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REVIEW ARTICLE

Hereditary spastic paraplegia

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Abstract
Hereditary spastic paraplegias (HSPs) are a group of neurodegenerative disorders which involve the corticospinal tracts and present with distinct spasticity and weakness of the lower extremities. The estimated prevalence of HSP is around 1.8/100,000 cases for both autosomal dominant and autosomal recessive types. Classification of HSP is based on inheritance pattern, clinical phenotype, and molecular pathophysiological mechanisms. The most common neuropathological sign is the axonal degeneration involving the lateral corticospinal tracts in both the cervical and thoracic spinal cord. The target of this review article is to provide a comprehensive overview of the HSP classification, neuropathology, and differential diagnosis.

Keywords Hereditary spastic paraplegia · Autosomal dominant HSP · Autosomal recessive HSP · X-linked · Differential diagnosis · Treatment

Introduction

Hereditary spastic paraplegias (HSPs) are a group of neurodegenerative disorders which involve the corticospinal tracts and present with distinct spasticity and weakness of the lower extremities [1, 2]. HSPs are inherited in an autosomal dominant (AD), autosomal recessive (AR), X-linked recessive (XLR), and mitochondrial inheritance manner with > 80 published loci or genes [2, 3].

Clinically HSPs are classified into a pure form and a complex form. Pure forms present with slowly progressive lower extremity weakness and spasticity, corticospinal tract signs, disturbance in vibration sense and proprioception, and a variable hypertonic urinary disturbance. Complex HSP form has leg spasticity and other complications like ataxia, a thin corpus callosum, extrapyramidal signs, chorioretinal dystrophy, peripheral neuropathy, and mental retardation. Complex forms of HSP most often present with AR inheritance rather than AD form [1, 2].

Historical perspective

Neurologist Ernst Adolf von Strumpell, in 1880, published the first case report of patients with HSP [4]. In 1886, Strumpell also described the pathological characteristics of HSP [5]. Maurice Lorrain in 1888 published the comprehensive clinical and anatomical study of the HSPs. HSP is also known as Strumpell-Lorrain disease [6].

Schwarz in 1952 published a detailed review on pathological characteristics of HSP and also established the fact that initially lesions are restricted to the spinal cord particularly affecting the corticospinal and posterior tracts, which differentiates the HSP from other diseases like cerebellar ataxias and motor neuron disorders [7].

Anita Harding in 1981 published the investigational study of pure HSP families; it was also reported from this study that the pure subtypes of HSPs are most commonly inherited through AD way [8]. Harding also confirmed that spasticity is the main cause of disability and not weakness, which also differentiates the HSP from other myelopathies. In 1983, Harding introduced the classification of HSP into pure and complicated forms. Along with spastic paraparesis, other neurological symptoms like vibration and proprioception deficits,

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sphincter dysfunction, and a slight distal amyotrophy are also reported in the pure form of HSP [6].

Schady et al., in 1991, reported the neurophysiological findings through transcranial magnetic stimulation by central motor conduction studies in HSP patients [8]. Jouet et al., in 1994, described that the three disorders X-linked paraplegia, X-linked hydrocephalus, and MASA syndrome (mental retardation, aphasia, shuffling gait, and adducted thumbs) are the allelic conditions which occurred due to the mutations in the gene for L1CAM (neuronal cell adhesion molecule) or SPG1 (spastic paraplegia gene) [9]. Casari et al., in 1998, discovered the first gene for autosomal recessive HSP, while cloning the HSP-SPG7 gene. SPG7 gene encodes paraplegin protein which is found in mitochondria and ragged red muscle fibers [10]. Hazan et al., in 1999, cloned the SPG4 gene, which responds to 60% of cases with AD inherited HSP [11].

In 2006, the German network for HSP developed a spastic paraplegia rating scale to quantify the clinical disease progression [10]. In 2014, Novarino discovered up to 18 new HSP-related genes. Currently, > 80 different loci along with > 50 genes related to HSP are discovered. Historical timeline of HSP clinical research over the last century is shown below in Table 1 [6, 10].

Epidemiology

There are limited studies of HSP and its prevalence rate varies based on the geographic location, patient's inclusion criteria, classification, and diagnosis. Worldwide, the estimated prevalence of HSP is around 1.8/100,000 cases for both AD and AR types. Few other studies suggested that the prevalence could range from 4.3 to 9.8/100,000 [12].

In Europe, there is an estimate of 3–10 HSP patients for 100,000 individuals. In Japan, it is estimated that there are 0.2 cases for 100,000 individuals [2]. Prevalence of AD-HSP is about 0.5 to 5.5/100,000 and for AR-HSP, it ranges from 0.0 to 5.3/100,000 population, with pooled average of 1.8/100,000 [13].

Classification

Classification of HSP is based on inheritance pattern, clinical phenotype, and other pathophysiological molecular mechanism. Classifications of HSP and its main subtypes are shown below in Table 2 [12].

Pure form of HSP presents with pyramidal signs like quadriparesis or paraparesis, brisk tendon reflexes, extensor plantar response, and spasticity along with deep sensory loss and sphincter disturbances [14, 15].

Complex or complicated form of HSP is characterized with both neurological and non-neurological signs. Neurological signs include the following [14, 16]:

- Cerebellar dysfunctions like tremor, ataxia, and nystagmus
- Cognitive impairment which includes dementia, intellectual disability, and mental retardation
- Epilepsy
- Axonal or demyelinating peripheral neuropathy involving dysautonomia and significant sensory disturbances
- Myopathic characteristics include ptosis and opthalmoparesis (chronic progressive external ophthalmoplegia-like phenotype)
- Psychiatric disturbances
- Extrapyramidal features like chorea, parkinsonism, and dystonia
- Brain and spine MRI abnormalities of distinct genetic subtypes are hypomyelination, leukodystrophy, thin corpus callosum, hydrocephalus, mild white matter changes, brain iron accumulation, cerebellar atrophy, and spinal cord atrophy

Non-neurological symptoms of complicated HSP include the following [15, 17]:

- Ophthalmological abnormalities like optic atrophy, cataracts, optic neuropathy, macular degeneration, and retinitis pigmentosa
- Dysmorphic features like macrocephaly, microcephaly, short stature, facial dysmorphisms, and other complex deformative syndromes
- Orthopedic anomalies include scoliosis, hip dislocation, and various foot deformities

Based on inheritance pattern, HSP is inherited through AD, AR, XLR, and maternal pattern trait disorders. AD forms of HSP are less common than the AR forms; pure phenotypic forms are significantly seen in AD-HSP form. AR inheritance is the most frequently seen HSP form and is commonly seen in consanguineous families. XLR inheritance is seen in isolated cases and has five genetic subtypes known so far. Mitochondrial maternal inheritance is so sporadic with almost all the cases having a complex HSP phenotype; numerous signs and symptoms are usually seen which point towards a mitochondrial disorder [12, 17].

Although various pathophysiological mechanisms are involved in the development of HSP, it is classified based on the intracellular mechanisms involved in the pathophysiology. Molecular mechanisms which are commonly involved are mitochondrial dysfunction, axonal transport, membrane trafficking and organelle shaping, myelination abnormalities, and lipid metabolism disturbances [12, 15].

Table 1 Historical timeline of HSP clinical research over the last century [6, 10]

1880- Strumpell published the first case report
1886- Strumpell described pathological hallmarks
1979- The complicated phenotypes
1983- Anita Harding introduced the clinical classification
1991- Schady reported central motor conduction studies
1994- Jouet discovered L1CAM gene
1998- Casari identified the first AR gene for HSP-SPG7 and paraplegin protein
1999- Hazan cloned the SPG4 gene
2004- DeLuca published the detailed pathology
2006- Shule introduced German Network for HSP Rating Scale
2015- Gaia Novarino found 14 new genes
2017- 80 different loci are discovered

AR autosomal recessive; *HSP* hereditary spastic paraplegia; *SPG* spastic paraplegia gene

Neuropathology

Postmortem studies in HSP patients most commonly showed degeneration of axons involving the lateral corticospinal tracts with maximum severity in the thoracic portion of the spinal cord distal ends and relatively with little severity in the cervical portion of the spinal cord [14, 18]. Axonal degeneration in fasciculus gracilis fibers are typically found and are most

Table 2 Classification of HSP and its subtypes [12]

Based on signs and symptoms (Harding's classification)
1. Pure (uncomplicated) HSP
- Spastic paraparesis along with sphincteral disturbances and mild to moderate sensory loss

2. Complicated (complex) HSP
- Spastic paraparesis along with additional neurological and systemic signs and symptoms

Based on spasticity onset age (Harding's classification)
1. HSP type I
- Early onset – starting before 35 years of age

2. HSP type II
- Classical – starting after 35 years of age

Based on inheritance pattern
1. Autosomal dominant HSP
- SPG3A, SPG4, SPG6, SPG8, SPG9, SPG10, SPG12, SPG13, SPG17, SPG19, SPG29, SPG31, SPG33, SPG36, SPG37, SPG38, SPG41, SPG42, SPG72, SPG73

2. Autosomal recessive HSP
- SPG5, SPG7, SPG11, SPG14, SPG15, SPG18, SPG20, SPG21, SPG23, SPG24, SPG25, SPG26, SPG27, SPG28, SPG30, SPG32, SPG35, SPG39, SPG43, SPG44, SPG45/SPG65, SPG46, SPG47, SPG48, SPG49, SPG50, SPG51, SPG52, SPG53, SPG54, SPG55, SPG56, SPG57, SPG58, SPG59, SPG60, SPG61, SPG62, SPG63, SPG64, SPG66, SPG67, SPG68, SPG69, SPG70, SPG71, SPG72, SPG74

3. X-linked HSP
- SPG1, SPG2, SPG16, SPG22, SPG34

4. Mitochondrial HSP
- MT-ATP6, MT-TI, MT-CO3, MT-ND4

Based on intracellular pathophysiological mechanisms
1. Membrane trafficking and organelle trafficking
- SPG3A, SPG4, SPG6, SPG11, SPG15, SPG18, SPG20, SPG31, SPG59, SPG60, SPG61, SPG62, SPG69, SPG72

2. Axonal transport
- SPG4, SPG10, SPG30, SPG58

3. Mitochondrial dysfunction
- SPG7, SPG20, SPG31

4. Lipid metabolism disturbances
- SPG5, SPG26, SPG28, SPG35, SPG39, SPG46, SPG54, SPG56

5. Myelination abnormalities
- SPG1, SPG2, SPG39, SPG42, SPG67

HSP hereditary spastic paraplegia; *SPG* spastic paraplegia gene

significant in the cervical portion of the spinal cord; demyelination of these fibers is correlated with the degree of axon degeneration instead of suggesting a disease of primary demyelinative cause [14].

Axonal degeneration in the spinal cord causes mild to distinct atrophy in both cervical and thoracic segments [19]. In few cases, corticospinal tract degeneration stretches rostrally into the internal capsule, cerebral peduncles, pons, and medulla; reduced amount of pyramidal neurons ("Betz cells") was also found in some specimens [14, 20].

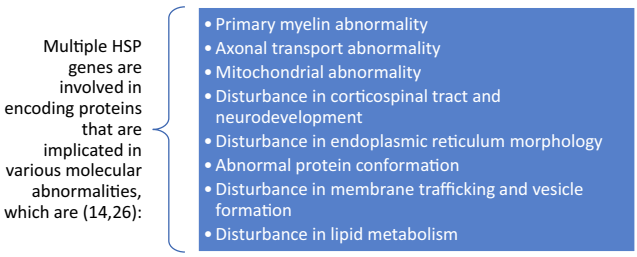
HSP showed distinct susceptibility towards the long, sensory and motor axons of the CNS and depicts primary axonopathy. HSP expands beyond the CNS and causes peripheral neuropathy as a common symptom in many subtypes of HSP [14, 21]. HSP also involves not so long neurons, particularly seen in the neurons of the cerebellum, basal ganglia, anterior horn cells, and Clarke's column (SPG4 subtype) [22].

Myelin abnormalities are frequently seen in HSP, specifically because of the genetic mutations in the neurons. Postmortem of a SPG2 HSP showed moderate cerebral atrophy, diffuse pallor of CNS myelin (corticospinal tract), and severe axonal degeneration of the corticospinal tract [23].

Few HSP abnormalities might be developmental instead of degenerative causes. Diameter of the spinal cord was relatively smaller in HSP subjects, which might be due to developmental disturbance in the spinal canal because of mutated induction in the development of the spinal cord [24]. Thin corpus callosum was believed to be an abnormality in development; however, Franca et al. have shown progressive thinning of the corpus callosum on serial brain MRI scans [25].

Genetics

HSP is inherited through AD, AR, XLR, and maternal pattern trait disorders [12]. HSP subtypes, inheritance mode, their gene encoded protein functions, and distinct clinical features are shown below in Table 3 [12, 26].



SPG4

SPG4 is inherited in an AD pattern and comprises 45% of pure HSP form. Mutations in the SPAST gene, which encode spastin, which is an ATPase-microtubule-severing protein family member engaged in intracellular motility, proteolysis, membrane trafficking, organelle biogenesis, endosomal tabulation, and fission and protein folding. Common presentation includes spastic paraparesis, sphincter disturbances, mild spastic dysarthria, and pes cavus; atypical symptoms include head tremor, nystagmus, depression, mental retardation, behavioral disturbances, psychosis, and cognitive decline with executive dysfunction; isolated symptoms are bulbar dysfunction, lower motor neuron syndrome, and restless leg syndrome [12, 14, 27].

Table 3 HSP subtypes, mode of inheritance, gene encoded protein functions, and their clinical features [12, 26]

HSP subtype (gene)	Mode of inheritance	Gene encoded protein and its function	Clinical features
SPG1 (L1CAM)	XLR	L1 cell adhesion molecule – guidance to axons	CRASH syndrome, MASA syndrome, Gareis-Mason syndrome; hydrocephalus, corpus callosum agenesis
SPG2 (PLP1)	XLR	Proteolipid protein 1 – oligodendrocyte progenitor cell migration, myelin component	Nystagmus, optic atrophy, severe hypomyelination
SPG3A (ATL1)	AD	Atlastin GTPase 1 - dendritic morphogenesis, formation of the tubular ER, inhibit BMP signaling	Seizures, thin corpus callosum, rarely optic atrophy
SPG4 (SPAST)	AD	Spastin – BMP signaling, microtubule dynamics	Classical "Strumpell-Lorrain disease"
SPG5A (CYP7B1)	AR	Cytochrome P450, family 7, subfamily B, polypeptide 1 – hydroxylase, cholesterol, and neurosteroid metabolism	Optic atrophy, spastic ataxia, and cerebellar ataxia
SPG6 (NIPA1)	AD	NIPA1/non-imprinted in Prader Willi/Angelman syndrome 1 – inhibitor of BMP pathway, Mg+2 transporter	Seizures, postural tremor
SPG7 (SPG7)	AR	Paraplegin – component of the m-AAA protease	Cerebellar atrophy, chronic progressive external ophthalmoplegia, and cerebellar ataxia
SPG8 (KIAA0196)	AD	Strumpellin – remodeling of actin	Lower limb distal amyotrophy
SPG9A (ALDH18A1)	AD		Cerebellar ataxia, ALS-like CMNSS, SPACGR
SPG9B (ALDH18A1)	AR		Corpus callosum atrophy, microcephaly, mental retardation, facial dysmorphism, tremor
SPG10 (KIF5A)	AD	Kinesin heavy chain isoform 5A – axonal transport, motor protein	Neuropathy, cerebellar ataxia, cognitive decline, distal amyotrophy, rarely with parkinsonism
SPG11 (SPG11)	AR	Spatacsin – lysosome shaping	"Ears of the lynx" sign, thin corpus callosum, cerebellar ataxia, mild white matter changes, distal amyotrophy, mental retardation, parkinsonism, maculopathy
SPG12 (RTN2)	AD	Reticulon 2 – helps in ER shaping	"Pure HSP"
SPG13 (HSPD1)	AD	Heat shock 60 kDa protein 1/chaperonin – helps in mitochondrial chaperone	"Pure HSP" and marked spasticity
SPG14, -	AR		Mental retardation, distal motor neuropathy
SPG15 (ZFYVE26)	AR	Spastizin – autophagy, lysosome shaping, cytokinesis	Thin corpus callosum, Kjellin syndrome, retinal degeneration, distal amyotrophy, levodopa-responsive parkinsonism, mild white matter changes, hearing loss, neuropathy, cerebellar ataxia, psychosis, epilepsy
SPG16 (SPG16)	XLR		Mental retardation, motor aphasia, short and thick distal phalanges, maxillary hypoplasia
SPG17 (BSCL2)	AD	Seipin – scaffolding protein for lipid metabolism and lipid droplet formation, ER protein	Silver syndrome, prominent thenar and interossei musculature wasting, ALS-like phenotype
SPG18 (ERLIN2)	AR	SPFH2 – ER-associated degradation pathway (ERAD)	Mental retardation, severe spasticity, multiple joint contractures, seizures
SPG19, -	AD		Mild neuropathy
SPG20 (SPG20)	AR	Spartin – BMP signaling, mitochondrial ca2+ homeostasis, cytokinesis, lipid droplet maintenance	Troyer syndrome, distal amyotrophy, multiple dysmorphisms, tongue dyspraxia, rarely cerebellar ataxia, mild white matter changes, cerebellar atrophy
SPG21 (ACP33)	AR	Maspardin – associated with markers of endocytic and trans-Golgi compartments	MAST syndrome, extrapyramidal and cerebellar signs, cognitive decline, neuropathy, frontotemporal atrophy, thin corpus callosum
SPG22 (SLC16A2)	XLSD	Solute carrier family 16 member 2 – acts as thyroid hormone transporter	Hypomyelinating leukodystrophy, cerebellar ataxia, typical dysmorphisms, mental retardation, dystonia
SPG23, -	AR		Lison syndrome, mental retardation, hyperpigmentation of exposed areas, patchy vitiligo, lentigenes, mild neuropathy, facial features
SPG24, -	AR		"Pure HSP"
SPG25, -	AR		"Familial intervertebral disk disease"
SPG26 (B4GALNT1)	AR	Beta-1,4-N-acetyl-galactosaminyl transferase – helps in ganglioside metabolism	Mental retardation, neuropathy, distal amyotrophy, cerebellar ataxia, nystagmus, dystonia, dyskinesias

Table 3 (continued)

HSP subtype (gene)	Mode of inheritance	Gene encoded protein and its function	Clinical features
SPG27, -	AR		"Typical pure HSP"
SPG28 (DDHD1)	AR	DDHD domain containing 1 – helps in lipid metabolism, phospholipase A1	"Typical pure HSP"
SPG29, -	AD		Genetic anticipation, hearing loss, hiatal hernia
SPG30 (KIF1A)	AR	Kinesin family member 1A – axonal anterograde transport, motor protein	Mild cerebellar ataxia, mild neuropathy, mild cerebellar atrophy
SPG31 (REEP1)	AD	Receptor expression-enhancing protein 1 – mitochondrial functions, ER-shaping	"Distal amyotrophy"
SPG32, -	AR		Mental retardation (mild)
SPG33 (ZFYVE27)	AD	ZFYVE27/zinc finger, FYVE domain containing 27/protrudin – neurite outgrowth, ER morphology	"Pure HSP"
SPG34, -	XLR		"Pure HSP," Brazilian family
SPG35 (FA2H)	AR	Fatty acid 2-hydroxylase – cell differentiation, myelin stability	FAHN syndrome, leukodystrophy, cognitive decline, optic atrophy, cerebellar ataxia, brain iron accumulation, dystonia, rarely seizures and strabismus
SPG36, -	AD		"Neuropathy"
SPG37, -	AD		"Pure HSP"
SPG38, -	AD		Silver syndrome-like, ALS-like phenotype
SPG39 (PNPLA6)	AR	Patatin-like phospholipase domain containing 6/neuropathy target esterase – membrane curvature, lipid metabolism	Troyer syndrome-like, marked distal amyotrophy, cerebellar and thoracic spinal cord atrophy
SPG40, -	AD		"Pure HSP," genetic anticipation
SPG41,	AD		"Pure HSP"
SPG42 (SLC33A1)	AD	Solute carrier family 33 acetyl-CoA transporter, member 1 – acts as acetyl-CoA transporter	"Pure HSP"
SPG43 (C190RF12)	AR	Chromosome 19 open reading frame 12 – (-)	Multiple contractures, severe amyotrophy, Malian and Brazilian families
SPG44 (GJC2)	AR	Gap junction protein, gamma 2, 47 kDa – oligodendrocyte connexin	Seizures, cerebellar ataxia, hearing loss, mental retardation, painful spasms, hypomyelinating leukodystrophy, thin carpus callosum
SPG45/SPG65 (NT5C2)	AR		Dysplastic corpus callosum, mental retardation, white matter changes, optic atrophy, strabismus, joint contractures, nystagmus
SPG46 (GBA2)	AR	Glucocerebrosidase 2 – helps in lipid metabolism	Cerebellar atrophy, thin corpus callosum, cerebellar ataxia, head tremor, mental retardation, congenital cataracts, small testicles, hearing loss
SPG47 (AP4B1)	AR	Adaptor-related protein complex 4, beta 1 subunit – helps in membrane trafficking	Thin corpus callosum, neonatal hypotonia, late-onset febrile seizures, mental retardation, spastic tongue protrusion, dysmorphisms, shy character, stereotypic laughter, dystonia, white matter changes
SPG48 (AP5Z1)	AR	Adaptor-related protein complex 5, zeta 1 subunit - membrane trafficking	"Pure HSP" and mild cervical spine hyperintensities
SPG49 (TECPR2)	AR	Cytochrome P450, family 2, subfamily U, polypeptide 1 – lipid metabolism	Seizures, mental retardation, cerebellar ataxia, complicated gastroesophageal reflux, dysmorphisms, recurrent respiratory infections, cerebellar atrophy, recurrent central apnea, thin corpus callosum
SPG50 (AP4M1)	AR	Adaptor-related protein complex 4, mu 1 subunit – membrane trafficking	Infantile-onset seizures, neonatal hypotonia, mental retardation, strabismus, dysmorphisms, thin corpus callosum, ventriculomegaly, white matter changes
SPG51 (AP4E1)	AR	Adaptor-related protein complex 4, epsilon 1 subunit – membrane trafficking	Seizures, neonatal hypotonia, cerebellar atrophy, mental retardation, shy character, short stature, stereotypic laughter, dysmorphisms, nystagmus, joint contractures, ventriculomegaly, marked leukodystrophy
SPG52 (AP4S1)	AR	Adaptor-related protein complex 4, sigma 1 subunit – helps in membrane trafficking	Shy character, neonatal hypotonia, smiling attitude, mental retardation, dysmorphisms, joint contractures

Table 3 (continued)

HSP subtype (gene)	Mode of inheritance	Gene encoded protein and its function	Clinical features
SPG53 (VPS37A)	AR	Vacuolar protein sorting 37 homolog A –ESCRT-1 complex member	Pectus carinatum, mental retardation, hypertrichosis, dystonia
SPG54 (DDHD2)	AR	DDHD domain containing 2 – helps in lipid metabolism, phospholipase	Optic nerve hypoplasia, mental retardation, strabismus, joint contractures, dysmorphisms, white matter changes, thin corpus callosum, abnormal lipid peaks
SPG55 (C12ORF65)	AR	Chromosome 12 open reading frame 65 – mediated ribosome rescue system member in mitochondria	Optic atrophy, progressive visual loss, strabismus, mental retardation, distal neuropathy, hypoplastic corpus callosum, mild facial dysmorphisms
SPG56 (CYP2U1)	AR		Mental retardation, dystonia, neuropathy, white matter changes, basal ganglia calcification, thin corpus callosum
SPG57 (TFG)	AR	TRK-fused gene –vesicle transport between ER and Golgi, ER morphology	Contractures, neuropathy, optic atrophy
SPG58 (KIF1C)	AR	Kinesin family member 1C – retrograde Golgi to ER transport, motor protein	Microcephaly, cerebellar ataxia, mental retardation, hypodontia, short stature, chorea, fragmentary clonus, white matter changes
SPG59 (USP8)	AR	Ubiquitin-specific peptidase 8 – acts as deubiquitination enzyme	"Pure HSP"
SPG60 (WDR48)	AR	WD repeat domain 48 – acts as deubiquitination enzyme	Neuropathy, nystagmus,
SPG61 (ARL6IP1)	AR	ADP-ribosylation factor-like 6 interacting protein 1 – ER morphology	Severe mutilating acropathy, severe neuropathy
SPG62 (ERLIN1)	AR	ER lipid raft associated 1 – helps in ER-associated degradation	Distal amyotrophy, cerebellar ataxia
SPG63 (AMPD2)	AR	Adenosine monophosphate deaminase 2 – helps in deamination of AMP to IMP in purine nucleotide metabolism	Thin corpus callosum, short stature, white matter changes
SPG64 (ENTPD1)	AR	Ectonucleosidase triphosphate diphosphorylase 1 – helps in hydrolyzing ATP and other nucleotides to regulate purinergic transmission	Mental retardation, microcephaly, delayed puberty, mild white matter changes
SPG66 (ARSI)	AR	Arysulfatase I – hydrolyses sulfate esters, hormone biosynthesis	Cerebellar hypoplasia, severe neuropathy, colpocephaly, thin corpus callosum
SPG67 (PGAP1)	AR	GPI inositol deacylase – GPI-AP sorting by ERES	Agenesis of the corpus callosum, global developmental delay, hand tremor, hypomyelination, cerebellar vermis hypoplasia
SPG68 (FLRT1)	AR	Fibronectin leucine-rich transmembrane protein 1 – FGF pathway	Optic atrophy, mild amyotrophy, nystagmus; without marked spasticity
SPG69 (RAB3GAP2)	AR	RAB3 GTPase activating protein subunit 2 – ER morphology	Mental retardation, deafness, cataracts
SPG70 (MARS)	AD	Methionyl-tRNA synthetase – acts as cytosolic methionyl-tRNA synthetase	Mild mental retardation, nephrotic syndrome
SPG71 (ZFR)	AR	Zinc finger RNA-binding protein – (-)	"Pure HSP," thin corpus callosum
SPG72 (REEP2)	AR/AD	Receptor expression-enhancing protein 2 – ER shaping	"Postural tremor"
SPG73 (CPT1C)	AD		Amyotrophy (mild)
SPG74 (IBA57)	AR	Iron-sulfur cluster assembly homolog	Optic atrophy, neuropathy
IAHSP (ALS2)	AR		Marked pyramidal hypersignal, ascending phenotype
SPOAN (KLC2)	AR		Brazil, Egypt; optic atrophy, marked acoustic startle reflex, nystagmus, hyperhidrosis, parkinsonism, distal amyotrophy, neuropathy, mild spine atrophy
CPSQ-I (GAD1)	AR		Multiple contractures, mental retardation, microcephaly, occasional seizures
Spastic paraplegia with deafness	XL		Deafness, hypogonadism, short stature, tremor, cataracts
BICD2-associated HSP	AR	Bicaudal D homolog 2 – adapter protein of the dynein-dynactin motor complex	"Amyotrophy"

Table 3 (continued)

HSP subtype (gene)	Mode of inheritance	Gene encoded protein and its function	Clinical features
CCT5-associated HSP	AR	Chaperonin containing TCP1, subunit 5 – acts as cytosolic chaperonin	Mutilating acropathy, cavanagh variant, vagal hyperactivity, severe neuropathy, mild spine atrophy
FAM1 34B-associated HSP	AR	FAM134B – Golgi protein	Mutilating acropathy, painless neuropathy, hyperhidrosis
EXOSC3-associated HSP	AR	Exosome component 3 – acts as core component of the RNA exosome complex	Distal amyotrophy, short stature, cerebellar ataxia, mental retardation, strabismus, tongue atrophy, cerebellar atrophy, adducted thumbs, enlarged cisterna magna
LYST-associated HSP	AR	Lysosomal trafficking regulator protein – helps in lysosome fusion or fission regulation	Neuropathy, cerebellar ataxia, thoracic spine and cerebellar atrophy
GRID2-associated HSP	AR		Lower motor neuron syndrome, cerebellar ataxia, ALS-like phenotype, frontotemporal dementia, cerebellar atrophy
IFIH1-related HSP	AD	Interferon-induced helicase C domain containing protein 1 – helps in interferon signaling	Multisystem inflammatory disorders, British families
ADAR1-related HSP	AD	Adenosine deaminase RNA-specific – RNA metabolism	"Pure HSP," high interferon-1 levels
RNASEH2B-related HSP	AD	Ribonuclease H2 subunit B – ribonucleotides metabolism	"Pure HSP," unspecific white matter changes
KLC4-associated HSP	AR		Marked pyramidal tract hypersignal, joint contractures, white matter changes, thin corpus callosum, dentate nucleus hypersignal, cerebellar atrophy
PMCA4-associated HSP	AD		Chinese families, "pure HSP"
MAG-associated HSP	AR	Myelin-associated glycoprotein – myelination	Amyotrophy, mental retardation, cerebellar ataxia
TUBB4A-related HSP	AR		Hypomyelinating leukodystrophy, cerebellar ataxia
FARS2-associated HSP	AR		"Pure HSP"
DNM2-associated HSP	AD		"Pure HSP"
MT-CO3 gene mutations	Mitochondrial	Cytochrome c oxydase III/complex IV - respiratory chain complex IV subunit	Mental retardation, Leigh-like features, ophthalmoplegia, severe lactic acidosis, COX deficiency
MT-T1 gene mutations	Mitochondrial	Isoleucine transfer RNA (mitochondrial) – mitochondria	Chronic progressive external ophthalmoplegia, cerebellar ataxia, mental retardation; normal muscle biopsy; hearing loss, cardiomyopathy, diabetes
MT-ND4 gene mutations	Mitochondrial		Visual loss (Leber-like features)
MT-ATP6 gene mutations	Mitochondrial	Complex V, ATP synthase, subunit ATPase 6 - respiratory chain complex V subunit	Neuropathy, normal lactate, normal muscle biopsy

AD autosomal dominant; *AR* autosomal recessive; *ALS* amyotrophic lateral sclerosis; *BMP* bone morphogenetic pathway; *CRASH* corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus; *CMNSS* cataracts with motor neuronopathy, short stature, and skeletal abnormalities; *ER* endoplasmic reticulum, *ERES* ER exit sites; *ESCRT* endosomal sorting complexes required for transport; *FAHN* fatty acid hydroxylase-associated neurodegeneration; *FGF* fibroblast growth factor; *GPI-AP* glycosylphosphatidylinositol-anchor protein; *IMP* inositol monophosphate; *(m)AAA* (mitochondrial) ATPase associated with diverse cellular activities; *MASA* mental retardation, aphasia, shuffling gait, and adducted thumbs; *SPACGR* spastic paraparesis with amyopathy, cataracts, and gastroesophageal reflux; *XLR* X-linked recessive; *XLSD* X-linked semi-dominant

SPG11

SPG11 is inherited in an AR pattern, which constitutes about 40% of AR-HSP form. Mutations in SPG11 gene encode spatacsin protein which causes intracellular trafficking, neuronal axonal growth, and function. Typical presentation is of slowly progressive spastic paraparesis, sphincter disturbances, cerebellar ataxia, parkinsonism, cognitive decline, mental retardation with learning disability, pes cavus, neuropathy, dysphagia, and pigmented macular degeneration leading to loss of visual acuity. Typical "ears-of-the-lynx" sign is seen on neuroimaging due to thin corpus callosum, symmetric periventricular white matter changes, cortical atrophy, and mild ventricular dilatation [17, 28].

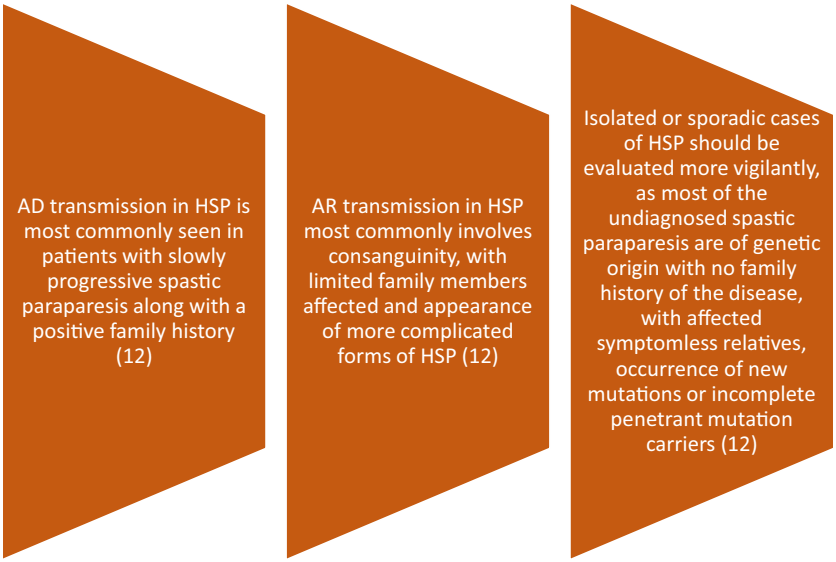


Table 4 Differential diagnosis of hereditary spastic paraplegia [12]

Acquired myelopathies	
Structural changes	• Cervical spondylotic myelopathy, Chiari type I malformation, atlanto-axial subluxation
Demyelinating disorders	• Neuromyelitis optica, multiple sclerosis
Neuroinfectious diseases	• HIV, CMV, HTLV-I/II, syphilis, schistosomiasis
Vascular diseases	• Fibrocartilaginous embolism, spinal cord infarction, arteriovenous shunts, posterior reversible encephalopathy syndrome with spinal cord involvement
Neoplastic diseases	• Astrocytoma, B cell lymphoma, ependymoma
Nutritional diseases	• Copper deficiency, cobalamin deficiency
Paraneoplastic syndromes	• Anti-amphiphysin, anti-CRMP-5/CV2, anti-Hu, anti-GAD
Inherited metabolic diseases (metabolic spastic paraparesis)	
Homocysteine remethylation defects	• Cobalamin C deficiency, methylene-tetrahydrofolate reductase (MTHFR) deficiency
Urea cycle disorders	• Hyperonithinemia-hyperammonemia-homocitrullinuria, arginase deficiency
Dopamine synthesis defects	• GTP-cyclohydrolase deficiency, tetrahydrobiopterin deficiency, sepiapterin reductase deficiency
Peroxisomal disorders	• Adrenomyeloneuropathy, adrenoleukodystrophy, alpha-methylacyl-CoA racemase deficiency
Lysosomal diseases	• GM1/GM2 gangliosidosis, Krabbe disease, metachromatic leukodystrophy, Gaucher's disease, adult onset polyglucosan body disease
Other neurometabolic disorders	Sjogren-Larsson syndrome, biotinidase deficiency, phenylketonuria, non-ketotic hyperglycinaemia, cerebral folate deficiency syndrome, cerebrotendinous xanthomatosis, homocarnosinosis
Other degenerative diseases	
Spastic ataxias	• ARSACS, SPAX
Motor neuron disease	• Juvenile familial amyotrophic lateral sclerosis, primary lateral sclerosis
Spinocerebellar ataxias	• SCA1, SCA3
Inherited dementias	• PSEN1-related disorders

ARSACS autosomal recessive spastic ataxia of Charlevoix–Saguenay; *SCA* spinocerebellar ataxias; *CMV* cytomegalovirus; *CRMP-5* collapsin response mediator protein-5; *GAD* glutamate decarboxylase; *HTLV* human T lymphotropic virus; *HIV* human immunodeficiency virus; *PSEN* presenilin; *SPAX* spastic ataxia

Clinical features

Main clinical feature of HSP is slowly, progressive spastic paraparesis which develops as a gait disturbance. Delayed motor milestones are seen in patients with early-onset HSP (childhood). Brisk jaw jerk and asymptomatic upper limb hyperreflexia without spasticity are commonly seen. Other neurological symptoms commonly seen in more than 50% of the cases are ataxia, cognitive impairment, neuropathy, seizures, and dysarthria [3, 29].

Vibration sensation impairment is usually seen in a few cases due to dorsal column degeneration and other sensory systems are seldom involved [3]. Urinary symptoms due to detrusor sphincter dyssynergia or instability are commonly seen in the late stages of the disease [30]. HSP subtypes and their typical clinical features are shown in Table 3 [12, 26].

Diagnosis

HSP molecular diagnosis depends mainly on distinguishing the pathogenic mutations in the SPG genes [31]. Clinical diagnosis of HSP depends on the existence of spastic paraparesis along with other neurological and systemic presentations with or without family history [12]. A detailed family and developmental history of the patient plays a key role in the diagnosis and an acute or subacute presentation points towards an acquired form of HSP [31].

Patients usually present with slowly, progressive leg stiffness, abnormal gait, or gait instability, but maintain muscle power in spite of high tone in the lower limbs. Age of presentation varies from the first year of age with slowed motor milestones to delayed onset of pure HSP [17].

Neuroimaging including magnetic resonance imaging (MRI) of the brain and spinal cord can help in differentiating the SPG types. MRI of the spinal cord can be normal or might show thinning in a large number of SPG types [31, 32]. The "ears of the lynx" sign shows the distinct pattern of hyperintensities at the anterior forceps of the corpus callosum, which is commonly seen in SPG11 and SPG15 [33].

Neurophysiological studies include central motor conduction times (CMCTs), somatosensory-evoked potentials (SSEPs), electromyography (EMG), and nerve conduction studies (NCS). Although abnormal neurophysiological tests are common in HSP, they are not specific to the subtypes of HSP. Mononeuropathy like carpel tunnel syndrome and multifocal compression neuropathy is also seen in some isolated cases of HSP [31].

Genetic testing with next-generation sequencing-based gene panels is being extensively used in the diagnosis of HSP. These panels screen the exons of a vast variety of genes causing HSP; however, they do not detect triplet repeat disorders, mutations in deep intronic or promoter regions, and copy number variants like large duplications or deletions and exon deletions. One should be vigilant while diagnosing HSP, as monogenic diseases which present with lower limb spasticity without abnormalities on spinal cord MRIs are not defined in the SPG classification [31, 34].

Differential diagnosis

The differential diagnosis of HSP is expansive and multiple complementary test panels should be performed to rule out various inherited and acquired etiologies. The main differential diagnoses of HSP are shown below in Table 4 [12].

Various diagnostic tests which are used in differentiating HSP from other diseases are neuroimaging studies of the brain, cervical and thoracic spinal cord MRI, lumbar puncture with CSF analysis, neurophysiological tests, complete ophthalmologic examination, and full metabolic screening for inherited neurometabolic disorders [12, 14, 35]. In some unique isolated cases, further investigations are required to establish the diagnosis of HSP, which include very long chain fatty acid (VLCFA) analysis in plasma, serum vitamin E and cobalamin, plasma lipoprotein and amino acid profiles, serum copper, ceruloplasmin analysis, human immunodeficiency virus (HIV), human T cell leukemia virus type I (HTLV-I), and serological tests for *Treponema pallidum* [12, 14, 20].

As HSP is a heterogeneous disease, genetic testing became a main component in the clinical assessment and diagnosis. Genetic testing panels along with newer techniques in genetic sequencing (whole-exome) are having a considerable effect in both pure and complicated forms of HSP [12].

Treatment

At present, there is no definitive disease-modifying therapy for HSP [12]. A multidisciplinary approach is necessary to address the symptoms of cramps, stiffness, spasms, and other deformities. Orthotics like ankle-foot orthoses and heel raises are beneficial in improving the mobility [31].

Current treatment

Oral antispasmodics comprising of baclofen and tizanidine have demonstrated benefit in HSP patients [31]. In cases of severe spasticity, intrathecal baclofen is effective in decreasing the tone, pain, and disability; in its usage in the earlier stages of wheelchair-requiring patients, it showed an improvement in gait [36]. Dalfampridine (4-aminopyridine) showed some advantage in a small group of HSP and large studies are needed to establish its role [37].

Botulinum toxin (Botox) injections are efficacious in selective problematic muscle groups alongside the hip, knee, and ankle. Both stretching exercises and injections into calf decrease muscle tone, and enhance gait velocity while preserving balance and strength [38]. Oxybutynin helps in decreasing urinary urgency after ruling out urinary infection and establishing there is no marked increase in post-micturition residual volume of urine [31].

Physical therapy along with an exercise program by neurophysiotherapists is recommended to build up and maintain the lower extremity strength, to improve the range of motion, and to enhance cardiovascular conditioning. Both ankle foot orthotics and peroneal nerve stimulation transcutaneously reduce the toe dragging [14].

Genetic testing and counseling help the patients and families in understanding the disease and risk of transmission to the next generations. Clinicians must be vigilant while providing counseling and prognosis as most of the HSP genetic types of complete phenotypic spectrum and genetic penetrance are unfamiliar. Caution is necessary while counseling about SPG7, as in a minority of cases it can cause an AD form of HSP, in addition to the more frequent recessive form [14].

Gene therapy and future directions

Although genotype-targeted therapy has made marked advances in neurological diseases like spinal muscular atrophy and Huntington's disease, HSP has not seen much progress because of genetic heterogeneity, rare form of genetic subtypes, mechanistic diversity, and a slow clinical disease progression [31].

In HSP-SPG4, microtubule severing causes partial loss of function, which might be corrected with gene therapy. Recent study showed that the human-induced plutipotent stem cells from a patient with spastin nonsense mutation with M1 or M87 isoform expressions redevelop the neurite numbers, length, branching, and reducing of the neuronal swelling [39].

SPG5 HSP is autosomal recessive and caused by the mutation in CYP7B1 gene encoding oxysterol-7α-hydroxylase which causes cholesterol degradation to primary bile acids and thus accumulating neurotoxic oxysterols. Management usually involves cholesterol-lowering drugs like atorvastatin which are used in reducing the levels of 27-hydroxycholesterol and chenodeoxycholic acid decreases the abnormal bile acid levels in SPG5 patients. More research studies are needed to establish the benefits of the combination therapies [31].

Paraplegin plays a key role in fine tuning the fast opening of the mitochondrial permeability transition pore, which can be pharmacologically modulated [31]. Study conducted by Pirozzi et al. showed that paraplegin delivery through the intramuscular route stops the neuropathology progression and also saves the peripheral nerve mitochondrial morphology [40].

Development of gene therapy for common recessive forms like SPG11, SPG15, and SPG7 offers vast possibilities for targeted gene editing or replacement. There is a need for all the international research groups to come together and get benefitted from the large clinical trials to achieve progress in gene therapy and other therapeutic areas [31].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval None

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We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.