

REVIEW

Hereditary spastic paraparesis: a review of new developments

CJ McDermott, K White, K Bushby, PJ Shaw

Hereditary spastic paraparesis (HSP) or the Strümpell-Lorrain syndrome is the name given to a heterogeneous group of inherited disorders in which the main clinical feature is progressive lower limb spasticity. Before the advent of molecular genetic studies into these disorders, several classifications had been proposed, based on the mode of inheritance, the age of onset of symptoms, and the presence or otherwise of additional clinical features. Families with autosomal dominant, autosomal recessive, and X-linked inheritance have been described.

Historical aspects

In 1880 Strümpell published what is considered to be the first clear description of HSP. He reported a family in which two brothers were affected by spastic paraplegia. The father was said to be "a little lame", suggesting autosomal dominant transmission.¹ Both Strümpell and Lorrain added similar cases to the literature in subsequent years.²⁻³ Shortly after these landmark descriptions, numerous reported cases of HSP appeared in the literature. However, Pratt, who considered the presence of additional neurological features to be incompatible with the original descriptions, labelled many of these as HSP plus syndromes.⁴ Early reviews of these and other cases attempted to identify "pure" cases as had been described by Strümpell. However, the definition of "pure" varied among authors.⁵⁻⁸ It was Harding in 1981 who, after detailed clinical evaluation of 22 families, suggested criteria for classifying HSP into pure and complicated forms which have since been adopted and are discussed below.⁹ Further subdivision of pure HSP was also suggested by Harding based on the age of onset of the disease. It was found that families could be separated into two groups, one with onset before 35 years (type I) and the other with onset after 35 years (type II). There seemed to be clinical differences between the groups, with the type I patients having a slow and variable course compared with the more rapidly evolving type II, in which muscle weakness, urinary symptoms, and sensory loss were more marked.⁹ Neither of these classifications are ideal, with many families not easily fitting the criteria. As is the case in other hereditary neurodegenerative disorders, the unravelling of the molecular genetic mechanisms underlying he-

reditary spastic paraparesis will no doubt provide a more useful and relevant classification.

Epidemiology

The prevalence of HSP varies in different studies. Such variation is probably due to a combination of differing diagnostic criteria, variable epidemiological methodology, and geographical factors. Some studies in which similar criteria and methods were employed found the prevalence of HSP/100 000 to be 2.7 in Molise Italy, 4.3 in Valle d'Aosta Italy, and 2.0 in Portugal.¹⁰⁻¹² These studies employed the diagnostic criteria suggested by Harding and utilised all health institutions and various health care professionals in ascertaining cases from the specific region. Polo *et al* in 1991 reported a higher prevalence of 9.6/100 000 in Cantabria, Spain.¹³ In their report only hospital records were used to ascertain cases, although many secondary cases were identified by examining all at risk relatives.

Clinical features

PURE HEREDITARY SPASTIC PARAPARESIS

Criteria which have been suggested for the diagnosis of pure HSP are included in table 1. Most patients present with difficulty walking or gait disturbance, noticed either by themselves or a relative. In those with childhood onset, a delay in walking is not uncommon. Other symptoms include stiffness of legs, urinary disturbance, and premature wear on footwear. Up to 25% of affected patients are asymptomatic, emphasising the often benign nature of the disease and the importance of careful clinical evaluation of families included in genetic studies. The age of onset can be from infancy to the eighth decade.⁹ The marked interfamilial variation in age of onset was one of the early pointers to genetic heterogeneity in this condition. This variation may also be partly due to difficulty in ascertaining an exact date of onset, particularly in older patients who have had the disease for decades, or may reflect other as yet unknown genetic or environmental modifying factors.

The cardinal abnormalities on examination of patients with pure HSP include spasticity, hyperreflexia, and extensor plantar responses, with weakness of a pyramidal distribution in

Department of
Neurology, Ward 11,
Royal Victoria
Infirmary, Newcastle
upon Tyne NE1 4LP,
UK

CJ McDermott
PJ Shaw

Department of Human
Genetics
K Bushby

Department of
Neurology, Manchester
Royal Infirmary,
Manchester UK
K White

Correspondence to:
Dr CJ McDermott
chrismcder@aol.com

Received 31 August 1999
Accepted 3 December 1999

Table 1 Suggested diagnostic criteria for pure hereditary spastic paraparesis and clinical features that would alert the clinician to possible alternative diagnoses

	Clinical features
Obligatory	Family history Progressive gait disturbance Spasticity of lower limbs Hyperreflexia of lower limbs Extensor plantar responses
Common	Paresis of lower limbs Sphincter disturbances Mild dorsal column disturbance Pes cavus Hyperreflexia of upper limbs Mild terminal dysmetria Loss of ankle jerks
Uncommon	Paresis of upper limbs Distal amyotrophy
Diagnostic alerts	Paresis greater than spasticity Prominent ataxia Prominent amyotrophy Prominent upper limb involvement Peripheral neuropathy Asymmetry Retinal pigmentation Extrapyramidal signs

the lower limbs. The lower limb spasticity is the prominent finding on examination, particularly in the hamstrings, quadriceps, and ankles. This pattern of hypertonicity is responsible for the classic gait with the affected person demonstrating circumduction and toe walking. Muscle weakness when present is seen in iliopsoas, tibialis anterior and, to a lesser extent, the hamstrings. A characteristic feature of HSP, which has been stressed by several authors, is the marked discrepancy between the often severe spasticity and only mild or absent muscle weakness.^{8 14} This is demonstrated by the patient with HSP who is wheelchair bound due to spasticity but on manual muscle testing has normal power.

Other features which some authors have included under the umbrella of pure HSP include: mild sensory abnormalities in the lower limbs, absent ankle jerks, pes cavus, urinary symptoms, mild ataxia in the upper limbs, and mild distal muscle wasting.^{9 15-18} This more inclusive approach seems to be validated by the multisystem involvement suggested by para-clinical investigations and neuropathological findings. Sensory impairment is seen in 10%-65% of cases of pure HSP and is found more commonly, but not exclusively, in patients with longstanding disease. It usually consists of diminished vibration sense and, less often, diminished joint position sense in the extremities of the lower limbs.^{9 15 16} In most patients nerve conduction studies are normal.^{9 15 19 20} This suggests that the abnormalities found on examination are due to a central axonopathy rather than peripheral nerve involvement. The uncommon finding of absent ankle jerks in patients with HSP probably reflects the same process.^{9 16} Pes cavus is not as common a finding as was originally suggested. Harding in her series found pes cavus in only one third of patients.⁹ Its presence may reflect the severity or duration of the illness. Urinary sphincter disturbance occurs in up to 50% of patients. This usually manifests as a combination of urgency, hesitancy, and frequency and is more common in longstanding disease.^{9 15-17 21 22} Anal

sphincter involvement is unusual in HSP, although Schetlens *et al* did report a family in which faecal urgency and incontinence were present and Schwarz had earlier described a man similarly afflicted. In both reports urinary symptoms were also present.^{23 24} Sexual dysfunction has only been described in one family. It occurred about 10-15 years after the onset of disease, and so the patient's reproductive capacity was not dramatically affected. The problem in affected males consisted of erectile failure with retained capacity to ejaculate.²⁵ Mild muscle wasting is well recognised although uncommon in HSP. When present it is found in distal muscles in the lower limbs, usually the small muscles of the foot and tibialis anterior. It is more common in patients who have had the disease for over 10 years.^{9 15} If muscle wasting is prominent and present early in the course of the disease, the diagnosis should be reconsidered. Upper limb involvement is relatively uncommon and usually consists of mild hyperreflexia, which may be present early in the disease. A trace of terminal dysmetria may also be found in the upper limbs, but more florid cerebellar signs are not seen. There are occasional reports of mild distal muscle atrophy but more marked involvement of the upper limbs with spasticity, weakness, or amyotrophy is not usually seen in pure HSP.⁹

Important negative findings on examination are normal cranial nerve function and no evidence of corticobulbar tract involvement. The possible involvement of the autonomic nervous system in HSP has not been systematically studied, although Cartledge and Bone, when reporting on the finding of sphincter disturbance in patients with HSP considered involvement of the autonomic nervous system in three patients and performed a battery of autonomic function tests which were normal.¹⁷

The prognosis and severity of HSP varies between families and, to a lesser extent, within the same family, although life expectancy is normal. Several authors have supported the observation by Harding that in early onset HSP (<35 years), disease progression is slow with most patients remaining ambulant through most of their lives, and with only a small proportion becoming confined to a wheelchair in elderly life. This contrasts with many cases of late onset HSP (>35 years), in whom disease progression can be rapid, with most patients losing the ability to walk in their 60s and 70s.^{9 16 20}

COMPLICATED HEREDITARY SPASTIC PARAPARESIS Whereas in pure HSP the spastic paraparesis is the prominent feature, in complicated HSP this is one component of a much more variable phenotype. Some types of complicated HSP are extremely rare and may have only been described in a single family. In some cases it could be argued that more than one inherited disorder may contribute to the clinical features. Hereditary spastic paraparesis has been associated with many conditions including optic atrophy, retinopathy, extrapyramidal disease, amyotrophy, dementia, ataxia, mental retarda-

Table 2 Clinical features which may be seen in addition to spastic paraparesis in complicated hereditary spastic paraparesis

Association	Disease/main feature	Description/references
Amyotrophy	Resembling hereditary motor and sensory neuropathy of small muscles of hands	Distal weakness and wasting combined with brisk reflexes, extensor plantar responses and pes cavus (AD). ²⁶⁻²⁸ Severe wasting of the small muscles of the hand with marked sparing of the lower limb musculature (AD). ²⁹
	Troyer syndrome	Distal wasting in the limbs with delayed development, spastic tetraparesis, pseudobulbar palsy, choreoathetosis and short stature in Amish people (AR). ³⁰
	Charlevoix-Saguenay syndrome	Similar to Troyer syndrome but found in Quebec. ³¹ Also associated with mental retardation. ³²
Cardiac defects	—	Dysarthria with a mild upper limb ataxia. ³³
Cerebellar signs	—	X-linked. ³⁴
Deafness	Sensorineural	
Dementia	Subcortical or cortical pattern	Dementia can occur in isolation with HSP, ³⁵⁻³⁸ when it tends to be of the subcortical type, or be part of a much more complex phenotype (AR and AD). ³⁹ Linkage to SPG4 locus in a number of families. ³⁸⁻⁴⁰
Epilepsy	Myoclonus	41-43
	Simple/complex partial	42
	Absence	41 44
	Grand mal	45 46
	Atonic episodes	41 43
Extrapyramidal signs	Choreoathetosis	47 48
	Dystonia and rigidity	
Ichthyosis	Sjögren-Larsson syndrome	Also with mental retardation and occasionally a pigmentary macular degeneration (AR). ⁴⁹
Sensory neuropathy	Asymptomatic	Sensory neuropathy detected only on clinical examination. ⁵⁰
	Childhood onset	With painless ulcers and deformities secondary to neuropathic bone resorption. ⁵¹
	Adult onset	Trophic skin changes and foot ulcers. ^{52 53}
Retinal changes	Optic atrophy	37 54 55
	Retinal degeneration	56 57
Others	Kallmann's syndrome	Hypogonadotropic hypogonadism and anosmia. ⁵⁸
	Hyperreflexia	Neonatal hypertonia and an exaggerated startle response (AD). ⁵⁹
	MASA syndrome	Mental retardation, aphasia, a shuffling gait and adducted thumbs. Caused by mutations in L1CAM gene (X-linked). ^{60 61}
	Mast syndrome	Dementia, dysarthria and athetosis in Amish people with onset in 2nd decade (AR). ⁶²
	Kjellin syndrome	Dysarthria, upper limb ataxia, dementia, retinal degeneration+amyotrophy (AR). ⁶³
	SPG9	Bilateral cataracts, gastro-oesophageal reflux and amyotrophy. ⁶⁴

AD=autosomal dominant; AR=autosomal recessive.

tion, deafness, ichthyosis, peripheral neuropathy, and epilepsy. References and brief descriptions of additional clinical features reported are given in table 2.

Epilepsy associated with HSP was not mentioned in earlier reviews, perhaps because with only rare case reports of one or two affected members in a pedigree, the association could have been coincidental, given the high prevalence of epilepsy in the community. However, over the past decade several authors have published case reports where epilepsy syndromes and HSP seem to be closely associated.^{39 41-44} No clear pattern is found between the families where this association exists. Both autosomal dominant and recessive inheritance is seen. There is no consistent seizure type associated with HSP and myoclonic, simple partial, complex partial, and generalised epilepsy have been reported. Different types of seizures have sometimes been described in affected members within the same family. Similarly, there is variability as to when the seizures commence, with examples of seizures predating and postdating the onset of the gait disturbance. Coexisting mental retardation or cognitive impairment has often been described in these families. Epilepsy is a characteristic feature of mitochondrial diseases (for example, MERRF), a group of diseases which often manifest with diverse symptoms not unlike complicated HSP. As will be discussed later, evidence for mitochondrial involvement has been found in some autosomal recessive HSP families and it will be interesting to determine whether mitochondrial dysfunction contributes to the pathogenesis of other forms of HSP.

There are families with HSP who do seem to have involvement of the peripheral nerves. Schady and Smith reported a family with

asymptomatic sensory involvement detected on clinical examination. All those within the family who underwent nerve conduction studies had decreased sensory action potentials. Three patients underwent a nerve biopsy, which showed decreased numbers of large and medium sized myelinated fibres with no evidence of demyelination, suggesting an axonal neuropathy.⁵⁰ Such families represent examples of complicated HSP. Earlier reports described a severe sensory neuropathy in association with HSP, with chronic painless cutaneous ulcers and neuropathic bone resorption occurring in early childhood.⁵¹ In a less severe form trophic skin changes and ulcers on the feet develop in adult life superimposed on a longer established spastic paraparesis.^{52 53}

Dementia has been associated with HSP in pedigrees where members may show additional features such as ataxia,⁶⁵ dysarthria,⁶⁶ dysarthria and mild facial immobility,⁴⁰ cardiac disease,³² epilepsy,³⁹ and in the Mast syndrome which consists of spastic paraplegia with dementia, dysarthria, and athetosis.⁶² Dementia has also been reported in both autosomal dominant and recessive families, as an isolated accompaniment to spastic paraparesis.³⁵⁻³⁸ In these families, similar patterns of cognitive deficits have been found. These include various combinations of defective recent memory, impairment of attention, poor perceptual speed, poor visuomotor coordination, and forgetfulness. In the descriptions of affected people there was an absence of features suggesting major cortical involvement such as dysphasia, agnosia, and dyscalculia. This would suggest that a subcortical dementia may characterise the complicated HSP phenotype of spastic paraplegia with dementia. It is possible that milder degrees of cognitive impairment may be

Table 3 Differential diagnosis of hereditary spastic paraparesis

Differential diagnosis	Investigation(s)
Cervical/lumbar spondylosis	MRI spine
Neoplasm; primary or secondary	MRI brain, spine
Arnold Chiari malformation	MRI brain, spine
Diplegic cerebral palsy	MRI brain, birth history
Spinal cord arteriovenous malformation	MRI/spinal angiography
Progressive multiple sclerosis	MRI, CSF analysis, evoked responses
Motor neuron disease	EMG
Spinocerebellar ataxias	Gene analysis
ALD, AMN	MRI brain, VLCFA
MLD	MRI brain, arylsulphatase
Krabbe leukodystrophy	MRI, galactocerebrosidase
Subacute combined degeneration of the cord	Vitamin B12
Arginase deficiency	Plasma arginine, aminoaciduria
Neurolethyrism	History of <i>Lathyrus sativus</i>
Abetalipoproteinemia	Lipoprotein electrophoresis
Dopa responsive dystonia	L-dopa trial, gene analysis
Vitamin E deficiency	Serum vitamin E level
Neurosyphilis	Syphilis serology
HTLV-1 infection (tropical spastic paraparesis)	Serum/CSF HTLV-1 antibodies
AIDS	HIV testing, CD4 count

ALD=adrenoleukodystrophy; AMD=adrenomyeloneuropathy; VLCFA=very long chain fatty acids; MLD=metachromatic leucodystrophy; HTLV-1=human T lymphotropic virus type1; AIDS=acquired immune deficiency syndrome; HIV=human immunodeficiency virus.

more frequent than previously recognised in those affected by HSP.³⁸ This problem has not yet been systematically evaluated. In one of the few studies which carefully evaluated cognitive function, asymptomatic impairment was demonstrated in five out of seven patients from four families with pure HSP.⁶⁷ It seems likely, therefore, that if patients are carefully evaluated for subclinical cognitive problems, that even pure HSP will turn out to be a multisystem disorder, with involvement outside the motor system. This phenomenon has increasingly been recognised in other apparently selective motor disorders, including motor neuron disease.^{68 69}

Findings on investigation

Investigations are useful in excluding alternative diagnoses, but do not otherwise add to the diagnostic certainty of HSP. Central motor conduction times have been reported by several authors to show either unrecordable, or delayed responses from the lower limbs, with usually normal values from the upper limbs.⁷⁰⁻⁷³ Somatosensory evoked potentials have been reported to be small or absent, with the abnormality again being mainly seen in the lower limbs.^{20 72 74} Nerve conduction studies and EMG are normal in most cases of pure HSP.^{9 20 73 75 76}

Analysis of CSF is usually unremarkable in HSP. However, occasional reports of abnormalities have included increased protein concentrations in complicated families and raised homocarnosine concentrations in a complicated family with spastic paraplegia, progressive mental deficiency, and retinal pigmentation.^{18 29 77 78}

On MRI the spinal cord may appear small, but other abnormalities are not usually seen. There are occasional reports of mild to moderate atrophy of intracranial structures, particularly the corpus callosum, and also of white matter lesions in the cerebral hemispheres.^{15 71 79 80} However, marked atrophy or changes in white matter on MRI require thorough exclusion of other conditions.

Rapid progress is being made in the molecular genetics of HSP, which will affect the way

we investigate and diagnose HSP in the future, and this is discussed later.

Differential diagnosis

Hereditary spastic paraparesis should be considered a diagnosis of exclusion. It is important to consider treatable disorders that can present in a similar manner, such as B12 deficiency, dopa responsive dystonia, and structural spinal cord disorders. Disorders, the prognosis of which differs significantly from HSP, such as multiple sclerosis and familial motor neuron disease should also be excluded. The necessity for investigations will vary depending on the individual clinical picture. Table 3 details investigations which may be useful in excluding other disorders in particular patients. Only once other diagnoses are confidently excluded can patients and their families be counselled appropriately.

Neuropathology

Hereditary spastic paraparesis is a disease which is compatible with a normal life expectancy, with most patients dying in old age from coincidental diseases. Given the chronicity of the condition and the paucity of treatment options, a large proportion of patients may not be under regular review by a neurologist. It is therefore not surprising that there are relatively few pathological reports in HSP. Schwarz and Lui reviewed the early pathological reports in 1952, identifying seven cases of pure HSP and added their own description of cases in 1956.^{81 24} Only a handful of pathological reports have been published since.^{80 82-84} The major neuropathological feature of pure HSP is axonal degeneration that is maximal in the terminal portions of the longest descending (corticospinal tracts) and ascending (dorsal column pathways) tracts within the spinal cord. Demyelination and gliosis can accompany the axonal loss. The most severely affected pathways are the crossed and uncrossed corticospinal tracts to the lower limbs and the fasciculus gracilis fibres from the lower limbs (figure). Involvement of spinocerebellar tracts is seen in about 50% of cases. Other less common reported findings have included decreased number of Betz cells in layer V of the motor cortex in four cases, marked neuronal loss in Clarke's column in another four cases, and one case in which the cerebellum and basal ganglia showed neuronal loss.⁸⁵ Dorsal root ganglia, posterior roots, and peripheral nerves are usually normal, as are anterior horn cells, although one report did demonstrate degeneration of anterior horn cells throughout the spinal cord of an affected person.²⁴

In the only quantitative study, the size of the pyramids in an affected person aged 57 was found to be comparable with the size in an average 2 year old. The total number of myelinated nerve fibres in the pyramid was 376 055 compared with 625 700 in a 20 year old man. In the same study the number of Betz cells was reduced to 23 652 in the left motor area compared with 34 562 in a 22 year old woman. The nature of the cellular degeneration is uncertain. The reduction of Betz cells could be explained



Midcervical spinal cord section from a case of chromosome 2 linked autosomal dominant pure HSP (SPG4), stained for myelin with Luxol fast blue. There is diffuse myelin pallor of crossed and uncrossed corticospinal tracts. In addition, the gracile fasciculi in the centre of the dorsal columns show prominent myelin pallor. Anterior horn cells are normal in number and morphology.

by retrograde degeneration, which can be seen when damage occurs to the spinal cord by several mechanisms. Given that the distal part of long axons in the corticospinal tracts, and sensory and spinocerebellar pathways are preferentially affected in HSP, it has been suggested that a process of “dying back” is occurring, with degeneration beginning distally and then proceeding towards the cell body.²⁴

Pathological reports have occasionally uncovered clinically unsuspected problems such as dorsal column degeneration in patients without detectable sensory abnormalities during life. One case had documented cerebellar and basal ganglia pathology at necropsy, without any documented clinical correlate.⁸⁵

Recently, new pathological changes have been described in a case of pure HSP, with autosomal dominant inheritance, linked to the chromosome 2 locus. The patient described had an early history entirely compatible with pure HSP, developing progressive spastic paraparesis from the age of 19 years. However, at the age of 72 years he developed a rapidly progressive dementing illness with several epileptic seizures in the preterminal stages. The spinal cord pathology was entirely in keeping with pure HSP. However, the brain pathology was unusual. The interesting features included a loss of neurons in the substantia nigra with associated Lewy and pale bodies, and hippocampal changes with tau immunoreactive neurofibrillary tangles. Another noteworthy feature was the presence of tau positive inclusion bodies in the limbic area and neocortex. These changes have not previously been demon-

strated in HSP and also do not correspond to the pathology characteristic of other defined forms of dementia. It is possible, therefore, that these cerebral pathological features are a direct result of the expression of the abnormal SPG4 gene product.⁴⁰

Genetics

The clinical heterogeneity of HSP is matched by genetic heterogeneity. Autosomal dominant, recessive, and X-linked families are well recognised with several loci described. A summary of the current genetic classification of HSP is shown in table 4.

Autosomal dominant HSP (ADHSP)

Autosomal dominant inheritance is the commonest mode of inheritance in HSP and has been linked to loci on chromosome 2p (SPG4),^{38-40 71 86-94} chromosome 14q (SPG3),^{88-90 95-97} chromosome 15q (SPG6),⁹⁸ chromosome 8q (SPG8),⁹⁹ chromosome 10q (SPG9),⁶⁴ and chromosome 12q (SPG10).¹⁰⁰

CHROMOSOME 2P LOCUS SPG4

The chromosome 2 locus (SPG4) is by far the commonest locus to which ADHSP families are linked, accounting for about 40% of pedigrees. Recently the gene responsible for HSP at the SPG4 locus has been identified using a positional cloning strategy. The gene, spastin, is located on chromosome 2p22-p21 and is composed of 17 exons spanning a region of 90 kb.¹⁰¹ Spastin is a member of a group of proteins known as the ATPases associated with diverse cellular activities (AAA). The AAA proteins act in various cellular functions, including cell cycle regulation, protein degradation, organelle biogenesis, and vesicle mediated protein function.¹⁰² All of these cellular mechanisms involve the assembly and function of protein complexes and it has been proposed that AAA family members act as chaperone proteins in these complexes.¹⁰³ The AAA proteins share a 230 amino acid domain which imparts the ATPase function. Outside this domain very little homology is seen, except among closely related proteins of the same AAA protein subfamily.¹⁰² Interestingly paraplegin, a member of another AAA protein subgroup, has been shown to be involved in SPG7 autosomal recessive HSP (see later).¹⁰⁴ Spastin shares little homology with paraplegin apart from within the AAA domain and unlike paraplegin, is predicted to have a nuclear localisation. Spastin shows greater homology to a particular subclass of AAA proteins that include the yeast 26S proteasome subunits.¹⁰¹ Nuclear AAA proteins which exhibit homology to 26S proteasome subunits have been suggested to play an indirect part in gene regulation, inducing proteolytic activation or degradation of transcription factors.¹⁰⁵

To date the spastin mutations identified include missense, nonsense, and splice site mutations in various exons leading to major changes in the amino acid sequence of the AAA domain. This suggests that SPG4 is caused by

Table 4 Current genetic classification of hereditary spastic paraparesis

Genome database designation	Chromosome	Inheritance	Phenotype	Genetic defect
SPG1	Xq28	X-linked	Complicated	L1CAM
SPG2	Xq22	X-linked	Both	PLP
SPG3	14q11.2-24.3	AD	Pure	Unknown
SPG4	2p22-21	AD	Both	Spastin
SPG5	8p12-q13	AR	Pure	Unknown
SPG6	15q11.1	AD	Pure	Unknown
SPG7	16q24.3	AR	Both	Paraplegin
SPG8	8q24	AD	Pure	Unknown
SPG9	10q23.3-24.2	AD	Complicated	Unknown
SPG10	12q13	AD	Pure	Unknown
(SPG11)	15q13-15	AR	Both	Unknown

L1CAM=L1 cell adhesion molecule; PLP=proteolipid protein; AD=autosomal dominant; AR=autosomal recessive; ()=genome database designation unconfirmed.

a loss of function implying that a threshold level of spastin protein expression is critical for axonal preservation in the corticospinal tract.¹⁰¹

Although most SPG4 pedigrees have pure HSP, there have been three families with complicated phenotypes also linked to this locus.^{38–40} In the pure HSP families linked to this locus there is marked interfamilial and intrafamilial variation in the severity and the presence or absence of features such as bladder symptoms and diminished vibration sense.

Not all the published studies comment on the severity of the motor dysfunction in affected persons and in those that do often it is not easy to directly compare different reports. There tends to be a range of severity with the majority of affected people retaining the ability to walk independently or with minimal support. At the extremes are asymptomatic patients with pyramidal signs in the lower limbs with a normal or only slightly abnormal gait and a few patients who are chairbound or bedridden.^{71–94}

There is marked variability in the age at onset of symptoms in chromosome 2p linked families. Several published pedigrees show age at onset of symptoms ranging over 5 or more decades in different members of the same family. The mean age at onset of symptoms from the published pedigrees ranges from 12 to 43 years, demonstrating interfamilial variation also. The cause of such interfamilial and intrafamilial variation is not known. It may represent allelic heterogeneity or the presence of modifying genes or environmental factors. Another factor may be the obvious difficulty in recognising the precise timing of onset of symptoms that begin insidiously and have often been present for many years.

In some families anticipation is reported whereby the age at onset decreases in subsequent generations.^{40–71–89–92} This is seen in other neurodegenerative diseases—for example, Huntington's disease, dentatorubral-pallidolusian atrophy (DRPLA), and Machado-Joseph disease (MJD). However, these diseases are caused by an abnormal CAG repeat expansion and it is the increase in length of the repeat expansion that correlates with the younger onset of disease in subsequent generations.^{106–108} Before the discovery of the spastin gene there were extensive searches for evidence that SPG4 was a trinucleotide repeat disorder. Both the clinical and molecular genetic evidence as to whether expanded CAG repeats were pathogenic in SPG4 were inconclusive.^{109–111} However, the spastin gene does not contain an abnormally expanded CAG repeat and an alternative explanation for the apparent anticipation seen in some SPG4 families must be sought. This could simply be that where anticipation is reported, this may actually represent ascertainment bias, in which the disease is noticed early in children of affected parents.

Interestingly, in three chromosome 2p linked families, HSP was associated with cognitive impairment. Webb *et al* described a large family with 12 affected members. One patient died of a dementing illness aged 62 and four family

members with HSP were found to have dementia of subcortical type on neuropsychological testing.³⁸ In the French family, described by Heinzleff *et al*, four out of seven affected family members had cognitive impairment whereas one had severe dementia with some cortical features. Three affected members with cognitive impairment also had epilepsy.³⁹ In the family reported by White *et al*, the index member with HSP died with a late onset severe dementing illness with cortical and extrapyramidal features. Two other family members had memory impairment in old age, although detailed information on motor symptoms in these members was not available. One other family member with HSP had borderline learning difficulties with mild impairment in all aspects of memory. As in the other families there were family members with HSP without cognitive changes. The pathological findings in the patient with dementia in this pedigree have been discussed earlier.⁴⁰

CHROMOSOME 14Q LOCUS SPG3

The first ADHSP locus to be discovered was SPG 3 on chromosome 14q and only five published families have been linked to this locus. The location of the SPG3 gene on chromosome 14q11.2–q24.3 has been narrowed to a 7 cM region.^{88–90–95–97} Among the five families there does seem to be a trend to a relatively early age at onset of the disease, with the mean usually within the first or second decade. There has been no evidence to suggest anticipation of age at onset in successive generations. Initially it was thought that the SPG 3 phenotype may also be more severe than other subtypes of HSP. However, Huang *et al* and Gispert *et al* have published pedigrees in which the proportion of severely affected cases (those requiring a wheelchair) is not dissimilar to that seen in some SPG4 linked pedigrees.

Comparing with other loci, where it has been mentioned, there seems to be an absence of bladder or sensory involvement in the SPG 3 phenotype.

CHROMOSOME 15Q LOCUS SPG6

Only one, large North American, family has been linked to SPG6. The locus has been mapped to a ~7.3 cM interval in the centromeric region of chromosome 15q.⁹⁸ The mean age at onset was 22 years (12–35) and on the whole the phenotype was of pure HSP, although the phenotype is relatively severe. Almost one third of affected members required a wheelchair, some as early as 40 years of age. Pes cavus was almost always present in affected members, perhaps a reflection of disease severity.

CHROMOSOME 8Q LOCUS (SPG8)

Two families have been linked to the SPG8 locus on chromosome 8q24. One large North American family and more recently a British family, which enabled the genetic locus to be refined to a 3.4cM region.^{99–112} The mean age at onset of symptoms in the SPG8 linked pedigrees was comparable with SPG4 families. The phenotype seemed to be fairly severe,

particularly in the American family, in which 10/15 affected members over 40 years required the use of a wheelchair, eight of them for more than 50% of the time.¹¹³ In both pedigrees the clinical features were typical of pure HSP with some family members having diminished vibration sense, bladder symptoms, and pes cavus. Magnetic resonance imaging demonstrated marked spinal cord atrophy in one patient with moderate symptoms from the American family linked to chromosome 8q. A reduction in cross sectional area of 50% at the T9 level, compared with age and sex matched controls, was found.¹¹³

Evidence of mitochondrial dysfunction as a mechanism of disease at this locus was not found on histochemical or biochemical analysis of a muscle biopsy taken from one affected member.¹¹³

CHROMOSOME 10Q LOCUS SPG9

One large Italian pedigree has been linked to the SPG9 locus on chromosome 10q23.3–24.2 in a region spanning 12 cM.⁶⁴ The mean age at onset of symptoms varies from the first to third decade of life and the authors suggest evidence for anticipation over the three generations. The clinical phenotype is one of complicated HSP with the spastic paraparesis being associated with bilateral cataracts, gastroesophageal reflux with persistent vomiting, and distal amyotrophy secondary to an apparent axonal motor neuropathy. A pedigree with a similar complicated phenotype of congenital cataracts and spastic paraparesis has previously been described which may also prove to be due to the same gene at the SPG9 locus.¹¹⁴

CHROMOSOME 12Q LOCUS SPG10

The latest ADHSP locus to be discovered is SPG10 on chromosome 12q13 spanning a 9.2 cM region in a British family.¹⁰⁰ The mean age at onset of symptoms in affected family members was younger than that seen in SPG4 pedigrees, at 10.8 (SD 9.6) years. The phenotype was one of pure HSP with a wide range of disease severity with some patients requiring a wheelchair whereas others remained asymptomatic at the age of 40 years.

Reid *et al* described a further pedigree in which linkage to all five known ADHSP loci had been excluded, suggesting the presence of at least one more as yet undiscovered ADHSP locus.¹⁰⁰

Autosomal recessive HSP (ARHSP)

The recessive disease is far less common than the dominant form. Both pure and complicated phenotypes are seen. There are consanguineous families linked to three loci, SPG5 on chromosome 8p,¹¹⁵ SPG7 on chromosome 16q¹¹⁶, and the recently discovered locus on chromosome 15q,¹¹⁷ which at present does not have an official genome database designation.

CHROMOSOME 8P LOCUS SPG5

The SPG5 locus is on chromosome 8p12–q13 and it spans an interval of 32cM. The four Tunisian families linked to SPG5 are of the pure phenotype with a mean age at onset rang-

ing from 1–20 years. There does not seem to be a difference between the clinical features of pure ADHSP and pure ARHSP.¹¹⁵

CHROMOSOME 16Q LOCUS SPG7

The SPG7 locus is on chromosome 16q24.3 and at present three families have been linked to this locus. The phenotype is heterogeneous with both pure and complicated families being found. The initial family linked to SPG7 was described as pure although there were additional features, not normally seen in pure HSP, present in this family, reported by DeMichele *et al*, which included dysarthria.¹¹⁶

The protein encoded by SPG7 has been given the name paraplegin. Recently a homozygous 9.5 kb deletion in the last five exons of the paraplegin gene on chromosome 16q has been described in this original SPG7 linked family. When further unrelated patients with HSP were screened using single stranded confirmation polymorphism (SSCP) analysis, two additional frameshift mutations in the paraplegin gene were identified. One occurred in a pure ARHSP family from Italy, affected members showing a 2 bp deletion in exon 6. Another was found in a complicated ARHSP family whose additional clinical features included optic atrophy, with cortical and cerebellar atrophy seen on imaging. This mutation consisted of an insertion in the coding region of the last exon. All three SPG7 mutations lead to major abnormalities of the paraplegin protein. Paraplegin is a member of the mitochondrial metalloproteases, which are a subgroup of the AAA protein family. Other members of this subgroup include the yeast mitochondrial proteins Afg3p and Rcalp, which exhibit both proteolytic and chaperone-like activity and localise to the mitochondrial inner membrane. Targeting and localisation studies have demonstrated that the paraplegin protein localises to the mitochondrial subcellular compartment. The finding of evidence of mitochondrial dysfunction in muscle biopsy tissue from affected members of these families supports mitochondrial involvement in the disease process. The muscle abnormalities consisted of the presence of fibres negative for cytochrome oxidase and ragged red fibres which showed intense staining for succinate dehydrogenase, changes which suggest mitochondrial OXPHOS impairment.¹⁰⁴ A muscle biopsy from a patient with ARHSP linked to chromosome 8q showed no evidence of mitochondrial dysfunction, suggesting an alternative mechanism of disease in this type of HSP.¹¹³

Mitochondrial dysfunction has been identified in some neurodegenerative disorders. In diseases such as Parkinson's disease it seems that there may be direct involvement of the respiratory chain complexes. In Friedreich's ataxia and Huntington's disease the defects in OXPHOS seem to be secondary to alterations in proteins other than respiratory chain enzymes.¹¹⁸

Recently a paraplegin related gene AFG3L2 has been identified on chromosome 18p11.¹¹⁹ The predicted gene product has homology with paraplegin, the yeast mitochondrial ATPases,

Afg3p and Rcalp, and AFG3L1, a related gene.^{119 120} AFG3L2 has also been shown to localise to the mitochondrial subcellular compartment. Further investigation is required to establish how common paraplegin defects are in the various forms of HSP and establish if AFG3L1 or AFG3L2 is also involved in causing HSP, particularly in families with a complicated phenotype, where the multisystem involvement may be reminiscent of clinical features found in other mitochondrial disorders.

This class of gene may be involved in other neurological diseases and it is interesting that AFG3L2 lies within the region of chromosome 18p to which a form of idiopathic torsion dystonia has been linked.¹²¹

CHROMOSOME 15Q

After the discovery of SPG5 and SPG7 there still remained ARHSP families unlinked to any loci. Murrilo *et al* have recently uncovered what at present seems to be the commonest locus for ARHSP on chromosome 15q13–15.¹¹⁷ They screened eight families and found evidence of linkage to this new locus in seven.

The phenotype in these families is variable with both pure and complicated forms being described. In the pure families the age at onset was in the first decade in one and at the age of 43 years in the other, in which only one family member was affected. There was also phenotypic variation between the complicated families, although there were some similar features present in more than one family. The most interesting was atrophy or agenesis of the corpus callosum demonstrated on MRI, seen in both affected siblings from one family and in one affected member from another. In this latter member, periventricular white matter changes were also found. Both these families had similar ages at onset of disease symptoms in their second decade and mental retardation was a feature noted in one member from each family. Other associations with spastic paraplegia at this locus were mixed motor and sensory neuropathy in one family and mild cerebellar dysfunction in another two.

The association of HSP linked to chromosome 15q with agenesis of the corpus callosum and mental retardation is interesting because a gene for Andermann's syndrome or agenesis of the corpus callosum and peripheral neuropathy (ACCPN) has been shown to also have linkage to chromosome 15q.¹²² It may be that this form of HSP and Andermann's syndrome are allelic disorders with different mutations in the same gene giving rise to the varying phenotypes.¹¹⁷ This is seen in X-linked HSP where different mutations in the PLP gene give rise to either a HSP phenotype or Pelizaeus-Merzbacher disease.

X-linked HSP

Although X-linked HSP is rare, its molecular genetic basis is relatively well understood.

There are two different loci identified for X-linked HSP, SPG1 and SPG2.^{60 123} Families with complicated HSP have been linked to

both SPG1 and SPG2, whereas the pure phenotype has only been linked to SPG2.

X-LINKED SPG2 LOCUS

Complicated HSP linked to SPG2 consists of a core phenotype of spastic paraparesis, cerebellar syndrome, and mental retardation. Interfamilial variation is seen with the core features occurring to various degrees with or without additional features such as optic atrophy. Similarly, intrafamilial variation occurs.^{124 125} This had been reported in earlier descriptions of X-linked families.¹²⁶

The gene at the SPG2 locus is the proteolipid protein (PLP) gene. Mutations, most commonly duplications, in this gene are known to cause Pelizaeus-Merzbacher disease (PMD). This is a dysmyelinating disease affecting the CNS, which consists of early onset cerebellar and pyramidal signs, with rapid progression resulting in death usually in infancy or childhood. Complicated HSP pedigrees linked to the SPG2 locus have been shown to have mutations in the PLP gene in exons 3b, 4, or 6.^{127 128} Therefore different mutations in the same gene can produce either a PMD phenotype or a complicated HSP phenotype. The PLP is a major myelin protein involved in both myelin maturation and maintenance in the CNS. The less severe phenotype and later development of signs in SPG2 compared with PMD is due to the fact that PLP has a smaller isoform, DM-20. In both SPG2 and PMD, PLP concentrations are reduced, whereas the concentration of DM-20 is only significantly reduced in PMD. It is thought that the two isoforms have slightly different effects on myelin. The DM-20 isoform seems to be predominantly involved in myelin maturation whereas the PLP isoform, which is expressed at a later stage of development, has a role in myelin sheet compaction and maintenance. Myelin sheaths missing the PLP protein will be assembled and although they can function these eventually undergo accelerated turnover.¹²⁹ These differences may explain the marked phenotypic variation between SPG2 and PMD.

A further complicated family has been found with linkage to a region containing the SPG2 locus, with no mutation identified in the PLP gene. The authors suggest this may represent evidence for a nearby third locus for X-linked HSP.¹³⁰ However, in a proportion of patients with PMD no mutations have been identified.^{131 132} This could be due to the presence of unrecognised mutations in non-coding areas of the gene, or due to a mutation in an adjacent gene involved in either PLP gene regulation or myelin formation.

Pure X-linked HSP is very rare, with only five families described in the literature to date.^{123 133–136} Two of these families have been linked to the SPG2 locus.^{123 133} In only one of these families a single base substitution was found in exon 5 of the PLP gene, showing this pedigree of pure HSP to be allelic to complicated HSP (SPG2) and PMD.

X-LINKED LOCUS SPG1

The family with complicated HSP linked to SPG1 has marked phenotypic differences compared with the earlier pedigrees, which included the absence of cerebellar involvement, severe mental retardation, and congenital musculoskeletal abnormalities, most notably the absence of extensor hallucis longus.⁶⁰ This phenotype is due to a mutation in exon 26 of the L1 cell adhesion molecule (LICAM) gene.⁶¹ LICAM is a transmembrane glycoprotein which is mainly expressed by neurons and Schwann cells. It plays an essential part in the development of the nervous system, being involved in axon outgrowth and pathfinding. Different mutations in this gene give rise to the syndromes of MASA (mental retardation, aphasia, shuffling gait, and adducted thumbs), X-linked hydrocephalus, and X-linked agenesis of the corpus callosum. There is much interfamilial and intrafamilial variability in families with mutations in the LICAM gene. It is possible to have members with the various phenotypes within one family. The diseases are now referred to as being part of the clinical syndrome CRASH (corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraplegia, and hydrocephalus).¹³⁷

Conclusion

It is no surprise that there were early difficulties in attempting to classify HSP, which represents a heterogeneous group of diseases that at best may share a final common pathway in the neuronal degenerative process. Molecular genetic classification is now beginning to define the limits of the conditions and their genotype/phenotype correlations.

At present, mutations in four genes; LICAM, PLP, paraplegin, and spastin have been identified as playing a part in the development of an HSP phenotype, with the identity of the genes at the other seven loci still unknown. The recent discovery of the spastin and paraplegin genes opens a new era of exciting opportunities in which we can begin to investigate the physiology of the motor system and the degenerative process it undergoes, hopefully offering opportunities for treatment. The discovery of the remaining genes and their products can be expected in the near future which will further our understanding of these diseases.

The presence of such genetic heterogeneity underlying HSP goes some way to explain the marked phenotypic variation seen between families. However, the finding of similar intrafamilial variation can only be explained by the presence of genetic modifying factors or an unknown interaction with the environment. Meyer *et al* demonstrated mutations in the glutamate transporter gene EAAT2, in two out of seven family members affected with pure HSP. They postulate that an interaction with the allelic variant of EAAT2 and the unknown primary genetic defect may be responsible for the phenotypic variation seen within their family.¹³⁸

Despite the progress in the genetics of HSP, up to now there has been relatively little of

diagnostic relevance. This may now change with the discovery of the spastin gene, mutations in which may account for up to 50% of ADHSP. When seeing a patient with possible HSP, the first step remains to exclude other diagnoses. Genetic analysis will offer the potential for precise diagnosis in cases where mutations are identified. This will ultimately offer the possibility of presymptomatic or even prenatal diagnosis in families who want to undergo such testing. However, until the full mutational range of these genes is understood, the technical feasibility of setting up such analyses remains unclear. These are multiexon genes with various mutations, so the identification of a mutation may not be particularly straightforward. The potential for precise diagnosis none the less heralds a new area of management in HSP. In the coming years further rapid progress can be expected, both in the identification of new HSP related genes and in the underlying cell biology of motor system degeneration.

PJS is supported by the Wellcome Trust as a Senior Fellow in Clinical Science.

- 1 Strümpell A. Beiträge zur Pathologie des Rückenmarks. *Archiv für Psychiatrie und Nervenkrankheiten* 1880;10:676–717.
- 2 Strümpell A. Ueber die hereditäre spastische Spinalparalyse. *Deutsche Zeitschrift für Nervenheilkunde* 1893;4:173–88.
- 3 Lorrain M. *Contribution à l'étude de la paraplégie spasmodique familiale*. Paris: Steinheil, 1898.
- 4 Pratt RTC. *The genetics of neurological disorders*. Oxford: Oxford University Press, 1967:44.
- 5 Holmes GL, Shaywitz BA. Strümpell's pure familial spastic paraplegia: case study and review of the literature. *J Neurol Neurosurg Psychiatry* 1977;40:1003–8.
- 6 Osvath K. Paralysis spinalis spastica familiaris. *Deutsche Zeitschrift für Nervenheilkunde* 1968;193:287–323.
- 7 Bell J, Carmichael EA. On hereditary ataxia and spastic paraplegia. *Treasury of Human Inheritance* 1939;IV:141–281.
- 8 Bickerstaff ER. Hereditary spastic paraplegia. *J Neurol Neurosurg Psychiatry* 1950;13:134–45.
- 9 Harding AE. Hereditary pure spastic paraplegia: a clinical and genetic study of 22 families. *J Neurol Neurosurg Psychiatry* 1981;44:871–83.
- 10 Filla A, DeMichele G, Marconi R, *et al*. Prevalence of hereditary ataxias and spastic paraplegias in Molise, a region of Italy. *J Neurol* 1992;239:351–3.
- 11 Leone M, Bottachi E, D'Alessandro G, *et al*. Hereditary ataxias and paraplegias in Valle d'Aosta, Italy: a study of prevalence and disability. *Acta Neurol Scand* 1995;91:183–7.
- 12 Silva MC, Coutinho P, Pinheiro CD, *et al*. Hereditary ataxias and spastic paraplegias: methodological aspects of a prevalence study in Portugal. *J Clin Epidemiol* 1997;50:1377–84.
- 13 Polo JM, Calleja J, Combarros O, *et al*. Hereditary ataxias and paraplegias in Cantabria, Spain. An epidemiological and clinical study. *Brain* 1991;114:855–66.
- 14 Sutherland JM. Familial spastic paraplegia. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology*. Amsterdam: North-Holland, 1975:421–31.
- 15 Dürr A, Brice A, Serdaru M, *et al*. The phenotype of pure autosomal dominant spastic paraplegia. *Neurology* 1994;44:1274–7.
- 16 Polo JM, Calleja J, Combarros O, *et al*. Hereditary pure spastic paraplegia: a study of nine families. *J Neurol Neurosurg Psychiatry* 1993;56:175–81.
- 17 Cartledge NEF, Bone G. Sphincter involvement in hereditary spastic paraplegia. *Neurology* 1973;23:1160–3.
- 18 Bruyn RPM, Scheltens PH. Hereditary spastic paraparesis (Strümpell-Lorrain). In: de Jong JMBV, ed. *Handbook of clinical neurology*. Amsterdam: Elsevier, 1991:301–17.
- 19 Bruyn RPM, van Dijk JG. Clinically silent dysfunction of dorsal columns and dorsal spinocerebellar tracts in hereditary spastic paraparesis. *J Neurol Sci* 1994;125:206–11.
- 20 Schady W, Sheard A. A quantitative study of sensory function in hereditary spastic paraplegia. *Brain* 1990;113:709–20.
- 21 Bushman W, Steers WD, Meythaler JM. Voiding dysfunction in patients with spastic paraplegia: urodynamic evaluation and response to continuous intrathecal baclofen. *Neurology and urodynamics* 1993;12:163–70.
- 22 Opjordsmoen S, Nyberg-Hansen R. Hereditary spastic paraplegia with neurogenic bladder disturbances and syndactylia. *Acta Neurol Scand* 1980;61:35–41.

- 23 Schetlens P, Bruyn RPM, Hazenberg GJ. A Dutch family with autosomal dominant pure spastic paraparesis (Strümpell's disease). *Acta Neurol Scand* 1990;**82**:169–73.
- 24 Schwarz GA, Liu CN. Hereditary (familial) spastic paraplegia. *Archives of Neurology and Psychiatry* 1956;**75**:144–62.
- 25 Boustany R-MN, Fleishnick E, Alper CA, et al. The autosomal dominant form of pure familial spastic paraplegia: clinical findings and linkage analysis of a large pedigree. *Neurology* 1987;**37**:910–15.
- 26 Harding AE, Thomas PK. Peroneal muscular atrophy with pyramidal features. *J Neurol Neurosurg Psychiatry* 1984;**47**:168–72.
- 27 Dyck PJ. Inherited neuronal degeneration and atrophy affecting peripheral motor, sensory, and autonomic neurons. In: Dyck PJ, Thomas PK, Lambert EH, et al, eds. *Peripheral neuropathy*. 2nd ed. Philadelphia: WB Saunders, 1984:1600–55.
- 28 Ueyama H, Kumamoto T, Asahara K, et al. Hereditary motor and sensory neuropathy type V with spinal cord atrophy on magnetic resonance imaging. *Eur Neurol* 1993;**33**:399–400.
- 29 Silver JR. Familial spastic paraplegia with amyotrophy of the hands. *J Neurol Neurosurg Psychiatry* 1966;**29**:135–44.
- 30 Cross HE, McKusick VA. The Troyer syndrome. A recessive form of spastic paraplegia with distal muscle wasting. *Arch Neurol* 1967;**16**:473–85.
- 31 Bouchard JP, Barbeau A, Bouchard R, et al. Autosomal recessive spastic ataxia of Charlevoix-Saguenay. *Can J Neurol Sci* 1978;**5**:61.
- 32 Sutherland JM. Familial spastic paraplegia. Its relation to mental and cardiac abnormalities. *Lancet* 1957;ii:169–70.
- 33 Harding AE. Hereditary spastic paraplegias. *Semin Neurol* 1993;**13**:333–6.
- 34 Wells CR, Jankovic J. Familial spastic paraparesis and deafness. A new X-linked neurodegenerative disorder. *Arch Neurol* 1986;**43**:943–6.
- 35 Arjundas G, Ramamurthi B, Chettur L. Familial spastic paraplegia (a review with four case reports). *J Assoc Physicians India* 1971;**19**:653–7.
- 36 Pridmore S, Rao G, Abusah P. Hereditary spastic paraplegia with dementia. *Aust N Z J Psychiatry* 1995;**29**:678–82.
- 37 Rothner AD, Yahr F, Yahr MD. Familial spastic paraparesis, optic atrophy and dementia: clinical observations of affected kindred. *N Y State J Med* 1976;**76**:756–8.
- 38 Webb S, Coleman D, Byrne P, et al. Autosomal dominant hereditary spastic paraparesis with cognitive loss linked to chromosome 2p. *Brain* 1998;**121**:601–9.
- 39 Heinzl O, Paternotte C, Mahieux F, et al. Mapping of a complicated familial spastic paraplegia to a locus SPG4 on chromosome 2p. *J Med Genet* 1998;**35**:89–93.
- 40 White KD, Ince PG, Cookson M, et al. Clinical and pathological findings in hereditary spastic paraparesis linked to chromosome 2p. *Neurology* 2000 (in press).
- 41 Sommerfelt K, Kyllerman M, Sanner G. Hereditary spastic paraplegia with epileptic myoclonus. *Acta Neurol Scand* 1991;**84**:157–60.
- 42 Webb S, Flanagan N, Callaghan N, et al. A family with spastic paraparesis and epilepsy. *Epilepsia* 1997;**38**:495–9.
- 43 Yih JS, Wang S-J, Su M-S, et al. Hereditary spastic paraplegia associated with epilepsy, mental retardation and hearing impairment. *Paraplegia* 1993;**31**:408–11.
- 44 Gigli GL, Diomedes M, Bernardi G, et al. Spastic paraplegia, epilepsy and mental retardation in several members of a family: a novel genetic disorder. *Am J Med Genet* 1993;**45**:711–6.
- 45 Skre H. Hereditary spastic paraplegia in western Norway. *Clin Genet* 1974;**6**:165–83.
- 46 Kuroda S, Kazahaya Y, Otsuki S, et al. Familial spastic paraplegia associated with epilepsy. *Acta Med Okayama* 1985;**39**:113–7.
- 47 Gilman S, Romanul FCA. Hereditary dystonic paraplegia with amyotrophy and mental deficiency: clinical and neuropathological characteristics. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology*. Amsterdam: North Holland, 1975:445–65.
- 48 Dick AP, Stevenson CJ. Hereditary spastic paraplegia. Report of a family with associated extrapyramidal signs. *Lancet* 1953;ii:921–3.
- 49 Sjögren T, Larsson T. Oligophrenia in combination with congenital ichthyosis and spastic disorders: a clinical and genetic study. *Acta Psychiatr Neurol Scand* 1957;**32**(suppl 113):1–112.
- 50 Schady W, Smith CML. Sensory neuropathy in hereditary spastic paraplegia. *J Neurol Neurosurg Psychiatry* 1994;**57**:693–8.
- 51 Cavanagh NPC, Eames RA, Galvin RJ, et al. Hereditary sensory neuropathy with spastic paraplegia. *Brain* 1979;**102**:79–94.
- 52 Khalifeh RR, Zellweger H. Hereditary sensory neuropathy with spinal cord disease. *Neurology (Minneapolis)* 1963;**13**:406–11.
- 53 Koenig RH, Spiro AJ. Hereditary spastic paraparesis with sensory neuropathy. *Dev Med Child Neurol* 1970;**12**:576–81.
- 54 Nyberg-Hansen R, Refsum S. Spastic paraparesis associated with optic atrophy in monozygotic twins. *Acta Neurol Scand* 1972;**48**(suppl):261–3.
- 55 Bruyn GW, Went LN. A sex-linked heredo-degenerative neurological disorder, associated with Leber's optic atrophy. *J Neurol Sci* 1964;**1**:59–80.
- 56 Macrae W, Stieffel J, Todorov AB. Recessive familial spastic paraplegia with retinal degeneration. *Acta Genet Med Gemellol (Roma)* 1974;**23**:249–52.
- 57 Mahloudji M, Chuke PO. Familial spastic paraplegia with retinal degeneration. *Johns Hopkins Med J* 1968;**123**:142–4.
- 58 Tuck R, O'Neill BP, Gharib H, et al. Familial spastic paraplegia with Kallmann's syndrome. *J Neurol Neurosurg Psychiatry* 1983;**46**:671–4.
- 59 Baxter P, Connolly S, Curtis A, et al. Co-dominant inheritance of hyperreflexia and spastic paraparesis. *Dev Med Child Neurol* 1996;**38**:739–43.
- 60 Kenwrick S, Ionasescu V, Ionasescu G, et al. Linkage studies of X-linked recessive spastic paraplegia using DNA probes. *Hum Genet* 1986;**73**:264–6.
- 61 Jouet M, Rosenthal A, Armstrong G, et al. X-linked spastic paraplegia (SPG1), MASA syndrome and X-linked hydrocephalus result from mutations in the L1 gene. *Nat Genet* 1994;**7**:402–7.
- 62 Cross HE, McKusick VA. The Mast syndrome: a recessively inherited form of pre-senile dementia with motor disturbances. *Arch Neurol* 1967;**16**:1–13.
- 63 Kjellin K. Familial spastic paraplegia with amyotrophy, oligophrenia and central retinal degeneration. *Arch Neurol* 1959;**1**:133–40.
- 64 Seri M, Cusano R, Forabosco P, et al. Genetic mapping to 10q23.3-q24.2, in a large Italian pedigree, of a new syndrome showing bilateral cataracts, gastroesophageal reflux, and spastic paraparesis with amyotrophy. *Am J Hum Genet* 1999;**64**:586–93.
- 65 Worster-Drought C, Greenfield JG, McMenemy W. A form of familial presenile dementia with spastic paralysis. *Brain* 1944;**67**:38–43.
- 66 Manson J. Hereditary spastic paraplegia with ataxia and mental defect. *BMJ* 1920;ii:477.
- 67 Tedeschi G, Allocca S, Di Costanzo A, et al. Multisystem involvement of the central nervous system in Strümpell's disease. *J Neurol Sci* 1991;**103**:55–60.
- 68 Cummings JL. Subcortical dementia. *Br J Psychiatry* 1986;**149**:682–97.
- 69 Neary D, Snowden JS, Mann DMA, et al. Frontal lobe dementia and motor neurone disease. *J Neurol Neurosurg Psychiatry* 1990;**53**:23–32.
- 70 Claus D, Waddy HM, Harding AE, et al. Hereditary motor and sensory neuropathies and hereditary spastic paraplegia: a magnetic stimulation study. *Ann Neurol* 1990;**28**:43–9.
- 71 Nielsen JE, Krabbe K, Jennum P, et al. Autosomal dominant pure spastic paraplegia: a clinical, paraclinical and genetic study. *J Neurol Neurosurg Psychiatry* 1998;**64**:61–6.
- 72 Pelosi L, Lanzillo B, Perretti A, et al. Motor and somatosensory evoked potentials in hereditary spastic paraplegia. *J Neurol Neurosurg Psychiatry* 1991;**54**:1099–102.
- 73 Schady W, Dick JPR, Sheard A, et al. Central motor conduction studies in hereditary spastic paraplegia. *J Neurol Neurosurg Psychiatry* 1991;**54**:775–9.
- 74 Aalfs CM, Koelman JHTM, Posthumus Meyjes FE, et al. Posterior tibial and sural nerve somatosensory evoked potentials: a study in spastic paraparesis and spinal cord lesions. *Electroencephalogr Clin Neurophysiol* 1993;**89**:437–41.
- 75 Mcleod JG, Morgan JA, Reye C. Electrophysiological studies in familial spastic paraplegia. *J Neurol Neurosurg Psychiatry* 1977;**40**:611–15.
- 76 Thomas PK, Jefferys JGR, Smith IS, et al. Spinal somatosensory evoked potentials in hereditary spastic paraplegia. *J Neurol Neurosurg Psychiatry* 1981;**44**:243–6.
- 77 Tyrer JH, Sutherland JM. The primary spinocerebellar atrophies and their associated defects, with a study of the foot deformity. *Brain* 1961;**84**:289–300.
- 78 Sjaastad O, Berstad J, Gjesdahl P, et al. Homocarnosinosis. 2. A familial metabolic disorder associated with spastic paraplegia, progressive mental deficiency, and retinal pigmentation. *Acta Neurol Scand* 1976;**53**:275–90.
- 79 Ormerod IEC, Harding AE, Miller DH, et al. Magnetic resonance imaging in degenerative ataxic disorders. *J Neurol Neurosurg Psychiatry* 1994;**57**:51–7.
- 80 Kramer W. Hereditary spinal spastic paraplegia (Strümpell-Lorrain's disease). *Neuropathol Appl Neurobiol* 1977;**3**:488–9.
- 81 Schwarz GA. Hereditary (familial) spastic paraplegia. *Arch Neurol Psychiatry* 1952;**68**:655–82.
- 82 Sack GH, Huether CA, Garg N. Familial spastic paraplegia: clinical and pathological studies in a large kindred. *Johns Hopkins Med J* 1978;**143**:117–21.
- 83 Bruyn RPM. The neuropathology of hereditary spastic paraparesis. *Clin Neurol Neurosurg* 1992;**94**(suppl):s16–18.
- 84 Behan WMH, Maia M. Strümpell's familial spastic paraplegia: genetics and neuropathology. *J Neurol Neurosurg Psychiatry* 1974;**37**:8–20.
- 85 Kahlstorf A. Klinischer und histopathologischer Beitrag zur hereditären spastischen Spinalparalyse. *Zeitschrift für die gesamte Neurologie und Psychiatrie* 1937;**159**:774–80.
- 86 Nance MA, Raabe WA, Midani H, et al. Clinical heterogeneity of familial spastic paraplegia linked to chromosome 2p21. *Hum Hered* 1998;**48**:169–78.
- 87 Matsuura T, Sasaki H, Wakisaka A, et al. Autosomal dominant spastic paraplegia linked to chromosome 2p: clinical and genetic studies of a large Japanese pedigree. *J Neurol Sci* 1997;**151**:65–70.
- 88 Hentati A, Pericak-Vance MA, Lennon F, et al. Linkage of a locus for autosomal dominant spastic paraplegia to chromosome 2p markers. *Hum Mol Genet* 1994;**3**:1867–71.
- 89 Hazan J, Fontaine B, Bruyn RPM, et al. Linkage of a new locus for autosomal dominant familial spastic paraplegia to chromosome 2p. *Hum Mol Genet* 1994;**3**:1569–73.

- 90 Lennon F, Gaskell PC, Wolpert C, et al. Linkage and heterogeneity in hereditary spastic paraparesis. *Am J Hum Genet* 1995;57(suppl):A217.
- 91 Dürr A, Davoine C-S, von Fellenger J, et al. Phenotype of autosomal dominant spastic paraplegia linked to chromosome 2. *Brain* 1996;119:1487-96.
- 92 Bürger J, Metzke H, Patternote C, et al. Autosomal dominant spastic paraplegia with anticipation maps to a 4-cM interval on chromosome 2p21-p24 in a large German family. *Hum Genet* 1996;98:371-5.
- 93 Kobayashi H, Garcia CA, Alfonso G, et al. Molecular genetics of familial spastic paraplegia: a multiple of responsible genes. *J Neurol Sci* 1996;137:131-8.
- 94 Reid E, Grayson C, Rogers MT, et al. Locus-phenotype correlations in autosomal dominant pure hereditary spastic paraplegia: a clinical and molecular genetic study of 28 United Kingdom families. *Brain* 1999;122:1741-55.
- 95 Hazan J, Lamy C, Melki J, et al. Autosomal dominant familial spastic paraplegia is genetically heterogeneous and one locus maps to chromosome 14q. *Nat Genet* 1993;5:163-7.
- 96 Huang S, Zhuyu, Li H, et al. Another pedigree with pure autosomal dominant spastic paraplegia (AD-FSP) from Tibet mapping to 14q11.2-q24.3. *Hum Genet* 1997;100:620-3.
- 97 Gispert S, Santos N, Damen R, et al. Autosomal dominant familial spastic paraplegia: reduction of the FSP1 candidate region on chromosome 14q to 7 cM and locus heterogeneity. *Am J Hum Genet* 1995;56:183-7.
- 98 Fink JK, Wu C-tB, Jones SM, et al. Autosomal dominant familial spastic paraplegia: tight linkage to chromosome 15q. *Am J Hum Genet* 1995;56:188-92.
- 99 Hedera P, Rainer S, Alvarado D, et al. Novel locus for autosomal dominant hereditary spastic paraplegia, on chromosome 8q. *Am J Hum Genet* 1999;64:563-9.
- 100 Reid E, Dearlove M, Rhodes M, et al. A new locus for autosomal dominant pure hereditary spastic paraplegia mapping to chromosome 12q13, and evidence for further genetic heterogeneity. *Am J Hum Genet* 1999;65:757-63.
- 101 Hazan J, Fonknechten N, Mavel D, et al. Spastin, a novel AAA protein, is altered in the most frequent form of autosomal dominant spastic paraplegia. *Nat Genet* 1999;23:296-303.
- 102 Patel S, Latterich M. The AAA team: related ATPases with diverse functions. *Cell Biology* 1998;8:65-71.
- 103 Neuwald AF, Aravind L, Spouge JL, et al. AAA: a class of chaperone-like ATPases associated with the assembly, operation and disassembly of protein complexes. *Genome Res* 1999;9:27-43.
- 104 Casari G, De Fusco M, Ciarmatori S, et al. Spastic paraplegia and OXPHOS impairment caused by mutations in paraplegin, a nuclear-encoded mitochondrial metalloprotease. *Cell* 1998;93:973-83.
- 105 Confalonieri F, Duguet M. A 200-amino acid ATPase module in search of a basic function. *Bioessays* 1995;17:639-50.
- 106 Maciel P, Gaspar C, DeStefano AL, et al. Correlation between CAG repeat length and clinical features in Machado-Joseph disease. *Am J Hum Genet* 1995;57:54-61.
- 107 Koide R, Ilkeuchi T, Onodera O, et al. Unstable expansion of CAG repeat in hereditary dentatorubral-pallidolusian atrophy (DRPLA). *Nat Genet* 1994;6:9-13.
- 108 Andrew SE, Goldberg YP, Kremer B, et al. The relationship between trinucleotide repeat (CAG) repeat length and clinical features of Huntington's disease. *Nat Genet* 1993;4:398-403.
- 109 Nielsen JE, Koefoed P, Abell K, et al. CAG repeat expansion in autosomal dominant pure spastic paraplegia linked to chromosome 2p21-p24. *Hum Mol Genet* 1997;6:1811-16.
- 110 Benson KF, Horwitz M, Wolff J, et al. CAG repeat expansion in autosomal dominant familial spastic paraparesis: novel expansion in subset of patients. *Hum Mol Genet* 1998;7:1779-86.
- 111 Trotter Y, Lutz Y, Stevanin G, et al. Polyglutamine expansion as a pathological epitope in Huntington's disease and four dominant cerebellar ataxias. *Nature* 1995;378:403-7.
- 112 Reid E, Dearlove AM, Whiteford ML, et al. Autosomal dominant spastic paraplegia. Refined SPG8 locus and additional genetic heterogeneity. *Neurology* 1999;53:1845-9.
- 113 Hedera P, DiMauro S, Bonilla E, et al. Phenotypic analysis of autosomal dominant hereditary spastic paraplegia linked to chromosome 8q. *Neurology* 1999;53:44-50.
- 114 Slavotinek AM, Pike M, Mills K, et al. Cataracts, motor system disorder, short stature, learning difficulties, and skeletal abnormalities: a new syndrome? *Am J Med Genet* 1996;62:42-7.
- 115 Hentati A, Pericak-Vance MA, Hung W-Y, et al. Linkage of pure autosomal recessive familial spastic paraplegia to chromosome 8 markers and evidence of genetic locus heterogeneity. *Hum Mol Genet* 1994;3:1263-7.
- 116 De Michele G, De Fusco M, Cavalcanti F, et al. A new locus for autosomal recessive hereditary spastic paraplegia maps to chromosome 16q24.3. *Am J Hum Genet* 1998;63:135-9.
- 117 Murillo F, Kobayashi H, Pegoraro E, et al. Genetic localization of a new locus for recessive familial spastic paraparesis to 15q13-15. *Neurology* 1999;53:50-6.
- 118 Schapira AHV. Mitochondrial involvement in Parkinson's disease, Huntington's disease, hereditary spastic paraplegia and Friedreich's ataxia. *Biochim Biophys Acta* 1999;1410:159-70.
- 119 Banfi S, Bassi MT, Andolfi G, et al. Identification and characterization of AFG3L2, a novel paraplegin-related gene. *Genomics* 1999;59:51-8.
- 120 Shah ZH, Migliosi V, Wang A, et al. Chromosomal locations of three human nuclear genes (RPSM12, TUFM, and AFG3L1) specifying putative components of the mitochondrial gene expression apparatus. *Genomics* 1998;48:384-8.
- 121 Leube B, Rudnicki D, Ratzlaff T, et al. Idiopathic torsion dystonia: assignment of a gene to chromosome 18p in a German family with adult onset, autosomal dominant inheritance and purely focal distribution. *Hum Mol Genet* 1996;5:1673-7.
- 122 Casaubon LK, Melanson M, Lopes-Cendes I. The gene responsible for a severe form of peripheral neuropathy and agenesis of the corpus callosum maps to chromosome 15q. *Am J Hum Genet* 1996;58:28-34.
- 123 Keppen LD, Leppert MF, O'Connell P, et al. Etiological heterogeneity in X-linked spastic paraplegia. *Am J Hum Genet* 1987;41:933-43.
- 124 Bonneau D, Rozet J-M, Bulteau C, et al. X-linked spastic paraplegia (SPG2): clinical heterogeneity at a single locus. *J Med Genet* 1993;30:381-4.
- 125 Goldblatt J, Ballo R, Sachs B, et al. X-linked spastic paraplegia: evidence for homogeneity with a variable phenotype. *Clin Genet* 1989;35:116-20.
- 126 Johnson AW, McKusick VA. A sex-linked recessive form of spastic paraplegia. *Am J Hum Genet* 1962;14:83-94.
- 127 Kobayashi H, Hoffman EP, Marks HG. The rumpshaker mutation in spastic paraplegia. *Nat Genet* 1994;7:351-2.
- 128 Saugier-Verber P, Munnich A, Bonneau D, et al. X-linked spastic paraplegia and Pelizaeus-Merzbacher disease are allelic disorders at the proteolipid protein locus. *Nat Genet* 1994;6:257-61.
- 129 Griffiths IR, Montague P, Dickinson P. The proteolipid protein gene. *Neuropathol Appl Neurobiol* 1995;21:85-96.
- 130 Steinmüller R, Lantigua-Cruz A, Garcia-Garcia R, et al. Evidence of a third locus in X-linked recessive paraplegia. *Hum Genet* 1997;100:287-9.
- 131 Hodes ME, Pratt VM, Dlouhy SR. Genetics of Pelizaeus-Merzbacher disease. *Dev Neurosci* 1993;14:383-94.
- 132 Boespflug-Tanguy O, Mimault C, Melki J, et al. Genetic homogeneity of Pelizaeus-Merzbacher disease: tight linkage to the proteolipoprotein locus in 16 affected patients. PMD clinical group. *Am J Hum Genet* 1994;55:461-7.
- 133 Cambi F, Tang X-M, Cordray P, et al. Refined genetic mapping and proteolipid protein mutation analysis in X-linked pure hereditary spastic paraplegia. *Neurology* 1996;46:1112-17.
- 134 Raggio JF, Thurmon TF, Anderson EE. X-linked hereditary spastic paraplegia. *J La State Med Soc* 1973;125:4-6.
- 135 Thurmon TF, Walker BA, Scott CL, et al. Two kindreds with a sex-linked recessive form of spastic paraplegia. *Birth Defects* 1971;7:219-21.
- 136 Zatz M, Penha-Serrano C, Otto PA. X-linked recessive type of pure spastic paraplegia in a large pedigree: absence of detectable linkage to Xg. *J Med Genet* 1976;13:217-22.
- 137 Franssen E, Lemmon V, Van Camp G, et al. CRASH syndrome: clinical spectrum of corpus callosum hypoplasia, retardation, adducted thumbs, spastic paraparesis and hydrocephalus due to mutations in one single gene, LI. *Eur J Hum Genet* 1995;3:273-84.
- 138 Meyer T, Munch C, Volkel H, et al. The EAAT2 (GLT-1) gene in motor neuron disease: absence of mutations in amyotrophic lateral sclerosis and a point mutation in patients with hereditary spastic paraplegia. *J Neurol Neurosurg Psychiatry* 1998;65:594-6.