Parallels and differences between facial onset sensory motor neuronopathy (FOSMN) and motor neuron disease (MND): neuropsychological profiles of two cases.

G. Fiamingo[1,2], G. Perini[1,2], A. Costa[1,2], A. Alfonsi[1], S. Bernini[1], E. Sinforiani[1], M. Ceroni[1,2], L. Diamanti[1,2]

[1] National Neurological Institute C. Mondino IRCCS, Pavia, Italy

[2] Department of Neurosciences and Behaviour, University of Pavia, Pavia, Italy

BACKGROUND AND AIM

Facial onset sensory and motor neuronopathy (FOSMN) syndrome is a rare neurological disorder heralded by development of sensory symptoms within the face (trigeminal nerve distribution), followed by evolution of sensory and motor deficits in a rostral-caudal direction (1). A primary neurodegenerative process is supposed. Recently, single cases of TDP-43-positive neuronal inclusions and mutation in SOD-1 gene have risen the hypothesis of a link between FOSMN and motor neuron disease (MND). Clinically, the evidence of some patients showing upper motor neuron (UMN) signs makes FOSMN an important MND mimic (2,3).

We aim to expand clinical and instrumental aspects of FOSMN, possibly able to differentiate it from MND.

CASE REPORTS

We describe two male patients, aged 72 and 81, with a 12- and 4-year history of symptoms respectively (Tab 1). Patient 1 presented with perioral numbness, followed by paresthesias in the trigeminal divisions bilaterally and progressively in the limbs. Patient 2 presented initially with weakness and cramps prevalent in the upper limbs. Both patients developed a mild weakness in proximally to distal manner and dysphagia.

- The **neurological examination** showed a reduced pinprick sensation in the trigeminal divisions bilaterally and absence of corneal reflexes in the former. In both patients was evident a global wasting of limb muscles bilaterally, with diffuse fasciculations and symmetrically reduced reflexes.
- Negative investigations included cervical imaging, broad serum screening tests for polyneuropathies (autoantibody screen, anti-neuronal and anti-GM1 antibodies, serum protein electrophoresis and HIV serology) and **CSF** findings in patient 1 (including tau, p-tau, β amyloid 1-42)
- **EMG/NCS** showed widespread neurogenic changes with acute denervation potentials in spinal and bulbar muscles, and reduced sensory and motor nerve action potentials in the limbs (Fig 1). **Trigeminal reflexes** were altered bilaterally (Fig 2).
- **Brain magnetic resonance** evidenced a mild superficial atrophy in patient 2 (Fig 3).
- **Neuropsychological profile** was normal, except for deficit in verbal short term memory in patient 1 and delayed verbal memory in patient 2 (Tab 2).

Table 1. Summary of the clinical features and results of the investigations in 2 patients with facial-onset sensory motor neuronopathy

	Age of onset, y/sex	Disease duration, y	Bulbar symptoms (Trigeminal sensory symptoms)	Neck flexion weak	Upper limb weakness	Lower limb weakness	Upper motor neuron signs	Trigeminal nerve reflexes	ENG/EMG	CSF	MEP	MRI	Neuropsychological tests	Genetic test
Patient 1	69/M	3	oral and pharyngeal dysphagia (Yes)	Yes	Yes	No	No	abnormal	neurogenic changes and loss of SNAP	normal	ND	normal	deficit in verbal short term memory	SOD1, C9orf72, FUS, TDP-43, AR negative
Patient 2	79/M	4	oral and pharyngeal dysphagia (No)	No	Yes	Yes	No	abnormal	neurogenic changes and loss of SNAP	ND	prolonged CMCT in upper and lower limbs	mild atrophy	deficit in delayed verbal memory	AR ongoing

Figure 1. ENG/EMG of patient 1

Sensory NCS

Nervo / Posizioni	Rec. Site	Latency ms	Amp.1-2 µV	Amp.2-3 µV	Distance cm	Dur. ms	Velocity m/s
D MEDIAN - Digit III (Palm)							
Palm	III	2,10	4,0	7,0	7	1,85	33,3
Wrist	III	3,45	6,1	12,3	7	2,65	51,9
S MEDIAN - Digit III (Palm)							
Palm	III	2,05	3,0	6,0	7	1,45	34,1
Wrist	III	3,20	5,7	9,0	5,5	2,55	47,8
D SURAL - Lat Malleolus							
Calf	Lat Malleolus	3,25	5,4	7,6	12,5	2,10	38,5
S SURAL - Lat Malleolus							
Calf	Lat Malleolus	3,95	5,9	4,8	15	2,20	38,0
D RADIAL - Thumb							
Forearm	Thumb	2,70	4,6	4,5	12,5	1,45	46,3
S RADIAL - Thumb							
Forearm	Thumb	2,25	11,4	8,7	12,5	1,65	55,6

Motor NCS

Nervo / Posizioni	Latency ms	Ampl mV	Distance cm	Velocity m/s
D MEDIAN - APB				
Polso	4,10	5,9		
Gomito	8,95	5,0	25,5	52,6
S COMM PERONEAL - EDB				
Ankle	3,85	5,6		
Fib Head	11,75	4,6	28	35,4
Knee	15,70	3,8	16,5	41,8
D COMM PERONEAL - EDB				
Ankle	3,85	6,0		
Fib Head	11,45	5,5	30	39,5
Knee	15,00	5,1	14,5	40,8

Needle EMG1

EMG Summary Table									
	Spontaneous					MUAP			Recruitment
	IA	Fib	PSW	Fasc	H.F.	Amp	Dur.	PPP	Pattern
D. DELTOID	N	None	None	2+ (fast)	None	2+	2+	2+	Reduced
D. SUPRASPINATUS	N	None	None	None	None	2+	2+	2+	Reduced
D. INFRASPINATUS	N	None	None	None	None	2+	2+	2+	1-
D. THOR PSP (M)	N	None	None	None	None	N	2+	2+	N
S. THOR PSP (M)	N	2+	2+	2+ (slow)	None	N	2+	2+	1-
S. DELTOID	N	None	None	2+ (slow)	None	2+	2+	2+	N
D. TIB ANTERIOR	N	None	None	2+ (fast)	None	2+	2+	2+	Reduced
D. TIB POSTERIOR	N	2+	2+	2+ (slow)	None	2+	2+	2+	Reduced
D. FIRST D INTEROSS	N	2+	2+	2+ (slow)	None	2+	2+	2+	Reduced
D. EXT POLL BREVIS	N	2+	2+	2+ (slow)	None	2+	2+	2+	Reduced
S. TIROARITENOIDEO	N	2+	2+	2+ (slow)	None	N	2+	2+	Reduced
S. TONGUE	N	None	None	2+ (slow)	2+	N	1+	1+	Reduced

Figure 2. The trigeminal nerve reflexes: the blink reflex, the masseter reflex, and the masseter inhibitory reflex

A Nervo / Posizioni	R1 ms	R2 ms	R2-R1 ms	Amp.1-2 mV
S SUPRAORBITAL				
3		49,70		
4	11,95	47,35	35,40	0,1
D SUPRAORBITAL				
1	12,35	55,80	43,45	0,2
2		56,30		

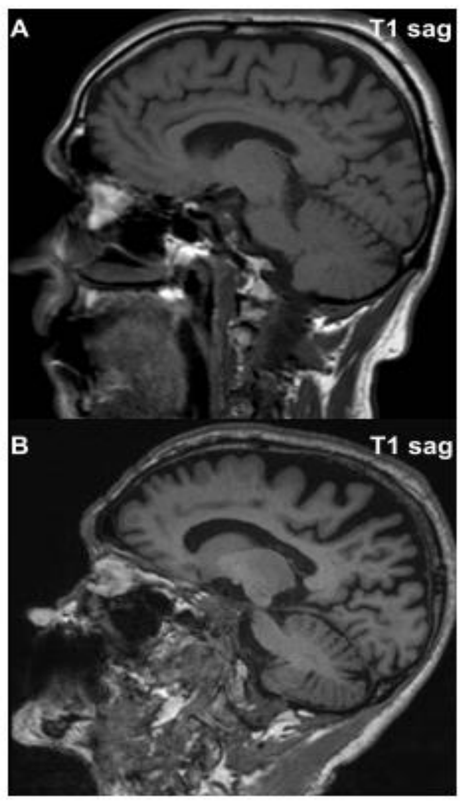
B Nervo / Posizioni	R1 ms	R2 ms	R2-R1 ms	Amp.1-2 mV
S SUPRAORBITAL				
3	10,30	34,90	24,60	0,0
4		35,15		
D SUPRAORBITAL				
7		40,65		
8	10,85	40,50	29,65	0,0

- The blink reflex: normal R1 and delayed ipsi-and contralateral R2 responses and normal R1 and R2 responses, in patient 1 and 2, respectively (A, B)
- The masseter reflex: absent in both patients
- The masseter inhibitory reflex: absent SP1 and SP2 in patient 1; increased in duration in patient 2

Table 2. Neuropsychological tests

	Patient 1	Patient 2
global cognitive efficiency (Mini-Mental State Exam)		
memory (Verbal Span, Digit Span, Corsi Test, Fifteen Item Memory Test, Story Recall Test, Rey Complex Figure delayed recall)	Deficit in verbal span	Deficit in story recall test
logical and executive functioning (Raven's Colored Matrices, Frontal Assessment Batter),		
attention (Trail Making Test A/B, Attentive Matrices, Stroop Test)		
visual-spatial perception (Rey Complex Figure copy)		

Figure 3. No atrophy and a mild superficial atrophy mainly in the posterior areas on T1 sequences in patient 1 and 2 , respectively (A, B)



DISCUSSION AND CONCLUSION

Patient 1 presents typical features of FOSMN. Patient 2 shows atypical features: sensory involvement was evidenced only by neurophysiological examination and UMN was involved as pointed out by MEP, similar to MND. Neuropsychological functions have never been studied in FOSMN patients (3). Our two cases represent the first reports of cognitive screening and show a substantially normal cognitive profile, despite the long disease duration. While data from a wider cohort of patients are advisable, the relative sparing of cognitive function in our cases may be interesting in view of the possible inclusion of FOSMN in the group of TDP-43 proteinopathies.

	Distinguishing features of FOSMN	Similarities between FOSMN and MND
Presentation	FOSMN usually presents with insidious onset of sensory disturbance affecting the mouth and face	Occasionally FOSMN presents with motor symptoms in the limbs and upper motor neurone signs. Fasciculations are typically in FOSMN
Progression	slow evolution in a rostral-caudal direction	FOSMN may progress rapidly
TMS and ENG/EMG	In contrast to MND, there is no evidence of cortical hyperexcitability in TMS studies of FOSMN cases. FOSMN usually have reduced and low amplitude SNAP	active denervation and chronic reinnervation can be observed in MND and FOSMN
Blink reflex	typically abnormal in FOSMN, with either a delayed R2 response or complete absence	only occasionally abnormal in the later stages of MND
Neuropathology/Genetics	most postmortem studies have not found features associated with MND/ no familial cases of FOSMN	one single case of TDP-43-positive neuronal inclusions/ one case of SOD-1 mutation

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12 – 14 MARZO 2020 - FIRENZE