as a framework. The characterization of all possible types of leukodystrophies and eventual atypical presentations is beyond the scope of this review.

**Step 1: Identify Symmetric White Matter Involvement**
Symmetric white matter involvement at MRI is a typical finding in patients with leukodystrophies. Thus, recognizing this involvement is important when leukodystrophies are suspected, although there are exceptions to this pattern (12). T2-weighted and fluid-attenuated inversion-recovery (FLAIR) MRI are the best sequences to use to determine white matter involvement, as shown in Figure 1, which illustrates symmetric white matter involvement compared with an asymmetric pattern. White matter lesions appear as hyperintensity on T2-weighted and FLAIR MR images and hypo- or isointensity on T1-weighted images. Depending on the cause and stage of the disease, signal intensity may vary. Familiarity with typical manifestations is important (13).

Important exceptions to this rule are genetically defined vasculopathies, such as CADA-SIL, in which abnormalities in signal intensity (ie, increased signal intensity on T2-weighted or FLAIR MR images) can be multifocal and asymmetric instead of symmetric, especially in the early phases of the disease. However, these diseases usually manifest with other distinctive MRI findings that can help in reaching the correct diagnosis.

In addition to recognizing symmetric white matter involvement, characterizing the white matter involvement pattern is necessary to continue with the differential diagnosis.

**Step 2: Look for a White Matter Involvement Pattern**
The next step in the diagnostic approach is to look for the pattern of white matter involvement. There are six patterns of white matter involvement with which radiologists should be aware to reduce the list of possible diagnoses, as shown in Figure 2. However, sometimes the same patient presents with more than one pattern during the time course of the disease, and a given leukodystrophy may manifest with more than one of these patterns. In this situation, searching for distinctive findings (step 3) helps to restrict the conditions to consider in the differential diagnosis and target the specific confirmatory tests.

**Parieto-occipital Pattern**

*X-linked Adrenoleukodystrophy.*—X-linked adrenoleukodystrophy (X-ALD), one of the most common adult leukodystrophies, is caused by a mutation in the adenosine triphosphate–binding cassette subfamily D member 1 gene (*ABCD1*), which codes for an adenosine triphosphate–binding cassette transporter and is located in the peroxisomal membrane. The biochemical hallmark of this condition is an elevation in serum levels of very long-chain fatty acids, which also accumulate in neural tissues and in the adrenal gland. Molecular confirmation of X-ALD is performed by sequencing the *ABCD1* gene (10,13,14).

In adults, there are different forms of X-ALD. The most common is “pure” adrenomyeloneuropathy, which manifests with slowly progressive spastic paraparesis, sensory disturbances, and bladder dysfunction. These patients usually experience spinal cord atrophy, mainly in its thoracic segment, but the brain shows no abnormalities. The cerebral manifestation of X-ALD is less frequent in adults and is characterized by psychiatric features followed by dementia, ataxia, seizures, and even death. In these patients, MR images of the brain are similar to those observed in children with ALD, and the spinal cord shows no abnormalities. Other patients present with intermediate forms of the disease that include involvement of the spinal cord and brain (3,15–17).

Approximately 80% of men with the cerebral form of X-ALD have abnormalities at MRI (ie, high signal intensity on T2-weighted or FLAIR MR images) in the parieto-occipital white matter, splenium of the corpus callosum, visual and audi-
Adult Krabbe disease can manifest as late as the 5th decade of life. Clinically late-onset forms manifest with pyramidal tract involvement and spastic paraparesis or tetraparesis. A peripheral demyelinating polyneuropathy occurs in up to 60% of patients and may be asymmetric and involve bulbar muscles. Progressive cognitive decline, seizures, and cortical blindness also can ensue. The disease progression is slow (22–27).

MRI may show bilateral white matter involvement or may be normal even when the patient has neurologic symptoms. Predominant parieto-occipital white matter changes and involvement of the splenium of the corpus callosum typically are observed (Fig 4). T2-hyperintense changes are observed along the corticospinal tracts, the

Krabbe Disease (Globoid Cell Leukodystrophy).—Krabbe disease is an autosomal recessive lysosomal storage disease caused by deficiency of the β-galactocerebrosidase enzyme, which leads to oligodendrocyte apoptosis and gliosis (21).
posterior limb of the internal capsule, and the pyramidal tracts in the brainstem (15,25,28).

Frontal Pattern

**X-ALD.**—Patients with X-ALD also may present with a frontal pattern of white matter involvement (Fig 5). The features of this disease were described in the parieto-occipital pattern section. Frontal white matter is involved in approximately 15% of children with X-ALD but also can be seen in adult patients (Fig 5).

When there is concomitant involvement of parieto-occipital and frontal white matter, patients usually experience rapidly progressive disease (13,18,19).

**Metachromatic Leukodystrophy.**—Metachromatic leukodystrophy is an autosomal recessive lysosomal condition due to arylsulfatase A (ARSA) gene mutations, resulting in deficiency of the enzyme arylsulfatase A (ASA) that leads to accumulation of 3-O-sulfogalactosylceramide (sulfatide) in oligodendrocytes, Schwann cells, and some neurons (29,30).

Adults account for approximately 20% of patients with metachromatic leukodystrophy. The initial symptoms are often behavioral and psychiatric changes, followed by a slow decline in memory and intellectual abilities. Later, the onset of motor symptoms including spastic paraparesis and cerebellar ataxia and peripheral neuropathy occur. Cholecystitis due to accumulation of sulfatide in the gallbladder wall is an important nonneurologic complication (31).

MRI findings consist of confluent, symmetric T2 hyperintensity in the frontal or periventricular white matter (Fig 6). The subcortical U fibers are spared, and frequently some frontal predominance is present in patients with adult-onset metachromatic leukodystrophy. Loss of white matter volume results in brain atrophy in the late stages of the disease (32,33).

**Leukoencephalopathy with Axonal Spheroids and Pigmented Glia.**—Leukoencephalopathy with axonal spheroids and pigmented glia also can show a frontal pattern; however, it will be discussed in step 3, because these additional
features are a more substantial diagnostic clue for this disease.

**Periventricular Pattern**

The periventricular pattern is probably the most prevalent of all patterns, and myriad distinct diseases, including diseases other than leukodystrophies, can manifest with periventricular involvement.

**Metachromatic Leukodystrophy.**—MRI findings in patients with metachromatic leukodystrophy also can reveal a periventricular white matter pattern without lobar predominance (32,33).

**Krabbe Disease.**—Less commonly, Krabbe disease can manifest as diffuse periventricular white matter involvement (7).

**Leukoencephalopathy with Brainstem and Spinal Cord Involvement.**—Leukoencephalopathy with brainstem and spinal cord involvement may manifest with a periventricular involvement pattern, as shown in Figure 2. However, because brainstem involvement is characteristic, it is discussed in the brainstem involvement section.

**Sjögren-Larsson Syndrome.**—Sjögren-Larsson syndrome is a rare autosomal recessive disorder characterized by spastic diplegia or tetraplegia, dementia, speech disturbance, and congenital ichthyosis. Sjögren-Larsson syndrome is caused by inactivating mutations in the aldehyde dehydrogenase 3 family member A2 gene (ALDH3A2), which encodes for fatty aldehyde dehydrogenase (FALDH) and results in abnormal metabolism of long-chain aliphatic aldehydes and alcohols (34,35).

At MRI, patients show diffuse white matter hyperintensity on FLAIR and T2-weighted MR images, mainly in the periventricular white matter of the frontal lobes and at the level of the centrum semiovale and corpus callosum (Fig 7).

MR spectroscopy allows disclosure of some ancillary changes that eventually can be of some help. Spectroscopic abnormalities consist of
lipid peaks in the white matter, which are related to the accumulation of lipid substrates that occurs in Sjögren-Larsson syndrome, especially a peak located at 1.3 ppm. N-acetyl aspartate peaks are usually relatively preserved, and elevated levels of creatine, choline, and myo-inositol can be seen (34,36).

**Subcortical Pattern**

L-2-hydroxyglutaric aciduria is a rare neuro-metabolic disorder with autosomal recessive inheritance (L-2-hydroxyglutarate dehydrogenase [L2HGDH] gene) that is characterized by leukoencephalopathy that predominantly affects subcortical white matter (Fig 8) (14).

Patients initially may appear asymptomatic or may have a static encephalopathy. The neurologic symptoms are progressive and include cerebellar ataxia and intellectual decline. Hearing loss is another possible symptom of the disease. In certain patients, these features become apparent only in adulthood. Increased L2-hydroxyglutaric acid in urine is diagnostic (37).

MRI in patients with L-2-hydroxyglutaric aciduria shows predominant subcortical white matter involvement, initially focal and evolving to become confluent. Periventricular white matter is spared. Increased signal intensity on T2-weighted or FLAIR MR images may be observed in the globus pallidus, and less importantly, in the caudate nucleus and putamen, with symmetric distribution. These same signal intensity abnormalities also may be observed in the dentate nucleus (38).

**Brainstem Involvement**

**Alexander Disease.**—Alexander disease is the result of an autosomal dominant mutation in
the glial fibrillary acidic protein (GFAP) gene. These mutations usually are de novo but may be hereditary in patients with adult-onset disease. This condition is characterized pathologically by diffuse Rosenthal fiber accumulation in astrocyte cytoplasms. Molecular testing is diagnostic, and a brain biopsy is no longer required to confirm the diagnosis (37,39).

The clinical presentation includes slowly progressive bulbar dysfunction (dysphagia, dysarthria, and dysphonia), pyramidal signs, and ataxia, with normal cognitive and intellectual functions. When present, palatal myoclonus is suggestive of this diagnosis (8,40,41).

MRI findings in patients who develop Alexander disease in adulthood differ substantially from those of the early-onset form of the disease (Fig 9). White matter signal intensity abnormalities (increased signal intensity on T2-weighted and FLAIR MR images) and mild to severe atrophy of the medulla oblongata extending caudally to the upper cervical spinal cord are the hallmarks of this condition. Middle cerebellar peduncle signal intensity abnormalities also may be observed, and patchy enhancement may be present in affected regions (39,42,43).

**Leukoencephalopathy with Brainstem and Spinal Cord Involvement.**—Leukoencephalopathy with brainstem and spinal cord involvement is a rare autosomal recessive disorder related to aspartyl-tRNA synthetase 2 (DARS2) mutations. Diagnostic criteria have been developed. This condition is a monogenic disease directly related to mutations in the gene encoding mitochondrial aminoacyl-tRNA synthetase (44). Patients with adult-onset disease have been reported to have progressive pyramidal, dorsal column, and cerebellar dysfunction. Symptoms include motor deterioration, progressive spastic ataxia, cognitive decline, and sensory neuropathy (45–47).

At the brainstem level, typical MRI findings include trigeminal mesencephalic tract hyperintensity on T2-weighted and FLAIR MR images.
Figure 9. Alexander disease in two patients. (a) Axial T2-weighted MR image in a 36-year-old woman shows atrophy of the medulla with some hyperintense areas. (b) Sagittal contrast-enhanced T1-weighted MR image in the same patient shows atrophy of the cervicomedullary junction (arrow), a common finding in patients with this condition. (c) Axial reformatted three-dimensional T2-weighted MR image in a 20-year-old man shows bilateral middle cerebellar peduncle involvement (arrows). (d) Axial contrast-enhanced T1-weighted MR image in the same patient shows enhancement foci (arrows) in the same region. (e) Axial FLAIR image in the same patient as in c and d shows hyperintense lesions in the mesencephalon (arrows).

Figure 10. Leukoencephalopathy with brainstem and spinal cord involvement in a 19-year-old woman. (a) Axial FLAIR image shows symmetric white matter involvement. (b) Axial T2-weighted MR image shows selective brainstem (arrowheads) and cerebellar (bent arrows) hyperintensities, including the intraparenchymal tracts of the trigeminal nerves bilaterally (straight arrow). (c) Cervical spine sagittal T2-weighted MR image shows cervical spinal cord involvement, characterized by hyperintense areas. (d) Proton MR spectroscopic image with a short echo time shows an increased lactate peak (Lac).
and medial lemniscus and pyramidal tract lesions (Fig 10). Involvement of the inferior and superior cerebellar peduncles and deep cerebellar white matter are frequently observed. There is also selective involvement throughout the entire length of the pyramidal tracts, including the spinal cord (14,37). MR spectroscopy occasionally allows visualization of lactate peaks.

**Adult-onset Autosomal Dominant Leukodystrophy.**—Adult-onset autosomal dominant leukodystrophy also has brainstem involvement, but it will be discussed under the associated spinal cord involvement section in step 3.

**Cerebellar Involvement (Including Middle Cerebellar Peduncles)**

**Cerebrotendinous Xanthomatosis.**—Cerebrotendinous xanthomatosis (CTX) is a treatable autosomal recessive disorder and is characterized as a lipid storage disease caused by a mutation of the cytochrome P450 family 27 subfamily A member 1 (CYP27A1) gene, which leads to a deficiency of the mitochondrial enzyme 27-hydroxylase. This enzyme catalyzes one of the first steps in the metabolism of sterols. CTX results in the development of a tendinous xanthoma, early cataracts, diarrhea, and leukoencephalopathy. If left untreated, patients might develop progressive dementia and psychiatric symptoms (7,48–50).

The earliest and most relevant MRI features of CTX are involvement of the cerebellar white matter (Fig 11). High signal intensity in the deep periventricular white matter and low or high signal intensity in the dentate nucleus on T2-weighted MR images is characteristic. T2-hypointense areas may be observed and probably represent hemosiderin deposition (15,37).

MR spectroscopy in patients with CTX shows increases in lactate and lipid peaks and a decreased N-acetyl aspartate peak, mainly in the cerebellum. The presence of lipid peaks is reasonable because CTX is a lipid storage disease (51).

**Alexander Disease.**—In Alexander disease, the involvement of the deep cerebellar white matter occasionally can be appreciated, as can middle cerebellar peduncle signal intensity abnormalities (7).

**Leukoencephalopathy with Brainstem and Spinal Cord Involvement.**—Leukoencephalopathy with
brainstem and spinal cord involvement is another entity that sometimes manifests as cerebellar white matter involvement (46).

**Adult-onset Autosomal Dominant Leukodystrophy.**—Adult-onset autosomal dominant leukodystrophy also has cerebellar involvement but will be discussed in step 3.

**L-2-Hydroxyglutaric Aciduria.**—L-2-hydroxyglutaric aciduria can manifest with involvement of the dentate nuclei, as can be seen in Figure 8.

**Fragile X–associated Tremor and/or Ataxia Syndrome.**—Fragile X-associated tremor and/or ataxia syndrome is caused by fragile X intellectual disability 1 (FMR1) gene permutations and leads to cerebellar ataxia, tremor, and peripheral neuropathy.

At MRI, diffuse symmetric middle cerebellar peduncle T2 hyperintensities are a radiologic hallmark of this disease, but they are not always present (Fig 12). Other radiologic findings include deep cerebellar white matter lesions and mild to moderate cerebellar atrophy (12,14,52).

### Step 3: Recognize Distinctive Features

In this section, we will review distinctive imaging findings that can further restrict the differential diagnosis of leukodystrophies. There are five types of distinctive findings that clinicians should recognize. These findings are illustrated in Figure 13.

**Lesions with Cerebrospinal Fluid Signal Intensity**

The presence of lesions that show signal intensity similar to that of cerebrospinal fluid on images from all MRI sequences can be a distinctive finding, although these lesions can have different causes and pathophysiologic mechanisms. FLAIR MR images are of paramount importance for the correct identification of these lesions, which can represent, among other entities, cysts, cavitations, or lacunae.
**Vanishing White Matter Disease.**—Vanishing white matter disease is related to eukaryotic translation initiation factor 2B subunit α 1–5 (EIF2B1–5) gene mutations. A mild variant of this disease has been described in adult patients. The symptoms in the adult-onset form are migraine, spasticity, psychiatric symptoms, cerebellar signs, seizures, and dementia. Pseudobulbar palsy and progressive spastic paraparesis also may be present (9,14,15).

T2-weighted MRI may show normal white matter signal intensity or diffuse increased white matter signal intensity and enlargement of the lateral ventricles (Fig 14). Over time, FLAIR MR images show progressive rarefaction and cystic degeneration until the white matter shows isointensity compared with that of the cerebrospinal fluid. Cerebellar white matter is relatively spared. Signal intensity abnormalities in the midbrain and the pons may be observed (53,54). In the end stage, cerebral hemispheric white matter may have vanished entirely, leaving only the ventricular walls and the cortex, with almost no white matter in between, replaced by this cystic degeneration (15).

**CADASIL.**—CADASIL is the most common hereditary cerebral small-vessel disease. CADASIL is caused by a mutation in the NOTCH3 gene and is the major cause of inherited vascular leukoencephalopathies (10,14).

Adult patients with CADASIL usually present with migraine with a mean patient age at onset of 30 years, while the age of onset for ischemic events usually is when patients are in their late 40s. As microvascular changes progress, patients may develop seizures, cognitive dysfunction, and psychiatric symptoms. MRI changes usually precede the onset of symptoms by 10–15 years (9,15).

At MRI, the first changes are round or oval lesions in the periventricular white matter and centrum semiovale, and these lesions are usually multifocal. These abnormalities subsequently become diffuse and symmetric and involve the external capsule and temporal poles (Fig 15).

Patients can present with lacunae secondary to small-vessel infarcts, which appear as areas of signal intensity similar to that of cerebrospinal fluid on images from all sequences. Another lesion with the same MRI signal intensity behavior in this disease is believed to be a distended subcortical perivascular space, which usually is found in the temporal poles (55).

Small foci of restricted diffusion that suggest recent infarcts and microhemorrhages on susceptibility-weighted images have been described as well. Microhemorrhages can be a distinctive finding for vasculopathy, and a T2* or susceptibility-weighted MRI sequence must be performed in every patient who presents with leukodystrophy (56,57).

**Leukoencephalopathy with Axonal Spheroids and Pigmented Glia.**—Besides the presence of small cysts that have similar signal intensity to that of cerebrospinal fluid, calcifications also can be detected in patients with this disease; for this reason, this disease is discussed in the next section (susceptibility signal intensity abnormalities).

**Leukoencephalopathy with Calcifications and Cysts.**—As suggested by the name, cysts that sometimes resemble cerebrospinal fluid signal intensity can be found with all sequences, as can calcifications (also discussed in the next section).

**Susceptibility Signal Intensity Abnormalities (Calcification and/or Microhemorrhage)**

Lesions that appear as susceptibility signal intensity abnormalities, which manifest as hypointensity
Leukoencephalopathy with Axonal Spheroids and Pigmented Glia.—Studies (58–61) have shown that these pathologically defined entities are the result of autosomal dominant mutations in the colony-stimulating factor 1 receptor (CSF1R) gene. Both familial and de novo mutations have been described. Unlike other leukodystrophies, this disease manifests exclusively in adults, with most cases occurring in patients in the 20–50-year age range. The clinical picture consists of behavioral changes, dementia, motor impairment (Parkinsonism, paraparesis or tetraparesis, and ataxia), and epilepsy (62).

MRI features include a frontal pattern of involvement of the white matter, which often is associated with restricted diffusion, in the early phases of the disease (Fig 16). There is confluent involvement of the white matter in the late phases, when some foci of restricted diffusion may persist. Small cysts, thinning of the corpus callosum, and calcifications also may be seen. The calcifications are described as small, symmetric, and mainly located adjacent to the anterior horns of the lateral ventricle and in the parietal subcortical white matter, exhibiting preserved basal ganglia. Thin-section CT may be useful for their detection (63).
Leukoencephalopathy with Calcifications and Cysts.—Leukoencephalopathy with calcifications and cysts is a genetic disorder related to a mutation in the small nucleolar RNA, C/D box 118 (SNORD118) gene, which was identified recently. This disease is considered a microangiopathy, and as can be observed of other vasculopathies, asymmetric involvement of white matter may be a characteristic on MR images (Fig 17) (64–66).

In addition to asymmetric diffuse bilateral leukoencephalopathy, calcifications and cystic changes with mass effect can be seen. The calcifications tend to be large and can be observed anywhere in the brain but mostly in the basal ganglia. Gadolinium contrast enhancement sometimes can be observed (64–66).

CADASIL.—Microhemorrhages are a good marker of a vasculopathy and can be a clue for the diagnosis of genetically inherited vasculopathies such as CADASIL (14).

Nasu-Hakola Disease.—Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy, or Nasu-Hakola disease, is a rare autosomal recessive disorder caused by mutations in the triggering receptor expressed on myeloid cells 2 (TREM2) and TYRO protein tyrosine kinase binding protein (TYROBP) genes. Bone pain and fractures usually arise between the 3rd and 5th decades of life, followed by development of presenile cognitive impairment and death by the 5th decade of life (10).

Bone imaging shows multiple cystic-like lesions leading to fractures in the wrists and ankles. In the brain, MRI shows nonspecific white matter involvement and cortical and corpus callosum atrophy, while calcifications in the basal ganglia can be seen at CT (Fig 18) (9,67,68).

Enhancement
Enhancement is a distinctive characteristic that can be found in a few adult leukodystrophies such as X-ALD (Fig 3), Alexander disease (Fig 9), and leukoencephalopathy with calcifications and cysts (Fig 17).

Abnormal Peaks at MR Spectroscopy
Abnormal peaks at MR spectroscopy can be found in patients with certain leukodystrophies. Although abnormal peaks are relatively non-specific most of the time, they can be a relevant ancillary finding in some clinical scenarios.

Figure 7 shows a patient with Sjögren-Larsson syndrome who has increased lipid peaks in the white matter; the peak at 1.3 ppm is somewhat distinctive in patients with the disease.

Figure 11 shows a patient with a diagnosis of CTX who shows increases in lactate and lipid peaks and a decreased N-acetyl aspartate peak.
in the cerebellum. These are nonspecific findings, but because this disease is related to lipid accumulation in the central nervous system, MR spectroscopy might be used as a potential noninvasive biomarker of treatment response in treatable diseases such as CTX (51). Occasionally, MR spectroscopy can show the presence of lactate peaks in patients with leukoencephalopathy with brainstem and spinal cord involvement, as shown in Figure 10.

**Associated Spinal Cord Involvement**

**Adult-onset Autosomal Dominant Leukodystrophy.**—Adult-onset autosomal dominant leukodystrophy is related to lamin B1 (*LMNB1*) gene duplication. The clinical presentation is characterized by autonomic dysfunction, pyramidal signs, and cerebellar ataxia in the 4th or 5th decade of life (69,70).

Signal intensity abnormalities (increased signal intensity on T2-weighted or FLAIR MR images) are most prominent in the frontoparietal white matter, cerebellar peduncles, corticospinal tracts, and corpus callosum (Fig 19). The changes in the uppermost corticospinal tracts underlying the motor cortex may represent the earliest imaging manifestation of the disease and can be seen in asymptomatic family members. Atrophy of the brainstem and spinal cord also may be observed. The MRI lesion pattern, in combination with the typical clinical symptoms and mode of
inheritance, is quite suggestive of the diagnosis of autosomal dominant leukodystrophy (69).

**Alexander Disease.**—In patients with Alexander disease, involvement of the upper cervical spinal cord occasionally can be appreciated, most often extending from the medulla (41).

**Leukoencephalopathy with Brainstem and Spinal Cord Involvement.**—As indicated by its name, this disease can manifest with signal intensity abnormalities in the spinal cord, which helps in diagnosing this disease (46).

**Conclusion**

Diagnosing adult leukodystrophies remains complex and challenging. Clinicians and radiologists should recognize MRI white matter involvement patterns and distinctive characteristics; in addition, they should work together when facing such a suspicion.

In summary, although not neglecting the complexity of the subject, our approach can be helpful as a starting point to provide an algorithmic analysis of MRI examinations of patients suspected of having adult leukodystrophy in an attempt to reduce the list of differential diagnoses and target specific confirmatory tests.

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**References**


