Hereditary Spastic Paraplegia

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Introduction

Hereditary spastic paraplegia (HSP) is a group of inherited neurodegenerative disorders characterized by spasticity (/Spasticity) and weakness in the lower extremities [1]. HSP may develop at any time throughout the lifespan. Generally speaking, if the disorder is developed in early childhood, the symptoms will be non-progressive, whereas the opposite holds true if developed later in life. HSP is classified as either uncomplicated (pure) or complicated. Uncomplicated HSP, as the name suggests, means the individual presents with symptoms most typically associated with HSP, including lower extremity spasticity and weakness, urinary disturbance, and mild deficits in lower extremity vibration sense [2]. Furthermore, uncomplicated HSP does not involve other deficits related to the upper extremities, speech, or swallowing [2]. Complicated HSP is distinguished by the presence of uncomplicated symptoms, in addition to many others, including ataxia, seizures, intellectual disability, dementia, muscular atrophy, extrapyramidal disturbance, and peripheral neuropathy [2]. Causes of additional symptoms are yet to be identified [2].

The first reported cases of HSP occurred in two middle aged siblings from the Estonia region and was documented in 1880 by a neurologist named Ernst Adolf Gustav Gottfried von Strümpell [1]. Later that decade, Maurice Lorrain went on to publish a more detailed account of HSP. Strümpell and Lorrain's early HSP research was essential to the current knowledge-base of HSP and is referred to as Strümpell-Lorrain disease today [3]. HSP has also been referred to as familial spastic paraparesis [4].

Clinically Relevant Anatomy

HSP is associated with severe degeneration of the corticospinal tract (/Corticospinal_Tract), and a usually less severe degeneration of the posterior column-medial lemniscus pathway [1]. The corticospinal tract is the major descending motor pathway that terminates on motor neurons and interneurons in the ventral horn of the spinal cord (/Spinal_cord_anatomy) and ultimately controls movement in the limbs and trunk [5]. On the other hand, the posterior column-medial lemniscus pathway ascends

from the periphery to the primary somatosensory cortex on the post-central gyrus and conveys sensory information of fine, discriminative touch, proprioception and vibration sense [6]. HSP patients experience a marked reduction in the area and axonal density of both the corticospinal and posterior column-medial lemniscus pathways [7], which accounts for the presentation of lower limb spasticity, followed by generally less severe weakness and reduced vibration sense [1].

Clinical Presentation

Individuals with HSP exhibit progressive spasticity in the lower limbs and gradually develop abnormal gait patterns [8]. Typically speaking, individuals with HSP walk on the tip of their toes with their ankles inverted [9]. HSP patients will also exhibit a reduced step length, increased step width, and a reduced range of motion in the knee with increased trunk range of motion in all planes [10]. Weakness most commonly occurs in the lower limbs, but mild upper limb weakness may also occur. The upper limbs may also experience poor coordination and hyperreflexia, although a positive Babinski sign may not be elicited in the majority of individuals with HSP. Urinary symptoms, such as incontinence, are present in up to 50% of individuals diagnosed with HSP [11]. In terms of sensation, decreased pallesthesia and proprioception (/Proprioception) are common in HSP [11], while vision loss and hearing deficits rarely occur [9]. It is also likely that an individual with HSP will exhibit the physical feature of a high foot arch (/Pes_cavus) [8]. Although infrequent, intellectual disabilities, dementia, seizures and peripheral neuropathy may also be developed [2][9].

Epidemiology

The global prevalence of HSP is difficult to quantify due to the lack of epidemiological studies of acceptable quality and the difficulty of diagnosing HSP, as it overlaps with other neurological diseases [12]. A systematic review by Ruano et al.[13], evaluated 22 articles from 16 different countries and found that the prevalence of HSP varies based on region and type of HSP. The estimated global prevalence of autosomal dominant (AD-HSP) lies at 0.5-5.5 per 100,000, whereas autosomal recessive (AR-HSP) has a prevalence of 0.3-5.3 per 100,000[13].

The most common form of HSP is spastic paraplegia autosomal dominant type 4 (SPG4) [13]. The highest prevalence of HSP (19.9 per 100,000) has been found in Sardinia, Italy [14], followed by Norway and Portugal [13]. The pure forms of HSPs are commonly found in northern Europe whereas the complicated forms are most often found in southern Europe [14]. The majority of studies used for prevalence rates were performed in Europe or Asia, thus some caution is required when interpreting these values since prevalence rates from other parts of the world are still unknown[13].

There is no significant difference in sex distribution of HSP [15][16].

Etiology

HSP, as the name indicates, is inherited genetically through the individual's parents. HSP, however, is unique to other hereditary disorders as there are multiple mechanisms responsible for this disorder's onset. Specifically, individuals can express the mutation if it was inherited in an autosomal dominant, recessive, X-linked, or maternal (mitochondrial) manner [2]. To date, there are 41 different inheritance patterns that have been identified as causes of HSP [2].

Each inheritance pattern has multiple different genes that may be affected. Each gene mutation is also associated with different presentations of the disease, including both complicated and uncomplicated classifications. The following are the most common clinical presentations associated with each inheritance pattern:

Autosomal Dominant (AD): The SPAST gene accounts for roughly 40% of AD HSP, and causes the uncomplicated form of the disorder. The onset typically occurs in early childhood, and the disease is progressive. Cognitive impairments may also develop later in life [2].

Autosomal Recessive (AR): The majority of the genes associated with AR HSP result in a complicated presentation. However, the most common form of AR HSP (50%) is caused by mutation of the SPG11 gene, which leads to an uncomplicated or slightly complicated form of HSP. Distinguishing factors of AR HSP include upper extremity weakness, dysarthria (speech complications) and nystagmus [2].

X-Linked: Far fewer genes are involved in the cause of X-linked HSP. A mixture of complicated and uncomplicated presentations associated with the common theme of intellectual disability is characteristic of X-linked HSP [2].

Maternal (Mitochondrial): Typically results in adult onset HSP and is progressive in nature. Symptoms range from mild to severe [2].

Diagnosis

The diagnosis of HSP is based on the individual's clinical presentation and a detailed investigation of family history [1]. A thorough physical assessment investigating the clinical features of HSP (see clinical presentation) and potential genetic testing or subjective family history should be implemented to strengthen the diagnosis. In the absence of a family history, exclusion of other myelopathy (/Myelopathy) conditions listed below can help confirm the diagnosis:[1]

- T-lymphotropic virus-related myelopathy
- Primary progressive multiple sclerosis
- Vitamin B12 deficiency
- Copper deficiency
- Spinal cord tumors or malformations

Prognosis

The extent of disability exhibited by HSP patients varies drastically. In 10-20% of cases the individual will present asymptomatically, while in severe cases (5%), the individual must completely rely on a wheelchair for ambulation [8]. Diagnosis of HSP before the age of 35 leads to a better prognosis compared to diagnosis later in life. Diagnosis after the age of 35 is associated with a more rapid progression of the disease and a greater likelihood of losing the ability to walk. Life expectancy in individuals

with HSP is normal [11].

Medical Management

As with any disease, medical management begins with an accurate diagnosis. Following the diagnosis, frequent physician follow-ups should occur to monitor the progression of the disease. Follow-up appointments should include reassessment, referrals and prescription/adjustment of medications as needed. Referrals may include, but are not limited to physiotherapy, chiropractic [17] or any other health care professional focused on improving/maintaining functional abilities. As previously mentioned, medications that manage the symptoms of HSP are also prescribed. Oral medications such as Baclofen, Tizanidine, Gabapentin/Pregabalin are prescribed as muscle relaxants to reduce spasticity. Botulinum toxin injections or an intrathecal baclofen pump implantation may also be utilized for HSP management depending on the severity of spasticity [18].

Physiotherapy Management

Physiotherapy management for HSP should focus on improving functional ability, managing spasticity, and preventing contracture development [8]. Exercise programs developed for HSP patients should be holistic in that they incorporate stretching and strengthening of the lower limbs, as well as cardiovascular training [19].

Pelvic floor physiotherapy plays an important role in treating HSP patients experiencing urinary incontinence and/or pelvic pain during intercourse [20]. Patient education of proper posture during defecation and micturition, along with avoiding over straining pelvic floor muscles has been shown to be effective [20]. Pelvic floor motor control exercises have also proven to be an effective treatment. Furthermore, the use of an insufflated vaginal probe has also been shown to be effective in stretching the pelvic floor muscles [20].

In a study completed by Yanxin and colleagues (2013), the use of 10 fourty-five minute hydrotherapy (/Hydrotherapy) sessions were shown to increase both the walking speed and step length in individuals with HSP. However, the aforementioned benefits were achieved via compensatory strategies rather than performance of a normal gait (/Gait) pattern [21]. Therefore, caution should be used when considering hydrotherapy to promote normal gait patterns in individuals with HSP. Instead, it may be recommended to prescribe general balance exercises completed on a daily basis [22]. These balance exercises may include a single-leg stance using a counter to provide stability as needed [22]. It is likely that physiotherapists will also need to prescribe and educate patients regarding the appropriate use of a gait-aid for ambulation [22].

In terms of managing contracture development, regular stretching exercises of the gastrocnemius (/Gastrocnemius), soleus (/Soleus), tibialis posterior, hamstrings (/Hamstrings), and hip adductors are recommended. Agility training has also been shown to improve range of motion [22]. The use of serial casting and splints may help stretch and improve the position of spastic muscles, while functional electrical stimulation may also reduce spasticity [23].

Outcome Measures

A variety of reliable and valid outcome measures may be administered to measure the severity and progression of HSP, as well as general balance, mobility, and degree of spasticity in HSP patients. The subsequently listed outcome measures may be categorized based on specificity to HSP and general balance, mobility and spasticity measures.

Specific HSP Measures: HSP Severity and Progression of the Disease

1. **Spastic Paraplegia Rating Scale (SPRS)** [24]
   The SPRS was created by Schüle and colleagues in 2006 to measure disease severity and progression [24]. This 13-item scale, however, was designed to measure functional impairments in only uncomplicated (pure) forms of HSP. The SPRS has high reliability and validity with no apparent floor or ceiling affects. This scale may be retrieved from the Schüle and colleagues (2006) journal article [24].

General Balance, Mobility and Spasticity Measures

1. **The Ashworth Scale**
   The Ashworth Scale is the most commonly administered tool for objective measures of spasticity. For more information, refer to the "Diagnostic Procedures" section of spasticity (/Spasticity).
2. **Berg Balance Scale** (/Berg_Balance_Scale) (BBS)
   The Berg Balance Scale may be used to objectively measure a patient's ability to safely balance during a series of 14 tasks. It is important to note that the BBS has not been validated specifically for use in this population, but may still provide useful information during balance assessment. For more information, refer to the Berg Balance Scale (/Berg_Balance_Scale).
3. **The Functional Mobility Scale (FMS)**
   The Functional Mobility Scale (FMS) was originally designed to measure functional mobility of children diagnosed with Cerebral Palsy (/Cerebral_Palsy_Outcome_Measures) at home, in school, and in the wider community. However, the FMS has more recently been deemed valid and reliable for measuring functional mobility in children with HSP [25]. Refer to https://www.schn.health.nsw.gov.au/files/attachments/the_functional_mobility_scale_version_2.pdf (https://www.schn.health.nsw.gov.au/files/attachments/the_functional_mobility_scale_version_2.pdf) for the full online version of the FMS.
4. **Gross Motor Functional Measure (GMFM)**
   The Gross Motor Functional Measure (GMFM) was originally designed to assess the capacity of children with Cerebral Palsy (/Cerebral_Palsy_Outcome_Measures) (CP) to perform specific functions. The GMFM is then utilized to monitor change in gross motor functioning in children with CP. Similar to the FMS, the GMFM has also recently been deemed valid and reliable for measuring gross motor functioning in children with HSP [25]. Refer to Cerebral Palsy (/Cerebral_Palsy_Outcome_Measures) for more information on the GMFM.
5. **Timed Up and Go Test (TUG)** (/Timed_Up_and_Go_Test_(TUG))
   The Timed Up and Go Test (TUG) provides objective information of a patient's ability to perform a sit-to-stand, and balance while ambulating. It is important to note that the TUG has not been validated specifically for use in this population, but may still provide useful information during balance assessment. For more information refer to the Timed Up and Go Test (TUG) (/Timed_Up_and_Go_Test_(TUG)).

List of Categories

1. Queen's University Neuromotor Function Project (/Queen%27s_University_Neuromotor_Function_Project)
2. Neurology

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Definition / Description Primary Lateral Sclerosis (PLS) is a neuromuscular disease characterized as a rare, non-hereditary, idiopathic, slow, and progressive degeneration of the upper motor neurons[1]. PLS lies on a continuum of sporadic motor neurone diseases. This spectrum includes other disorders such as progressive muscular atrophy, which involves only lower motor neurons,