Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Motor neuron diseases

Hereditary spastic paraplegia: More than an upper motor neuron disease

L. Parodi [a], S. Fenu [a,b], G. Stevanin [a,b,c], A. Durr [a,b,*]

[a] Institut du Cerveau et de la Moelle épinière, ICM, Sorbonne Université, UPMC Univ Paris 06, UMRS_1127, INSERM, U 1127, CNRS, UMR 7225, Pitié-Salpêtrière University Hospital, 75013 Paris, France
[b] APHP, Genetics Departement, Pitié-Salpêtrière University Hospital, 75013 Paris, France
[c] PSL Research University, EPHE, 75014 Paris, France

INFO ARTICLE

Article history:
Received 2 March 2017
Accepted 31 March 2017
Available online 24 April 2017

Keywords:
Spastic paraplegia
SPG
Motor neuron disease
Amyotrophic lateral sclerosis
Neurodegeneration
Motor neuron

ABSTRACT

Hereditary spastic paraplegias (HSPs) are a group of rare inherited neurological diseases characterized by extreme heterogeneity in both their clinical manifestations and genetic backgrounds. Based on symptoms, HSPs can be divided into pure forms, presenting with pyramidal signs leading to lower-limb spasticity, and complex forms, when additional neurological or extraneurological symptoms are detected. The clinical diversity of HSPs partially reflects their underlying genetic backgrounds. To date, 76 loci and 58 corresponding genes [spastic paraplegia genes (SPGs)] have been linked to HSPs. The genetic diagnosis is further complicated by the fact that causative mutations of HSP can be inherited through all possible modes of transmission (autosomal-dominant and -recessive, X-linked, maternal), with some genes showing multiple inheritance patterns. The pathogenic mutations of SPGs primarily lead to progressive degeneration of the upper motor neurons (UMNs) comprising corticospinal tracts. However, it is possible to observe lower-limb muscle atrophy and fasciculations on clinical examination that are clear signs of lower motor neuron (LMN) involvement. The purpose of this review is to classify HSPs based on their degree of motor neuron involvement, distinguishing forms in which only UMNs are affected from those involving both UMN and LMN degeneration, and to describe their differential diagnosis from diseases such as amyotrophic lateral sclerosis.

1. Introduction

Hereditary spastic paraplegias (HSPs) were first described in the late 1800s by German neurologist Adolf Strümpell through observations of degeneration of spinal cord nerve fibers in two brothers presenting with gait disorders and spasticity in the lower limbs.

The latest estimate of the global prevalence of HSPs is 1–5:100,000 population, depending on the country [1], although there is still no information on its incidence in large parts of the world. HSPs refer to a very heterogeneous group of

* *Corresponding author at*: Institut du Cerveau et de la Moelle épinière, ICM, Sorbonne Université, UPMC Univ Paris 06, UMRS_1127, INSERM, U 1127, CNRS, UMR 7225, Pitié-Salpêtrière University Hospital, 75013, Paris, France.
E-mail address: alexandra.durr@icm-institute.org (A. Durr).
http://dx.doi.org/10.1016/j.neurol.2017.03.034

diseases, and the literature on HSPs highlights the extreme complexity that characterizes them, including both the observable set of clinical features in affected patients and their underlying genetic features.

The neurodegeneration that characterizes HSP patients is the result of a progressive distal axonopathy that mainly involves the corticospinal tracts, leading to spasticity of the lower limbs when walking, the hallmark of the disease. Moreover, a wide range of neurological and extraneurological features can be manifested by HSP patients that sometimes overlap with those of other diseases.

A high degree of genetic diversity underlies the observed phenotypic heterogeneity, with more than 70 loci and 50 genes involved in the onset of HSPs that can be inherited through autosomal-dominant and -recessive, X-linked and maternal modes of transmission [2].

No treatment is yet available to prevent or slow the neural degeneration. Drug therapy to alleviate spasticity, coupled with physiotherapy and rehabilitation, is therefore the only current strategy to ameliorate patients' quality of life (QoL).

2. Clinical classification and diagnosis

HSPs were initially classified into two groups, pure and complex (complicated), based on the clinical phenotype. In pure HSP forms, pyramidal signs predominantly affect the lower limbs, causing spasticity, weakness and, in some cases, sphincter disturbances [3]. The major features that define this pure form on neurological examination include increased lower-limb muscle tone (especially in the hamstrings, quadriceps, gastrocnemius–soleus and adductors) and weakness (in the iliopsoas, hamstrings and tibialis anterior), as well as hyperreflexia, extensor plantar responses and attenuated vibratory sensation in the ankles. Spasticity, usually more prominent when walking than at rest, allows the distinction between HSPs and multiple sclerosis.

Additional neurological symptoms define the complex forms of HSP, especially spastic ataxia, characterized by the association of cerebellar ataxia and dysarthria with core HSP symptoms. The presence of dystonia or other extrapyramidal features, such as cognitive disability and/or deterioration, optic atrophy, cataract and hearing impairment, among many other symptoms, are responsible for the wide clinical heterogeneity of these forms of the disease.

Furthermore, both the age at onset and disease progression are extremely variable among HSP patients, even among those with the same genetic background. High intrafamilial variability is often observed: mutation carriers may experience early onset and rapid progression or be asymptomatic, suggesting the influence of as yet unidentified modifying factors.

Because of the clinical overlap of HSPs with other neurological diseases, clinical diagnosis is sometimes difficult. The association of gait spasticity with other neurological signs, a positive familial history and ancillary tests, such as brain and spinal cord magnetic resonance imaging (MRI), electromyography (EMG), nerve conduction studies and ophthalmological examination, are therefore crucial for correct patient classification.

Cerebrospinal fluid (CSF) analysis may also be performed to differentially diagnose HSPs from multiple sclerosis or to detect the presence of human T-cell leukemia virus (HTLV)-1, responsible for tropical spastic paraparesis. In addition, specific plasma biomarker concentrations can be measured to support the diagnosis of some HSPs or HSP-related forms. These include increased levels of very long-chain fatty acids (VLCFA) in adrenoleukodystrophy (resulting from *ABCD1* gene mutations) and cholestanol in cerebrotendinous xanthomatosis (due to *CYP27A1* mutations), as well as 25- and 27-hydroxycholesterol in the spastic paraplegia type 5 (*SPG5*) gene (resulting from *CYP7B1* mutations).

3. Genetics of HSPs

Linkage analysis was the first strategy to allow the identification of genomic regions harboring causative genes of HSPs. The subsequent introduction of next-generation sequencing (NGS) revolutionized the genetic diagnosis of HSPs: the combination of NGS and the use of screening panels of genes involved in HSPs, or allelic diseases, greatly increased the power of genetic diagnosis and is now steadily increasing the number of new candidate genes. Yet, despite these advances, the difficulty in connecting an observed phenotype with a specific candidate gene, and the occasional uncertainty surrounding the inheritance pattern, make research into the genetic causes of HSPs particularly arduous, leaving most HSP patients without a genetic diagnosis [1,4]. To date, 76 genomic loci and 58 corresponding genes have been linked to HSPs, highlighting the extreme heterogeneity in the mode of transmission of HSPs and the role played by SPG-encoded proteins.

Autosomal-dominant HSPs (ADHSPs) are linked to mutations in 19 SPG genes, leading mostly to the onset of a pure form of the disease. Among ADHSPs, SPG4/*SPAST*, SPG3A/*ATL1*, SPG31/*REEP1* and SPG10/*KIF5A* are those most frequently mutated, and responsible for almost 57% of ADHSP cases.

A total of 57 loci and 52 genes are responsible for autosomal-recessive HSPs (ARHSPs), which often lead to more complicated phenotypes. SPG11/*KIAA1840*, SPG5A/*CYP7B1*, SPG7 and SPG15/*ZFYVE26* account for almost 34% of causative mutations in ARHSP-affected patients [2,5]. However, the frequency of *SACS* mutations in patients with spastic ataxia is probably underestimated because of the misclassification of such patients as having either ataxia or an HSP based on the clinical picture [6].

Rare forms of HSP include X-linked and maternally inherited HSPs with five loci responsible for X-linked HSPs, most frequently due to mutations in SPG1/*L1CAM* and SPG2/*PLP1*, both leading mostly to a complicated form of HSP [7,8].

To date, only one gene encoded by the mitochondrial genome has been clearly shown to be responsible for HSP; complicated spastic paraplegia was indeed observed in a family harboring mutations of *MT-ATP6*, which codes for a component of the adenosine triphosphate (ATP) synthase complex [9].

Multiple inheritance patterns have been observed in patients carrying mutations in both SPG58/*KIF1C* and SPG72/*REEP2*, leading to HSPs when present in either a heterozygous