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Genetic Leukoencephalopathies in Adults

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ABSTRACT

Purpose of Review: More than 100 heritable disorders can present with abnormal white matter on neuroimaging. While acquired disorders remain a more common cause of leukoencephalopathy in the adult than genetic causes, the clinician must remain aware of features that suggest a possible genetic etiology.

Recent Findings: The differential diagnosis of heritable white matter disorders in adults has been revolutionized by next-generation sequencing approaches and the recent identification of the molecular cause of a series of adult-onset disorders.

Summary: The identification of a heritable etiology of white matter disease will often have important prognostic and family counseling implications. It is thus important to be aware of the most common hereditary disorders of the white matter and to know how to distinguish them from acquired disorders and how to approach their diagnosis.

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INTRODUCTION

While acquired demyelinating conditions are more common than genetic etiologies in the adult population, a growing number of heritable leukoencephalopathies have been identified. The clinician caring for patients with multiple sclerosis (MS) and other conditions of the white matter should be aware of these conditions and adept at identifying potential genetic mimickers of white matter disease in the adult population. Next-generation sequencing technologies and their ability to provide rapid and broad-based genetic information have revolutionized this field and provide a broad differential diagnosis in heritable leukoencephalopathies. Thus, this review should be considered a current view of genetic leukoencephalopathies that are potential mimickers of MS and other adult disorders, subject

to revisions as the field advances in the coming years.

Broadly characterized, genetic mimickers of white matter disease in adults may be divided into two groups. The first includes genetic disorders that present with primarily multifocal white matter abnormalities and can closely mimic acquired demyelinating disorders such as MS or ischemic vascular disease (**Table 12-1**¹). These disorders can present at various ages and may ultimately evolve toward confluency, but at initial presentation they are often nondiffuse with isolated multifocal white matter lesions.

The second group of disorders, with some overlap with the first group, includes adult presentations of leukodystrophies (**Table 12-2**). Often, even disorders that present in the pediatric population with diffuse or confluent white matter lesions may

TABLE 12-1 Leukoencephalopathies With Multifocal Onset^a

► **Progressive (May Evolve to Confluency)**

Hereditary diffuse leukoencephalopathy with spheroids
Adult-onset polyglucosan body disease
L2-Hydroxyglutaric aciduria
Leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate
Urea cycle disorders
Hydroxymethylglutaryl coenzyme A lyase deficiency
Histiocytosis
Incontinentia pigmenti
Vasculopathies (eg, CADASIL, CARASIL, Fabry disease)
Multiple sclerosis, neuromyelitis optica (NMO), acute disseminated encephalomyelitis (ADEM), progressive multifocal leukoencephalopathy
Mitochondrial diseases
Subacute sclerosing panencephalitis

► **Static**

18q deletion syndrome
Sjögren-Larsson syndrome
RNASET2-deficient leukoencephalopathy
Congenital Cytomegalovirus

► **Prominent Perivascular Spaces**

Mucopolysaccharidoses
Chromosomal abnormalities or genetic mosaicism
Lowe syndrome
PTEN-associated disorders
Histiocytosis
Disorders of branched chain amino acids

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy.

^a Data from Vanderver A, et al, GeneReviews.¹ www.ncbi.nlm.nih.gov/books/NBK184570/?report=reader.

KEY POINTS

- Clinicians caring for patients with multiple sclerosis and other conditions of the white matter should be aware of, and adept at identifying, potential genetic mimickers of white matter disease (heritable leukoencephalopathies) in the adult population.
- Broadly characterized, genetic mimickers of white matter disease in adults may be divided into two groups. The first includes genetic disorders that present with primarily multifocal white matter abnormalities and can closely mimic acquired demyelinating disorders such as multiple sclerosis or ischemic vascular disease. The second group of disorders, with some overlap with the first group, includes adult presentations of leukodystrophies.
- Adult-onset presentations of typically pediatric leukodystrophies usually do not follow the standard clinical and neuroimaging features usually seen in children and may be paucisymptomatic with limited radiologic abnormalities.

present in older patients with more restricted areas of signal abnormality. In these cases, the likelihood of a heritable disorder may not be considered until disease evolution alerts the

clinician to a degenerative condition. Together, these two groups should be considered as a nonexhaustive list of heritable white matter disease affecting the adult population.

KEY POINT

■ Inherited disorders of the white matter can present as asymmetric multifocal conditions of the white matter in certain specific conditions.

TABLE 12-2 A Nonexhaustive List of Adult-Onset Leukodystrophies and Leukoencephalopathies

► **With Typical Adult Onset**

Hereditary diffuse leukoencephalopathy with spheroids
 Adult-onset polyglucosan body disease
 Dentatorubral-pallidoluysian atrophy
 Autosomal dominant leukodystrophy
 Cerebrotendinous xanthomatosis
 Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
 Fabry disease
SPG11-related hereditary spastic paraplegia

► **With Special Presentations in the Adult Population**

Metachromatic leukodystrophy
 Globoid cell leukodystrophy (Krabbe disease)
 G_{M1}/G_{M2} gangliosidosis
 Alexander disease
 X-linked adrenoleukodystrophy/adrenomyeloneuropathy
 L2-Hydroxyglutaric aciduria
 Leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate and other tRNA synthase disorders
 Hypomyelinating conditions, including Pelizaeus-Merzbacher disease; hypomyelination, hypogonadotropic hypogonadism, and hypodontia syndrome; and hypomyelination with atrophy of the basal ganglia and cerebellum
 Peroxisomal biogenesis disorders
 Kearns-Sayre syndrome and other mitochondrial disorders
 Vanishing white matter disease

tRNA = transfer ribonucleic acid.

HERITABLE DISORDERS WITH MULTIFOCAL PRESENTATIONS

A number of heritable disorders that can have multifocal white matter abnormalities have such distinct clinical presentations, typically affecting the very young, that it makes them unlikely to be mistaken for more common disorders such as MS or ischemic vascular disease. Other heritable disorders that include multifocal white matter signal

abnormalities have milder systemic presentations more likely to be mistaken for acquired disorders. In most of these conditions, white matter changes will ultimately evolve to become confluent, but early in the disease course they may be strikingly multifocal in appearance.

L2-Hydroxyglutaric Aciduria

Clinical. L2-Hydroxyglutaric aciduria is an inborn error of small molecule

metabolism. Patients may initially appear normal or may have a static encephalopathy. Over time, cerebellar ataxia and progressive intellectual decline become apparent. Patients may also have hearing loss. In some cases, these features only become apparent in young adulthood.

Neuroimaging. MRI in L2-hydroxyglutaric aciduria demonstrates predominant subcortical white matter involvement, initially focal and evolving to be confluent. Periventricular tissue remains spared. Increased signal is seen in the globus pallidus and less significantly in the caudate and putamen. Signal change may also be seen in the dentate nucleus.²

Diagnosis. Urine organic acids demonstrating increased L2-hydroxyglutaric acid are diagnostic. L2-Hydroxyglutaric acid is increased in urine, plasma, and CSF. Plasma amino acids may demonstrate increased lysine.

Mechanism/genetics. L2-Hydroxyglutaric aciduria is caused by a deficiency of L2-hydroxyglutarate dehydrogenase, encoded by *L2HGDH*. It is inherited in an autosomal recessive manner.

Leukoencephalopathy With Brainstem and Spinal Cord Involvement and Elevated White Matter Lactate

Clinical. Leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate presents in childhood or adolescence with motor deterioration and a progressive spastic ataxia, cognitive decline, and sensory neuropathy. Mild elevations of serum or CSF lactate are known to occur on occasion.

Neuroimaging. On MRI, cerebral white matter is involved in a patchy inhomogeneous fashion. Selective involvement of the pyramidal tracts

through their entire length including the spinal cord, sensory tracts through their entire trajectory including the medial lemniscus, the superior and inferior cerebellar peduncles, and the intraparenchymal trajectory of the trigeminal nerve, among others, may be seen (**Figure 12-1**). Cerebellar white matter is often involved. Magnetic resonance spectroscopy (MRS) demonstrates elevated lactate in the affected white matter.³

Diagnosis. The diagnosis of leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate is made based on the typical MRI features and sequencing of the causative gene.

Mechanism/genetics. Leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate is caused by mutations in *DARS2*, encoding mitochondrial aspartyl tRNA synthase.⁴ It is inherited in an autosomal recessive manner.

Hypomyelinating Leukodystrophy With Brainstem and Spinal Cord Involvement and Leg Spasticity

Clinical. Hypomyelinating leukodystrophy with brainstem and spinal cord involvement and leg spasticity is clinically and radiologically similar to leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate. Patients can present in infancy with a disorder with neurologic regression, often disproportionately affecting the lower extremities with spasticity and ataxia. Cognition may be spared, or children may be encephalopathic. Over time, a loss of reflexes without nerve conduction abnormalities may develop. Patients may also present in adolescence with a picture more reminiscent of spastic paraplegia, but often with episodic decline. These episodes of functional decline have led to confusion

KEY POINTS

- L2-Hydroxyglutaric aciduria is an inborn error of small molecule metabolism. Patients may initially appear normal or may have a static encephalopathy. Over time, cerebellar ataxia and progressive intellectual decline become apparent.
- Certain features, such as basal ganglia or dentate nucleus involvement in patients with otherwise multifocal leukoencephalopathies, should alert the clinician to the possibility of an underlying genetic diagnosis.
- Leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate presents in childhood or adolescence with motor deterioration and a progressive spastic ataxia, cognitive decline, and sensory neuropathy.

KEY POINTS

- Hypomyelinating leukodystrophy with brainstem and spinal cord involvement and leg spasticity is clinically and radiologically similar to leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate. Patients can present in infancy with a disorder with neurologic regression, often disproportionately affecting the lower extremities with spasticity and ataxia.
- Certain leukodystrophies, in particular hypomyelinating leukodystrophy with brainstem and spinal cord involvement and leg spasticity, can appear to respond to treatment with IV steroids similar to acquired inflammatory brain disorders. An atypical MRI feature, such as whole cord T2 signal changes or tract involvement along the entire length in the brain and brainstem, should alert the clinician to the possibility of an underlying genetic condition.

FIGURE 12-1 Leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate. T2-weighted images show longitudinally extensive whole cord involvement on sagittal views of the spine (A, C, *thin arrows*) as well as anterior and posterior tract involvement in the brainstem and cervical cord (B, D, *thick arrows*) on axial views.

with MS, and patients have been treated with IV steroids, often with partial recovery.⁵

Neuroimaging. In the adolescent-onset variant, MRI shows cerebral white matter involvement in a patchy inhomogeneous fashion. Selective involvement of the pyramidal, sensory, and brainstem tracts is seen, much as in leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate. In the early-onset variant, patients may have a diffuse leukoencephalopathy involving the entirety of the supratentorial white matter.

Diagnosis. The diagnosis of hypomyelinating leukodystrophy with

brainstem and spinal cord involvement and leg spasticity is made based on the typical MRI features and sequencing of the causative gene.

Mechanism/genetics. Hypomyelinating leukodystrophy with brainstem and spinal cord involvement and leg spasticity is caused by mutations in *DARS*, encoding a cytoplasmic aspartyl tRNA synthase.⁶ Similarities with leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate, caused by mutations in the same tRNA synthetase but for the mitochondrial compartment *DARS2*, offer intriguing insight into possible pathogenesis. It is inherited in an autosomal recessive manner.

AARS2-Related Leukoencephalopathy

Clinical. Patients with AARS2-related leukoencephalopathy present with a progressive spastic diplegia, dystonia, and ataxia. Significant dysarthria and bulbar dysfunction often restrict communication and make feeding more difficult over time. Over time, patients develop a progressive encephalopathy.

Neuroimaging. On MRI, cerebral white matter is involved in a patchy inhomogeneous fashion predominating in the frontal and parietal regions. Selective involvement of the corpus callosum and longitudinal involvement of the frontopontine, pyramidal, or parieto-occipitopontine tracts may be seen. Diffusion-weighted images often show multiple small areas of restricted diffusion in the cerebral white matter and corpus callosum. Variable cerebellar atrophy can be seen.⁷

Diagnosis. The diagnosis of AARS2-related leukoencephalopathy is made based on the typical MRI features and sequencing of the causative gene.

Mechanism/genetics. AARS2-related leukoencephalopathy is caused by mutations in AARS2, encoding a mitochondrial alanyl-tRNA synthase.⁷ It is inherited in an autosomal recessive manner.

Trends: Leukoencephalopathies Caused by tRNA Synthase Defects

It is important to note that leukoencephalopathy with brainstem and spinal cord involvement and elevated white matter lactate, hypomyelinating leukodystrophy with brainstem and spinal cord involvement and leg spasticity, and AARS2-related leukoencephalopathy are part of a growing group of disorders caused by defects in tRNase synthases. These currently include the genes *MARS*, *AARS*, and *EARS2* in addition to *DARS2*. Each is

responsible for loading its cognate amino acid. Given the rapid accumulation of these disorders in the leukoencephalopathy family, it is reasonable to expect that more disorders in this family are likely to be included. The reason for the large number of neurologic disorders, and specifically leukoencephalopathy disorders, caused by mutations in these genes remains unknown. It should also be noted that improvement with steroids has been noted in hypomyelinating leukodystrophy with brainstem and spinal cord involvement and leg spasticity and is being explored in other tRNA synthase defects.

Hereditary Diffuse Leukoencephalopathy With Spheroids

Pathologic and now genetic data suggest that hereditary diffuse leukoencephalopathy with spheroids is the same as a disorder with another name, orthochromatic leukodystrophy.⁸

Clinical. Initial manifestations of this disorder are neurobehavioral and evolve to include spasticity and extrapyramidal features, although progressive dementia often overshadows other neurologic features, as demonstrated in **Case 12-1**.⁹

Neuroimaging. White matter signal abnormalities on MRI are most prominent at the precentral and postcentral gyri or in the frontal white matter. Abnormalities may be patchy and asymmetric. Atrophy of the frontal lobe may be seen. Abnormalities may extend into the posterior limb of the internal capsule and the pyramidal tracts of the brainstem (**Figure 12-2**).^{9,10}

Diagnosis. In the past, the diagnosis of hereditary diffuse leukoencephalopathy with spheroids was often made in familial cases in which an affected patient had undergone brain biopsy documenting excessive

KEY POINTS

- Patients with AARS2-related leukoencephalopathy present with a progressive spastic diplegia, dystonia, and ataxia.
- Persistent areas of restricted diffusion in an individual in whom a genetic leukoencephalopathy is suspected should raise concern for a toxic-metabolic defect, including mitochondrial cytopathies and tRNase synthetase defects.
- Hereditary diffuse leukoencephalopathy with spheroids can present as a frontotemporal dementia syndrome, and patients with this type of neuropsychiatric presentation in the context of compelling white matter changes should be tested for this condition.

Case 12-1

A 44-year-old woman presented with a several-year history of cognitive changes. Approximately 5 years before presentation, the patient and family began noting social withdrawal and disengagement even from the parenting of her then-teenaged daughters. This was initially attributed to depression and resulted in the patient losing her position as a nurse. In the subsequent years, she developed a progressive gait apraxia as well as spasticity and had progressive cognitive difficulties, with reported changes in short-term memory and sequencing of tasks, disorientation in time, and significant abulia. More recently, she had progressive motor difficulties, with a slow shuffling gait evolving to complete inability to initiate movement, despite apparently normal strength.

Her general examination was unremarkable. On mental status, she had slow responses and no spontaneous initiation of conversation. She was unable to perform simple calculations and serial 7's. She had abnormal glabellar response and a snouting response. She had slow saccades to pursuit, but cranial nerves were otherwise normal to examination. She had motor impersistence for all tasks. She was unable to correctly perform rapid alternating movements and simple motor sequences. When she was helped to a standing position, she was unable to initiate walking, although when supine, full movements were demonstrated. Sensory and cerebellar testing were normal.

Extensive biochemical testing was normal. MRI demonstrated multifocal but fairly symmetric white matter signal abnormalities with increased signal on T2 and decreased signal on T1 involving the periventricular and deep white matter fibers with sparing of the subcortical fibers. White matter abnormalities had a clear frontal predominance, particularly in the involvement of the corpus callosum with significant atrophy of the frontal lobes. Nonspecific abnormalities were reported on an outside brain biopsy, but when results were reviewed again, clear axonal spheroids were seen.

Comment. Based on the clinical features with a predominance of frontal lobe symptoms (psychiatric manifestations, severe motor apraxia, frontal release signs on neurologic examination), biopsy findings, and MRI evidence of a multifocal leukodystrophy with involvement of the pyramidal tracts, testing of the *CSF1R* gene was recommended. A pathogenic heterozygous change was identified, confirming a diagnosis of hereditary diffuse leukoencephalopathy with spheroids.

axonal spheroids in appropriate clinical conditions, although these are not a unique feature of this disorder. Recently, hereditary diffuse leukoencephalopathy with spheroids families have been shown to harbor mutations affecting the tyrosine kinase domain of the colony stimulating factor 1 receptor (encoded by *CSF1R*).¹¹ The diagnosis is now made based on identification of mutations in *CSF1R* in the appropriate clinical circumstances.

Mechanism/genetics. Hereditary diffuse leukoencephalopathy with spheroids is caused by mutations in *CSF1R*.¹¹ The mechanism of this disorder is unknown, although mutations in a myeloid lineage gene suggest the possibility that central nervous system microglia are important in this condition. The disorder is inherited in an autosomal dominant fashion. Because no treatment for this condition exists at this time, descendants of patients

FIGURE 12-2 Hereditary diffuse leukoencephalopathy with spheroids. Fluid-attenuated inversion recovery (FLAIR) (A, B) and T2-weighted images (C, D) show asymmetric white matter abnormalities and frontal predominance as well as frontal atrophy. The right frontal regions show evidence of the surgical biopsy (D, arrow) that helped establish the diagnosis in this patient.

KEY POINT

■ A patient presenting with a strong neuropsychiatric prodrome prior to the development of obvious motor impairment should lead the clinician to suspect hereditary diffuse leukoencephalopathy with spheroids or lysosomal leukoencephalopathies, such as G_{M1} gangliosidosis, G_{M2} gangliosidosis, globoid cell leukodystrophy, or metachromatic leukodystrophy.

with hereditary diffuse leukoencephalopathy with spheroids need to be carefully counseled regarding the impact of a diagnosis prior to testing.

Adult-Onset Polyglucosan Body Disease

Clinical. Adult-onset polyglucosan body disease is a disorder typically

presenting in the fifth to seventh decades of life. Patients present with gait difficulties with both lower and upper motor neuron involvement and peripheral neuropathy, with sensory deficits predominantly in the lower extremities, neurogenic bladder, and dementia. The combination of upper and lower motor neuron signs can

KEY POINT

■ Adult-onset polyglucosan body disease is a disorder typically presenting in the fifth to seventh decades of life. Patients present with gait difficulties with both lower and upper motor neuron involvement and peripheral neuropathy, with sensory deficits predominantly in the lower extremities, neurogenic bladder, and dementia. The combination of upper and lower motor neuron signs with leukoencephalopathy should lead the clinician to suspect adult-onset polyglucosan body disease.

sometimes be mistaken for amyotrophic lateral sclerosis. CSF protein may be elevated, and electrophysiologic studies are abnormal. A skin or nerve biopsy can help identify polyglucosan bodies, although genetic testing is now the mainstay of diagnosis.

Neuroimaging. White matter abnormalities in polyglucosan body dis-

ease tend to be most evident in the periventricular white matter. They are often multifocal and poorly defined initially and progress to confluency. Significant abnormalities are often seen in the brainstem and cerebellar white matter (**Figure 12-3**).¹²

Diagnosis. Diagnosis is typically made by molecular screening of

FIGURE 12-3 Adult-onset polyglucosan body disease. A, The relatively hypointense normal body of the pons within the affected brainstem on sagittal fluid-attenuated inversion recovery (FLAIR) images is a classic feature of the disease. B, C, D, Confluent white matter disease is seen in this advanced case with significant brainstem and cerebellar signal abnormalities on axial T2-weighted images.

GBE1, the gene encoding the glucan branching enzyme.^{13,14} Abnormalities of glucan branching enzyme activity are not constant, so this measurement is not an ideal test for the condition.

Mechanism/genetics. Deficiency of glucan branching enzyme also causes glycogen storage disease type IV. These patients have no glucan branching enzyme activity. Patients with adult-onset polyglucosan body disease may have normal or decreased glucan branching enzyme activity, and it is unclear what leads to the formation of the typical abnormality, accumulation of polyglucosan bodies. Adult-onset polyglucosan body disease is inherited in an autosomal recessive manner.

Dentatorubral-Pallidoluysian Atrophy

Clinical. Patients may present with dentatorubral-pallidoluysian atrophy (DRPLA) from the first to the sixth decades, but most patients present in adulthood. Patients present with heterogeneous features, including myoclonic epilepsy, choreoathetosis, cerebellar ataxia, and cognitive/behavioral decline. In adult-onset cases, ataxia, choreoathetosis, and dementia are the most prominent features.¹⁵

Neuroimaging. MRI features include atrophy of the tegmentum of the midbrain, pons, dentate nucleus, superior cerebellar peduncles, and cerebellum. T2 signal increase of the globus pallidus and thalamus is present. White matter changes may be initially patchy and periventricular and evolve to confluency.

Diagnosis. Diagnosis is suggested by typical MRI manifestations and clinical history and confirmed by genetic testing that can detect trinucleotide expansions. Exome testing, which does not detect trinucleotide repeat disorders, will not detect DRPLA. DRPLA is the only genetic leuko-

encephalopathy caused by a trinucleotide repeat disorder.

Mechanism/genetics. DRPLA is an autosomal dominant disorder caused by expansion of a CAG repeat in the *ATN1* (*DRPLA*) gene.¹⁶ The CAG repeat ranges from 48 to 93 in affected persons. Some cases are sporadic, but in familial cases, anticipation may occur. Transmission is autosomal dominant.

Autosomal Dominant Leukodystrophy

Clinical. Autosomal dominant leukodystrophy is an adult-onset leukodystrophy with early autonomic involvement, such as urgency in urination, impotence, constipation, anhidrosis, and postural hypotension, and progressive gait disturbance associated with spasticity and ataxia.¹⁷

Case 12-2 provides an example of a typical clinical course.

Neuroimaging. Notable radiologic features include confluent white matter changes in supratentorial regions, predominantly affecting the deep white matter, with relative sparing of the periventricular white matter and the subcortical fibers. In some cases, predominance in the perirolandic regions and pyramidal tracts is seen at onset, evolving over time into diffuse white matter abnormalities. The corpus callosum is relatively spared but can show posterior abnormalities. The posterior limb of the internal capsule is often involved. Abnormal signal is seen in brainstem tracts, and the upper and middle cerebellar peduncles are often involved (**Figure 12-4**).^{18,19}

Diagnosis. The diagnosis of autosomal dominant leukodystrophy is suggested by typical MRI features, family history, and clinical characteristics and is confirmed by mutation testing.

Mechanism/genetics. Autosomal dominant leukodystrophy is caused by duplications in the gene encoding

KEY POINTS

- Adult-onset polyglucosan body disease is allelic with a childhood-onset condition, glycogen storage disease type IV, with very different symptom manifestations, demonstrating the phenotypic spectrum of disorders affecting the white matter of the brain.
- Patients may present with dentatorubral-pallidoluysian atrophy from the first to the sixth decades, but most patients present in adulthood. In adult-onset cases, ataxia, choreoathetosis, and dementia are the most prominent features.
- Exome testing, which does not detect trinucleotide repeat disorders, will not detect dentatorubral-pallidoluysian atrophy. Dentatorubral-pallidoluysian atrophy is the only genetic leukoencephalopathy caused by a trinucleotide repeat disorder.
- Autosomal dominant leukodystrophy is an adult-onset leukodystrophy with early autonomic involvement, such as urgency in urination, impotence, constipation, anhidrosis, and postural hypotension, and progressive gait disturbance associated with spasticity and ataxia.

Case 12-2

A 50-year-old man presented with a 10-year history of progressive neurologic deterioration. His first symptoms were nocturnal enuresis followed by erectile dysfunction. Progression of symptoms included gradual worsening of urinary symptoms, with diurnal incontinence and recurrent urinary tract infections, constipation, impotence, and, later, a progressive spastic diplegia. These symptoms and the lack of a spinal cord lesion on neuroimaging led to imaging of the brain, which documented a leukoencephalopathy. The patient was initially clinically suspected to have multiple sclerosis, but he was later reevaluated and established to have a leukodystrophy of unknown cause. He became wheelchair dependent approximately 1 year before presentation and in recent months became unable to transition himself from bed to wheelchair. Autonomic symptoms, including cold and burning extremities, orthostatic symptoms, urinary and bowel dysfunction and impotence, continued to evolve. He had no relevant family history, but his parents both died in their fifties of non-neurologic causes.

On examination, he was orthostatic (blood pressure sitting 110/70, standing 90/40). His affect was mildly labile, but mental status examination was otherwise normal. He had mildly reduced muscle bulk distally in both lower extremities, but his general examination was otherwise unremarkable. His cranial nerve examination was notable for mild dysarthria. Tone was remarkable for increased tone and decreased strength in the lower greater than upper extremities. Deep tendon reflexes were brisk

FIGURE 12-4 Autosomal dominant adult-onset leukodystrophy. T2-weighted MRI images demonstrate classic brainstem and middle cerebellar peduncle signal abnormalities accompanying diffuse central white matter signal abnormalities at a late stage. Images from three unrelated individuals demonstrate the stereotypical brainstem (A) and supratentorial (B) signal abnormalities, such as seen in the patient in **Case 12-2**.

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throughout. He had decreased recognition on sensory testing of sharp versus dull sensation, decreased temperature sensation, and subjective burning of his feet in a stocking distribution and an area over the left thigh. He had ataxia while sitting and was unable to stand. He also had mild dysmetria on finger-to-nose testing and was unable to perform heel to shin.

Extensive biochemical testing was unrevealing. MRI of the brain demonstrated confluent white matter changes in the supratentorial regions. Individual brainstem tracts had abnormal signal. The middle cerebellar peduncles were also involved (**Figure 12-4**).

Comment. Based on the clinical features of an individual with initial symptoms of autonomic dysfunction and progressive spastic tetraparesis with neuroimaging remarkable for a leukoencephalopathy with confluent white matter abnormalities and prominent brainstem and middle cerebellar peduncle involvement, *LMNB1* duplication testing was performed and confirmed a diagnosis of autosomal dominant leukodystrophy.

lamin B1 (*LMNB1*).²⁰ The mechanism of disease remains poorly understood. Lamin B1 is overexpressed in autosomal dominant leukodystrophy. This protein is an intermediate filament expressed in the nuclear lamina within the nuclear envelope. Believed to be involved in either altered nuclear envelope stability or in transcriptional regulating, lamin B1 duplications have a yet unknown mechanism that disrupts myelin homeostasis. Available histopathologic reports suggest loss of myelin in the cerebrum and cerebellum, preserved oligodendrocytes, and mild astrogliosis. No evidence of inflammation is seen. Inheritance is autosomal dominant. Apparent de novo cases are reported in addition to cases of autosomal inheritance. Because no treatment for this condition exists at this time, descendants of individuals with autosomal dominant leukodystrophy should be carefully counseled regarding the impact of a diagnosis prior to testing.

Cerebrotendinous Xanthomatosis

Clinical. Cerebrotendinous xanthomatosis is an inborn error of metabolism. Patients often have a history of prolonged cholestatic jaundice in infancy as well as unexplained chronic diarrhea. In late childhood or early adolescence, patients may begin to manifest more specific features of the disease,

but these may come to medical attention only in adulthood. Patients develop cataracts and xanthomas of the tendons, as well as neurologic dysfunction, most often including spastic paresis, cerebellar ataxia, posterior column dysfunction, peripheral neuropathy, seizures, and progressive dementia. Premature atherosclerosis and coronary artery disease have been reported.

Neuroimaging. The hallmark and earliest MRI features of cerebrotendinous xanthomatosis are involvement of the cerebellar white matter. T2 hyperintensity of the dentate nucleus and cerebellar white matter are seen, along with cerebellar atrophy. Occasionally, T2 hypointensity can be seen in the dentate. If this is present along with cerebellar white matter hyperintensity, it is highly suggestive of cerebrotendinous xanthomatosis. Brainstem lesions may involve the corticospinal tracts and the medial lemniscus. Ill-defined symmetric but sometime patchy periventricular T2 hyperintensity may be seen in the supratentorial white matter.²¹

Diagnosis. Measurement of serum cholestanol, the 5 alpha-dihydro derivative of cholesterol, can be performed, and elevations are diagnostic of the disorder in addition to normal to low plasma cholesterol concentrations,

KEY POINTS

- Significant symmetric involvement of the middle cerebellar peduncles in an adult-onset leukodystrophy should raise concern for autosomal dominant leukodystrophy.
- Cerebrotendinous xanthomatosis is an inborn error of metabolism. In late childhood or early adolescence, patients may begin to manifest more specific features of the disease, but these may come to medical attention only in adulthood.

KEY POINTS

- Patients with cerebrotendinous xanthomatosis develop cataracts and xanthomas of the tendons, as well as neurologic dysfunction, most often including spastic paresis, cerebellar ataxia, posterior column dysfunction, peripheral neuropathy, seizures, and progressive dementia. Carefully soliciting the history of cataracts in patients, which may have been diagnosed and treated decades earlier, may be a clue to the diagnosis of cerebrotendinous xanthomatosis.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is characterized by a history of migraines, middle adult-onset cerebrovascular disease, progressive dementia, diffuse white matter lesions, and subcortical infarcts.
- Involvement of the extreme capsule and multifocal white matter changes perpendicular to the gray-white matter junction should raise concern for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

decreased chenodeoxycholic acid, and increased concentration of bile acids.

Mechanism/genetics. Cerebrotendinous xanthomatosis is characterized as a lipid storage disease caused by deficiency of the mitochondrial enzyme 27-hydroxylase, which catalyzes one of the first steps in the metabolism of sterols. The sterol 27-hydroxylase gene (*CYP27A1*) can be sequenced for mutations or deletions for confirmation of the diagnosis. Recognition of this disorder is important because long-term treatment with chenodeoxycholic acid improves neurologic outcome.

Trends. Because evidence exists that early long-term treatment with chenodeoxycholic acid improves outcome, this disorder should be actively sought so that a potentially treatable condition is not missed. In particular, history of previous cataract removal should be sought. Cerebrotendinous xanthomatosis should not be discounted because of absence of the typical xanthomas of the tendons and ocular manifestations. Some experts maintain that cholestanol should be measured in all patients with unexplained cataracts and neurologic decline with white matter changes.

Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy

Clinical. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is characterized by a history of migraines, middle adult-onset cerebrovascular disease, progressive dementia, diffuse white matter lesions, and subcortical infarcts. Skin biopsies demonstrate electron-dense granules in the media of arterioles on electron microscopy.

Neuroimaging. MRI in CADASIL may show extensive abnormalities in the white matter without large cortical infarcts. Subcortical lacunar lesions, characteristically aligned at the junction of the gray and white matter, are typically seen. Cerebral microbleeds are most commonly seen in the thalamus. Symmetric involvement of the centrum semiovale, external capsules, temporal lobes, and basal ganglia are seen.²²

Diagnosis. The diagnosis of CADASIL previously required a skin biopsy documenting electron-dense granules. Currently, molecular testing is the mainstay of diagnosis.

Mechanism/genetics. More than 90% of individuals have mutations in *NOTCH3*,²³ and molecular genetic testing is available. CADASIL is inherited in an autosomal dominant manner. Because no treatment exists at this time for this condition, descendants of individuals with CADASIL need to be carefully counseled regarding the impact of a diagnosis prior to testing.

Fabry Disease

Clinical. Although Fabry disease has systemic symptoms, often with onset in childhood, the white matter abnormalities are typically seen in later decades. This X-linked disorder typically presents in affected males with symptoms including angiokeratomas, chronic acral paresthesia, recurrent gastrointestinal symptoms, hypohidrosis, cardiovascular disease, and renal failure. Heterozygous females may have some of the above features.

Neuroimaging. CT and MRI may suggest calcification of the pulvinar, globus pallidus, cerebellar-corticomedullary junction, and cerebral subcortical-cortical junction. MRI demonstrates progressive lacunar infarctions that, with time, can progress to confluency.¹²

Diagnosis. Diagnosis is made based on deficient activity of α -galactosidase A and molecular analysis of *GLA*.

Mechanism/genetics. Deficient activity of α -galactosidase results in progressive lysosomal deposition of globotriaosylceramide. The disorder is transmitted in an X-linked fashion.

3-Hydroxy-3-Methylglutaryl Coenzyme A Lyase Deficiency

Clinical. Patients with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) lyase deficiency have metabolic acidosis without ketonuria, hypoglycemia, and a characteristic pattern of elevated urinary organic acid metabolites. Features of presentation can also include hepatomegaly, seizures, or acute encephalopathy/coma. There have been reported cases in which this diagnosis has been unrecognized into adulthood,²⁴ although the advent of universal newborn screening for organic acidemias should greatly decrease this possibility in coming years.

Neuroimaging. Axial T2-weighted MRI shows multifocal increased signal intensity in periventricular and subcortical areas of the white matter. In certain cases, treatment with a leucine-restricted diet has normalized the abnormalities on neuroimaging.²⁵

Diagnosis. Diagnosis can be made by the detection of 3-hydroxy-3-methylglutaric acid, 3-methylglutaconate, 3-hydroxyisovalerate, and 3-methylglutarate in urine organic acid analysis.

Mechanism/genetics. Hydroxymethylglutaryl-CoA lyase is deficient, and molecular analysis of *HMGCL* can confirm the diagnosis.

HERITABLE DISORDERS WITH ENLARGED PERIVASCULAR SPACES

An important cause of multifocal white matter abnormalities is the

presence of enlarged perivascular spaces, with surrounding white matter signal changes. This group of disorders has very similar imaging features overall, with numerous different etiologies. The mucopolysaccharidoses are the most striking example of this abnormality, and other systemic manifestations often result in an appropriate diagnosis. However, other disorders may be more subtle in presentation. Patients with almost any chromosomal abnormality, including fairly common sex chromosome aneuploidy (eg, XXY) may have enlarged perivascular spaces and multifocal white matter abnormalities. Additionally, disorders with cognitive impairment and developmental abnormalities, such as Lowe syndrome, Coffin-Lowry syndrome, and *PTEN*-associated hamartoma syndrome, can all be associated with enlarged perivascular spaces (**Figure 12-5**).

HERITABLE LEUKOENCEPHALOPATHIES WITH SPECIAL PRESENTATIONS IN THE ADULT POPULATION

A number of leukodystrophies typically associated with onset in the pediatric age group can present in older adolescents or throughout the adult decades. They may have typical phenotypic presentations or may present with symptom complexes very different from their pediatric counterparts. In many cases, they present at disease onset with less confluent white matter changes than in pediatric cases and should be considered, in select cases, as part of the differential diagnosis of MS and other presentations of abnormal white matter in adults.

Metachromatic Leukodystrophy

Clinical. Metachromatic leukodystrophy can be seen in any age group, although it classically presents in the infantile period. Late juvenile- and

KEY POINTS

- Fabry disease is one of only three X-linked leukoencephalopathies presenting in adulthood, in addition to X-linked adrenoleukodystrophy and Pelizaeus-Merzbacher disease. It typically presents in affected males with symptoms including angiokeratomas, chronic acral paresthesia, recurrent gastrointestinal symptoms, hypohidrosis, cardiovascular disease, and renal failure.
- Patients with 3-hydroxy-3-methylglutaryl coenzyme A lyase deficiency have metabolic acidosis without ketonuria, hypoglycemia, and a characteristic pattern of elevated urinary organic acid metabolites. Features of presentation can also include hepatomegaly, seizures, or acute encephalopathy/coma.
- Adults and adolescents with 3-hydroxy-3-methylglutaryl coenzyme A deficiency may not have benefited from the expanded newborn screening protocols now in place, and urine organic acids should be ordered if this diagnosis is considered.

KEY POINTS

- A number of leukodystrophies typically associated with onset in the pediatric age group can present in older adolescents or throughout the adult decades. They may have typical phenotypic presentations or may present with symptom complexes very different from their pediatric counterparts. In many cases, they present at disease onset with less confluent white matter changes than in pediatric cases and should be considered, in select cases, as part of the differential diagnosis of multiple sclerosis and other presentations of abnormal white matter in adults.
- In contrast to early-onset cases of metachromatic leukodystrophy, in which motor features predominate early on, later-onset cases demonstrate significant behavioral and cognitive deficits at symptom onset. Over time, spasticity, seizures, movement disorders, cerebellar ataxia, and peripheral neuropathy may develop.

FIGURE 12-5 Enlarged perivascular spaces in a patient with Lowe syndrome. The areas with decreased T1 signal (A) and increased T2 signal (B) have small nonenhancing cystic regions that are isointense with the CSF, corresponding to increased perivascular spaces.

adult-onset cases exist. In contrast to early-onset cases, in which motor features predominate early on, later-onset cases demonstrate significant behavioral and cognitive deficits at symptom onset. Over time, spasticity, seizures, movement disorders, cerebellar ataxia, and peripheral neuropathy may develop. Absence of peripheral reflexes is a suggestive finding. Increased CSF protein, commonly seen in early-onset cases, is an inconsistent finding in later-onset metachromatic leukodystrophy.

Neuroimaging. MRI of the brain in infantile metachromatic leukodystrophy is characterized by diffuse white matter abnormalities with an appearance of radiating stripes (tigroid pattern), sparing of subcortical white matter, and involvement of the corpus callosum and pyramidal tracts in the brainstem.²⁶ Isolated involvement of cranial nerves, radicular nerves, and cauda equina is increasingly recognized as an initial presentation in some patients.²⁷ Juvenile- and adult-onset metachromatic leukodystrophy

are notable for frontal predominance of white matter abnormalities, an absence of characteristic radiating stripes, and the presence of pyramidal tract involvement. This is similar to that seen in globoid cell leukodystrophy (Figure 12-6). Significant atrophy may be present.

Diagnosis. The diagnosis of metachromatic leukodystrophy is based on demonstration of decreased arylsulfatase A levels in blood leukocytes²⁸ and increased urinary sulfatides. Care should be taken to include urinary sulfatides in diagnosis as arylsulfatase A level activity that is 5% to 20% of controls can be seen in normal individuals and is classified as pseudo-deficiency. Molecular genetic testing of the *ARSA* gene may be performed.

Mechanism/genetics. Mutations in the *ARSA* gene cause loss of arylsulfatase A activity. This, in turn, results in accumulation of sulfatated lipids that are a constitutive part of the myelin sheath and is presumed to result in the degradation of myelin in patients with metachromatic leukodystrophy. The

FIGURE 12-6 Globoid cell leukodystrophy (Krabbe disease). *A*, Axial T2-weighted MRI of infantile-onset globoid cell leukodystrophy with diffuse white matter involvement sparing the subcortical fibers, atrophy, and dentate signal abnormality. *B*, Axial T2-weighted MRI of adult-onset globoid cell leukodystrophy demonstrating selective parietal involvement.

disorder is inherited in an autosomal recessive pattern.

Globoid Cell Leukodystrophy

Clinical. Globoid cell leukodystrophy, or Krabbe disease, can be seen in any age group, but the early-infantile presentation is most common. In later-onset cases, the presentation may be very variable. Initial signs may include spastic paraparesis, visual impairment, cerebellar ataxia, seizures, behavioral or cognitive decline, and peripheral neuropathy. In contrast to metachromatic leukodystrophy, motor or visual dysfunction is more often the initial manifestation.¹² The rate of disease

deterioration may be variable but is relentlessly progressive. Increased CSF protein, a hallmark of early-infantile cases, is an inconsistent finding in later-onset cases.

Neuroimaging. Later-onset globoid cell leukodystrophy may manifest as hyperdensity of the basal ganglia and thalamus on CT as seen in early-onset cases. Juvenile- and adult-onset globoid cell leukodystrophy may be characterized by predominant involvement on MRI of the parietooccipital regions or even selective involvement of corticospinal tracts (Figure 12-6).²⁹ Pyramidal tract involvement may extend from the motor cortex through

KEY POINT

- Pseudodeficiency of arylsulfatase is not causative of disease and should not be confused with a diagnosis of metachromatic leukodystrophy.

KEY POINTS

- Globoid cell leukodystrophy, or Krabbe disease, can be seen in any age group. In later-onset cases, the presentation may be very variable. Initial signs may include spastic paraparesis, visual impairment, cerebellar ataxia, seizures, behavioral or cognitive decline, and peripheral neuropathy.
- In adult-onset cases of G_{M1} gangliosidosis, gait disturbance and speech impairment are often the first clinical signs. In adult-onset cases of G_{M2} gangliosidosis, symptoms may be highly variable and include ataxia, spasticity, weakness, muscle atrophy, fasciculations, dystonia, and psychosis.
- Alexander disease can be seen in any age group, and a growing number of publications have documented adult-onset cases. Adult-onset Alexander disease tends to manifest with predominantly bulbar and autonomic disturbances, as well as more typical long-tract signs.

the posterior limb of the internal capsule and into the brainstem. Involvement of the splenium of the corpus callosum may be seen.

Diagnosis. The diagnosis of globoid cell leukodystrophy is made by demonstrating decreased activity of galactocerebroside β -galactosidase (galactocerebrosidase or *GALC*) in leukocyte lysosomal assays. Molecular genetic testing can also be performed of the *GALC* gene.

Mechanism/Genetics. Globoid cell leukodystrophy is caused by mutations in *GALC*. In late-onset globoid cell leukodystrophy, a mutation c.809G>A is often seen.^{30,31} Psychosine, which accumulates as a result of deficiency of galactocerebrosidase, is hypothesized to be toxic to oligodendrocytes, but the exact mechanism of toxicity to the oligodendrocytes, and in particular the role played by the multinucleated cells typical of this disorder (globoid), remains unclear. The disorder is inherited in an autosomal recessive fashion.

Lysosomal Disorders With White Matter Abnormalities

Trends. Because of their slow onset of disease manifestations, juvenile- or adult-onset cases of these disorders may be partially responsive to disease management approaches such as bone marrow transplantation. Thus, these disorders should be actively sought so that a potentially treatable or modifiable disease condition is not missed. Additionally, the advent of newborn screening for metachromatic leukodystrophy and globoid cell leukodystrophy in many states will identify some patients with uncertain outcomes who will need to be followed into adulthood to establish the absence of disease. Thus the adult neurologist should become familiar with this group of disorders.

G_{M1} Gangliosidosis/ G_{M2} Gangliosidosis

Clinical. G_{M1} and G_{M2} gangliosidoses typically present in the pediatric population, but adult-onset variants do occur. In G_{M1} adult-onset cases, gait disturbance and speech impairment are often the first clinical signs. On physical examination, extrapyramidal features predominate. Typical bony abnormalities, visceromegaly, cherry red spots, and facial dysmorphisms are not usually seen. In G_{M2} adult-onset cases, symptoms may be highly variable and include ataxia, spasticity, weakness, muscle atrophy, fasciculations, dystonia, and psychosis. Abnormal urinary oligosaccharides are seen but may be less abundant than in early-onset cases.

Neuroimaging. Characteristics of MRI in G_{M1} and G_{M2} adult-onset cases are nearly identical. Slight white matter T2 signal increase and diffuse atrophy are seen. T2 signal hyperintensity may be seen in the caudate nucleus and the putamen, while hypointensity may be seen in the globus pallidus.¹²

Diagnosis. The diagnosis of G_{M1} and G_{M2} gangliosidoses is made by analysis of β -galactosidase or hexosaminidase A enzyme activity, respectively. Rarely, G_{M2} can be caused by deficiency of an activator protein (G_{M2} AB variant). An alternative is molecular sequencing of the *GLB1* and *HEXA* genes.

Mechanism/genetics. β -Galactosidase and hexosaminidase A enzyme deficiency result in excessive neuronal glycolipid storage. Both disorders are inherited in an autosomal recessive fashion.

Alexander Disease

Clinical. Alexander disease can be seen in any age group, and a growing number of publications have documented adult-onset cases. Adult-onset

Alexander disease tends to manifest with predominantly bulbar and autonomic disturbances, as well as more typical long-tract signs. Patients present with palatal myoclonus, swallowing difficulties, dysphonia, obstructive sleep apnea, unexplained syncope, and gait disturbance. Biochemical and standard laboratory evaluations will be unrevealing.

Neuroimaging. MRI of the brain may demonstrate typical Alexander disease findings. These include frontal predominance of white matter abnormalities, contrasting T2 signal hypointensity/T1 signal hyperintensity around the peritrial white matter, basal ganglia and brainstem signal abnormalities, and contrast enhancement of specific intracranial structures (Figure 12-7A).³² More often than in early-onset Alexander disease, MRIs in adult-onset Alexander disease will show space-occupying lesions of the brainstem, brainstem atrophy, or cerebellar white matter abnormalities. In adults, supratentorial white matter changes may be absent on typical MRI sequences (Figure 12-7B).^{33,34} If sought, signal abnormalities of the basal ganglia and contrast enhancement of Alexander disease–suggestive structures may often help in the diagnosis. In rare instances, posterior fossa involvement may be so significant as to cause confusion with brainstem gliomas.

Diagnosis. The diagnosis of Alexander disease can be confirmed by sequencing of the *GFAP* gene, encoding glial fibrillary acidic protein (GFAP).³⁵

Mechanism/genetics. Heterozygous mutations cause gain of function in *GFAP*, and accumulation of mutant GFAP along with other proteins in Rosenthal fibers is thought to be pathogenic to astrocytes. In early-onset cases, mutations are often sporadic, but in adult-onset cases, autosomal do-

minant inheritance patterns can be seen; familial cases should be sought once a proband is identified.

X-linked Adrenoleukodystrophy/Adrenomyeloneuropathy

Clinical. X-linked adrenoleukodystrophy often presents in a rapidly progressive childhood cerebral-onset form; however, up to 40% to 45% of affected male subjects will manifest a slower later-onset form called adrenomyeloneuropathy. Less frequently, adult males may present with a rapidly progressive cerebral form much like the childhood-onset presentation. Female heterozygotes may also present with an adrenomyeloneuropathy-like phenotype. At any age, cerebral X-linked adrenoleukodystrophy typically first presents with significant behavioral changes that may be misdiagnosed as attention deficit hyperactivity disorder, psychiatric illness, or, in older patients, primary dementia. Deteriorating cognitive function, gait changes, or visual loss may be the first indication of an organic neurologic disorder. Rapid deterioration ensues and typically results in severe dementia and spastic quadriplegia over a period of months. In contrast, adrenomyeloneuropathy presents with symptoms and signs of myelopathy and neuropathy. In all presentations, adrenal insufficiency may accompany neurologic features. Isolated Addison disease may also be seen in this disorder. Because of the clinical implications, adrenal function should be investigated in any subject affected by or suspected to be affected by X-linked adrenoleukodystrophy.

Neuroimaging. Classic MRI features in cerebral X-linked adrenoleukodystrophy are predominantly parietooccipital white matter abnormalities involving the splenium of the corpus callosum and often sparing the

KEY POINTS

- Adult patients with Alexander disease may lack supratentorial white matter changes and instead present with symptoms mainly attributable to brainstem involvement. Palatal myoclonus, dysphonia, swallowing difficulties, and sleep apnea are strongly suggestive of this condition.
- Adult-onset Alexander disease may not show typical MRI manifestations but may show brainstem-predominant lesions.
- Many adult-onset leukodystrophies and leukoencephalopathies, including cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, hereditary diffuse leukoencephalopathy with spheroids, adult-onset polyglucosan body disease, autosomal dominant leukodystrophy, adult-onset Alexander disease, and others, are autosomal dominant inherited conditions. These may occur sporadically or a consistent family history may exist, but regardless, these disorders have a 50% recurrence risk in the proband's descendants.

FIGURE 12-7 Adult-onset Alexander disease. *A*, In some cases, MRI features resemble early-onset Alexander disease with classic characteristics including frontal preponderance, contrasting T2 signal hypointensity relative to the remainder of the abnormal white matter signal around the peritrial white matter, and basal ganglia signal abnormalities. *B*, In other cases, MRI abnormalities are predominantly in the posterior fossa, with few supratentorial white matter signal abnormalities.

KEY POINT

■ Cerebral X-linked adrenoleukodystrophy typically first presents with significant behavioral changes that may be misdiagnosed as attention deficit hyperactivity disorder, psychiatric illness, or, in older patients, primary dementia.

arcuate fibers (Figure 12-8). Less common (15%) is frontal predominance with a similar pattern, mostly in adolescents and young adults presenting with cerebral X-linked adrenoleukodystrophy. Careful attention to abnormal white matter permits identification of two zones, a central zone with more severe demyelination and a relatively preserved peripheral zone. The hallmark of cerebral X-linked adrenoleukodystrophy is contrast enhancement of the border between these two zones. In adrenomyeloneu-

ropathy, the principal abnormality is spinal cord atrophy, but patients with adrenomyeloneuropathy may also have brain involvement, including involvement of corticopontine and corticospinal fibers and tracts as well as parietooccipital white matter and the splenium of the corpus callosum. MRI features are crucial in the monitoring of patients with X-linked adrenoleukodystrophy, and the presence of specific criteria may determine eligibility for therapeutics such as bone marrow transplant.

FIGURE 12-8 X-linked adrenoleukodystrophy. Axial MRIs show features seen in adult-onset presentations of cerebral adrenoleukodystrophy with frontal rather than parietal signal abnormalities on T2-weighted imaging (A, C), while still having the typical features of callosal involvement on fluid-attenuated inversion recovery (FLAIR) imaging (genu rather than splenium, B) and contrast enhancement of affected white matter on T1 imaging with contrast (D).

KEY POINTS

- Isolated Addison disease should prompt testing for X-linked adrenoleukodystrophy.
- Classic MRI features in cerebral X-linked adrenoleukodystrophy are predominantly parietooccipital white matter abnormalities involving the splenium of the corpus callosum and often sparing the arcuate fibers.

Diagnosis. The diagnosis of X-linked adrenoleukodystrophy and adrenomyeloneuropathy is typically made by testing very-long-chain fatty acids in plasma, with characteristic elevations in the concentration of C26:0 and the ratios of C24:0 to C22:0 and C26:0 to C22:0.³⁶

Mechanism/genetics. X-linked adrenoleukodystrophy and adrenomyeloneuropathy are caused by mutations in the gene *ABCD1*, a peroxisomal

transporter protein. Mutation testing for this gene is clinically available. When a proband is identified, careful attention to family history and evaluation of other potentially affected males should be performed.

Trends. With the advent of successful bone marrow transplantation in the management of X-linked adrenoleukodystrophy when caught early in the disease course and the need for urgent medical management of potential

KEY POINTS

- Patients with Kearns-Sayre syndrome present with ptosis and progressive external ophthalmoplegia, pigmentary degeneration of the retina, cardiac conduction block, developmental delay, growth failure, sensorineural hearing loss, endocrine dysfunction, and nonspecific neurologic abnormalities.
- Vanishing white matter disease, also known as childhood ataxia with cerebral hypomyelination, is a disorder in which presentation classically occurs in early childhood, manifesting by acute decompensations after falls or febrile illnesses.

mineralocorticoid deficiency, the identification of X-linked adrenoleukodystrophy has become a medical emergency. If an individual potentially affected by X-linked adrenoleukodystrophy has been identified, measures to test for and manage endocrine disturbances should immediately be put into place. Additionally, the patient should be urgently transferred to the care of a center with experience in bone marrow transplantation in patients with metabolic disease where decisions regarding the appropriateness of transplantation based on disease state can be made. Finally, the clinician should be diligent in searching for and testing other potentially affected individuals within the family of the proband, such that even if the index case cannot be fully treated because of disease advancement, other members of the family might be better managed.

Kearns-Sayre Syndrome

Clinical. Patients with Kearns-Sayre syndrome present with ptosis and progressive external ophthalmoplegia, pigmentary degeneration of the retina, cardiac conduction block, developmental delay, growth failure, sensorineural hearing loss, endocrine dysfunction, and nonspecific neurologic abnormalities. Blood and CSF lactic acid are usually elevated. CSF protein is elevated. EMG may demonstrate myopathy, and nerve conduction studies may demonstrate peripheral neuropathy. ECG may show various types of conduction abnormalities.

Neuroimaging. CT may demonstrate calcifications of the globus pallidus and caudate nucleus. MRI often shows a characteristic pattern of symmetric lesions of the globus pallidus and thalamus along with subcortical white matter abnormalities. The splenium of the corpus callosum

is often involved. Brainstem tracts and the cerebellum may also be involved (Figure 12-9).¹²

Diagnosis. Kearns-Sayre syndrome is one of three overlapping phenotypes, including also Pearson syndrome and progressive external ophthalmoplegia, caused by mitochondrial DNA deletions. Characteristic clinical features may be helpful in establishing a diagnosis, along with supportive evidence such as ragged red fibers on muscle biopsy and decreased activity of respiratory chain complexes.

Mechanism/genetics. Approximately 90% of individuals with Kearns-Sayre syndrome have a large deletion of mitochondrial DNA.³⁷ Often, lymphocytes used for blood testing of the mutant DNA do not carry a deletion, and other tissue must be biopsied for diagnosis. Kearns-Sayre syndrome is usually sporadic but when inherited is transmitted by maternal inheritance.

Other Mitochondrial Syndromes

Other mitochondrial syndromes that can present with leukoencephalopathy in the adult age group include mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), and other mutations in nuclear mitochondrial genes. A complete discussion of these phenotypes is beyond the scope of this article.

Vanishing White Matter Disease

Clinical. Vanishing white matter disease, also known as childhood ataxia with cerebral hypomyelination³⁸ is a disorder in which presentation classically occurs in early childhood, manifesting by acute decompensations after falls or febrile illnesses.³⁹ Patients can present with altered mental status, acute paresis, or hypotonia or may even develop coma in the initial

FIGURE 12-9 Kearns-Sayre syndrome. T2-weighted MRIs show cerebellar and globus pallidus involvement. Cerebral white matter is selectively involved in the subcortical regions, with preservation of the periventricular white matter and deep white matter to a lesser degree.

period of illness. Death may ensue, or the patient may experience partial neurologic recovery, followed by repeated episodes and a progressive neurologic decline. Paucisymptomatic adult forms exist, which may present with a progressive spastic paraparesis, cognitive changes, or even isolated ovarian failure.

Neuroimaging. MRI demonstrates diffuse white matter T2 signal increase. Over time, fluid-attenuated inversion recovery (FLAIR) images show progres-

sive rarefaction and cystic degeneration until white matter is replaced with signal isointense to the CSF spaces (**Figure 12-10**). Cerebellar white matter is relatively spared. Signal abnormality in the midbrain and the pons may be seen. More rarely, signal abnormality may be seen in the thalamus and the globus pallidus. These MRI features are seen across all age groups, except early-onset vanishing white matter disease, which may have a distinct MRI picture.¹²

FIGURE 12-10 Vanishing white matter disease. T2-weighted images of the pediatric presentation of the disorder show white matter signal that is isointense with CSF spaces, giving the impression that it has “vanished” (A). Fluid-attenuated inversion recovery (FLAIR) imaging documents rarefaction of affected white matter (B). Adult-onset cases show T2 hyperintensity (C), with abnormal signal and loss of white matter volume on FLAIR (D) but without the characteristic rarefaction.

Diagnosis. Diagnosis in vanishing white matter disease is based on classic MRI features and sequencing of the related genes (*EIF2B1* to *EIF2B5*),^{40,41} encoding a eukaryotic translation initiation factor eIF2B with five components: alpha, beta, gamma, delta, and epsilon.

Mechanism/genetics. eIF2B is a critical rate-limiting factor for protein translation that is modulated by the endoplasmic reticulum stress response.⁴² The mechanism by which mutations in a ubiquitous housekeeping gene result in fairly selective glial cell dysfunction remains unknown.

The disorder is inherited in an autosomal recessive manner.

Spastic Paraplegia SPG11

Although not considered leukodystrophies, hereditary spastic paraplegias, including SPG11, are occasionally misdiagnosed as such because of the prominent periventricular white matter abnormalities seen in these conditions.

Clinical. SPG11 is characterized by childhood onset of progressive spastic paraparesis, cognitive deterioration, cerebellar signs, peripheral neuropathy/neuronopathy, and central retinal degeneration. Several patients with an early-onset primarily extrapyramidal phenotype have also been described, on occasion associated with abnormalities on neurochemistry of CSF.⁴³

Neuroimaging. Patients with SPG11 have signal changes of periventricular white matter in the frontal region centered in the area of the forceps minor of the corpus callosum. They also have a characteristic thin corpus callosum, more pronounced in the mid and anterior portions with relative sparing of the splenium, giving a beaked appearance to the anterior portion of the corpus callosum. White matter atrophy is seen.

Diagnosis. The diagnosis of SPG11 is based on classic MRI features and sequencing of the related gene. It should be noted that overlapping phenotypic features with other hereditary spastic paraplegias exist, in particular SPG15, and that sequencing of more than one gene may be indicated in a tiered fashion or using a panel of genes.

Mechanism/genetics. SPG11 is caused by mutations in *SPG11* encoding spatacsin. SPG15 is caused by mutations in *ZFYVE26* encoding spastizin. Both are inherited in an autosomal recessive fashion. While limited information exists on the pathogenic mechanism in both of these

conditions, recent studies suggest a lysosomal trafficking or storage defect may be present.⁴⁴

Hypomyelinating Leukodystrophies

Special consideration should be given to the hypomyelinating leukodystrophies, including Pelizaeus-Merzbacher disease; hypomyelination, hypogonadotropic hypogonadism, and hypodontia (4H syndrome); and hypomyelination with atrophy of the basal ganglia and cerebellum, seen commonly in the pediatric population, as in adults they may present without the characteristic clinical features seen in their childhood-onset counterparts.

Clinical. Features are often predominantly motor, with significant spastic paraplegia and extrapyramidal features. In some cases, these motor features are superimposed on a chronic encephalopathy with learning disability or autistic features that went undiagnosed in childhood. In other cases, cognitive status is normal until adulthood. Specific clinical features, such as the hypogonadotropic hypogonadism and myopia commonly seen in 4H syndrome, should alert the neurologist to a specific clinical condition. Adult teeth may be normal in 4H syndrome, so an antecedent history of abnormalities of eruption in the primary teeth should be sought. Pelizaeus-Merzbacher disease is an X-linked disorder and should be considered in affected males. Hypomyelination with atrophy of the basal ganglia and cerebellum has no extraneurologic manifestations and may be more difficult to suspect clinically.

Neuroimaging. Neuroimaging in adult-onset cases of hypomyelination may be less striking, without the accompanying cerebellar and basal ganglia changes seen in pediatric disease, or may even have relatively

KEY POINTS

- Although not considered leukodystrophies, hereditary spastic paraplegias, including SPG11, are occasionally misdiagnosed as such because of the prominent periventricular white matter abnormalities seen in these conditions.
- Certain symptom complexes, such as hereditary spastic paraplegia, may be more amenable to testing groups of genes rather than single genes because of overlapping disorders.
- In adults, the hypomyelinating leukodystrophies may present without the characteristic clinical features seen in their childhood-onset counterparts.

normal appearing myelination with abnormalities restricted to the corticospinal tracts.

Diagnosis. A broad approach should be taken in these conditions, with either panel or tiered testing for *PLP1* (in males), *TUBB4A*, *POLR3A*, and *POLR3B* at least.^{45–48} Other etiologies of hypomyelination, such as Salla disease, *GJC2*-related disease, and *SOX10*-related disease, are less likely to present in the adult. No biochemical testing is available for these conditions.

Mechanism/genetics. Pelizaeus-Merzbacher disease is caused by X-linked mutations in *PLP1*. *PLP1* encodes one of the major protein constituents of mature myelin, proteolipid protein, and misfolding and mis-targeting of this protein is thought to result in oligodendrocyte-related disease. 4H syndrome is caused by autosomal recessive mutations in *POLR3A*, *POLR3B*, and the more recently identified *POLR1C*, although this has only been seen in early-onset cases. These genes encode components of the polymerase III (Pol III), thought to result in disease through its role in protein synthesis. Hypomyelination with atrophy of the basal ganglia and cerebellum is caused by de novo sporadic mutations in *TUBB4A*, encoding a tubulin essential to oligodendrocyte and neuronal maintenance, although how these mutations affect cell stability and trafficking remains to be established. Although sibling pairs have been seen in hypomyelination with atrophy of the basal ganglia and cerebellum, these have been demonstrated to be caused by low-level parental mosaicism, so the genetic counselor should be alert to this possibility.

CONCLUSION

A variety of inherited leukoencephalopathies may present to the adult

neurologist as mimickers of MS or other acquired leukoencephalopathies. The etiologic diagnosis of leukodystrophies or leukoencephalopathies remains challenging in any age group. A diagnosis remains important for family counseling and treatment of these devastating disorders. With careful attention to clinical features and MRI pattern recognition for described disorders, diagnosis can be achieved in a large proportion of cases. Additionally, when MRI and clinical features do not suggest a specific disorder or targeted testing does not result in an etiologic diagnosis, agnostic testing using next-generation sequencing approaches such as whole exome sequencing is warranted. Although currently not all are curable, an increasing number of these disorders have etiologic treatment, and all the disorders respond to symptom management. Thus, early and rapid diagnosis is the mainstay of these conditions, and the treating neurologist should seek expert help in reaching a diagnosis, if necessary.

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REFERENCES

1. Vanderver A, Tonduti D, Schiffmann R, et al. Leukodystrophy overview. In: Pagon RA, Adam MP, Ardinger HH, et al, eds. GeneReviews. Seattle, WA: University of Washington, Seattle; 2014:1993–2016. www.ncbi.nlm.nih.gov/books/NBK184570/?report=reader. Accessed April 3, 2016.
2. Steenweg ME, Salomons GS, Yapici Z, et al. L-2-Hydroxyglutaric aciduria: pattern of MR imaging abnormalities in 56 patients. *Radiology* 2009;251(3):856–865. doi:10.1148/radiol.2513080647.
3. van der Knaap MS, van der Voorn P, Barkhof F, et al. A new leukoencephalopathy with brainstem and spinal cord involvement and high lactate. *Ann Neurol* 2003;53(2):252–258. doi:10.1002/ana.10456.

4. Scheper GC, van der Klok T, van Andel RJ, et al. Mitochondrial aspartyl-tRNA synthetase deficiency causes leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation. *Nat Genet* 2007;39(4):534–539. doi:10.1038/ng2013.
5. Wolf NI, Toro C, Kister I, et al. DARS-associated leukoencephalopathy can mimic a steroid-responsive neuroinflammatory disorder. *Neurology* 2015;84(3):226–230. doi:10.1212/WNL.0000000000001157.
6. Taft RJ, Vanderver A, Leventer RJ, et al. Mutations in DARS cause hypomyelination with brain stem and spinal cord involvement and leg spasticity. *Am J Hum Genet* 2013;92(5):774–780. doi:10.1016/j.ajhg.2013.04.006.
7. Dallabona C, Diodato D, Kevelam SH, et al. Novel (ovario) leukodystrophy related to AARS2 mutations. *Neurology* 2014;82(23):2063–2071. doi:10.1212/WNL.0000000000000497.
8. Wider C, Van Gerpen JA, DeArmond S, et al. Leukoencephalopathy with spheroids (HDLS) and pigmentary leukodystrophy (POLD): a single entity? *Neurology* 2009;72(22):1953–1959. doi:10.1212/WNL.0b013e3181a826c0.
9. van der Knaap MS, Naidu S, Kleinschmidt-Demasters BK, et al. Autosomal dominant diffuse leukoencephalopathy with neuroaxonal spheroids. *Neurology* 2000;54(2):463–468. doi:10.1212/WNL.54.2.463.
10. Freeman SH, Hyman BT, Sims KB, et al. Adult onset leukodystrophy with neuroaxonal spheroids: clinical, neuroimaging and neuropathologic observations. *Brain Pathol* 2009;19(1):39–47. doi:10.1111/j.1750-3639.2008.00163.x.
11. Rademakers R, Baker M, Nicholson AM, et al. Mutations in the colony stimulating factor 1 receptor (CSF1R) gene cause hereditary diffuse leukoencephalopathy with spheroids. *Nat Genet* 2011;44(2):200–205. doi:10.1038/ng.1027.
12. van der Knaap MS, Valk J. Magnetic resonance of myelination and myelin disorders. 3rd edition. Berlin, Germany: Springer; 2011.
13. Bruno C, Servidei S, Shanske S, et al. Glycogen branching enzyme deficiency in adult polyglucosan body disease. *Ann Neurol* 1993;33(1):88–93. doi:10.1002/ana.410330114.
14. Lossos A, Barash V, Soffer D, et al. Hereditary branching enzyme dysfunction in adult polyglucosan body disease: a possible metabolic cause in two patients. *Ann Neurol* 1991;30(5):655–662. doi:10.1002/ana.410300505.
15. Uyama E, Kondo I, Uchino M, et al. Dentatorubral-pallidoluysian atrophy (DRPLA): clinical, genetic, and neuroradiologic studies in a family. *J Neurol Sci* 1995;130(2):146–153. doi:10.1016/0022-510X(95)00019-X.
16. Koide R, Ikeuchi T, Onodera O, et al. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidoluysian atrophy (DRPLA). *Nat Genet* 1994;6(1):9–13. doi:10.1038/ng0194-9.
17. Melberg A, Hallberg L, Kalimo H, Raininko R. MR characteristics and neuropathology in adult-onset autosomal dominant leukodystrophy with autonomic symptoms. *AJNR Am J Neuroradiol* 2006;27(4):904–911.
18. Bergui M, Bradac GB, Leombruni S, et al. MRI and CT in an autosomal-dominant, adult-onset leukodystrophy. *Neuroradiology* 1997;39(6):423–426. doi:10.1007/s002340050437.
19. Schwankhaus JD, Patronas N, Dorwart R, et al. Computed tomography and magnetic resonance imaging in adult-onset leukodystrophy. *Arch Neurol* 1988;45(9):1004–1008. doi:10.1001/archneur.1988.00520330094015.
20. Padiath QS, Saigoh K, Schiffmann R, et al. Lamin B1 duplications cause autosomal dominant leukodystrophy. *Nat Genet* 2006;38(10):1114–1123. doi:10.1038/ng1872.
21. Barkhof F, Verrips A, Wesseling P, et al. Cerebrotendinous xanthomatosis: the spectrum of imaging findings and the correlation with neuropathologic findings. *Radiology* 2000;217(3):869–876. doi:10.1148/radiology.217.3.r00dc03869.
22. Sabbadini G, Francia A, Calandriello L, et al. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). Clinical, neuroimaging, pathological and genetic study of a large Italian family. *Brain* 1995;118(pt 1):207–215. doi:10.1093/brain/118.1.207.
23. Joutel A, Corpechot C, Ducros A, et al. Notch3 mutations in CADASIL, a hereditary adult-onset condition causing stroke and dementia. *Nature* 1996;383(6602):707–710. doi:10.1038/383707a0.
24. Bischof F, Nägele T, Wanders RJ, et al. 3-hydroxy-3-methylglutaryl-CoA lyase deficiency in an adult with leukoencephalopathy. *Ann Neurol* 2004;56(5):727–730. doi:10.1002/ana.20280.
25. Zafeiriou DI, Vargiami E, Mayatepek E, et al. 3-Hydroxy-3-methylglutaryl coenzyme A lyase deficiency with reversible white matter changes after treatment. *Pediatr Neurol* 2007;37(1):47–50. doi:10.1016/j.pediatrneurol.2007.02.007.

26. Kim TS, Kim IO, Kim WS, et al. MR of childhood metachromatic leukodystrophy. *AJNR Am J Neuroradiol* 1997;18(4):733–738.
27. Morana G, Biancheri R, Dirocco M, et al. Enhancing cranial nerves and cauda equina: an emerging magnetic resonance imaging pattern in metachromatic leukodystrophy and Krabbe disease. *Neuropediatrics* 2009;40(6):291–294. doi:10.1055/s-0030-1249654.
28. Austin J, McAfee D, Armstrong D, et al. Low sulfatase activities in metachromatic leukodystrophy (MLD). A controlled study of enzymes in 9 living and 4 autopsied patients with MLD. *Trans Am Neurol Assoc* 1964;89:147–150.
29. Kapoor R, McDonald WI, Crockard A, Moseley IF. Clinical onset and MRI features of Krabbe's disease in adolescence. *J Neurol Neurosurg Psychiatry* 1992;55(4):331–332.
30. Wenger DA. Krabbe disease. GeneReviews. Seattle, WA: University of Washington, Seattle; 2000. www.ncbi.nlm.nih.gov/books/NBK1238/. Updated March 31, 2011. Accessed April 3, 2016.
31. Wenger DA, Rafi MA, Luzi P, et al. Krabbe disease: genetic aspects and progress toward therapy. *Mol Genet Metab* 2000;70(1):1–9. doi:10.1006/mgme.2000.2990.
32. van der Knaap MS, Naidu S, Breiter SN, et al. Alexander disease: diagnosis with MR imaging. *AJNR Am J Neuroradiol* 2001;22(3):541–552.
33. van der Knaap MS, Ramesh V, Schiffmann R, et al. Alexander disease: ventricular garlands and abnormalities of the medulla and spinal cord. *Neurology* 2006;66(4):494–498. doi:10.1212/01.wnl.0000198770.80743.37.
34. van der Knaap MS, Salomons GS, Li R, et al. Unusual variants of Alexander's disease. *Ann Neurol* 2005;57(3):327–338. doi:10.1002/ana.20381.
35. Brenner M, Johnson AB, Boespflug-Tanguy O, et al. Mutations in GFAP, encoding glial fibrillary acidic protein, are associated with Alexander disease. *Nat Genet* 2001;27(1):117–120. doi:10.1038/83679.
36. Moser HW, Moser AB, Frayer KK, et al. Adrenoleukodystrophy: increased plasma content of saturated very long chain fatty acids. *Neurology* 1981;31(10):1241–1249. doi:10.1212/WNL.31.10.1241.
37. DiMauro S, Hirano M. Mitochondrial DNA deletion syndromes. GeneReviews. Seattle, WA: University of Washington, Seattle; 2003. www.ncbi.nlm.nih.gov/books/NBK1203/. Updated May 3, 2011. Accessed April 3, 2016.
38. Schiffmann R, Moller JR, Trapp BD, et al. Childhood ataxia with diffuse central nervous system hypomyelination. *Ann Neurol* 1994;35(3):331–340. doi:10.1002/ana.410350314.
39. van der Knaap MS, Barth PG, Gabreëls FJ, et al. A new leukoencephalopathy with vanishing white matter. *Neurology* 1997;48(4):845–855. doi:10.1212/WNL.48.4.845.
40. van der Knaap MS, Leegwater PA, Köst AA, et al. Mutations in each of the five subunits of translation initiation factor eIF2B can cause leukoencephalopathy with vanishing white matter. *Ann Neurol* 2002;51(2):264–270. doi:10.1002/ana.10112.
41. van der Knaap MS, Leegwater PA, van Berkel CG, et al. Arg113His mutation in eIF2Bepsilon as cause of leukoencephalopathy in adults. *Neurology* 2004;62(9):1598–1600. doi:10.1212/01.WNL.0000123118.86746.FC.
42. van der Voorn JP, van Kollenburg B, Bertrand G, et al. The unfolded protein response in vanishing white matter disease. *J Neuropathol Exp Neurol* 2005;64(9):770–775.
43. Vanderver A, Tonduti D, Auerbach S, et al. Neurotransmitter abnormalities and response to supplementation in SPG11. *Mol Genet Metab* 2012;107(1–2):229–233. doi:10.1016/j.ymgme.2012.05.020.
44. Renvoisé B, Chang J, Singh R, et al. Lysosomal abnormalities in hereditary spastic paraplegia types SPG15 and SPG11. *Ann Clin Transl Neurol* 2014;1(6):379–389. doi:10.1002/acn3.64.
45. Bernard G, Chouery E, Putorti ML, et al. Mutations of POLR3A encoding a catalytic subunit of RNA polymerase Pol III cause a recessive hypomyelinating leukodystrophy. *Am J Hum Genet* 2011;89(3):415–423. doi:10.1016/j.ajhg.2011.07.014.
46. Tétreault M, Choquet K, Orcesi S, et al. Recessive mutations in POLR3B, encoding the second largest subunit of Pol III, cause a rare hypomyelinating leukodystrophy. *Am J Hum Genet* 2011;89(5):652–625. doi:10.1016/j.ajhg.2011.10.006.
47. Daoud H, Tétreault M, Gibson W, et al. Mutations in POLR3A and POLR3B are a major cause of hypomyelinating leukodystrophies with or without dental abnormalities and/or hypogonadotropic hypogonadism. *J Med Genet* 2013;50(3):194–197. doi:10.1136/jmedgenet-2012-101357.
48. Simons C, Wolf NI, McNeil N, et al. A de novo mutation in the β -tubulin gene TUBB4A results in the leukoencephalopathy hypomyelination with atrophy of the basal ganglia and cerebellum. *Am J Hum Genet* 2013;92(5):767–773. doi:10.1016/j.ajhg.2013.03.018.