

HEREDITARY SPASTIC PARAPLEGIA: FROM GENE TO CLINIC

TONEKABONI Seyed Hassan MD

Associate Professor of Pediatric Neurology, Pediatric Neurology Research Center, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran

Corresponding Author:
TONEKABONI Seyed Hassan MD
Mofid Children Hospital, Tehran, Iran
Tel: +98 21 22909559
Email: shtonekaboni@yahoo.com

Received: 08-Feb- 2010
Last Revised: 10-Feb- 2010
Accepted: 17-Feb- 2010

Abstract

Objective

Hereditary Spastic Paraplegia (HSP) is a degenerative disease of genetic origin affecting the corticospinal tracts in the spinal cord. There are three forms of inheritance: Autosomal dominant HSP, Autosomal recessive HSP and X-linked HSP.

This disease is characterized by progressive spasticity of leg muscles with varying degrees of stiffness and weakness of other muscle groups. In this review, we will discuss the latest findings on the pathophysiology of axonal degeneration and all the responsible genetic defects in HSP.

Keyword: Hereditary spastic paraplegia, degenerative disease, inheritance

Introduction

Hereditary spastic paraplegia (HSP) encompasses a heterogeneous group of neurodegenerative diseases of genetic origin that are clinically characterized by progressive spasticity and weakness of lower limbs (1). Hereditary spastic paraplegia (HSP) is also called familial spastic paraparesis and Strümpell-Lorrain syndrome.

HSP causes degeneration of the ends of the corticospinal tracts within the spinal cord. The ends of the longest fibers, which supply the lower extremities, are affected to a much greater extent than are the fibers to the upper body. Although some degeneration of the fibers supplying the arms commonly takes place, most people with HSP do not have symptoms in hands or arms.

Pyramidal weakness with hyperreflexia and extensor plantar reflexes is the key diagnostic clinical findings. The genetics of HSP are complex and all mendelian modes of inheritance (X-Linked, autosomal dominant and autosomal recessive) have been discovered (2).

The prevalence of HSP worldwide is unknown, but few studies on the epidemiological status of HSP in Europe show a prevalence of 3-10 cases per 100,000 population (3,4). Our experience in Mofid Children Hospital in Tehran shows that it is not a rare disease, probably due to the high prevalence of consanguineous marriages in Iran. The disease begins from early childhood through to 70 years of age and therefore is a major source of neurodisability. In this review, we discuss its clinical and diagnostic features as well as the genes that have been identified and the pathophysiology of the disease.

Clinic and paraclinic

HSP has been traditionally divided into pure (uncomplicated) and complicated

types, depending on the presence of concomitant and neurological findings in addition to spastic paraplegia. Spasticity is an increase in muscle tone with resulting stiffness. Muscle tone refers to the mild contraction that muscles continue to have even when at rest. A reflex between nerve endings in the muscle and spinal cord regulates muscle tone. Normally, the corticospinal nerves control and reduce sensitivity of this reflex. Because HSP causes deterioration of the corticospinal nerves, the reflex is not reduced as it should be, the result being an exaggerated reflex and increased muscle tone (5).

The disease onset is subtle with progressive leg stiffness or abnormal wear of the shoes (6). Increasing stiffness in legs is associated with frequent tripping, particularly when the patient is walking on uneven terrain. Uncontrollable shaking of the legs may be noted during ambulation. Dragging of the feet, scissoring of the legs during walking, weakness and giving way at the ankles, flexor spasms of the legs during the night, and a sense of unsteadiness during ambulation are also common (5). A common symptom of HSP is a decreased sense of balance. For many people, this is the first symptom that they notice. Many people with HSP have an impaired sense of position in their feet. If the brain does not receive accurate signals about the body's position, it may not be able to respond properly to those signals, and loss of balance occurs. The patient's gait shows a circumduction pattern owing to a difficulty with hip flexion and ankle dorsiflexion.

Neurologic examination reveals crossed adductor reflexes, ankle clonus, and extensor plantar responses. Hoffman and Tromner signs may be observed. High-arched feet (pes cavus) are generally present and are usually prominent in older patients (5).

No evidence of cranial nerve dysfunction, reduced cognition, speech disturbance, difficulty swallowing, or frank corticobulbar tract dysfunction is noted in uncomplicated forms. Upper extremity muscle tone and strength are usually normal. In the lower extremities, muscle tone is increased at the hamstrings, quadriceps, and ankles. Results of manual muscle testing are difficult to assess because of the increased tone; however, weakness is occasionally demonstrated in the legs. Weakness is most notable at the iliopsoas muscles, the tibialis anterior muscles, and, to a lesser extent, the

hamstring muscles. Muscle wasting may occur in patients with pure HSP, but is mild and limited to atrophy of the shins in the elderly, wheelchair-dependent patients. Peripheral nerves are normal in patients with pure HSP, although decreased perception of sharp stimuli below the knees is occasionally noted. Vibratory sensation is often mildly diminished in the distal lower extremities. When it occurs, this deficit provides a diagnostic sign that helps to distinguish HSP from other disorders. Slight terminal dysmetria is occasionally observed on finger-to-nose testing in older affected individuals. Deep tendon reflexes may be brisk (2+ to 3+) in the upper extremities but are pathologically increased (3+ to 4+) in the lower extremities. Some people also experience incontinence (sense of urgency even when bladder is not full) (e medicine).

In comparison with other etiologies of spastic paraplegia (spinal injury and MS), muscle power is relatively preserved despite the significant increased tone in the legs, particularly in patients with an early-onset disease (1).

Etiologic approach to any spastic paraplegia is based upon age and nature of the disease, onset, progression of symptoms, presence of a family history and associated clinical findings. Onset in infancy with delayed motor milestones is more suggestive of cerebral palsy, especially if there is a static clinical course.

In pure forms of HSP, some other clinical findings have been described: mild sensory abnormalities of the lower limbs (reduced vibration sense), urinary symptoms (reported in up to 50% of the cases in later disease), Pes cavus, and a mild cognitive decline. Upper limbs might show hyper-reflective, but cranial nerves are rarely involved in HSP (1-6).

Complicated HSP describes a large group of conditions in which spastic paraplegia is accompanied by other clinical signs and symptoms such as optic atrophy, pigmentary retinopathy, ataxia, mental retardation, severe amyotrophy, deafness, dementia, epilepsy, peripheral neuropathy, extrapyramidal signs and ichthyosis (2-6).

Patients with HSP may have several possible complications including the following: Gastrocnemius-soleus contracture, cold feet, fatigue, back and knee pain, stress and depression, which should be treated appropriately.

These forms are often autosomal recessive and rare in North America and Europe. We should be aware that the presence of additional neurological findings plus spastic paraplegia might indicate other possible diagnoses.

The following list denotes some major differential diagnoses of HSP in children: Structural abnormalities of the brain or spinal cord, Leukodystrophy, B12 deficiency, Tropical spastic paraplegia (caused by HTLV1 infection), Dopa-responsive dystonia (also known as hereditary progressive dystonia with marked diurnal variation or “Segawa disease”), Amyotrophic lateral sclerosis (ALS), Primary lateral sclerosis (PLS), Arginase deficiency, Friedreich ataxia, and Machado-Joseph disease (SCA3)(1).

A significant proportion of undiagnosed patients with spastic paraplegia are likely to be of genetic origin, and detailed family history is therefore crucial. The presence of a slowly progressive gait disorder with relatively few sensory symptoms or signs favors the diagnosis of HSP. Acute or sub acute onset of spasticity favors vascular or inflammatory causes, respectively, and in these cases weakness is often more marked. Similarly, spinal cord compression also has a more aggressive course, often accompanied by sensory signs and symptoms plus spinal or referred pain, which is unusual in HSP (1).

In a family with several affected members, it is easy to make the diagnosis of HSP, but for a patient to whom there is no reliable or verifiable family history, further investigation is required. This investigation includes plasma amino acids, serum lipoprotein analysis, very long chain fatty acids, white cell enzymes, vitamin B₁₂ or vitamin E, copper and ceruloplasmin, serum serology for syphilis, human T-cell leukemia virus 1, HIV and neuro ophthalmological consult (1).

The most common MRI finding in HSP is thinning of the cervical and thoracic spinal cord (7).

Electromyography and nerve conduction studies are normal in the majority of pure HSP patients (8). Cerebrospinal fluid analysis is also usually normal in HSP, although increased protein is noted in some patients. Central motor conduction times have been reported to be delayed or unrecordable from the lower limbs and lower extremity somatosensory evoked potentials show a conduction delay in dorsal column fibers (9).

Pathophysiology

The main neuropathological finding in HSP is axonal degeneration of the terminal portions of the long descending (corticospinal tracts) and ascending (dorsal columns) pathways in the spinal cord (10). Studies on some genes implicated in hereditary spastic paraplegia have revealed that membrane trafficking and axonal transport defects are implicated in many cases of HSP (11). As a result of the unique morphology of spinal neurons, the long axons (which can measure up to 1 m in length) are likely to have considerable dependence on membrane trafficking, microtubule-associated transport, and cytoskeletal organization. Membrane trafficking and axonal transport depend on the appropriate function of mitochondrial function. Thus, membrane trafficking, axonal transport, mitochondrial function and their meticulous interaction are potentially important factors in HSP pathophysiology (figure 1)(11).

Membrane trafficking (1): All cells have a regulated, dynamic membrane trafficking system that allows interactions between the plasma membrane and other membrane-bound compartments. This trafficking is highly organized and starts with vesicle budding, followed by transport of the vesicle, tethering, and fusion with the target membrane. Endocytosis begins with vesicle formation at the plasma membrane which contains receptors and/or other transmembrane proteins and is reliant on the vesicle coat protein, clathrin. Vesicles are transported along the microtubule cytoskeleton, as described below, and then tethering and fusion of endosomes occur to deliver cargo to various sub-cellular locations. These processes depend on families of proteins, such as the Rab family of small GTPases, that mediate the intracellular destination of the vesicles and ESCRT (endosomal sorting complex required for transport)-associated proteins, which sort proteins targeted for ubiquitin-dependent degradation. The secretory pathway flows in the opposite direction to endocytosis, from the endoplasmic reticulum (ER) and Golgi apparatus, and allows the delivery of newly synthesized proteins, carbohydrates, and lipids to the cell surface, endosomes, and lysosomes.

Axonal transport (1): Axonal transport mainly depends on microtubule tracks and is powered by two distinct classes of molecular motors, namely dynein (retrograde transport) and kinesins (mainly anterograde

transport). Cytoplasmic dynein is a ubiquitous motor of the AAA (ATPase associated with various cellular activities) family, and comprises many subunits that are responsible for attachment to microtubules and cargo recruitment. Dynein is necessary for a wide variety of cellular processes, such as cell division and Golgi maintenance, and neurons are highly dependent on the proper function of this molecular complex for their axonal transport. Indeed, dynein has been shown to be involved in the axonal transport of numerous cargoes, such as neurotrophin-signalling endosome. The kinesin family comprises several members, some of which are responsible for the delivery of material to nerve terminals. Kinesin 1 is composed of two kinesin heavy chains and two kinesin light chains. The maintenance of the cytoskeletal tracks also depends on molecular motors, which are responsible for the transport of short microtubules and neurofilaments to where they are required for growth and repair.

Important components of the process of microtubule remodeling are those proteins that divide microtubules into short lengths.

8 HSP genes: Spastin (SPAST), Atlastin GTPase1 (ATL1), Kinesin Family Member 5A (KIF5A), Non imprinted in Prader-Willi/Angelman syndrome1 (NIPA1), Zinc Finger FYVE domain-containing 26 (ZFYVE26), SPG20, SPG21 and SPG11 support dysfunction of axonal transport and membrane trafficking as causes of HSP (11). SPAST-associated cases account for approximately 40% of autosomal dominant HSP patients, making mutation in these genes the most common cause of HSP. Over 150 mutations have been described in SPST which encodes spastin, a member of the ATPase-Associated (AAA) family of proteins, which is a component of the dynein motor and is involved in axonal retrograde Cargo transport (12). Different SPAST mutations lead to either haploinsufficiency or gain of function (13). Mutations in another gene, ATL1, cause ~ 10% of autosomal dominant HSP cases with an early-onset pure phenotype (SPG3A) (14). The primary role of Atlastin 1 is in endoplasmic reticulum and Golgi morphogenesis, but it also has a role in neurite outgrowth (15). Interestingly, Atlastin and Spastin directly interact, which suggests a common pathway of HSP pathogenesis. HSP cases associated with KIF5A (SPG10) were initially only reported in early-

onset pure HSP. But recently, mutations were reported in 10% of cases of complicated HSP in patients of European descent (16). KIF5A is a sub unit of Kinesin 1 and in vitro studies indicate that expression of its mutant forms leads to reduced Cargo flux along microtubules.

Mitochondrial function (11): Three HSP causative genes (SPG7, heat shock 60-kDa protein 1 (HSPD1) and Receptor Expression-Enhancing Protein 1 (REEP1)) support a role for mitochondrial dysfunction. Mutations in SPG7, which encodes paraplegin, account for ~5% of autosomal recessive HSPs. These mutations produce both pure and complicated HSP forms (17). Paraplegin is part of the metalloprotease AAA complex, which is an ATP-dependent proteolytic complex that is located on the inner mitochondrial membranes and that controls protein quality and ribosomal assembly (18).

The disease is due to the loss of Paraplegin function and both axonal transport and mitochondrial dysfunction may be implicated. SPG13 cases are associated with HSPD1, which participates in the folding of mitochondrial proteins, and are usually late-onset, pure forms (19).

Other cellular dysfunction in HSP: Two HSP causative genes, L1 Cell Adhesion Molecule (L1CAM) and Proteolipid Protein 1 (PLP1)), which underlie two X-linked forms of HSP encode membrane myelin proteins expressed in schwan cell. The L1CAM-associated HSP (SPG1) is the most common form of complicated HSP (11). Mutations in cytochrome P450, family 7, subfamily b, polypeptide 1 (CYP7B1) are found in families with autosomal recessive HSP (SPG5A). SPG5A was originally viewed as a pure HSP form with a variable age of onset and slow progression, but it is now believed to have both pure and complex forms. CYP7b1 mutants are proposed to affect cholesterol homeostasis because the normal protein is involved in myelin formation (20).

Genetic

The various Spastic Paraplegia (SPG) loci are associated with different forms of HSP which are listed in table 1 and recently, 45 SPG loci and 20 causative genes have been identified (B). The identification of these genes has led to insight into potential pathological mechanisms. HSP can be inherited as an autosomal dominant, recessive, or X-linked recessive trait. Autosomal dominant HSP is the

most prevalent form and represents around 70% of the cases. Most cases of pure HSP are autosomal dominant, whereas complicated forms tend to be autosomal recessive. We will describe clinical phenotypes of more common genetic subtypes of HSP in the following paragraphs.

Autosomal dominant HSP

SPAST-associated HSP (SPG4) is the most common type (40–45%) of pure autosomal dominant HSP and is the form that has been clinically more studied. The onset SPAST-associated HSP is usually in childhood through to late adult life (21). Overall, more than half of mutation carriers do not develop symptoms until after the age of 30 years. In most cases, the phenotype is slowly progressive spasticity in the lower limbs with loss of mobility around two decades after the onset of symptoms. Symptoms consistently found in a small number of patients with a longer disease duration include urinary urgency, upper limb hyper-reflexia, decreased vibration sense, and muscle wasting in the lower limbs (21). Complex phenotypes, including cerebellar ataxia, epilepsy, thinning of the corpus callosum, and mental retardation, have been described in several families with a mutation in the SPAST gene which encodes the Spastin Protein (1).

SPG3A-associated HSP is the second most common cause of autosomal dominant HSP, accounting for approximately 10% of the cases (22). It usually has a pure phenotype but an earlier onset, often before the age of 10 years. Typically, symptoms progression is relatively slow.

Mutations in NIPA1 (formerly SPG6) are also a cause of pure HSP that progresses slowly but can become severe (23). Penetrance is age dependent and high. Similarly, HSP associated with mutations in KIAA0196 (formerly SPG8) is characterized by more severe spasticity and a reduced vibration sense. HSP associated with mutations in the gene for Heat Shock Protein 60 (HSPD1; formerly SPG13) typically has a late onset without additional features (19). A Gly563Ala missense variant was recently reported to be associated with an earlier age of onset in patients carrying SPAST mutations, although this was not pathogenic by itself. Mutations in BSCL2 (formerly SPG17) cause a complicated form of HSP that

is characterized by additional amyotrophy of the small muscles of the hands and feet with onset in the early teens to the late thirties (Silver syndrome). Mutations in the BSCL2 gene also cause hereditary motor neuropathy type V and the autosomal recessive condition Berardinelli-Seip congenital lipodystrophy (1). Mutations in REEP1 (formerly SPG31) lead to a pure form of HSP with a variable age of onset. It is relatively common, and mutations in the REEP1 gene have been identified in 3% of a sample of unrelated patients with HSP, which increased to 8.2% in pure HSP if those with SPG3A and SPAST mutations were excluded (24). Other forms of autosomal dominant HSP are summarized in the table (associated with KIF5A, SPG9, SPG12, SPG18, SPG19, SPG29, SPG34, SPG36–SPG38, and SPG41 genes).

Autosomal recessive HSP

A number of families have autosomal recessive HSP that is associated with mutations in the CYP7B1 (formerly SPG5A) gene. This is a pure form with a variable age of onset and slow progression. To date, it has been recorded in about 20 families (25). Mutations in the SPG7 gene, which encodes Paraplegin, account for around 5% of autosomal recessive HSP. This type produces both pure and complicated HSP phenotypes. Cerebellar signs (dysarthria, nystagmus, and ataxia), pale optic discs, and peripheral neuropathy are common complicating features (26). SPG11-associated HSP, which is characterized by a thin corpus callosum, is a common and clinically distinct form that is linked to the SPG11 locus on chromosome 15 in most families. Other common features include cognitive impairment and severe axonal neuropathy (27–28). HSP associated with mutations in ZFYVE26 (formerly SPG15) has a characteristic autosomal recessive complicated phenotype (Kjellin syndrome), in which spastic paraplegia is accompanied by mental impairment, pigmentary retinopathy, cerebellar signs, and distal amyotrophy (29).

SPG20-associated HSP and SPG21-associated HSP are two complicated forms that have been identified in members of the Old Order Amish. A single mutation in SPG20, which encodes the Protein Spartin, causes Troyer syndrome(31), whereas a mutation in SPG21 (encoding the Protein Maspardin) causes Mast syndrome(32). Troyer syndrome is characterized by spastic tetraparesis,

dysarthria, distal amyotrophy, short stature, and learning difficulty. Mast syndrome is associated with dementia, cerebellar and extrapyramidal signs, and thin corpus callosum.

The remaining recessive forms of HSP (associated with SPG14, SPG23–SPG28, SPG30, SPG32, SPG35, and SPG39) are very rare, and have each been described in only one or two families. Any distinguishing clinical feature is listed in the table 1.

X-linked HSP

HSP caused by mutations in L1 Cell Adhesion Molecule (L1CAM) (formerly SPG1) is characterized by spasticity of the legs, mental retardation, hydrocephalus, and adducted thumbs. L1CAM is a transmembrane glycoprotein protein that is expressed in neurons and schwann cells and is believed to have a role in the development of the central nervous system (CNS). The phenotypic spectrum of L1 syndrome also includes X-linked hydrocephalus with aqueduct of Sylvius stenosis, MASA syndrome (mental retardation, aphasia, spastic paraplegia, and adducted thumbs), and X-linked agenesis of the corpus callosum (30).

Mutations in the Proteolipoprotein gene (PLP1; formerly SPG2) at Xq21–q22 have been found in families with a mainly complicated HSP in which there can be associated white matter changes on MRI and peripheral neuropathy. Mutations (usually duplications) of this gene also give rise to a dysmyelinating condition known as Pelizaeus-Merzbacher disease (PMD), which is characterized by congenital hypotonia, psychomotor deterioration, and progressive pyramidal, cerebellar, and dystonic signs. Death usually occurs in infancy or childhood. The variation in phenotype between PMD and PLP1-linked HSP is thought to arise from the differential effect that mutations can have on the two isoforms of the protein product, Proteolipoprotein 1 (PLP1) and DM20. Both are integral membrane proteins that account for ~50% of the protein content of adult CNS myelin. Mutations in exon 3b of PLP1 might predominantly result in SPG2 rather than PMD because this exon is excluded from DM20, which is thought to therefore be left intact. PMD is thought to arise only when DM20 is also affected by mutation (31).

Treatment

Currently, there is no specific treatment to prevent, retard, or reverse HSP's progressive disability. Nonetheless, treatment approaches used for chronic paraplegia from other causes are useful. Antispasticity medications can be useful. However, one of the limitations of these agents is that some patients find that the stiffness of spasticity helps them to overcome the muscle weakness that also occurs in HSP. When patients are medicated to reduce spasticity, walking may become more difficult. Adverse effects can also be a problem. If the patient does well with the medications, however, discomfort associated with spasticity can generally be reduced, mobility can be improved, and the effectiveness of physical therapy can be enhanced. Patients in relatively early stages of the illness have achieved symptomatic improvement with oral Dantrolene, as well as with oral and intrathecal Baclofen. Tizanidine has also provided some reduction of spasticity in HSP patients. Tizanidine is a centrally acting muscle relaxant metabolized in the liver and excreted in urine and feces. Baclofen may induce hyperpolarization of the afferent terminals and inhibit monosynaptic and polysynaptic reflexes at the spinal level. Dantrolene Sodium stimulates muscle relaxation by modulating skeletal muscle contractions at the site beyond the myoneural junction and acts directly on muscle itself. Some patients benefit from injections of Botulinum toxin type A. Botulinum toxin binds to receptor sites on motor nerve terminals and inhibits the release of acetylcholine, which in turn inhibits the transmission of impulses in neuromuscular tissue. This agent is most useful for treating spasticity in the gastrocnemius and soleus muscles and less effective in larger muscles (e.g. quadriceps). Bladder spasticity may be improved with Oxybutynin.

Regular physical therapy (PT) is important for maintaining and improving range of motion (ROM) and muscle strength. Furthermore, PT is necessary to maintain aerobic conditioning of the cardiovascular system. Although PT does not reduce the degenerative process within the spinal cord, individuals with HSP must maintain an exercise regimen performed at least several times each week as guided by their physical therapist. Exercise can help the patient to retain or improve muscle strength, minimize atrophy of the muscles caused by

disuse, increase endurance, reduce fatigue, prevent spasms and cramps, and maintain or improve range of motion. Exercise also has a positive psychological effect, helping to reduce stress and produce a feeling of well-being. Patients with HSP may experience spasticity and weakness (i.e. increased muscle tone and reduced muscle strength). Because of the increased resistance to passive stretching, spasticity may make it difficult for patients to exercise certain muscles. Antispasmodic drugs may help the patient to reduce the spasticity and may allow weakened muscles to be targeted in order to improve the effectiveness of PT. Different types of exercises incorporated into PT programs for patients with HSP may include strengthening, stretching, and aerobic exercises, as follows:

- Strengthening exercises - These help to strengthen muscles that have not yet weakened. Strengthened muscles help to compensate for muscles that have weakened, decreasing the rate of functional impairment. Exercise may also help to slow the

development of disuse atrophy, which occurs in muscles that are not being used (e.g. calf muscles of the people who are wheelchair-bound). Back-strengthening exercises may help to reduce or eliminate back pain associated with HSP. Such pain is probably not due to HSP itself but to strain on the back resulting from HSP (e.g. poor gait, poor posture, and use of a mobility device).

- Stretching exercises - These help to maintain or increase ROM and to reduce such problems as tendinitis, bursitis, and muscle cramps.
- Aerobic exercises - These improve cardiovascular fitness, reduce fatigue, and increase endurance and general fitness. Walking, bicycle riding, water aerobics, and swimming are among many excellent forms of aerobic exercises.

In patients with pure HSP, life expectancy is typically unaffected by the disease. This prognosis can not be generalized to complicated HSP patients, because each case has its own unique symptoms.

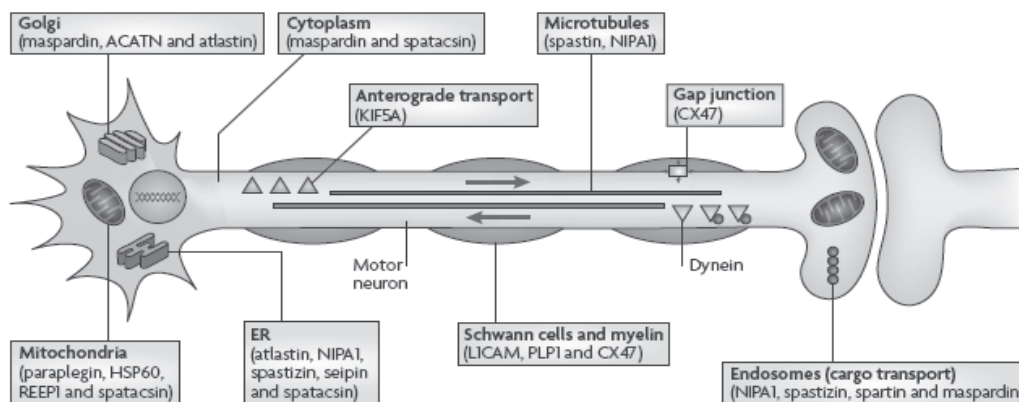


Fig 1. Potential Pathogenic mechanisms in heredity spastic paraplegia. The genes known to predispose to hereditary spastic paraplegia (HSP) support the view that defects at various cellular sites can be detrimental to the long axons of upper motor neurons. This representation of a motor neuron shows where these HSP-predisposing proteins have been suggested to reside or function. Motor neurons have a regulated, dynamic membrane-trafficking system that involves HSP-predisposing proteins that function in the endoplasmic reticulum (ER) and Golgi. Endosomes are transported along the microtubule cytoskeleton to various subcellular locations. A process that involves HSP-predisposing proteins that are located on endosomes and microtubules. Motor neurons rely on mitochondria to drive the efficient transport of signals. Molecules and organelles to and from nerve terminals, and this process also involves HSP-predisposing proteins that function in mitochondria. For other HSP-predisposing proteins (for example, strumpellin, connexin 47(CX47) and cytochrome P450, family7,subfamily B, polypeptide1(CYP7B1): not shown). Their location is unclear and/ or their contribution to motor neuron disease is not yet understood. ACATN.acetyl-CoA transporter:HSP60. Heat shock protein 60: KIF5A. Kinesin family member SA: LICAM. L1 cell adhesion molecule:NIPA1.non –imprinted in Prader-Willi/Angelman syndrome region protein1: PLP1.Proteolipid protein 1: REEP1.receptor expression-enhancing protein1 (11).

Table 1. Genetic causes of other motor neuron disease: AD.autosomal dominant,ALS.amyotrophic lateral sclerosis: AR.autosomal recessive, BSCL2. Berardinelli-Seip congenital contravtiture syndrome, MSA.mental retardation.aphasi. shuffling gait and adducted thumbs,PLP1.proteolipid protein1, PLSA1.adult primary lateral sclerosis,PNPLA5. phospholipase domain-containing6, SBMA.spinal bulbar muscular atrophy, SMA. Spinal muscular atrophy, SPG. spstic paraplegia, ZFVEZ6.zinc finger. FYVE domain-contaning26 (11).

Disease	Chromosome	Gene	Protein	Inheritance	Associated clinical features	Refs
SPG1	Xq28	L1CAM	L1 cell adhesion molecule	X-linked	MASA syndrome and X-linked hydrocephalus	124
SPG2	Xq22	PLP1	Myelin proteolipid protein	X-linked	Pure and complicated (mental retardation and seizures) HSP	125
SPG3A	14q12-q21	ATL1	Atlastin	AD	Pure and complicated HSP with early onset and slow progression	99
SPG4	2p22	SPAST	Spastin	AD	Mainly pure HSP with variable onset	92
SPG5A	8q21.3	CYP7B1	Cytochrome P450, family 7, subfamily B, polypeptide 1	AR	Pure HSP with variable onset	128
SPG6	15q11.2-q12	NIPA1	Non-imprinted in Prader-Willi/Angelman syndrome region protein 1	AD	Pure HSP with adult onset	106
SPG7	16q24.3	SPG7	Paraplegin	AR	Pure and complicated HSP (optic, cortical and cerebellar atrophies)	118
SPG8	8q24	KIAA0196	Strumpellin	AD	Pure HSP with adult onset (marked spasticity)	133
SPG10	12q13	KIF5A	Kinesin family member 5A	AD	Pure and complicated HSP with early onset	104
SPG11	15q21.1	SPG11	Spatacsin	AR	Pure HSP with variable onset and thin corpus callosum with early onset	117
SPG13	2q24-q34	HSPD1	Heat shock protein 60	AD	Pure HSP with adult onset	122
SPG15	14q24.1	ZFYVE26	Spastizin	AR	Complicated HSP (Kjellin syndrome) with adolescent onset	111
SPG17	11q12-q14	BSCL2	Seipin	AD	Complicated HSP (Silver syndrome) with variable onset	134
SPG20	13q12.3	SPG20	Spartin	AR	Complicated HSP (Troyer syndrome) with childhood onset	112
SPG21	15q21-q22	SPG21	Maspardin	AR	Complicated HSP (Mast syndrome) with early adult onset	113
SPG22	Xq13.2	SLC16A2	Solute carrier family 16, member 2	X-linked	Allan-Herndon-Dudley syndrome (AHDS)	135
SPG31	2p12	REEP1	Receptor expression-enhancing protein 1	AD	Pure HSP with variable onset	136
SPG39	19p13	PNPLA6	Neuropathy target esterase	AR	Very rare HSP with marked distal wasting in all four limbs	138
SPG42	3q25.31	SLC33A1	Acetyl-CoA transporter	AD	Pure HSP with variable onset	129
SPG44	1q42.13	GJC2	Connexin 47	AR	Complicated HSP (ataxia, dysarthria and seizures) with late onset	132
JPLS	2q33.1	ALS2	Alsin	AR	Juvenile ALS2 and infantile-onset ascending spastic paralysis	41
PLSA1	4ptel-p16.1	Unknown	Unknown	AD	Progressive asymmetric spastic paraparesis and weakness of the lower limbs followed by upper limb involvement	140
SMA	5q12.2-q13.3	SMN1	Survival of motor neuron protein 1, telomeric	AR	SMA type I, II, III and IV	148
SBMA	Xq11-q12	AR	Androgen receptor	X-linked	Kennedy disease (X-linked recessive form of SMA)	150
LCCS1	9q34	GLE1	GLE1	AR	Lethal arthrogryposis with anterior horn cell disease	153
LCCS2	12q13	ERBB3	ERBB3	AR	Early fetal hydrops and akinesia with anterior horn disease with neurogenic bladder defects	155
LCCS3	19p13.3	PIP5K1C	Phosphatidylinositol-4-phosphate 5-kinase, type I, gamma	AR	Similar to LCCS2 but without neurogenic bladder defects	154

References

1. Sara Salinas, Christos Proukakis, Andrew Crosby, Thomas T Warner : Hereditary spastic paraplegia: clinical features and pathogenetic mechanisms . *Lancet Neurol* 2008; 7: 1127–38.
2. Fink JK. Advances in the hereditary spastic paraplegias. *Exp Neurol* 2003;184 (suppl 1):S106-10.
3. McMonagle P, Webb S, Hutchinson M. The prevalence of pure HSP in the island of Ireland. *J Neurol Neurosurg Psychiatry* 2002; 72: 43–46.
4. Silva M, Coutinho P, Pinheiro CD, Neves JM, Seneno P :Hereditary ataxias and spastic paraplegias: methodological aspects of a prevalence study in Portugal . *J Clin Epidemiol* 1997;50:1377–84.
5. Paik NJ, Lim JY. Hereditary Spastic Paraplegia. *Emedicine*. Jul 29, 2008. Available from URL: emedicine.medscape.com/article/306713-overview.
6. Harding AE. Hereditary spastic paraplegias. *Semin Neurol* 1993; 13: 333–36.
7. Hedera P, Eldevik OP, Maly P, Rainier S, Fink JK. Spinal cord MRI in autosomal dominant hereditary spastic paraplegia. *Neuroradiology* 2005; 47: 730–34.
8. Sartucci F, Tavani S, Murri L, Saggliocco L. Motor and somatosensory evoked potentials in autosomal dominant hereditary spastic paraplegia linked to chromosome 2p, SPG4. *Brain Res Bull* 2007; 74: 243–49.
9. Sartucci F, Tavani S, Murri L, Saggliocco L. Motor and somatosensory evoked potentials in autosomal dominant hereditary spastic paraplegia linked to chromosome 2p, SPG4. *Brain Res Bull* 2007; 74: 243–49.
10. Deluca GC, Ebers GC, Esiri MM. The extent of axonal loss in the long tracts in hereditary spastic paraplegia. *Neuropathol Appl Neurobiol* 2004 Dec; 30(6):576-84.
11. Patrick A. Dion, Hussein Daoud and Guy A. Rouleau; Genetics of motor neuron disorders: new insights into pathogenic mechanisms. *Nature Reviews* 2009 Nov; 10:769-782.
12. Van Niekerk E A, Willis D E, Chang J H, Reumann K, Heise T, Twiss J L. Sumoylation in axons triggers retrograde transport of the RNA-binding protein. *La Proc Natl Acad Sci USA* 2007;104(31):12913–12918.
13. Svenson I K, Ashley-Koch AE, Pericak-Vance M A, Marchuk DA. A second leaky splice-site mutation in the spastin gene. *Am J Hum Genet* 2001; 69:1407–1409.
14. Zhao X, Alvarado D, Reinier SH, Lemons R, Hedera P, Weber CH, et al. Mutations in a newly identified GTPase gene cause autosomal dominant hereditary spastic paraplegia. *Nature Genet* 2001; 29:326–331.
15. Namekawa M, Muriel MP, Janer A, Latouche M, Dauphin A, Debeir T, et al. Mutations in the SPG3A gene encoding the GTPase atlastin interfere with vesicle trafficking in the ER/Golgi interface and Golgi morphogenesis. *Mol Cell Neurosci* 2007; 35:1–13.
16. Reid E, Kloos M, Ashley-Koch A, Hughes L, Bevan S, Svenson K I, et al. A kinesin heavy chain (KIF5A) mutation in hereditary spastic paraplegia (SPG10). *Am J Hum Genet* 2002; 71: 1189–1194.
17. Wilkinson P A, Crosby AH, Turner C, Bradley LJ, Ginsberg L, Wood NW, et al. A clinical, genetic and biochemical study of SPG7 mutations in hereditary spastic paraplegia. *Brain* 2004;127:973–980.
18. Koppen M, Metodiev MD, Casari G, Rugarli E I, & Langer T. Variable and tissue-specific subunit composition of mitochondrial m-AAA protease complexes linked to hereditary spastic paraplegia. *Mol. Cell Biol* 2007; 27: 758–767.
19. Hansen J J, Durr A, Cournu-Rebeix I, Georgopoulos C, Ang D, Nielsen MN, et al. Hereditary spastic paraplegia SPG13 is associated with a mutation in the gene encoding the mitochondrial chaperonin Hsp60. *Am J Hum Genet* 2002;70:1328–1332.
20. Tsaousidou MK, Ouahchi K, Warner TT, Yang Y, Simpson MA, Laing NG, et al. Sequence alterations within CYP7B1 implicate defective cholesterol homeostasis in motor-neuron degeneration. *Am J Hum Genet* 2008;82: 510–515.
21. Mc Dermott CJ, Burness CE, Kirby J, Cox LE, Rao DG, Hewamadduma C, et al. Clinical features of hereditary spastic paraplegia due to spastin mutations. *Neurology* 2006; 67: 45–51.
22. Namekawa M, Ribai P, Nelson I, Forlani S, Fellmann F, Goizet C, et al. SPG3A is the most frequent cause of hereditary spastic paraplegia with onset before age of 10 years. *Neurology* 2006; 66: 112–14.
23. Reed JA, Wilkinson PA, Patel H, Simpson MA, Chatonnet A, Robay D, et al. A novel NIPA1 mutation

- associated with a pure form of autosomal dominant hereditary spastic paraplegia. *Neurogenetics* 2005; 6:79–84.
24. Beetz C, Schule R, DeConnit T, Tran-Viet KN, Zhu H, Kremer BP, et al. REEP1 mutation spectrum and genotype/phenotype correlation in HSP31. *Brain* 2008; 131: 1078–86.
 25. Hentati A, Pericak-Vance MA, Hung WY, et al. Linkage of pure autosomal recessive spastic paraplegia to chromosome 8 markers and evidence of genetic locus heterogeneity. *Hum Mol Genet* 1994; 3: 1263–67.
 26. Wilkinson PA, Crosby AH, Turner C, et al. A clinical, genetic and biochemical study of SPG7 mutations in hereditary spastic paraplegia. *Brain* 2004; 127: 973–80.
 27. Paisan-Ruiz C, Dogu O, Yilmuz A, Houlden H, Singleton A. SPG11 mutations are common in familial cases of complicated hereditary spastic paraplegia. *Neurology* 2008;70:1384–89.
 28. Stevanin G, Montagna G, Azzedine H, Valente EM, Durr A, Scarano V, et al. Spastic paraplegia with thin corpus callosum: description of 20 new families, refinement of the SPG11 locus, candidate gene analysis and evidence of genetic heterogeneity. *Neurogenetics* 2006 Jul;7(3):149–56. Epub 2006 May 13.
 29. Hanein S, Martin E, Boukhris A, et al. Identification of the SPG15 gene, encoding spastizin, as a frequent cause of complicated autosomal recessive spastic paraplegia, including Kjellin syndrome. *Am J Hum Genet* 2008; 82: 992–1002.
 30. Jouet M, Rosenthal A, Armstrong G, et al. X-linked spastic paraplegia (SPG1) MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. *Nat Genet* 1994; 7: 402–07.
 31. Inoue K. PLP1-related inherited dysmyelinating disorders: Pelizaeus–Merzbacher disease and spastic paraplegia type 2. *Neurogenetics* 2005;6:1–16.