

## CASE REPORTS

### Hereditary spastic paraplegia

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#### Abstract

Hereditary spastic paraplegia (HSP) or Strümpell–Lorrain syndrome is a heterogeneous group of inherited disorders, with prevalence ranged from 4.3 to 9.6 cases per 100 000 population. A common feature of these disorders is the slowly progressive and often severe spasticity, noticeably especially in the low limbs. Conventionally, HSP is divided into two clinical groups, uncomplicated (pure spastic paraparesis) or complicated HSP depending on the presence of other neurological features in addition to spastic paraparesis. Inheritance may be autosomal dominant, autosomal recessive or rarely X-linked, but autosomal dominant inheritance is most commonly associated with pure forms of the disease, whereas autosomal recessive HSP shows greater phenotypic variability, including several well-defined syndromes. Genetic studies have revealed as many as 31 different chromosomal HSP loci. We investigated two subjects, brother and sister, who were diagnosed using the criteria for a diagnosis of HSP proposed by Fink (1996), as “definitely affected” with HSP. As some particularities, we noticed an iliopsoas pseudohypertrophy in male patient and a mild atrophy in female, maybe due to degeneration of anterior columns. Family history recorded the presence of same manifestations in relatives. The pedigree of patients revealed some anomalies that could be related with the pathology. Our findings supported the diagnosis of complicated form of HSP in both cases.

**Keywords:** hereditary spastic paraplegia, magnetic resonance imaging, gene mutations, neurological features.

#### □ Introduction

Hereditary spastic paraplegia (HSP) is a heterogeneous group of inherited disorders, with prevalence ranged from 4.3 to 9.6 cases per 100 000 population [1, 2].

Before the advanced molecular genetic studies, several classifications of HSP had been proposed, based on the mode of inheritance, the age of symptoms onset, and the presence of additional clinical features. The essential clinical findings for diagnosis are the slowly progressive spasticity, pyramidal weakness, hyperreflexia and extensor plantar responses, with little or no involvement of the upper limbs [3]. Conventionally, HSP are divided into two clinical groups, *uncomplicated* (pure spastic paraparesis) or *complicated* HSP depending on the presence of other neurological features in addition to spastic paraparesis [4].

In pure HSP, the age of onset can be from infancy to the eighth decade, with a marked interfamilial variation due to genetic heterogeneity in this condition. The key neuropathological feature of pure HSP is the distal axonal degeneration, maximal in the terminal part of the spinal cord corticospinal tracts and dorsal ascending tracts. Important negative findings on examination are normal cranial nerve function and no evidence of corticobulbar tract involvement [5].

Complicated HSP includes a considerable number of conditions in which spasticity is accompanied by central and peripheral nervous system involvement: muscle amyotrophy, optic atrophy, pigmentary retinopathy,

mental retardation, extrapyramidal disease, ataxic syndrome, dementia, deafness, ichthyosis, peripheral neuropathy and epilepsy [5].

Inheritance may be autosomal dominant, autosomal recessive or rarely X-linked, but autosomal dominant inheritance is most commonly associated with pure forms of the disease, whereas autosomal recessive HSP shows greater phenotypic variability, including several well-defined syndromes [6].

#### □ Patients and Methods

Subjects – brother and sister – were diagnosed, using the criteria for a diagnosis of HSP proposed by Fink JK *et al.* (1996) [7], as “definitely affected” with HSP if (1) all alternative disorders have been excluded, (2) the family history supports an inherited disorder, (3) subjects report a progressive gait disturbance, and (4) neurological examination shows a frank corticospinal tract deficit in the lower limbs, including grade 4 hyperreflexia and extensor plantar responses.

The patients were fully investigated for spastic paraparesis. Tests included full blood count, electrolytes, liver function tests, glucose, blood urea and nitrogen, erythrocyte sedimentation rate, thyroid function tests, syphilis serology, HTLV (human T-cell lymphocytotropic virus), vitamin B12 and folate, visual evoked responses, neuroimaging studies including MRI of the brain and spinal cord or myelogram of the complete spinal cord.

## ■ Results

### Case no. 1

A 21-year-old man presented in our clinic with progressive spastic paraparesis for evaluation and rehabilitation. He was born of non-consanguineous marriage and the delivery was full-term and vaginal without any neonatal hypoxia or jaundice. There were no unusual problems in his perinatal period and he experienced no serious illnesses or injuries in his childhood. Based on collateral history, the patient sister and two first male cousins are affected, the maternal grandfather was affected. He had a borderline mental retardation and by the age 15, he developed a slowly progressive spastic paraparesis.

On actual examination, he had pronounced intellectual impairment and his speech was dysarthric, impoverished, and lacked spontaneity. He has a short stature (165 cm), thoracic kyphosis (Figure 1) and genu



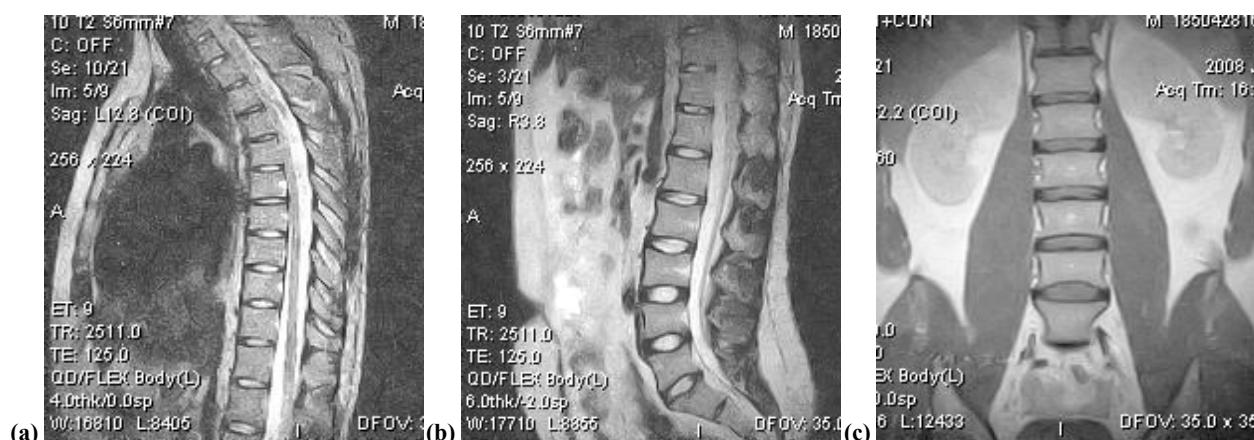
**Figure 1 – Thoracic kyphosis.**

recurvatum (Figure 2). Physical examination of the lower extremity showed a bilateral equinovarus deformity, paraparesis, severe spasticity, hyperreflexia with clonus (4+ DTR) of the both ankles, extensor plantar responses and positive Babinski, mild diminution of lower-extremity vibration and joint position sensation, without fasciculation or involvement of upper extremities and bulbar muscles. Hypertonic urinary disturbance with inability to completely empty the bladder was noted. He walked with difficulty using canes. Laboratory investigations, as mentioned before, were normal. EEG, visual evoked responses, ophthalmoscopic exam, electromyography (EMG), and nerve conduction studies were normal.

Cranial magnetic resonance imaging (MRI) revealed a thin corpus callosum and medial frontal atrophy. Magnetic resonance imaging of the spinal cord were normal but showed pseudohypertrophy of iliopsoas muscle (Figure 3).



**Figure 2 – Genu recurvatum.**



**Figure 3 – Sagittal T2 weighted image shows normal spinal cord (a, b) and coronal T1-weighted (c), demonstrating pseudohypertrophied iliopsoas muscles.**

Patient's karyotype revealed a deletion on chromosome 11q, in all analyzed metaphases (Figure 4).

After all diagnostic work-up (brain and spine MRI, evoked potentials, EMG, laboratory investigation) other disorders presenting with spastic paraparesis (amyotrophic lateral sclerosis ALS, funicular myelosis, multiple sclerosis, Friedreich ataxia, lues, etc.) were excluded, allowing, on the ground of the family history

and the clinical features, the diagnosis of hereditary spastic paraparesis.



**Figure 4 – Extract from karyotype 46, XY, 11q del.**

## Case no. 2

A 25-year-old woman (the first case's sister who had been referred to our clinic and at the same time as mentioned for case no. 1) was affected with the same problems as his brother, but she developed spasticity and balance difficulty by the age 16.

Physical examination revealed bilateral equinovarus deformity and pes cavus (Figure 5).

On neurological evaluation, she presented a severe spasticity and hyperreflexia of the lower limbs with extensor plantar responses and distal sensory deficits. Vibration and proprioception were reduced bilaterally. On detailed neuropsychological examination no cognitive decline was revealed. She also complained of increasing urinary incontinence.

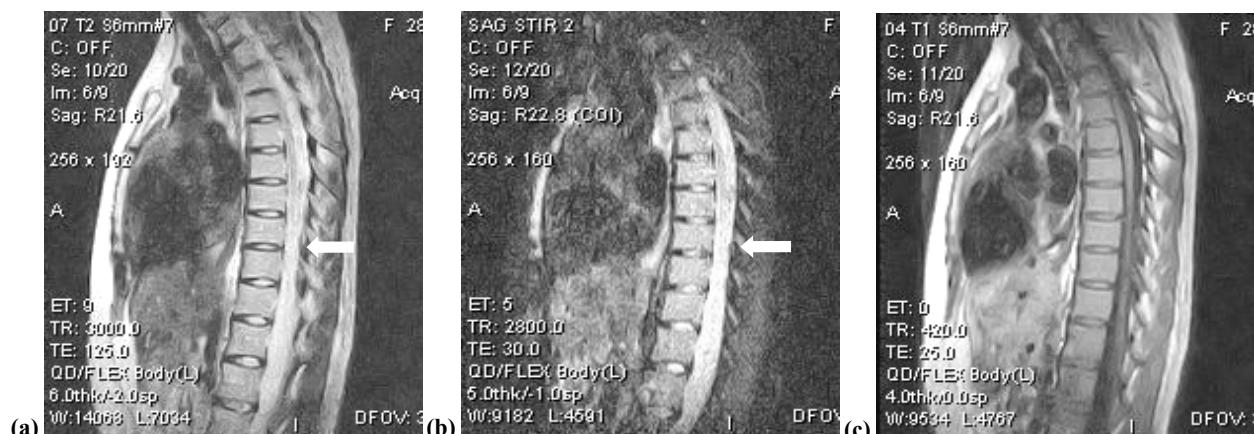
Other paraclinical investigations were also normal.

Magnetic resonance imaging of the brain showed a marked atrophy of the splenium corporis callosi with hypertense T2-signal and no contrast enhancement. Magnetic resonance imaging of the spinal cord demonstrated a mild atrophy of the thoracic spinal

cord (Figure 6). The sagittal diameters at the thoracic levels were less than 5.0 mm markedly (60–70%) reduced compared to publish data from normal control subjects.



**Figure 5 – Bilateral equinovarus deformity and pes cavus.**



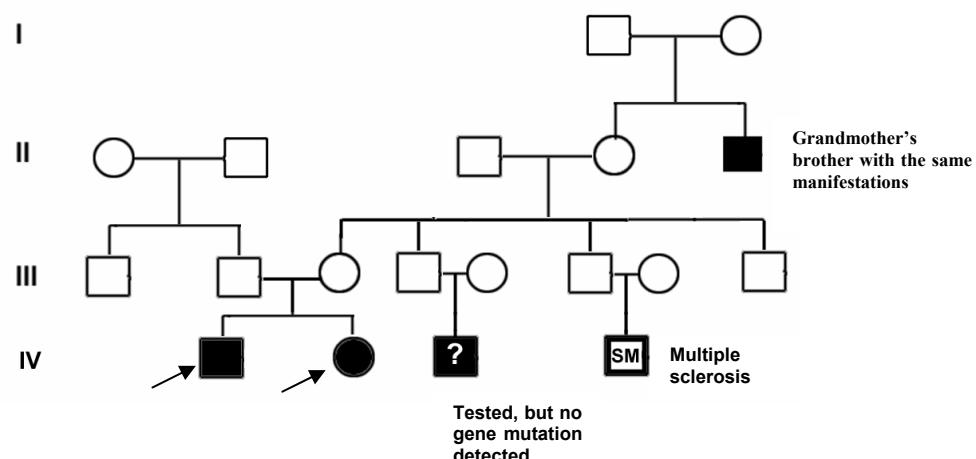
**Figure 6 – Cervical and thoracic spinal cord MRI in the sagittal plane (a–c) of the female patient showing cord mild atrophy in thoracic region.**

Both brothers (cases no. 1 and no. 2) had been clinically diagnosed as having hereditary spastic paraplegia.

Family history, recording in patients' notes, revealed the presence of same manifestations in two cousins and

grandmother's brother (Figure 7). One of the cousins has been recorded with multiple sclerosis, underlining the problem of differential diagnosis. Second cousin has been investigated in a molecular diagnostic laboratory, but no gene mutation was identified.

**Figure 7 – Family pedigree.**



## Discussion

Pathologic changes in hereditary spastic paraparesis are mostly limited to the spinal cord with degeneration of the distal ends of corticospinal tracts and dorsal columns. Involvement of the brain, such as corpus callosum atrophy or white matter lesions, has also been described. A broader use of magnetic resonance imaging has allowed the *in vivo* description of such lesions. Considering the involvement of the spinal cord, several radiological studies have documented either normal spinal cord findings or a mild atrophy of the cervical and thoracic segments [8].

In pure HSP, the patients present lower limb spasticity, particularly in the hamstrings, quadriceps, and triceps surae, muscle weakness in iliopsoas and tibialis anterior, walking difficulty or gait disturbance, stiffness of legs, mild sensory abnormalities in the lower limbs, absent ankle jerks, pes cavus, and urinary sphincter disturbance [5].

The most severely affected pathways in pure HSP are the crossed and uncrossed corticospinal tracts to the lower limbs and the fasciculus gracilis fibres from the lower limbs. Demyelination and gliosis can accompany the axonal loss and involvement of spinocerebellar tracts is seen in about 50% of cases [5]. It was suggested that may also be found a mild loss of anterior horn cells and decreased numbers of Betz cells [9]. Dorsal root ganglia, posterior roots, and peripheral nerves are usually normal.

We have to consider the multiple dysfunctions involving also central and peripheral nervous system associated with the main condition in our patients and we can interpret them as a complicated form of HSP.

As particularities of cases, we noticed iliopsoas pseudohypertrophy in male patient and marked atrophy in thoracic spinal cord due to anterior columns degeneration in female patient.

Genetic studies have revealed as many as 31 different chromosomal HSP loci [10]. Twenty HSP loci and nine HSP genes have been discovered, in which five genes identified for autosomal dominant subtypes [3, 11]. Mutations in the genes *spastin* (*SPG4*) and *atlastin* (*SPG3A*) account for up to 50% of all HSP cases. HSP due to *SPG4* mutations is generally described as a pure form of the disease [12]. More than 150 different mutations have been identified in all exons of the *SPG4* gene, all types of DNA alterations being observed, including missense, non-sense, splice-site mutations, and small insertions or deletions with a haplo-insufficiency pathogenic mechanism [12]. Mutations in *KIF5A*, *HSP60* and *NIPA1* occur in <1% of HSP cases [13–15] and mutation *REEP1* mutations occurred in 6.5% of cases [16].

Although, there are no chromosomal mutations noticed in HSP, presence of a deletion on chromosome 11 in one patient could be discussed regarding the complexity of the symptoms associated with the main pathology. However, there are some known candidate genes for HSP on chromosome 11, involved in progressive joint contractures and dysarthria. SPOAN syndrome (spastic paraparesis, optic atrophy, and

neuropathy) is a complicated form of HSP, which present also progressive joint contractures and spine deformities [17]. Chromosomal locus involved is 11q13. First symptoms of HSP appear in infancy, progressive neuropathy in childhood through adolescence, and dysarthria in the third decade [11].

## Conclusions

Raising knowledge regarding molecular bases of HSP made the classification of this pathology more complex, but without a direct impact on clinical practice. First step to a correct diagnosis in HSP is to exclude other similar pathologies, with the same signs and symptoms. Differential diagnosis is still based on neurological exam, correct interpretation of cranial and spinal cord magnetic resonance imaging and biochemical tests proposed by *HSP Working Group*. Recent molecular studies can contribute to decipher the mechanisms of corticomotor degenerescence in hereditary spastic paraparesis.

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