Facial Onset Sensory and Motor Neuronopathy: Further Evidence for a TDP-43 Proteinopathy

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Key Words
Facial onset sensory and motor neuronopathy · Motor neurone disease · TDP-43 proteinopathy

Abstract
Three patients with the clinical and investigation features of facial onset sensory and motor neuronopathy (FOSMN) syndrome are presented, one of whom came to a post-mortem examination. This showed TDP-43-positive inclusions in the bulbar and spinal motor neurones as well as in the trigeminal nerve nuclei, consistent with a neurodegenerative pathogenesis. These data support the idea that at least some FOSMN cases fall within the spectrum of the TDP-43 proteinopathies, and represent a focal form of this pathology.

Introduction
Facial onset sensory and motor neuronopathy (FOSMN) is a slowly progressive disorder characterised by facial sensory deficits which may spread to affect the neck, the upper trunk and the limbs, with the development later in the course of the disease of bulbar symptoms such as dysarthria and dysphagia, muscle weakness, cramps and fasciculation [1]. Because of these latter features, parallels between FOSMN and motor neurone disease (MND) have been drawn, although sensory features are not a feature of MND and the onset and progression of FOSMN appear to be slower than those of MND [2].
The pathogenesis of FOSMN is uncertain. Based on the limited currently available clinical and investigative evidence [1–12] and the lack of therapeutic response to immunosuppressive agents in most (but not all) [4] cases, an underlying neurodegenerative process has been suggested in FOSMN, although cases with neuropathological examinations are very few [2, 6, 9]. We report 3 further cases of FOSMN, one with a post-mortem examination, suggesting that at least some of these cases fall within the spectrum of the transactive response DNA binding protein 43 (TDP-43) proteinopathies.

Case 1

A 62-year-old man presented with a 3-year history of perioral numbness and paraesthesia progressing to involve all divisions of the trigeminal nerve bilaterally. Over a similar interval, he also developed bilateral global upper limb weakness, muscle twitching and cramps. Twelve months prior to presentation, he described progressive slurring of speech, dysphagia and weight loss of 7 kg as well as complete loss of taste and smell. There was no past medical history of note.

A neurological examination showed a decreased sensation to pinprick and light touch in all divisions of the trigeminal nerve bilaterally. Corneal reflexes were absent. Eye movements were normal. He had a spastic dysarthria with tongue atrophy and fasciculation. There was wasting of the periscapular muscles bilaterally, with widespread fasciculation in the upper limbs and occasional fasciculation in the quadriceps bilaterally. Power was preserved throughout. Reflexes were globally brisk with bilateral flexor plantar responses.

Normal or negative investigations included an autoantibody screen, anti-ganglioside antibodies, serum immunoglobulins, cerebrospinal fluid (CSF) analysis (opening pressure, cell count, protein, glucose), and MRI of the brain and the cervical spine. Needle electromyography and nerve conduction studies (EMG/NCS) showed widespread neurogenic changes without evidence of a neuropathy. Motor evoked potentials were normal.

The patient died at the age of 64, approximately 6 years after symptom onset. A neuropathological examination exhibited that the number of cervical, thoracic, and lumbar spinal motor neurones was reduced by approximately 40%. Some of the remaining spinal cord motor neurones displayed characteristic intracytoplasmic extranuclear inclusions that stained positive for TDP-43 (fig. 1a) as well as for p62 antibodies (fig. 1b); TDP-43 inclusions were also seen in hypoglossal nucleus motor neurones (fig. 1c). In addition, p62 and TDP-43-positive inclusions could be detected in neurones of the trigeminal nuclei (not shown).

Case 2

A 38-year-old woman presented with a 3-month history of right lower facial and oral cavity numbness. Over the next 3 years, she developed sensory loss involving the upper and lower limbs as well as a wasting of the small muscles of the hand. She described decreased upper limb strength, and it progressed to a point when she was unable to wash her hair or dress without help. There was a progressive spread of sensory loss to her arms, neck and trunk. Over the next 8 years, she developed lower limb weakness, more prominent distally than proximally; she mobilised with a frame.

A neurological examination showed mild dysarthria, but no tongue weakness. Pinprick sensation was reduced in all divisions of the trigeminal nerve bilaterally. Horizontal saccades were slow, with normal vertical saccades and smooth pursuit eye movements. There
was fasciculation and weakness of the facial muscles bilaterally. Her neck flexion was weak.
In the upper limbs, there was fasciculation, global muscle wasting and flaccid weakness with
finger drop of the ring finger and little finger on the right. In the lower limbs, the weakness
was more marked distally than proximally and with areflexia. There was a reduced pinprick
and temperature sensation to the knees and elbows and over the trunk, with preserved joint
position and vibration sensation.

Normal or negative investigations included autoantibody screen, anti-neuronal and anti-
GM1 antibodies, serum protein electrophoresis, lysosomal storage enzymes, HIV and syphilis
serology, CSF examination, MRI of the brain, and neurogenetic tests (PMP-22, P0, CMT-X,
mitofusin, SCA 1, 2, 3, 6, 7, 17, and frataxin). An MRI of the spinal cord showed an atrophy of
the cervical and thoracic cord with no evidence of a syrinx. A muscle biopsy (left quadriceps)
showed denervation changes only, with no evidence of COX negative or abnormal NADH
staining and no polyglucosan bodies. EMG/NCS showed neurogenic changes and a loss of
sensory action potentials.

There was no clinical response to 3 monthly intravenous immunoglobulin (IVIg) infusions given over 12 months.

Case 3

A 69-year-old man presented with a 4-month history of numbness affecting his left
cheek, gradually progressing to involve the right cheek, tongue, jaw, and forehead, associat-
ed with difficulty swallowing.

A neurological examination showed a reduced sensation to pinprick and light touch
throughout the distribution of the trigeminal nerve bilaterally, and also over the tongue.
Speech was dysarthric. An initial examination was otherwise normal, but over the following
year, he developed wasting and fasciculation of the tongue and widespread wasting of the
upper limbs. Reflexes remained symmetrical with flexor plantar responses. His dysphagia
deteriorated over the same interval, causing a weight loss of 19 kg, requiring a percutaneous
endoscopic gastrostomy insertion for nutritional support.

Normal or negative investigations included autoantibody screen, thyroid autoantibod-
ies, onconeural and anti-glutamic acid decarboxylase antibodies, serum electrophoresis,
serum angiotensin-converting enzyme, complement, HIV and lyme serology, brain MRI, CT of
the chest/abdomen/pelvis, bronchoscopy, and CSF analysis. EMG/NCS showed no neurogen-
ic changes 1 year after symptom onset; further electrophysiological examination after onset
of the tongue and upper limb fasciculation was declined.

There was no response to treatment with steroids and IVIg; treatment with riluzole was
subsequently commenced.

Discussion

We have presented 3 cases with clinical and investigation features consistent with the
syndrome of FOSMN first described by Vucic et al. in 2006 [1], namely trigeminal sensory
symptoms followed by a lower motor neurone disorder with bulbar onset (table 1). None of
our patients had any clinical features of autonomic dysfunction.

The characteristic features in the limited number of cases reported to date [1–12] are
those of a sensory and motor neurone disorder, with sensory loss in the trigeminal nerve
distribution, with subsequent peripheral facial weakness which may spread to affect other
bulbar muscles, neck, upper and lower limbs. The disease is, with exceptions, usually slowly progressive (but with exceptions) [8]. Onset is usually in later life, although childhood onset has been described [11].

Neurophysiological findings in FOSMN syndrome include diminished sensory nerve action potential amplitudes in the upper limbs. There are also reports of widespread axonal, 

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specifically looking for subtle subclinical signs of frontal dysfunction as found in some MND progression and a relatively good prognosis with appropriate supportive care. To pursue this potential nosology, it might be of interest to examine cognitive function in FOSMN cases, specifically looking for subtle subclinical signs of frontal dysfunction as found in some MND cases [16].

However, since FOSMN has rightly been described as a syndrome [1], this does not exclude the possibility that other examples of FOSMN may have a different pathogenesis, including possibly inflammatory disorders which may on occasion respond to immunotherapy [4]. Anti-ganglioside antibodies were checked in 2 of our patients (cases 1 and 2) and were negative. Nevertheless, an assay of anti-ganglioside antibodies, especially those associated with facial and bulbar weakness (GD1a and GT1a respectively), might be reasonable in FOSMN cases, although unlike FOSMN, the associated clinical syndromes are not chronic progressive disorders.
Further neuropathological studies are critical to clarify disease mechanisms. We suggest that this might be facilitated by identifying possible cases of FOSMN, for example cases currently being followed up with a diagnostic label of ‘atypical’ or ‘benign’ bulbar MND. The possibility of identifying a subpopulation of patients with a better prognosis mandates searching MND clinic databases for such patients as well as a careful review of the history for sensory symptoms in each new ‘bulbar MND’ case.

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Disclosure Statement

The authors declare no competing interests.

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Table 1. Summary of clinical characteristics and treatment response

|                         | Case 1                | Case 2                | Case 3                |
|-------------------------|-----------------------|-----------------------|-----------------------|
| Gender/age at onset, years | Male/62               | Female/38             | Male/69               |
| Disease duration, years | Deceased at 6 years   | Alive at 16 years     | Alive at 6 years      |
| Trigeminal sensory symptoms | Yes: first symptom   | Yes: first symptom   | Yes: first symptom   |
| Bulbar symptoms         | Yes                   | Yes                   | Yes                   |
| Neck flexion weakness at last follow-up | No                   | Yes                   | No                    |
| Fasciculation and wasting at last follow-up | Yes                   | Yes                   | Yes                   |
| Upper limb weakness at last follow-up | No                   | Yes                   | No                    |
| Lower limb weakness at last follow-up | No, but fasciculation present | Yes                   | No                    |
| Upper motor neurone signs at last follow-up | No, except brisk reflexes | No improvement with IVlg | No improvement with steroids/IVlg |
| Immunotherapy           | No treatment          | No improvement with IVlg | No improvement with steroids/IVlg |

Fig. 1. Motor neurones in the spinal cord (a, ai, b, bi) and hypoglossal nucleus (c) of case 1. Immunohistochemistry for TDP-43 (a, ai, c) and p62 (b, bi). Physiological intranuclear TDP-43 staining (arrowhead in a) and pathological aggregations of phosphorylated TDP-43 (arrows in c) are seen, with strong intracytoplasmic extranuclear positivity for TDP-43 (ai) and p62 (bi). Original magnification: ×400 (a, b), ×600 (c); scale bars: 50 μm (a, b), 20 μm (c).