Clinical Neurology and Neurosurgery 120 (2014) 14–19

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

# Hereditary spastic paraparesis in adults. A clinical and genetic perspective from Tuscany

Daniele Orsucci [a], Loredana Petrucci [a], Elena Caldarazzo Ienco [a], Lucia Chico [a], Paolo Simi [b], Antonella Fogli [b], Fulvia Baldinotti [b], Costanza Simoncini [a], Annalisa LoGerfo [a], Cecilia Carlesi [a], Alessia Arnoldi [c], Maria Teresa Bassi [c], Gabriele Siciliano [a], Ubaldo Bonuccelli [a], Michelangelo Mancuso [a,*]

[a] Neurological Clinic, University of Pisa, Italy
[b] U.O. Laboratorio Genetica Medica, Santa Chiara Hospital, Pisa, Italy
[c] IRCCS E. Medea, Laboratory of Molecular Biology, Bosisio Parini, Lecco, Italy

ARTICLE INFO

*Article history:*
Received 20 April 2013
Received in revised form 14 January 2014
Accepted 8 February 2014
Available online 17 February 2014

*Keywords:*
4SMD
Hereditary spastic paraparesis
Hereditary spastic paraplegias
HSP
SPG
Strumpell-Lorrain

ABSTRACT

*Objective:* Hereditary spastic paraparesis or paraplegias (HSPs) are a group of neurogenetic conditions with prominent involvement of the pyramidal tracts. Aim of this study is the clinical and molecular characterization of a cohort of patients with HSP. Moreover, we aim to study the minimum prevalence of HSP in our area and to propose a schematic diagnostic approach to HSP patients based on the available data from the literature.
*Methods:* Retrospective/perspective study on the subjects with clinical signs and symptoms indicative of pure or complicated HSP, in whom other possible diagnosis were excluded by appropriate neuroradiological, neurophysiologic and laboratory studies, who have been evaluated by the Neurogenetic Service of our clinic in last two years (2011–2012).
*Results:* 45 patients were identified. The minimum prevalence of HSP in our area was of about 2.17–3.43/100,000. The SF-36 (quality of life) and SPRS (disease progression) scores were inversely related; the time-saving, four-stage scale of motor disability could predict the SPRS scores with a high statistical significance, and we encourage its use in HSP. Our study confirms *SPG4* as the major cause of HSP. All *SPG4* patients had a pure HSP phenotype, and the dominant inheritance was evident in the great majority of these subjects. *SPG7* was the second genetic cause. Other genotypes were rarer (*SPG10*, *SPG11*, *SPG17*).
*Conclusion:* Exact molecular diagnosis will allow a more accurate patient counseling and, hopefully, will lead to specific, targeted, therapeutic options for these chronic, still incurable diseases.


## 1. Introduction

Hereditary spastic paraparesis (HSPs), describes a heterogeneous group of neurogenetic disorders caused by degeneration of the corticospinal tracts [1]. The key clinical findings are lower limb spasticity, with hyperreflexia and extensor plantar responses [1]. Urinary urgency is also frequent. Age at onset is extremely variable, from childhood through to late adult life. Traditionally, these conditions have been divided into pure HSPs and complicated HSPs, depending on the presence of adjunctive neurological features (such as ataxia, thin corpus callosum, peripheral neuropathy, distal amyotrophy, retinopathy, optic atrophy, extrapyramidal signs, cognitive dysfunction, deafness, epilepsy) [2].

HSP prevalence has been estimated 3–10/100,000 in Europe [3,4], but few epidemiological studies are available. A recent population-based, cross-sectional study performed in Southeast Norway showed a prevalence of 7.4/100,000 [5], and another study in Estonia of 4.4/100,000 [6].

The best-characterized molecular mechanisms in HSPs are impairment of transport of macromolecules and organelles, disturbance of mitochondrial function, or abnormalities of the developing axon [1]. The genetics of HSP is complex and all mendelian modes of inheritance have been described [1]. Most cases of autosomal dominant HSP are pure, whereas complicated forms tend to be autosomal recessive; *SPG4* (*SPAST*, spastin), *SPG3A* and *SPG31* (*REEP1*) are the most common causes of

* Corresponding author. Tel.: +39 50 992443.
*E-mail address:* mancusomichelangelo@gmail.com (M. Mancuso).

http://dx.doi.org/10.1016/j.clineuro.2014.02.002
0303-8467/

autosomal dominant pure HSP [1]. Mutations in the *SPG7* gene (paraplegin) are the most common cause of autosomal recessive HSP, with both pure and complicated phenotypes [1]. Moreover, a significant number of apparently sporadic cases has an *SPG* mutation, suggesting that these patients should not be excluded from genetic studies [7].

Aim of this study is the clinical and molecular characterization of a big cohort of patients with HSP evaluated at the Neurogenetic Service of our clinic in last two years (2011–2012). Moreover, we aim to study the minimum prevalence of HSP in our area and to propose a schematic diagnostic approach to HSP patients based on the available data from the literature.

## 2. Methods

### 2.1. Patients

We retrospectively reviewed the clinical and genetic data of subjects with clinical signs and symptoms indicative of pure or complicated HSP, in whom other possible diagnosis (i.e., multiple sclerosis, leucodystrophy, mitochondrial diseases, etc.) were excluded by appropriate neuroradiological, neurophysiologic and laboratory studies. Those HSP cases ($n = 45$) have been evaluated in last two years (2011–2012).

A simple, four-stage functional scale of motor disability (1 = mild symptoms, walking without aid; 2 = walking without aid but unable to run; 3 = walking with aid; 4 = wheelchair-dependent) [5] has been utilized (Table 1). Moreover, in a subset of patients perspectively evaluated in 2012, we could also perform standardized functional evaluations by means of the SF-36 scale of health-related quality of life [8] and the spastic paraplegia rating scale (SPRS) [9].

Magnetic resonance imaging (MRI) of the brain and the spinal cord, as well as appropriate neurophysiological and laboratory investigations (including in some instances genetic studies for spino-cerebellar ataxias, Friedreich's ataxia, ARSACS, mitochondrial DNA mutations, etc.), have been performed in all patients in order to exclude secondary cases of the paraparesis and to find eventual "complicating" features (e.g., neuropathy, thinning of the corpus callosum, etc.). Patients without genetically confirmed

**Table 1**
Clinical features of HSP patients in our group.

| No. | Onset (years) | Last eval. | Follow up | Pure/compl. | Sex | 4SMD | SF36 | SPRS | Family history | Screened genes (*SPG*)[a] | Genetic diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 40 | 48 | 6 | Pure | F | 1 | 618 | 3 | AD | | *SPG4* |
| 2 | 44 | 46 | 2 | Pure | F | 2 | 387 | 11 | AD | 7 | *SPG4* |
| 3 | 30 | 50 | 19 | Pure | F | 3 | 516 | 22 | AD | | *SPG4* |
| 4 | 25 | 34 | 7 | Pure | F | 2 | 374 | 16 | AD | | *SPG4* |
| 5 | 42 | 44 | 2 | Pure | M | 1 | 446 | 6 | AD | | *SPG4* |
| 6 | 43 | 48 | 3 | Pure | F | 1 | 629 | 3 | AD | | *SPG4* |
| 7 | 45 | 62 | 13 | Pure | M | 3 | 394 | 23 | AD | | *SPG4* |
| 8 | 10 | 61 | 5 | Pure | M | 2 | 604.5 | 8 | No | | *SPG4* |
| 9 | 42 | 47 | 5 | Pure | M | 1 | 498 | 5 | AD | | *SPG4* |
| 10 | 50 | 76 | 10 | Pure | F | 3 | | | AD | | *SPG4* |
| 11 | 65 | 70 | 2 | Pure | F | 1 | 230 | 11 | AD | | *SPG4* |
| 12 | 30 | 53 | 10 | Pure | M | 2 | 661 | 17 | AD | | *SPG4* |
| 13 | 37 | 40 | 3 | Pure | M | 2 | 362 | 16 | No | | *SPG4* |
| 14 | 27 | 38 | 10 | Compl. | M | 2 | 323 | 14 | ar | 7 | *SPG7* |
| 15 | 35 | 57 | 5 | Compl. | F | 2 | 532 | 9 | ar | 7,17 | *SPG7* |
| 16 | 46 | 51 | 5 | Pure | M | 2 | 175 | 21 | No | 7 | *SPG7* |
| 17 | 53 | 59 | 4 | Compl. | M | 1 | 638 | 1 | No | 7 | *SPG7* |
| 18 | 34 | 37 | 2 | Pure | M | 2 | | | No | 7 | *SPG7* |
| 19 | 26 | 38 | 5 | Pure | M | 2 | 393 | 10 | AD | 7,10,17 | *SPG10* |
| 20 | 26 | 38 | 10 | Pure | F | 4 | 302 | 29 | No | 7,10,11 | *SPG11* |
| 21 | 27 | 69 | 13 | Compl. | M | 3 | 244 | 23 | AD | | *SPG17* |
| 22 | 24 | 33 | 9 | Compl. | F | 3 | | | No | 7,11 | Unknown |
| 23 | 55 | 60 | 5 | Pure | F | 3 | 164 | 24 | No | 7,10,11 | Unknown |
| 24 | 46 | 69 | 16 | Pure | F | 2 | 233 | 14 | No | 7,10,11 | Unknown |
| 25 | 43 | 64 | 21 | Compl. | F | 2 | 256 | 20 | AD | 7,10 | Unknown |
| 26 | 12 | 41 | 9 | Pure | F | 2 | 200 | 4 | No | 7,10,11 | Unknown |
| 27 | 50 | 65 | 6 | Pure | M | 3 | 409 | 23 | AD | 7,10 | Unknown |
| 28 | 49 | 50 | 1 | Pure | M | 1 | | | No | 7 | Unknown |
| 29 | 58 | 68 | 10 | Compl. | F | 1 | | | No | 6,7,13 | Unknown |
| 30 | 55 | 58 | 2 | Compl. | F | 3 | 397 | 13 | No | 7,11,15 | Unknown |
| 31 | 58 | 67 | 7 | Pure | M | 2 | 450 | 14 | No | 7,10,11 | Unknown |
| 32 | 32 | 34 | 2 | Pure | M | 3 | 310 | 22 | No | 7 | Unknown |
| 33 | 16 | 30 | 2 | Compl. | F | 3 | 467 | 23 | No | 7,10,11 | Unknown |
| 34 | 12 | 43 | 10 | Pure | F | 2 | | | No | 5,7,10,11 | Unknown |
| 35 | 62 | 64 | 1 | Pure | M | 2 | 223 | 11 | No | 7,10,11 | Unknown |
| 36 | 29 | 33 | 2 | Compl. | F | 2 | 441 | 14 | No | 7 | Unknown |
| 37 | 30 | 49 | 10 | Pure | M | 2 | | | No | 7 | Unknown |
| 38 | 21 | 42 | 20 | Compl. | F | 2 | | | No | 6,7,10,11,13,15 | Unknown |
| 39 | 53 | 58 | 5 | Pure | F | 1 | | | No | 7,10,11 | Unknown |
| 40 | 63 | 66 | 3 | Pure | F | 4 | 410 | 30 | AD | 7,10 | Unknown |
| 41 | 24 | 28 | 4 | Pure | F | 2 | 613 | 15 | No | 7,10,11 | Unknown |
| 42 | 12 | 41 | 16 | Pure | F | 2 | 527 | 17 | No | 7 | Unknown |
| 43 | 10 | 51 | 2 | Compl. | F | 2 | 600.5 | 10 | No | 7, 10,11 | Unknown |
| 44 | 50 | 62 | 4 | Pure | M | 2 | 587 | 10 | No | 7,10,11 | Unknown |
| 45 | 40 | 64 | 9 | Pure | F | 2 | 501 | 9 | No | 7,10,11 | Unknown |

[a] Apart from *SPG4*, *3A*, *31* (analyzed in all patients). 4SMD, four-stage scale of motor disability (see text); AD, autosomal dominant; ar, autosomal recessive. Complicating features (compl.): cerebellar atrophy in patients 14, 15, 17 and 36; distal amyotrophy and hearing loss in patient 21; white matter involvement in patients 21, 22, 38 and 43; dysarthria in patients 25 and 30; cognitive involvement in patients 29 and 30; thin corpus callosum in patient 30; ataxia (without cerebellar atrophy) in patient 33.