Hereditary Spastic Paraplegias

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Hereditary spastic paraplegias (HSP) comprise a genetically and clinically heterogeneous group of neurodegenerative disorders characterized by progressive spasticity and hyperreflexia of the lower limbs.

Clinically, HSPs can be divided into two main groups: pure and complex forms. Pure HSPs are characterized by slowly progressive lower extremity spasticity and weakness, often associated with hypertonic urinary disturbances, mild reduction of lower extremity vibration sense, and, occasionally, of joint position sensation. Complex HSP forms are characterized by the presence of additional neurological or non-neurological features. Pure HSP is estimated to affect 9.6 individuals in 100,000. HSP may be inherited as an autosomal dominant, autosomal recessive or X-linked recessive trait, and multiple recessive and dominant forms exist. The majority of reported families (70-80%) displays autosomal dominant inheritance, while the remaining cases follow a recessive mode of transmission. To date, 24 different loci responsible for pure and complex HSP have been mapped. Despite the large and increasing number of HSP loci mapped, only 9 autosomal and 2 X-linked genes have been so far identified, and a clear genetic basis for most forms of HSP remains to be elucidated.

Keywords
Hereditary Spastic Paraplegia (HSP), SPG loci, Strümpell-Lorrain syndrome, pure and complex forms, genetic heterogeneity.

References
progressive axonal degeneration mainly evident at the distal ends of the corticospinal tracts. Mild loss of the distal ends of the dorsal column fibers and of anterior horn cells may occur. Clinically, HSPs can be divided into two main groups: pure and complex, also referred to as uncomplicated and complicated forms, respectively. Pure HSPs are characterized by slowly progressive lower extremity spasticity and weakness, often associated with hypertonic urinary disturbances, mild reduction of lower extremity vibration sense, and, occasionally, of joint position sensation. Pes cavus is sometimes present, and scoliosis may develop in some cases. Pure HSP can be highly disabling but does not shorten life span. In complex HSPs, this clinical picture is associated with other neurological or non-neurological signs and symptoms, such as seizures, dementia, deafness, amyotrophy, extrapyramidal signs, peripheral neuropathy, in the absence of other co-existing diseases (Bundey 1992; Harding 1993; Reid 1997).

**Classification**

Genetically, HSPs are divided by mode of inheritance (autosomal dominant, autosomal recessive and X-linked) and sub-divided by chromosomal locus or causative gene (if already identified). All genetically defined HSPs are assigned the symbol “SPG” (spastic gait) followed by a progressive number. Twenty-four SPG symbols have been assigned so far, each one identifying a different locus/gene. Considering both clinical and genetic classifications, five HSP groups are defined:

- autosomal dominant pure (SPG3; SPG4; SPG6; SPG8; SPG10; SPG12; SPG13; SPG19),
- autosomal dominant complex (SPG9; SPG17),
- autosomal recessive pure (SPG5; SPG11; SPG24),
- autosomal recessive complex (SPG14; SPG15; SPG20; SPG21; SPG23)
- X-linked complex (SPG1/L1CAM; SPG2/PLP1; SPG16).

SPG7, due to mutations in the “paraplegin” gene, is an autosomal recessive form that can present either with a pure or with a complex phenotype. SPG17, also called Silver Syndrome, is usually transmitted in an autosomal dominant fashion, but can occasionally be autosomal recessive.

**Differential diagnosis**

Several neurological conditions must be ruled out for establishing HSP diagnosis. The following is a list of some of the most important conditions to consider in the differential diagnosis of HSP:

- Structural abnormalities of the brain or the spinal cord (due to trauma, tumors, malformations etc). These can be detected by a brain and spinal cord MRI, a CT scan or other appropriate neuroimaging techniques.

**Multiple sclerosis** (MS). In the first stages, this disorder may selectively involve the upper motor neurons or pyramidal tracts projecting to the lower limbs, therefore mimicking HSP. Although the clinical progression of MS is usually different, with a relapsing-remitting course, some patients may have a slowly progressive course. However, a brain and spinal cord MRI scan and laboratory testing of the cerebrospinal fluid will clarify the diagnosis.

Vitamin B12 deficiency can result in a neurological syndrome sharing some clinical features with HSP, such as leg spasticity and extensor plantar responses. The phenotype is usually complicated by sensory and motor neuropathy, with reduced tendon responses at ankles, megaloblastic anemia, gastrointestinal problems, mental retardation or encephalopathy in children, cognitive impairment in adults. Vitamin B12 levels can be assessed by measuring the serum vitamin levels and other specific metabolites, and spinal cord MRI shows typical lesions which mostly resolve after an 8 to 12 month-therapy.

**Dopa-responsive dystonia** has to be considered in children with progressive gait abnormalities of unknown etiology. However, the neurological examination will show a dystonic posture of lower limbs and/or parkinsonian signs instead of upper motor neuron signs, and a trial with small doses of Levodopa will lead to a massive improvement of symptoms.

**Amyotrophic lateral sclerosis** (ALS), **primary lateral sclerosis** (PLS) and infantile-onset ascending hereditary spastic paralysis (IAHSP) have to be considered in differential diagnosis, as they typically lead to an upper motor neuron degeneration. However, in ALS lower motor neuron signs are invariably present, and the disease is more rapidly progressive and mostly sporadic. PLS and IAHSP share with pure HSPs the selective involvement of upper motor neurons, but usually involve also upper extremities and bulbar muscles (speech and swallowing) as disease progresses, and there is no family history. Bladder function is also normal until late in disease. Viral spastic paraplegia (i.e., HTLV1 infection). Lower limbs spasticity can be a clinical manifestation of some viral infections of the central nervous system (CNS), and are usually part of a more complex neurological picture. These cases are usually sporadic, and a careful collection of personal history may help in...

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suspecting a particular viral infection and performing specific diagnostic tests. Leukodystrophies, such as adrenomyelo-neuropathy, metachromatic leukodystrophy, Pelizaeus-Merzbacher disease (etc.) can present with lower limb spasticity as part of a more complex neurological phenotype. Brain MRI will show the typical abnormalities of the white matter, which are absent in HSP. Specific laboratory and genetic testing are available for several leukodystrophies.

Prevalence
Pure HSP is estimated to affect 9.6 individuals in 100,000 (Polo et al. 1991).

Clinical description
In pure HSP, age of onset is widely variable, ranging from early childhood to late adulthood and the disease usually progresses slowly over the years, without exacerbations or remissions. Neurological examination shows bilateral lower limb weakness, which can be mild to severe, increased muscle tone, lower limb hyperreflexia and extensor plantar responses. In some cases, there is a decrease of joint position and vibration sense in the distal lower extremities, while other sensation modalities are normal. Strength and dexterity of the upper limbs are usually spared, although mild hyperreflexia and decreased vibration sense can be occasionally present. The bulbar district is always normal. Lower extremity paresthesias may occur. Affected individuals experience progressive difficulty in walking and can eventually require canes, walkers or wheelchairs. Urinary symptoms are frequent and range from urinary urgency to incontinence. Most patients report that their symptoms (often referred to as “stiffness” and “rigidity” of lower limbs) are worsened by stress and anxiety. Intra-familial phenotypic variability has been often described, especially in autosomal dominant forms. Among the eight autosomal dominant pure HSPs, the principal phenotypic difference is represented by the mean age of onset of symptoms, ranging from the first decade (as in SPG3, SPG10 and SPG12) to the fourth-fifth decade (as in SPG19). Other forms, such as SPG4, SPG8 and SPG13, are characterized by a much wider range of ages of onset, spanning several decades. Minor clinical differences concern the percentage of urinary disturbances, upper limb hyperreflexia, and the overall disability. Other than family history, no clinical features can help distinguishing between autosomal dominant and autosomal recessive pure HSPs. One exception is SPG11, which is characterized by HSP and a thin corpus callosum in the vast majority of families. In the single family so far described linked to SPG24, a peculiar feature was the very early onset at about 1 year of age in all affected individuals. In complex HSP, the clinical picture is highly variable, depending on the accompanying neurological and non-neurological clinical symptoms. Among autosomal dominant complex HSPs, SPG9 is characterized by congenital bilateral cataracts, gastro-esophageal reflux with persistent vomiting and atrophy, while SPG17 presents with characteristic distal amyotrophy of hands and feet. Among autosomal recessive complex forms, patients with SPG7 can have optic atrophy, bulbar involvement, cerebellar and cortical atrophy, or simply present with a pure HSP phenotype. Mild mental retardation, neuropsychological impairment, and a distal motor neuropathy with onset around the third-fourth decade, are features suggestive of SPG14, while SPG15 generates a more complex clinical presentation with lower limb spastic paraparesis associated with distal upper limbs weakness, pigmented maculopathy, dysarthria, mental retardation and progressive intellectual decline, mild ataxia and, occasionally, dystonia, epilepsy or psychosis. Cerebellar signs, distal amyotrophy, short stature and mild developmental delay with emotional lability and onset in early childhood are found in SPG20 patients. SPG21, or MAST syndrome, is characterized by spasticity of lower limbs and often of upper limbs as well, dementia and extrapyramidal signs. Onset is usually in the late teens or twenties with slow progression, but the disease may have a later onset in the third or even fourth decade of life. MRI shows thin corpus callosum, gray matter atrophy and white matter demyelination. Spastic paraplegia with pigmented abnormalities are the peculiar signs of SPG23, also called Lison syndrome. This complex form is in fact characterized by patchy vitiligo, areas of skin hyperpigmentation and lentigines, premature graying of body hair. The skin abnormalities can be apparent at birth, while spasticity usually has an onset in childhood. Other inconstant features may include microcephaly, facial dysmorphisms such as thin face, micro- or retrognathia, mild cognitive impairment and mild peripheral neuropathy. All X-linked HSPs are complex forms. SPG1 is characterized by spastic paraplegia plus mental retardation and adducted thumbs, and is allelic to several other conditions such as X-linked hydrocephalus, MASA syndrome (Mental retardation, Aphasia, Shuffling gait and Adducted thumbs) and CRASH syndrome (Corpus callosum hypoplasia, Retardation,
Adducted thumbs, Spastic paraparesis and Hydrocephalus). According to the HUGO Gene Nomenclature Committee, the approved locus symbol has been recently changed to L1CAM. SPG2 can give rise to a phenotype ranging from a nearly pure HSP to Pelizaeus-Merzbacher disease, a severe condition characterized by nystagmus, hypotonia, cognitive impairment, severe spasticity and ataxia, with onset in early childhood and shortened life span. According to the HUGO Gene Nomenclature Committee, the approved locus symbol has been recently changed to PLP1. SPG16 also has onset in early childhood and presents with facial hypotonia, strabismus and reduced vision, bowel dysfunction, skeletal abnormalities (maxillary hypoplasia, short thick distal phalanges), mental retardation, aphasia and restlessness.

Management including treatment
There is currently no "cure" for HSP. All treatments are symptomatic. Physical therapy and/or a regular exercise and stretching program play an important role in treating HSP symptoms. While exercise or physical therapy do not prevent or reverse the damage to the nerve fibers, it will help HSP patients in maintaining mobility, retaining or improving muscle strength, minimizing atrophy of the muscles due to disuse, increasing endurance (and reducing fatigue), preventing spasms and cramps, maintaining or improving range of motion, and providing cardiovascular conditioning. Exercise also has a positive psychological effect, helping to reduce stress and to produce feelings of well being. Anti-spasticity drugs may improve the results of physical therapy or exercise by reducing the spasticity and allowing the weak muscles to be targeted, especially in cases where spasticity is quite severe. A limitation to the use of anti-spasticity drugs is that leg spasticity helps in some cases to overcome the problem of muscle weakness. In these patients, anti-spastic drugs may sometimes have negative rather than positive effects on walking. Side effects such as excessive sleepiness and increased weakness can also be a problem. However, if their dosage and prescription are appropriate, the anti-spasticity drugs can reduce the pain associated with spasticity, improve mobility, and increase the effectiveness of physical therapy. Baclofen, Diazepam, Tizanidine, Dantrolene Sodium and Gabapentin are among the most frequently prescribed anti-spastic drugs. Botulinum Toxin injections can greatly improve spasticity in selected muscles, and it is advised to address specific problems (i.e. major gait difficulties due to equinovarus foot).

Other drugs can be effective in solving urinary problems. Among these, the most important are some anticholinergic drugs (Oxybutynin chloride, Tolterodine tartrate), which inhibit bladder contractions and delay or decrease the urge to void. The most common side effect is dry mouth, other side effects include headache, dry eyes, constipation and indigestion. The benefit of vitamins, antioxidants, creatine and Coenzyme Q10 in treating HSP have not been demonstrated.

Diagnostic methods
Pure HSP is diagnosed on the basis of clinical, neurological examination (see “Clinical description”), family history and exclusion of other diagnoses (see “Differential diagnosis”), a very important criterion, as HSP is a diagnosis of exclusion in most cases. Brain and spinal cord MRI are usually normal, even if a thinning of the spinal cord, especially in the thoracic area, has been observed in some patients. Motor evoked potentials (MEPs) are severely delayed or absent when recording from lower limbs, whereas they are generally normal in the upper limbs. MEPs can be very useful to confirm the diagnosis in mild cases or at early stages of the disease. Needle electromyography (EMG), peripheral sensory and motor neurography and somato-sensory evoked potential are usually normal. In complex forms, as the clinical picture of pure HSP is associated with other neurological and non-neurological signs and symptoms, the diagnostic procedures will be chosen on the basis of the phenotype (i.e. EMG, sensory and motor nerve conduction velocities, fundus oculi examination, electroencephalography (EEG), skeletal X-ray, neuropsychological and cognitive testing, auditory test, etc).

Etiology
The genetic loci ascribed to the different HSP forms are given in the following tables:
Loci described for HSP autosomal dominant pure forms:

<table>
<thead>
<tr>
<th>HSP form</th>
<th>Locus</th>
<th>MIM</th>
<th>References</th>
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<tbody>
<tr>
<td>SPG3</td>
<td>14q11.2-q24.3</td>
<td>182600</td>
<td>Hazan et al. 1993</td>
</tr>
<tr>
<td>SPG4</td>
<td>2p22</td>
<td>182601</td>
<td>Hazan et al. 1994</td>
</tr>
<tr>
<td>SPG5</td>
<td>16q24.3</td>
<td>602783</td>
<td>De Michele et al. 1998</td>
</tr>
<tr>
<td>SPG6</td>
<td>15q13-q15</td>
<td>604360</td>
<td>Martinez Murillo et al. 1999</td>
</tr>
<tr>
<td>SPG7</td>
<td>2q24</td>
<td>605280</td>
<td>Fontaine et al. 2000</td>
</tr>
<tr>
<td>SPG8</td>
<td>9q33-q34</td>
<td>607152</td>
<td>Valente et al. 2002</td>
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</tbody>
</table>

Loci described for HSP autosomal recessive pure forms:

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<tbody>
<tr>
<td>SPG5</td>
<td>8p12-q13</td>
<td>270800</td>
<td>De Micheile et al. 1998</td>
</tr>
<tr>
<td>SPG7</td>
<td>16q24.3</td>
<td>602783</td>
<td>De Micheile et al. 1998</td>
</tr>
<tr>
<td>SPG11</td>
<td>15q13-q15</td>
<td>604360</td>
<td>Martinez Murillo et al. 1999</td>
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<tr>
<td>SPG24</td>
<td>13q14</td>
<td>607584</td>
<td>Hodgkinson et al. 2002</td>
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Loci described for HSP autosomal dominant complex forms:

<table>
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<tbody>
<tr>
<td>SPG9</td>
<td>10q23.3-q24.2</td>
<td>601162</td>
<td>Seri et al. 1999</td>
</tr>
<tr>
<td>SPG17</td>
<td>11q12-q14</td>
<td>270685</td>
<td>Patel et al. 2001</td>
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Loci described for HSP autosomal recessive complex forms:

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<tbody>
<tr>
<td>SPG14</td>
<td>3q27-q28</td>
<td>605229</td>
<td>Vazza et al. 2000</td>
</tr>
<tr>
<td>SPG15</td>
<td>14q22-q24</td>
<td>606859</td>
<td>Hughes et al. 2001</td>
</tr>
<tr>
<td>SPG20</td>
<td>13q12.3</td>
<td>275900</td>
<td>Patel et al. 2002</td>
</tr>
<tr>
<td>SPG21</td>
<td>15q21-q22</td>
<td>248900</td>
<td>Simpson et al. 2003</td>
</tr>
<tr>
<td>SPG23</td>
<td>1q24-q32</td>
<td>270750</td>
<td>Blumen et al. 2003</td>
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Despite the large and increasing number of HSP loci mapped, only 9 autosomal and 2 X-linked genes have been identified to date (Crosby and Proukakis 2002; Simpson et al. 2003; Windpassinger et al. 2004), and a clear genetic basis for most HSP forms remains elusive. Mutations in a gene encoding for paraplegin, a protein with mitochondrial localization and a chaperone-like function, have been found in both pure and complex forms of autosomal recessive HSP linked to SPG7 (Casari et al. 1998). This protein contains an AAA (ATPases associated with diverse cellular activities) domain, which is common to a group of molecules involved in protein degradation and trafficking, and organelle biogenesis. In particular, mitochondrial AAA proteins show chaperone-like activity ensuring the specificity of proteolysis and the activation of respiratory chain complexes (Leonhard et al. 1999). Muscle biopsies of SPG7 patients showing typical alteration of mitochondrial disorders (Casari et al. 1998) and preliminary reports of electron microscopy studies in mice lacking paraplegin (Ferreirinha et al. 2004) show that the paraplegin protein plays a role in mitochondrial function.

A mitochondrial involvement has also been demonstrated in a pure autosomal dominant form of HSP (SPG13) by the identification of a mutation in the heat shock protein 60 (Hsp60), a mitochondrial chaperone, in affected individuals (Hansen et al. 2002). The recent identification of new HSP genes suggests that other different pathogenetic mechanisms could be responsible for HSP. In particular, aberrant intracellular-trafficking dynamics has been postulated to represent a common process for the specific pattern of neurodegeneration observed in HSP phenotypes (Crosby and Proukakis 2002).

The gene responsible for the autosomal dominant SPG4-linked HSP encodes a protein named spastin, which is a member of the AAA protein family (Hazan et al. 1999). A recent study has shown that wild-type spastin interacts transiently with microtubules and probably is involved in microtubules dynamics (Errico et al. 2002) since its overexpression results in a microtubule-disassembly phenotype. In contrast, spastin mutants are able to bind constitutively to microtubules and recent data indicate the N-terminal region of spastin as responsible for microtubule binding (Errico et al. 2002). No functional domains have been identified in this portion with the exception of an ESP domain localized close to the N-terminal region of spastin.

Interestingly, an ESP domain is also present in the N-terminal portion of the spartin protein, which is responsible for a complex autosomal recessive form of HSP (SPG20; Troyer.
of the hand's and occasionally also of the lower limbs (SPG17), has been recently identified (Windpassinger et al. 2004). Heterozygous missense mutations in the BSCL2 gene have been described in patients affected with Silver syndrome as well as in patients with autosomal dominant distal hereditary motor neuropathy (dHMN). Null mutations in the BSCL2 gene were previously reported to cause autosomal recessive Berardinelli-Seip congenital lipodystrophy type 2, a disorder clinically unrelated to dHMN and Silver syndrome. The BSCL2 gene encodes the protein seipin, an integral membrane protein of the endoplasmic reticulum (Windpassinger et al. 2004). The missense mutations identified in Silver syndrome and in dHMN patients affect glycosylation of seipin and result in aggregate formation leading to neurodegeneration (Windpassinger et al. 2004).

The two SPG1 and SPG2 X-linked forms have been shown to be caused by mutations in the genes for L1 cell adhesion molecule (L1CAM) and the proteolipidic protein (PLP1), respectively (Jouet et al. 1994; Saugier-Weber et al. 1994). They represent the first genes demonstrated to be responsible for HSP phenotypes. L1CAM is a transmembrane glycoprotein with extracellular immunoglobulin and fibronectin type III repeat (Casari and Rugarli, 2001). It is expressed during development on the surface of long axons and growth cones, including those of the corticospinal tract. Furthermore, L1 mediates cell adhesion and neurite growth. Neuropathological studies and the analysis of transgenic animals have suggested that this molecule is required for normal development of corticospinal tract (Casari and Rugarli, 2001). Conversely, the PLP1 gene encodes one of the major components of myelin and mutations in this gene are also responsible for Pelizaeus-Merzbacher disease, a genetic disorder characterized by significant hypomyelination of the CNS with a reduced number of mature oligodendrocytes. An important step in understanding the pathogenesis of HSP caused by PLP1 mutations has been the generation of the knockout animals that do not express any PLP. Surprisingly these animals have normal CNS function but assemble compact myelin sheaths and subsequently develop widespread axonal swelling and degeneration, most likely secondary to impaired axonal transport (Casari and Rugarli, 2001).

**Genetic counseling**

Many HSPs cases are referred annually to the outpatient Genetic Clinics for genetic counseling. Due to the wide heterogeneity, the genetic classification of the different HSP patients remains difficult. As mentioned in the "clinical
description" section, the age of onset in some patients as well as the presence of additional features specific for several complex forms could help in the classification of affected individuals and families.

In most familial cases, segregation analysis is sufficient to establish the pattern of inheritance and to calculate an accurate risk of recurrence. Sometimes, in such pedigrees linkage analysis could be useful in order to confirm the segregation of the disease phenotype with a previously mapped HSP locus. Sporadic cases represent the majority of HSP patients in genetic counseling. They could represent recessive cases with a risk of recurrence for their parents of 25%, but without risk with an extremely low risk of recurrence for their children. Conversely, they could correspond to autosomal dominant cases due to a de novo mutation in a HSP gene. In this case, their parents do not show specific risks for other pregnancies but they do have a risk of 50% to transmit the disorder. Sporadic HSP male patients could be due to mutations in X-linked HSP genes suggesting that their mothers could be carriers with a risk of 50% to have an additional affected son. Finally, similar to other neurodegenerative disorders such as Parkinson disease, amyotrophic lateral sclerosis, or Alzheimer’s disease, sporadic HSP cases may represent multifactorial/multigenic phenocopies of the monogenic diseases. In such cases, recurrence risk is expected to be extremely low.

The identification of a mutation in sporadic patients by direct sequencing of the identified HSP genes could clarify the pattern of inheritance and the risk of recurrence.

Antenatal diagnosis

Due to the late onset of the disorder and to the wide clinical and genetic heterogeneity, prenatal diagnosis of HSP cases has to be discussed in specific cases.

References


Chai JH, Locke DP, Grelley JM, Knoll JH, Ohta T, Dunai J, Yavor A, Eichler EE, Nichols RD. (2003) Identification of four highly conserved genes between breakpoint hotspots BP1 and BP2 of the Prader-Willi/Angelman syndromes deletion region that have undergone evolutionary transposition mediated by flanking duplicons. Am J Hum Genet, 73:898-925


http://www.orpha.net/data/patho/GB/uk-HSP.pdf


