MGZ

Medical Genetics Center

Clinician Information

HEREDITARY SPASTIC PARAPLEGIA (HSP)

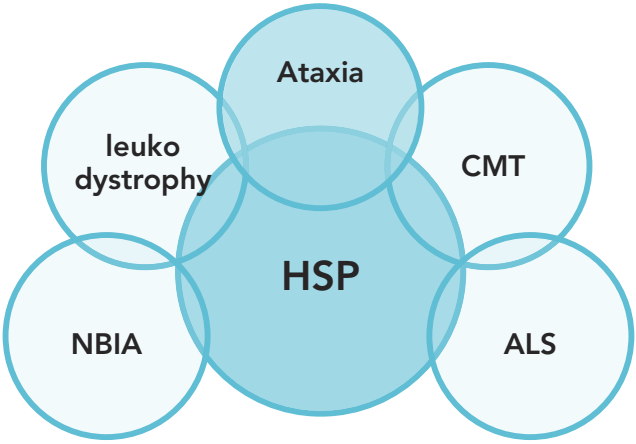
LEADING SYMPTOM PROGRESSIVE SPASTIC PARAPLEGIA

Genetic Differential Diagnosis: Hereditary Spastic Paraplegia (HSP)

Clinically, the pure forms are distinguished from complicated forms of progression:

- **Pure form of HSP**: Prominent features are the consequences of pyramidal tract damage (lower extremity spasticity, neurogenic bladder disorder). These symptoms can be accompanied by mild sensory deficits (disturbance of pallesthesia).

- **Complicated form of HSP**: In addition, there are very variable neurological and non-neurological symptoms: most commonly ataxia (in about 50% of patients), frequently peripheral neuropathy or dysarthria (each in about 30% of patients). Furthermore, cognitive impairment, psychosis, epilepsy, optic atrophy or extrapyramidal motor symptoms are possible manifestations. The genetic causes and phenotypic spectrum of complicated HSP thus overlap with other neurological disorders, most notably hereditary ataxias.



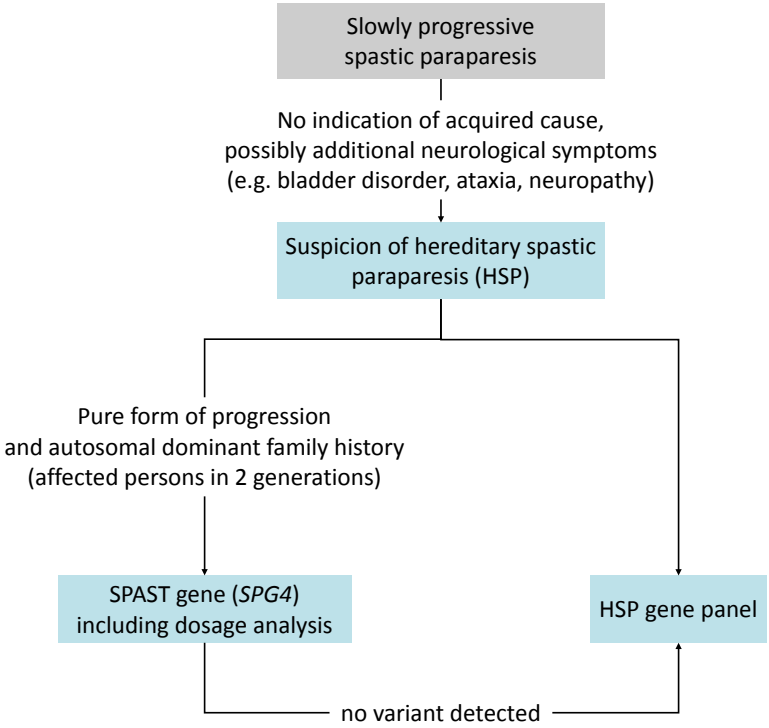
Overlap of genetic causes and phenotypic spectrum of HSP with other neurological disorders, modified according to - Schüle R und Schöls L. Nervenarzt 2017; 88:720-727

DIAGNOSTIC STRATEGY

Diagnostic Algorithm

The diagnosis of HSP is primarily to be based on a human genetic examination.

With more than 150 known disease genes or gene loci, HSPs are, genetically, very heterogeneous. The classic forms are categorized as SPG1 to SPG78 (SPG = spastic paraplegia gene). In most cases, an assignment to a specific gene based on clinical phenotype is not possible. For this reason, the diagnostic process often includes next-generation sequencing (NGS)-based procedures (panel diagnostics), which allow several genes implicated in the disease to be studied simultaneously.



A pure progressive form in a patient with positive family history, suggesting an autosomal dominant inheritance (2 generations affected), justifies a single gene analysis of the SPAST gene (SPG4), as about 50% of cases in this constellation are attributed to a pathogenic variation of this gene. In addition to sequencing, a dosage analysis of the SPG4 gene should be performed, as about 20% of the pathogenic variants of the SPAST gene are deletions. In contrast, primary changes in the SPAST gene are much less common in sporadic patients, making primary panel diagnostics a useful tool.

Mutation detection rate

A lack of proof of mutation does not completely exclude an HSP, as there are still some scientifically unexplained genetic causes. The mutation detection rate for all known HSP genes is currently estimated to be about 70% for autosomal dominant cases, and 50% and 30% lower for autosomal recessive and sporadic cases.

Non-genetic differential diagnosis

HSPs are to be distinguished from the common non-genetic neurological disorders associated with spasticity. Common causes of damage to motor pathways include stroke, multiple sclerosis, traumatic brain injury, hypoxic brain damage, and spinal cord injury, e.g. due to tumors or inflammation. In rare cases, metabolic disorders can also lead to the appearance of a spastic spinal paralysis.

Clinical Utility / Clinical value of human genetic diagnosis

Therapeutic options depend on the cause of spastic spinal paralysis.

- The diagnosis of HSP is important to differentiate between genetic conditions from acquired forms of spastic spinal paralysis, which require fundamentally different treatment.
- Depending on the genetically defined subtype, the patient will be faced with different consequences with regard to disease progression, prognosis, disease-related risks and risk of recurrence for family members and offspring.
- Apart from a few exceptions, there is no causal treatment available for the majority of HSPs, and symptomatic medical management with oral antispastics, botulinum toxin injections or intrathecal anti-spastic therapy is required.

References:

– Schüle R und Schöls L. Nervenarzt 2017; 88:720-727
– Fink JK. Hereditary Spastic Paraplegia Overview. 2000 Aug 15 [Updated 2014 Feb 6]. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. GeneReviews® [www.ncbi.nlm.nih.gov/books/NBK1509/].

PROFILE: HEREDITARY SPASTIC PARAPLEGIA (HSP)

Leading Symptom

Progressive spastic paraplegia (HSP)

Genetic Causes

With more than 150 known disease genes or loci, HSPs are, genetically, very heterogeneous

Frequency

The prevalence of HSPs is estimated at up to 1:10,000. It is therefore relatively common among the "rare diseases".

Inheritance

Dependent on underlying genetic changes. All modes of inheritance are possible (autosomal dominant, autosomal recessive, X-linked, mitochondrial).

Manifestation

From childhood to later adulthood. Disease onset peaks in childhood and around the age of 40.

Progression

Dependent on underlying genetic changes. In early onset of the disease, symptoms may be non-progressive, similar to infantile cerebral palsy. Generally, early manifested forms progress slowly (only partial loss of walking ability after decades, no limitation of life expectancy). More severe progression forms with quicker progression are expected in complicated HSP and/or when onset first occurs at a later age.

SELF-HELP GROUPS/USEFUL ADDRESSES

- Orphanet. The portal for rare diseases and orphan drugs:
  www.orpha.net

INFORMATION MATERIAL

On our website, you will find additional information on other clinical topics as well as organizational information.

Visit us at www.mgz-muenchen.com

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