Syndrome of the month

Pure hereditary spastic paraplegia

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The hereditary spastic paraplegias are a group of neurological conditions which are characterised by the presence of progressive spasticity, predominantly affecting the legs. They may be subclassified into pure and complicated forms based on the presence of additional neurological or non-neurological features.[1]

Pure hereditary spastic paraplegia (pHSP)

The first clear description of pHSP was by Strümpell in 1880,[2] who reported a family in which two brothers were affected by a late onset spastic paraplegia. Autosomal dominant inheritance was likely, since their mother was "a little lame". Subsequent reports have described autosomal dominant, autosomal recessive, and X linked recessive patterns of inheritance.[1][3-12] Autosomal dominant inheritance accounts for approximately 70-80% of families, with autosomal recessive inheritance being responsible for most of the remainder.[5][8] X linked recessive inheritance is very rare.

PREVALENCE

Pure hereditary spastic paraplegia is the most common form of hereditary spastic paraplegia (HSP).[13] A rigorously conducted epidemiological study in the Cantabria region of Spain suggested a prevalence for pHSP of 9.6 per 100 000.[14]

CLINICAL FEATURES

The principal clinical feature of pHSP is, by definition, the presence of a progressive spastic paraplegia. Often this is of insidious onset and the abnormal gait is frequently noticed by relatives before the affected person becomes aware of it.[5][8][9] Age at onset may range from early childhood, with delayed motor milestones and "clumsiness", to adult life.[5][8][9] Age at onset is not consistent between families, although it is consistent within some families.[5][8][9] There is also considerable variation in disease severity. Affected subjects may range from entirely asymptomatic (10-20% of cases) to chairbound (10-15% of cases).[5][8][9] Although severity tends to increase with disease duration, considerable variation is present even when people who have been affected for the same length of time are compared.[5][8][9] Urinary symptoms are common, and 50% of patients may be affected by urinary frequency, urgency, or hesitancy.[5][8][9][15-17] Anal sphincter disturbances have been reported but are rare.[7] Erectile impotence may occur, although its frequency is unknown.[6]

Physical examination findings are typical of a spastic paraplegia. However, the degree of hypertonicity is often out of proportion to weakness, and is frequently the most disabling feature.[5] Weakness and hypertonicity are usually restricted to the legs, although there have been occasional reports of mild upper limb weakness, and upper limb hyperreflexia is common.[5][8][9] Pes cavus is present in 30-50% of cases.[5][8] Mild upper limb incoordination may occur and mild distal amyotrophy is well recognised, though rare.[5] Unexpected physical signs may be found; ankle jerks are absent and Babinski reflexes plantar in a small proportion of patients.[5][8][9] Additional neurological abnormalities, indicating involvement of systems other than the motor tracts, are frequent. A significant proportion of patients (20-65%) have diminished vibration sense, and a small number have diminished joint position sense.[5][8][9] Subclinical sensory abnormalities affecting these and other modalities may be present in the majority of cases.[18]

Attempts have been made to subclassify autosomal dominant pHSP on the basis of clinical features. Harding[5] found a bimodal distribution of age of onset and used this to divide families into type I, with age of onset predominantly below 35 years, and type II, with age of onset predominantly over 35 years. Subjects from type II families had a disorder which progressed more rapidly and was more commonly associated with somatosensory and urinary sphincter disturbances than subjects from type I families. Muscular weakness predominated in type II families, while hypertonicity was more marked in type I families. However, there was considerable overlap between these two groups and subsequent studies have not consistently supported the concept of two distinct types of pHSP.[8][9] No consistent clinical differences are apparent between families with different inheritance patterns.

PATHOLOGY

Pathological reports for pHSP are scant and have usually described patients with long

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standing disease. The principal pathological finding is of axonal degeneration involving the terminal ends of the longest fibres of the corticospinal tracts and dorsal columns. The spinocerebellar tracts are involved to a lesser degree. The cell bodies of the degenerating fibres are apparently normal; the process has been described as "dying back" of the nerve fibre endings. There is no evidence of primary demyelination and no abnormality of peripheral nerves, dorsal roots, or dorsal root ganglia has been reported.[1][19]

DIFFERENTIAL DIAGNOSIS AND INVESTIGATIONS

The diagnosis of pHSP in a family where several members have typical clinical features is relatively straightforward. Standard neurological investigations should be used selectively to exclude alternative diagnoses. Magnetic resonance imaging may show spinal cord atrophy, particularly in the cervical region.[13] Peripheral nerve conduction studies are almost always normal.[5][20][21] Cervical somatosensory evoked potentials and central motor conduction studies are abnormal in the majority of cases, although unfortunately do not provide a means for early detection of affected family members.[21-24] Interestingly, brain stem auditory evoked potentials and visual evoked potentials are abnormal in a minority of cases.[9]

Other genetic conditions to be considered in the differential diagnosis include dopa responsive dystonia, which should actively be excluded in families where age of onset is early and sensory signs are absent, particularly if there is marked diurnal variation of spasticity. Dramatic and sustained improvement of symptoms occurs with small doses of L-dopa.[25] The clinical picture should allow exclusion of the spinocerebellar syndromes and Machado-Joseph disease, in which ataxia is a much more prominent feature. Adult onset forms of adrenoleucodystrophy, Krabbe's leucodystrophy, and metachromatic leucodystrophy may rarely present with spastic paraplegia, and can be detected with appropriate biochemical tests.[26] Atypical Friedreich's ataxia should also be considered, since a proportion of patients homozygous for the frataxin gene triplet repeat expansion have retained or exaggerated lower limb reflexes and upgoing plantar responses.[27]

The differential diagnosis is more extensive in sporadic cases of spastic paraplegia and, in addition to the above, includes structural spinal cord lesions, intracranial parasagittal space occupying lesions, multiple sclerosis, myelopathies associated with deficiencies of vitamin B12 or E, and abetalipoproteinaemia. Infective conditions including tertiary syphilis, HTLV1 infection causing tropical spastic paraparesis, and the myelopathy associated with the acquired immune deficiency syndrome should be considered, although the clinical picture would be not entirely typical of pHSP.[26]

DIAGNOSIS IN AT RISK FAMILY MEMBERS

Criteria for the diagnosis of pHSP in at risk family members have been proposed, although they are perhaps most useful for standardisation in a research setting (table 1).[26] The

Table 1 Suggested diagnostic criteria for family members from families with pHSP.[26] Alternative diagnoses should first be excluded and the family history should be consistent with autosomal dominant, autosomal recessive, or X linked recessive inheritance. These criteria are perhaps most useful for standardisation in a research setting and are open to criticism. Many definitely affected subjects lack grade 4 hyperreflexia. The criteria for the definitely unaffected category are insufficiently rigorous in view of the wide range in age of onset which may occur in some families

Status	Criteria
Definitely affected	Progressive gait disturbance + Frank corticospinal tract involvement of lower limbs, including grade 4 hyperreflexia and extensor plantar reflexes
Probably affected	Subjects lacking history of **progressive** gait disturbance, or asymptomatic subjects with signs of spastic paraparesis, examined only once and so not proven to have a progressive gait disturbance + Frank corticospinal tract involvement of lower limbs, including grade 4 hyperreflexia and extensor plantar reflexes. Serial examinations may allow recategorisation as definitely affected
Possibly affected	Asymptomatic + Normal gait + Questionably abnormal corticospinal tract signs, eg mild hyperreflexia, non-sustained clonus, but downward plantar reflexes
Definitely unaffected	Asymptomatic + Normal neurological examination + Age greater than maximal age of symptoms in family
Probably unaffected	Asymptomatic + Normal neurological examination + Age younger than maximal age of symptoms in family

insidious onset of the condition can lead to diagnostic uncertainty. Clues from the history can be helpful. Patients may note poor athletic ability at school, tripping more often than normal, and the presence of clonus at the knee or ankle joint. Relatives may have made comments about an at risk subject having the "family walk". Many affected people rapidly wear out shoes, particularly at the toe, and footwear should be examined.[8] Physical examination findings in at risk relatives must be carefully interpreted. Anxiety may cause mildly increased muscle tone, hyperreflexia, and non-sustained clonus and these findings should be viewed with caution in subjects who lack one of the "hard" physical signs of sustained clonus ($\geq$ five beats), bilateral upgoing plantar responses, or progressive gait disturbance. If doubt remains, serial examinations should help.

MANAGEMENT

No therapy is available which slows disease progression. Treatment is aimed at maximising functional ability and preventing complications such as contractures. Referral to a neurological physiotherapist, for an appropriate exercise programme, is essential. Some patients increase functional activity with antispastic drugs such as the GABA agonist baclofen, or newer alternatives.[13] Anecdotal reports in small numbers of patients have described a useful functional response to continuous intrathecal baclofen, although there have been no good clinical trials of this treatment.[17][28] Intramuscular botulinum toxin may improve function for carefully selected patients, although its use has not been fully evaluated in pHSP.[29][30] Ortho-

Table 2 Risks of having disease gene for clinically normal offspring of affected subjects, based on cumulative age of onset curve for autosomal dominant pHSP. For use with families in which age of onset is predominantly under 35 years. Modified from Harding[5]

Age (y)	Risk of having disease gene (%)
20	24
25	22
30	19
35	13
40	11
45	9

paedic surgery, usually release of contractures and tenotomies, may rarely have a role, but requires very careful assessment of the likely consequences of the procedure on gait.

GENETIC COUNSELLING

The often late onset of pHSP and the variability of age of onset within families showing dominant inheritance means that it may be impossible to reassure clinically normal young adults who are at 50% prior risk of having inherited the disease gene. The data of Harding[5] on type I families indicate that the clinically normal offspring of an affected parent have, at the age of 20, a 24% chance of having the abnormal gene, and at the age of 45, a 9% chance of having inherited the abnormal gene (table 2).[5] It should be emphasised that these data are only applicable to families in which the age of onset for the condition is predominantly under 35 years. The risk figures are almost certainly overestimates, since they are derived from an age at onset of symptoms cumulative frequency curve. The degree of reduction which can be made when an at risk patient has no signs is unknown. Predictive testing may be feasible for at risk subjects from large families where definite linkage is established.

The frequent occurrence of asymptomatic subjects means that every effort should be made to examine both parents of sibs with apparently recessive pHSP. If both parents are normal, recessive inheritance is most likely. Non-penetrance (only a few well documented cases exist[8 13]) or gonadal mosaicism in a parent are alternative possibilities. If both parents of affected sibs cannot be examined, empirical figures derived by Harding[5] (and only applicable to type I families) indicate a 1/6 chance that one parent was affected. The risks to the offspring of the affected sibs are therefore 1/12. No empirical figures are available for the risks to offspring of apparently sporadic cases, where in addition to non-penetrance in a parent a new dominant mutation is a possibility.

Although X linked inheritance cannot be excluded in many families, it would appear to be rare and only a few convincing pedigrees have been described.[11 12] Those obligate carrier females examined have been almost always normal neurologically and none has had clear cut signs of spastic paraplegia.[11 12] However, because X linked pedigrees are so sparse and because examination findings in carrier females have not always been reported, it is difficult to be certain that carrier females never have definite signs of spastic paraplegia.[11 12]

Complicated HSP

Complicated HSP consists of a large number of rare conditions, which tend to be inherited in an autosomal recessive fashion. They have been well reviewed by Bundey[31] and by Harding,[13] whose proposed classification is given in table 3.

Molecular genetics of HSP

Three autosomal dominant genes causing pHSP have been mapped, on chromosomes 2p, 14q, and 15q (to regions of 4 cM, 7 cM, and 7

cM respectively).[35-38] Linkage results have been published in complete form for 34 families.[35-42] Strong evidence of linkage to one of the three known loci has been found in approximately half of these families, with weaker evidence of linkage being found in a proportion of the remainder. Of those families showing evidence of linkage, most are linked to chromosome 2,[35 36 40-42] with small numbers showing linkage to chromosomes 14 (three families)[36 37 39] and 15 (one family).[38] Linkage to all three loci has been excluded in a number of families, strongly suggesting the existence of at least one further locus.[43 44] Anticipation has been postulated to occur for a proportion of the families where the disease gene maps to chromosome 2[35 40 41 45] and to chromosome 14,[39] suggesting the intriguing possibility that the underlying genetic abnormality might involve a trinucleotide repeat expansion, as has been described for several other neurodegenerative conditions.

There may be some correlation between genetic locus and clinical phenotype, although assessment of this is hampered by scanty clinical details in mapping reports. All three of the families showing linkage to the chromosome 14 locus had a very early mean age at onset, under 10 years old.[36 37 39] On the other hand, families showing linkage to chromosome 2 have considerable inter- and intrafamilial variation in age of onset, corresponding to both types I and II of Harding, and further weakening the argument that these types of pHSP are distinct.[35 36 40 41] In none of these families was the mean age of onset as early as the chromosome 14 linked families. The single family showing linkage to chromosome 15 had a unimodal age of onset (mean 22 years) and was characterised by the relative severity of the condition, with approximately 30% of its members being chairbound.[38]

A gene for autosomal recessive pHSP has been mapped to the pericentric region of chromosome 8 in three consanguineous and one non-consanguineous Tunisian families.[46] Again there is evidence of locus heterogeneity, with linkage to chromosome 8 markers being excluded in a fifth consanguineous Tunisian family. The clinical picture was homogeneous in all five families, with an early age of onset (between 1 and 20 years), loss of vibration sense and proprioception, and bladder sphincter disturbance in all affected members.[46]

While X linked spastic paraplegia is rare, it is important because its molecular pathology is more completely understood than that of the other forms. Mutations in the gene encoding the neural cell adhesion molecule L1 (L1-CAM) at Xq28 are responsible for a complicated form of spastic paraplegia, in which paraplegia is accompanied by mental retardation and absence of the extensor pollicis longus muscle.[33] Different mutations in the same gene are responsible for the MASA syndrome (mental retardation, aphasia, shuffling gait, adducted thumbs) and X linked hydrocephalus.[33] The same L1-CAM mutation may result in either an X linked hydrocephalus phenotype or a MASA phenotype.[47] L1-CAM is a cell surface glycoprotein which is expressed on the

Table 3 Classification of complicated spastic paraplegias, updated and modified from Harding,[1] [13] with additional references[32-34]

Type	Clinical features	Inheritance pattern
With amyotrophy		
Resembling peroneal muscular atrophy	Mild paraparesis accompanied by features resembling Charcot-Marie-Tooth disease	AD
Of small hand muscles	Mild paraparesis with moderate/severe amyotrophy of small hand muscles	AD
Troyer syndrome	Early onset with motor and speech delay. Severe spasticity and distal amyotrophy of all 4 limbs. Pseudobulbar palsy, dysarthria, and emotional lability. Described in Amish	AR
Charlevoix-Saguenay syndrome	Early onset. Dysarthria, nystagmus, cerebellar ataxia. Amyotrophy in all 4 limbs. Spasticity prominent in legs. Defective vertical pursuit eye movements. Occurs in an isolated area of Quebec	AR
Resembling amyotrophic lateral sclerosis		AR/AD
Sjögren-Larsson syndrome	Congenital ichthyosis, severe mental retardation and usually non-progressive spastic paraplegia	AR. Caused by mutations in fatty aldehyde dehydrogenase gene[32]
MASA syndrome	Mental retardation, aphasia, spasticity, and adducted thumbs. Allelic with X linked hydrocephalus	XLR. Caused by mutations in L1-CAM gene[33]
With cerebellar signs	Cerebellar dysarthria, mild upper limb ataxia and spastic paraplegia. Distal wasting may occur	AR/AD
Kjellin syndrome	Mental retardation, progressive spastic paraplegia from 20s, distal neurogenic atrophy of limbs, dysarthria, central retinal degeneration	AR
With optic atrophy	Rare. Associated with a variety of additional features in different family reports	AR/AD
With choreoathetosis/ dystonia	Additional features may occur in some families. Consider dopa responsive dystonia as an alternative diagnosis!	AR/AD
Mast syndrome	Dementia, dysarthria, athetosis, and spastic paraplegia. Described in Amish population	
With sensory neuropathy	Sensory neuropathy often affects all modalities and may lead to trophic ulceration and mutilation. Trophic ulcers may have early onset	AR/AD
With disordered skin pigmentation	Two separate conditions reported. First with generalised depigmentation at birth, becoming patchily pigmented. Second with hypopigmented skin below knee	AR/AD
With hyperekplexia	A single family described in which hyperekplexia and spastic paraplegia cosegregate	AD. Caused by mutations in gene coding for the α1 subunit of glycine receptor[34]

AR=autosomal recessive, AD=autosomal dominant, XLR=X linked recessive.

axons of postmitotic neurones and which is involved in neuronal migration and neurite extension.[48] It is highly expressed in the developing corticospinal tracts of rats and the congenital onset of the three conditions comprising the "L1-CAM" syndrome is consistent with the molecule's proposed role in neuronal development.[49]

Pelizaeus-Merzbacher disease is a dysmyelinating disorder of the central nervous system, characterised by congenital hypotonia, nystagmus, slow psychomotor deterioration, and progressive pyramidal, dystonic, and cerebellar signs. Mutations in the proteolipid protein (PLP) gene, which maps to Xq21-q22, have been found in families with this condition, in a family with pHSP and in families with complicated forms of spastic paraplegia.[50-52] The PLP gene codes for two myelin proteins, PLP and DM20. These proteins are thought to play a major role in oligodendrocyte maturation and, later in development, in myelin sheet compaction.[51] It has been suggested that mutations or duplications which affect the role of the PLP gene in oligodendrocyte maturation give rise to the more severe Pelizaeus-Merzbacher phenotype, while those which affect only myelin compaction give rise to the milder spastic paraplegia phenotypes, although this issue has not yet been resolved.[42] It is possible that further X chromosome pHSP genes exist. In a second X linked pHSP family, the responsible gene mapped tightly to the PLP gene region.[52] However, no mutation in either the coding sequence or intron/exon boundaries of the PLP gene was found, raising the possibility that the disease causing mutation may have been in a non-coding portion of the PLP gene, or that pHSP may also be caused by a second gene in the same region.[52]

Thus, the X linked hereditary spastic paraplegias indicate that mutations in the same gene may be responsible for both pure and complicated forms of HSP, as well as other neurological conditions. In addition, they suggest that cell adhesion molecule genes and myelin genes are likely candidates for other forms of spastic paraplegia.

Conclusion

Knowledge of the genetics of the hereditary spastic paraplegias is advancing rapidly. Eventually, an understanding of the molecular pathology underlying these conditions may allow better genetic counselling for at risk family members, rational development of more effective treatments, and insight into the function of the spinal cord in health and disease.

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