Clinical and neurophysiologic characterization of an European family with hereditary sensory neuropathy, paroxysmal cough and gastroesophageal reflux

Caracterização clínica e neurofisiológica de uma família europeia com neuropatia sensitiva hereditária, tosse paroxística e refluxo gastroesofágico

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ABSTRACT
In 2002, Spring et al reported a family with an autosomal dominant form of hereditary sensory neuropathy; patients also presented adult onset of gastroesophageal reflux and cough. Since then, no further families have been described. Objective: To study a new Portuguese family with these characteristics. Method: To describe the clinical and neurophysiologic characteristics of one family with features of sensory neuropathy associated with cough and gastroesophageal reflux. Results: Three of five siblings presented a similar history of paroxysmal cough (5th decade). About a decade later they experienced numbness and paraesthesia in the feet and in all cases there was evidence of an axonal sensory neuropathy. A history of gastroesophageal reflux of variable severity and age of onset was also present. Discussion: Molecular genetic studies have demonstrated genetic heterogeneity between the hereditary sensory neuropathy type 1 subtypes. The identification of these families is of major importance because further work is required to identify the underlying genetic defect. Keywords: cough, hereditary sensory neuropathy, reflux.

RESUMO
variable, even within families. In patients with marked distal muscle weakness, the presence of prominent sensory abnormalities and foot ulcerations is crucial to differentiate HSN type 1 from hereditary motor and sensory neuropathy (HMSN; Charcot-Marie-Tooth syndrome). HSN type 1 is slowly progressive but is often disabling after many years of disease evolution. In HSN type 1, there is a wide variability of electrophysiological abnormalities. Sensory potentials are usually absent in the lower limbs but can be normal in the upper limbs. Previous reports illustrated clinical and genetic heterogeneity of HSN 1. At this time, three gene loci and two genes (SPTLC 1 and RAB 7) are identified. A subdivision into HSN 1A, 1B, 1C and 1D which is based on the different genetic background and also clinical characteristics has been proposed.

In 2002, Spring et al. reported a family with an autosomal dominant form of HSAN; patients had distal sensory loss usually without foot ulceration, adult onset of gastroesophageal reflux (GOR) and cough and no motor symptoms. The disease locus in this family was linked to a 3.42 cM interval on chromosome 3p22-p24 in 2003, and was also confirmed in a second family with a similar phenotype. The gene involved in this disease remains to be identified. Here we describe clinical and neurophysiologic characteristics of a European family with a similar phenotype.

METHOD

One Portuguese family has been identified with features of sensory neuropathy associated with cough and GOR. The family is originally from Fiães (Santa Maria da Feira, northern Portugal). The ancestry is from the same geographic region, with the exception of the paternal grandfather, who was born in another Portuguese city (interior central region of the country).

Our diagnostic requirement for sensory neuropathy was the presence of clinical signs of distal sensory loss, with an axonal neuropathy on nerve conduction studies (NCS); cough was required to have been present for at least 5 years with no medication or condition found to account for the cough; significant GOR was defined as symptoms of heartburn or regurgitation at least once a week.

RESULTS

III: 5 - Index Case: This 74 year-old man had a history of bilateral deafness since his 20 years old. At age 50 he complained of severe heartburn; a gastroscopy had shown reflux oesophagitis and he underwent anti-reflux surgery, with partial benefit in his heartburn complaints (he remained medicated with important doses of proton-pump inhibitors). He complained of a recurrent (almost daily), violent, paroxysmal dry cough since age 52; it was often triggered by inhalation of strong odours such as cigarette smoke, and by eating dry food. Episodes occurred up to twenty times per day and were often very violent and prolonged causing an important impact in his quality of life. There were occasional episodes of cough syncope and prolonged paroxysmal cough episodes could be induced by pressure of objects such as cotton bud in the external auditory canal. From the age of 62 he had experienced numbness and paraesthesia in the feet with intermittent shock-like pain. On examination, there was evidence of a stocking sensory neuropathy. There was sensory loss for all modalities in a stocking pattern, with absence of ankle jerks; mild sensory ataxia and positive Arnold’s sign.

NCS demonstrated a pure sensory axonal neuropathy (absent bilateral sural, superficial peroneal, median and ulnar sensory nerve action potentials (SNAP’s)). Motor studies were normal (see Table 1). Audiometry revealed a bilateral sensorineural hearing loss.

We performed extensive laboratory investigation of common causes of neuropathy, including: complete blood count, biochemistry (renal function, liver enzymes, C-reactive protein, erythrocyte sedimentation rate, thyroid function), virological studies (HIV, HBV, HCV), immunological study, serum immunoelectrophoresis, HbAlc, vitamin B12, acid malonic, homocysteine and folic acid; all of these investigations were normal/negative in this patient in all other affected patients. There was no history of alcohol or neurotoxins consumption. He was screened and found to have no mutations in genes of known CMT1 loci, CMT1A, 1B (including the Thr124Met mutation), 1D or 2I/2J as well as for mutation in the SPTLC1 and RAB 7 genes.

III-I: This 80 year old woman had a history of paroxysmal cough since age 50. The paroxysmal cough episodes (up to 5 a day) were of moderate intensity; there was not a clear history of episodes triggered by inhalation of strong specific odours but the patient reported that they could be induced by pressure of objects such as cotton bud in the external auditory canal. There was no history of cough syncope but many of these episodes forced her to stop activity. She complained of heartburn since her sixties; gastroscopy revealed very slight signals of GOR. By the age of 65 she experienced numbness and paraesthesia in the feet; sometime later initiates a history of falls, especially in the dark. On examination, there was evidence of a glove and stocking sensory neuropathy; there was extensive sensory loss for all modalities in a glove and stocking pattern, with absence of ankle jerks; very serious sensory ataxia (requiring unilateral support) and positive Arnold’s sign. NCS demonstrated a pure sensory axonal neuropathy (absent bilateral sural, superficial peroneal, median and ulnar SNAP’s). Motor studies were normal (see Table 1). Audiometry revealed a mild bilateral sensorineural hearing loss.
III-7: Very similar history to III-1 (paroxysmal cough since 5th decade – mild heatburn complaints – sensory axonal neuropathy with very important sensory ataxia).

II-1: died at 66 years (probable prostate cancer). He had paroxysmal cough and complaints of numbness and paraesthesia in the feet since age 55.

IV-1; 2; 3; 4 – Asymptomatic; normal NCS.

**DISCUSSION**

Since the report, in 2005, by Spring et al., of two families with the combination of a dominantly inherited sensory axonal neuropathy with cough and GOR, with intermittent throat clearing, hoarse voice and sensorineural hearing loss, no other families were reported. Nevertheless, even in these two families there was a variable clinical presentation. For instance, in the first described family, the index case presented with a predominantly small fibre, glove and stocking sensory neuropathy but, on the other hand, his paternal aunt presented with an extensive sensory loss for all modalities up to the shoulders (more extensive on the right than left). In this Portuguese family, and although the NCS showed similar findings in the affected family members, clinical sensory ataxia was much more severe in patients III-1 and III-7.

Spring et al. reported that pure sensory axonal neuropathy on nerve conduction studies (NCS) was the “rule” in the Australian families – NCS demonstrated a pure sensory axonal neuropathy in all but one of these subjects, who was one of the youngest in his generation and had a suspected small fibre neuropathy. Motor studies were all normal apart from the reduced common peroneal compound motor action potential (CMAP) amplitude in one subject. We want to highlight the fact that patients in this Portuguese family have been evaluated at a much higher age than the affected patients in the Australian families, which can contributed to an even more disparity in the sensory vs motor NCS. It’s known that, in other forms of hereditary sensory neuropathy, sensory loss initially affects pain and temperature perception but it involves all modalities as the disease progresses. The sensory neuropathy shows similarity to the other dominant HSN’s, but it can be distinguished by the lack of motor involvement and also acral mutilation and ulceration. Like in the Australian families, the neuropathy usually presented later than the cough and GOR with a mean time delay of 12 and 15 years, respectively. As reported by Spring et al., this form of HSN has minimal evidence of an autonomic neuropathy on autonomic studies apart from distal hypohidrosis. Although we have not performed autonomic studies, it is important to emphasize that patients denied complaints of impotence, urinary urgency, impaired lacrimation or lower gastrointestinal disturbances.

Cough has been reported as a feature of neurological disorders that affect the autonomic nervous system and this

<table>
<thead>
<tr>
<th>Motor NCS (III-5/III-1)</th>
<th>DL (ms)</th>
<th>Amp (mV)</th>
<th>CV (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right median</td>
<td>3.7/3.3</td>
<td>6.8/4.7</td>
<td>57.8/45.5</td>
</tr>
<tr>
<td>Right posterior tibial</td>
<td>3.9/4.2</td>
<td>8.1/5.6</td>
<td>47.3/36.2</td>
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<tr>
<td>Right peroneal</td>
<td>4.2/5.4</td>
<td>2.8/2.0</td>
<td>39.7/36.6</td>
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<tr>
<td>Left peroneal</td>
<td>5.4/5.3</td>
<td>2.5/1.9</td>
<td>42.9/36.8</td>
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</tbody>
</table>

<table>
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<tr>
<th>Sensory NCS (III-5/III-1)</th>
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<th>Amp (uV)</th>
<th>CV (m/s)</th>
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</thead>
<tbody>
<tr>
<td>Right median (2nd finger)</td>
<td>-/-</td>
<td>-/-</td>
<td>-/-</td>
</tr>
<tr>
<td>Right ulnar (5th finger)</td>
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</tr>
<tr>
<td>Right radial</td>
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<tr>
<td>Right superficial peroneal</td>
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<tr>
<td>Left superficial peroneal</td>
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<tr>
<td>Right sural</td>
<td>-/-</td>
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<tr>
<td>Left sural</td>
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</table>

DL: distal latencies; AMP: amplitude; CV: conduction velocity.

**Table 1.** Motor and sensory Nerve Conduction Studies (NCS) of patients III-5 and III-1.
includes a variant of neuropathy associated with the Thr124Met mutation in the peripheral myelin protein zero (MPZ) gene. In this form of HSN 1, cough usually begins between the second and fourth decade; in this family, the paroxysmal cough episodes began somewhat later, in the 5th decade. The stereotyped features of attacks being triggered by inhalation of noxious odours and by tactile stimulation of the external auditory canal are similar to the descriptions of the MPZ mutation family members, but as already pointed this mutation was screened and was absent. In rare cases, cough can be the initial and only manifestation of GOR, and is a strong possibility that GOR may have contributed, in some measure, to chronic cough in these patients. The "Arnold's ear-cough reflex", that can be elicited in some patients of these families, occurs in 1.7-4.2% of the general population, but its presence in multiple family members is not common. Baloh et al hypothesized that a "prominent ear-cough reflex may result from impaired C fibre sensory innervations of the upper airways or oesophagus leading to denervation hypersensitivity of the neurons in the nucleus solitaries". As previously suggested by some authors, a possible alteration in the pattern of lower oesophageal sphincter relaxation may be the mechanism for GOR in these patients.

In conclusion, molecular genetic studies in the past years have demonstrated genetic heterogeneity between the HSN type 1 subtypes. In this family, presenting with an inherited HSN, linkage to known HSN 1 and CMT loci was excluded. The identification of these families is definitely important because further work is required to identify the underlying genetic defect, since this may lead to improvements in knowledge of neural structures involved. In addition, these patients (as was the case) are likely to be followed in multiple specialties, performing multiple diagnostic tests for conditions which initially seem to be unrelated. Greater knowledge of this entity may allow a faster diagnosis and spare unnecessary investigations.

References