Current insights into familial spastic paraparesis: new advances in an old disease

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Accepted for publication: February 14, 2003

Summary

Hereditary spastic paraparesis (HSP) comprises a clinically and genetically heterogeneous group of disorders characterized by progressive spasticity and hyperreflexia of the lower limbs. The past few years have witnessed an exponential increase in knowledge of this disease and we can now list 19 loci mapped on the human genome and eight genes cloned. However, this wider knowledge of the molecular basis of HSP has had limited impact on clinical practice: the use of antispastic drugs and regular physiotherapy still remain crucial in the therapeutic management of patients. Nonetheless, the identification of new genes mutated in HSP furthers comprehension of the pathomechanisms involved and helps in genetic counseling, especially of asymptomatic individuals who request molecular analyses.

KEY WORDS: Autosomal dominant, autosomal recessive and X-linked inheritance, hereditary spastic paraparesis, defective trafficking.

Introduction

The term hereditary spastic paraparesis (HSP) (or Strümpell-Lorrain syndrome) is used to describe a group of inherited disorders of which slowly progressive spastic paraparesis is the pivotal clinical hallmark. Before the advent of molecular genetic studies, classifications were based on clinical features only, such as the age at onset, and the presence of additional, non neurological signs, as well as on the mode of inheritance. In the past few years, we have witnessed an exponential increase in knowledge of this disease and we can now list 19 HSP loci mapped on the human genome and eight genes cloned. This research has stimulated a better understanding of several different aspects of the biology of corticospinal axons, revealing distinct, possibly interconnected, pathways relevant to the pathogenesis of HSP. All this makes HSP one of the most rapidly expanding fields of neurogenetics.

In this review, we will present recent genetic advances in the different forms of HSP and focus on recent knowledge of the different gene functions.

Classification

During the 120 years since the initial description by Strümpell and Lorrain (1,2), a number of different clinical forms of HSP have been described. However, only 20 years ago an initial nosographic approach was undertaken with the classification into “pure” and “complicated” forms (3). Pure forms present with signs of isolated or prevalent pyramidal tract involvement such as brisk reflexes, Babinski sign, spasticity, and motor deficits in the lower limbs. Additional, though not obligatory, features are pes cavus, deep sensory impairment, sphincter disturbances and sometimes upper limb dysmetria. Complicated forms also manifest extraneurological clinical features including epilepsy, peripheral neuropathy, and mental retardation. Further, pure HSP is also subdivided into type I, with onset before age 35 years, and type II, when onset is after 35 years of age. Type I patients usually have a slower and more variable clinical course than the rapidly evolving type II patients. However, many families do not easily fit strict diagnostic criteria and only the advent of molecular genetics has allowed a more useful and complete classification.

Epidemiology

The prevalence of HSP is difficult to establish. It is estimated at 1.5-2.7x10^5 when strict clinical criteria are adopted, with variations between countries often depending on
the method of ascertainment used. Pure autosomal dominant HSPs are certainly the most frequent forms in northern Europe, whereas autosomal recessive complicated forms are more easily observed in southern Europe (4,5).

Clinical presentation

The prognosis and severity of HSP varies between and within families, but life expectancy is normal. Importantly, about 30% of patients are asymptomatic, emphasizing the often benign nature of the disease and the need for careful clinical evaluation of families included in genetic studies. A recent review (6) has proposed useful inclusion criteria for pure HSP, distinguishing between obligatory criteria such as a positive family history, progressive gait disturbance, spasticity and hyperreflexia of lower limbs, and extensor plantar responses, and common diagnostic criteria such as sphincter disturbances, pes cavus, hyperreflexia of upper limbs, and mild terminal dystymetria. Uncommon features include paresis of upper limbs and distal amyotrophy. Difficulties in walking or gait disturbances are present in most patients. A delay in walking is frequent in childhood. Sensory involvement, comprising diminished vibration sense and impaired joint position sense in the extremities of the lower limb, seems to be present in 10-65% of patients with the pure form, more commonly in those with a long disease duration. Urinary sphincter disturbances occur in up to 50% of patients, more commonly in those with a long-standing disease, and are usually described as a combination of urgency, hesitancy and frequency. Interestingly, cranial nerves and corticobulbar tracts are never involved. In complicated HSP, the spastic paraparesis is only one component of a much more variable phenotype. The interfamilial variation is however marked. Many conditions have been associated with HSP, including optic atrophy, retinopathy, extrapyramidal disease, ataxia, deafness, and ichthyosis. Myoclonic seizures but also partial or generalized epilepsies have been reported in association with HSP. Mental retardation or early cognitive impairment have been described in these families (7,8). Peripheral nerve involvement is well documented in families with HSP. Nerve biopsy usually showed decreased numbers of large and medium-sized myelinated fibers with no evidence of demyelination, suggesting an axonal neuropathy (9). Dementia has also been described in association with HSP in pedigrees where members may show additional features such as ataxia (10), dysarthria and mild facial immobility (11), and cardiac disease (12). Cognitive decline often consists of memory impairment, attention deficit, poor perceptual speed, poor visuomotor coordination, and frank dementia (13). However, the presence of cognitive impairment has not been systematically evaluated. It would likely emerge as a common feature if one were to adopt appropriate neuropsychological testing to evaluate subclinical deficits.

Differential diagnosis

Differential diagnosis is now becoming easier because of the availability of more precise and sophisticated neuroradiological investigation techniques and biochemical tests. The latter contribute to the identification of several metabolic diseases that mimic HSP, particularly adrenoleukodystrophy, adrenomyeloneuropathy, metachromatic leukodystrophy, and Krabbe’s disease. Some treatable disorders clinically resembling HSP, such as vitamin B12 deficiency, dopa-responsive dystonia and structural spinal cord disorders, carefully excluded upon neuroradiological investigations, should be considered in the differential diagnosis. Conditions with a different prognosis, such as multiple sclerosis and amyotrophic lateral sclerosis, must also be ruled out. Clinical features that should be considered for differential diagnosis are paraparesis greater than spasticity, evidence for manifest ataxia, amyotrophy, or prominent upper limb involvement. Peripheral neuropathy, asymmetry, and retinal pigmentation are additional clinical signs that would alert the clinician to a possible alternative diagnosis.

Molecular genetics

Autosomal dominant, autosomal recessive and X-linked families are described, showing the genetic heterogeneity of HSP. Nineteen chromosomal loci have been mapped so far — SPG1 through SPG20 (Table I) — but only eight genes cloned. These encode L1 cell adhesion molecule (L1CAM), proteolipid protein (PLP), paraplegin (SPG7), spastin (SPAST), heat-shock 60-kD protein (HSP60), atlastin (SPG3A), spartin (SPART), and the recently identified KIF5A encoding a subunit of the kinesin heavy chain protein (KHC). L1CAM and PLP are responsible for two X-linked complicated forms of HSP, paraplegin and spastin are involved in autosomal recessive forms, while spastin is mutated in the vast majority of autosomal dominant cases (42%), followed by atlastin (9%), Hsp60 and KHC (1%). Although X-linked HSP is rare, its molecular genetic basis is relatively well understood. There are three different loci identified: SPG1 (14), SPG2 (15) and SPG16 (16). SPG1 results from mutations in the L1CAM gene on chromosome Xq28 and can manifest as pure HSP or, more often, in association with a complex phenotype such as the MASA syndrome (mental retardation, adducted thumbs, spasticity and aphasia) or the GRASH syndrome (gorus callosum hypoplasia, mental retardation, adducted thumbs, spastic paraplegia and hydrocephalus) (17). The SPG2 form of HSP maps on chromosome Xq22 and results from mutations in PLP, a major component of myelin in the central nervous system (CNS). PLP, and its splicing variant DM20, are thought to stabilize the structure of the CNS myelin. Pure and complicated forms of HSP are associated with mutations in the PLP gene, though this condition is rare. SPG2 is allelic to Pelizaeus-Merzbacher disease (PMD), characterized by significant hypomyelination of the CNS, which manifests with onset in infancy of nystagmus, psychomotor retardation, spasticity, and ataxia. As yet unknown is the mutated gene in the SPG16 form, mapping on chromosome Xq11.2 (16).

Autosomal dominant transmission is the most common mode of inheritance of HSP in European countries, being responsible for 70-80% of the families studied. Eight of the ten loci identified manifest as a pure HSP. Although the number of families with linkage to most of these loci is very limited, some preliminary considerations can be drawn in terms of genotype-phenotype correlations. It appears that the SPG8 families exhibit a severe phenotype, but also incomplete penetrance.
As occurs in SPG3 families, the single kindred with linkage to markers on chromosome 19q13 (SPG12) (18) is characterized by early onset, and a relatively benign course, even in cases with long disease duration, with no need of a wheelchair. Age at onset is later (range 17-68) in the single SPG13 family on chromosome 2q24 (19), in which the disease is often severe. The disease usually starts in the third decade of life with evidence of anticipation in two SPG9 families. The phenotype is complicated by the presence of congenital cataract and gastroesophageal reflux (20). The SPG17 locus, on chromosome 11q12-q14, is associated with the Silver syndrome, a complicated form characterized by spastic gait, pyramidal tract signs, and distal amyotrophy of hands and feet (21). Bladder disturbance and onset in the early twenties seem frequent in the single North American kindred with pure HSP linked to the SPG6 locus on chromosome 15q11.1 (22), while the single Italian SPG19 family shows onset in the fourth decade (range 36-55) with a slowly progressive syndrome characterized by frequent urinary disturbances, and low incidence of pes cavus, muscular weakness and upper limb hyperreflexia.

Four genes are known for autosomal-dominant HSP: SPAST (SPG4), SPG3A (SPG3), KIF5A (SPG10), and HSP60 (SPG13). The SPG4 locus on chromosome 2p accounts for about 40% of pedigrees. Most SPAST patients present with a pure HSP phenotype, with remarkable variation in age at onset and severity of the disease. In some families, late-onset dementia was observed and in one case an unusual cortical pathology was found consisting of tau-immunoreactive neurofibrillary tangles in the hippocampus and tau-immunoreactive balloon cells in the limbic neocortex (23). The SPAST gene encodes a 616-aminoacid protein, termed spastin, a putative member of the AAA (ATPase associated with diverse cellular activities) protein family, believed to be involved in microtubule dynamics (24). Spastin appears to be ubiquitously expressed in fetal and adult tissues. To date more than 80 different heterozygous mutations have been detected in SPAST, scattered throughout all the coding exons (Fig. 1, see over). About 30% of the mutations are missense and all are located in the conserved AAA cassette. The S44L mutation exceptionally appears to cause disease only in the homozygous state (25). Nonsense mutations outnumber the missense ones, and tend to promote rapid mRNA degradation, suggesting that haploinsufficiency is the molecular mechanism in the disease (26). Accordingly, whenever the level of spastin mRNA has been tested in tissues from patients, it has been found to be drastically reduced. It is reasonable to speculate that a threshold for spastin is critical for axonal preservation in the corticospinal tract (24). Mutations in the SPG3A gene have been identified in a few families (27, 28). SPG3A encodes atlastin, a protein predominantly expressed in the CNS. Atlasin shows significant homology with several GTPases, in particular the guanylate binding protein 1 (GBP1), a member of the dynamin family of large GTPases. Dynamins are essential for receptor mediated endocytosis and endosome trafficking to the trans-Golgi network (29). In addition, dynamins have been associated with cytoskeletal elements, including actin and microtubules (30). Very re-

### Table I - Genetic classification of hereditary spastic paraparesis.

<table>
<thead>
<tr>
<th>Locus</th>
<th>Inheritance</th>
<th>Gene</th>
<th>Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPG1</td>
<td>Xq28</td>
<td>X-linked</td>
<td>L1CAM</td>
</tr>
<tr>
<td>SPG2</td>
<td>Xq22</td>
<td>X-linked</td>
<td>PLP</td>
</tr>
<tr>
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<td>14q11-q21</td>
<td>A.D.</td>
<td>SPG3A</td>
</tr>
<tr>
<td>SPG4</td>
<td>2p21-p22</td>
<td>A.D.</td>
<td>SPAST</td>
</tr>
<tr>
<td>SPG5</td>
<td>8p12-q13</td>
<td>A.R.</td>
<td>?</td>
</tr>
<tr>
<td>SPG6</td>
<td>15q11.1</td>
<td>A.D.</td>
<td>?</td>
</tr>
<tr>
<td>SPG7</td>
<td>16q24.3</td>
<td>A.R.</td>
<td>SPG7</td>
</tr>
<tr>
<td>SPG8</td>
<td>8q24</td>
<td>A.D.</td>
<td>?</td>
</tr>
<tr>
<td>SPG9</td>
<td>10q23.3-q24.2</td>
<td>A.D.</td>
<td>?</td>
</tr>
<tr>
<td>SPG10</td>
<td>12q13</td>
<td>A.D.</td>
<td>KIF5A</td>
</tr>
<tr>
<td>SPG11</td>
<td>15q13-q15</td>
<td>A.R.</td>
<td>?</td>
</tr>
<tr>
<td>SPG12</td>
<td>19q13</td>
<td>A.D.</td>
<td>?</td>
</tr>
<tr>
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<td>A.D.</td>
<td>HSP60</td>
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<tr>
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<td>A.R.</td>
<td>?</td>
</tr>
<tr>
<td>SPG15</td>
<td>14q22-q24</td>
<td>A.R.</td>
<td>?</td>
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<tr>
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<td>X-linked</td>
<td>?</td>
</tr>
<tr>
<td>SPG17</td>
<td>11q12-q14</td>
<td>A.R.</td>
<td>?</td>
</tr>
<tr>
<td>SPG19</td>
<td>9q33-q34</td>
<td>A.D.</td>
<td>?</td>
</tr>
<tr>
<td>SPG20</td>
<td>13q12.3</td>
<td>A.R.</td>
<td>SPART</td>
</tr>
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(17). As occurs in SPG3 families, the single kindred with linkage to markers on chromosome 19q13 (SPG12) (18) is characterized by early onset, and a relatively benign course, even in cases with long disease duration, with no need of a wheelchair. Age at onset is later (range 17-68) in the single SPG13 family on chromosome 2q24 (19), in which the disease is often severe. The disease usually starts in the third decade of life with evidence of anticipation in two SPG9 families. The phenotype is complicated by the presence of congenital cataract and gastroesophageal reflux (20). The SPG17 locus, on chromosome 11q12-q14, is associated with the Silver syndrome, a complicated form characterized by spastic gait, pyramidal tract signs, and distal amyotrophy of hands and feet (21). Bladder disturbance and onset in the early twenties seem frequent in the single North American kindred with pure HSP linked to the SPG6 locus on chromosome 15q11.1 (22), while the single Italian SPG19 family shows onset in the fourth decade (range 36-55) with a slowly progressive syndrome characterized by frequent urinary disturbances, and low incidence of pes cavus, muscular weakness and upper limb hyperreflexia.
families with a pure HSP phenotype and onset in the early twenties (34). The SPG14 locus on chromosome 14q22-q24, has been described only in one complicated recessive HSP phenotype. A recent survey of 40 families from Italy and葡萄牙 and Algeria (33) identified five major recessive HSP phenotypes: early onset (<20 years) or late onset (>20 years) pure forms; phenotypes complicated with mental retardation and peripheral neuropathy or with cerebellar ataxia; and a much rarer fifth group with unique, complex clinical features.

At least six loci have been identified in autosomal recessive HSP families display a more variegated phenotype. A recent survey of 40 families from Portugal and Algeria (33) identified five major recessive HSP phenotypes: early onset (<20 years) or late onset (>20 years) pure forms; phenotypes complicated with mental retardation and peripheral neuropathy or with cerebellar ataxia; and a much rarer fifth group with unique, complex clinical features.

At least six loci have been identified in autosomal recessive HSP families. Linkage to chromosome 8p12-q13 (SPG5) has been found in four Tunisian and two Italian families with a pure HSP phenotype and onset in the early twenties (34). The SPG14 locus on chromosome 3q17-q28 has been identified in an Italian family with a form complicated by mental impairment and motor neuropathy (35) while the SPG15 locus, on chromosome 14q22-q24, has been described only in one complicated Irish family (36). A complex form of recessive HSP with thin corpus callosum (TCC), first described in Japanese families with linkage to chromosome 15q13-q15 (37), has been considered allelic to a recessive HSP locus (SPG11) in Italian and North American families with and without TCC (38). We recently investigated a total of 18 affected and 30 healthy individuals from 12 unrelated Italian families with HSP-TCC (39). Five families were consistent with linkage, defining a 19.8 cM region between markers D15S1007 and D15S978 encompassing the SPG11 interval. In one consanguineous family, linkage could be firmly excluded, corroborating genetic heterogeneity in HSP-TCC. Our findings suggested that, though HSP-TCC cannot totally be identified with SPG11, it is the most frequent Italian form of complicated recessive HSP.

The first recessive gene to be identified in HSP was SPG7, associated with pure and complicated phenotypes. SPG7, on chromosome 16q24.3, encodes para-plegin, a mitochondrial member of the AAA metalloproteases (40). Muscle specimens from affected family members showed typical signs of mitochondrial dysfunction such as ragged-red fibers, intense succinate dehydrogenase-stained areas (indicating proliferating mitochondria), and cytochrome oxidase negative fibers. The severity of muscle mitochondrial signs correlated well with the HSP severity within the family so that less severely affected patients showed mild to no evidence of muscular mitochondrial disorder. The identification of pathogenic mutations in a mitochondrial metalloprotease suggested that oxidative phosphorylation (OXPHOS) alterations might underlie HSP in a subgroup of patients. This was further corroborated by our recent findings of isolated complex I deficiency in recessive patients negative for SPG7 mutations (41). A second recessive gene (SPART, on chromosome 13q12.3) has been identified in the rare Troyer syndrome, a disorder complicated by dysarthria, distal amyotrophy, and short stature in the Amish population (42).

Concluding remarks

Wider knowledge on the molecular basis of HSP has increased the complexity of its classification, and had no clear impact on clinical practice. Differential diagnosis still relies on neurological examination, the appropriate use of brain and spinal cord imaging, and on the extensive list of biochemical screening tests proposed by the HSP Working Group (27). The use of antispastic drugs and regular physiotherapy still remain crucial in the therapeutic management of patients. Nonetheless, the identification of new disease genes can help in genetic counseling. For instance, by combining direct testing of SPAST and SPG3A, at least 50% of dominant families can now receive appropriate genetic diagnosis. Another important consequence of the recent molecular findings is that we can start to imagine the possible interrelated mechanisms that make corticomotor degeneration in HSP possible. The preferential degeneration of long axons may be explained by their high energy requirements and may arise as a result of inadequate fueling of axonal transport. The involvement of
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aberrant mitochondrial processes in neurodegenerative diseases is well established, and paraplegin and Hsp60 mutations offer evidence for the involvement of this mechanism in HSP. With the recent identification of new genes underlying different forms of HSP, evidence is accumulating to link defective trafficking dynamics with the neurodegeneration seen in the disease (32). Overall, at least three scenarios can be imagined:

i. Alterations of signaling molecules in axon outgrowth and pathfinding.

L1CAM, the SPG1 disease gene, is a transmembrane glycoprotein which appears to mediate cell adhesion, neurite outgrowth, and axon pathfinding (43). Neuro-pathological studies in SPG1 patients showed that the pyramids were absent or severely reduced in size suggesting an abnormal development of the corticospinal tracts (44). In transgenic animals, loss of L1 function impairs guidance of corticospinal axons across the pyramidal decussation, so that a substantial proportion of axons fail to cross the midline and therefore descend ipsilaterally. Moreover, projection of the axons below the cervical levels is severely reduced. An association between the trafficking capability of mutant PLP, the gene mutated in SPG2, and the severity of the phenotype has been described both in human diseases and in spontaneous animal models (such as the jumpy mouse, and the rumpshaker mouse) (45). PLP knock-out animals assemble compact myelin sheaths, but subsequently develop widespread axonal swelling and degeneration, most likely secondary to impaired axonal transport. These data showed that correct expression of the L1CAM and PLP proteins is needed in oligodendrocytes to provide local support to myelinated axons. Thus, disruption of intimate glial to axon interactions underlies the axonal degeneration observed in SPG2 patients. The relationships with signaling molecules involved are still unknown but their identification should have important implications for understanding additional forms of HSP.

ii. Impaired endosomal trafficking and microtubule dynamics.

Early last year it was reported that spastin, the first dominant HSP gene identified, acts as a microtubule-severing protein, like katanin, another ATPase involved in the regulation of the microtubule dynamics (46). Spastin and katanin actually share structural homologies in the AAA domain. Spastin mutants lacking the ATPase function or the whole AAA domain revealed a stable microtubule association. Overexpression of wild-type spastin caused microtubule disassembly in transfected cells. Moreover, spastin and spartin, the SPG20 protein, share important homologies with mammalian proteins with microtubule-binding capacity and show functional domains present in endosomal-associated molecules (42). Atlantin, the second dominant gene identified in HSP, may be involved, as a putative dynamin, in processes crucial for neurotransmission and maintenance of synaptic membrane morphology and may well have a function in vesicular transport (28). A mutated kinesin, part of the anterograde transport machinery, in SPG10 corroborates the hypothesis of a pathogenetic role for hampered trafficking dynamics in HSP (32).

iii. Defective protein proof-reading and quality control.

The evidence that two of the eight genes cloned in HSP encode mitochondrial proteins with putative chaperon activity supports the hypothesis that a subset of HSP are “chaperonopathies”. Because of its homologies with yeast mitochondrial AAA proteins, paraplegin potentially has chaperon-like activity – for example it can activate the assembly of respiratory chain complexes, and can participate in protein quality control by binding unfolded peptides and ensuring specificity of proteolysis (47). The mitochondrial dysfunction in HSP patients could result from impaired protein quality control, causing accumulation of misfolded proteins within the mitochondrial matrix. The relatively late age at onset of this form of HSP (35-40 years) is consistent with the hypothesis of impaired protein quality control: age-dependent accumulation of mtDNA mutations due to poor proof-reading control may result in increased misfolded proteins that are not properly degraded by the mutated paraplegin within the mAAA complex. The primary motoneuron, with its high energy requirement in order to propagate electric signals, might represent a preferential target for this form of mitochondrial neurodegeneration (48). A defective transportation of fuel molecules along the road could also be hypothesized. Similarly, the detection of the first disease-causing mutation in a biochemically well characterized chaperonin (Hsp60) may make it possible to investigate the mechanisms by which mutations in the various chaperon genes predominantly manifest in the distal regions of the very long axons of the corticospinal tract.

Summarizing, the wide range of possible gene functions in HSP seemed until now to disagree with the quite uniform pattern of neurodegeneration observed in patients. A number of discoveries, however, seem to lend weight to the notion that blocks or burdened quality control of the vital process of trafficking along microtubules play an important role in the disease pathomechanisms. Certainly, the increased pace of identification of responsible genes in HSP has led to the availability of new diagnostic tools to substantiate a clinical diagnosis and to the prospect of a more up-to-date, molecular-based reclassification of this condition. Clinical management of HSP patients is still based on trials of physical therapy, baclofen and electrical stimulation for spasticity inhibition (49). Hopefully, further studies will open the way for new treatments in the near future.

Acknowledgments

Clinical and experimental work in our laboratories was partially supported by grants from the Italian Ministry of Health (Ricerca Corrente), MIUR (ex-40%, Progetto Giovani Ricercatori 2001 to D.F., and Ricerca di Ateneo e di Facoltà). Prof. Morocutti is gratefully acknowledged for his continuous support.
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