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Childhood-onset Hereditary Spastic Paraplegia and Its Treatable Mimics

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Abstract

Early-onset forms of hereditary spastic paraplegia and inborn errors of metabolism that present with spastic diplegia are among the most common "mimics" of cerebral palsy. Early detection of these heterogenous genetic disorders can inform genetic counseling, anticipatory guidance, and improve outcomes, particularly where specific treatments exist. The diagnosis relies on clinical pattern recognition, biochemical testing, neuroimaging, and increasingly next-generation sequencing-based molecular testing. In this short review, we summarize the clinical and molecular understanding of: 1) childhood-onset and complex forms of hereditary spastic paraplegia (SPG5, SPG7, SPG11, SPG15, SPG35, SPG47, SPG48, SPG50, SPG51, SPG52) and, 2) the most common inborn errors of metabolism that present with phenotypes that resemble hereditary spastic paraplegia.

Keywords

hereditary spastic paraplegia; spasticity; inborn error of metabolism; urea cycle disorders; biotinidase deficiency; cerebrotendinous xanthomatosis

INTRODUCTION

The hereditary spastic paraplegias (HSP) are a genetically heterogeneous group of over 80 disorders characterized by progressive spasticity due to corticospinal tract dysfunction [1–3]. Though many subtypes are rare or even ultra-rare disorders, collectively HSP is estimated to affect about 2-8:100,000 individuals worldwide [4, 5]. On a molecular level, several pathways are known to be impacted by mutations that give rise to HSP, including membrane

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trafficking, mitochondrial function, the cytoskeleton, autophagy and lysosomal function, RNA metabolism and myelination [6]. Inborn errors of metabolism (IEM) represent a rare and often under-appreciated cause of spastic paraparesis in children and adults. Motor neurons and the corticospinal tracts with their long axons and high energy demand seem particularly vulnerable to metabolic defects. IEM can therefore lead to phenotypes that resemble pure forms of HSP (isolated pyramidal signs) or, more commonly, complex, syndromic forms of HSP, where spastic paraplegia is accompanied by other neurological or systemic symptoms and signs. Most forms of spastic paraplegia caused by an IEM present in childhood but it is important to recognize that some may manifest in adulthood and with milder phenotypes. Recognition of these cases is often challenging leading to significant diagnostic delay. Early-onset forms of HSP and IEM that resemble HSP are often misdiagnosed as “cerebral palsy” until progressive features are recognized or molecular testing is pursued. Early detection of HSP caused by IEM can improve outcomes, particularly where specific treatments exist [7, 8], and can inform genetic counseling and anticipatory guidance. The diagnosis relies on clinical pattern recognition and laboratory and imaging studies and increasingly, next-generation sequencing-based molecular testing. In this short review, we summarize the clinical and molecular understanding of 1) childhood-onset and complex forms of HSP and 2) the most common IEM that present with phenotypes that resemble HSP.

CHILDHOOD-ONSET COMPLEX HSP

A detailed review of all forms of HSP is beyond the scope of this review. Here we focus on major forms of complex HSP that present in childhood (Table 1), which includes several that present with metabolic defects (Supplementary Table 1 provides an overview of pathways involved in all HSPs). Complex forms of HSP encompass syndromes that present with progressive limb spasticity (usually beginning in the legs) and weakness accompanied by other neurological symptoms that results from central- and peripheral nervous system dysfunction. This often includes developmental delay and later intellectual disability, cerebellar dysfunction, ataxia, dystonia, seizures, peripheral neuropathy, retinopathy and others.

Clinical features of complex HSP manifest in an age-dependent manner and may resemble “cerebral palsy” early on. Findings on history and neurological exam that distinguish complex HSP from cerebral palsy, however, may include: 1) absence of risk factors of pre- or perinatal brain injury, 2) onset of motor symptoms or regression after a period of normal development, 3) a family history of similarly affected individuals or parental consanguinity, 4) prominent ataxia or cerebellar dysfunction, 5) presence of peripheral neuropathy or optic nerve atrophy, 6) a syndromic presentation not readily explained by sequelae of prematurity, 7) brain MR imaging findings that are normal or inconsistent with acquired injury. Generally, in HSP there is a pattern of clinical progression that may be different from the clinical pattern seen in cerebral palsy. Clinically, the spasticity in childhood-onset HSP usually starts in the distal lower extremities leading to a clumsy gait or toe walking in young children. Over time the knees and hips become involved leading to impaired ambulation, if ever fully achieved, and the need for assistive devices including walkers or wheelchairs. Involvement of the upper extremities usually occurs later in the disease course

and is variable. Certain neuroimaging findings, including thinning of the corpus callosum, or characteristic patterns of signal abnormalities in the periventricular white matter in some, can provide an important clue into complex forms of HSP. Research on HSP is advancing at a rapid pace, with discovery of additional causative genes and better delineation of clinical and molecular characteristics. Summarized below are the most common childhood-onset and complex forms of HSP; other less common forms are summarized in Table 1.

SPG5 *(CYP7B1)*

Although often classified as a “pure” form of HSP, several studies on SPG5 (OMIM # 270800) have documented the presence of clinical features beyond spastic paraplegia including dorsal column dysfunction that is more severe compared to other forms of pure HSP, a prominent sensory ataxia, and behavioral symptoms [9–11]. Neurogenic bladder dysfunction and incontinence are relatively common [9]. The age at onset is highly variable with no genotype-phenotype correlation established yet, though a homozygous founder mutation observed in the Han Chinese population of Taiwan may be associated with greater disease severity (*CYP7B1* (NM_004820.5): c.334C>T, (p.Arg112Ter)) [11]. Most patients present in adolescence [9, 10] with insidious-onset gait difficulties, spasticity in the distal legs, and pyramidal signs on examination. There is early dorsal column involvement with impaired joint position and vibration sense in the lower extremities. The disease typically progresses slowly and most patients are able to walk without assistance for many years. After a disease duration of ~20-30 years, spasticity and functional handicap are usually moderate to severe [10]. Wheelchair-dependency is reached at a median disease duration of ~33 years [9]. Spasticity typically stays confined to the lower extremities. MR brain imaging shows hyperintense signal in the periventricular white matter on T2 and FLAIR sequences, particularly of the posterior supratentorial regions. In some cases, mild cerebellar atrophy and spinal cord atrophy are found. Nerve conduction studies are typically normal.

SPG5 is caused by biallelic loss-of-function variants in *CYP7B1* which encodes the enzyme oxysterol-7-α-hydroxylase that is involved in the degradation of cholesterol into primary bile acids. Specifically, oxysterol-7-α-hydroxylase mediates the hydroxylation of 25-hydroxycholesterol (25-OHC) and 27-hydroxycholesterol (27-OHC). Elevation of oxysterol-7-α-hydroxylase substrates can be detected in serum and CSF of SPG5 patients and can serve as a biomarker [9, 12–14]. Levels of 27-OHC seem to be associated with disease severity as measured using the Spastic Paraplegia Rating Scale [9].

A randomized and placebo-controlled phase 1/2 trial of atorvastatin in 14 patients with SPG5 showed a reduction of serum 25-OHC and 27-OHC levels. No effects were seen on clinical outcome parameters which was attributed to the short study duration [9]. An earlier phase 2 trial used an open-label three-treatment crossover design to test atorvastatin, resveratrol and chenodeoxycholic acid in 12 SPG5 patients and found a moderate reduction in 27-OHC levels [14]. These trials provide a solid basis for future investigations into cholesterol lowering drugs. A phase 1/2 trial of the PCSK9 inhibitor, evolocumab, is currently underway (ClinicalTrials.gov Identifier: NCT04101643).

SPG7 *(SPG7)*

One of the most studied forms of HSP, SPG7 (OMIM #602783) often presents with prominent ataxia, dysarthria, abnormal saccades and nystagmus in addition to spasticity [15–19]. This underscores the often-overlapping spectra of the hereditary spinocerebellar ataxias and HSP [20]. In SPG7, loss of peripheral muscle bulk, sensory deficits, progressive external ophthalmoplegia (primarily horizontal eye movements), dysphonia, dysphagia and sphincter dysfunction are findings that may develop over time. Other manifestations such as cervical or limb dystonia, parkinsonism, intellectual disability, and optic nerve atrophy are rare and present the severe end of the spectrum. Onset of spasticity or ataxia is typically in the second or third decade of life; however, patients with pediatric onset have also been reported [19]. Progression is slower than in other forms of complex HSP and loss of ambulation is less common. Nerve conduction studies are normal or may show a sensorimotor axonal neuropathy. Brain MR imaging is significant for cerebellar atrophy of varying severity in about 80% of cases [15, 19, 21].

SPG7 is caused by biallelic loss-of-function variants in *SPG7*. *SPG7* encodes a mitochondrial inner membrane metalloprotease termed paraplegin. Not surprisingly many of the clinical features, i.e., external ophthalmoplegia, overlap with mitochondrial disorders and it has been suggested that SPG7 may be a disorder of mitochondrial DNA maintenance [22]. On muscle biopsy mitochondrial abnormalities and respiratory chain dysfunction are evident [19]. Neuropathology of a single case showed degenerative changes of the cerebellum with loss of Purkinje cells, as well as degeneration of the corticospinal tracts and optic nerves [17].

SPG11 *(SPG11)*, SPG15 *(ZFYVE26)* and SPG48 (*AP5Z1*)

SPG11 (OMIM #604360) is thought to be the most common cause of autosomal recessive HSP and a major cause of HSP with a thin corpus callosum [23, 24]. SPG11 results from biallelic loss-of-function variants in the *SPG11* gene (also *KIAA1840*) [25], encoding the spatacsin protein. Spatacsin has been shown to act in complex with the proteins encoded by *ZFYVE26* and *AP5Z1*, the two genes responsible for SPG15 (OMIM #270700) [26] and SPG48 (OMIM #613647) [27]. Not unexpectedly the clinical features of all three disorders are overlapping [24, 28–30] and SPG11 and SPG15 are indistinguishable on clinical grounds alone.

All three disorders are characterized by progressive spasticity that begins in the lower extremities and is associated with several symptoms resulting from central and peripheral nervous system dysfunction. For SPG11 and SPG15, onset is typically in mid to late childhood or adolescence, though subtle symptoms, such as developmental delay or learning disability, may be present earlier and often precede motor symptoms. Cases with onset of symptoms in adulthood have also been reported. Though detailed natural history data are not available yet, SPG11 and SPG15 are thought to be progressive disorders.

First symptoms are often poor balance, clumsiness, and gait impairment, typically in mid to late childhood. Over time this evolves into progressive lower extremity weakness and spasticity with associated pyramidal signs. Bulbar or cerebellar dysarthria often

develops along with the spastic paraplegia. Most individuals, over the course of years, become non-ambulatory and ultimately require mobility aids or a wheelchair. Spasticity progresses to involve the upper extremities in some cases, resulting in a spastic tetraplegia, though continues to be more severe in the legs. Associated complications may include dysphagia, contractures secondary to progressive spasticity, scoliosis, foot deformities, and dysregulation of bladder and bowel function. The degree of cognitive impairment associated with SPG11 and SPG15 is variable and ranges from learning disabilities to mild or moderate intellectual disability. A subset of patients shows cognitive decline with disease progression. Cerebellar signs are found in over half of patients and range from dysarthria, dysmetria, dysdiadochokinesia, intention tremor, nystagmus to cerebellar ataxia. A subset of patients may present with extrapyramidal movement disorders which may include focal dystonia or parkinsonism. A peripheral neuropathy is present in a subset and nerve conduction studies, where available, show an axonal sensorimotor neuropathy of the lower extremities. With disease progression there is often a loss of muscle bulk, particularly in the distal lower extremities. Loss of vibration sense is often found. A pigmentary retinopathy, classically described as part of Kjellin syndrome, may be present in a subset of patients and is likely underdiagnosed as it may not present with overt deficits early on. Other ocular anomalies reported include early-onset cataracts. Sensorineural hearing impairment is found in a subset of patients. Seizures are uncommon in SPG11 and SPG15, which is an important distinguishing feature for comparison with other forms of complex HSP. The most common neuroimaging findings include: 1) thinning of the corpus callosum, 2) signal abnormalities of the periventricular white matter, and 3) cerebral and cerebellar atrophy. While these findings are not specific, they can help guide a differential diagnosis. The thinning of the corpus callosum tends to affect the anterior parts, which contrasts the adaptor protein complex-4 (AP-4) related HSP (SPG47, SPG50, SPG51 and SPG52) and others which typically affect the posterior parts [31]. In SPG11 and SPG15 the signal abnormalities in the periventricular white matter can have a characteristic appearance involving the forceps minor. This is known as the *Ears of the Lynx* sign which consists of hypointense signal on T_1-weighted and hyperintense signal on FLAIR images which, on axial views, resembles the shape of the ears of a lynx with its characteristic apical hair tuft [32].

The above clinical findings are overlapping greatly with other complex forms of HSP with a thin corpus callosum and with congenital disorders of autophagy [33, 34]. Several converging lines of evidence from work on SPG11, SPG15 and AP-5 are in support of this by showing that the SPG11/ZFYVE26/AP-5 complex is involved in autophagy and the reformation of lysosomes from autolysosomes and endolysosomes [35–37]. Also notable are reports of secondary abnormalities in neurotransmitter metabolites with clinical benefit using L-dopa and sapropterin supplementation in SPG11 [38].

SPG35 (FA2H)

Another important form of early-onset form of complex HSP is SPG35 (OMIM #612319), caused by mutations in *FA2H* [39] which encodes the endoplasmic reticulum (ER) associated enzyme fatty acid 2-hydroxylase. Described in less than 100 cases thus far, children with SPG35 present in early childhood with first symptoms evident in the first 5 years of life in the vast majority of cases [24, 40, 41]. The clinical spectrum consists

of progressive spastic diplegia and later tetraplegia, cerebellar ataxia, dysarthria, slow horizontal saccades, dysphagia and progressive cognitive decline. Extrapyramidal movement disorders such as dystonia, rigidity and a resting tremor may evolve. A peculiar recently described feature is that of bristle hair with structural abnormalities on electron microscopy [40]. There are usually no prominent sensory deficits. Disease progression is relativity rapid with loss of ambulation and involvement of the upper extremities within less than a decade [40]. On brain MR imaging there are features commonly seen in other complex HSP including a thin corpus callosum, cerebral and ponto-cerebellar atrophy, white matter changes but also a T2*/SWI hypointense signal in the globus pallidus [40, 41]. FA2H is involved in the synthesis of sphingolipids, which are particularly abundant in myelin. *Fa2h* knockout mice display loss of myelin with late-onset axonal degeneration and behavioral symptoms that resemble spastic paraplegia [42].

AP-4-associated HSP (*SPG47, SPG50, SPG51, SPG52*)

An emerging group of childhood-onset complex HSP are the four adaptor protein complex 4 (AP-4) associated HSP caused by biallelic loss-of-function variants in the subunits of this obligate protein complex [43]. This includes *AP4B1*-associated SPG47 (OMIM #614066), *AP4M1*-associated SPG50 (OMIM #612936), *AP4E1*-associated SPG51 (OMIM #613744) and *AP4S1*-associated SPG52 (OMIM #614067). A loss of AP-4 complex function is common to all four disorders; hence they share a common phenotype. Although the genetic causes of AP-4 deficiency had been delineated a decade ago [44–46], the phenotypic spectrum has only recently been described in detail [31, 47]. The AP-4-associated HSP are an important genetic mimic of cerebral palsy given their age at symptom onset, nonspecific initial presentation and relatively slow progression. Most children with AP-4-associated HSP present with early-onset developmental delay with delayed motor milestones and absent or delayed speech development. Most eventually learn to walk with assistance but only about half of patients ever achieves independent ambulation [31]. About a third of patients remain non-verbal with their receptive language often being much more developed. Intellectual disability is usually in the moderate to severe range. From a motor standpoint, there is usually a history of truncal hypotonia in infancy that over time evolves into a distal spastic paraplegia that progresses from the ankles upward. By the age of 5-10 years, most patients display a spastic paraplegia and many go on to require a wheelchair. Along with spasticity of the lower extremities, there are pyramidal signs and distal contractures. Involvement of the arms tends to occur later and is variable in severity. Extrapyramidal symptoms include limb dystonia and some patients may present with ataxia [31]. Seizures are found in about two thirds of patients with the initial presentation often consisting of complex, often prolonged febrile seizures in the first 5 years of life. While many go on to develop unprovoked seizures as well, these tend to be well controlled with standard anti-seizure medications and in many cases will become less frequent in late childhood [31]. Seizures are of variable semiology and include both focal and generalized seizures. There are no specific EEG findings. Of clinical importance, a subset of patients presents with malformations of cortical development, including bilateral perisylvian polymicrogyria. In these cases, seizures can be refractory to anti-seizure medications which heralds greater overall disease severity [31]. Neuroimaging can be helpful to distinguish AP-4-associated HSP from cerebral palsy. A thin corpus callosum is found in over 90% of cases and typically involves the splenium

more than anterior parts [31]. There is often a loss of periventricular white matter leading to ex-vacuo ventriculomegaly of the lateral and third ventricles. This is often more evident in posterior regions leading to asymmetric colpocephaly with enlarged occipital horns. Cerebral atrophy may be present though is typically mild. Cerebellar atrophy is rare [31].

The diagnosis of AP-4-associated HSP is confirmed if biallelic mutations in *AP4B1*, *AP4M1*, *AP4E1* or *AP4S1* are found. A functional assay for AP-4 function in fibroblasts is available on a research basis and can help evaluate novel variants [48, 49]. Recent work has identified several cargo proteins that depend on the AP-4 for their intracellular transport [48, 50–54]. This includes the autophagy-associated protein ATG9A and a working model for how AP-4 deficiency leads to HSP has emerged: (1) AP-4 is required for sorting of ATG9A from the trans-Golgi network; (2) loss-of-function variants in any of the four AP-4 subunits lead to a loss of AP-4 assembly and function; (3) ATG9A accumulates in the trans-Golgi network leading to a reduction of axonal delivery of ATG9A; (4) lack of ATG9A at the distal axon impairs autophagosome biogenesis and impairs axonal function leading to length-dependent axonal degeneration. This model has parallels to many other forms of HSP that result from defective protein trafficking, organelle dysfunction or impaired axonal transport (Supplementary Table 1).

INBORN ERRORS OF METABOLISM THAT RESEMBLE HSP

There are several IEM that can resemble HSP. Highlighted here are treatable conditions that fall in this category (Table 2). Others are covered in recent reviews [7, 8, 55].

Urea Cycle Disorders (*ARG1*-associated arginase 1 deficiency and *SLC25A15*-associated HHH syndrome)

Among the urea cycle disorders, several have been reported to resemble a slowly progressive complex form of HSP, at least in a subset of cases. Two of these conditions are *ARG1*-associated arginase 1 deficiency and *SLC25A15*-associated hyperornithinemia-hyperammonemia–homocitrullinuria (HHH) syndrome.

Arginase 1 deficiency (OMIM #207800) stands out among the urea cycle disorders for the relatively rare occurrence of hyperammonemic crises. Disease onset is typically in early childhood, often with an insidious onset distal spastic diplegia [56]. Because of the slow progression of the spastic diplegia and later tetraplegia, the condition is sometimes mistaken for cerebral palsy [57]. Along with spasticity most patients present with developmental delay and later intellectual disability and seizures. Extrapyramidal movement disorders such as dystonia and ataxia have also been reported [56].

The combination of hyperornithinemia, hyperammonemia, and homocitrullinuria is pathognomonic for HHH syndrome (OMIM #238970) [58] caused by biallelic variants in *SLC25A15* encoding the mitochondrial ornithine/citrulline antiporter ORC1. Loss of ORC1 function impairs ornithine transport through the mitochondrial membrane thus interrupting the urea cycle. A systematic retrospective review of over 100 reported cases found a wide spectrum, both in terms of disease onset and severity [59]. First symptoms are usually present in early childhood, including the neonatal period. HHH can present acutely with

hyperammonemic crises and liver dysfunction or with a more indolent, slowly progressive course. Neurologically, HHH is characterized by progressive spasticity with pyramidal signs [59–62]. This is accompanied by learning disability or intellectual disability and there is also often cerebellar dysfunction with ataxia, dysarthria, nystagmus and poor fine motor coordination, and epilepsy [59].

Upon laboratory testing, arginase 1 deficiency is characterized by hyperargininemia, while HHH syndrome shows the typical combination of hyperornithinemia, hyperammonemia, and homocitrullinuria. Increased plasma ammonia may be associated with abnormal liver function tests in HHH syndrome, especially during attacks, while they are usually normal in arginase 1 deficiency. Brain MRI may reveal diffuse white matter abnormalities or atrophy in some patients. Molecular testing can confirm the diagnosis.

Both conditions are managed with a restriction of protein intake and supplementation of essential amino acids. Patients with arginase 1 deficiency who are diagnosed and treated early generally remain asymptomatic. Patients with HHH syndrome are additionally treated with citrulline and arginine supplementation [63].

Disorders of Cofactors and Vitamins (Biotinidase Deficiency)

Biotinidase deficiency (OMIM # 253260) represents an inherited defect in the metabolism of biotin, resulting in multiple carboxylase deficiencies [64]. Biotinidase deficiency usually manifests during infancy or early childhood. Presenting symptoms include a neurocutaneous syndrome with eczematous skin rash, developmental delay, seizures, hypotonia, ataxia, optic atrophy, and hearing impairment. Skin manifestations include alopecia, skin rash due to seborrhea, atopic dermatitis and glossitis. Delayed-onset cases have been reported and mainly present with a progressive myelopathy with spastic paraplegia [65, 66]. The diagnosis of biotinidase deficiency is usually made by newborn screening or with a direct enzyme assay. Brain and spine MR imaging can be helpful, particularly in later-onset presentations, showing diffuse white matter abnormalities consistent with dysmyelination. The condition is successfully managed with biotin, which can result in the prevention of disease progression when administrated early.

Disorders of bile acid biosynthesis (*CYP27A1*-associated cerebrotendinous xanthomatosis)

Cerebrotendinous xanthomatosis (CTX) (OMIM # 213700) is caused by biallelic loss-of-function variants in the *CYP27A1* gene [67], which encodes the mitochondrial enzyme sterol 27-hydroxylase that is involved in the bile synthesis pathway by converting cholesterol to cholic acid and chenodeoxycholic acid (CDCA). Decreased synthesis of bile acid, inadequate feedback inhibition of cholesterol production, and subsequently abnormal deposition of cholestanol and cholesterol in tissues and organs are the hallmark features of CTX.

The clinical presentation is usually one of insidious-onset but progressive with a combination of neurological and non-neurological manifestations. Typical non-neurological features include neonatal jaundice, bilateral childhood-onset cataracts, and chronic diarrhea, and the presence of tendon xanthomas (these occur late in the disease course). The disease

produces various neurological manifestations, including progressive spastic paraparesis with onset typically in adolescence, cognitive decline, cerebellar ataxia, dystonia/parkinsonism, psychiatric symptoms, seizures, and a peripheral neuropathy [68–70].

The diagnosis of CTX may be challenging due to the slowly progressive course of the disease and the wide range of presenting symptoms. A combination of at least two out of the following four clinical hallmarks are suggestive of CTX: tendon xanthomas, early-onset cataracts, intractable diarrhea, and progressive neurological manifestations [71].

MRI often shows cortical and cerebellar atrophy, white matter abnormalities in the brain and spinal cord, and symmetric T2 hyperintensities in the dentate nuclei [72]. Plasma cholestanol levels are elevated and, together with low levels of bile alcohols in plasma or urine, are usually diagnostic. Confirmation is obtained by sequencing of *CYP27A1*. Although treatment with chenodeoxycholic acid can lower cholestanol levels and can prevent progression, the effect on existing symptoms is variable.

Peroxisomal Disorders (*ABCD1*-related adrenoleukodystrophy)

Adrenoleukodystrophy (OMIM #300100) is an X-linked leukodystrophy caused by impaired oxidation of very long chain fatty acids (VLCFA) leading to their accumulation in the central nervous system, adrenal glands, and other tissues. The responsible gene is *ABCD1*, which encodes the peroxisomal transporter protein ATP-binding cassette subfamily D member 1. The accumulation of VLFCA in the central nervous system is thought to have a neurotoxic effect, causing demyelination and eventually leading to a slowly progressive dying-back axonopathy, affecting ascending and descending spinal pathways [73]. The childhood-onset cerebral form of adrenoleukodystrophy often begins in mid childhood and is characterized by progressive inflammatory demyelination leading to cognitive decline, behavioral dysregulation, vision impairment, and progressive spasticity with gait impairment. Seizures are seen in a subset of patients and most have adrenal insufficiency. Late-onset forms can present as slowly progressive paraparesis in adults, mimicking pure HSP [74–76].

MRI of the brain shows diffuse white matter lesions in the parieto-occipital regions, often involving the splenium of the corpus callosum in the childhood-onset form. The detection of increased plasma VLFCA levels is typical for adrenoleukodystrophy and the diagnosis is confirmed by the presence of a pathogenic variant in *ABCD1*.

It is generally accepted that allogeneic hematopoietic cell transplantation is the only effective treatment for the cerebral forms of the disease and when it is performed early it can prevent disease progression. *Ex vivo* gene therapy may be a safe and effective alternative to allogeneic stem-cell transplantation in patients with early-stage cerebral adrenoleukodystrophy [77].

GCH1-associated dopa-responsive dystonia

Disorders of neurotransmitter metabolism are among the most classic inborn errors of metabolism that present with movement disorders [78]. Autosomal-dominant GTP cyclohydrolase 1 (GCH1) deficiency (Segawa's disease or DYT-*GCH1*, OMIM #128230)

is an important treatable disorder that results from impaired synthesis of tetrahydrobiopterin. Classically, the age at onset is between 5 and 10 years and there is a well-established female preponderance [79, 80]. Postural dystonia of the extremities, most commonly of the legs, with diurnal fluctuation and worsening in the evening is the typical initial presentation. Craniocervical dystonia (including cervical dystonia, blepharospasm or oromandibular dystonia) is less common. If left untreated, there is often progression from focal to segmental and finally to generalized dystonia. Atypical presentations may include retrocollis or oculogyric crises and features of parkinsonism (particularly in older individuals). Adult-onset cases may present with writer's cramp or tremor only.

Early in the disease course, it can be difficult to distinguish dystonia from spasticity and it is increasingly appreciated that a subset of patients presents with lower limb spasticity rather than dystonia [81–83]. Deep tendon reflexes can be brisk and other pyramidal signs may be present, sometimes leading to a diagnosis of cerebral palsy [84]. A recent analysis of 400 Canadian HSP patients via exome sequencing revealed three cases of *GCH1*-associated dopa-responsive dystonia [82]. This argues for consideration of a levodopa trial and inclusion of the *GCH1* gene in multigene panels for HSP or cerebral palsy spectrum disorders [82].

The diagnosis of *GCH1*-associated dopa-responsive dystonia relies on a combination of clinical features, biochemical and genetic tests, and is supported by a levodopa trial. Neuroimaging is typically normal. CSF testing may show low levels of homovanillic acid, biopterin and neopterin, with a normal plasma level of phenylalanine. A phenylalanine load is sometimes used to further support the diagnosis. Genetic testing for variants in *GCH1* confirms the diagnosis. Therapy with levodopa often leads to a quick and sustained improvement of the dystonia, and from a diagnostic standpoint establishes the cardinal feature of dopa responsiveness. Interestingly, the reported spasticity seen in a subset of patients was also ameliorated [81, 82].

CLINICAL IMPLICATIONS AND CONCLUSION

There have been remarkable advances in the understanding of the clinical and molecular spectrum of childhood-onset HSP. Much of this is fueled by the advent and increasing availability of next-generation sequencing based multigene panels or clinical exome sequencing. With the list of HSP genes growing steadily, the latter might be advantageous in many situations provided that comparable depth of DNA sequencing coverage exists. In clinical practice it is important to distinguish HSP from cerebral palsy and to identify treatable IEM that mimic both. Differentiation from dystonia may not be apparent, especially in early stages, and some patients with a suspected clinical diagnosis of HSP may have dopa-responsive dystonia and benefit from a trial of L-dopa [7, 81, 82]. While the diagnosis of HSP relies on the identification of pathogenic mutations in SPG-designated genes, acquired causes of progressive spasticity should be ruled out as a first step. Recognition of symptoms beyond spasticity is crucial and "red flag" features on history and examination can guide further diagnostic steps including biochemical testing, brain imaging and molecular testing. Attention needs to be paid to atypical presentations of treatable disorders including the ones discussed here. Treatment of childhood-onset complex HSP is

largely symptomatic with several novel disease modifying agents being developed including small molecules and gene replacement strategies. A correct clinical and molecular diagnosis, and a better understanding of the clinical spectrum and natural history are thus of paramount importance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS:

CDCA	chenodeoxycholic acid
CSF	cerebrospinal fluid
CTX	cerebrotendinous xanthomatosis
HHH	hyperornithinemia, hyperammonemia, and homocitrullinuria
HSP	hereditary spastic paraplegia
IEM	inborn error of metabolism
OHC	hydroxycholesterol
SPG	spastic paraplegia
VLCFA	very long chain fatty acids

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Table 1.

Autosomal-Recessive Childhood-Onset Complex HSP – Key Clinical, Molecular And Neuroimaging Findings

HSP	Gene	Molecular / metabolic defect	Major clinical manifestations *	Major neuroimaging findings	Key References
SPG5 (OMIM #270800)	*CYP7B1*	Defect in cholesterol metabolism	Prominent dorsal column dysfunction with sensory ataxia, cerebellar dysfunction	Periventricular white matter changes (often posterior), mild cerebellar atrophy, spinal cord atrophy	[9–11, 14]
SPG7 (OMIM #607259)	*SPG7*	Defect in mitochondrial metabolism	Cerebellar dysfunction, chronic progressive external ophthalmoplegia-like phenotype, optic nerve atrophy, dystonia	Cerebellar atrophy, periventricular white matter changes	[15–18]
SPG11 (OMIM #604360) SPG15 (OMIM #270700) SPG48 (OMIM #613647)	*SPG11*	Defect in endosome, autophagosome, lysosome biology	Cognitive impairment (broad range), dysarthria, cerebellar dysfunction, peripheral neuropathy, retinopathy	Thin corpus callosum, periventricular white matter changes (ears of the lynx sign), cerebral and cerebellar atrophy	[24]
	ZFYVE26				[26, 85]
	AP5Z1				[27, 28]
SPG18 (OMIM #611225)	*ERLIN2*	Defect in ER-associated calcium signaling	Developmental delay / intellectual disability, cerebellar dysfunction	Thin corpus callosum	[86]
SPG21 (OMIM #248900)	*ACP33*	Defect in endosome and lysosome biology	Progressive cognitive impairment, cerebellar dysfunction, psychiatric symptoms	Thin corpus callosum	[87]
SPG26 (OMIM #609195)	*B4GALNT1*	Defect in biosynthesis of complex gangliosides	Learning disabilities / intellectual disability, psychiatric/behavioral symptoms, peripheral neuropathy	Cerebral atrophy, periventricular white matter changes	[88, 89]
SPG28 (OMIM #609340)	*DDHD1*	Defect in phospholipid metabolism	Cerebellar dysfunction, peripheral neuropathy	n.a.	[90]
SPG35 (OMIM #612319)	*FA2H*	Defect in sphingolipid metabolism	Cognitive impairment, cerebellar dysfunction, dysphagia, extrapyramidal movement disorders, optic nerve atrophy	Thin corpus callosum, cerebral and cerebellar atrophy	[40]
SPG46 (OMIM # 614409)	*GBA2*	Defect in glucosylceramide metabolism	Cerebellar dysfunction, cataracts, hypogonadism in males	Thin corpus callosum	[91]
SPG47 (OMIM #614066), SPG50 (OMIM #612936), SPG51 (OMIM #613744), SPG52 (OMIM #614067)	*AP4B1, AP4M1, AP4S1, AP4E1*	Defect in intracellular protein trafficking / autophagy	Developmental delay / intellectual disability, postnatal microcephaly, epilepsy, extrapyramidal movement disorders	Thin corpus callosum, periventricular white matter changes, ventriculomegaly (colpocephaly)	[31]
SPG49 (OMIM #615031)	*TECPR2*	Defect in autophagy	Developmental delay / intellectual disability, hypotonia, autonomic dysfunction, central apneas	Thin corpus callosum	[92]
SPG54 (OMIM #615033)	*DDHD2*	Defect in phospholipid metabolism	Developmental delay / intellectual disability, cerebellar dysfunction, short statue	Thin corpus callosum, periventricular white matter changes	[93]
SPG55 (OMIM #615035)	*C12orf65*	Defect in mitochondrial function	Peripheral neuropathy, optic nerve atrophy	n.a.	[94]

HSP	Gene	Molecular / metabolic defect	Major clinical manifestations *	Major neuroimaging findings	Key References
SPG56 (OMIM #615030)	*CYP2U1*	Defect in lipid metabolism	Developmental delay / intellectual disability, peripheral neuropathy, dystonia	Thin corpus callosum, periventricular white matter changes	[90]

* All patients present with spastic paraplegia and associated pyramidal signs.

Table 2.

Treatable IEM That Resemble HSP

Inborn error of metabolism	Gene / Inheritance	Clinical manifestations	Treatment
Adrenoleukodystrophy (OMIM #300100)	*ABCD1* / X-linked	Childhood cerebral form: Progressive spasticity, cognitive decline, behavioral dysregulation, vision impairment, seizures, adrenal insufficiency	Allogeneic HSCT [95, 96] Ex-vivo gene therapy [77]
Arginase 1 deficiency (OMIM #207800)	*ARG1* / autosomal-recessive	Spasticity (progressing from a spastic diplegia to tetraplegia), DD/ID, seizures	Protein restriction [63] Pegzilarginase [97]
Biotinidase deficiency (OMIM #253260)	*BTD*	Spasticity, developmental delay / intellectual disability, seizures, ataxia, vision impairment, hearing loss, cutaneous abnormalities	Biotin [64]
Cerebrotendinous xanthomatosis (OMIM #213700)	*CYP27A1* / autosomal-recessive	Spasticity, ataxia, parkinsonism, cognitive impairment, seizures, peripheral neuropathy, tendon xanthomas, neonatal jaundice, bilateral childhood-onset cataracts, childhood-onset chronic diarrhea	Supplementation with chenodeoxycholic acid [68]
Dopa-responsive dystonia (OMIM #128230)	*GCH1* / autosomal-dominant	Dystonia (often involving limbs first, often with diurnal fluctuation, responsive to levodopa), parkinsonism, spasticity	Levodopa/carbidopa [79]
Hyperornithinemia-hyperammonemia–homocitrullinuria (HHH) syndrome (OMIM #238970)	*SLC25A15* / autosomal-recessive	Progressive spasticity with pyramidal signs, cognitive impairment, cerebellar signs, epilepsy.	Protein restriction, citrulline and arginine supplementation [63]