REVIEW ARTICLE

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Hereditary Myelopathies

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ABSTRACT

PURPOSE OF REVIEW: **This article guides clinicians in the clinical recognition and differential diagnosis of hereditary myelopathies.**

RECENT FINDINGS: **Rather than a disease, a disease process, or relating to specific cellular vulnerability, the term *hereditary myelopathy* refers to diverse inherited disorders in which major aspects of the clinical syndrome reflect disturbance of elements within the spinal cord (specifically, the dorsal columns and dorsal root ganglia, corticospinal tracts, and anterior horn cells). It is important to note that the clinical features of almost all hereditary myelopathies reflect not only disturbance of elements within the spinal cord but also disturbance of extraspinal structures (particularly, but not limited to, peripheral nerves and the cerebellum) and that these extraspinal clinical features can be very helpful in recognizing specific myelopathy syndromes. The value of classifying disorders as inherited myelopathies lies primarily in facilitating their clinical recognition and differential diagnosis. It is useful to recognize that many hereditary myelopathies conform to one of four clinical paradigms: (1) spinocerebellar ataxia, (2) motor neuron disorder, (3) leukodystrophy, or (4) distal motor-sensory axonopathy predominantly affecting the central nervous system. Although they are myelopathies, spinal dysraphisms such as spina bifida and myelomeningocele are not included in this context because they are not usually due to single-gene mutation and have low hereditability.**

SUMMARY: **This article illustrates clinical paradigms of hereditary myelopathy with clinical examples emphasizing the spectrum, clinical recognition, and differential diagnosis of hereditary myelopathies.**

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INTRODUCTION

Hereditary myelopathies are diverse genetic disorders in which the major clinical features are due to disturbance of elements that occur entirely within, emanate from, or traverse the spinal cord. Although the word *hereditary* implies genetic causation as the disease mechanism, the term *myelopathy* is strictly a clinical syndromic designation describing particular signs and symptoms localizing to the spinal cord and therefore does not imply common neuropathologic processes or radiographic findings. As with most neurologic syndromes, correlation between the distribution of neuropathology, radiographic findings, and nature of the clinical disorder is imperfect. For example, some forms of "pure" cerebellar ataxia have postmortem evidence of more widespread neurodegeneration involving dorsal columns. Conversely, not all inherited disorders that cause radiographic abnormalities involving the spinal cord in fact manifest as

myelopathies.[1] As used in this article, hereditary myelopathy is a clinical term describing a pattern of signs and symptoms.

The term hereditary myelopathy does not imply that clinical features exclusively relate to spinal cord disturbance: clinical neurologic involvement in nearly all hereditary myelopathies reflects disturbance in structures outside the spinal cord. In fact, the nature of these extraspinal neurologic signs is very helpful in classifying and diagnosing hereditary myelopathies.

HEREDITARY MYELOPATHY CLINICAL PARADIGMS

Myelopathies are recognized by variable combinations of upper motor neuron–pattern functional motor disturbance, impaired vibration or proprioception, and lower motor neuron–pattern motor impairment that are not attributable (by the remainder of neurologic symptoms and examination findings) to another localization (ie, brain or peripheral nerve). The magnitude of each of these elements is highly variable between and within different types of inherited myelopathy. For example, in primary lateral sclerosis (PLS), upper motor neuron–pattern motor impairment is severe and occurs in the absence of significant dorsal column or lower motor neuron impairment. In the spinal muscular atrophies, anterior horn cell degeneration causing lower motor neuron–pattern motor impairment occurs in the absence of upper motor neuron or dorsal column disturbance.

Variable presence and degree of these elements (upper motor neuron, lower motor neuron, and dorsal column [or dorsal root ganglia] disturbance) cause most inherited myelopathies to conform to one of four syndromes: spinocerebellar degeneration, motor neuron disorder, leukodystrophy, and central nervous system (CNS)–predominant distal motor-sensory axonopathy (TABLE 8-1[2-19]).

Spinocerebellar Degeneration

The prefix *spino-* of spinocerebellar degeneration indicates involvement of one or more of the following: corticospinal tracts in the spinal cord, dorsal columns (or dorsal root ganglia), or anterior horn cells. As clinical syndromes, spinocerebellar disorders are contrasted with much less common "isolated" or "pure" cerebellar ataxia syndromes (eg, spinocerebellar ataxia type 15 [SCA15, Mendelian Inheritance in Man (MIM) 606658] and SCA41 [MIM 616410])[20] and distinguished from clinical olivopontocerebellar disorders that involve the cerebellum and other brainstem structures (eg, multiple system atrophy, cerebellar type) and disorders involving the cerebellum and other areas of the nervous system that do not have clinical manifestations of spinal cord involvement (eg, Niemann-Pick disease type C). Classifications of spastic ataxias (in which ataxia is prominent)[1] and complicated forms of hereditary spastic paraplegia (HSP) associated with cerebellar involvement (in which spastic paraparesis is prominent) overlap.[15,16]

Inherited spinocerebellar degenerations (eg, Friedreich ataxia, SCA3 [also known as Machado-Joseph disease] [CASE 8-1], Bassen-Kornzweig syndrome, and vitamin E deficiency [occasionally familial]) are recognized by a combination of progressive cerebellar ataxia, peripheral neuropathy, dorsal column impairment, and variable corticospinal tract involvement.

It is important to recognize that both between individuals who share the same disorder and between individuals with genetically unrelated types of

spinocerebellar degeneration, these diagnostic elements (cerebellar ataxia, peripheral neuropathy, dorsal column impairment, and signs of upper motor neuron disturbance) exist in variable proportions, that some of the diagnostic elements may be absent entirely, and that diagnostic elements may appear asynchronously as the disorder evolves.

Friedreich ataxia is often associated with hypertrophic cardiomyopathy (present in the patient in CASE 8-2 but absent in the patient in CASE 8-3). The significantly different, yet overlapping, neurologic and systemic involvement in the two patients presented in these cases illustrates the important clinical variation in Friedreich ataxia. Each patient had evidence of marked impairment of the dorsal columns, an important feature of Friedreich ataxia. These patients differed, however, in the occurrence of cardiomyopathy, generalized areflexia, and prominent cerebellar deficits (present in the patient in CASE 8-2 but not in the patient in CASE 8-3) and the occurrence of corticospinal tract impairment (hyperreflexia, in contrast to areflexia) in the patient in CASE 8-3 but not in the patient in CASE 8-2.

Recognition that upper motor neuron signs ranging from simply extensor plantar responses to progressive lower extremity spasticity are common in Friedreich ataxia represents an evolution of our understanding of this disorder.

Prior to discovery of the causative gene mutation, Friedreich ataxia was diagnosed clinically as an autosomal recessive disorder (ie, ascertained either in sibships or as a single affected individual in a family without similarly affected parents or children) marked by ataxia (both cerebellar ataxia and sensory ataxia) and areflexia (owing to peripheral neuropathy and dorsal root ganglia involvement). Following discovery of the *FXN* gene, mutation-based diagnosis led to recognition that many individuals not only had preserved reflexes, but some had lower extremity hyperreflexia and spasticity. Indeed, some individuals with Friedreich ataxia present with progressive spastic gait instead of progressive ataxia. Typically, severe dorsal column (and dorsal root ganglia) involvement in Friedreich ataxia contrasts with the typically mild distal vibration impairment that usually accompanies uncomplicated HSP.

FXN encodes a mitochondrial protein. The vast majority of patients with Friedreich ataxia have expanded trinucleotide repeats (GAA) on both *FXN* alleles (CASE 8-2). The patient described in CASE 8-3 is not homozygous for this trinucleotide repeat and instead has compound heterozygosity with an expanded GAA repeat on one *FXN* allele and a point mutation on the other allele. Point mutations (rather than GAA expansion) are responsible for only 2% of patients with Friedreich ataxia. The frataxin trinucleotide repeat is GAA instead of the more common polyglutamine expansion (CAG) repeat responsible for Huntington chorea and many other spinocerebellar ataxias. Furthermore, the frataxin GAA trinucleotide repeat occurs in an intron (frataxin intron 1) and does not alter the frataxin coding sequence. Nonetheless, this intronic mutation leads to reduced frataxin messenger RNA (possibly through locally increased DNA methylation leading to reduced transcription),[24] iron accumulation in mitochondria, and an apparent increased vulnerability to oxidative stress.

Motor Neuron Disorders

Motor neuron disorders involve degeneration of the corticospinal tracts or anterior horn cells, or both.[2,4,8] Cortical motor neurons may also be involved, although generally to a lesser extent. Various motor neuron disorder syndromes

KEY POINTS

- In addition to symptoms arising from disturbance within the spinal cord, neurologic involvement in nearly all hereditary myelopathies includes structures outside the spinal cord.
- Many hereditary myelopathic syndromes can be recognized as one of four clinical paradigms: (1) spinocerebellar ataxia, (2) motor neuron disorder, (3) leukodystrophy, or (4) central nervous system–predominant distal motor-sensory axonopathy.
- Spinocerebellar degenerations (eg, Friedreich ataxia, spinocerebellar ataxia type 3, Bassen-Kornzweig syndrome, and vitamin E deficiency) are recognized by a combination of progressive cerebellar ataxia, often accompanied by peripheral neuropathy; dorsal column (or dorsal root ganglia) impairment (which may cause sensory ataxia); and variable corticospinal tract involvement.
- Spinocerebellar ataxia type 3 is caused by a trinucleotide repeat (CAG) expansion that, like other polyglutamine expansions, is thought to be pathogenic through protein misfolding.
- The vast majority of patients with Friedreich ataxia are homozygous for expanded trinucleotide repeat in the *FXN* gene, which encodes a mitochondrial protein. Rarely, individuals will have an expanded trinucleotide repeat in one *FXN* allele and a point mutation in the other *FXN* allele.

TABLE 8-1 **Syndromic Classification of Hereditary Myelopathies**[a]

Major syndrome	Representative examples	Diagnostic testing
Spinocerebellar ataxias (SCAs)[3]	SCA 1 through 48	Genetic testing for specific SCA gene mutation; neuroimaging to demonstrate cerebellar atrophy
	Machado-Joseph disease (SCA3)	Genetic testing for specific SCA gene mutation; neuroimaging to demonstrate cerebellar atrophy
	Friedreich ataxia	*FXN* gene analysis
	Familial vitamin E deficiency	Serum vitamin E
	Abetalipoproteinemia (Bassen-Kornzweig syndrome)	Lipoprotein electrophoresis
	Autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS)	Genetic testing
Motor neuron disorders[4–8]	Spinal muscular atrophy	Survival motor neuron (*SMN1*, *SMN2*) gene analysis
	Familial amyotrophic lateral sclerosis	*C9orf72*, *SOD1*, and other gene analysis
	Primary lateral sclerosis (rarely familial)	*ALSIN* gene analysis (for juvenile familial primary lateral sclerosis); *FIG4*, *C9orf72*, *SPG7* analysis
	Hereditary spastic paraplegia (HSP)	HSP gene analysis
	Spinal bulbar muscular atrophy (Kennedy disease)	Androgen receptor gene mutation (CAG repeats)
	Partial hexosaminidase deficiency	Leukocyte hexosaminidase assay
Leukodystrophies[9–11]	Subacute combined degeneration (rarely familial)	Serum vitamin B_{12}, methylmalonic acid
	5-Methyltetrahydrofolate reductase deficiency (*MTHFR*)[12]	Plasma homocysteine, methionine, vitamin B_{12}, methylmalonic acid, folate; urine homocysteine
	Cobalamin C deficiency (*MMACHC* gene mutation)[13]	Plasma methylmalonic acid, homocysteine
	Multiple sclerosis (occasionally familial)	MRI of brain and spinal cord, CSF analysis, clinical course
	Adrenoleukodystrophy, adrenomyeloneuropathy	Serum very long chain fatty acid analysis
	Krabbe disease	Leukocyte β-galactosidase assay
	Metachromatic leukodystrophy	Leukocyte arylsulfatase assay
	Pelizaeus-Merzbacher disease/SPG2 HSP due to *PLP1* gene mutation	Proteolipid protein gene analysis
	Cerebrotendinous xanthomatosis	Serum cholestanol
	Alexander disease[14]	MRI, *GFAP* gene analysis

CONTINUED ON PAGE 189

CONTINUED FROM PAGE 188

Major syndrome	Representative examples	Diagnostic testing
Central nervous system-predominant, distal motor-sensory axonopathies[15,16]	Hereditary spastic paraplegia	HSP gene analysis
Other	Mitochondrial myelopathy[17]	Magnetic resonance spectroscopy (brain), muscle biopsy for ragged red fibers and histochemical evidence of oxidative phosphorylation deficit; mitochondrial gene analysis
	Leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (*DARS2* mutation) (FIGURE 8-1A)[18]	*DARS2* gene analysis, spinal MRI
	Autosomal dominant leukodystrophy (multiple sclerosis mimic)[19]	Brain and spinal cord MRI, *LMNB1* gene analysis (including copy number analysis); *LMNB1* quantification in white blood cells
	Adult polyglucosan body disease due to *GBE1* gene mutation	Brain and spinal cord MRI, nerve conduction studies and EMG, *GBE1* gene analysis
	Variant Alzheimer disease with spastic paraplegia due to *PSEN1* mutation	*PSEN1* gene analysis
	Hyperzincemia	Serum zinc
	Neurofibromatosis type 2	MRI scan
	Hereditary exostosis with spinal cord compression	CT and MRI scans
	Hereditary hemorrhagic telangiectasia	MRI scan
	Von Hippel-Lindau (hereditary hemangiomata)	MRI scan and *VHL* gene analysis
	Tropical spastic paraplegia (due to human T-cell lymphotropic virus type 1 [HTLV-1] infection; may occur in familial clusters)	HTLV-1 antibody testing
	Arginase deficiency	Increased plasma arginine, reduced red blood cell arginase
	Biotinidase deficiency	Reduced serum biotinidase
	Syringomyelia (rarely familial)	MRI scan
	Sjögren-Larsson syndrome	Clinical features of congenital ichthyosis, mental deficiency, and spastic diplegia or tetraplegia (typically accompanied by additional features) and demonstrating enzyme (fatty aldehyde dehydrogenase) defect in cultured fibroblasts

CSF = cerebrospinal fluid; CT = computed tomography; EMG = electromyography; MRI = magnetic resonance imaging.
[a] Updated from Fink JK, Continuum (Minneap Minn).[2] © 2008 American Academy of Neurology.

differ in the relative combination of upper motor neuron versus lower motor neuron involvement and the variable occurrence of additional neurologic disturbance. In PLS, for example, progressive spastic weakness, usually beginning in the legs and later involving the arms, speech, and swallowing, reflects corticospinal and corticobulbar tract involvement and, to a lesser extent, loss of cortical motor neurons (CASE 8-4). In PLS, in contrast to amyotrophic lateral sclerosis (ALS), there is either no evidence of lower motor neuron involvement or, at most, minimal evidence on EMG of chronic denervation late in the disease. Conversely, spinal muscular atrophy is characterized by muscular weakness and atrophy due to anterior horn cell degeneration with relative preservation of corticospinal tracts.

CASE 8-1

A 30-year-old woman presented for an initial neurologic evaluation for difficulty with balance and handwriting. She first noted the insidious onset of a very slowly progressive balance disturbance at approximately age 26, followed several years later by mildly impaired handwriting. Although she was fully able to ascend and descend stairs and walk long distances independently, neurologic examination at age 30 showed slightly wide-based gait and impaired ability to walk in tandem. Ocular dysmetria and saccadic intrusions into pursuit eye movements were also noted. The remainder of neurologic examination, including finger-to-nose, heel-to-shin, sensory, and reflex testing, was normal.

Serial evaluations were performed over the next 20 years. During this time, her balance impairment slowly worsened, her speech became increasingly dysarthric, and she gradually lost the ability to stand and walk (requiring a walker by age 48 and a wheelchair in her fifties). In addition, progressive dystonia, axial rigidity, impaired distal sensation, and generalized hyperreflexia gradually emerged.

By age 47, she had begun to experience involuntary movements of her face, neck, and upper extremities. Examination at this time showed prominent axial rigidity, particularly affecting neck movements; dystonia affecting the neck, face, and bilateral upper extremities; and cogwheel rigidity in her upper extremities. In addition to ataxic dysarthria and ataxia affecting upper and lower extremities, she had grade 3 hyperreflexia throughout except at the ankles, which were hyporeflexic, and decreased sensation to pinprick and vibration in a stocking distribution below the knees. She was able to stand with great difficulty and was able to take a few steps but had marked balance impairment and tendency to fall.

Neurologic examination at age 53 showed facial bradykinesia, generally reduced movements of the extremities, marked ataxic dysarthria, marked saccadic intrusions into smooth pursuit, very slow ocular saccades, and generalized hyperreflexia (grade 3) except absent ankle deep tendon reflexes. She required significant assistance to stand, had a wide-based stance, and required maximum assistance to take a couple of steps.

Disorders collectively known as the amyotrophic lateral scleroses typically involve degeneration of both anterior horn cells and corticospinal tracts and, to a lesser degree, loss of cortical motor neurons. Although motor neuron, corticospinal tract, and corticobulbar tract degeneration are the major features and primary cause of death in ALS, neuropathology is often not limited to the motor system. Many forms of ALS (eg, *C9orf72* expansion-related ALS) also involve other brain areas (particularly the frontal lobes) and manifest clinically as frontal lobe dementia.

Approximately 10% of ALS is familial, in which affected individuals have similarly affected first-degree relatives. The majority of familial ALS is dominantly inherited, often due to *SOD1* mutation or pathogenic expansion in the *C9orf72*

Family history was notable for similar symptoms in the patient's brother and mother, who also had progressive ataxia and dysarthria. The brother had died at age 40 and the mother died at age 55. The patient's maternal aunt and several cousins were also similarly affected. Postmortem examination of the patient's mother had showed degenerative changes in cerebellum and spinal cord.

Genetic testing revealed pathologic CAG repeat expansion ($[CAG]_{75}$) in *ATXN3*, and the patient was diagnosed with spinocerebellar ataxia type 3 (SCA3).

COMMENT

Localization indicated deficits affecting the cerebellum midline (ocular dysmetria, saccadic intrusions, ataxic dysarthria) and cerebellar hemispheres (upper extremity dysmetria), peripheral nerves (stocking gradient to pinprick and vibration below the knees, absent ankle deep tendon reflexes), corticospinal tracts (generalized hyperreflexia except at the ankles), and extrapyramidal system (dystonia in the neck, face, extremities, axial rigidity).

SCA3 is caused by a trinucleotide repeat (CAG) expansion that, like other polyglutamine expansions, is thought to be pathogenic through protein misfolding.[21] SCA3 phenotypes vary from spastic paraparesis (which dominated the first decade of this patient's symptoms) to complex syndromes involving elements of cerebellar ataxia, extrapyramidal disturbance (eg, nigrostriatal pathway disturbance), and peripheral neuropathy. Symptoms in SCA3, as in many degenerative neurologic disorders, often evolve as the disorder progresses and other neurologic regions become involved. This patient's neurologic signs for the first 15 years were limited to disturbance of the cerebellum (ataxic speech and ataxia of upper and lower extremities) and a minor degree of peripheral neuropathy. These features are shared with many forms of spinocerebellar ataxia. It was only after approximately 15 years that features that tend to distinguish SCA3 from other spinocerebellar ataxias (ie, axial rigidity, dystonia, and mild corticospinal tract impairment [hyperreflexia]) began to appear.

repeat. More than 50 other genes have been implicated in familial ALS.[8] Genetic factors also contribute to the disease in many individuals with apparently sporadic ALS (ie, ALS ascertained in individuals who do not have ALS-affected first-degree relatives). Specifically, among individuals with apparently sporadic ALS, 1% to 3% have *SOD1* mutations and approximately 5% have pathogenic *C9orf72* expansions. Additional genes (eg, *TARDBP*, *FUS*, *HNRNPA1*, *SQSTM1*, *VCP*, *OPTN*, and *PFN1*) have also been implicated in apparently sporadic ALS.[8]

Overlap exists between the classifications of motor neuron disorder and distal motor-sensory axonopathy affecting the CNS (eg, HSP). The primary differences are the degree to which anterior horn cells are lost (a major aspect of spinal muscular

CASE 8-2

A 13-year-old girl presented with very slowly worsening gait and balance. She reported some stumbling and occasionally dropping things. She had a history of mild clumsiness in childhood that did not rise to the level of medical concern. A heart murmur had been discovered at age 10. Echocardiography identified hypertrophic cardiomyopathy.

Examination was notable for pes cavus, mild scoliosis, mild hypophonia and dysarthria, mild nystagmus, mild weakness of intrinsic hand muscles and tibialis anterior muscles, mildly ataxic heel-to-shin and finger-to-nose movements, mild truncal titubation, and markedly impaired vibration perception (absent below the knees and absent in her hands). Deep tendon reflexes were absent throughout. Although she was able to ambulate independently, her gait was mildly ataxic. Romberg sign was present.

Her gait and balance slowly worsened, and she required the use of a wheelchair at approximately age 17. Examination at age 21 showed mild ataxic dysarthria; saccadic intrusions into smooth pursuit; and weakness of hip flexion, foot dorsiflexion, and wrist extension. She had mild hypotonia in the legs, generalized areflexia, ataxia in upper and lower extremities, and pes cavus with hammer toe formation. She could stand with assistance but was not able to walk even with support. Localization indicated deficits referable to the cerebellar midline, cerebellar hemispheres, and dorsal columns serving the upper and lower extremities.

Genetic analysis showed expansions in both *FXN* alleles (*FXN* $[GAA]_{766}$ and $[GAA]_{533}$). The normal GAA repeat number is approximately 8 to 30, with pathologic expansions measuring 170 to 1700 repeats.[22] The patient was diagnosed with Friedreich ataxia.

COMMENT

This individual manifests classic symptoms of Friedreich ataxia: adolescent onset, slowly progressive gait disturbance associated with areflexia, dorsal column impairment, cerebellar ataxia, scoliosis, pes cavus, and cardiomyopathy. Following the discovery of the *FXN* gene, the classic clinical presentation of Friedreich ataxia was expanded with recognition that some individuals with pathologic *FXN* gene mutations had late-onset symptoms and retained deep tendon reflexes or even hyperreflexia and spasticity (**CASE 8-3**).

CASE 8-3

A 24-year-old woman began to notice insidiously progressive difficulty with walking and balance beginning at approximately 12 years of age. There was no previous illness and no family history of similar symptoms. Although able to walk and run, she noted that she had to concentrate on keeping her balance. Within the next 2 years she began noticing a tingling sensation in both legs. Classmates began commenting that she walked as if she were drunk. Gait disturbance continued to worsen slowly.

Her neurologic examination at age 24 revealed normal speech and normal cranial nerves with the exception of saccadic intrusions into smooth pursuit. Muscle bulk, tone, and strength were normal in the upper extremities. In the lower extremities, however, muscle tone was increased (particularly at the hamstrings and ankles and to a lesser extent at the quadriceps), and she had marked weakness of tibialis anterior, moderate weakness of iliopsoas, and mild weakness of hamstring muscles. She had profound impairment of distal vibratory sensation (she was able to perceive vibratory sensation applied to her shins but not to her toes) and moderately impaired distal proprioception. She had subjectively decreased pinprick sensation in the distal aspects of the lower extremities. Deep tendon reflexes were 1 to 2+ at the biceps, triceps, and brachioradialis; 3+ at the knees; and absent at the ankles. Finger-to-nose testing was normal. Heel-to-shin testing was minimally abnormal. Plantar responses were extensor bilaterally. Nerve conduction studies and EMG were consistent with a sensorimotor polyneuropathy. MRI of the brain was normal.

COMMENT

Localization indicated deficits referable to corticospinal tracts serving bilateral lower extremities (weakness, increased tone, extensor plantar responses); dorsal columns and/or dorsal roots (marked vibration and proprioception impairment, which were out of proportion to subtle diminution in pinprick perception); and peripheral nerves (absent ankle deep tendon reflexes and stocking distribution of subjectively decreased pinprick sensation) and subtle midline cerebellar disturbance (saccadic intrusions into smooth pursuit and mild heel-to-shin abnormality). Note that the gradient of hyperreflexia (increased in the legs relative to the arms) suggests length-dependent central axonopathy. Furthermore, reflexes that are diminished distally (ie, 3+ at knees and absent at ankles), suggests co-occurrence of length-dependent corticospinal tract and peripheral nerve deficits in addition to severe dorsal column or dorsal root ganglia disturbance.

Genetic analysis revealed compound heterozygous *FXN* mutations, with one *FXN* allele with an expanded repeat ($[GAA]_{962}$) and the other *FXN* allele having a missense mutation resulting in amino acid substitution (G130V).The patient was diagnosed with Friedreich ataxia, the most common form of autosomal recessive spinocerebellar ataxia.[23]

Case updated from Fink JK, Continuum (Minneap Minn).[2]

CASE 8-4

A 64-year-old man began experiencing initially subtle but slowly worsening gait disturbance. Neurologic examination showed generalized hyperreflexia (3+) and mild symmetric weakness and spasticity in his legs. Speech articulation; swallowing ability; and upper extremity strength, tone, and dexterity were normal. Sensation was normal throughout. Brain MRI showed areas of T2 signal intensity in periventricular regions consistent with chronic small vessel ischemia and age-related changes. Cervical and thoracic spine MRI showed degenerative changes but no evidence of spinal cord compression or spinal cord signal change.

One year later (approximately 6 years after symptom onset [age 70]), he began to experience subtle difficulty speaking, slight impairment of handwriting and hand dexterity, and emotional lability. Neurologic examination at that time showed mild slowing of finger tapping, the presence of Hoffman and Trömner signs, generalized hyperreflexia, and continued weakness and spasticity in the legs. Worsening gait disturbance required use of a walker.

By age 74 (approximately 10 years after symptom onset), the patient reported dysphagia, emotional lability (suggestive of pseudobulbar affect), and worsened ability to use his upper extremities. Examination demonstrated marked spastic dysarthria and hypophonia, very slow hand opening and closing, the emergence of spasticity in the upper extremities, and worsening of spasticity to a marked degree in the legs. Marked spastic gait required intermittent use of a wheelchair. There was no family history of similar disorder.

EMG within approximately 1 year of symptom onset and again after symptoms had progressed for at least 5 years showed only mild sensory-motor neuropathy without evidence of amyotrophic lateral sclerosis.

COMMENT

Neurologic findings localized to the corticospinal tracts serving all extremities (the legs initially and most severely) and corticobulbar tracts serving speech.

In this patient, the absence of generalized white matter disturbance on neuroimaging argued against a leukodystrophy, and the absence of lower motor neuron involvement on EMG argued against amyotrophic lateral sclerosis. Involvement of upper extremities and speech and the absence of dorsal column involvement argued against a form of hereditary spastic paraplegia. The onset after age 30, exclusion of other disorders, limitation of neurologic symptoms to corticobulbar and corticospinal tracts, and involvement of three body segments fulfill diagnostic criteria for primary lateral sclerosis.[25]

atrophy, an important feature of ALS, and a minimal feature of PLS and which can occur insidiously and symmetrically in some complicated forms of HSP) and the degree of sensory (eg, dorsal column) involvement (a finding common in hereditary spastic paraplegia but absent in ALS). In individuals with both upper and lower motor neuron involvement, the occurrence of additional neurologic disturbance such as peripheral neuropathy and cerebellar ataxia, features not associated with ALS or PLS, would suggest a complicated form of HSP.

For most individuals, PLS is an "apparently sporadic" adult-onset disorder,[25] being diagnosed in individuals without similarly affected relatives. Rarely, PLS begins in early childhood and occurs in families, where it appears to be an autosomal recessive disorder. Yang and colleagues[26] identified mutations in the *ALSIN* gene in patients with autosomal recessive juvenile PLS. Depending on the precise location of the *ALSIN* gene mutation, patients either exhibit a phenotype of pure upper motor neuron impairment (PLS phenotype) or also manifest lower motor neuron disturbance (consistent with a juvenile-onset, autosomal recessive ALS phenotype).

The vast majority of adults with PLS do not have identified gene mutations. However, with increasing analysis of large candidate gene panels and whole-exome sequencing, gene mutations have been identified in approximately 5% of individuals with PLS. Interestingly, although rare, these mutations have been in genes implicated in HSP (eg, *SPG7*) and ALS (eg, *C9orf72* and *FIG4*). This observation indicates that for some individuals, ALS, PLS, and HSP may share similar underlying molecular processes and represent a clinical spectrum.

Although PLS is often regarded as an exclusively upper motor neuron disorder, the variable occurrence of cognitive disturbance (usually in the frontotemporal dementia pattern of deficits that also occurs in ALS)[27] and relatively common occurrence of pseudobulbar affect in PLS indicate involvement in nonmotor brain areas. Pseudobulbar affect occurs in individuals with a variety of disorders (eg, multiple sclerosis, stroke, ALS, PLS). Although it occurs in individuals with upper motor neuron impairment, pseudobulbar affect is unlikely to be caused by upper motor neuron impairment.

The precise neuroanatomic localization of pseudobulbar affect is uncertain[28] and includes the dorsal globus pallidus as well as descending pathways from frontal lobes to the brainstem, pontine nuclei, and cerebellum (corticopontine cerebellar pathways). Regarding the localization and frequent occurrence of pseudobulbar affect in patients with PLS, Floeter and colleagues[29] wrote "[Pseudobulbar affect] is common in PLS. Imaging findings showing disruption of corticopontocerebellar pathways support the hypothesis that [pseudobulbar affect] can be viewed as a 'dysmetria' of emotional expression resulting from cerebellar dysmodulation."

In other words, although pseudobulbar affect is common in individuals whose neurologic syndrome includes upper motor neuron impairment (eg, ALS and PLS), the present understanding is that pseudobulbar affect is not due to disturbance in the upper motor neurons but reflects co-occurrence of impairment in other brain areas (likely corticopontocerebellar pathways).

KEY POINT

- In primary lateral sclerosis, there is either no evidence of lower motor neuron involvement, or, at most, minimal evidence of chronic denervation is seen on EMG late in the disease. At the other extreme, spinal muscular atrophy is characterized by muscular weakness and atrophy due to anterior horn cell degeneration with preservation of corticospinal tracts.

Leukodystrophies

Leukodystrophies are disorders in which the primary or major abnormality involves myelin development (dysmyelination) or myelin degeneration (demyelination) of central nerves occurring alone or in combination with

demyelinating peripheral neuropathy.[9,10] As discussed below, primary myelin abnormality may cause degeneration of the long axons, manifesting clinically as the syndrome of HSP (CNS-predominant distal motor sensory axonopathy) instead of a leukodystrophy syndrome.

Leukodystrophies have extremely variable clinical presentations, including progressive cognitive disturbance and signs of corticospinal and corticobulbar tract deficits. Early corticobulbar tract involvement argues against disorders causing distal motor-sensory axonopathy (ie, types of HSP). Although the complete constellation of insidiously progressive cognitive impairment, spasticity, optic neuropathy, and demyelinating peripheral neuropathy is suggestive of generalized leukodystrophy (affecting both the CNS and peripheral nervous system), often all elements of this constellation are not present. In particular, demyelinating peripheral neuropathy, which typically accompanies childhood-onset leukodystrophies (eg, Krabbe disease and metachromatic leukodystrophy), may be absent in the rare adolescent- and adult-onset forms of these disorders.[30]

Whereas it is not uncommon for inherited leukodystrophies to eventually cause spastic paraparesis or tetraparesis, it is much more common for inherited leukodystrophies (eg, CADASIL [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy], adrenoleukodystrophy, Krabbe disease, metachromatic leukodystrophy, Pelizaeus-Merzbacher disease, mitochondrial disorder [eg, *DARS2* mutation (**FIGURE 8-1**)], and Alexander disease) to manifest initially and predominantly with cerebral symptoms (ie, cognitive impairment). Notable exceptions occur when the primary myelin disturbance (eg, due to proteolipid protein [*PLP1*] mutation) results in progressive axon degeneration involving corticospinal tracts.[31] In these individuals, primary myelin impairment (ie, leukodystrophy) manifests as a myelopathy. When cognitive disturbance is minimal or absent, leukodystrophies may be difficult to distinguish from hereditary CNS distal axonopathy (ie, HSP). Certainly, demyelinating optic neuropathy and deafness, which are not uncommon in leukodystrophies but quite atypical of HSP, would aid the differential diagnosis. Brain and spinal cord MRI (**FIGURE 8-1**), brainstem and visual evoked potentials, and nerve conduction studies are valuable in evaluating individuals suspected of having leukodystrophy.

ADRENOLEUKODYSTROPHY AND ADRENOMYELONEUROPATHY. Childhood-onset adrenoleukodystrophy and adolescent- and adult-onset adrenomyeloneuropathy are X-linked disorders in which *ABCD1* gene mutation leads to impaired peroxisomal beta-oxidation and accumulation of very long chain fatty acids systemically.[32,33] Adrenoleukodystrophy/adrenomyeloneuropathy phenotypes include rapidly progressive childhood, adolescent, and adult cerebral forms (**CASE 8-5**); slowly progressive myelopathic forms (characterized by slowly progressive spastic paraparesis and peripheral neuropathy, often with complete sparing of the brain); and isolated adrenal insufficiency. The patient in **CASE 8-5** had confluent leukodystrophy on brain MRI and conforms to the adult-onset cerebral form of adrenoleukodystrophy/adrenomyeloneuropathy.

Potentially treatable leukodystrophies include multiple sclerosis, cerebrotendinous xanthomatosis, vitamin B_{12} deficiency, folate deficiency, 5-methylenetetrahydrofolate reductase (MTHFR) deficiency,[12] Wilson disease (occasionally causes demyelination), and mitochondrial disorders (less treatable). For this reason, serum vitamin B_{12}, methylmalonic acid, folate, very

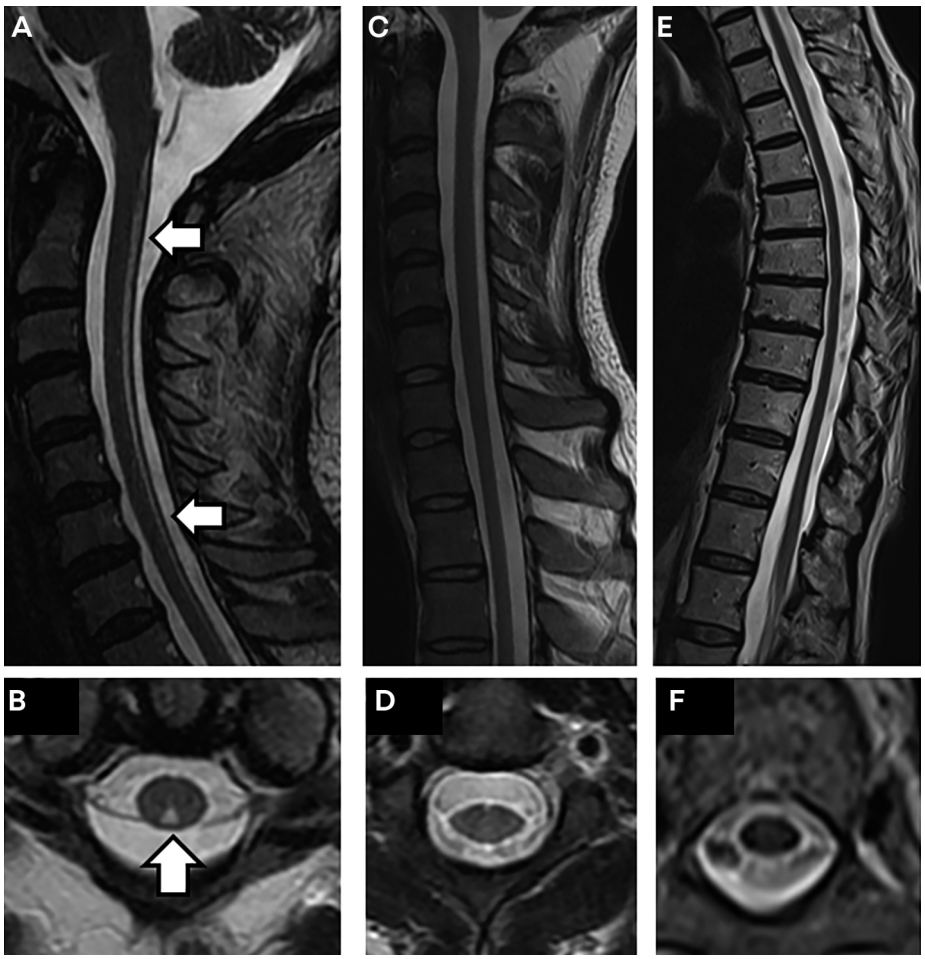

FIGURE 8-1

MRI examples of hereditary myelopathies. Sagittal (*A*) and axial (*B*) T2-weighted images of the cervical spine show spinal cord atrophy accompanied by dorsal T2 hyperintensity (*A, B, arrows*) in a patient with a leukoencephalopathy with brainstem and spinal cord involvement and high lactate associated with the *DARS2* gene mutation. Sagittal (*C*) and axial (*D*) T2-weighted images of the cervical spine show moderate cervical cord atrophy in a young man with X-linked adrenomyeloneuropathy. Sagittal (*E*) and axial (*F*) T2-weighted images of the thoracic spine show diffuse spinal cord atrophy in a patient with hereditary spastic paraplegia accompanied by a mutation in the *SPG7* gene.

Figure courtesy of Eoin Flanagan, MBBCh.

long chain fatty acids, lactate, pyruvate, serum copper, plasma amino acids (including homocysteine and methionine), urine amino acids, and serum cholestanol should be checked in all patients with unexplained spastic paraplegia and those with leukodystrophy.

CNS-Predominant Distal Motor-Sensory Axonopathies

Distal axonopathy predominantly affecting long CNS fibers[2,15,16] in the spinal cord may be entirely motor (eg, PLS) or involve both long motor (corticospinal) and sensory (dorsal column) fibers (eg, uncomplicated HSP). The term *distal* refers to neuropathologic findings that show greater axonal degeneration in the distal ends of these fibers. Postmortem studies (although limited to relatively few of the nearly 100 genetic types of HSP) have shown axonal degeneration that is maximal in corticospinal tracts in distal thoracic segments and only mild

KEY POINTS

- Demyelinating peripheral neuropathy, which may accompany childhood-onset leukodystrophies (eg, Krabbe disease and metachromatic leukodystrophy), may be absent in the rare adolescent- and adult-onset forms of these disorders.
- Childhood-onset adrenoleukodystrophy and adolescent- and adult-onset adrenomyeloneuropathy are X-linked disorders in which *ABCD1* gene mutation leads to impaired peroxisomal beta-oxidation and accumulation of very long chain fatty acids systemically.
- Adrenoleukodystrophy/adrenomyeloneuropathy phenotypes include rapidly progressive childhood, adolescent, and adult cerebral forms; slowly progressive myelopathic forms (characterized by slowly progressive spastic paraparesis and peripheral neuropathy, often with complete sparing of the brain); and isolated adrenal insufficiency.

CASE 8-5

A 46-year-old man presented with a 13-year history of progressive gait disturbance, urinary urgency, dementia, and dysphagia. He first noted symptoms at age 33, when he noticed difficulty driving because his foot would "jump" repetitively when pressing the gas and brake pedals. This was followed by very slowly progressive gait impairment and urinary urgency. Within the previous year, he had quit working (after age 46) because of progressive inability to walk and stand and frequent urinary incontinence. Over the 6 months before presentation, he developed new symptoms of progressive dementia and dysphagia. These symptoms began at approximately age 46 and became severe over the next 6 months.

His family history was significant for a brother who died at age 12 and a maternal cousin (son of his mother's sister) who died in childhood of a neurodegenerative disorder.

Neurologic examination at age 46 demonstrated full alertness, markedly impaired cognition with very slow verbal replies, and difficulty following simple commands. Cranial nerves, including extraocular movements, were normal. Muscle strength was preserved. He had mild spasticity in the arms and moderate to marked spasticity in the legs. Sensory testing was considered unreliable. Deep tendon reflexes were hyperactive (3+) throughout his upper and lower extremities. He was able to stand and take steps (consistent with mild spastic gait) but was quite unsteady and required a wheelchair.

Brain MRI showed diffuse white matter abnormality, including areas of contrast enhancement. Laboratory studies demonstrated increased plasma very long chain fatty acids.

COMMENT

In this patient, neurologic deficits involved corticospinal tracts (symmetric, four-limb spastic weakness with hyperreflexia) and cerebral hemispheres, particularly frontal lobes (subacutely progressive dementia).

Increased very long chain fatty acids indicate peroxisomal disease. The 13-year course of insidiously progressive spastic gait is typical of adrenomyeloneuropathy and is considered the "default pathway" or typical neurologic presentation of individuals with an *ABCD1* mutation. The subsequent rapidly progressive dementia and dysphagia with MRI indicating diffuse brain white matter abnormality are consistent with transition to cerebral adrenoleukodystrophy, which occurs in a small percentage of individuals with adrenomyeloneuropathy. Areas of contrast enhancement in brain white matter are consistent with active inflammatory demyelination, typical of cerebral adrenoleukodystrophy. As they are X-linked disorders, individuals with adrenoleukodystrophy and adrenomyeloneuropathy may have no family history of similarly affected relatives, either because the disorder is transmitted through asymptomatic or mildly symptomatic mothers or because the condition is due to de novo *ABCD1* gene mutation. In this case, the history of a neurodegenerative disorder affecting the patient's brother and maternal cousin was consistent with transmission through unaffected mothers and therefore supportive of an X-linked disorder.

corticospinal tract axonal degeneration in cervical spinal cord segments as well as axonal degeneration of dorsal column fibers that is maximal at the distal ends (in the cervicomedullary region) of the longest fibers (affecting fasciculus gracilis fibers more than shorter fibers [fasciculus cuneatus]). Similar findings are noted in phenotypically similar adrenomyeloneuropathy (FIGURE 8-1B). Clinically, length-dependent axonopathy predominantly involving distal ends of corticospinal tracts may be apparent as an upper-to-lower extremity gradient of upper motor neuron signs; much greater (or much earlier onset) upper motor neuron–pattern impairment is seen in the legs compared to the arms.

Distinguishing between leukodystrophies and CNS-predominant motor-sensory axonopathies at the bedside may be difficult but is important in formulating a differential diagnosis. Signs of corticospinal tract impairment (eg, spastic weakness, hyperreflexia, extensor plantar responses, Hoffman and Trömner signs) are typical of both leukodystrophies and axonopathies. Clinically distinguishing leukodystrophies from CNS-predominant distal motor-sensory axonopathies is based on the presence of additional neurologic findings, particularly cognitive impairment and sensory disturbance. For example, patients with generalized leukodystrophies (those affecting myelin of both the CNS and peripheral nervous system) may also have (although not always) progressive cognitive impairment and may have demyelinating peripheral neuropathy, which usually manifests as stocking distribution of hypesthesia and a gradient of deep tendon reflexes, being reduced in the ankles compared to the

CASE 8-6

A former college football player experienced insidious-onset progressive gait impairment beginning in his late twenties. There was no family history of similar disorder and no parental consanguinity. Neurologic examination demonstrated normal cranial nerves; normal upper extremity muscle strength, tone, and dexterity; bilaterally symmetric lower extremity spasticity (hamstrings, quadriceps, adductors) without weakness; minimally reduced distal lower extremity vibration sensation with normal light touch perception; lower extremity hyperreflexia; and a marked spastic gait. Brain and spinal cord MRI were normal.

COMMENT

Examination showed neurologic deficits referable to corticospinal tracts serving bilateral lower extremities and, to a lesser extent, dorsal column fibers serving bilateral lower extremities. Genetic testing demonstrated a potentially pathogenic mutation in *SPAST* that was absent in his parents. This suggests that the patient's adult-onset apparently sporadic spastic paraplegia was due to a de novo spastin gene mutation causing adult-onset apparently sporadic uncomplicated spastic paraplegia.

SPAST hereditary spastic paraplegia is an autosomal dominant disorder. Therefore, despite having no previous family history of spastic paraparesis, this individual has an approximately 50% risk of transmitting this disorder to each child. This emphasizes the need to consider genetic causes in individuals with possible myelopathy even when there is no family history of similar disorder.

knees. On the other hand, sensory impairment in motor-sensory axonopathies (eg, uncomplicated forms of HSP) is typically predominantly limited to dorsal column impairment affecting longer fibers (fasciculus gracilis) and manifests as mildly impaired vibration perception in the toes with preservation of other sensory modalities. Note is made, however, that peripheral neuropathy may be a complicating feature of many forms of HSP.

The HSPs are a group of nearly 100 disorders in which lower extremity spastic weakness is a major clinical feature.[15,16] There are autosomal dominant, autosomal recessive, X-linked, and maternally inherited (mitochondrial) forms of HSP. When

CASE 8-7

A 13-year-old girl presented for evaluation of gait disturbance, upper extremity tremor and declining hand dexterity. She had been born at 35 weeks gestation after an induced delivery because of premature placental aging. Her speech and developmental milestones had been mildly delayed, and she had mild cognitive impairment that required special education. She was nonetheless fully ambulatory, social, and able to perform self-care activities. By the age of 13 she was noted to have a gait disturbance with incomplete extension of her knees and a tendency to keep her arms flexed while walking. She also was noted to have upper extremity tremors and slowed hand dexterity with impaired ability to write.

Initial neurologic examination at age 13 showed upper extremity tremor, mild dysarthria, and increased tone in the upper and lower extremities, with preserved strength, generalized hyperreflexia, and ankle clonus. Sensory and cerebellar testing were normal. Her balance was impaired, and her gait was slow, narrow-based, and associated with dystonic arm postures.

Slowly, over many years, her cognition, speech, swallowing, gait, and functional use of the upper extremities progressively declined, ultimately causing profound disability. Examination at age 22 showed marked cognitive impairment, marked hypophonia, very slow arm movements, coarse tremor in the hands, mild spasticity in the arms, and marked spasticity in the legs. She had marked weakness in the legs and was unable to lift her legs against gravity or bend her knees. She had generalized hyperreflexia, including a hyperactive jaw jerk, and was nonambulatory. EMG and nerve conduction studies showed only left median neuropathy. Brain MRI at age 23 showed a thin corpus callosum (FIGURE 8-2A) and focal T2 signal hyperintensity anterior to the anterior horns of the lateral ventricles consistent with the ears of the lynx sign (FIGURE 8-2B).[34] At age 31, she was nearly aphonic and was only able to very slowly move her right arm, turn her head, and slowly partially open and close her hands. She had dystonia in her hands and marked spasticity in upper and lower extremities. Progressive dysphagia and weight loss necessitated gastrostomy feeding. Repeat EMG and nerve conduction studies showed length-dependent motor-predominant neuropathy.

The diagnosis of *SPG11* autosomal recessive hereditary spastic paraplegia was made. Genetic testing at age 28 revealed compound heterozygous *SPG11*/spatacsin mutations each causing protein truncation (c.6299 T>A, pLeu2100Stop and c.6598 A>T, p.Lys2200Stop).

HSP symptoms begin in early childhood, gait disturbance may be nonprogressive and resemble spastic diplegic cerebral palsy. HSP symptoms that begin after early childhood typically progress slowly over a number of years. Neurologic examination demonstrates signs of upper motor neuron impairment as various degrees of hyperreflexia, spasticity, and weakness that are exclusively present or markedly greater in the legs than the arms. For example, in the presence of spasticity, weakness, and grade 3 to 4 reflexes in the legs, upper extremities are typically entirely asymptomatic yet show mildly brisk deep tendon reflexes. This is often accompanied by subtle decrease in vibration perception in the toes.

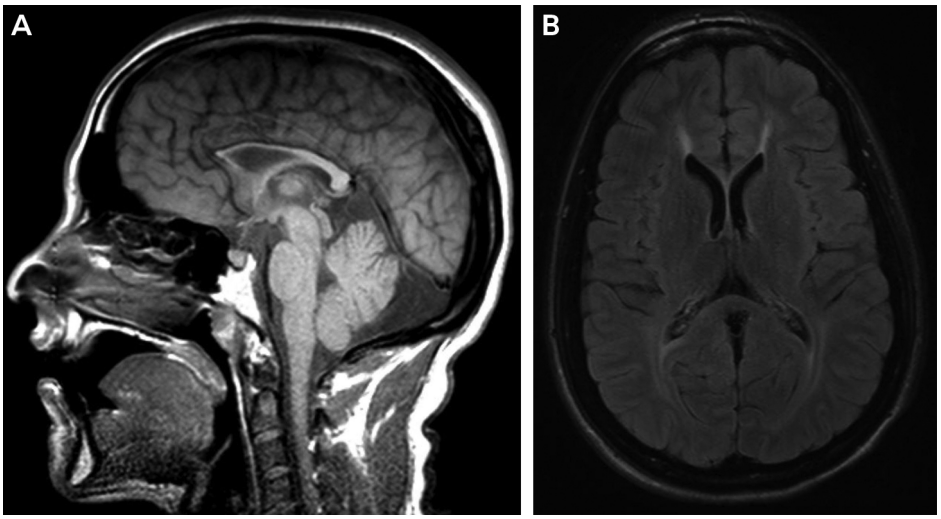

FIGURE 8-2
Imaging of the patient in CASE 8-7. *A*, Sagittal T1-weighted MRI shows a thin corpus callosum. *B*, Axial fluid-attenuated inversion recovery (FLAIR) MRI shows the ears of the lynx sign.

COMMENT

This patient's findings indicated neurologic deficits involving corticospinal tracts serving all extremities (with earlier-appearing and more severe deficits affecting the legs compared to the arms), corticobulbar tracts, extrapyramidal system (dystonia and tremor), and cerebral hemispheres (serving cognition). In addition, EMG and nerve conduction studies provided evidence of motor neuropathy.

SPG11 HSP, the diagnosis in this patient, is among the most common causes of autosomal recessive HSP.[35] Although some individuals have uncomplicated spastic paraparesis, it is typical for patients with *SPG11* HSP to have complicated phenotypes in which progressive spastic paraplegia is associated with other deficits, including cognitive impairment, a thin corpus callosum, extrapyramidal features[36] (which may resemble dopa-responsive dystonia[37] and dopa-unresponsive parkinsonism[38]), upper extremity and bulbar muscle involvement, and peripheral motor neuropathy.[39] Motor neuron degeneration in *SPG11* HSP may mimic ALS.[40,41]

KEY POINTS

- Clinical distinction of leukodystrophies from axonopathies is based on the presence of additional neurologic findings, particularly cognitive impairment, optic neuropathy, deafness, and sensory disturbance.
- Sensory impairment in uncomplicated motor-sensory axonopathies (eg, uncomplicated hereditary spastic paraplegia) typically results in mild dorsal column impairment affecting longer fibers and manifests as impaired vibration perception in the toes with preservation of other sensory modalities.
- *ATL1*/atlastin gene mutation is the most common cause of childhood-onset autosomal dominant hereditary spastic paraplegia. *ATL1* hereditary spastic paraplegia usually causes nonprogressive infantile-onset spastic gait and resembles spastic diplegic cerebral palsy.
- Central nervous system–predominant distal motor-sensory axonopathy (eg, uncomplicated hereditary spastic paraplegia) can be considered analogous to Charcot-Marie-Tooth disease type 2, in which axonopathy affects predominantly the distal ends of long motor and sensory fibers in the peripheral nervous system.
- *SPAST* mutations are the most common cause of autosomal dominant hereditary spastic paraplegia.

HSP's pattern of CNS-predominant motor and sensory axonopathy particularly affecting the distal ends of very long CNS fibers (corticospinal tracts and dorsal columns, respectively) can be considered analogous to Charcot-Marie-Tooth disease type 2, in which distal motor-sensory axonopathy is limited to the peripheral nervous system.

Numerous types of complicated HSP have neurologic involvement in addition to corticospinal tract and dorsal column disturbance. These abnormalities include, for example, peripheral neuropathy, cerebellar ataxia, cognitive impairment, dementia, and distal muscle wasting.[15,16]

SPAST mutations are the single most common cause of dominantly inherited HSP, present in approximately 35% to 45% of such individuals with HSP.[15,16] Individuals with *SPAST* HSP typically manifest with a slowly progressive uncomplicated spastic paraparesis (CASE 8-6).

Recognizing HSP is straightforward when the patient has similarly affected first-degree relatives, neurologic involvement is limited to progressive corticospinal tract impairment (often accompanied by urinary urgency and subtle impairment of vibration perception), and other disorders are excluded by laboratory testing and neuroimaging (FIGURE 8-1C). Recognizing HSP is more difficult when patients have no family history (which may be the case when HSP is autosomal recessive, X-linked, or due to de novo mutation [CASE 8-6]) and when diverse neurologic symptoms are (or eventually become) indicative of more extensive CNS involvement (CASE 8-7).

GENETIC TESTING

Genetic testing is often able to establish a precise diagnosis for patients with hereditary myelopathy. Depending on the clinical syndrome (ie, whether cerebellar ataxia, spastic paraparesis, or cognitive impairment is the predominant symptom), the clinician may choose to either analyze a large panel of genes implicated in spinocerebellar ataxias, HSPs, leukodystrophies, or motor neuron disorders or proceed with whole-exome analysis. Next-generation sequencing (either of gene panels or whole-exome analysis) may not sensitively detect gene copy number variation (deletion or duplication). Chromosome microarray analysis may be useful in this regard.

In general, genetic testing has the highest likelihood of yielding unambiguous information when a clinical diagnosis is made, and syndrome-specific candidate genes are analyzed. It is often difficult to interpret the significance of gene variations (such as those identified in whole-genome or whole-exome sequencing) that have little or no known association with the specific syndrome. It is important to note that identifying a precise genetic cause of the syndrome often does not indicate the extent and severity of the individual's symptoms. Each of these syndromes is highly variable. Significant variation may be seen even between individuals who share exactly the same mutation. For most conditions, little is known about genotype-phenotype correlation and the contribution of modifying genes and potentially modifying environmental factors. For this reason, a cautious approach to prognosis is advised.

CONCLUSION

The clinical and genetic diversity of hereditary myelopathies limits useful generalizations. Nonetheless, it is notable that in the patients described in the

cases in this article (SCA3, autosomal dominant HSP due to *SPAST* mutation, autosomal recessive HSP due to *SPG11* mutation, cerebral adrenoleukodystrophy, Friedreich ataxia, and PLS), spastic gait disturbance was an early and prominent symptom. Identifying associated features (eg, subtle dorsal column signs in HSP; cognitive impairment in cerebral adrenoleukodystrophy; marked dorsal column impairment in Friedreich ataxia; upper extremity and bulbar muscle involvement in PLS; and cognitive, extrapyramidal, and peripheral motor neuropathy in *SPG11* HSP) is essential to clinical recognition of these disorders.

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REFERENCES

1 Marelli C, Salsano E, Politi LS, Labauge P. Spinal cord involvement in adult-onset metabolic and genetic diseases. J Neurol Neurosurg Psychiatry 2019;90(2):211-218. doi:10.1136/jnnp-2018-318666

2 Fink JK. Hereditary myelopathies. Continuum (Minneap Minn) 2008;14(3):58-70. doi:10.1212/01.CON.0000324124.55065.09

3 Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. Nat Rev Dis Primers 2019;5(1):24. doi:10.1038/s41572-019-0074-3

4 Garg N, Park SB, Vucic S, et al. Differentiating lower motor neuron syndromes. J Neurol Neurosurg Psychiatry 2017;88(6):474-483. doi:10.1136/jnnp-2016-313526

5 Tiryaki E, Horak HA. ALS and other motor neuron diseases. Continuum (Minneap Minn) 2014;20(5 Peripheral Nervous System Disorders):1185-1207. doi:10.1212/01.CON.0000455886.14298.a4

6 Verschueren A. Motor neuropathies and lower motor neuron syndromes. Rev Neurol (Paris) 2017;173(5):320-325. doi:10.1016/j.neurol.2017.03.018

7 Peters OM, Ghasemi M, Brown RH Jr. Emerging mechanisms of molecular pathology in ALS. J Clin Invest 2015;125(5):1767-1779. doi:10.1172/JCI71601

8 Taylor JP, Brown RH Jr, Cleveland DW. Decoding ALS: from genes to mechanism. Nature 2016;539(7628):197-206. doi:10.1038/nature20413

9 Raymond GV. Leukodystrophy: basic and clinical. Adv Neurobiol 2017;15:365-382. doi:10.1007/978-3-319-57193-5_14

10 Köhler W, Curiel J, Vanderver A. Adulthood leukodystrophies. Nat Rev Neurol 2018;14:94-105. doi:10.1038/nrneurol.2017.175

11 Lyon G, Fattal-Valevski A, Kolodny EH. Leukodystrophies: clinical and genetic aspects. Top Magn Reson Imaging 2006;17(4):219-242. doi:10.1097/RMR.0b013e31804c99d4

12 Gales A, Masingue M, Millecamps S, et al. Adolescence/adult onset MTHFR deficiency may manifest as isolated and treatable distinct neuro-psychiatric syndromes. Orphanet J Rare Dis 2018;13:29. doi:10.1186/s13023-018-0767-9

13 Cui J, Wang Y, Zhang H, et al. Isolated subacute combined degeneration in late-onset cobalamin C deficiency in children: two case reports and literature review. Medicine (Baltimore) 2019;98(39):e17334. doi:10.1097/MD.0000000000017334

14 Messing A. Alexander disease. Handb Clin Neurol 2018;148:693-700. doi:10.1016/B978-0-444-64076-5.00044-2

15 Fink JK. Upper motor neuron disorders: hereditary spastic paraplegia and primary lateral sclerosis. In: Johnston MV, Adams HP, Fatemi A, editors. Neurobiology of disease. 2nd ed. Oxford University Press, 2016: 236-240.

16 Fink JK. The hereditary spastic paraplegias. In: Rosenberg RN, Pascual JM, editors. Rosenberg's molecular and genetic basis of neurologic and psychiatric disease. 6th ed. Academic Press, 2020:891-902.

17 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

18 Isohanni P, Linnankivi T, Buzkova J, et al. DARS2 mutations in mitochondrial leucoencephalopathy and multiple sclerosis. J Med Genet 2010;47(1):66-70. doi:10.1136/jmg.2009.068221

19 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

20 Bird TD. Hereditary ataxia overview. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews. University of Washington, Seattle; 1993-2020. Published October 28, 1998. Updated July 25, 2019. Accessed December 7, 2020. ncbi.nlm.nih.gov/books/NBK1138/

21 Paulson H. Machado-Joseph disease/spinocerebellar ataxia type 3. Handb Clin Neurol 2012;103:437-449. doi:10.1016/B978-0-444-51892-7.00027-9

22 Cossée M, Schmitt M, Campuzano V, et al. Evolution of the Friedreich's ataxia trinucleotide repeat expansion: founder effect and premutations. Proc Natl Acad Sci U S A 1997;94(14):7452-7457. doi:10.1073/pnas.94.14.7452

23 Cook A, Giunti P. Friedreich's ataxia: clinical features, pathogenesis and management. Br Med Bull 2017;124(1):19-30. doi:10.1093/bmb/ldx034

24 Greene E, Mahishi L, Entezam A, et al. Repeat-induced epigenetic changes in intron 1 of the frataxin gene and its consequences in Friedreich ataxia. Nucleic Acids Res 2007;35(10):3383-3390. doi:10.1093/nar/gkm271

25 Turner MR, Barohn RJ, Corcia P, et al. Primary lateral sclerosis: consensus diagnostic criteria. J Neurol Neurosurg Psychiatry 2020;91(4):373-377. doi:10.1136/jnnp-2019-322541

26 Yang Y, Hentati A, Deng HX, et al. The gene encoding alsin, a protein with three guanine-nucleotide exchange factor domains, is mutated in a form of recessive amyotrophic lateral sclerosis. Nat Genet 2001;29(2):160-165. doi:10.1038/ng1001-160

27 de Vries BS, Spreij LA, Rustemeijer LMM, et al. A neuropsychological and behavioral study of PLS. Amyotroph Lateral Scler Frontotemporal Degener 2019;20(5-6):376-384. doi:10.1080/21678421.2019.1620284

28 Lapchak PA. Neuronal dysregulation in stroke-associated pseudobulbar affect (PBA): diagnostic scales and current treatment options. J Neurol Neurophysiol 2015;6(5):323. doi:10.4172/2155-9562.1000323

29 Floeter MK, Katipally R, Kim MP, et al. Impaired corticopontocerebellar tracts underlie pseudobulbar affect in motor neuron disorders. Neurology 2014;83(7):620-627. doi:10.1212/WNL.0000000000000693

30 Lyon G, Hagberg B, Evrard P, et al. Symptomatology of late onset Krabbe's leukodystrophy: the European experience. Dev Neurosci 1991;13(4-5):240-244. doi:10.1159/000112167

31 Garbern JY, Yool DA, Moore GJ, et al. Patients lacking the major CNS myelin protein, proteolipid protein 1, develop length-dependent axonal degeneration in the absence of demyelination and inflammation. Brain 2002;125(pt 3):551-561. doi:10.1093/brain/awf043

32 Moser HW, Mahmood A, Raymond GV. X-linked adrenoleukodystrophy. Nat Clin Pract Neurol 2007;3(3):140-151. doi:10.1038/ncpneuro0421

33 Engelen M, Kemp S, de Visser M, et al. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. Orphanet J Rare Dis 2012;7:51. doi:10.1186/1750-1172-7-51

34 Pascual B, de Bot ST, Daniels MR, et al. "Ears of the lynx" MRI sign is associated with SPG11 and SPG15 hereditary spastic paraplegia. AJNR Am J Neuroradiol 2019;40(1):199-203. doi:10.3174/ajnr.A5935

35 Stevanin G. Spastic paraplegia 11. In: Adam MP, Ardinger HH, Pagon RA, et al, editors. GeneReviews. University of Washington, Seattle; 1993-2020. Published March 27, 2008. Updated December 19, 2019. Accessed December 7, 2020. ncbi.nlm.nih.gov/books/NBK1210/

36 Faber I, Martinez ARM, de Rezende TJR, et al. SPG11 mutations cause widespread white matter and basal ganglia abnormalities, but restricted cortical damage. Neuroimage Clin 2018;19:848-857. doi:10.1016/j.nicl.2018.05.031

37 Wijemanne S, Shulman JM, Jimenez-Shahed J, et al. SPG11 mutations associated with a complex phenotype resembling dopa-responsive dystonia. Mov Disord Clin Pract 2015;2(2):149-154. doi:10.1002/mdc3.12144

38 Faber I, Martinez ARM, Martins CR Jr, et al. SPG11-related parkinsonism: clinical profile, molecular imaging and l-dopa response. Mov Disord 2018;33:1650-1656. doi:10.1002/mds.27491

39 Manole A, Chelban V, Haridy NA, et al. Severe axonal neuropathy is a late manifestation of SPG11. J Neurol 2016;263(11):2278-2286. doi:10.1007/s00415-016-8254-5

40 Branchu J, Boutry M, Sourd L, et al. Loss of spatacsin function alters lysosomal lipid clearance leading to upper and lower motor neuron degeneration. Neurobiol Dis 2017;102:21-37. doi:10.1016/j.nbd.2017.02.007

41 Daoud H, Zhou S, Noreau A, et al. Exome sequencing reveals SPG11 mutations causing juvenile ALS. Neurobiol Aging 2012;33(4):839.e5-839.e9. doi:10.1016/j.neurobiolaging.2011.11.012