**Spastic paraplegia pdf**

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Symptoms describe an individual’s experience of a medical disorder. Signs are the objective evidence of the disorder, documented, for example by physician examination, laboratory studies, or magnetic resonance images (MRI). The primary symptom of HSP is difficulty walking due to weakness and tightness (spasticity) in the legs. Both legs are affected, usually to a relatively similar degree.The term “paraplegia” means severe weakness in both legs including paralysis. “Paraparesis” indicates weakness in both legs of lesser severity than paraplegia. Although the disorder is typically referred to as hereditary spastic paraplegia the degree of weakness is variable and ranges from no weakness (full strength) to marked weakness (paraplegia).When present, weakness does not affect all leg muscles, but rather is most obvious in muscles of hip flexion (iliopsoas), hip abduction (gluteus medius), knee flexion (hamstrings), and foot dorsiflexion (bending the foot back toward the shin via tibialis anterior muscle). In contrast, muscles of leg extension (quadriceps) and foot extension (gastrocnemius-soleus) usually are not affected in uncomplicated HSP.Spasticity primarily affects muscles of leg extension (quadriceps), knee flexion (hamstrings), hip adduction (bringing the knees together, thigh adductor muscles), and muscles that extend the feet (gastrocnemius-soleus [Achilles tendon]).Walking pattern described as “spastic gait” occurs in which the following elements are present, each to variable degree in different individuals: a) heel strike is shifted forward (landing on the mid-foot or even further forward on the balls of the feet); b) there is reduced foot dorsiflexion (not bending the toes up, but instead tending to drag the toes, often catching them on carpet or when stepping over curbs, and causing the toes of the shoes to be worn out); c) stride length may become shorter; d) there may be “circumduction” or “scissoring”, with one leg crossing into the path of the other; e) there is a tendency for the knees to be maintained flexed (not fully extended in mid-stride), f) for thighs to be close together (adductor tightness), and g) hip flexion (knee lifting) to be reduced. Balance difficulty, often worse when walking in the dark or on uneven surfaces is not uncommon in individuals with HSP.Tightness in the legs and leg muscle spasm (often at night) are not uncommon. The consequences of abnormal walking pattern cause strain on the ankles, knees, hips, and back and often cause pain in these areas.Urinary urgency, the symptom of experiencing a very short interval between the sensation of need to urinate and difficulty remaining continent, is very common in HSP and occasionally may be an early symptom. Bowel urgency is less common but may occur. Medications such as oxybutynin may reduce urinary urgency. If urinary urgency is severe or accompanied by difficulty initiating urination, consultation with a urologist is recommended. Some genetic types of HSP tend to cause only spastic weakness in the legs and urinary urgency. These syndromes are referred to as “uncomplicated HSP”. Other genetic types of HSP tend to be associated with additional symptoms (“complicated HSP”) including difficulty with coordination (“ataxia”), impaired vision, seizures (epilepsy), muscle atrophy, disturbance of the nerves in the arms and legs (neuropathy), and disturbance cognitive ability (intellectual impairment and dementia). Previously, it was considered that HSP caused symptoms only in the legs, and therefore, did not affect the strength or coordination of the arms and hands, or speech or swallowing. As the number of HSP types has grown, it is now recognized that the arms, hands, and speech and swallowing may be affected in some genetic types of complicated HSPPattern of symptom progression (course of the disorder): When HSP begins in very early childhood (before age two years, for example), symptoms may not worsen even over many years or decades. Individuals with this “non-progressive” (non-worsening) pattern may resemble subjects with spastic cerebral palsy, a life-long disorder that also remains relatively stable. One caveat however: although early childhood-onset forms of HSP may be “non-progressive”, the degree of spasticity may increase slowly if adequate range-of-motion is not maintained through stretching exercises and muscle spasticity reduction.In contrast, when HSP symptoms begin after early childhood (in adolescence or adulthood), symptoms usually worsen very slowly over a number of years. Sudden onset or rapid worsening over weeks or months is not typical of HSP and suggests an alternate disorder or co-existing condition. After a number of years of very gradual worsening, the rate of worsening appears to slow down for many (not all) subjects. These subjects seem to reach a “functional plateau” beyond which the degree of worsening seems to be similar to that expected for age and similar degrees of physical exercise. Nonetheless, not all patients reach an apparent “leveling off” or functional plateau but instead experience continuous worsening of walking ability due to very slowly progressive muscle weakness and tightness . There may be significant variability in the type of symptoms and their severity. For example, symptoms may remain mild in some patients or become quite severe in others patients. This variability may occur between different genetic types of HSP as well as in between individuals with the same genetic type of HSP including family members who share not only the same genetic type of HSP but also precisely the same genetic mutation.There is not a perfect correlation between the genetic type of HSP and the pattern of symptoms. For example, while some genetic types of HSP (e.g. dominantly inherited HSP due to SPG4/spastin mutation) usually are associated with “uncomplicated” HSP syndromes, some patients with these types of HSP develop additional neurologic symptoms. As another example, although SPG7 and SPG11 typically are associated with additional neurologic symptoms (ataxia, neuropathy, cognitive impairment, for example), some subjects with mutations in these genes have uncomplicated HSP (only spastic weakness in the legs). There also may be variation in severity and the nature of symptoms between affected family members. Therefore, it is generally not possible to predict with certainty the severity or exact nature of symptoms associated with given genetic type of HSP. A cautious, “wait and see” approach, combined with pro-active, individualized physical therapy is recommended.Prognosis: predicting symptoms and course of HSP As noted above, there is significant variation in HSP symptoms and their severity. This limits the certainty of making predictions. In general however, some genetic types of HSP are usually associated with only leg weakness, spasticity, and urinary urgency (“uncomplicated HSP”). Other types of HSP are usually associated with other neurologic disturbances in addition to these symptoms (“complicated HSP”). Although there are exceptions (discussed above), an individual with a genetic type of HSP usually associated with “uncomplicated” syndrome would be expected to have only spastic weakness and urinary urgency.Symptoms of HSP vary from mild to severe. Individuals with severe symptoms may be unable to walk independently. In general, however, HSP does not shorten lifespan. HSP causes degeneration of the ends of the corticospinal tracts within the spinal cord. The ends of the longest fibers, which supply the lower extremities, are affected to a much greater extent than are the fibers to the upper body. Although some degeneration of the fibers supplying the arms commonly takes place, most people with HSP do not have symptoms in the hands or arms. Impaired cellular membrane trafficking, more particularly, axonal transport of macromolecules and organelles, is the best-characterized genetic mechanism of HSP. Several proteins, such as spastin (SPG4) and atlastin-1 (SPG3A), which shape membranes of the endoplasmic reticulum or endosomes, are known as such candidates. [10, 11] Mitochondrial dysfunction is the second process that leads to HSPs. Paraplegin (SPG7) is a candidate for the development of such dysfunction. It is part of the m-AAA protease, an adenosine triphosphate (ATP)- dependent proteolytic complex located at the mitochondrial inner membrane, which controls protein quality and regulates ribosome assembly. [12, 13] In most cases of HSP, the primary problem may be disturbance of the ends of the long axons, with little or no loss of myelin and no abnormal myelin. A rare type of X-linked HSP, however, has been associated with a myelin protein gene mutation. Patients with this form of HSP generally show evidence of myelin abnormalities, which are known to affect axon function. Although genes involved with myelination of the central nervous system (CNS) are less likely to be involved with HSP than are those associated with axonal stability, these genes must be considered. A study by Agosta et al suggested that the various neurologic disorders designated as HSP share a common neurodegenerative cascade. Magnetic resonance imaging (MRI) revealed that in patients with different clinical pictures, a similar involvement existed for the motor, association, and cerebellar white matter pathways and for the cervical cord, in relation to healthy controls. [14] Presently, more than 80 genetic loci have been identified. There are families with autosomal dominant patients and with autosomal recessive and sporadic patients. In a report on HSP in Japan, Koh et al stated that causative genes could not be found in 35% of autosomal dominant patients or in 52% of autosomal recessive and sporadic patients. [7, 15, 16, 17, 18, 19, 20, 21, 22] Most cases of pure HSP are autosomal dominant, whereas complicated forms tend to be autosomal recessive. With regard to pure, autosomal dominant HSP, SPG4, SPG3A, and SPG6 account for 70-80% of families. [13] SPG4 HSP is the single most common dominantly inherited HSP, representing approximately 40% of such cases. Hazan and colleagues discovered that mutations in a novel gene designated SPG4 (protein, spastin) are the cause of this disorder. [23] Insights into the SPG4 phenotype and spastin function can yield useful information relating to hypotheses for axonal degeneration in SPG4 HSP, such as direct cytoskeletal instability, abnormal mitochondrial distribution, and other consequences of abnormal axonal transport. [16, 13, 24, 25] A second autosomal dominant HSP (SPG3A) shows a linkage to band 14q11-q21 and accounts for approximately 10% of cases. This is also a pure HSP. Symptoms usually begin in early childhood and are often nonprogressive. Genetic testing for SPG3A is commercially available. A third autosomal dominant HSP, SPG6, shows a linkage to band 15q11.1. Symptoms begin in late teenage years. This kindred contains a number of affected members who have developed more severe disability than typical HSP families with other linkages. Penetrance is age dependent and high. Other genes involved in autosomal dominant HSPs are SPG8, SPG10, SPG13, SPG31, and SPG33. SPG5, SPG7, and SPG11 are involved in autosomal recessive HSPs. A family with pure HSP demonstrated a linkage to band 8q12-q13 (SPG5 HSP). SPG7 HSP has been linked to mutations in the gene encoding for paraplegin and accounts for around 5% of autosomal recessive HSPs. [16, 26] This type of mutation produces both pure and complicated HSP phenotypes. Mutations in the gene result in impaired oxidative phosphorylation. SPG11 HSP, which is characterized by a thin corpus callosum, is a clinically distinct form that includes cognitive impairment and severe axonal neuropathies. [18, 27, 28]  A study by Faber et al indicated that in SPG11 HSP, selective neuronal vulnerability exists, with white matter involvement being precocious and widespread and subsequent gray matter degeneration being restricted but progressive. [29] X-linked HSP is complex but rare, and the border between pure and complicated HSP syndromes is blurred. SPG1 HSP is linked to mutations in the gene for the L1 cell adhesion molecule (L1CAM); these mutations are associated with hydrocephalus, spasticity, ataxia, mental retardation, and adducted thumbs. SPG2 HSP is linked to a duplication mutation in the gene for proteolipid protein, which is located on band Xq21-q22. Mutations in this gene are also related to complicated X-linked HSP and to the dysmyelinating condition Pelizaeus-Merzbacher syndrome. One other rare X-linked form of HSP has been described (associated with SPG16). Affected individuals have quadriplegia, motor aphasia, reduced vision, mild mental retardation, and sphincter disturbance. [30] Preliminary genotype-phenotype correlations With the identification of HSP loci on chromosome X and 2p, 8q, 14q, 15q, and 16q, a comparison of phenotypes is possible in families for whom the disorder is linked to one of these loci, as well as in HSP families for whom these loci are excluded. [31] Thus far, genetically diverse types of autosomal dominant HSP (those linked to 2p, 14q, and 15q) appear to be clinically and electrophysiologically similar. This observation suggests that the different abnormal gene products may interact in a common biochemical cascade that results in similar patterns of neuronal degeneration. The disorder may be more severe in the 15q-linked kindred than in kindreds linked with 14q. In a study of the kindred with disease linked to 14q, only 1 patient needed a wheelchair. [32] In contrast, 9 of the patients affected in a kindred HSP linked to 15q required a wheelchair (for some patients, the need began in their 40s). Kindreds with autosomal dominant HSP linked to 2p have exhibited (1) the prototypical adolescent- or adult-onset, progressive form and (2) the less common childhood-onset, relatively nonprogressive form. The significant variations in patients' ages at symptom onset and the degree of progression in these kindreds indicate that the complete phenotype is influenced by different mutations in the same gene or by the effects of modifying genes.