

## Essay on the hereditary spastic paraplegia

Please add 'Hereditary spastic paraplegia' to the A-Z Disorders list for the Australian Brain Foundation

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### **What is it?**

Hereditary spastic paraplegia (HSP) is a group of disorders in which the main clinical feature is progressive stiffness (spasticity) in the legs. HSP can be divided into 'pure' and 'complicated' forms. For the pure form of HSP the doctor will usually find signs of spasticity in the legs such as stiffness, brisk reflexes, and upgoing toes (plantars). The age of onset can vary from infancy to the eighth decade, although the majority of patients experience their first symptoms between the second and fourth decades. Patients will often notice stiffness in the legs, difficulty walking, easily worn-out shoes, toe walking, and pins and needles below the knees. There may also be a disturbance to bladder function such as urgency, frequency and hesitancy. The arms are typically not affected. There may be delayed motor milestones for those patients affected in infancy. For the 'complicated' forms of HSP, there are additional neurological features, such as dementia, seizures, deafness, abnormalities in the nerves of the arms and legs (peripheral neuropathy) or abnormalities in the nerve at the back of the eye (optic neuropathy). HSP is a rare condition, and the prevalence varies according to the country tested. For example, a study from Western Norway found that the prevalence of this condition is 11.9 per 100,000 people, whereas a study from Italy found the prevalence to be only 1 per 100,000.

### **What causes HSP?**

It is now recognised that there are many different genetic causes for HSP. In fact, up to 52 different genetic loci (locations), including 27 genes, have been identified so far! There are also many ways in which the condition can be inherited, including autosomal dominant, autosomal recessive, x-linked (sex chromosome), and mitochondrial (maternal). For autosomal dominant, you only need one copy of the abnormal gene to get the disease, and one of your parents may also be symptomatic. The most common cause of autosomal dominant disease is Spastic Paraplegia 4 (SPG4), causing about 45% of cases. SPG4 is due to mutations in the *spastin* gene. The spastin protein is involved in severing (cutting) microtubules, which form part of the cytoskeleton or the 'scaffolding' of the cells. Mutations in the *spastin* gene may affect several important protein functions, such as transport inside cells (cellular trafficking) and modulating the growth of nerve cells (axon outgrowth). Another relatively common cause is SPG3A due to mutations in the *atlastin* gene, accounting for about 10% of autosomal dominant cases. SPG3A is the most common type in patients with onset at less than 10 years of age. For autosomal recessive disease, you need two abnormal copies of the gene to get the disease. The first gene identified as a cause of autosomal recessive HSP was the *paraplegin* gene (SPG7), which affects the energy producing unit of the cell (mitochondria). More recently,

researchers identified mutations in the *CYP7B1* gene (SPG5) as a cause of autosomal recessive disease. The product of the *CYP7B1* gene is involved in cholesterol breakdown in the liver. Some types of autosomal recessive HSP (SPG11 and SPG15) are associated with a change on MRI of the brain in which a bundle of nerve fibres is thinner than normal (thin corpus callosum). Other forms of HSP are probably much less common; some are associated with distinctive syndromes such as Kjellin syndrome (SPG15), Silver Syndrome (SPG17), Troyer Syndrome (SPG20), Mast Syndrome (SPG21) and Charlevoix-Saguenay syndrome.

### **What tests might the doctor order if this condition is suspected?**

The doctor may consider a few different tests including blood tests, MRI of the brain and the spinal cord and electrical tests of the nerves (e.g. nerve conduction studies and motor evoked potentials). These tests might be important to investigate for other conditions that might look like HSP, or to search for complications of HSP. Sometimes, the doctor might think that genetic testing and genetic counselling are also worthwhile.

### **What is the prognosis?**

The prognosis is quite variable because there are many different forms of HSP and different complications can occur. Most patients will experience a slow, gradual progression of symptoms. Some patients suffer from severely restricted mobility and may require a wheelchair. Life expectancy is usually not affected.

### **What treatments are available?**

Unfortunately, there are no treatments currently available that target the underlying disease process. However, there are treatments for the symptoms of the condition such as anti-spasticity drugs to treat leg spasticity and physiotherapy. Patients often find that community support groups are very helpful, such as the Australian HSP Community which is associated with the HSP Research Foundation (see web resources below).

### **What does the future hold for HSP?**

There are now new genetic technologies such as exome sequencing, in which we can test the entire 'coding' part of the genome in a single experiment. This has allowed researchers to identify new genetic causes of HSP in families where several family members are affected. Another promising development is the use of induced pluripotent stem (iPS) cells. Researchers can take skin biopsies (fibroblasts) or nose biopsies (olfactory neurospheres) from patients and turn them back into iPS cells, which can then be turned into nerve cells (neurons). These nerve cells can then serve as a biologically accurate model to study the disease. With these exciting new developments, we hope to

learn more about what causes HSP. This offers up the potential to develop new treatments in the future, so that can halt or even reverse the underlying disease processes.

### **Web Resources**

HSP Research Foundation

<http://www.hspersunite.org.au/>

Spastic Paraplegia Foundation, Inc.

<http://www.sp-foundation.org/>

WE MOVE: Hereditary Spastic Paraplegia

<http://www.wemove.org/hsp/>