Hereditary Spastic Paraplegia

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The hereditary spastic paraplegias (HSPs) comprise a large group of inherited neurologic disorders. HSP is classified according to the mode of inheritance, the HSP locus when known, and whether the spastic paraplegia syndrome occurs alone or is accompanied by additional neurologic or systemic abnormalities. Analysis of 11 recently discovered HSP genes provides insight into HSP pathogenesis. Hereditary spastic paraplegia is a clinical diagnosis for which laboratory confirmation is sometimes possible, and careful exclusion of alternate and co-existing disorders is an important element in HSP diagnosis. Treatment for HSP is presently limited to symptomatic reduction of muscle spasticity, reduction in urinary urgency, and strength and gait improvement through physical therapy. Prenatal genetic testing in HSP is possible for some individuals with the increasing availability of HSP gene analysis.

Introduction

The hereditary spastic paraplegias (HSPs) comprise a large group of inherited neurologic disorders in which the predominant symptom is lower extremity spastic weakness [1••,2–4] (http://www.geneclinics.org/profiles/hsp/ and http://www.med.umich.edu/hsp and http://www.sp-foundation.org). The prevalence of HSP has been estimated to range from 1.27 to 9.6 per 100,000 [5,6].

Classification by Mode of Inheritance, HSP Syndrome, and Genetic Locus

Hereditary spastic paraplegia is classified according to the mode of inheritance (autosomal dominant, autosomal recessive, and X-linked HSP), according to the HSP locus when known (designated SPG loci 1 through 30 in order of their discovery, Table 1), and according to whether the spastic paraplegia syndrome occurs alone ("uncomplicated" HSP, which may be accompanied by urinary urgency and decreased vibration sensation in the toes) or is accompanied by additional neurologic or systemic abnormalities ("complicated HSP"). For example, "complicated HSP" included syndromes in which spastic paraplegia is accompanied by mental retardation, ataxia, peripheral neuropathy, deafness, cataracts, or muscle atrophy.

In general, families with well-documented "uncomplicated" HSP do not appear to be at risk of transmitting "complicated" HSP syndromes. There is some controversy, however, as our understanding of the full phenotypic spectrum of uncomplicated HSP syndromes emerges. For example, although the majority of SPG4/spastin subjects have uncomplicated HSP, some SPG4 HSP patients also have cognitive impairment, ataxia, epilepsy, and even lower motor neuron disturbance [7,8].

Neuropathology

Postmortem studies of uncomplicated HSP show axon degeneration limited to the central nervous system(CNS) affecting primarily the distal ends of the longest descending motor fibers (corticospinal tracts, with maximal involvement in the thoracic spinal cord) and the distal ends of the longest ascending fibers (fasciculus gracilis fibers, with maximal involvement in the cervico-medullary region) [9–15]. Demyelination of fibers undergoing degeneration occurs in uncomplicated HSP and is considered to be the consequence of primary axonal degeneration in uncomplicated HSP. Decreased numbers of cortical motor neurons and anterior horn cells have been observed in HSP [12,13].

The neuropathology of uncomplicated HSP (distal degeneration of long sensory and motor axons in the CNS) is parallel to that of Charcot-Marie-Tooth (CMT) type II, in which distal motor and sensory axon degeneration is limited to the peripheral nervous system. Indeed, there is evidence that at least one form of HSP may share similar pathophysiologic mechanisms with CMT type II: SPG10 HSP is due to mutation in kinesin heavy chain (KIF5A) [16], a molecular motor involved in axonal transport; mutations in another kinesin (KIF1B) cause CMT type 2A1 [17].

Table 1. HSP loci

Spastic gait (SPG) locus	HSP syndrome	Protein name and function	Gene testing	Study
Autosomal dominant HSP				
SPG3A (14q11-q21)	Uncomplicated HSP: symptoms usually begin in childhood (and may be nonprogressive); symptoms may also begin in adolescence or adulthood and worsen insidiously. Genetic nonpenetrance reported. De novo mutation reported presenting as spastic diplegic cerebral palsy.	Atlastin: unknown function, appears to be Golgi protein that shares homology with guanylate binding protein 1, a dynamin family GTPase	ADL	[57,70,103,104]
SPG4 (2p22)	Uncomplicated HSP, symptom onset in infancy through senescence, single most common cause of autosomal dominant HSP (40%); some subjects have late-onset cognitive impairment.	Spastin: cytosolic (or possibly nuclear) protein with AAA domain that appears to interact with microtubules and may play a role in microtubule severing.	ADL	[20,27,43,60,71, 105,106]
SPG6 (15q11.1)	Uncomplicated HSP: prototypical late-adolescent, early-adult onset, slowly progressive uncomplicated HSP.	NIPA1: neuron specific protein of unknown function, 9 alternating hydrophobic-hydrophilic domains predicts integral membrane localization	ADL	[72,107–109]
SPG8 (8q23-q24)	Uncomplicated HSP	Unknown	No	[110,111]
SPG9 (10q23.3-q24.2)	Complicated: spastic paraplegia associated with cataracts, gastroesophageal reflux, and motor neuronopathy	Unknown	No	[112]
SPG10 (12q13)	Uncomplicated HSP or complicated by distal muscle atrophy	Kinesin heavy chain (KIF5A): is a molecular motor that participates in axonal transport of organelles and macromolecules	Research	[113,114]
SPG12 (19q13)	Uncomplicated HSP	Unknown		[111]
SPG13 (2q24-34)	Uncomplicated HSP: adolescent and adult onset	Chaperonin 60 (also known as heat shock protein 60): mitochondrial protein	Research	[31,115]
SPG17 (11q12-q14)	Complicated: spastic paraplegia associated with amyotrophy of hand muscles (Silver syndrome)	BSCL2/seipin: integral membrane protein in endoplasmic reticulum	Research	[55,56,116]
SPG19 (9q33-q34)	Uncomplicated HSP	Unknown	No	[117]
SPG29 (1p31.1-21.1)	Complicated: spastic paraplegia associated with hearing impairment and persistent vomiting due to hiatal hernia inherited	Unknown	No	
SPG29 (2p12)	Uncomplicated HSP	Unknown	No	[118]
Autosomal recessive HSP				
SPG5 (8p)	Uncomplicated	Unknown	No	[34,119–121]
SPG7 (16q)	Uncomplicated or complicated: variably associated with mitochondrial abnormalities on skeletal muscle biopsy and dysarthria, dysphagia, optic disc pallor, axonal neuropathy, and evidence of "vascular lesions," cerebellar atrophy, or cerebral atrophy on cranial MRI	Paraplegin: mitochondrial metalloprotease	Research	[36,122]
SPG11 (15q)	Uncomplicated or complicated: spastic paraplegia variably associated with thin corpus callosum, mental retardation, upper extremity weakness, dysarthria, and nystagmus; 50% of autosomal recessive HSP is considered to be SPG11	Unknown	No	[123,124]

*Including DuPont Nemours Clinic and Baylor University.
ADL—Athena Diagnostics Laboratory; HSP—hereditary spastic paraplegia; L1CAM—L1 cell adhesion molecule.

Table 1. HSP loci ***(continued)***

Spastic gait (SPG) locus	HSP syndrome	Protein name and function	Gene testing	Study
SPG14 (3q27-28)	Complicated: spastic paraplegia associated with mental retardation and distal motor neuropathy	Unknown	No	[125]
SPG15 (14q)	Complicated: spastic paraplegia associated with pigmented maculopathy, distal amyotrophy, dysarthria, mental retardation, and further intellectual deterioration (Kjellin syndrome).	Unknown	No	[126]
SPG20 (13q)	Complicated: spastic paraplegia associated with distal muscle wasting (Troyer syndrome)	Spartin: N-terminal region similar to spastin; homologous to proteins involved in the morphology and trafficking of endosomes	Research	[30,54,127,128]
SPG21	Complicated: spastic paraplegia associated with dementia, cerebellar and extrapyramidal signs, thin corpus callosum, and white matter abnormalities (Mast syndrome)	Maspardin: protein localizes to endosome/trans-Golgi vesicles, may function as protein transport and sorting.	Research	[129]
SPG22 (19q13.3)	Complicated: spastic paraplegia accompanied by distal wasting	Neuropathy target esterase	Research	[130]
SPG23 (1q24-q32)	Complicated: childhood onset HSP associated with skin pigment abnormality	Unknown	No	[131]
SPG24 (13q14)	Complicated: childhood onset HSP variably complicated by spastic dysarthira and pseudobulbar signs	Unknown	No	[132]
SPG26 (12p11.1-12q14)	Complicated: childhood onset progressive spastic paraparesis with dysarthria and distal amyotrophy in both upper and lower limbs, intellectual impairment	Unknown	No	[133]
SPG27 (10q22.1-q24.1)	Uncomplicated or complicated: adult-onset, uncomplicated spastic paraplegia; or spastic paraplegia associated with dysarthria	Unknown	No	[134]
SPG28 (14q21.3-q22.3)	Uncomplicated: childhood-onset progressive spastic gait	Unknown	No	[135]
SPG29	Uncomplicated: childhood onset	Unknown	No	[136]
SPG30	Complicated: spastic paraplegia, distal wasting, saccadic ocular pursuit, peripheral neuropathy, mild cerebellar signs	Unknown	No	[137]
SPOAN syndrome (11q23)	Complicated: spastic paraplegia, optic atrophy, neuropathy (SPOAN)	Unknown	No	[138]
X-linked HSP				
SPG1 (Xq28)	Complicated: associated with mental retardation, and variably, hydrocephalus, aphasia, and adducted thumbs	L1CAM	Research	[139]
SPG2 (Xq28)	Complicated: variably associated with MRI evidence of central nervous system white matter abnormality; may have peripheral neuropathy	Proteolipid protein	Several laboratories*	[39,140–142]
SPG16 (Xq11.2-q23)	Uncomplicated or complicated: associated with motor aphasia, reduced vision, nystagmus, mild mental retardation, and dysfunction of the bowel and bladder	Unknown	No	[143,144]

*Including DuPont Nemours Clinic and Baylor University.
ADL—Athena Diagnostics Laboratory; HSP—hereditary spastic paraplegia; L1CAM—L1 cell adhesion molecule.

Insights into HSP Pathophysiology

Analysis of 11 recently discovered HSP genes (Table 1) provides insight into HSP pathogenesis [10]. Rather than conforming to one extended gene or protein family, HSP proteins are diverse. This suggests that diverse biochemical abnormalities produce axon degeneration in various genetic types of HSP [18]. These abnormalities include primary axonal transport abnormality, disturbance in Golgi function, mitochondrial abnormality, dysmyelination, and disturbance in corticospinal tract development. It is likely, though as yet unproven, that these disparate biochemical disturbances converge into one or more common pathways.

Disturbance in axonal transport or axonal cytoskeleton was initially proposed as an HSP mechanism because degeneration is maximal at the ends of the longest CNS axons. The clearest examples of axonal transport disturbance are autosomal dominant SPG10 HSP due to KIF5A mutation, and autosomal dominant SPG4 due to spastin mutation. KIF5A is a molecular motor component involved in axonal transport of organelles and macromolecules. Spastin has been shown to interact with microtubules and to be involved in microtubule severing [19–28].

A role for Golgi abnormality in HSP pathophysiology is suggested by SPG3A HSP due to SPG3A/atlastin mutation, and SPG17 due to SPG17/spartin mutation. Although the functions of these proteins are unknown, both atlastin and spartin have been shown to be localized to Golgi [29,30].

Evidence that primary mitochondrial abnormality underlies at least some forms of HSP is indicated by the fact that two HSP genes encode integral mitochondrial proteins: chaperonin 60/heat shock protein 60, mutations in which cause autosomal dominant uncomplicated SPG13 HSP [31]; and paraplegin, mutations in which cause autosomal recessive SPG7 HSP [32–35]. Some SPG7 HSP subjects have morphologic and histochemical abnormalities of mitochondria in skeletal muscle biopsy [36].

Axon degeneration in at least one form of HSP arises from glial abnormality rather than intrinsic neuron abnormality. Proteolipid protein (PLP; mutations in which cause X-linked SPG2) is an intrinsic myelin protein. PLP gene mutations cause both Pelizaeus-Merzbacher disease [37], an X-linked infantile-onset dysmyelinating disorder; and a childhood onset slowly progressive spastic gait disorder (X-linked SPG2 HSP) [38–40].

At least one form of HSP appears to reflect disturbance in corticospinal tract development rather than being a progressive degenerative disorder. L1 cell adhesion molecule (L1CAM) is involved in neuronal migration and corticospinal tract development. L1CAM mutations cause a variety of X-linked neurologic disorders including a complicated form of HSP (SPG1) and X-linked hydrocephalus [41].

Symptoms and Course of Uncomplicated HSP

Gait disturbance is the hallmark feature of uncomplicated HSP. Symptom may begin at any age, from very early childhood through the eighth decade. When symptoms begin in very early childhood (before age 2 years) they may be essentially nonprogressive. The relatively nonprogressive spastic gait (toe walking) of early-onset HSP may closely resemble that of spastic diplegic cerebral palsy [42]. On the other hand, when symptoms begin after early childhood (after age 6 years), gait disturbance usually worsens insidiously over many years. Onset and progression of symptoms over weeks or months has not been reported for HSP and would suggest alternative or co-existing disorders. Many individuals report that lower extremity spasticity increases in cold weather, following exertion, and in the evening.

Urinary urgency is a common symptom of HSP and occasionally is an early or presenting symptom. Cognitive impairment may be a feature of SPG11 HSP (the most common type of recessively inherited HSP) and several other forms of complicated HSP (Table 1). In addition, cognitive disturbance and late-onset dementia have been reported in some patients with SPG4 HSP, which is the most common form of dominantly inherited HSP [43–50]. The prevalence of cognitive impairment in this and other forms of otherwise uncomplicated HSP is not known.

Neurologic Examination

Neurologic examination of HSP subjects begins with gait analysis because gait disturbance is the primary symptom of HSP. Though spastic gait is observed in all subjects with HSP, the manner in which gait is abnormal is often variable between individuals [51]. HSP subjects generally exhibit reduced stride length due to difficulty lifting the legs and dorsiflexing the feet, variable degrees of anteriorly shifted foot strike (ranging from striking the floor with the mid-lateral plantar surface, the balls of the feet, or toe-walking), and a tendency to drag their toes (due to decreased hip flexion and foot dorsiflexion). Circumduction, "scissoring" (due to adductor muscle spasticity), hyperlordosis, and hyperextension at the knees may also be seen. The ability to walk on the heels is generally compromised. Careful analysis of each patient's gait is useful to provide specific exercise recommendations and to determine which subjects would benefit most from spasticity-reducing medication, and which subjects would benefit from ankle-foot orthotic devices.

Neurologic examination of individuals with uncomplicated HSP reveals lower extremity hyperreflexia, spasticity (particularly in the hamstrings, adductor, and gastrocnemius-soleus muscles), weakness (particularly in the hamstrings, iliopsoas, and tibialis anterior muscles), and extensor plantar responses (rarely, plantar responses remain flexor despite obvious lower extremity spasticity and pathologic hyperreflexia). Lower extremity involve-

ment is typically symmetric (or nearly symmetric). Pes cavus (high arched feet) is common in HSP, although it may be absent in definitely affected subjects.

Spasticity and weakness occur in variable proportions in HSP [13,52]. Whereas some patients have significant weakness, other patients have only marked spasticity with no demonstrable weakness. Assessing the relative contributions of weakness versus spasticity helps determine which patients' gait would benefit from spasticity reducing medication.

It is common for subjects with uncomplicated HSP to have mildly increased reflexes (grade 3+) in their upper extremities. Nonetheless, mild upper extremity hyperreflexia in uncomplicated HSP is not accompanied by upper extremity spasticity, weakness, slowness of movement, or reduced dexterity and produces no functional disturbance. Spastic paraplegia that becomes associated with slowly progressive, functionally limiting, upper extremity spasticity and weakness would suggest a diagnosis of primary lateral sclerosis (PLS) rather than uncomplicated hereditary spastic paraplegia.

Mildly decreased vibratory sensation in the toes is often observed in uncomplicated HSP. Proprioception and other sensory modalities are normal. Vibratory sensation impairment, when present and not attributable to other causes (such as peripheral neuropathy or cervical spondylosis), is a helpful sign distinguishing HSP from early phases of amyotrophic lateral sclerosis (ALS) and PLS, neither of which involve dorsal column impairment [53]. Distal vibratory sense impairment in uncomplicated HSP is mild. Severe dorsal column disturbance is not typical of uncomplicated HSP and would suggest alternative diagnoses (such as Friedreich's ataxia, subacute combined degeneration, and tertiary syphilis) or co-existing disorders.

Clinical Variability of HSP

Hereditary spastic paraplegia has significant clinical variability. As with any large group of genetically heterogeneous disorders, there may be significant clinical variation between different genetic types of HSP. Such clinical differences include age of symptom onset, course, degree of disability, and presence of other neurologic deficits of systemic involvement. Although some forms of "uncomplicated" HSP (eg, uncomplicated SPG4, SPG8, and SPG6 HSP) are extremely similar and not reliably distinguished by clinical parameters, various forms of complicated HSP are recognized by unique clinical syndromes. For example, autosomal recessive SPG20 HSP and autosomal dominant SPG17 HSP have distal muscle wasting (conforming to Troyer [30,54] and Silver syndromes [55,56] respectively) that is not a feature of SPG3A, SPG4, SPG6, or SPG8 "uncmomplicted" HSP.

The age at which HSP symptoms begin may vary significantly between different genetic types of HSP. For example, gait disturbance in SPG10, SPG3A, and SPG12 HSP4 typically begins in childhood whereas symptom onset in SPG4, SPG13, SPG8, and SPG6 HSP is typically in late adolescence, or adulthood. Nonetheless, within a given type of HSP there is a wide range of ages at which symptoms begin. For example, although SPG3A typically begins in early childhood, some SPG3A HSP patients have symptom onset in late childhood, adolescence, or adulthood [57–59]. Similarly, although the average age of symptom onset for SPG4 HSP is usually between age 20 and age 40 years [4], symptom onset has ranged from age 2 to 70 years [60].

The causes of clinical variation in a given type of HSP are usually not known. For SPG4 HSP, meta-analysis of 75 families did not show a correlation between spastin mutation class (missence, aberrant splicing, frameshift, premature truncation mutations) and age-of-symptom onset [61]. On the other hand, unique phenotypes may at times be associated with specific mutations. For example, although SPG4 and SPG3A HSP are typically "uncomplicated," ataxia is associated with SPG4/spastin mutation GLN490Stop7 and peripheral axonal neuropathy has been associated with SPG3A/atlastin mutation M408V [62].

In some HSP families, the age of symptom onset and severity are relatively uniform. This is most often seen with very early onset HSP. In other families, the range of age of symptom onset may vary by two decades or more. The cause of this variation is uncertain, although the effect of modifying genes is likely. One source of modifying genes is the HSP genes themselves. Recently, benign variations in the SPG4/spastin gene (L44 and Q45) were associated with markedly earlier symptom onset in subjects with pathogenic mutations in SPG4/spastin's AAA domain [63].

Disability due to HSP is age dependent and may be variable between different genetic types of HSP as well as within a given family [4]. For example, we have seen SPG3A and SPG6 HSP families in which several elderly subjects were only mildly affected whereas most subjects had moderate to marked disability.

Complicated forms of HSP are often variable within a given family. For example, although SPG9, SPG10, and SPG17 are characterized by spastic paraplegia associated with motor neuropathy or distal wasting, these "complicating features" may not be present in each affected subject. In such families, therefore, affected subjects may have either complicated or uncomplicated HSP.

Some HSP families exhibit progressively younger age of symptom onset in succeeding generations, a pattern that is consistent with genetic anticipation [64]. It is notable that in such cases where the gene mutation is identified, it is due to a point mutation and not a tandem repeat expansion (which cause genetic anticipation in many other inherited neurologic disorders).

HSP Diagnostic Criteria

Hereditary spastic paraplegia is a clinical diagnosis for which laboratory confirmation is sometimes possible.

Diagnostic criteria for HSP are 1) the presence of HSP symptoms (spastic weakness affecting both legs approximately symmetrically, often accompanied by urinary urgency) that may be either essentially nonprogressive (when HSP begins in very early childhood) or insidiously progressive; 2) neurologic signs of bilateral (typically symmetric) lower extremity spasticity, hyperreflexia, extensor plantar responses (rarely flexor), often accompanied by mildly decreased vibration sensation in the toes; 3) family history of the same disorder; and 4) exclusion of other disorders. In addition to these criteria, complicated forms of HSP are recognized by syndrome-specific signs (Table 1).

The absence of family history does not exclude the diagnosis of HSP. Family history may be absent because of incomplete ascertainment, de novo mutation, late age of symptom onset (children are sometimes affected before a parent is affected), mild and nondisabling symptoms that are attributed to other etiologies, autosomal recessive inheritance (carriers are typically asymptomatic), and X-linked inheritance. "Apparently sporadic spastic paraplegia" refers to subjects who have all signs and symptoms of HSP but who do not have apparent family history of the disorder. Mutations in HSP genes are identified in approximately 5% to 10% of such subjects.

The diagnosis of HSP should be questioned, however, when the course is atypical (abrupt symptom onset, salutatory worsening, or marked symptom progression over several months), when neurologic involvement is unilateral or markedly asymmetric, when spasticity and weakness involve upper extremities (beyond asymptomatic upper extremity hyperreflexia) or bulbar muscles, or in the presence of spinal sensory level.

The presence of significant muscle atrophy and fasciculations in a subject with lower extremity spasticity would suggest alternative disorders (such as ALS) rather than uncomplicated HSP. Significant muscle atrophy is not regarded as a typical feature of uncomplicated HSP. There are notable exceptions, however. SPG3A HSP, though usually "uncomplicated," has been associated with distal wasting in some subjects with SPG3A/atlastin mutation M408V [62]. Late-onset, slowly progressive ALS has been reported in a subject with SPG4/spastin mutation [8].

In contrast to "uncomplicated" HSP, it is now apparent that lower motor neuron involvement occurs in many forms of "complicated" HSP. Troyer syndrome (SPG20) and Silver syndrome (SPG17) are autosomal recessive and autosomal dominant forms, respectively, of HSP associated with distal muscle wasting [54,55]. In addition, peripheral motor axon degeneration and/or muscle wasting have been reported in SPG7, SPG10, SPG14, SPG15, and SPG26 HSP [10].

Differential Diagnosis

Careful exclusion of alternate and co-existing disorders is an important element in HSP diagnosis. The differential diagnosis includes disorders with significantly different prognosis (eg, ALS and PLS) and conditions for which specific treatments are available (eg, vitamin B_{12} deficiency and dopa-responsive dystonia).

The differential diagnosis primarily includes 1) structural disorders of the brain and spinal cord (eg, tethered cord syndrome, spinal cord compression from degenerative spondylosis or neoplasm); 2) disturbance of CNS white matter (eg, vitamin B_{12} deficiency, multiple sclerosis, adrenomyeloneuropathy) [65,66]; 3) infectious diseases (tropical spastic paraplegia due to HTLV1 infection, which may be familial, and pachymeningitis due to tertiary syphilis); 4) other degenerative neurologic disorders (eg, Friedreich's ataxia, which may have spasticity rather than arreflexia [67], Machado-Joseph disease, PLS [53], ALS, and spinal cord arteriovenous malformation); and 5) environmental toxins (such as lathyrism and organophosphate-induced delayed neuropathy). It is always important to consider the possibility of dopa-responsive dystonia [68], particularly when evaluating childhood-onset gait disturbance [69].

HSP gene analysis

Gene analysis for HSP is increasingly available. For example, analysis of SPG3A/atlastin [70], SPG4/spastin [71], and SPG6/NIPA1 [72] genes (available through Athena Diagnostics Laboratory, Boston, MA) will confirm the diagnosis of HSP in 60% of subjects for whom the disorder is dominantly inherited. PLP gene analysis (to diagnose SPG2 HSP) is performed at various centers, including the DuPont Nemours Clinic. When an HSP gene mutation is identified in an affected subject, this information can be applied to prenatal genetic testing [73,74].

Despite its utility, there are important limits to HSP gene testing. Presently, gene testing is commercially available for only a subset of HSP genes and only examines the coding sequences and intron-exon splice junctions of these genes. Sequence abnormalities in gene promoter and other gene regulatory elements (implicated in approximately 10% of SPG4 HSP) are not assessed. Therefore, although identification of an HSP gene mutation can confirm the clinical diagnosis of HSP, the absence of a detectable mutation among currently available HSP genes does not exclude the diagnosis.

There is increasing recognition of incomplete genetic penetrance (the existence of asymptomatic subjects who have pathogenic HSP gene mutations) in dominantly inherited HSP (the existence of asymptomatic subjects who have pathogenic HSP gene mutations) as well clinical variability including late age of symptom onset and mild symptoms. Furthermore, there is usually no reliable association between specific mutations (eg, which specific SPG4/spastin gene mutation) and clinical features such as disease severity and age of symptom onset. Therefore, although an asymptomatic subject shown to possess an HSP gene mutation previously identified in affected

family members would be considered at increased risk of developing HSP, it would not be possible to predict with certainty when symptoms would begin or the extent of disability. For these reasons, HSP gene testing is usually reserved for confirming the diagnosis in affected subjects and is generally not recommended for asymptomatic subjects in HSP families.

Laboratory, neuroimaging, and neurophysiologic studies

The primary role of laboratory, neuroimaging, and neurophysiologic studies is to exclude alternative disorders. In addition, neuroimaging and neurophysiologic studies are useful to assess the extent of neurologic involvement, and to classify more precisely the type of HSP. This information is helpful when estimating the prognosis. Routine laboratory evaluations such as serum lactate, pyruvate, long chain fatty acids, and cerebrospinal fluid examination are normal in subjects with HSP.

Magnetic resonance imaging of the brain and spinal cord are important to exclude alternative disorders including multiple sclerosis, leukodystrophies, and structural abnormalities affecting the brain or spinal cord. Conventional brain MRI is normal in uncomplicated HSP. Brain MRI in several forms of complicated HSP reveals syndrome-specific abnormalities such as thin corpus callosum in SPG11 [75], cerebral or cerebellar abnormalities in SPG7, and hydrocephalus in SPG1. MRI of the spinal cord in uncomplicated HSP may be entirely normal or show atrophy, particularly involving the thoracic spinal cord [7,43,49,76].

Electromyography (EMG) nerve conduction studies (NCS) are usually normal in uncomplicated HSP. Subclinical sensory neuropathy in otherwise uncomplicated HSP has been described [77,78]. In contrast to "uncomplicated" HSP, a number of forms of "complicated" HSP (eg, SPG10, SPG14, SPG15, and SPG26 HSP) are associated with peripheral neuropathy and evidence of lower motor neuron involvement (Table 1).

Axon degeneration in uncomplicated HSP often involves dorsal column fibers in addition to corticospinal tracts. Not unexpectedly, somatosensory evoked potentials recorded from the lower extremities often show delayed conduction [79–83]. When present, this finding helps distinguish HSP subjects from those in which lower extremity spasticity is a phase of PLS or ALS (in which vibration sensation and dorsal column function are normal) [53].

Corticospinal tract conduction velocity, measured by cortical evoked potentials, is often reduced in HSP. Whereas cortical evoked potentials recorded from the legs often show reduced conduction velocity and amplitude [84–87], those recorded from cervical spinal segments are typically normal or show only mildly reduced conduction velocity [86].

Muscle biopsy in some but not all subjects with SPG7 HSP (due to mutations in the mitochondrial metalloprotease paraplegin) shows ragged red fibers and cytochrome oxidase C negative fibers [36]. Mitochondrial abnormality is not a general feature of all types of HSP. Muscle biopsies and analysis of oxidative phosphorylation enzymes have been normal in autosomal dominant "uncomplicated" SPG3A, SPG4, SPG6, and SPG8 HSP.

Treatment

Treatment for HSP is presently limited to symptomatic reduction of muscle spasticity (through muscle stretching exercises and medications such as lioresal (oral or intrathecal), dantrolene, or tizanidine [88–90]; reduction in urinary urgency (through medications such as oxybutyinin); and strength and gait improvement through physical therapy. Individuals with HSP consistently report the benefits of stretching for 10 minutes twice a day and daily physical exercise designed to improve lower extremity strength and general cardiovascular conditioning. Ankle-foot orthotic devices are often useful to reduce toe dragging in HSP subjects.

Prognosis

Subjects who experience HSP symptom onset in the first several years of life often show very little worsening through the first two decades. Thereafter, gait may worsen slowly, owing in part to advancing spasticity and general muscular deconditioning. When HSP symptoms begin after early childhood they typically worsen slowly over many years. Recognition of the often significant variation in severity within and between HSP families requires caution when estimating the degree of eventual disability. We and others have evaluated families in which some members had progressively disabling spastic paraparesis and others had mild, nondisabling spastic gait. Often, the ability to provide prognosis is limited by the analysis of small families in which the potential range of severity and age of symptom onset may not be appreciated. It must be recognized that subjects may have lower extremity hyper-reflexia for many years before gait becomes impaired. In addition, prognosis must consider the benefit of physical therapy and spasticity-reducing medication. In general, affected subjects from families with well-documented "uncomplicated" HSP are not considered at risk for developing a "complicated" HSP phenotype. Diagnosing "uncomplicated" HSP carries with it the prognosis that upper extremity strength and dexterity, speech, and swallowing will remain normal, and that life span will not be reduced.

Genetic Counseling

Genetic counseling in HSP is improved for many individuals by the availability of HSP gene analysis. If the disorder is one for which an HSP gene mutation is identi-

fied (presently limited to SPG3A, SPG4, SPG6, and SPG2 HSP), this information can be applied to prenatal diagnosis and genetic counseling. As discussed previously, identifying an HSP gene mutation indicates the increased risk of developing HSP but does not indicate the age at which symptoms will begin or disease severity.

Genetic counseling in HSP must consider the mode of inheritance (X-linked, dominant, recessive), the frequency of spontaneous mutations for dominantly inherited HSP, the degree of genetic penetrance, and the extent of clinical variability. As many as 12% of individuals with apparently sporadic spastic paraplegia have been shown to have a mutation for dominantly inherited HSP [28,91–93].

Genetic penetrance in "uncomplicated" HSP is age-dependent, high (70%–85% for SPG4 HSP [94]), but sometimes incomplete. Incomplete penetrance has been reported for SPG4 [95], SPG8 [96], and SPG3A HSP [97–102].

Genetic counseling must also consider that genetic anticipation has been observed in some (a minority) SPG464and SPG3A HSP families. Genetic anticipation carries with it the possibility that affected individuals in succeeding generations may be more severely affected and develop symptoms at an earlier age. In addition, it is possible that children may be affected before their parents. Diagnosing SPG3A HSP in a child, for example, may imply that one of the parents possesses the SPG3A/HSP gene and is thus at risk of developing HSP.

Conclusions

The hereditary spastic paraplegias are genetically and clinically heterogeneous disorders whose primary feature is lower extremity spastic weakness. More than 30 different genetic types of HSP have been identified. Whereas "complicated" forms of HSP may be recognized by specific clinical features, many forms of "uncomplicated" HSP are very similar and may not be reliably distinguished by clinical parameters alone. The neuropathology of "uncomplicated" HSP involves axonal degeneration involving the ends of the longest motor (corticospinal tract) and sensory (dorsal column fibers) in the spinal cord. Recent identification of 11 HSP genes suggests that different primary biochemical abnormalities may be responsible for this distal axonopathy in different genetic types of HSP. These include cytoskeletal and axonal transport abnormalities, mitochondrial disturbance, altered Golgi function, primary myelin disturbance, and corticospinal tract developmental abnormality.

Diagnosing "uncomplicated" HSP carries with it the prediction that although lower extremity spasticity may progress and become disabling, upper extremity strength and dexterity, speech, and swallowing will remain normal and that life expectancy will not be reduced.

Gene testing is available for SPG2 (X-linked), SPG3A, SPG4, and SPG6 HSP (autosomal dominant) and can confirm the diagnosis in SPG2 X-linked HSP and in approximately 60% of dominantly inherited HSP. Genetic test results can be applied to prenatal diagnosis. Advances in HSP gene testing notwithstanding, HSP is a diagnosis of exclusion for most subjects. The differential diagnosis includes treatable disorders as well as those whose prognosis is quite different than HSP. Presently, treatment for HSP is symptomatic and includes physical therapy and the use medications to reduce spasticity and urinary urgency.

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have been highlighted as:

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