Title

Hereditary spastic paraplegia: from diagnosis to emerging therapeutic approaches

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Summary

Hereditary spastic paraplegia (HSP) describes a heterogeneous group of genetic neurodegenerative diseases characterised by progressive spasticity of the lower limbs. The pathogenic mechanism, associated clinical features and imaging abnormalities vary significantly according to the affected gene. Here, we describe the clinical and imaging characteristics of the more common forms of HSP. We discuss how to approach the diagnosis and management of a suspected case of HSP in the era of next generation sequencing, before discussing treatment and the potential of emerging therapeutic options for specific causes of HSP based on their underlying molecular mechanism.

Introduction

The hereditary spastic paraplegias (HSPs) are a heterogeneous group of monogenic neurological diseases with a combined prevalence of 2-5 cases per 100,000 worldwide.[1,2] They are characterised by length-dependent corticospinal tract and dorsal column degeneration that manifests with the core clinical features of bilateral lower limb spasticity, hyperreflexia and extensor plantar responses.[3] HSPs can present in infancy, childhood, adolescence, or adulthood and autosomal dominant, autosomal recessive, or X-linked modes of inheritance are seen, with 13-40% of cases being sporadic (i.e. with no family history).[4,5]

The genetic classification for HSP is based on sequential numbering of chromosomal loci or specific genes, as they were identified, using an *SPG* designation. Up to *79 SPG* genes have been described so far. Many of these have only been identified in single families, and so are perhaps best regarded as HSP candidate genes.[6] Several other groups of monogenic neurological diseases, other than HSP, are associated with spasticity, usually in the context other cardinal clinical features, and are not the focus of this review. Despite the selective use of next generation sequencing-based HSP gene panels or whole exome sequencing, a genetic diagnosis is not made in up to half of all suspected cases of HSP, with or without a positive family history.[4,5,7,8]

Clinical characteristics

The majority of cases present with a slowly progressive gait disturbance of insidious onset. Onset in early childhood may manifest with delayed motor milestones and may initially be misdiagnosed as cerebral palsy. The spasticity, which can be slightly asymmetrical, may occur in the absence of limb weakness and may only be demonstrable on walking. Asymptomatic upper limb hyperreflexia without spasticity is common and a brisk jaw jerk can occasionally be seen.[8] Urinary symptoms related to detrusor instability and/or detrusor sphincter dyssynergia are frequent, usually occurring later in the disease course.[9] Asymptomatic, or mildly symptomatic, impairment of vibration sensation caused by dorsal column degeneration is also common, while central pathways conveying other sensory modalities are less frequently involved.[4]

Additional neurological features such as cognitive impairment, ataxia, dysarthria, neuropathy, or seizures are seen in more than half of cases and may be the presenting feature.[4] The clinical classification proposed by Harding and colleagues divides cases into *pure* or *complicated*, later revised to *pure* or *complex*, HSP on this basis.[10] These specific clinical features are sometimes helpful for differentiating the underlying aetiology, although significant phenotypic variation can occur between individuals with the same *SPG* type or specific mutation, and some features may be subtle or subclinical, or may only emerge later in the disease course.[7,11] The association between various different clinical features and the majority of *SPG* types, up to *SPG78*, has been covered in recent comprehensive review.[12]

Cellular pathogenetic mechanisms mirror the complex phenotypic and genotypic heterogeneity, making development of generic disease modifying treatments for HSP challenging. This review focuses on the more common HSPs encountered in clinical practice, highlighting clinical, neuroimaging and neurophysiological, features. These are divided according to inheritance patterns given that a positive family history can immediately narrow the differential diagnosis. We propose a simple diagnostic algorithm using clinical and neuroimaging features, and describe cellular pathogenetic themes and the therapeutic landscape, including the prospect of genotype specific treatments.

Autosomal-dominant HSP subtypes

SPG4 (SPAST, Spastin) is the most common HSP and is inherited as an autosomal dominant (AD) trait.[13–15] It accounts for up to a third of all HSP cases, including 60% of AD-HSP and 15% of sporadic cases.[4] The mean age

of onset is 31·7 years, with a range from 0 to 70 years, and it usually presents with isolated lower limb spasticity, with or without bladder/sensory dysfunction.[8] In a cohort of 196 cases of mostly German origin, ataxia or peripheral motor involvement were seen in 5-10% of cases and cognitive involvement, extrapyramidal involvement, dysarthria, or dysphagia were seen in fewer than 5% of cases.[4]

SPG3A (ATL1, Atlastin) is the second most common AD-HSP making up around 5-10% of AD-HSP cases that test negative for *SPG4* mutations.[8] Similarly, it usually presents with isolated lower limb spasticity, with or without bladder/sensory dysfunction, however an axonal motor neuropathy is seen in up to 25% of cases.[4] The mean age of onset for *SPG3A* is significantly lower than *SPG4* (5·6 vs 31·7 years), meaning that SPG3A and SPG4 mutations occur with roughly equal frequency in AD-HSP presenting in the first decade of life , while AD-HSP presenting after the fourth decade is unlikely to be caused by *SPG3A*.[4]

SPG31 (REEP1) is the third most common AD-HSP.[16,17] Like *SPG3A*, it usually presents as a pure phenotype, with or without bladder/sensory dysfunction, but is associated with an axonal neuropathy in up to 50% of cases.[18] It appears to have a bimodal distribution with peaks in the first and fourth decades, although onset in a nonagenarian has been reported, and the age of onset can also vary significantly within individual families.[19] Interestingly, several patients with *SPG31* have been reported to have COX-deficient fibres on muscle biopsy suggestive of mitochondrial dysfunction.[18]

Autosomal-recessive HSP subtypes

SPG11 (Spatacsin) is the one of the most prevalent autosomal recessive HSP and accounts for up to 8% of all HSP cases, with a higher prevalence in populations with significant consanguinity.[1,5] It presents between the ages of 4 and 36 years. The phenotype can vary between family members but is invariably complex. The majority of cases present with cognitive impairment or learning difficulties with lower limb spasticity emerging later, typically in the second decade.[20] Over 50% develop dysarthria, ataxia, axonal motor neuropathy, or prominent urinary symptoms.[4,7,20] Progression to upper limb involvement is common and levodopa-responsive parkinsonism, oromandibular dystonia, seizures, and visual failure secondary to optic atrophy have also been reported.[7]

SPG15 (ZFYVE26) presents in a similar fashion to *SPG11,* although the axonal neuropathy may be more prominent and levodopa-responsive parkinsonism is more frequent.[20] It can also cause adducted thumbs, an unusual sign seen in cases of *SPG1*, an X-linked HSP also known as mental retardation, aphasia, shuffling gait, and adducted thumbs (MASA) syndrome.[7,21]

SPG7 (Paraplegin) presents later than other HSPs, with a mean age of onset of 41·7 years,[4,22] and appears to be more common in males.[23] It usually manifests with a combination of lower limb spasticity, which can be relatively mild, and cerebellar ataxia.[24] Cerebellar signs were seen in 57-90% and dysarthria in 37-76% of cases at presentation in the two largest cohorts of 42 and 49 patients from England and the Netherlands, respectively.[23,25] A waddling gait associated with proximal myopathic weakness is also common and progressive external ophthalmoplegia (PEO) is also seen, and can be a useful diagnostic clue.[26] These features reflect underlying mitochondrial dysfunction that can be confirmed on muscle biopsy.[27,28] Visual loss due to optic neuropathy is a rare presentation of *SPG7*,[25] but subclinical abnormalities in ocular coherence tomography (OCT) were identified in all cases from one French cohort of 10 patients.[22]

SPG7 was previously considered to be a rare autosomal-recessive HSP,[29] however, the carrier frequency of the Ala510Val mutation, which is suspected to be pathogenic, was recently predicted to be as high as 3-4% in the UK population.[30–32] This raises the possibility of reduced penetrance in individuals who are homozygous for this mutation, which has been suggested to act as a hypomorphic allele. Autosomal dominant inheritance has also been reported in several families.[22] In at least one case this was related to a segregating third allele, i.e. pseudo-dominant inheritance, however some relatives with a single heterozygous Ala5210Val mutation in these families also developed a late-onset and relatively mild cerebellar ataxia, although it is possible that an alternative genetic diagnosis was present in these cases.[22,25,33] Perhaps some caution is therefore advised when providing genetic counselling, but in view of the high prevalence of Ala510Val, it seems very unlikely that heterozygous carriers of the mutation are at significantly increased risk of a neurological condition.

SPG5 (CYP7B1) is an autosomal-recessive HSP that is relatively rare in most cohorts but made up 28 of 101 autosomal-recessive cases in a large Chinese cohort of 531 patients[4,5,7,34,35] An international cohort of 34, predominantly European, patients was described by Schols and colleagues.[36] The median age of onset was 13 years with range 1 to 33 years. Dorsal column dysfunction was seen in 32 cases (94%) and was unusually severe, 16 patients (47%) presenting with a sensory ataxia in the lower limbs. Urinary symptoms were also prominent

and five patients (15%) also reported rectal urgency or incontinence. Cognitive impairment does not appear to be a prominent feature.[4,36]

Diagnosis

The identification of pathogenic mutations in an *SPG*-designated gene is required to confirm a molecular diagnosis of HSP. However, the clinical priority should always be to exclude acquired causes for progressive spastic paraparesis in the first instance. This includes a range of structural, inflammatory, and infectious aetiologies, in addition to amyotrophic or primary lateral sclerosis, arteriovenous fistulas, vitamin B12, and copper deficiency (table 1). Assessment of very long chain fatty acids (VLCFAs) should be considered in any family in which there is no documented male to male transmission of the disease to exclude adrenoleukodystrophy. A detailed developmental and family history may provide important clues to a diagnosis of HSP whereas acute or subacute deterioration suggests acquired causes.

Neuroimaging

Magnetic resonance imaging (MRI) of the spinal cord is normal or shows thinning of the spinal cord for the vast majority of *SPG* types,[37] with the notable exception of *SPG2* (PLP1), a rare X-linked HSP and variant of Pelizaeus-Merzbacher disease, which may be associated with a diffuse pattern of hypomyelination.[38] T2-weighted hyperintensities in the spinal cord should prompt careful re-consideration of acquired causes. Other rare genetic and metabolic causes associated with T2-weighted abnormalities in the spinal cord were recently reviewed by Marelli and colleagues.[39]

MRI of the brain can help differentiate *SPG* types, although there are very few pathognomonic changes. Cerebellar atrophy is seen in 39-95% of *SPG7* cases, mostly as mild atrophy of the cerebellar vermis (figure 1),[23,25] however this has also been reported other rarer HSPs. The dentate nucleus, which is usually hypointense on T2-weighted imaging, appeared isointense or hyperintense relative to pontine white matter in 86% of cases in a recent series of 42 patients with *SPG7,* and may be a more specific finding.[23] Thinning of the corpus callosum and periventricular white matter hyperintensities are seen in nearly all cases of *SPG11* and *SP15* (figure 1), as well as in other rarer subtypes of complex HSP.[20] The 'Ears of the lynx' sign, corresponding to a specific pattern of T2-weighted hyperintensities at the anterior forceps of the corpus callosum, is associated with *SPG11* and *SPG15*.[40] Non-specific white matter lesions are also seen in up to 50% of complex *SPG5* cases.[34] We recommend interpretation by a neuroradiologist with expertise in leukodystrophy if white matter abnormalities of uncertain significance are identified.

Neurophysiology

Neurophysiological findings were systematically studied in an Italian cohort of 70 HSP patients (the majority *SPG4* and *SPG11)* by Martinuzzi and colleagues.[41] Central motor conduction times (CMCTs) were absent or delayed in the lower limbs in 31 of 32 cases. The patient with normal CMCTs had an *SPG4* mutation with a very mild phenotype. CMCTs were abnormal in the upper limbs in 14 of the 31 cases with abnormal lower limb studies. Somatosensory evoked potentials (SSEPs) were abnormal in 30 of 44 patients. Electromyography (EMG) and nerve conductions studies (NCS) identified distal axonal motor neuropathy and associated neurogenic changes in 23 of 49 patients with HSP. This included the majority of *SPG7*, *SPG11* and *SPG15* cases and some *SPG3A*, *SPG4*, and *SPG5* cases. A recent neurophysiological study of *SPG31* HSP identified at least one focal mononeuropathy in all eight cases, including features of carpal tunnel syndrome in seven cases (13 of 16 hands), and one case of multifocal compression neuropathy, suggesting a peripheral predisposition to pressure palsies.[42] Abnormalities in neurophysiological testing are therefore common in HSP but do not appear to be specific to subtypes, with the exception of focal mononeuropathy, particularly of the upper limb, which appears to be common in *SPG31* cases.

Genetic testing

Several different approaches to genetic testing for HSP may be employed.[16,43] Next generation sequencing-based gene panels for HSP are increasingly cost-efficient and now widely available. They are most commonly used to screen the exons of a large number of genes associated with HSP but have their limitations; they will generally not identify copy number variants (i.e. large deletions or duplications, including exon deletions), mutations in promotor or deep intronic regions, and triplet repeat disorders.[44] This is a particular problem for *SPG4,* where exon deletions are relatively common. Multiplex ligation-dependent probe amplification is recommended for this gene if sequencing approaches give normal results.[45] Some centres currently use first generation sequencing

methods in a small number of targeted genes for initial genetic testing and consider next generation sequencing-based gene panel if results are inconclusive. We propose that the diagnostic algorithm in figure 2 may be particularly helpful in this scenario.

Clinicians also need to be aware that several other groups of monogenic diseases can present with slowly progressive lower limb spasticity without spinal cord imaging abnormalities and are not represented in the *SPG* classification. They may not be comprehensively covered by some next-generation sequencing panels and include the spinocerebellar ataxias, autosomal recessive ataxias, spastic ataxias, demyelinating and hypomyelinating leukodystrophies, and other rare metabolic and neurodegenerative disorders (table 2).[46–53] Several of the diseases in these groups, such as SCA1 (ATXN1), SCA3 (ATXN3), and Friedreich's ataxia (FXN) are triplet repeat disorders and may not therefore be covered by gene panels, even if they are extended to include wider groups of monogenic diseases associated with spasticity.[54–56]

Particular attention should however be given to atypical presentations of treatable diseases in which lower limb spasticity occurs, often in the context of other clinical features, in the absence of T2-weighted imaging abnormalities in the spinal cord. These include adrenoleukodystophy (ABCD1),[57] arginase deficiency (ARG1),[58] cerebrotendinous xanthomatosis (CYP27A1),[59] dopa-responsive dystonia (GCH1, TH, and other genes),[60] phenylketonuria (PAH),[61] biotinidase deficiency (BTD),[62] cobalamin-related remethylation disorders,[63] methylenetetrahydrofolate reductase deficiency (MTHFR),[64] and primary coenzyme Q10 deficiencies.[65]

Disease progression and prognosis

There is limited data on the prognosis for individual *SPG* types, except that *SPG11* is associated with a higher disease severity, as determined by the Spastic Paraparesis Rating Scale (SPRS), relative to other HSPs.[4] Disease progression in HSPs overall is usually slow although a later onset is associated with earlier loss of independent walking. The average rate of disease progression was observed to be slower for *SPG3A* than *SPG4* cases in one cohort, but there was no difference when comparing cases with onset before 20 years.[8] In the largest retrospective cohort, the median disease duration until loss of independent walking was 22 years.[4] This German cohort of 608 patients included 198 (33%) *SPG4*, 28 (5%) *SPG7* and 15 (2%) *SPG11* cases, among numerous rarer *SPG* types. After a disease duration of 20 years, 48% used a walking aid and 12% used a wheelchair. After a disease duration of 40 years, 72% used a walking aid and 29% used a wheelchair.[4]

Management of HSP

This section will discuss the current symptomatic therapies available and evidence supporting their use, and then consider potential future opportunities using a personalized medicine approach to some of the common forms of HSP discussed above.

Symptomatic treatment

The ideal approach is in a multidisciplinary spasticity clinic where the stiffness, cramps, spasms, and deformities can be addressed. An exercise programme supervised by neurophysiotherapists, focused initially on stretches, and later balance, is optimal. Use of orthotics such as ankle-foot orthoses and heel raises are also valuable for mobility.

Oral antispasmodics including baclofen and tizanidine have an established role, although the majority of patients do not gain significant benefit. Gabapentin has been used for spasticity in multiple sclerosis and spinal cord injury, but a double blind crossover trial in a small cohort of *SPG4* HSP cases found no difference in effect from placebo.[66] An open label trial of dalfampridine (4-aminopyridine) in a mixed cohort of HSP (*SPG4, SPG7, SPG11)* over 2 weeks, suggested some benefit and deserves more rigorous testing.[67] With more severe spasticity intrathecal baclofen can be effective in reducing very high tone and associated pain and disability. It is often used for patients requiring wheelchairs, but also has been shown to improve gait if used earlier.[68]

Botulinum toxin injections can be helpful for targeting specific problematic muscle groups around the ankle, knee, and hip. One trial enrolled patients with *SPG4, SPG3A* and *SPG8* and studied the combination of injections into the calf and stretching exercises, showing this improved gait velocity, reduced muscle tone, whilst preserving strength and balance.[69]

Functional electrical stimulation (FES) may improve gait disturbance in HSP patients. In a small crossover study 11 patients with spastic paraparesis from the UK, including six participants with a positive family history, bilateral

common peroneal stimulation or another preferred pattern of stimulation (hip abductors, lumbar extensor muscles or the flexor withdrawal reflex) improved toe clearance and dorsiflexion in the swing phase and significantly improved walking speed.[70] The use of transcutaneous direct current spinal stimulation (tcDCS) has also been shown to have a positive effect on spasticity in a recent crossover study with 11 HSP patients from Italy, although tcDCS did not affect a walking test.[71]

The value of the MDT approach to HSP patients was shown in a recent publication that found that detailed clinical information and profiling, associated with combined therapies with oral medication and botulinum toxin, plus physiotherapy improved patients' gait and reduced falls.[72]

The complexity of the problems with gait has been highlighted by a study of 29 patients (mainly *SPG4*, but also *SPG3A, SPG5, SPG7,* and *SPG31*) and 30 controls with kinematics and EMG of 12 leg muscles whilst walking. The findings showed that degeneration of corticospinal tracts in HSP was associated with widening of spinal locomotor output to muscles spreading from caudal to rostral segments, starting in sacral region.[73] This evolving process may be one reason why antispasmodic medication is not as efficacious compared to an acute inflammatory or traumatic spinal event. It may require a more targeted approach, such as retraining other pathways including the reticulospinal tract,[74] or robotic gait training for HSP patients which has shown benefit to both balance and walking.[75] [72]

Whilst most attention has focused on managing the spasticity and gait, there has been little consideration of other symptoms, especially urinary. A recent study of 71 HSP patients from Germany, including 34 *SPG4* cases, highlighted this need using validated rating scales. One or more urinary symptoms were seen in 53 patients (75%), incontinence was higher in women, and females and *SPG4* mutation carriers were associated with worse symptoms.[76] Over one third of patients had received no treatment for their urinary problems. These urinary problems can often be considerably improved by oxybutynin or equivalent drugs, after exclusion of urinary tract infection and ensuring that there is not significantly increased post-micturition residual volume of urine.

Genotype specific therapies

The significant genetic and clinical heterogeneity of HSP reflects a variety of pathogenic mechanisms that underlie the slow terminal axonal degeneration. While these processes may eventually resolve into a few pathogenic pathways, at present the cellular processes implicated in the axonopathy include membrane trafficking, mitochondrial function, organelle biogenesis and shaping, axonal transport, and lipid/cholesterol metabolism, and these have recently been comprehensively reviewed.[12]

Whilst a number of genetic neurological disorders, such as Huntington's disease and spinal muscular atrophy have seen dramatic advances in bespoke genotype targeted therapy, the same is not true for HSP. This may relate to the relative rarity of specific HSP genetic subtypes, extensive genetic heterogeneity and consequent mechanistic diversity, and slowly progressive clinical course of most cases. However, there has been increasing research investigating specific treatments for genetic HSP subtypes, including those attempting to address pathophysiological mechanisms, and gene therapy. The following sections summarise the molecular pathogenesis and potential therapeutic targets for the common HSP subtypes highlighted in this review.

Mechanistic approaches to therapy

SPG4 HSP

The *SPAST (SPG4)* gene encodes spastin, a member of the ATPases associated with diverse cellular activities (AAA) protein family. Spastin is involved in microtubule severing and regulating microtubule dynamics.[77] Reduced levels of spastin in cell models are associated with lower numbers of dynamic microtubules and increased stable acetylated microtubules.[78] Spastin is believed to control a range of microtubule dependent processes including axonal transport, endosomal recycling, lysosomal function, cytokinesis, and endoplasmic reticulum shaping. It has two cellular isoforms, full length (M1), and the smaller M87 isoform, generated by a complex transcriptional mechanism. All forms of spastin possess a microtubule interacting and trafficking (MIT) domain that binds ESCRT proteins, which play a role in the recognition and sorting of ubiquitin–conjugated proteins into internal vesicles of the late endosome, a critical process for receptor degradation in lysosomes.[79] The MIT domain is also involved in recruitment of spastin to endosomes and, during cell division, cytokinetic midbodies. In addition, spastin regulates axonal and synaptic growth, and neurite branching,[80,81] and recently spastin variants have been implicated in defective BMP and neuropilin 1 signalling affecting motor axon navigation.[82] Finally,

spastin is involved in regulating axonal transport of receptors, vesicles and organelles including mitochondria which can be found in axonal swelling in models of *SPG4* HSP.[83]

An unbiased approach using null SPAST homologues in *C.* elegans, drosophila and zebrafish to identify drugs that could rescue the HSP phenotype, screening with compounds known to modulate endoplasmic reticulum (ER) stress, has been performed.[84] Locomotor defects and lifespan in all three models could be partially rescued by phenazine, methylene blue, N-acetyl-cysteine, guanabenz, and salubrinal, and markers of ER stress levels correlated with improved locomotor activity. Future work is needed in mammalian models to assess relevance, but the use of FDA-approved compounds in this study holds the promise of rapid translation to human therapy if further work yields positive results.

The role of spastin in microtubule stability has also been investigated in drosophila, as well as neurons derived from human induced pluripotent and olfactory stem cells. This work showed that microtubule destabilizing drugs including vinblastine attenuated the mutant spastin-associated phenotype, demonstrating the potential for mechanistic targeting.[85,86] Furthermore, use of vinblastine and nocodazole rescued focal axonal swellings associated with impaired axonal transport in cortical neurons from spastin knockout mice.[87]

It is widely believed that *SPG4* HSP is, in most cases, mediated by haploinsufficiency and partial loss of function in microtubule severing. If true, this opens the possibility of gene therapy to rescue the loss of function. One study in neurons derived from human induced plutipotent stem cells from a patient with a spastin nonsense mutation found that overexpression of the M1 or M87 spastin isoforms, restored neurite length, branching, numbers of primary neurites and reduced swellings in neuronal cells.[88] However, this work has not been pursued further in animal models. This approach may, of course, not be the best therapeutic strategy in the case of a subset of spastin missense mutations, where dominant-negative or (perhaps less likely) gain of function mechanisms may contribute to their pathogenesis.[13]

SPG5 HSP

Potentially, one of the most treatable forms of HSP is *SPG5* HSP. This autosomal recessive form of HSP caused by mutations in the gene *CYP7B1* encoding oxysterol-7α-hydroxylase, which is involved in the degradation of cholesterol into primary bile acids and leads to accumulation of neurotoxic oxysterols.[36] The metabolic defect can be detected by increased concentrations of 25- and 27-hydroxycholesterol (25- and 27-OHC) in the plasma and cerebrospinal fluid (CSF). Treatment with cholesterol lowering drugs (atorvastatin) reduced the concentration of plasma 27-OHC.[36,89] Another study also detected abnormal bile acids profile in *SPG5* patients, which could be corrected by chenodeoxycholic acid, and suggested that combination therapy with atorvastatin and chenodeoxycholic acid might be beneficial.[90] Long term trials are required to determine whether these strategies improve clinical outcomes.

SPG3A & SPG31 HSP

SPG3A encodes atlastin-1, an integral membrane, ER-localised GTPase, enriched in the CNS,[91] which is involved in the fusion of ER tubules to form polygonal ER network. Numerous HSP proteins localise to the tubular ER and interact with each other to help create and regulate the tubular ER network, including M1 spastin, atlastin-1, REEP-1, and others. Mutations in the genes encoding these proteins can disrupt correct ER morphology, and have been proposed to cause axonopathy by altering the function of axonal ER[92–94] Perhaps related to these ER phenotypes, abnormalities in lipid droplets, which form at the ER, have been reported in REEP-1 null mice and atlastin models.[95,96] Finally, a potential therapeutic effect of MT destabilising drugs vinblastine and taxol was demonstrated in rescue of axon growth defects in neurons derived from patient iPSC with atlastin mutation.[97]

SPG7 HSP

The protein product of the *SPG7* gene is paraplegin, a metalloprotease of the inner mitochondrial membrane. Oxidative phosphorylation defects in muscle from patients have been demonstrated, and *SPG7* null mice have mitochondrial filled axonal swellings, linking transport to mitochondrial function.[28,98] Paraplegin is also an essential component of the mitochondrial permeability transition pore,[99] and a variant which escapes normal processing leads to higher ATP and reactive oxygen species production. This variant is also associated with non-neurological disease including type 2 diabetes, coronary artery disease, and toxicity of chemotherapeutic agents.[100] This loss of function mitochondrial disorder can affect central and peripheral neurons, and one study using AAV-mediated intramuscular delivery of paraplegin in a mouse model halted progression of neuropathology and rescued mitochondrial morphology in peripheral nerves.[101]

SPG11 & SPG15 HSP

The clinical similarity between *SPG11* and *15* HSP reflects a common underlying pathogenetic mechanism. Both of the encoded proteins, spatacsin and spastizin, interact with the AP5 vesicle adapter complex.[102] They both affect cellular autophagic processes, in particular autophagic lysosome reformation, a pathway that generates new lysosomes in the cell. Spatacsin loss of function appears to produce lysosome depletion through abnormal lysosomal lipid clearance,[103,104] which affects initiation of lysosomal tubulation.[105] Loss of function of spastizin has been recently found to affect processes involving the intersection between endocytosis and autophagy.[106]

One recent study attempted to target the pathogenesis of *SPG11* based on work using iPSC-derived neural precursor cells (NPC). Reduced NPC proliferation in *SPG11* was found to be mediated by increased GSK3β activity followed by impaired β-catanin signaling.[107] Pozner and colleagues tested the GSK3β inhibitor tideglusib on neuronal lines from *SPG11* patient iPSC and gene edited lines.[108] This treatment rescued neuritic pathology in the cells, as well as decreasing cell death, suggesting tideglusib (or similar molecules) as a candidate for further translational work.

Conclusions and future directions

HSP is a phenotypically and genotypically diverse group of monogenic diseases with emerging opportunities to provide targeted molecular therapies and personalised medicine. The advances in molecular biology over the last 20 years have benefitted diagnosis and gene identification for numerous HSP subtypes. The rapid increase in known causal genes has led to identification of a large number of potential mechanisms for axonal degeneration. This heterogeneity has meant identifying tractable generic therapeutic targets for HSP is challenging.

The field is also hampered by the fact that, despite being a disabling group of motor neuron disease, in most cases progression is slow. A clinical trial of a disease-modifying agent would be difficult to envisage for many forms as there are few biomarkers that would change over a reasonable period of time. Therefore, effort should be focused on exemplar HSP genotypes where work could be used to identify biomarkers (rating scales, blood and CSF) which are sensitive to change. One example of this is the Pre-*SPG4* study in Germany looking at the longitudinal course and biomarkers in pre-symptomatic *SPG4* mutation carriers (ClinicalTrials.gov NCT03206190).

Choosing subtypes amenable to therapy, such as *SPG5,* where a biochemical approach may benefit, are important. For developing gene therapy the more common recessive forms *SPG11*, *SPG15* and *SPG7*, where there is clear loss of function, also offer opportunities for targeted gene replacement or editing. It would be advantageous for international groups to pool resources into these areas and develop trial ready cohorts to take advantage of progress in gene therapy or other therapeutic areas. Such efforts are beginning.

The next years will, no doubt, see the identification of yet more HSP loci. However, we also hope that they will bring the beginning of rationally-designed therapeutic approaches for HSP.

Search strategy and selection criteria

References for this Review were identified by searches of PubMed between August, 2008 and October, 2018 and references from relevant articles. The search terms “hereditary spastic paraplegia”, “hereditary spastic paraparesis”, “SPG3”, “SPG3A”, “SPG4”, “SPG7”, “SPG11”, “SPG15”, and “SPG31” were used. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this review.

Contributors

SS and TTW performed the literature searches and drafted the manuscript. SS designed the figures and tables with input from HH. All authors commented on and revised the final manuscript.

Declarations of Interests

SS, AHC, HH and TTW declare no conflicts of interest. ER has received funding from Takeda for HSP-related research.

Acknowledgements

We wish to thank all the clinicians, scientists, and families that have contributed to research on HSP in the aforementioned studies.

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Figure legends

Figure 1 Brain imaging in patients with *SPG7* and *SPG15* HSP. A T1 sagittal image (A) showing cerebellar atrophy in a patient with *SPG7* HSP. T2 axial (B) and FLAIR axial (D) images showing white matter hyperintensities and a T1 sagittal image (B) showing a thin corpus callosum in a patient with *SPG15* HSP. The same abnormalities are seen in *SPG11* HSP.

Figure 2. Diagnostic algorithm for the more common HSPs combining the inheritance pattern and additional clinical features with associated brain imaging abnormalities at presentation. We propose that this approach can be applied where single gene testing is required as a prelude to full panel or genome sequencing, or, where panel sequencing has given normal results and the clinician needs to identify which genes should be tested for copy number variants, for example by multiple ligation-dependent probe amplification. This algorithm may also be helpful in situations where mutations of uncertain significance are identified through whole exome sequencing and require correlation with phenotype.