Autosomal Dominant Spastic Paraplegias

A Review of 89 Families Resulting From a Portuguese Survey

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Importance: Hereditary spastic paraplegias (HSPs) are a group of diseases caused by corticospinal tract degeneration. Mutations in 3 genes (SPG4, SPG3, and SPG31) are said to be the cause in half of the autosomal dominant HSPs (AD-HSPs). This study is a systematic review of families with HSP resulting from a population-based survey. Novel genotype-phenotype correlations were established.

Objective: To describe the clinical, genetic, and epidemiological features of Portuguese AD-HSP families.

Design: Retrospective medical record review.


Participants: Families with AD-HSP.

Main Outcome Measure: Mutation detection in the most prevalent genes.

Results: We identified 239 patients belonging to 89 AD-HSP families. The prevalence was 2.4 in 100 000. Thirty-one distinct mutations (26 in SPG4, 4 in SPG3, and 1 in SPG31) segregated in 41% of the families (33.7%, 6.2%, and 1.2% had SPG4, SPG3 and SPG31 mutations, respectively). Seven of the SPG4 mutations were novel, and 7% of all SPG4 mutations were deletions. When disease onset was before the first decade, 31% had SPG4 mutations and 27% had SPG3 mutations. In patients with SPG4 mutations, those with large deletions had the earliest disease onset, followed by those with missense, frameshift, nonsense, and alternative-splicing mutations. Rate of disease progression was not significantly different among patients with SPG3 and SPG4 mutations in a multivariate analysis. For patients with SPG4 mutations, disease progression was worst in patients with later-onset disease.

Conclusions and Relevance: The prevalence of AD-HSP and frequency of SPG3 and SPG4 mutations in the current study were similar to what has been described in other studies except that the frequency of SPG4 deletions was lower. In contrast, the frequency of SPG31 mutations in the current study was rare compared with other studies. The most interesting aspects of this study are that even in patients with early-onset disease the probability of finding a SPG4 mutation was higher than for patients with SPG3 mutations; there was no difference in disease progression with genotype but an association with the age at onset; 7 new SPG4 mutations were identified; and for the first time, to our knowledge, the nature of the SPG4 mutations was found to predict the age at onset.


Hereditary spastic paraplegias (HSPs) are heterogeneous diseases characterized by progressive spasticity and lower limb weakness due to corticospinal tract degeneration. They are divided into pure and complex forms according to the absence or presence of features besides the corticospinal signs. Hereditary spastic paraplegias are inherited in an autosomal dominant (AD), recessive, or X-linked manner. Nearly 50 loci have been mapped. In AD-HSP, 19 loci and 11 genes were identified. Three of them are reported as representing about 50% of the mutations in all AD-HSP families, SPG4 being the cause in 40%; SPG3 in 10%, and SPG31 in 4.5% to 6% of all families studied.1-15

SPG4 maps to chromosome 2p22-p21 and encodes spastin, which belongs to the AAA protein family (adenosine triphosphatase associated with various cellular activities). It is implicated in the remodeling of protein complexes and in axonal microtubule interactions with endoplasmic reticulum.16 Approximately 250 mutations have been reported.17 SPG3 links to chromosome 14q12-q21 and encodes atlastin-1, a Golgi guanosine tri-
phosphatase\textsuperscript{18} involved in vesicle trafficking, and is probably a spastin partner.\textsuperscript{19} About 25 mutations were described.\textsuperscript{19} SPG31 maps to chromosome 2p11.2 and encodes a receptor expression enhancing protein 1 (REEP1) of mitochondrial localization and unknown function.\textsuperscript{20}

This study aimed to estimate AD-HSP prevalence in Portugal and the frequency of the most prevalent genes, describe the main clinical features, and analyze the genotype-phenotype correlations.

METHODS

PATIENT ASCERTAINMENT

From 1993 to 2004, a population-based systematic survey of hereditary ataxias and spastic paraplegias was conducted in Portugal. We included all families ascertained during that survey, as well as those identified after. Their methods are discussed elsewhere.\textsuperscript{21}

CLINICAL STUDIES

Patients were examined by the same team of neurologists. Blood samples were collected after written consent. Diagnosis of HSP was based on published criteria\textsuperscript{22,23}; accordingly, 3 patients without family history and without an identified mutation were excluded. Diseases mimicking HSP were excluded by radiological and biochemical investigations.

Onset was systematically defined as the start of any change of gait pattern, walking difficulties, unexplained falls, or cramps noticed by the patients or relatives. Early onset was considered to have occurred before age 20 years (other patients were classified as having late-onset disease). We considered a complex family to be those with 2 or more patients with symptoms besides the corticospinal syndrome, in the absence of any other explanation for the changes found.

The motor severity of disease was classified on a scale from 0 to 7\textsuperscript{24} and transformed into a percentage (dividing by the maximum value of 7). Annual rate of disease progression was calculated by dividing the percentage from the scale of severity by disease duration and was expressed as a percentage per year. Patients with disease duration shorter than 5 years were excluded from this analysis. Spasticity was quantified from 0 to 4, according to the modified Ashworth Scale of Muscle Spasticity.\textsuperscript{25} Muscle strength was graded from 0 to 5, using the Medical Research Council Scale for Muscle Strength.\textsuperscript{26} Asymptomatic individuals (n=19) with abnormal neurological examination findings were excluded.

MUTATION SCREENING

Genomic DNA was extracted from blood, according to standard procedures.\textsuperscript{27} Mutation screening was performed by polymerase chain reaction amplification of all coding regions, followed by denaturant high-performance liquid chromatography and bidirectional direct sequencing of altered profiles for SPG3 and SPG4. More recently, mutation detection was performed by direct sequencing of SPG3, SPG4, and SPG31 coding sequences and exon-intron boundaries. Each fragment was amplified by polymerase chain reaction with HotStarTaq Master Mix (Qiagen), directly sequenced with the BigDye Terminator kit version 1.1 (Applied Biosystems), and loaded on a 3130xl Genetic Analyzer (Applied Biosystems). In patients in whom no mutation was found, we performed multiplex ligation-dependent probe amplification to detect large deletions or duplications.\textsuperscript{28} Patients in whom the 3 loci were tested and excluded are referred to as patients without an identified mutation.

STATISTICAL ANALYSES

A t test was used to compare the distributions of severity score and progression rate by genotype. Univariate analysis of variance was performed for the association between age at onset and genotype. Multivariate analysis of variance was performed for the distribution of age at onset adjusting for the effect of all other possible variables (genotype, family within each genotype, and sex) and disease progression and also for the distributions of disease progression and age at onset in patients with SPG4 mutations, adjusting for mutation type. The significance level used for statistical analysis was $P \leq .05$. To assist with the analysis, we used IBM-SPSS Statistic 19.

SUBJECTS AND FAMILIES

We identified 89 families with AD-HSP. Clinical data from 239 patients, 109 women (45.6%) and 130 men (54.4%), were available. The mean (SD) age of patients was 50.7 (17.9) years.

EPIDEMIOLOGY

The estimated prevalence of AD-HSP in Portugal, based on preliminary unpublished results from the survey, was 2.4 in 100 000 inhabitants, distributed all over the country, though not proportional to the density of various regions.

CLINICAL RESULTS

Age at and Mode of Onset

The mean (SD) age at onset for all patients was 29.9 (18.6) years and its distribution had a bimodal shape (Figure 1). Onset was late (> 20 years) in 62% of patients and early in 38%. The initial symptoms were almost always a feeling of trapped leg or shuffling gait. The other first symp-
Neurological Examination

Mental examination findings were normal in 94% of patients. Brisk jaw reflex was present in 19%, and its rate of progression was not different from those with a normal reflex. Dysarthria was present in 6% of patients, half of whom also had dysphagia. Weakness and spasticity of the upper limbs were only present in patients with dysarthria (6%). Upper limb hyperreflexia occurred in 54% of patients, who showed no difference in disease progression compared with those with normal reflexes. In the lower limbs, the average weakness score was 4; quantification of spasticity, often asymmetrical, was possible in 60% of patients, and the average score was 2.2. Approximately 10% of patients did not have spasticity at rest but it was visible when walking. Vibration sense was abolished at the ankles in 12%, sphincter changes were present in 25%, and pes cavus was seen in 30% of patients.

Severity Score and Annual Rate of Disease Progression

The mean motor severity score was 3.5 for all patients. Eighty-eight percent of patients could walk (53.7% walked with no aid, 18.3% required a unilateral aid, and 16% required bilateral assistance). The remaining 12% could not walk (9.1% were wheelchair bound and 2.9% were bedridden). The average rate of disease progression was 4.1% per year (minimum, 0.43% per year, maximum, 28% per year).

Clinical Forms

Eighty-eight percent of patients had a pure form of disease, 58% of whom had late onset. Twelve percent of patients had complex forms of disease; the majority (54%) also had late onset. Nine patients from 4 families had moderate mental retardation. Dementia was present in 6 patients from 2 families; in most patients, it started years after the onset of motor difficulties and the prognosis was bad, leading to a severe pseudobulbar tetraplegic stage. Eight patients from 5 families had moderate lower limb ataxia. A generalized epilepsy and tremor were found in 4 patients in 2 families. Except for families with dementia, the others had patients with complex and pure forms of disease.

GENETIC RESULTS

Mutations were searched in 80 of 89 families (Table 1). There were mutations in 33 families (41%). Mutations were most frequent in SPG4, found in 27 families (33.7%), followed by SPG3 mutations, found in 5 families (6.2%), and SPG31 in 1 family (1.2% of index patients). Among the 31 distinct mutations identified, 26 were in the SPG4 gene (8 missense, 6 nonsense, 6 frameshift, 1 splicing mutation, and 2 large deletions [7.7%]) including 7 novel mutations. Four previously reported mutations (3 missense and 1 frameshift) were found in SPG3 and 1 nonsense in SPG31.

Genotype-Phenotype Correlations

The mean duration of illness (23.3 years) and the average lower limb weakness scores were similar in all genotypes (Table 2). The mean lower limb spasticity score was 1.9 in patients with SPG4 mutations and 2.4 in patients with SPG3 mutations. Two of the 4 families with mental retardation (S39 and S48) had SPG3 missense mutations. These mutations were different from those described in complex SPG3 disease forms and were related to a pure phenotype when published. Another family with mental retardation (S36) had the largest SPG4 deletion we found, suggesting that major exonic defects may cause major pathological effects, although the opposite has been described.

No SPG mutation, or mutation in dementia-related genes (presenilin 1, presenilin 2, amyloid precursor protein, microtubule-associated protein tau, progranulin), was identified in families with dementia. Also, no SPG mutations were found in patients with HSP with ataxia, epilepsy, and tremor or in patients with cranial nerve dysfunction or weakness and spasticity of the upper limbs, except for 1 family with an SPG4 mutation.

Age at Onset and Genotypes

Patients with SPG3 mutations had a lower mean age at onset (5.6 [16.7] years) than patients with SPG4 mutations (31.7 [10] years) and patients with no identified mutation (30.4 [18.9] years) (P < .001). Only 1 patient with an SPG3 mutation had a late disease onset (in the fourth decade). A great number of patients with SPG4 mutations had early-onset disease as well. When the onset was before the age of 15 years, 34% had SPG4 mutations and 20% had SPG3 mutations. When the onset was before the first decade, 31% had SPG4 mutations and 27% had SPG3 mutations.

We found a homogeneity of ages at onset in related patients (P < .0001). There was no association with sex and affected parent age at onset.

Age at Onset and SPG4 Mutation Type

The mean age at onset was significantly influenced by the nature of the mutation (P < .0001): 15.8 years in patients with large deletions, 28.6 years for missense, 35.6 years for frameshift, 38.6 years for nonsense mutations, and 42.7 years for patients with alternative splicing mutations; 70% of mutations were located in the AAA spastin domain, and these patients had a trend to an earlier disease onset (P = .02).

Severity and Disease Progression

On average, motor severity score was not significantly different among genotypic groups: 3.8 for patients with SPG3 mutations; 3.4 for patients with SPG4 mutations; and 3.7 for patients without an identified mutation. Even in older patients (> 40 years), we found no differences in this score between the genotypes.

In patients with SPG3 mutations, patients with SPG4 mutations, and patients without an identified mutation, we found no significant association of the rate of disease progression...
with sex, generation, age at onset of the affected parent, and type of mutation. We found, however, an association of the disease progression within the family ($P = .001$).

Excluding patients with less than 5 years of disease duration, an association between a late disease onset and a faster progression was found in patients with SPG4 mutations (Figure 2) ($P < .0001$), but not in patients with SPG3 mutations and patients without identified mutations.

### Progression of Disease in Patients With SPG3 and SPG4 Mutations

The average rate of disease progression was 4.5% per year in patients with SPG4 mutations and 4.3% per year in those without identified mutations, faster than in patients with SPG3 mutations, with 1.7% per year ($P < .001$). As shown, patients with SPG4 mutations with an earlier disease onset had a slower progression than patients with a later onset. Comparing only patients with early disease onset (< 20 years), the disease progression rate of patients with SPG4 mutations (n = 24) was 2.7%, not significantly different ($P = .54$) from the progression rate of patients with SPG3 mutations (n = 13) (1.7%). In this respect, the patients with SPG4 mutations resemble patients with SPG3 mutations; the slower average progression of these patients with SPG4 mutations could be attributable to their younger disease onset.

### Table 1. Mutations Found in Patients With AD-HSP

<table>
<thead>
<tr>
<th>Gene</th>
<th>Family Code</th>
<th>Mean Age at Onset, y</th>
<th>Mean Disease Progression Rate</th>
<th>Location Exon/Intron</th>
<th>AAA Cassette</th>
<th>Nucleotide Change</th>
<th>Predict Protein Change</th>
<th>Mutation Type and Source</th>
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**Abbreviations:** AD-HSP, autosomal dominant hereditary spastic paraplegia; NA, not available.

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**COMMENT**

The prevalence of AD-HSP in Portugal is 2.4 in 100,000. Prevalence in other studies ranges from 0.3 to 5.3 in 100,000, but only 3 studies have a solid population base. In Portugal, the prevalence is higher than in Ireland (12,13,18) and Spain, but only 3 studies have a solid population base. In Portugal, the prevalence is higher than in Ireland (12,13,18) and Spain, but only 3 studies have a solid population base. In Portugal, the prevalence is higher than in Ireland (12,13,18) and Spain, but only 3 studies have a solid population base. In Portugal, the prevalence is higher than in Ireland (12,13,18) and Spain, but only 3 studies have a solid population base.
land (1.27 in 100 000) and, in spite of an active search for patients, is lower than in Norway (5.5 in 100 000). Isolated patients are almost nonexistent. Included in the majority of the series, these patients have uncertain clinical significance. Their nonexistence was probably due to the personal observation of most families, at their health centers or at home, facilitating the recording of a detailed family history. Frequently, persons unaware of the medical condition of other relatives were picked and registered in the same large family tree.

The frequency of SPG3 (5.6%) and SPG4 (33.3%) mutations in this study is similar to what was described in other countries but the percentage of SPG4 deletions (7%) is far below the other studies. One study found that 20% of SPG4 mutations were deletions, admitting that the 40% frequency of SPG4 mutations was due to this high number of deletions. Different percentages (2.5%-23.5%) in non–population-based studies were found by others. SPG31 mutations were rare in our population (about 1%). In French patients, a frequency of 4.5% was recently reported.

This study was soundly based on a population survey. Therefore, the epidemiological results and gene frequencies are probably accurate for the Portuguese population and should represent some of the most reliable estimates published in this area. Nevertheless, several of the clinical variables used could have some limitations. The age at onset is always difficult to assess in HSP. We use uniform criteria; however, there is still a considerable amount of subjectivity involved. The severity scale evaluates only motor impairment and does not reflect cognitive decline. In spite of this, we think that it still captures most of the patient's disability, because cognitive impairment was found to be rare. The analysis of disease progression may be affected by errors in evaluation of disease onset and severity.

After 20 years of disease, only 12% of patients could not walk. Moderate corticospinal signs above the lower limbs, although signifying a higher corticospinal lesion, do not indicate a poor prognosis. Complex disease forms have a worse course than pure forms only when associated with dementia. These patients form a clinically distinct subgroup needing further investigation. Their rate of disease progression accelerates after several years of disease. With the exception of this small group, we have no sufficient longitudinal data to evaluate if disease progression is linear over time.

Age at onset and progression of the disease were associated with each family. In spite of variation among and within families, there was a significant trend for an intrafamilial aggregation of age at onset and the rate of disease progression.

Association of mutational class of each gene with any phenotypic trait has never been possible, with the exception of a possible earlier disease onset in SPG4 miss-
sense mutations. Patients with large SPG4 deletions had the earliest age at onset, followed by missense, frameshift, and nonsense mutations, with patients with alternative splicing mutations having the latest onset. The early age at onset of the missense mutations group may be due to a very early onset in 2 particular mutations (p.Leu380Pro and p.Ser445Asn), one novel and the other previously described, both located in the AAA cassette. SPG4 mutations were not associated with a different rate of disease progression.

Even before the genes’ identification, it was suggested that when onset was after age 35 years the disease progresses more rapidly. Patients with SPG4 mutations and with unidentified mutations had a faster progression than those with SPG3 mutations. When making a multivariate analysis, however, there is no difference in the rate of progression with genotype but instead an association with age at onset. The patients with SPG4 and SPG3 mutations could have a quite similar progression of disease if the onset was at the same age. The differences in progression rates could be caused by the confounding factor of age at onset.

CONCLUSIONS

SPG3 mutations have been considered the most frequent cause of AD-HSP, with onset during the first decade. However, the probability of finding SPG4 mutations is higher than for SPG3 even when the disease begins before age 10 years. As a rule, we should start the genetic study by searching for SPG4 mutations. Some authors have suggested that rare late-onset forms legitimize the study of SPG3 mutations in all the SPG4 mutation–negative families. This has little justification according to our experience. Mutations in the SPG31 gene can hardly be regarded as the third most frequent cause of AD-HSP, since there are still 63% of families that remain without a molecular diagnosis. This large number of families reinforces the high genetic heterogeneity of HSP. The low interfamilial variability does not allow for the organization of distinct phenotypic groups, making the identification of novel genes a challenging task.

There is no significant difference in disease progression with genotype but an association with the age at onset. In patients with SPG4 mutations, an earlier onset pointed to a slower disease progression and a later onset, to a faster disease progression.

We identified 7 new SPG4 mutations, we found for the first time, to our knowledge, that the nature of the SPG4 mutations predicts the age at onset, and we verified a trend to an earlier disease onset when mutations are located in the AAA spastin domain.

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