CASE

FOSMN

A possible TDP-43 proteinopathy to consider in a patient with facial sensory symptoms

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Facial onset sensory and motor neuronopathy (FOSMN) is a recently described syndrome, first reported by Vucic et al.[1]

Clinical features

Usually around the 5th decade of life, patients begin with facial sensory disturbances, such as paresthesia and numbness, which slowly spread to the scalp, neck, upper trunk, and upper limbs in a rostral-caudal progression. Reduced or absent corneal reflex is the main pathognomonic feature. After a variable period, commonly from 2 to 5 years later, patients develop bulbar dysfunction, with dysarthria and dysphagia as main symptoms. Eventually, lower motor neuron signs such as fasciculation, weakness, and atrophy are seen, especially in the upper extremities. FOSMN slowly progresses over the years until death, generally due to respiratory failure.

Electrodiagnostic features

Patients with FOSMN have a decreased or absent blink reflex from the early stages of the disease. As it progresses, electrodiagnostic tests typically show a sensory and motor neuronopathy.[2]

Pathogenesis and anatomopathologic findings

FOSMN is a neurodegenerative process whose etiopathogenesis remains unknown. Anatomopathologic findings demonstrate atrophy of the cranial nerves' nuclei in the pons and medulla oblongata and gliosis and neuron loss in the dorsal root ganglia of the brainstem and cervical spinal cord, as well as in cervical anterior horns and roots.[3]

There are only 4 patients with FOSMN whose autopsy findings are reported. Three of them, described by Rossor et al., Ziso et al., and Sonoda et al., have revealed the presence of TAR-DNA binding protein (TDP-43).[3–5] The fourth one disclosed no evidence of TDP-43.[6] Here, we report a case of FOSMN with postmortem neuropathologic examination showing TDP-43 inclusions, and we compare the clinicopathologic features of previously reported patients (table).

PRACTICAL IMPLICATIONS

Facial onset sensory and motor neuronopathy should be considered in the differential diagnosis of facial sensory disturbances, unilateral or bilateral, especially when blink reflex is pathologic. Because bulbar and lower motor neuron dysfunction may appear years after the facial sensory onset, long follow-up is recommended in suspected patients.

Case

A 66-year-old man presented with a 13-year history of perioral paresthesias that over the time increased in intensity and spread bilaterally to both territories of the trigeminal nerve.

At that moment, no clinical or electrophysiologic signs of multiple mononeuropathy or polyneuropathy were present. Brain MRI showed small vessel ischemic disease. Blink reflex showed

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Table Clinical features of our patients and the patients with TDP-43 inclusions reported in the literature

	Case 1	Case 2	Case 3	Case reported in Ref. 5	Case reported in Ref. 4	Case reported in Ref. 3
Age in years/sex	53/M	62/W	63/W	45/W	59/M	45/M
Follow-up (y)	16	11	4	3	6	9
Initial facial symptoms	Bilateral perioral paresthesias	Perioral paresthesias on the right side	Perioral paresthesias on the left side	Perioral paresthesias on the right side and paresthesias on the right hand	Bilateral perioral paresthesias	Perioral paresthesias on the left side
Bulbar symptoms	Dysphagia and dysarthria	Dysphagia and dysarthria	Dysphagia and dysarthria	Dysphagia and dysarthria	Dysarthria	Dysphagia and dysarthria
Lower motor neuron symptoms	Fasciculations in the tongue and upper and lower limbs	Fasciculations in the tongue and upper limbs	No	Generalized fasciculations	Fasciculations in the tongue and upper and lower limbs	Fasciculations in the tongue
	Upper limb weakness and muscular atrophy			Upper limb weakness and muscular atrophy		Upper limb weakness and muscular atrophy
Cognitive impairment	No	No	No	Not reported	Not reported	Personality change
SNAPs in upper limbs	Decreased amplitudes	Normal	Normal	Not evoked in the upper right limb	Not reported	Normal
Blink reflex	Bilateral R1 absent	Right R1 absent	Left R1 decreased	Bilaterally absent	Not reported	Bilaterally absent
TDP-43 location	Bulbar and cervical spinal cord motor neurons	No neuropathologic data available; the patient is still under clinical observation	No neuropathologic data available; the patient is still under clinical observation	Cervical spinal cord motor neurons	Bulbar and spinal motor neurons (anterior horn cells)	Spinal motor neurons (anterior horn cells) and sensory neurons (dorsal root ganglion)
				Hypoglossal nucleus	Trigeminal and hypoglossal nucleus	Basal ganglia
						Frontal cortex

Abbreviations: SNAP = sensory nerve action potential; TDP-43 = TAR-DNA binding protein.

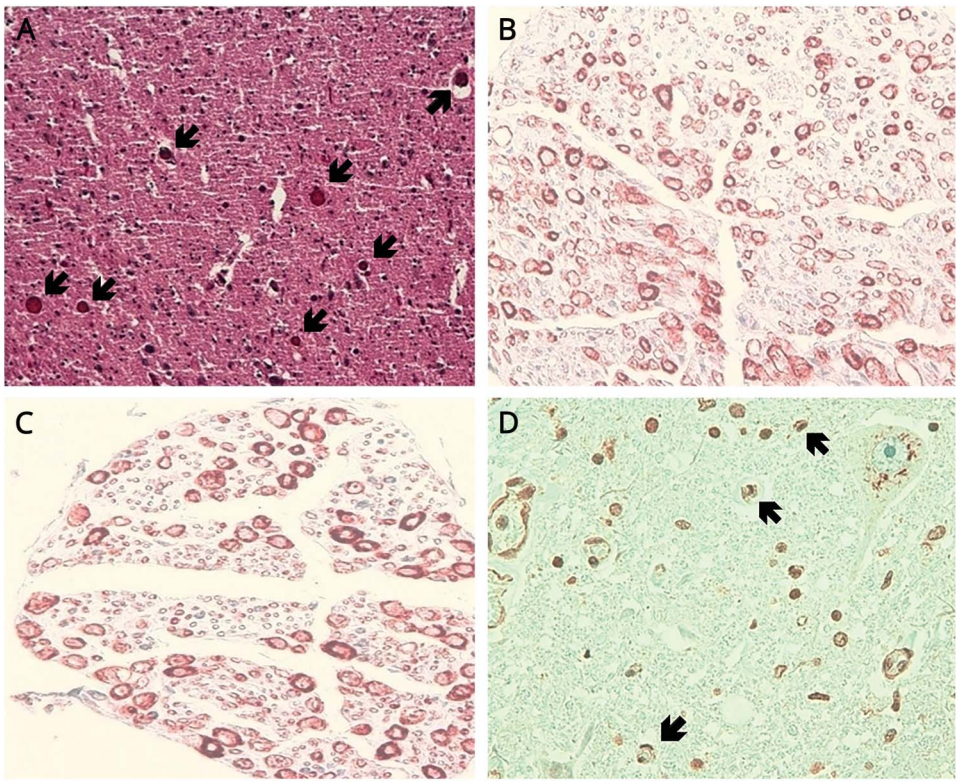
bilateral absent R1. Extensive etiologic evaluation, including CSF analysis, was unremarkable. One year later, the patient developed paresthesia and numbness in upper limbs. Nerve conduction studies showed decreased sensory nerve action potential amplitudes in the upper extremities, and electromyogram of the 4 limbs was normal. During the follow-up, 15 years after the facial sensory symptoms' onset, the patient developed bilateral facial paralysis, bulbar symptoms (dyspnea, dysarthria, and dysphagia), and proximal and distal weakness of upper extremities. Atrophy and fasciculations were evident in the tongue and both upper and lower limbs. The patient died due to respiratory failure at age 69 years.

Postmortem pathologic examination (figure) showed atrophy and axonal loss in the anterior horns and in the anterior and posterior roots of the cervical spinal cord. In the brainstem, trigeminal and hypoglossal nuclei were atrophic. Representative sections of the brain and spinal cord were immunostained for TDP-43, observing TDP-43–positive cytoplasmic inclusions in the bulbar and cervical lower motor neurons. Sensory neuronopathy and lower motor neuron disease with TDP-43 inclusions support the diagnosis of FOSMN. FOSMN is suspected in 2 additional patients in our department whose clinical features are described in the table.

Discussion

FOSMN is a rare sensory and motor neuronopathy. The pattern of the sensory and motor abnormalities and the distribution of atrophy and neuronal loss in neuropathologic examinations are well correlated in FOSMN.[1] Nevertheless, the presence of TDP-43 inclusions that has been recently

Figure Postmortem neuropathologic findings of our patient



(A) Trigeminal nucleus with atrophic and reduced neuronal population (arrows). (B) Axonal loss in the posterior roots of the spinal cord. (C) Axonal loss in the anterior roots of the spinal cord. (D) TDP-43–positive cytoplasmic inclusions in the lower motor neurons (arrows), observed by immunohistochemistry. TDP-43 = TAR-DNA binding protein.

reported in a few cases[3–5] has brought up new questions related to the underlying mechanisms of the disease. This case we present reinforces the hypothesis that FOSMN is within the spectrum of TDP-43 proteinopathies. In the 4 patients with FOSMN with TDP-43 inclusions reported in the literature (including our case), TDP-43 is observed in the cervical spinal motor neurons invariably[3–5] (table). Clinicopathologic findings suggest that it might be a focal form of a slowly progressive motor neuron disease (with associated sensory involvement, without first motor neuron symptoms).[6] Whether TDP-43 inclusions in FOSMN may also imply a neurocognitive decline at the end stages of the disease should also be assessed in future research.

Mutations have been detected in the *SOD1*, *TARDBP*, and *SQSTM1* genes in a few patients with FOSMN.[7] Considering the relationship of these genes with motor neuron disease and frontotemporal dementia, it would be highly interesting to perform genetic testing in patients with FOSMN, including *TARDBP*, *FUS*, *C9ORF72*, *SOD1*, and *SQSTM1* genes.

Clinical neurologists should consider FOSMN while evaluating a patient with facial paresthesias and absent or reduced blink reflex. Long-term follow-up may be required to assess the progression of the disease, as well as for early detection of possible cognitive impairment, due to the potential relationship between FOSMN and TDP-43 proteinopathies.[3–5]

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Continued

Appendix *(continued)*

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