A Hundred Faces for a Unique Disorder: Hereditary Spastic Paraplegia

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1. Introduction

Hereditary Spastic Paraplegia (HSP), also known as Hereditary Spastic Paraparesis, Familial Spastic Paraplegia, and Strumpell-Lorrain syndrome, refers to a group of inherited neurodegenerative disorders characterized by lesions of the pyramidal tract. The disorder manifests with progressive lower limb spasticity and weakness, and exhibits wide clinical and genetic variability [1–4]. Von Strumpell [5] is credited with reporting the first cases of HSP, followed by Lorrain [6], who contributed significantly to the study of this disorder. The term Strumpell-Lorrain syndrome has been used, but Hereditary Spastic Paraplegias (HSPs) is now the more common name. The prevalence of this disorder ranges from 0.1 to 9.6 per 100,000 individuals [7] with epidemiological results varying widely based on different methods and geographical factors [8]. According to Fink [3], HSPs are defined as a genetically and clinically heterogeneous group of slowly progressing neurological disorders. In the “pure” form, HSP is characterized by pyramidal signs (weakness, spasticity, brisk tendon reflexes, and extensor plantar responses) predominantly affecting the lower limbs, with possible association of sphincter disturbances and deep sensory loss. In the “complex” form, additional neurological or non-neurological features are present. HSP has also been reported as a feature of more complex neurodegenerative or neurodevelopmental disorders. Neuropathological analysis in uncomplicated forms of HSP may show axonal degeneration prevalent in the terminal portion of the longest descending tracts [7].

2. Genetic Causes

HSPs are classified based on hereditary factors; various genetic types of HSP may be inherited with autosomal dominant, autosomal recessive, X-linked recessive, and maternal (mitochondrial) traits. Genetic loci involved in HSP are numerous and are constantly being identified. More than 80 genes have been associated with HSP so far. The codified proteins interfere with several physiological processes such as axonal transport, myelination, endomembrane trafficking, mitochondrial function, vesicle transport, and metabolism of complexes lipids and nucleotides, causing the basis of the clinical events [3]. Mutations in four genes LICAM, PLP, paraplegin, and spastin have been shown to be involved in the pathogenesis of HSP. Table 1 (Ref. [9]) shows the most frequent HSP gene-diseases, HSP and Alzheimer’s disease (AD), Autosomal Recessive (AR), X-linked, and mitochondrial types of inheritance, as presented by Hedera [9].

3. Clinical Presentation

The clinical course of the disorder has been reported to be usually slower in childhood onset than in adult onset, but this is not always the rule. We present the course of two brothers who were followed from childhood to adulthood, and who directly and serially manifested the uncomplicated HSP type. The clinical presentation is reported herein as an example of the long-lasting clinical course in HSP patients. The two brothers, born to consanguineous parents (first cousins), were affected by uncomplicated HSP. The parents were clinically normal and refused to undergo genetic analysis for themselves and their sons. The affected brothers were diagnosed in childhood and serially followed in this Institution from the ages of 5 and 7 years old to their current adult ages of 36 and 38 years. The patients initially came to the clinic with mild weakness, increased muscle tone in the lower limbs, brisk patellar tendon reflexes, but no urinary disturbances. Their general condition was good, with normal strength in the upper extremities. During the course of the disease, electrophysiological studies as well as neuroimaging did not show specific anomalies. A very slow progression was noted. At their current ages they show normal cognitive function, mild weakness, and spasticity in the lower limbs. They walk with difficulty, presenting an anserine and falcina gait, use of canes, and frequent urinary urgency. The older brother has shown behavioral disturbances since the age of 18 consisting of severe aggressivity, phobic episodes, and sleep disturbances. They have refused any type of treatment.

In most cases, as reported in the literature, the initial symptoms of HSP include impaired walking with motor-developmental delay and balance problems [3]. During clinical examinations the patients manifest spasticity, hyperreflexia, and extensor plantar responses, with weakness in a pyramidal distribution in the lower limbs. Diagnostic
Table 1. Hereditary Spastic Paraplegia (HSP): frequency of autosomal dominant, autosomal recessive, X-linked, and maternally inherited (mitochondrial) forms, and related genes, as reported by Hedera [9].

<table>
<thead>
<tr>
<th>Type of HSP</th>
<th>Frequency of affected individuals</th>
<th>Genes/Variants</th>
</tr>
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<tbody>
<tr>
<td><strong>Autosomal dominant HSP</strong></td>
<td>- 75–80% of the affected</td>
<td>- Spastic paraplegia 4 (SPG4), caused by a pathogenic variant in \textit{SPAST}</td>
</tr>
<tr>
<td></td>
<td>individuals</td>
<td>- SPG30 caused by a pathogenic variant in \textit{KIF1A}</td>
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<td>- SPG31 caused by a pathogenic variant in \textit{REPP1}</td>
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<td>- Other types of autosomal dominant HSP are relatively rare and most of them account for 1% or less of all</td>
</tr>
<tr>
<td><strong>Autosomal recessive HSP</strong></td>
<td>- 25–30% of all individuals with</td>
<td>- SPG5A caused by pathogenic variant in \textit{CYP7B1}, accounts for 7.3% of all autosomal recessive HSP and 3% of apparently sporadic pure spastic paraplegia</td>
</tr>
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<td></td>
<td>HSP</td>
<td>- SPG7 caused by pathogenetic variant in \textit{SPG7}, accounts for approximately 5% of all autosomal recessive HSP</td>
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<td>- SPG11 caused by pathogenic variant in \textit{SPG11} accounts for 3–5% of all autosomal recessive HSP. The variant has been reported in 75% of individuals with all types of HSP manifesting thin or absent corpus callosum at the neuroradiological examination</td>
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<tr>
<td><strong>X-linked HSP and mitochondrial</strong></td>
<td>1–2% of all individuals affected</td>
<td>- e.g., those associated with pathogenic variants in \textit{ATL1, SPG7, and ALDH18A1} may be inherited as either autosomal recessive or autosomal dominant disorders [9]</td>
</tr>
<tr>
<td><strong>HSP</strong></td>
<td>by HSP</td>
<td></td>
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<tr>
<td><strong>Other</strong></td>
<td>- Several types of HSP</td>
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criteria have been suggested by McDermott et al. [8], with obligatory, common, and uncommon signs. Obligatory signs include a family history, progressive gait disturbance, spasticity of lower limbs with hyperreflexia, and extensor plantar responses; common signs include paresis of lower limbs, sphincter disturbances, mild dorsal column disturbances, pes cavus, hyperreflexia in the upper limbs, mild terminal dystymria, loss of ankle jerks; uncommon signs, manifest with upper limbs paresis and distal amyotrophy.

Differences in clinical presentation are reported based on age of onset, whether it is early or later, and the clinical type “uncomplicated” or “complicated”. The clinical differentiation according to the age of presentation was first reported by Harding [10]. Those authors described 22 families with the “pure” form of HSP. The autosomal dominant inheritance was found in 19 families and autosomal recessive in three. In the group of dominant HSP, the authors recognized two forms according to the age: Type I, with age of onset mostly below 35 years; and Type II, with onset usually over 35 years. In patients with Type I, delay in walking was common, with spasticity of the lower limbs more prevalent than weakness. Additionally, symptoms were slowly progressive and extremely variable in severity. In patients with Type II, the clinical development was more rapid with muscle weakness, urinary symptoms, and sensory loss being more marked than in Type I. These different clinical characteristics were confirmed by Hedera [9], who noted that when symptoms begin in very early childhood (early onset), they may be non-progressive, in contrast with symptoms beginning in later childhood or after, in which they usually tend to progress slowly and steadily. Hedera maintained that in several cases of HSP, it is not uncommon for patients to reach a “functional plateau” after a period of progressively worsening gait.

In the uncomplicated HSP type, the main clinical signs consist of progressive weakness and spasticity localized in the lower limbs, with gait disturbances, paresthesia, and urinary dysfunction. In the complicated HSP type, spastic paraparesis is a sign of a variable, complex, and heterogeneous clinical manifestation that may be associated with intellectual disability, ataxia, seizures, muscle atrophy, peripheral neuropathy, extrapyramidal disease, optic atrophy, deafness, and ichthyosis [9].

4. Diagnosis and Nervous System Hallmarks

Early diagnosis of HSP is based on the presence of gradually progressive weakness and stiffness in the lower limbs, a positive family history of a similar disorder, exclusion of other possible neurological diseases, and genetic analysis. Electrophysiological examinations, and brain and spinal MRIs may be useful in the differential diagnosis of other neurological disorders but they are not specific for diagnosing HSP [8]. Motor- and sensory-conduction studies [11] performed on 10 patients ranging in age from 4 to 41 years, from three families, with a diagnosis of uncomplicated HSP showed normal results. Karle et al. [12] reported on motor evoked potentials recorded from arms and legs in a cohort of 128 HSP patients genetically confirmed or clinically probable. They found normal results in 27% and broad spectrum with axonal and demyelinating features in the remaining 73%. In individuals with uncomplicated HSP, the brain and spinal cord MRIs are usually normal or nonspecific. In some patients, atrophy of the corpus callosum, mild-to-moderate brain atrophy, and spinal cord atrophy may be found [3]. Genetic diagnosis is not usually obtained early due to the difficulty of recognizing the initial symptoms of the HSP. In a group of 18 patients with a symptom-onset median age of 18 months (2 to 84 months), Kilic et al. [13] showed a lag between symptoms onset and confirmed genetic diagnosis of 5.8 years (5 months to 17 years).

The differential diagnosis of HSP includes: the diplegic form of cerebral palsy; structural, vascular abnormalities and demyelinating disorders; amytrophic lateral sclerosis; multiple sclerosis; nutritional disorders (including copper deficiency, Vitamin B12, and E deficiencies); and the large group of metabolic disorders for some of which an early diagnosis and early treatment may prevent the progression of the clinical signs [9].

5. Treatment and Prognosis

There is currently no definite cure for HSP. Symptomatic treatments aim to reduce symptoms severity and prevent complications. Available treatment may be used to manage symptoms: amelioration of spasticity; physical therapy including strengthening, stretching, balance, and agility exercise [3]; reducing urinary urgency; and prevention of complications related to secondary cardiac dysfunction and to orthopedic complications. Antispastic medications are useful and include the use of baclofen. The active ingredients of Lioresal are: baclofen, a gamma-aminobutyric acid receptor (GABAb receptor) agonist that acts by suppressing hyperexcitation; tizanidine, a centrally acting α2-adrenergic receptor agonist; and dantrolene sodium, 1-(5-nitrophenyl)furfurylidend amino) hydantoin sodium hydrate, which is used in chronic disorders of skeletal muscle spasticity; and botulinum A and B toxin, produced by Clostridium botulinum and consisting of a complex mixture of proteins containing botulinum neurotoxin and various non-toxic proteins by injection. Drugs used to block urinary urgency include: oxybutynin, an anticholinergic drug; solifenacin, a competitive muscarinic receptor antagonist; mirabegron, a β3-adrenergic receptor agonist; and intrabladder botulinum injections [9,14]. In patients with HSP, the use of dalfampridine (4-aminopyridine, a potassium channel blocker) in combination with physiotherapy has been reported to improve muscle spasticity and walking speed [15].

The prognosis is variable, with some individuals severely disabled and others experiencing mild to moder-
ate disability. Most individuals with uncomplicated HSP have a normal life expectancy.

6. Conclusions

HSP is a rare and diverse clinical disorder that can manifest at different ages with a slow and insidious progression, leading to delays in diagnosis. An early diagnosis and treatment can be beneficial in reducing the symptoms associated with this disorder.

Author Contributions

Conceptualization: RF and PP; methodology: AP; validation: AP, PP and RF; investigation: AP, PP; writing—original draft preparation: RF, PP, AP; writing—review and editing: AP, RF, and PP; supervision: PP. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

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References