

Phenotypic Spectrum and Clinical Approach to Early-Onset Hereditary Spastic Paraplegia

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Abstract: Background: Early-onset hereditary spastic paraplegias (HSPs) are an underrecognized cause of progressive spasticity, gait impairment, and movement disorders in children and young adults. HSPs frequently mimic cerebral palsy or genetic, metabolic, and acquired disorders, resulting in diagnostic delay. Their broad phenotypic spectrum, encompassing dystonia, parkinsonism, and neurodevelopmental features, makes them highly relevant to movement disorder practitioners across the lifespan.

Objectives: This review summarizes the phenotypic spectrum of early-onset HSP, outlines a practical diagnostic approach for clinicians, and discusses therapeutic strategies.

Methods: We conducted a narrative review of PubMed-indexed literature through February 2026, supplemented by expert consensus. HSPs typically presenting in childhood and adolescence, inclusive of forms presenting across a broader age spectrum, with attention to subtypes presenting with movement disorders, were considered.

Results: Early-onset HSPs encompass both pure and complex forms, with SPG4 (SPAST) and SPG11 (SPG11/KIAA1840) among the most prevalent etiologies. Diagnostic challenges include distinction from cerebral palsy and other movement disorders including dopa-responsive dystonia, and identification of neuroimaging signatures in specific subtypes. A multidisciplinary management approach remains central, with spasticity, movement disorder, and neurological comorbidities each requiring targeted consideration. Disease-modifying therapies are emerging, including gene replacement strategies and antisense oligonucleotide approaches for select subtypes.

Conclusions: Early-onset HSPs represent a clinically and genetically heterogeneous group with substantial overlap with movement disorder practice. Awareness of characteristic phenotypes, early genetic testing, and an individualized multidisciplinary approach are essential. Recent advances in natural history characterization and mechanism-targeted therapeutics signal a transition toward disease-modifying treatment strategies and offer cautious optimism for affected individuals.

The HSPs comprise a clinically and genetically heterogeneous group of inherited neurological disorders affecting approximately 2–9 per 100,000 individuals worldwide, although the true prevalence is likely higher.¹ They are progressive conditions unified by predominant dysfunction of the corticospinal tracts, resulting in lower extremity spasticity, weakness, and

characteristic gait impairment due to a length-dependent axonopathy of corticospinal tract axons. These clinical manifestations may occur in relative isolation (pure HSPs) or with additional neurological or systemic features (complex HSPs). Age at symptom onset can vary widely, ranging from infancy to late adulthood.²

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HSPs are notable for their marked genetic heterogeneity. To date, more than 90 causative genes have been identified across autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance patterns, historically designated SPG1 through SPG93 in order of discovery. Advances in next-generation sequencing over the past two decades have substantially accelerated gene discovery and improved diagnostic yield. Despite this diversity, many HSP-associated gene products converge on a limited number of shared cellular pathways, including axonal transport, membrane trafficking, lipid metabolism, and organelle dynamics, providing a biological framework for emerging therapeutic strategies.² Historically underrecognized, HSPs are now diagnosed with increasing frequency as genetic testing becomes more accessible and systematically integrated into clinical practice.

We conducted a narrative review of PubMed-indexed literature through February 2026, supplemented by reference review and expert consensus. Although early descriptions of HSP largely focused on adult-onset disease, there has been growing recognition of early-onset forms.³ For this review we define “early-onset HSPs” as forms of HSP that commonly present in childhood or adolescence, inclusive of forms with a broader phenotypic spectrum that may present into young adulthood. Retrospective cohort studies from diverse populations, including Italian and Chinese pediatric cohorts, have demonstrated that both autosomal dominant and autosomal recessive HSPs are well represented among children with early symptom onset.^{4,5} Across these studies, SPG4 remains the most common autosomal dominant cause and typically presents with a pure phenotype, while SPG11 is the most frequent autosomal recessive etiology and is often associated with complex neurological features. A recent prospective natural history study⁶ has broadened the phenotype associated with common and rare forms of early-onset HSP,^{7–13} showing that several additional HSP subtypes have onset during childhood and distinct neurodevelopmental phenotypes.

These observations have important implications for neurologists and movement disorder specialists. Notably, many individuals with early-onset HSP lack a positive family history, underscoring the importance of including HSP in the differential diagnosis of otherwise unexplained spastic gait or progressive lower extremity spasticity. This absence of family history reflects several factors: the higher prevalence of autosomal recessive inheritance in pediatric cohorts, the occurrence of *de novo* variants in common autosomal dominant forms such as SPG3A and SPG4, and age-dependent penetrance, whereby affected parents may remain asymptomatic or minimally symptomatic at the time of their child's presentation.

Disease Course in Early-Onset HSPs: Developmental and Degenerative Components

A unifying feature across early-onset HSP subtypes is predominant or exclusive lower limb spasticity, often accompanied by

weakness, resulting in abnormal gait, significant motor delay, or loss of previously acquired motor milestones. The age of symptom onset varies widely among subtypes, ranging from infancy to late adolescence, and can provide important diagnostic clues. In particular, very early onset with delayed acquisition of motor milestones should prompt consideration of adaptor protein complex 4 (AP-4)-related HSPs (SPG47, SPG50, SPG51, and SPG52), which may closely mimic CP in early childhood.⁸ As a rare disorder with substantial phenotypic overlap with other pediatric movement disorders, the diagnosis of HSP is often markedly delayed, an average of 5.8 years in one study¹⁴ and 8.2 years in another¹⁵ after symptom onset. This delay reflects both clinical heterogeneity and overlap with more prevalent causes of childhood spasticity, most notably cerebral palsy (CP), as well as a range of genetic, metabolic, and acquired disorders.

Complex HSP phenotypes account for a substantial proportion of early-onset cases and are characterized by neurological or systemic features extending beyond corticospinal tract dysfunction.^{16,17} These associated manifestations can assist in subtype recognition. For example, peripheral motor neuropathy is frequently observed in SPG11 or SPG15 and sensory-motor or predominantly sensory neuropathy is seen in SPG10 or SPG30.^{18–20} Ocular involvement also provides useful diagnostic clues, with cataracts commonly seen in SPG46, optic atrophy in SPG30, and pigmentary retinal changes in SPG11 or SPG15.^{21–23} Movement disorders are common in complex early-onset HSP and represent an important point of overlap with movement disorders practice.¹⁰ Dystonia, often involving the face and upper limbs, is most frequently observed in SPG11, SPG15, and SPG35, while parkinsonism, occasionally levodopa-responsive, has been reported in SPG11 and SPG15.¹⁰ In contrast, chorea, athetosis, and tremor are rare in childhood-onset HSP.¹⁰ Additional orthopedic or dysmorphic features may further narrow the differential diagnosis, including adducted thumbs in SPG1, short stature in SPG20, and combined short stature with dysmorphic facies in AP-4-related HSPs.^{8,24,25} Key clinical features supporting subtype recognition are summarized in Table 1, noting that individual features must be interpreted in the context of the overall clinical phenotype.

From a pathophysiological perspective, adult-onset pure HSP is classically considered a neurodegenerative disorder, supported by gradual clinical progression and pathological evidence of axonal swellings, gliosis, and axonal loss within long spinal tracts.^{26,27}

After a prolonged presymptomatic phase, disease manifestations typically follow a slowly progressive course.²⁸

In contrast, many recessive early-onset HSPs present with prominent neurodevelopmental features. This is particularly evident in complex subtypes such as the AP-4-related HSPs, where delayed motor development, intellectual disability, and dysmorphic features are common.⁸ Notably, corpus callosum thinning and other developmental brain malformations observed prenatally and in early childhood are consistent with a significant neurodevelopmental component.^{29,30}

Importantly, neurodevelopmental involvement does not preclude later neurodegeneration. Most early-onset HSPs demonstrate subsequent clinical progression, leading to the current view

TABLE 1 Characteristic clinical and neuroimaging features of selected early-onset hereditary spastic paraplegia subtypes

	HSP subtype (gene)	Typical age at onset
Clinical feature		
Hydrocephalus, adducted thumbs	SPG1 (<i>L1CAM</i>)	Infancy
Nystagmus, ataxia, cognitive decline	SPG2 (<i>PLP1</i>)	Infancy/Early childhood/ Adolescence
Pure phenotype	SPG3A (<i>ATL1</i>)	Childhood
Peripheral (predominantly sensory) neuropathy	SPG10 (<i>KIF5A</i>), SPG30 (<i>KIF1A</i>)	Childhood/Adolescence
Distal motor neuropathy, obesity, cognitive decline, parkinsonism	SPG11 (<i>SPG11/KIAA1840</i>)	Childhood/Adolescence
Pigmentary retinal changes	SPG15 (<i>ZFYVE26</i>)	Childhood/Adolescence
Short stature, skeletal deformities	SPG20 (<i>SPG20</i>)	Childhood
Optic atrophy, Peripheral (predominantly sensory) neuropathy and developmental delay	SPG30 (<i>KIF1A</i>)	Infancy/Early childhood
Dystonia	SPG35 (<i>FA2H</i>)	Childhood
Ataxia, cataracts and ichthyosis	SPG46 (<i>GBA2</i>)	Childhood/Adolescence
Severe global developmental delay, facial dysmorphism, microcephaly and short-stature	SPG47-52	Infancy/Early childhood
Neuroimaging feature		
Diffuse hypomyelination	SPG2 (<i>PLP1</i>)	Infancy/Early childhood/ Adolescence
Thin corpus callosum + “Ears of the lynx” sign	SPG11 (<i>SPG11/KIAA1840</i>)/ SPG15 (<i>ZFYVE26</i>)	Childhood/Adolescence
Leukodystrophy	SPG35 (<i>FA2H</i>), SPG54 (<i>DDHD2</i>)	Infancy/Childhood
Thin splenium of the corpus callosum + Absent/thin anterior commissure + “Ears of the grizzly” sign + Periventricular white matter abnormalities	SPG47-52	Infancy/Early childhood
Cerebellar atrophy	SPG30 (<i>KIF1A</i>), SPG46 (<i>GBA2</i>), SPG56 (<i>CYP2U1</i>)	Infancy/Childhood

Representative clinical manifestations and characteristic neuroimaging findings associated with selected early onset hereditary spastic paraplegia (HSP) subtypes. Features are intended to aid diagnostic recognition and are not universally present in affected individuals.

that these disorders represent a mixed pathophysiological continuum, with developmental abnormalities predominating early and degenerative processes emerging later.³ This distinction has important implications for diagnosis, prognostication, and the timing and selection of disease-modifying therapies.

Some HSP subtypes, including autosomal dominant SPG4, span both early-onset and adult-onset presentations. Genotype appears to influence disease course in these cases, with missense *SPAST* variants enriched among individuals with early-onset disease.^{31,32} Outside a subset with rapid progression due to reasons still incompletely understood,⁹ data from a pediatric cohort in Portugal demonstrated that children with early-onset SPG4 experienced prolonged plateau phases with minimal progression, in some cases appearing largely non-progressive.³³ In contrast, those with adult-onset SPG4 had continuous progression from symptom onset and more rapid functional decline.³³ On the

other hand, in complex early-onset HSPs, particularly AP-4-related disorders, earlier onset is associated with greater disease severity and faster progression.⁸

Neuroimaging

Clues to early-onset HSP diagnosis can be obtained from brain MRI (Table 1). White matter abnormalities and corpus callosum thinning are often found.^{34,35} There are additional characteristic findings that suggest specific genotypes. For example, the “ears of the lynx” sign has high sensitivity (79–97%) and specificity (91–100%) for SPG11 and SPG15.³⁶ A recent study identified characteristic imaging features of AP-4 related HSPs, with the presence of two out of four features (1. Ears of the grizzly sign,

2. Thin splenium of the corpus callosum, 3. Absent or thin anterior commissure, 4. Periventricular white matter abnormalities) 99% sensitive for this diagnosis (Fig. 1).²⁹ Although HSP is considered a distal axonopathy of the corticospinal tracts, spinal cord imaging typically contributes little to the diagnosis and characterization of affected patients and is obtained primarily to rule out structural processes.

Differential Diagnosis

Cerebral Palsy

CP, defined as a motor disability due to a non-progressive disturbance of the developing brain, is a particularly common mimic of early-onset HSPs. HSP is distinguished by primary corticospinal tract dysfunction and at least some degree of clinical progression, in contrast to the more static nature of CP. In many cases, differentiation based on history is straightforward. Children with CP typically exhibit motor delays from infancy, with a

relatively stable developmental trajectory that aligns with their Gross Motor Function Classification System (GMFCS) level, which is generally established by 5–6 years of age.³⁷ By contrast, HSPs often present a little later with progressive lower extremity spasticity, gait deterioration, and loss of previously acquired motor skills, resulting in crossing of GMFCS trajectories over time (Fig. 2).

Neurologic exam may aid distinction. Upper extremity and bulbar involvement are common in spastic CP but often absent or minimal in (pure) HSP. On confrontational testing, individuals with CP may be impaired by spasticity and decreased selective motor control, but true weakness is generally absent with maximal effort. In contrast, individuals with HSP often have true weakness in addition to spasticity. While gait patterns in spastic diplegic CP are largely overlapping with HSP (Fig. 3), a recurvatum gait, where the knee is hyperextended in stance phase, is highly suggestive of HSP as it is rarely seen in individuals with CP who have not had orthopedic surgery.³⁸ This knee hyperextension is thought to be due to quadriceps weakness. Additionally, individuals with HSP may have reduced knee flexion during swing phase and increased trunk movement compared with individuals with CP (Video 1).³⁸ However, in many

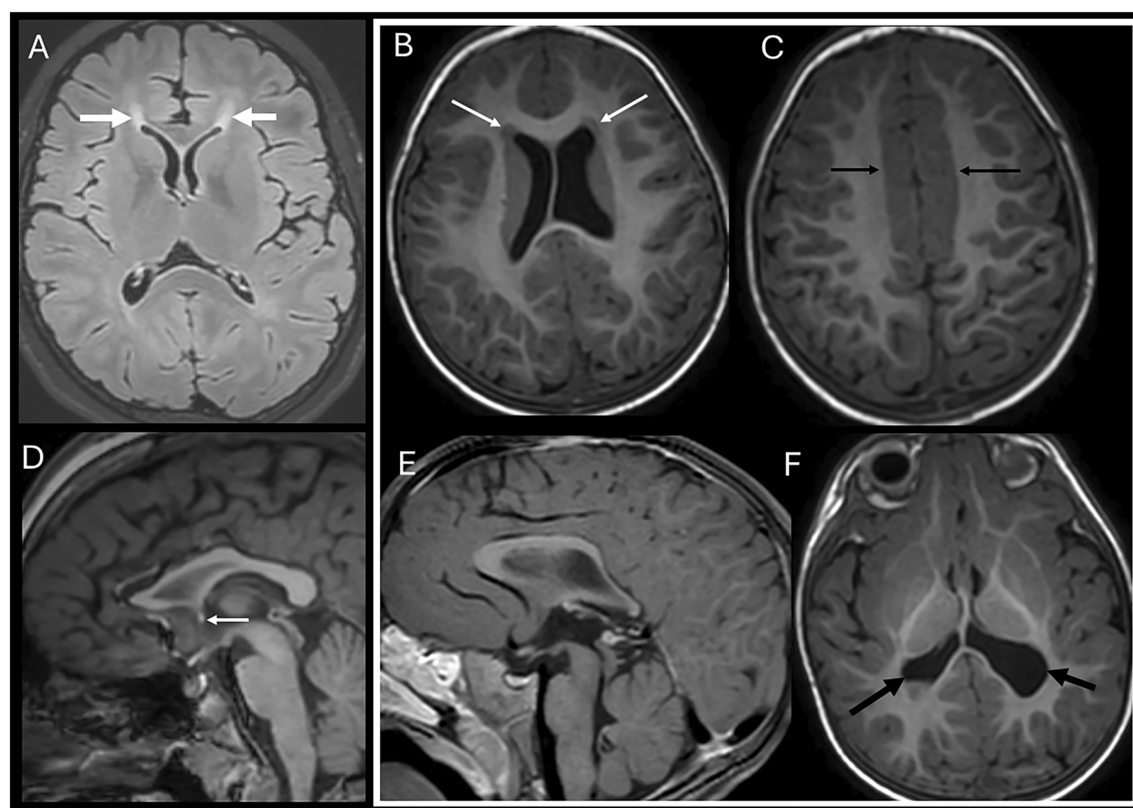


Figure 1. Characteristic magnetic resonance imaging findings of hereditary spastic paraplegias. Findings of SPG11 and SPG15 in (A, D) include flair hyperintense signal in the forceps minor (“ears of the lynx” sign) (A, thick white arrows) and thinning of the corpus callosum on sagittal T1 sequence (D) with presence of anterior commissure (thin white arrow). Findings of AP-4-associated HSP (SPG50) shown in (B, C, E, F) include rounded T1 hypointense signal in the forceps minor (hyperintense on T2/flair sequence) termed “ears of the grizzly” sign (B, thin white arrows), malformation of cortical development (C, thin black arrows), thinning of the corpus callosum with absence of the anterior commissure (E), and posterior ventricular enlargement due to white matter volume loss (F, thick black arrows).

cases, particularly in very early-onset or complex HSP phenotypes clinical history and examination alone may be insufficient, necessitating neuroimaging and genetic testing for accurate diagnosis.

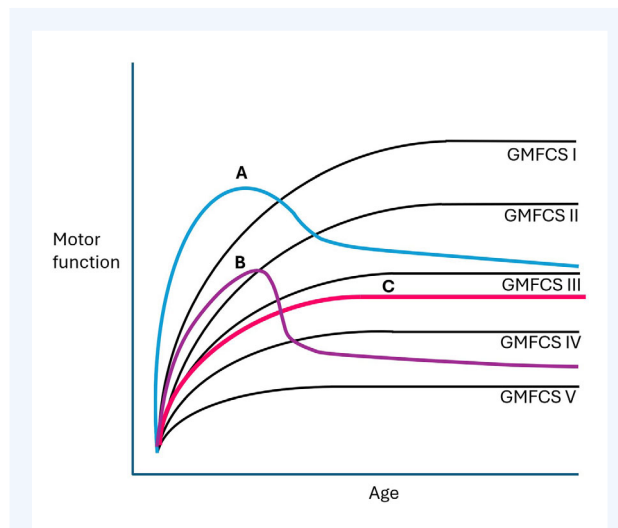


Figure 2. Cerebral palsy and hereditary spastic paraplegia motor developmental curves Black lines: CP motor curves by GMFCS level. HSP developmental curves (color) may cross GMFCS lines. Curve A (blue) shows typical early development, then loss of function in childhood. Curve B (purple) shows early delayed development, then significant regression in later childhood. Both A and B may be seen in pure HSP. Curve C (pink) is indistinguishable from the GMFCS curve, as can be seen with complex HSP. CP curves adapted from Rosenbaum et al. 2002 (ref 38). CP, cerebral palsy. GMFCS, gross motor function classification system.

Differential Diagnosis

Beyond CP, a broad differential diagnosis should be considered in children and adolescents with suspected HSP (Table 2). This includes genetic, metabolic, and acquired conditions, several of which are potentially treatable.^{39–45} Important considerations include dopa-responsive dystonia, biotinidase deficiency, arginase deficiency, vitamin B₁₂ or copper deficiency, structural spinal cord abnormalities such as tethered cord syndrome, selected leukodystrophies, and autoimmune or demyelinating disorders.^{16,46} Among these, dopa-responsive dystonia deserves particular emphasis as pyramidal features are common and may lead to misdiagnosis as CP or HSP. Clinicians should therefore have a low threshold for initiating an empirical trial of levodopa in children presenting with new or progressive gait dysfunction accompanied by spasticity and/or dystonia.

Diagnostic Evaluation

The diagnostic approach must be individualized. When there is a known family history of HSP, spastic CP, or unexplained loss of ambulation, it is reasonable to pursue genetic testing as the initial diagnostic evaluation, with consideration of neuroimaging to exclude structural causes. In the absence of such a history, in the child with lower extremity spasticity, neuroimaging is typically performed first, with MRI of the brain and entire spine to exclude structural, inflammatory, or metabolic mimics and to identify imaging features suggestive of specific HSP subtypes.

If neuroimaging is normal or nonspecific, genetic testing should be pursued without delay using either an HSP gene panel, whole-exome sequencing (WES), or whole-genome

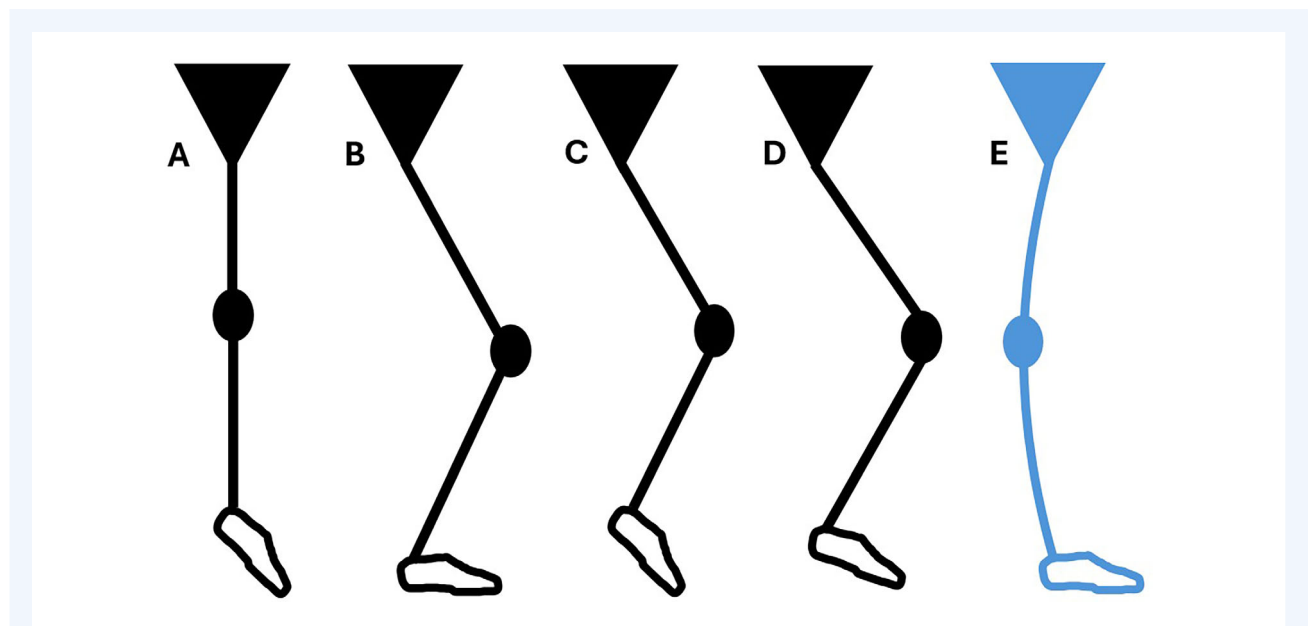


Figure 3. Gait patterns include (A). Equinus (knee extension, foot plantarflexion), (B) Crouch (knee flexion/foot dorsiflexion in stance), (C) Jump (knee flexion/foot plantar flexion in stance), (D) Apparent jump (knee flexion/foot neutral or dorsiflexed, but without heel contact), and (E) Recurvatum (knee hyperextension in stance). Recurvatum is rarely seen in CP but a common pattern in HSP.

TABLE 2 Differential diagnosis for early-onset hereditary spastic paraplegia

Clinical features		Investigations	Treatment
Metabolic/genetic			
Dopa-responsive dystonia	Toe walking, hyperreflexia, striatal toe	<i>GCH1</i> sequencing CSF neurotransmitters	Levodopa
Arginase deficiency	Hyperammonemia, poor growth, spasticity, dev delay	Plasma arginine (NBS) <i>ARG1</i> sequencing	Protein restriction Citrulline, arginine
Biotinidase deficiency	Optic atrophy, rash, seizures, hypotonia, ataxia, spastic paraparesis	Biotinidase activity (NBS) <i>BTBD</i> sequencing	Biotin
Leukodystrophies			
XLD	Regression, adrenal insufficiency	VLCFA, <i>ABCD1</i> sequencing	Stem cell/gene therapy
CTX	Seizures, neuropathy, cataracts, xanthomas	Cholesterol, <i>CYP27A1</i>	Chenodeoxycholic acid
PMD	Nystagmus, spasticity, dev delay	<i>PLP1</i> sequencing	Symptomatic
SCAs			
SCA3 ^{51,53}	Spasticity, dystonia, ataxia, ophthalmoplegia, vision loss, ataxia, spasticity, neuropathy	<i>ATXN3</i> repeat testing	Symptomatic
SCA7 ^{50,52}		<i>ATXN7</i> repeat testing	Symptomatic
GLUT1 deficiency ⁴⁰	Seizures, microcephaly, paroxysmal eye movements, dev delay, ataxia, spasticity	<i>SLC2A1</i> sequencing CSF:serum glucose	Ketogenic diet
BPAN ⁴¹	Dystonia, spasticity, seizures, dev delay	<i>WDR45</i> sequencing	Symptomatic
PLAN ⁴²	Nystagmus, regression, hypotonia, spasticity	<i>PLA2G6</i> sequencing	Symptomatic
Aicardi-Goutières syndrome ⁴³	Encephalopathy, spasticity, dystonia, dev delay, microcephaly, cerebral calcifications, chilblains; HSP-like phenotype described	Interferon, CSF neopterin, AGS gene panel or WES/WGS	Symptomatic, interferon-directed therapies investigational
Structural			
Tethered cord syndrome	Toe walking, ankle tightness, constipation, pain	MRI lumbar spine	Surgical filum lysis
Spinal cord dural AVF	Spasticity, pain, weakness, sensory loss	MRI spine	Surgical/endovascular
Infectious			
HIV ⁴⁴	HIVE: dev delay, microcephaly, LE spasticity	HIV antibody/antigen testing	Antiretroviral therapy
HTLV-1 ⁴⁵	Dermatitis, LE spasticity, bladder/bowel symptoms	HTLV antibody testing	Symptomatic
Nutritional/toxic			
Copper deficiency ⁴⁶	Cytopenias, LE spasticity, sensory ataxia	Serum copper	Copper
Autoimmune/demyelinating			
MOGAD/ NMO/MS	Dependent on lesion location	MRI, CSF/serum antibodies	Immunomodulation

Genetic, metabolic, structural, infectious, inflammatory, and neurodegenerative conditions that may mimic early onset hereditary spastic paraplegia.

Abbreviations: AGS, Aicardi-Goutières syndrome; AVF, arteriovenous fistula; BPAN, beta-propeller protein-associated neurodegeneration; CSF, cerebrospinal fluid; dev, development; HIV, human immunodeficiency virus; HIVE, human immunodeficiency virus encephalopathy; HSP, hereditary spastic paraplegia; HTLV-1, human T-lymphotropic virus 1; LE, lower extremity; MMA, methylmalonic acid; MOGAD, myelin oligodendrocyte glycoprotein antibody-associated disease; MRI, magnetic resonance imaging; MS, multiple sclerosis; NBS, newborn screen; NMO, neuromyelitis optica; PLAN, PLA2G6-associated neurodegeneration; SCAs, spinocerebellar ataxias; WES, whole exome sequencing; XLD, x-linked adrenoleukodystrophy.

sequencing (WGS) depending on availability. Targeted HSP panels generally provide coverage of high-yield genes, but we generally favor WES and WGS as first-line investigations as they offer a broader scope and may identify additional diagnoses not included on commercial panels.

In cases with strong clinical suspicion for HSP such as the presence of characteristic neuroimaging findings including the “ears of the lynx” or the “ears of the grizzly”²⁹ sign an HSP panel may be considered initially, with reflex to WES or WGS if results are nondiagnostic.^{47,48}

When first-line genetic testing is unrevealing, additional investigations may be warranted in selected cases. Chromosomal microarray analysis can detect copy number variants not reliably captured by WES. In addition, trinucleotide repeat testing may be appropriate when ataxia is a prominent feature, as juvenile-onset SCA7 often presents with both spasticity and ataxia and childhood-onset spinocerebellar ataxia SCA3 may initially manifest with spasticity.^{49–52} Although uncommon, acquired causes of spasticity should remain in the differential diagnosis throughout the evaluation. A therapeutic trial of levodopa may be considered at any stage of the diagnostic process, particularly when dystonia accompanies spasticity.

It should be noted that about 30–40% of children with suspected HSP do not receive a diagnosis by clinical genetic testing,^{47,53,54} indicating the presence of additional HSP related genes or variants that escape detection. Regular reanalysis of genomic data and research-based investigations can reduce this diagnostic gap.⁵⁴ A suggested diagnostic algorithm is described in Figure 4.

There are some important considerations in genetic counseling for familial HSP. SPG4 (and possibly SPG3) can demonstrate pseudo-anticipation, in which subsequent generations experience earlier onset of disease.^{55,56} As a result, a newly diagnosed child may inherit the pathogenic variant from a pre-symptomatic or mildly symptomatic parent. The mechanisms involved are not certain as the gene sequence remains unchanged. In addition, some children may present pre-

symptomatically in the setting of parental HSP. If there are no interventions to decrease morbidity, testing should be deferred for the child until symptoms develop or they reach adulthood and can provide informed consent after appropriate genetic counseling.⁵⁷

Clinical Management

A multidisciplinary team approach is central to the management of early-onset HSP.⁵⁸ Core team members typically include a movement disorder specialist or neurologist, physiatrist, orthopedist, geneticist or genetic counselor, physical and occupational therapists, and a social worker. Many patients require involvement of additional subspecialists, including urology, ophthalmology, audiology, gastroenterology, developmental pediatrics, and psychology or psychiatry, depending on associated neurological or systemic features. Physical therapy plays a foundational role, with goals focused on maintaining strength and range of motion, optimizing gait and functional mobility, managing pain, and addressing equipment and bracing needs such as orthotics to support ambulation.

Spasticity

The primary goals of spasticity management in early-onset HSP are to alleviate discomfort, preserve or improve function, and

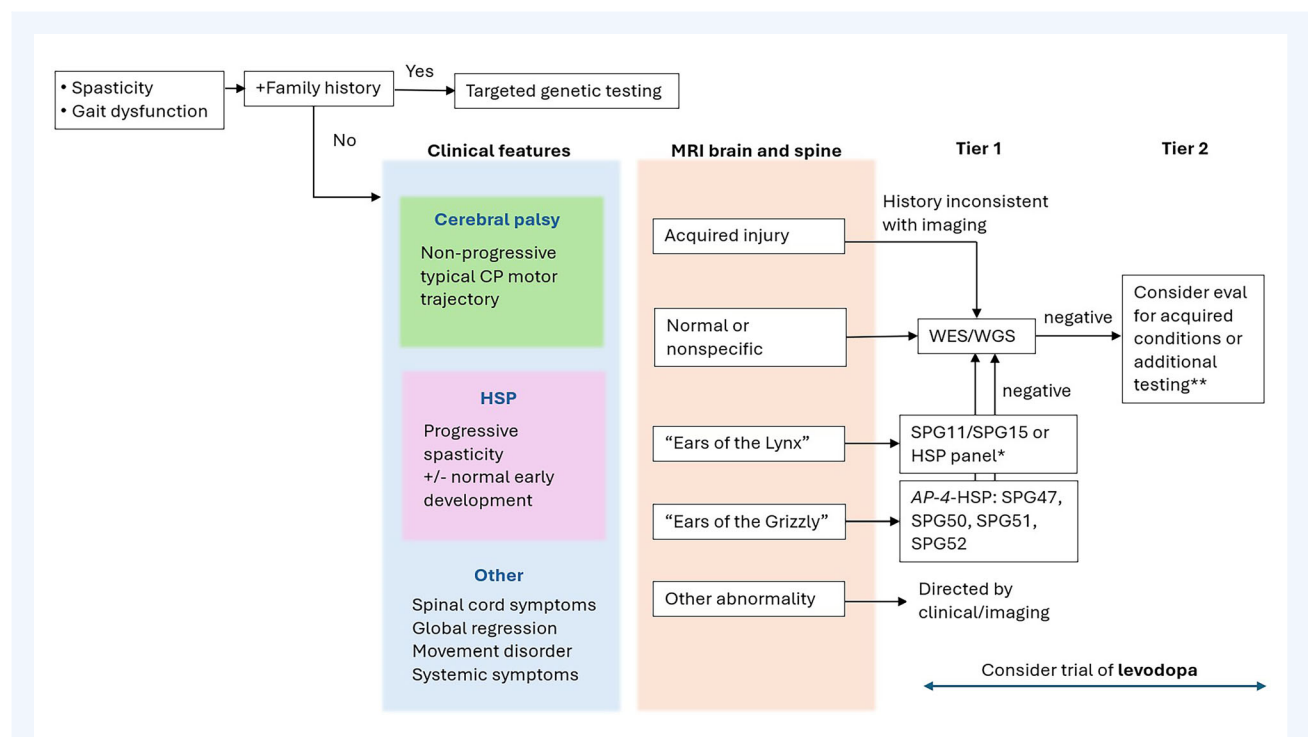
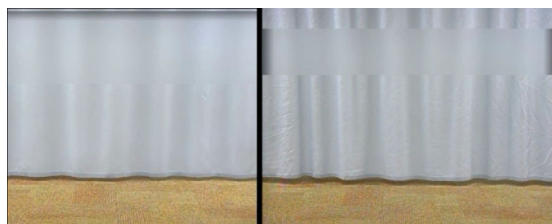


Figure 4. Suggested diagnostic algorithm for hereditary spastic paraplegia *May consider panel with reflex to WES/WGS **Consider further testing for infectious, nutritional, autoimmune causes. Consider chromosomal microarray and testing for trinucleotide repeat disorders. More invasive testing (e.g., EMG/NCS, spinal fluid analysis, etc.) may be indicated in some scenarios.



Video 1. The first clip shows a side-by-side comparison of a jump gait pattern in spastic diplegic cerebral palsy, characterized by knee flexion and ankle equinus during stance phase, and hereditary spastic paraplegia (HSP) on the right, distinguished by greater knee extension during stance and increased trunk movement. The second and third clips show a 5-year-old and a 15-year-old with HSP, respectively, both demonstrating knee recurvatum (highlighted in the freeze frames). The 15-year-old also demonstrates proximal lower-extremity weakness, evident when rising from the floor. These features may help distinguish HSP from cerebral palsy. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.70827>

prevent secondary orthopedic complications. Evidence guiding spasticity treatment in children with HSP is limited. A randomized crossover controlled trial of gabapentin in adults with SPG4-linked HSP demonstrated no benefit over placebo across multiple outcome measures,⁵⁹ and pediatric-specific trial data are lacking. In clinical practice, oral antispasticity agents commonly used in children including baclofen, tizanidine, and dantrolene may be considered for spasticity-related discomfort or functional impairment, with careful attention to sedation, weakness, and other adverse effects.

Botulinum toxin injections have shown modest benefits in reducing spasticity and improving gait parameters in small adult HSP studies, although treatment may unmask underlying weakness and worsen function in some individuals.⁶⁰ In early-onset HSP, limited retrospective data suggest transient improvements in spasticity and gait after botulinum toxin injections, lasting up to 6 months.⁶¹ Botulinum toxin may therefore be considered for targeted, goal-directed indications, such as improving brace tolerance or addressing focal spasticity. However, clinicians should remain mindful of potential risks. Systemic adverse effects have been reported in approximately 4% of children treated for spasticity related to cerebral palsy^{62,63} and experimental and clinical data suggest that repeated injections may alter muscle composition and size, with uncertain long-term effects on gait and motor development.⁶⁴

Intrathecal baclofen (ITB) is an invasive therapy commonly used for severe spasticity in cerebral palsy and has been reported in small series of adults and children with HSP. In adults, ITB has generally reduced spasticity, though sustained functional benefit has not been consistently observed.⁶⁵ Limited pediatric reports similarly describe reductions in spasticity.^{65,66} ITB may be considered in carefully selected children with severe, refractory spasticity who demonstrate a positive response to an intrathecal test dose. However, complication rates in pediatric cerebral palsy cohorts range from 30% to 70% underscoring the need for a cautious, individualized approach.^{67,68}

Selective dorsal rhizotomy (SDR) permanently reduces lower extremity spasticity by interrupting afferent spinal reflex pathways and is an established intervention for selected ambulatory children with spastic diplegic cerebral palsy. SDR has also been applied to spasticity associated with HSP and other non-CP conditions.⁶⁹ The largest reported series included 37 patients, 27 of whom were children.⁷⁰ While most patients experienced reduced spasticity (89%) and stable gross motor function (73%), functional improvement was uncommon (6%), and a subset (11%) experienced functional decline. Notably, the patients experiencing functional deterioration included individuals with the common HSP subtypes SPG4, SPG7, and SPG11. Additional reports describe transient improvement followed by disease progression in children with ALS2-related IAHP.⁷¹ Overall, SDR is likely to reduce spasticity in HSP but does not reliably improve function and may worsen outcomes in some patients. At present, predictors of benefit including genetic subtype remain undefined, and SDR should be approached with considerable caution in the HSP population. Combined ventral and dorsal rhizotomy is a palliative surgical option for non-ambulatory patients with severe spastic paraparesis and may offer an alternative to ITB, with potential advantages including lower healthcare costs, fewer complications, and reduced resource utilization,⁷² although HSP-specific data are lacking.

Movement Disorder

The extrapyramidal features of HSPs may be impairing and warrant treatment. Parkinsonism in SPG11 and SPG15 is sometimes dopa-responsive, and a formal levodopa trial is warranted when parkinsonism is suspected.⁷³ Other HSP subtypes which may respond to L-dopa include SPG7, SPG8 and SPG30.^{74–76} One patient with an adolescent-onset movement disorder due to SPG11 was treated with pallidal deep brain stimulation with improvement in dystonia, tremor and dyskinesias.⁷⁷

Dalfampridine (4-aminopyridine), a potassium channel blocker used to improve gait in multiple sclerosis through a proposed mechanism of increasing action potential conduction, has been investigated in adult-onset HSP. A few small, uncontrolled prospective studies showed improvements in spasticity, perceived walking ability, walking speed and dexterity.^{78,79} One randomized controlled trial of eight adults with HSP demonstrated that the dalfampridine treated group had significantly greater improvements in walking speed, muscle strength and spasticity, compared to placebo.⁸⁰ However, experience with dalfampridine has not been reported in early-onset HSP.

Non-Motor Features

Neurogenic bladder dysfunction is common in adults with HSP but is reported far less frequently in children. In complicated forms, such as AP-4-related HSP, urinary incontinence has been described in up to 81% of patients; this may, however, reflect the degree of intellectual disability rather than true neurogenic bladder.⁸¹ Providers should routinely ask about urinary symptoms

and refer to pediatric urology if there is concern about neurogenic bladder dysfunction. Urodynamic testing and/or treatment with anticholinergic medications may be indicated.

There may be additional manifestations of autonomic dysfunction. Impaired pain sensation was reported in 38% of children with AP4-HSP.⁸¹ One study in adults with SPG4 found that peripheral autonomic fibers are impacted based on abnormal Quantitative Sudomotor Axonal Reflex Test (QSART) and increase likelihood of sympathetic skin response (SSR). However, autonomic symptoms were not reported to a greater degree than controls apart from urinary symptoms, so the degree and significance of autonomic dysfunction in children with HSP is uncertain.⁸²

Other symptoms reported in HSP, although less well studied in early-onset disease, include constipation, restless leg syndrome, fatigue, and depression.^{83,84} These symptoms should be routinely assessed and managed according to standard clinical practice.

Complex HSPs: Additional Notes

The needs of children with complex HSP often resemble those of children with other neurodevelopmental disabilities and require multidisciplinary care. Depending on the individual's clinical features, involvement of feeding specialists may be needed to address dysphagia, gastroenterology for constipation and reflux, pulmonology for aspiration risk, epilepsy for epilepsy management, orthopedics for surveillance of musculoskeletal complications such as hip displacement and scoliosis, and rehabilitation medicine to facilitate bracing, mobility equipment, and other assistive devices. Ophthalmologic and audiologic evaluations should be performed to assess for visual and hearing impairments.

In addition to physical therapy, occupational therapy plays an important role in addressing fine motor skills, activities of daily living, and sensory needs. Caregivers of children with complex HSP due to *SPAST* mutations identified communication as the greatest contributor quality of life,⁸ highlighting the importance of speech-language therapy for all affected children and early consideration of augmentative and alternative communication. Given frequent cognitive deficits and executive dysfunction, testing through neuropsychology or developmental pediatrics is recommended to guide therapeutic and educational interventions.⁹ Specific tests should be selected by the assessing provider and tailored to the individual. A pediatric psychologist or behavioral specialist may benefit some children with psychiatric or behavioral symptoms.

Palliative Care

Individuals with a new diagnosis of HSP must adjust to living with a progressive neurologic condition which significantly impacts mobility and quality of life. Palliative care can provide valuable support at the time of diagnosis or at any stage of the disease, helping individuals and families navigate symptoms, clarify goals of care, and make informed decisions while receiving ongoing disease-directed management. For children with complex HSP and severe neurodevelopmental disability, palliative care can play a particularly important role in incorporating family values to aid in shared decision-making that optimizes quality of life.

Transition of Care

Most children with HSP generally have a life expectancy into adulthood and accumulate increasing disease-related needs over time, making the transition from pediatric to adult care a critical juncture in disease management. Transition planning should ideally begin by early adolescence, and include a structured hand-over to receiving adult providers. Key elements include documentation of the specific genetic diagnosis and inheritance pattern, a summary of prior spasticity interventions and their outcomes, current functional status and assistive equipment needs, and any active subspecialty involvement. For patients with complex HSP in whom movement disorder features such as dystonia or parkinsonism may emerge or progress in adulthood, timely referral to a movement disorder specialist is particularly important. Ideally, care is delivered within lifespan clinics capable of managing HSP from childhood through adulthood. Where this is not feasible, pediatric HSP programs should establish formal transition protocols in partnership with adult neurology and movement disorder services, with the goal of ensuring continuity of multidisciplinary expertise, preserving functional gains achieved in childhood, and maintaining access to emerging disease-modifying therapies as they enter clinical practice.

Emerging Therapies

Disease-modifying therapies remain a major unmet need for early-onset HSP. Historically, therapeutic development has been limited by the rarity of individual subtypes, incomplete understanding of disease mechanisms including distinctions between loss- and gain-of-function biology and the absence of robust natural history data.⁸⁵ Over the past decade, coordinated efforts by international research groups have begun to address these barriers. For a subset of HSPs, longitudinal clinical data and mechanistic insights are now available, supporting rational therapeutic targeting.⁸⁶ In parallel, the therapeutic landscape for monogenic neurological disorders has expanded beyond small molecules to include antisense oligonucleotides and gene replacement strategies. These approaches have already translated into effective treatments for related conditions such as spinal muscular atrophy and *SOD1*-associated amyotrophic lateral sclerosis, providing a framework for therapeutic development in HSP.^{87,88} Taken together, these innovations pave the way for the development of effective HSP therapies.

Supplements and Drug Repurposing

SPG5 is caused by pathogenic variants in *CYP7B1*, a gene involved in cholesterol and bile acid metabolism. A phase 2 study of 12 individuals found that atorvastatin, chenodeoxycholic acid and resveratrol normalized some biomarkers, although whether this translates to improvement in symptoms is not yet clear.⁸⁹ A case series of patients with complicated HSP due to severe methylenetetrahydrofolate reductase (MTHFR) deficiency (adult-onset) demonstrated clinical

improvement when treated with vitamin B₁₂, folic acid, folinic acid and betaine (only betaine improved biomarkers).⁹⁰ Subsequently, two young adults with severe MTHFR deficiency were reported to benefit from betaine and vitamins.⁹¹ Individuals with SPG56 (*CYP2U1*) have been shown to exhibit cerebral folate deficiency; two patients treated with folinic acid had a better than expected disease trajectory.⁹² Additionally, early treatment of a mouse model of SPG56 with folinic acid prevented cognitive deficits.⁹³ Dosages are provided in the Table S1. Note that these treatments are not applicable to other HSP subtypes.

Gene Replacement and Gene Editing

Although most HSP-directed drug development programs remain at preclinical stages, several gene-based therapies have recently entered early clinical testing. Clinical trial readiness programs and biomarker discovery are paving the way for more clinical stage testing.⁶ The first gene replacement therapy evaluated in humans targeted SPG50, an AP-4-related HSP caused by biallelic loss of function variants in *AP4M1*. This therapy employed an adeno-associated virus serotype 9 (AAV9) vector carrying the *AP4M1* coding sequence and was administered as a single intrathecal dose. One-year outcomes from the first treated patient—a 4-year-old child (disease duration approximately 3 years)—demonstrated an acceptable safety profile.⁹⁴ While data on efficacy remain limited, these initial findings supported program expansion, and clinical trials are currently underway ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT06692712) identifier NCT06692712).

Additional AP-4-related HSPs are now approaching clinical translation. A phase 1/2 study is initiating for SPG47, evaluating the safety and preliminary efficacy of an AAV9-based gene therapy designed to restore *AP4B1* expression.⁹⁵ In this program, the investigational product is delivered via stereotactic intracisternal magna injection ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT06948019) identifier NCT06948019). There are several barriers to bringing gene therapy to more than a small subset of individuals with HSP as current technology for gene therapy development requires a gene-by-gene approach, is exceedingly expensive, and is in the early stages of understanding efficacy and safety. Nonetheless, these studies mark a critical milestone in the transition of HSP therapies from pre-clinical proof-of-concept to human clinical trials.

Antisense Oligonucleotides (ASOs)

Antisense oligonucleotides (ASOs) have also been explored as therapeutic candidates for selected autosomal dominant HSPs driven by toxic gain-of-function mechanisms, including SPG3A and early-onset SPG30. The therapeutic strategy for these disorders centers on allele-specific silencing of the pathogenic transcript. While most ASO programs for HSP remain in

preclinical development, a single-patient report described intrathecal administration of a customized ASO in an individual with *KIF1A*-associated neurological disorder (KAND)—presenting with features overlapping SPG30—due to the de novo *KIF1A* variant p.Pro305Leu.⁹⁶ Over 9 months of treatment, the ASO was well tolerated, with improvements noted in some clinical measures, although no significant change was observed in 6-min walk distance. This case highlights both the feasibility and current limitations of individualized RNA-targeted therapies for HSP and underscores the need for systematic evaluation in larger cohorts. However, ASOs are not expected to be a universal treatment approach as they are generally not applicable to HSPs with loss of function mechanisms and treatment requires regular, indefinite intrathecal administration of the ASO.

Conclusions

Early-onset hereditary spastic paraplegias represent an important and likely underrecognized cause of gait impairment and spasticity in children and adolescents, with wide phenotypic variability and heterogeneous disease trajectories. Accurate diagnosis requires careful clinical assessment, early consideration of genetic testing, and awareness of disorders that mimic HSP. Multidisciplinary care remains central to management, addressing motor dysfunction, associated neurological features, and long-term functional needs. While disease-modifying therapies are currently available for only a small subset of HSPs, recent advances in natural history studies, molecular characterization, and gene- and RNA-based therapeutics signal a transition toward mechanism-informed treatment strategies and provide cautious optimism for future therapeutic development.

Author Roles

(1) Review: A. Conception, B. Organization, C. Execution; (2) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

JW: 1A, 1B, 1C, 2A, 2B.

CB: 1A, 1B, 1C, 2A, 2B.

DE: 1A, 1B, 1C, 2A, 2B.

MF: 1A, 1B, 1C, 2A, 2B.

Disclosures

Ethical Compliance Statement: Institutional review board approval was not required. Informed patient consent was not necessary for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Table S1. Treatment dosing for metabolic HSP

Data S1. ICMJE disclosure form.