SHORT REPORT

Heterozygous D90A-SOD1 mutation in a patient with facial onset sensory motor neuronopathy (FOSMN) syndrome: a bridge to amyotrophic lateral sclerosis

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ABSTRACT

Objective To describe a patient with facial onset sensory motor neuronopathy (FOSMN) syndrome associated with a heterozygous D90A mutation in superoxide dismutase (SOD1) gene.

Methods The patient underwent neurological and neurophysiological examinations, including blink and jaw reflexes, sural nerve and skin biopsies, and analysis of TARDBP, FUS and C9ORF72 genes.

Results Neurological examination showed diffuse fasciculations, bulbar signs, hypotrophy and weakness of facial, neck, shoulder girdle and first interosseous muscles, and absent corneal reflex. Neurophysiologic studies demonstrated abnormal blink and jaw reflexes and reduced sensory nerve action potentials at upper limbs. Sural nerve and skin biopsies revealed mild loss of large and small nerve fibres. Genetic analysis demonstrated a heterozygous D90A-SOD1 mutation.

Conclusions FOSMN syndrome has been recently described in patients with slowly progressive bulbar and upper limb amyotrophy. Sensory symptoms, mainly involving the trigeminal territory, typically precede the onset of motor weakness by months or years. The pathogenesis of FOSMN syndrome is unknown and possible immune-mediated mechanisms have been claimed. Our findings support the hypothesis that FOSMN syndrome is a primary degenerative disorder that widers the spectrum of motor neuron diseases.

INTRODUCTION

Facial onset sensory motor neuronopathy (FOSMN) syndrome, first described in 2006,1 is a condition characterised by early sensory symptoms followed, after a variable number of months or years, by wasting and weakness of bulbar and upper limb muscles. The clinical picture appeared quite stereotypic and the survival much longer than in amyotrophic lateral sclerosis (ALS), with median survival of 8–21 years.2 FOSMN syndrome may be underdiagnosed yet, with about 20 patients described thus far. No familiar case has been reported. The pathogenesis of this disease remains obscure, though clinical course and pathological findings suggested a primary neurodegenerative disease.3 4 Transient response to immune-modulatory treatment and evidence of autoantibodies at low titre in some patients raised also the hypothesis of a possible immune-mediated involvement.3 5

Here we report the first-ever patient presenting with FOSMN syndrome and harbouring a heterozygous D90A mutation in the superoxide dismutase (SOD1) gene. Our observation strongly supports the hypothesis that FOSMN syndrome is a variant of ALS characterised by the involvement of trigeminal and, for a less extent, small and large size dorsal root ganglion (DRG) neurons.

CASE REPORT

A 53-year-old man presented with 5-year history of nearly constant mild tingling at lips and near nose region. His familiar and personal history was unremarkable; 3 years later, he complained of 10 kg weight loss over a period of about 5 months, without diet changes and apparent dysphagia. A few months later he was hospitalised for acute pneumonia. In that period, the patient started reporting generalised asthenia and weakness in the upper limbs. Symptoms slowly worsened over time, with slight and transient difficulty in swallowing, until he was again hospitalised for acute pneumonia. Laboratory screening ruled out metabolic, infectious and connective diseases and solid or haematological malignancies. Serum immunofixation detected IgG-k monoclonal gammopathy of undetermined significance. Total body CT and gastroscopy were negative. Brain and spinal cord MRI were negative.

When referred to us, the neurological examination showed mild dysarthria and rhinolalia, tongue hypotrophic at the edges and weak, absent corneal reflex bilaterally, diffuse fasciculations on chin and shoulder girdle muscles, hypotrophy and weakness (Medical Research Council (MRC)=4) of facial, neck, shoulder girdle and first interosseous muscles. Sensory symptoms, mainly involving the trigeminal territory, typically preceded the onset of motor weakness by months or years. The pathogenesis of FOSMN syndrome is unknown and possible immune-mediated mechanisms have been claimed. Our findings support the hypothesis that FOSMN syndrome is a primary degenerative disorder that widers the spectrum of motor neuron diseases.
(EMG) revealed acute denervation (fibrillation and positive sharp waves) in upper limb and genioglossus muscles, and chronic neurogenic changes (increased motor unit potential duration and amplitude, reduced voluntary recruitment) at all limbs. Cranial nerve neurophysiologic examination showed altered trigeminal-facial and trigeminal-trigeminal responses at blink reflex and jaw reflex recording, respectively, with normal facial CMAP amplitude and latency (table 1). Motor evoked magnetic potential examination demonstrated normal central and peripheral motor conduction. Nocturnal oximetry resulted normal (SaO2 >90% for >4% of the overnight recorded time).

Sural nerve biopsy demonstrated axonal rearrangement with relative loss of large size myelinated fibres without inflammatory cell infiltrates (eg, LCA, CD45Ro, CD20 and CD68 cells), evidence of vasculitis (eg, fibrinoid necrosis of wall vessels) or amyloid deposition. Skin biopsy, performed with a 3-mm disposable punch, showed decreased intraepidermal nerve fibre (IENF) density at the lower limb (3 IENF/mm) compared with available gender and age adjusted normative values (5th centile 3.5 IENF/mm)\(^6\) (figure 1). Mutational assay of SOD1 gene identified a known nucleotide variant in heterozygosis causing aspartate-alanine substitution at codon 90 (pD90A). The genetic analysis of TARDBP, FUS and C9ORF72 genes was negative. The clinical picture worsened over the following 6 months with severe dysphagia and moderate nocturnal respiratory insufficiency, needing percutaneous gastrostomy and non-invasive ventilation. Due to previous reports demonstrating the lack of benefit from immune-modulatory or immune-suppressive treatments\(^5\) \(^4\) \(^7\) and the evidence of D90A-SOD1 mutation, no therapy was performed.

**DISCUSSION**

FOSMN syndrome, as originally described\(^1\) and later confirmed in further case series,\(^2\) \(^5\) \(^7\) \(^9\) has a quite stereotypical presentation with mild sensory disturbances in the trigeminal territory and upper limbs, often with asymmetric distribution. Sensory symptoms present months, or more frequently years, before the onset of motor weakness in bulbar, neck and upper limbs. These latter, causing progressive impairment and disability (eg, dysarthria, dysphagia, impaired hand movements), commonly lead patients to see a neurologist. At this stage, the burden of muscle waste and weakness and the neurophysiologic evidence of diffuse acute and chronic neurogenic changes may cloud the presence of sensory disturbances which are a clue for diagnosing FOSMN syndrome.

Hallmark of the syndrome is the absence of the corneal reflex. It is elicited by gently stimulation of the cornea leading to involuntary and consensual eyelid blinking. The corneal reflex is mediated by afferent fibres in the nasociliary branch of the ophthalmic branch of the trigeminal nerve and efferent fibres in the temporal branch of the facial nerve. The corresponding trigeminal-facial neurophysiologic response is evaluated by electrical stimulation of the supra-orbital nerve and measuring of ipsilateral early R1 component and the ipsilateral and contralateral late R2 components, both generated by the same facial motor neurons and mediated by interneurons in the pons and caudal medulla, respectively. Trigeminal nerve lesion on one side can reduce or abolish early ipsilateral component and late components on both sides, whereas unilateral facial nerve palsy does not abolish the contralateral late component. However, demyelinating neuropathies (eg, hereditary) involving both facial nerves can produce a similar pattern. Our patient showed normal CMAP amplitude and latency of facial nerves, confirming that blink reflex abnormalities were caused by a dysfunction in the trigeminal pathway not detectable by MRI. Altered jaw reflex demonstrated the failure of the arc relayed by the trigeminal mesencephalic nucleus through afferent sensory muscle spindle fibres and efferent motor axons. ALS patients do not show blink reflex alterations, except in the late stage of the disease when bilateral facial nerve palsy occur.\(^10\) Our patients showed reduced SNAP amplitude at upper limb nerves reflecting peripheral sensory axon loss, which has been previously observed in almost all FOSMN syndrome patients, whereas should not be found in ALS patients.

Diaphragm muscles were not examined. The patient did not show the classical signs of dyspnoe (hypoventilation, or bulbar and upper limb muscle weakness and impairment).

Previous pathologicial findings in FOSMN syndrome\(^1\) \(^4\) revealed loss of 5th, 7th, 9th, 12th nuclei, loss of cervical motor neurons and anterior root atrophy, Nageotte nodules and neuronal loss in DRG, and mild loss of large nerve fibres without regeneration cluster in sural nerve biopsy. Our morphometric assay of sural nerve confirmed the mild loss of large fibres, whereas skin biopsy demonstrated the involvement of unmyelinated sensory nerves that was not yet reported in FOSMN syndrome.

Several findings support the hypothesis that FOSMN syndrome is a primary degenerative disorder which widens the spectrum of motor neuron diseases.\(^2\) They include the anecdotal observation of TAR DNA-binding protein 43 inclusions in one patient,\(^3\) the disproportion between almost negligible sensory symptoms and progressive bulbar and upper limb muscle waste and weakness, and the dismal prognosis. Moreover, FOSMN syndrome appeared not responsive to immune-modulatory and immune-suppressive treatments,\(^5\) \(^4\) \(^7\) except in single cases over

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**Table 1** Facial nerve conduction, blink and jaw reflex, and sensory nerve conduction studies.

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Latency (ms)</th>
<th>Amplitude (mV)</th>
<th>Conduction velocity (m/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. facial</td>
<td>Zygomatic-orb. oculi</td>
<td>3.5 (4.0)</td>
<td>2.2 (2)</td>
</tr>
<tr>
<td>L. facial</td>
<td>Zygomatic-orb. oculi</td>
<td>3.5 (4.0)</td>
<td>2.0 (2)</td>
</tr>
<tr>
<td>Blink reflex</td>
<td>R. Supra-orbital</td>
<td>absent</td>
<td>46.2 (40)</td>
</tr>
<tr>
<td>L. Supra-orbital</td>
<td>10.0</td>
<td>47.4 (40)</td>
<td>51.2 (41)</td>
</tr>
<tr>
<td>Jaw reflex</td>
<td>R. Masseter</td>
<td>8.2 (7)</td>
<td>–</td>
</tr>
<tr>
<td>L. Masseter</td>
<td>absent (7)</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>L. superficial peroneus</td>
<td>Leg-foot</td>
<td>2.8</td>
<td>10.6 (3)</td>
</tr>
<tr>
<td>R. Sural</td>
<td>Leg-malleolus</td>
<td>3.1</td>
<td>10.2 (6)</td>
</tr>
<tr>
<td>L. Sural</td>
<td>Leg-malleolus</td>
<td>3.1</td>
<td>12.1 (6)</td>
</tr>
<tr>
<td>R. Ulnar</td>
<td>Wrist-fifth finger</td>
<td>3.0</td>
<td>11.9 (16)</td>
</tr>
<tr>
<td>L. Ulnar</td>
<td>Wrist-fifth finger</td>
<td>3.1</td>
<td>9.2 (16)</td>
</tr>
<tr>
<td>R. Median</td>
<td>Third finger-wrist</td>
<td>2.8</td>
<td>5.9 (12)</td>
</tr>
<tr>
<td>L. Median</td>
<td>Third finger-wrist</td>
<td>3.0</td>
<td>6.1 (12)</td>
</tr>
</tbody>
</table>

Alterations are reported in bold. Lower normal values are reported in brackets. Distal latencies and conduction velocity were normal in all nerves.
Figure 1  Sural nerve biopsy from patient (D) and age-matched control (A), and corresponding myelinated nerve fibre histograms (B and E); skin biopsy at 10 cm above the lateral malleolus in the territory of the sural nerve from patient (F) and age-matched control (C). Qualitative examination of sural nerve biopsy in the patient (D) showed cluster of regeneration (arrows) and relatively more small fibres, in the absence of clear-cut evidence of fibre loss. Myelinated fibre histogram, obtained on randomly chosen fields covering about 10% of the total transverse fascicular area using a semiautomatic programme (NIS Element BR, Nikon Japan), demonstrated in the patient (E) a left-side displacement with unimodal distribution, indicating a mild decrease in large size fibres. Skin biopsy showed mild decreased of intraepidermal nerve fibres (arrows) in the patient (F) compared with age and gender matched healthy subject.

short follow-up periods.5 8 Our finding of heterozygous D90A-SOD1 mutation in a sporadic case presenting with clinical and neurophysiologic features of FOSMN syndrome strengthened the link with ALS. The pathogenicity of the homozygous D90A mutation has been established and associated with very slow ALS progression.3,5 When in heterozygous form, it has variable penetrance and the clinical phenotype may include numbness, paraesthesia and pain symptoms, and altered findings at NCS and sural nerve biopsy in some patients.12–14 However, ALS can include non-clinically meaningful abnormalities of the somatosensory system15–17 suggesting the existence of protective cellular pathways in DRG or, alternatively, their loss in motor neurons. The pathogenicity of heterozygous D90A mutation has been recently challenged by its presence in non-affected ALS family members18 and its co-occurrence with C9ORF72 expansion in one patient.17 Our patient did not harbour any variant in TARBP, FUS and C9ORF72 genes. However, we cannot exclude that the heterozygous D90A mutation is part of an oligogenic pattern. Indeed, multiple mutations involving the main ALS-related genes were recently reported to be responsible for other ALS cases.17

In conclusion, we propose that FOSMN syndrome can be considered a variant of ALS with slow progression and early sensory symptoms at face and upper limbs. Anyhow, this diagnosis should be considered in patients with bulbar amyotrophy, sensory impairment and abnormal corneal reflex.

Contributors AR and VM contributed in the diagnostic and clinical assessment followed the patient; MM and SS processed and analysed sural nerve biopsy; CG performed genetic analyses; GM contributed in the diagnostic and clinical assessment; EDB and GL made the diagnosis, performed and analysed skin biopsy, and wrote the paper.

Competing interests The authors have no competing interests.

Patient consent Obtained.

Ethics approval The work has been approved by the institutional review board.

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