Hereditary Spastic Paraplegia

Hereditary spastic paraplegia (HSP) is a group of clinically and genetically heterogeneous conditions, with prevalence of 10 cases per 100,000 population. The key diagnostic clinical findings are of lower limb spasticity and pyramidal weakness, hyperreflexia and extensor planter responses. HSP can be divided into uncomplicated (pure) or complicated HSP depending on the presence of other neurological features in addition to spastic paraparesis. Even amongst individuals categorised as having uncomplicated HSP, mild sensory abnormalities of the lower limbs (e.g. reduced vibration sense), urinary symptoms, pes cavus, and mild to moderate cognitive decline are recognised. However, cranial nerves are almost never involved in HSP.

Complicated HSP comprises a large number of conditions in which spasticity is accompanied by other features including muscle wasting (amytrophy), optic atrophy, pigmentary retinopathy, mental retardation, extrapyramidal disease, ataxia, dementia, deafness, ichthyosis, peripheral neuropathy and epilepsy. Perhaps unsurprisingly, this has led to overlap in classification schemes, leading to rather confusing dual classification: hereditary motor neuronopathy with spasticity (HMN type V) and SPG17 (HSP with distal amyotrophy) describe the same condition. Complicated forms of HSP are usually autosomal recessive and rare.

Clinical features

HSP has onset from early childhood onwards, with insidious development of leg stiffness and/or abnormal wear of the shoes. There often appears to be relative preservation of power despite dramatically increased tone in the legs. Important clues to the cause of spastic paraplegia are age and nature of onset, progression of symptoms, family history and presence of other clinical features. It is helpful to ask about athletic ability in childhood, as poor performance or lack of interest in sport may indicate a longstanding motor disability. There is a high incidence of urinary symptoms in HSP, reported in <40% of cases, but is rarely marked in early disease.

The differential diagnoses according to age of onset are listed in Table 1. Spastic paraplegia developing over the age of 20 years is a relatively frequent clinical problem in neurological practice. It is likely that a significant proportion of cases of undiagnosed paraplegia are of genetic origin and detailed family investigations are critical, and sometimes leads to identification of an asymptomatic affected individual. The presence of a slowly progressive gait disorder with few sensory symptoms and signs favours HSP. Sudden onset of spasticity favours a vascular, inflammatory or mechanical cause, and in these cases there is frequently more marked weakness, sensory signs, and spinal or referred pain.

A family history compatible with autosomal dominant transmission in the context of adult onset spastic paraplegia, is almost always due to HSP. However, HSP can show autosomal dominant, recessive and X-linked inheritance. For the apparently sporadic case of spastic paraplegia, HSP is a diagnosis of exclusion (see Table 1).

Investigations

The diagnosis of pure HSP in a family in which several members have typical clinical features presents few difficulties. For an isolated case with young adult onset, MRI scanning of brain, cervical and thoracic cord is important to exclude the main differential diagnoses. In HSP, the most common MRI abnormality is of thinning of the cervical and thoracic spinal cord. Studies in dominant HSP kindreds have also suggested that there is loss of volume of the corpus callosum and a higher incidence of cerebral white matter lesions. In most cases of pure HSP, nerve conduction studies and EMG are normal, but central motor conduction times can be delayed or unrecordable from the lower limbs, and lower limb somatosensory evoked potentials small. Blood investigations (vitamin B12, very long chain fatty acids, serology where appropriate) may be required. CSF analysis is usually normal in HSP. The mapping and cloning of HSP genes has led to specific molecular genetic tests which will allow more focused investigation of potential cases of HSP.

Genetic subtypes of HSP

HSP can be inherited as an autosomal dominant, recessive or X-linked recessive trait and currently 33 SPG loci have been mapped. Autosomal dominant HSP is the most prevalent form and represents around 70% of cases. Most cases of pure HSP are autosomal dominant, whilst complicated forms tend to be autosomal recessive. The more common genetic forms are considered below:

Autosomal dominant HSP (AD-HSP)

SPG4 HSP: The locus on chromosome 2p22-p23 (SPG4) is the most important and accounts for around 45% of AD-HSP kindreds. The gene encodes the protein spastin and has 17 exons spanning about 90kb. Most pedigrees with spastin mutations have pure HSP, with onset from childhood to old age (typical age of onset 26-35 years). SPG4 HSP cannot be reliably differentiated from other forms of AD-HSP by clinical features alone. Cognitive impairment, dementia and epilepsy have been reported in some families. The severity and age of onset can vary markedly, even within one family, suggesting the effect of modifying genes or environmental factors.

The function of spastin is unknown, but it is a member of a group of proteins known as the ATPases Associated with diverse cellular Activities (AAA). These AAA proteins act in various cellular functions, including cell cycle regulation, protein degradation, organelle biogenesis and vesicle mediated protein function. Mutations within the spastin gene that have been identified include missense, nonsense and frame shift mutations, and in some pedigrees, duplications and deletions.

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Table 1: Differential diagnoses for childhood and adult onset spastic paraplegia

<table>
<thead>
<tr>
<th>Childhood Onset:</th>
<th>Adult Onset:</th>
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<tbody>
<tr>
<td>Diplegic cerebral palsy</td>
<td>Cervical spine degenerative disease</td>
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<tr>
<td>Structural: Chiari malformation, atlanto-axial subluxation</td>
<td>Multiple sclerosis</td>
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<tr>
<td>Hereditary spastic paraplegia</td>
<td>Motor neurone disease</td>
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<tr>
<td>Leukodystrophy: e.g Krabbe’s</td>
<td>Neoplasm: primary/secondary tumour, parasagittal meningioma</td>
</tr>
<tr>
<td>Metabolic: arginase deficiency, abetalipoproteinemia</td>
<td>Dural arteriovenous malformation</td>
</tr>
<tr>
<td>Dopa-responsive dystonia</td>
<td>Chiari malformation</td>
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<tr>
<td>Infection: myelitis</td>
<td>Adrenoleukodystrophy</td>
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<tr>
<td></td>
<td>Hereditary spastic paraplegia</td>
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<tr>
<td></td>
<td>Spinocerebellar ataxias</td>
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<td></td>
<td>Vitamin deficiency: B12 and E</td>
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<td></td>
<td>Lathyrism</td>
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<td></td>
<td>Dopa-responsive dystonia</td>
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<td></td>
<td>Infection: syphils, HTLV, HIV</td>
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splice site mutations in various exons which usually lead to major amino acid sequence changes in the AAA domain or truncation of the protein. Deletions have become increasingly recognised. This implies that there is a loss of function and a threshold level of spastin required to maintain axonal integrity, although there is also evidence for a dominant negative effect.

Other forms of AD-HSP

The SPG3A gene on chromosome 14q11.2-q24.3 encodes the protein atlastin, in which a number of missense mutations have been identified.1 The phenotype is of pure HSP with childhood onset (usually < 10 years of age) and a relatively benign course, such that most affected individuals remain ambulant. It has been estimated to cause 10% of AD-HSP. A small proportion of families with uncomplicated AD-HSP are caused by mutations in the SPG6 and SPG10 genes, which encode the proteins NIPA1 and neuronal kinesin heavy chain (KIF5A), respectively. Complicated forms of AD-HSP are all rare. SPG17 (Silver syndrome) describes HSP plus intellectual disability by atrophy of the small muscles of the hands and feet with onset usually in the second to fourth decades. Mutations were identified in the BSCL2 gene on chromosome 11q12-q14 and can also cause HMN type V.2

Autosomal recessive HSP (AR-HSP)

AR-HSP is rarer than AD-HSP, many of the genetic loci relate to single consanguineous families. The more common forms are:
- SPG3A: This locus on chromosome 8p12-q13 causes pure HSP with onset in first two decades.
- SPG7: Mutations in SPG7 gene leads to a complicated form of AR-HSP with additional neurological features of ataxia, dystrophy, optic disc pallor, axonal neuropathy. Onset is between 20 and 40 years of age, leading to progressive disability. The gene encodes paraplegin, a mitochondrial ATPase protein.3 Studies suggest that SPG7 HSP accounts for <10% of AR-HSP.4
- SPG11: Mapped to chromosome 15q13-q15, this locus cause a characteristic phenotype with onset in first two decades associated with mental retardation and agenesis of the corpus callosum.5
- SPG15: Another characteristic (Kjellin) syndrome maps to chromosome 14q22-q24 and the HSP is associated with a retinal degeneration and mental retardation.6

X-linked HSP

X-linked recessive HSP is very rare, although SPG1 and SPG2 were the first HSP genes cloned. SPG1 encodes the L1 cell adhesion molecule (L1CAM) and mutations cause a complicated form of HSP with mental retardation and absence of the extensor pollicis muscle.7 SPG2 mutations are within the proteolipidoprotein gene and can cause both pure and complicated forms of HSP. Mutations (usually duplications) of this gene also give rise to the dysmyelinating condition Pelizaeus-Merzbacher disease (PMD), which is characterised by congenital hypotonia, psychomotor deterioration and progressive pyramidal, dystonic and cerebellar signs.8

Pathophysiology

The main neuropathological finding in HSP is axonal degeneration of the terminal portions of the long descending (corticospinal) tracts and ascending (dorsal columns) pathways in the spinal cord. There have also been reports of degeneration of spinocerebellar tracts and loss of Betz cells in motor cortex layer V. Any pathophysiological mechanism must explain why the brunt of the disease falls upon the longest neurons in the spinal cord. The current hypothesis is that the different mutant proteins disrupt axonal transport of macromolecules and organelles, which selectively affects the distal axon.9 This view has come from study of a number of genes, in particular SPG4. Spastin (SPG4) appears to play a key role in the dynamics of microtubule turnover, which make up the intracellular cytoskeleton, and along which axonal transport occurs.10,11 Wild type spastin can sever microtubules, a property lost in mutant forms, and recent studies suggest this leads to excessive amounts of stabilised MTs occurring distally in terminal axons leading to altered distribution of organelles and other axonal cargoes.12,13 A tantalising finding was that, in a Drosophila model of SPG4 HSP, the abnormal phenotype and pathological changes were ameliorated by vinblastine, a drug which destabilises microtubules.14

Atlastin (SPG3A) is a dynamin expressed in the Golgi, and may be involved in vesicular transport. Recent evidence suggests its pathogenic effect is mediated by an interaction with spastin.15,16 Transgenic mouse models of other forms of HSP, including mutant paraplegin (SPG7) and proteolipidoprotein (SPG15) also appear to disrupt axonal transport.

Management and testing

There is no disease modifying therapy currently available for HSP. Physiotherapy is important to maximise function and prevent complications such as contractures. Anti-spasticity drugs such as baclofen, tizanidine, and to a lesser extent diazepam and dantrolene, can be helpful, as can botulinum toxin injections into specific muscles. Footdrop can be helped by orthoses. Occasionally surgery is required to release contractures or tendons. Early referral to continence advisory clinics is helpful to deal with urinary problems.

In appropriate circumstances, and with adequate counselling, molecular genetic testing can be performed and prevent extensive investigations. Testing is available for SPG4 (spastin), SPG3A (atlastin) and SPG6 (NIPA1) for families with pure AD-HSP. Other testing (e.g SPG7 and SPG17) may be available on a research basis. Testing for mutations in spastin (SPG4) should also be considered in cases of sporadic progressive spastic paraplegia where no cause has been identified, as mutations have been detected in <10% of apparently sporadic cases of pure HSP.

Summary

The HSPs are a heterogeneous group of degenerative disorders with a common pathogenetic theme of abnormalities of axonal transport leading to axonal dying back of long spinal neurons. Greater understanding their aetiology will shed light on the function of these long spinal neurons in both health and disease.

References