Electrodiagnostic findings in facial onset sensory motor neuronopathy (FOSMN)

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HIGHLIGHTS
• Blink reflexes are abnormal in over 90% of patients with FOSMN.
• In FOSMN, upper motor neuron dysfunction is not evident clinically, but it can be detected in up to 50% of patients on neurophysiological testing.
• Upper limb somatosensory evoked potential central conduction times increase on interval testing in FOSMN and might be used for monitoring disease progression.

ABSTRACT
Objective: To determine the electrodiagnostic characteristics of facial onset sensory and motor neuronopathy (FOSMN).
Methods: Electrophysiological data from 10 FOSMN patients in Newcastle-upon-Tyne and Sydney were reviewed. Relevant literature was reviewed.
Results: Findings on standard electrophysiological assessment were in broad agreement with those published: blink reflexes were abnormal in all but one patient; sensory nerve action potentials were reduced but compound muscle action potentials preserved; mixed acute and chronic neurogenic change was identified on needle electromyography in bulbar and cervico-thoracic muscles in approximately 50% of patients.
Upper limb somatosensory evoked potential (SEP) central conduction times were increased (n = 4) and progressed on repeat testing (n = 3). Upper motor neuron dysfunction was revealed by several measures [ipsilateral motor evoked potentials (MEPs) (n = 1); reduced short interval intra-cortical inhibition on threshold-tracking transcranial magnetic stimulation (n = 2); absent beta-band intermuscular coherence (n = 3)].
Conclusions: Electrodiagnostic investigation of FOSMN should include blink reflex testing, SEPs and tests of upper motor neuron function. The combination of progressive lower motor neuron disease and upper motor neuron disease on neurophysiological investigation provides further support for the contention that FOSMN is a rare variant of motor neurone disease.
Significance: These findings will aid the neurologist and neurophysiologist in making a confident diagnosis of FOSMN, thus expediting appropriate care.

1. Introduction

Facial onset sensory and motor neuronopathy (FOSMN) is a rare clinical syndrome initially described in a seminal case series of five
patients who presented with facial sensory deficits, followed by motor deficits, evolving rostro-caudally (Vucic et al., 2006b). Over the intervening 15 years, a range of individual cases and small case series have been reported (Barca et al., 2012; Bélenotti et al. 2010; de Boer et al., 2021; Broad and Leigh, 2015; Cruccu et al., 2014; Dalla Bella et al., 2016, 2014, 2019; Dobrev et al., 2012; Fluchere et al., 2011; Hokinohara et al., 2008; Isoardo and Troni, 2008; Karakis et al., 2014; Knopp et al., 2013; Lange et al., 2020; Ohashi et al., 2020; Olney et al., 2018; Pinto et al., 2019; Rossor et al., 2019; Sonoda et al., 2013; Truini et al., 2015; Vázquez-Costa et al., 2019; Vucic et al., 2012; Watanabe et al., 2018; Zhang et al., 2019; Ziso et al., 2015). Clinical, genetic and neuropathological data strongly suggest that FOSMN is a rare phenotype of motor neurone disease (MND)/amyotrophic lateral sclerosis (ALS) (Dalla Bella et al., 2014; Pinto et al., 2019; Rossor et al., 2019; Sonoda et al., 2013; Vázquez-Costa et al., 2019; Vucic, 2014; Zhang et al., 2019; Ziso et al., 2015).

Given the non-specific initial clinical presentation and lack of formal diagnostic criteria, patients with FOSMN are likely to experience even longer diagnostic delays than are generally seen in patients with MND/ALS [median of 11.5 months] (Pagani et al., 2014). This further delays the provision of optimal care through a multidisciplinary MND/ALS clinic (Martin et al., 2017) in patients with the FOSMN variant.

Neurophysiological examination plays a pivotal role in the diagnosis of MND/ALS and its contribution has been enhanced in successive international diagnostic criteria, specifically the Revised El Escorial (Brooks et al., 2000), Awaji-Shima (de Carvalho et al., 2011; Hokonohara et al., 2008; Isoardo and Troni, 2008; Karakis et al., 2014; Knopp et al., 2013; Lange et al., 2020) and Gold Coast criteria (Shefner et al., 2020).

Herein we review the published electrodiagnostic data for FOSMN and report detailed electrophysiological data from two cohorts with this syndrome, one from Newcastle-upon-Tyne (United Kingdom) and the other from Sydney (Australia). We propose a specific approach to electrophysiological testing in patients who present with facial sensory symptoms which should help to identify those patients who require follow-up and ultimately expedite the diagnosis of FOSMN, thus enabling earlier referral to a specialist clinic and improved patient care.

2. Methods

2.1. Ethics Statement

All data were collected from patients referred for electrophysiological investigations as part of routine clinical care and have been anonymised. Informed consent for electrophysiological testing was obtained from all patients.

2.2. Patients

Patients were included if they presented initially with facial sensory symptoms in isolation and conformed phenotypically to the original description of the syndrome by Vucic and colleagues (Vucic et al., 2006b). The clinical diagnosis of FOSMN was made by a neurologist subspecialising in MND/ALS, following detailed clinical assessment and investigation to refute alternative diagnoses. Patients from the Newcastle cohort were under the care of the Newcastle Motor Neurone Disease Care and Research Centre and patients from the Sydney cohort were reviewed in the Westmead Hospital Neuromuscular Clinic.

Patients included in this series were assessed for the first time at either the Royal Victoria Infirmary or Westmead Hospital between February 2006 and March 2019 and were identified through their respective clinic databases.

2.3. Nerve conduction studies (NCS)/Needle electromyography (EMG)

These investigations are widely used in routine clinical practice and follow international standards (Chen et al., 2016; Daube, 2000; Dillingham et al., 2016; Tankisi et al., 2020). Hence, detailed descriptions of relevant methods are not included here.

Nerves tested included the median and ulnar nerves in the upper limbs (motor and sensory), the peroneal and tibial nerves (motor), and the sural nerves (sensory) in the lower limbs. Needle EMG was performed at the discretion of the neurophysiologist; specific muscles examined for each patient at each time point can be found in Supplementary Table 1.

2.4. Somatosensory evoked potentials (SEPs)

SEP data were obtained using a clinical data acquisition system (Sierra Summit; Cadwell, Kennewick, USA) and followed published standards (American Clinical Neurophysiology Society, 2006).

For upper limb SEPs, recording electrodes were positioned at Erb’s point, over the vertebra prominens and on the scalp 2 cm posterior to the C3 (right upper limb SEPs) and C4 (left upper limb SEPs) locations; each were referenced to Fz. Lower limb SEPs were recorded using electrodes positioned 2 cm anterior to Cz and 2 cm posterior to Cz, each referenced to Oz. Stimulator pads (Alpine Biomed, Denmark) were used to stimulate the median nerve at the wrist for upper limb SEPs, and the posterior tibial nerve or common peroneal nerve at the ankle for lower limb SEPs. The stimulus current was set at a level above motor threshold such that there was a reliable and visible movement of the thumb or toes. Standard cortical SEP waveforms following upper (N9, N11, N13, P16, N20 and P25) and lower limb (N0, P1, N1, P2, N2) stimulation were easily identified in each patient. Latencies and amplitudes were documented and interpreted relative to normal upper limb (n = 50) and lower limb (n = 20) datasets obtained using the same acquisition system.

SEPs were considered abnormal where latencies were significantly prolonged compared to the control population mean, or where there was a significant difference between right and left SEPs, provided the peripheral component of the SEP was normal. The N20 was therefore abnormal if the latency was above 22.1 ms (mean + 3SD) from the median nerve at the wrist, and the P1 latency was abnormal if it was greater than 50.3 ms (common peroneal nerve at ankle; mean + 3SD) or 46.7 ms (posterior tibial nerve at ankle; mean + 3SD).

In the upper limbs the central sensory conduction time (CSTC) was also assessed. This was calculated by subtracting the latency of the volley recorded at Erb’s point from the N20 latency. This removes any contribution from peripheral nerve to the SEP and accentuates abnormalities attributable to central pathology (Supplementary Fig. 1). Moreover, because most of the variation in upper limb SEP latencies between individuals can be attributed to arm length (i.e., the peripheral conduction delay), CSTC also controls for these differences allowing the direct comparison of SEPs between individuals.

2.5. Blink reflexes

Blink reflexes were tested using a standard clinical EMG acquisition system (Newcastle: Myoquick; Micromed, Mogliano Veneto, Italy; Sydney: Synergy; Nicolet EDX by Natus, Pleasanton, CA, USA). EMG was recorded simultaneously from orbicularis oculi (OO) on both sides using self-adhesive disposable surface disc electrodes (type 019–400400; Natus, Middleton, USA). On each side, the active electrode was placed just below the palpebral fissure halfway between the inner canthus and the outer canthus, with the
reference electrode placed just lateral to the outer canthus. EMG signals were bandpass filtered at 3Hz–10 kHz.

The normal blink reflex, as measured using EMG from OO, comprises two components: the direct ipsilateral R1 response (latency 12.1 ± 0.96 ms; mean ± 1SD); and the indirect bilateral R2 response (latency 35.83 ± 2.45 ms; mean ± 1SD) (Kimura et al., 1969). To visualise both the R1 and R2 responses, a sweep of 100 ms was used with a gain of 500 μV per division.

A large handheld bipolar stimulating electrode (type 16893 T; Lifelines, Louisville, USA) was used to stimulate the supraorbital nerve. The cathode was placed over the supraorbital notch and the anode was located on the forehead. Stimuli were delivered with a pulse duration of 0.2 ms, an initial intensity of approximately 5 mA, and an inter-stimulus interval of no less than 8–11 seconds to prevent habituation of the responses, particularly the R2. The stimulus intensity was gradually increased by 3–5 mA until consistent R1 and R2 responses were observed. In our experience, a reliable R1 response is usually obtained at a stimulus intensity of between 5–10 mA, whereas a consistent R2 response is often not achieved until a stimulus intensity of 18–20 mA is used. Input-output curves of stimulus intensity versus R2 response (amplitude and/or area) were then constructed.

2.6. Motor evoked potentials (MEPs)

MEPs were only tested in the Newcastle cohort. Magnetic stimulation was delivered using a Magstim 200 stimulator (Magstim, Whitland, United Kingdom). Cervical and lumbosacral nerve root compound muscle action potentials as well as upper limb contralateral motor cortical evoked potentials (cMEPs) were assessed using a circular coil (130 mm diameter).

For upper limb cMEPs, the circular coil was held over the vertex and once positioned, there was very little coil movement in any plane. Clockwise and anti-clockwise coil currents (as viewed from above) were used to stimulate the right and left hemisphere, respectively. Upper limb ipsilateral MEPs (iMEPs) were tested using a figure-of-eight coil (70 mm diameter for each winding) to minimise spread of the magnetic field to the contralateral hemisphere. The coil handle was orientated posteriorly (i.e. optimised for evoking D waves); once the hotspot for evoking MEPs had been identified, the position was marked on the scalp and the coil was clamped manually to the head to minimise any movement of the coil relative to the head. Lower limb cMEPs were investigated using a double-cone coil.

Responses were recorded from first dorsal interosseous (FDI), abductor pollicis brevis (APB), extensor digitorum communis (EDC) and flexor digitorum superficialis (FDS) in the upper limbs and tibialis anterior (TA), medial gastrocnemius (MG), extensor digitorum brevis (EDB) and abductor hallucis (AH) in the lower limbs.

For iMEP assessment in the upper limbs, recordings were also made from biceps brachii (BB). Resting motor threshold (RMT) was determined as the percentage of maximum stimulator output able to elicit a threshold MEP (approximately 50 μV in 5 out of 10 trials) at rest. To ensure that the minimum cMEP latency was recorded, the patient was asked to produce a gentle background muscle contraction (~5% maximum voluntary contraction) and the magnetic stimulator was set at 120% RMT. To record iMEPs, a slightly stronger background muscle contraction is required. Patients were therefore asked to activate the relevant upper limb muscles at 10–20% of maximum voluntary contraction during iMEP assessment. Central motor conduction times (CMCTs) were calculated as previously described and were compared to published normative datasets (Eisen and Shtybel, 1990; Jaiser et al., 2015).

2.7. Threshold tracking transcranial magnetic stimulation (ttTMS)

Threshold tracking transcranial magnetic stimulation (ttTMS) was used to measure cortical excitability on the Sydney cohort according to a previously published technique (Vucic et al., 2012, 2006a). The motor cortex was stimulated by a 90 mm circular coil with MEPs recorded over APB. RMT was defined as the stimulus intensity required to produce and maintain a target response of 0.2 mV ±20%. Short-interval intracortical inhibition (SICI) and intracortical facilitation (ICF) were measured using the paired-pulse threshold tracking protocol (Vucic et al., 2006a).

2.8. Intermuscular (EMG-EMG) coherence

Beta-band intermuscular coherence (BIMC) was first proposed as a method for assessing the integrity of the corticospinal tract in MND/ALS in 2012 (Fisher et al., 2012). Assessment is straightforward and involves the simultaneous recording of the surface EMG from a set of muscles in a given limb whilst the subject is performing either a sustained low force contraction or repeated auxotonic contractions, followed by post-acquisition signal processing (Issa et al., 2017; Jaiser et al., 2016). Subsequent studies, from a number of centres worldwide, have further highlighted the potential utility of BIMC in a range of motor neuron disorders (Issa et al., 2017; Jaiser et al., 2019; Rong and Pattee, 2021).

Coherence was estimated from EMG recordings performed during a precision grip task (upper limb) or a foot rocking task (lower limb). For the upper limb, coherence spectra were calculated between EDC and FDI, as well as between FDS and FDI; for the lower limb, they were computed between MG and EDB, and between TA and EDB. Detailed methods have been previously published (Jaiser et al., 2016).

2.9. Literature review

Pubmed was searched using the terms “facial onset sensory and motor neuronopathy” or “FOSMN”. Published cases were excluded if no electroneurographic and electromyographic findings were reported, or if the diagnosis of FOSMN had been reached through retrospective reassessment of case notes alone; retrospective histological diagnoses were permitted.

3. Results

Ten patients with FOSMN were included (six from Newcastle, four from Sydney). Conventional neurophysiological examinations were completed in all patients as an essential component of diagnostic investigation. Additionally, blink reflex testing, SEPs, MEPs, ttTMS and BIMC were performed on a subgroup of FOSMN syndrome patients. A summary of the neurophysiological examinations performed in patients presented in this series can be found in Supplementary Table 2.

3.1. NCS and needle EMG

Upper limb sensory nerve action potentials (SNAPs) were abnormal in one of the nine patients in whom upper limb NCS were completed, while lower limb (LL) SNAPs were abnormal in two of ten patients (Fig. 1A, Fig. 2A and Table 1). By contrast, sensory nerve conduction velocities (SNCVs) were within normal limits (Fig. 2C). On repeated testing, neither SNAPs nor SNCVs decreased over time (Fig. 2B and 2D). Upper and lower limb compound muscle action potentials (CMAPs) were normal in all ten patients (Fig. 1A and Table 1).
Concentric needle EMG revealed acute (fibrillation potentials and positive sharp waves) and chronic neurogenic changes in five patients and chronic neurogenic changes in two patients. EMG findings were normal in only one patient; EMG was not performed in two patients (Fig. 3A, Table 1; Supplementary Table 2). In the 7 patients in whom neurogenic changes were identified, changes were more frequently observed in the bulbar and cervicothoracic regions (71.4% of patients) than in the lumbar region (28.6% of patients; Fig. 3B and Table 1). In cases where EMG was repeated after an interval, neurogenic changes progressed to involve previously spared areas (e.g., upper limb in Patient 1, tongue in Patient 6; see Table 1).

### 3.2. Blink reflexes

Blink reflexes were abnormal in five of the six patients in whom they were tested (Fig. 1A and Table 1). Abnormalities were characterised by prolonged R1 and R2 responses, requirement for higher stimulus intensities, or absence of R1 and/or R2 responses (Fig. 4). Importantly, abnormal blink reflexes were observed in the context of normal facial nerve CMAP responses, suggesting dysfunction in the afferent limb of the blink reflex pathway (i.e., ophthalmic division of the trigeminal nerve).
Table 1

| Patient | Age/Sex | Time from SO (m) | Blink Reflex | SNAPs UL | SNAPs LL | CMAPs UL | CMAPs LL | Fibrillation potentials | Fasciculation Potentials | Motor Unit Action Potentials |
|---------|---------|-----------------|--------------|----------|----------|----------|----------|------------------------|--------------------------|-----------------------------|
| 1       | 60/M    | 114             | ND           | Normal   | Normal   | Normal   | Normal   | Tongue                 | Tongue                  | Acute and chronic neurogenic |
| 2       | 59/M    | 37              | ND           | Normal   | Normal   | Normal   | Normal   | Upper limbs            | Upper limbs             | Acute and chronic neurogenic |
| 3       | 48/F    | 22.5            | Abnormal     | Normal   | Normal   | Normal   | Normal   | None                   | None                    | Chronic neurogenic          |
| 4       | 52/M    | 38.5            | Abnormal     | Normal   | Normal   | Normal   | Normal   | Face, right upper limb | None                    | Chronic neurogenic          |
| 5       | 62/M    | 2.5             | ND           | Normal   | Normal   | Normal   | Normal   | Tongue, upper limbs    | None                    | Chronic neurogenic          |
| 6       | 64/M    | 32              | ND           | Normal   | Normal   | Normal   | Normal   | Upper limbs            | Upper and lower limbs     | Acute and chronic neurogenic |
| 7       | 60/M    | 48              | ND           | Normal   | Normal   | Normal   | Normal   | Tongue, temporalis     | None                    | Chronic neurogenic          |
| 8       | 63/M    | 128             | ND           | Normal   | Normal   | Normal   | Normal   | Upper limbs            | None                    | Chronic neurogenic          |

When examination was conducted more than once, the result was recorded as abnormal if it was found to be so at any time point. Further information on timepoints at which such neurophysiological examination was conducted can be found in Supplementary Table 1. These data are also graphically displayed in Figs. 1 and 3. Age given for individual patients refers to age at symptom onset.

3.3. SEPs

Upper limb SEPs were performed in four patients; repeat assessments were performed in three patients (Table 2). The results of upper limb SEPs are summarised in Fig. 2E. All four patients had CSCTs which were delayed in at least one arm. Moreover, CSCTs tended to increase with time from symptom onset (Fig. 2E), and the rate of change of CSCT (ACSCCT/month) correlated with disease duration (Fig. 2F). Lower limb SEPs were tested in four patients and found to be normal (Table 2). No SEP data were available for two patients who had reduced lower limb SNAPs (Tables 1 and 2). Strikingly, only one patient had reduced upper limb SNAPs (Table 1), thus emphasising the higher sensitivity of SEPs as an electrodiagnostic test of sensory dysfunction.

3.4. MEPs

MEPs were tested in four patients from the Newcastle cohort. Examples of upper limb MEPs recorded from Patient 1 are illustrated in Fig. 5A and 5B. Whilst the cMEPs appeared polyphasic, MEP latencies (CMCTs) were within normal limits [left: BB 13 ms (7 ms), EDC 14.8 ms (4.8 ms), FDS 16 ms (7.1 ms), FDI 25.5 ms (9.2 ms); right: BB 12.5 ms (6.5 ms), EDC 16.8 ms (6.8 ms), FDS 15.3 ms (8.6 ms), FDI 28.4 ms (9.7); (Eisen and Shytel, 1990)].

Patient 1 had iMEPs recordable from the right upper limb (latencies: BB 49 ms, EDC 75 ms, FDS 73 ms, FDI 85 ms) but not from the left upper limb. These iMEP latencies equate to iMEP CMCTs of 43 ms (BB), 65 ms (EDC), 64.1 ms (FDS) and 68.7 ms (FDI). Although the iMEP CMCT recorded from biceps brachii was markedly increased, it is within the range reported previously in a large series of ALS patients (Krampl et al., 2004). However, iMEP CMCTs of >50 ms, as recorded from forearm and hand muscles in this patient, have not previously been reported in ALS. Whilst cMEPs were normal, the presence of iMEPs in the right upper limb in Patient 1 is indicative of disease affecting corticospinal tract neurons in the primary motor cortex in the right hemisphere.

3.5. tTMS

Threshold tracking TMS was performed on 4 previously reported patients (Vucic et al., 2012), referred to as historical patients, and two new patients from the Sydney cohort (Patients 7 and 10 in this series). Cortical function was normal in 4 (66.7%) of the assessed patients as indicated by mean SICI (interstimulus interval 1–7 ms) of 7.1 ± 1.8% (normal > 5.2%, Fig. 5C), and mean ICF (interstimulus interval 10–30 ms) of −2.3 ± 2.5% (normal > −2.3%) (Vucic et al., 2012). Cortical dysfunction was evident in 2 (33.3%) patients, with mean SICI being −4.1% and −6.8% (Fig. 5C). Additionally, the RMT was reduced in one of the new patients (36.7%) assessed and was normal (61.4%) in the other patient. Interestingly, ICF was preserved in the two new patients.

3.6. Beta-band intermuscular coherence (BIMC)

BIMC data from the upper limb of four patients and from the lower limb of one of these patients is illustrated in Supplementary Fig. 2. Results varied between patients. Upper limb coherence was preserved in Patient 2, and reduced or absent in most muscle pairs in the other three patients. Lower limb coherence was only examined in Patient 4, in whom it was absent.

In Patient 1, intermuscular coherence was absent in the left upper limb muscles, consistent with disease affecting corticospinal projections arising from the right motor cortex, thus co-localising with the pathology identified by the presence of iMEPs in this patient (see Section 3.4).
3.7. Review of neurophysiologic findings in FOSMN patients reported in the literature

A review of the literature identified 52 patients in whom the results of neurophysiologic testing was reported. The findings of this review are summarised in Supplementary Table 3, Fig. 1B and Fig. 3C and D.

Blink reflexes were abnormal in all patients in whom they were tested (Fig. 1B, Supplementary Table 3). Upper limb SNAPs were reduced in 65% of those tested, whereas lower limb SNAPs were abnormal in 31% of those tested. These findings are consistent with a rostral to caudal pattern of dysfunction, with lower limb responses being relatively preserved (Fig. 1B, Supplementary Table 3). By contrast, there did not appear to be a clear rostro-caudal distribution, being more common in the bulbar musculature (40.4% of patients) and cervicothoracic musculature (48.1% of patients) and less frequent in the lumbosacral musculature (21.2% of patients).

Fig. 4. Blink reflexes. Illustrative examples of blink reflex responses acquired from patients 1 and 4. Responses were recorded from left (L) and right (R) orbicularis oculi (OO) following stimulation of the supraorbital nerve at a range of intensities. In both patients, ipsilateral and contralateral R2 responses were only seen at high stimulation intensities, and their onset (vertical red lines) was delayed. Direct supramaximal stimulation of the facial nerve elicited normal compound muscle action potentials (shown at the bottom of each cascade). This suggested that the efferent limb of the R2 blink reflex pathway was intact.
caudal pattern of change in CMAPs, with reduced CMAPs documented in only 20% of patients (Fig. 1B, Supplementary Table 3). Neurogenic changes were identified on EMG in all patients reported in the literature, with the prevalence of such changes again displaying a rostral to caudal distribution (Fig. 3D, Supplementary Table 3). There were findings of both acute and chronic neurogenic change, similar to that observed in MND/ALS, in 49% of patients (Fig. 3D). Motor evoked potentials have previously been reported as normal in all patients tested (Dalla Bella et al., 2014; Fluchere et al., 2011; Vázquez-Costa et al., 2019). Cortical excitability, as measured by threshold tracking TMS, was comparable to healthy controls in previously reported patients (Vucic et al., 2012). The results of somatosensory evoked potential testing have not previously been reported in the FOSMN literature.

4. Discussion

The present study reiterates the importance of electroneurography, EMG and blink reflex testing in making the diagnosis of FOSMN, while also identifying the potential utility of additional investigations not described in previously published cases, including somatosensory evoked potentials (SEPs), motor evoked potentials (MEPs) and beta-band intermuscular coherence (BIMC).

Our observations are in broad agreement with previously published results of neurophysiological examination conducted in 52 patients (Supplementary Table 3), where on electroneurography, SNAPs were more affected than CMAPs and blink reflexes were found to be abnormal in most of the patients tested (Vucic et al., 2012). The new patients demonstrated cortical hyperexcitability, implying the presence of TDP43 proteinopathy.

Table 2

| PT | Time from SO (m) | Side | Erb's P. (ms) | N13 (ms) | N20 (ms) | CSCT (ms) | N0 (ms) | P1 (ms) | N1 (ms) | P2 (ms) | N2 (ms) |
|----|-----------------|------|--------------|---------|---------|-----------|---------|---------|---------|---------|---------|
| 1  | 91              | RT   | 12.4         | 13.3    | 24      | 11.6      | 34.3    | 39.6    | 49.3    | 56.3    | 64.4    |
|    |                 | LT   | 11.9         | 15.3    | 21.5    | 9.6       | 35.8    | 44      | 48.5    | 57.5    | 65.4    |
| 3  | 63              | RT   | 8.6          | 13      | 18.7    | 10.1      | 31.8    | 39.6    | 49.2    | 71.3    | 82.9    |
|    |                 | LT   | 9            | 12.5    | 18.9    | 9.9       | 31.9    | 40.6    | 51.5    | 64.9    | 76.8    |
| 96 |                 | RT   | 9            | 13.6    | 20.3    | 11.3      | 33.7    | 40.1    | 48.2    | 65.3    | 76.3    |
|    |                 | LT   | 9.2          | 13      | 21      | 11.9      | 34.5    | 41.7    | 51.7    | 64.5    | 80.6    |
| 4  | 24              | RT   | 11           | 15.2    | 20.9    | 9.9       | 30.6    | 43.7    | 50.2    | 63      | 73.1    |
|    |                 | LT   | 10.2         | 14.9    | 20.3    | 10.1      | 33.5    | 47.6    | 58.9    | 68.7    | 81      |
| 32 |                 | RT   | 11.35        | 14.75   | 22.2    | 10.85     | 4.95    | 48.6    | 57      | 72.4    | 89.65   |
|    |                 | LT   | 11.85        | 16.5    | 22.5    | 10.65     | 49.9    | 54.45   | 63.1    | 79.95   | 92.8    |
| 5  | 63              | RT   | 11.1         | 16.3    | 22.6    | 11.5      | 52.7    | 56.8    | 66.3    | 74.9    | 86.1    |
|    |                 | LT   | 11           | 14.8    | 22.6    | 11.6      | NR      | NR      | NR      | NR      | NR      |
| 82 |                 | RT   | 10.2         | 15.6    | 23.8    | 13.5      | 36.6    | 46.6    | 55.1    | 70      | 78.7    |
|    |                 | LT   | 9.6          | 14.4    | 22.6    | 13.1      | 37.6    | 43.3    | 51.4    | 57.7    | 69.4    |

SEPs were measured in four FOSMN patients from the Newcastle and Sydney cohorts and at two time points in three patients. CSCTs were delayed or at the upper limit of normal in all three patients and the rate of change in CSCT correlated with disease duration (displayed graphically in Fig. 2). N0, P1, N1, P2 and N2 responses were not recorded (NR) for Patient 5 at 21 months from symptom onset due to technical reasons.

Key: PT - patient; SO - symptom onset; m - months; ms - millisecond; P - point; CSCT - central sensory conduction time; RT - right; LT - left.

Fig. 5. Contralateral and ipsilateral (A and B) motor cortical evoked potentials (MEPs) and (C) threshold tracking transcranial magnetic stimulation (ttTMS). Examples of MEPs recorded from contralateral and ipsilateral upper limb muscles. (A) A figure-of-eight TMS coil was discharged over the hand area of the right primary motor cortex whilst the patient activated his upper limb muscles (10–20% maximum voluntary contraction). Latencies of contralateral MEPs (cMEPs): biceps 13 ms; extensor digitorum communis (EDC) 14.8 ms; flexor digitorum superficialis (FDS) 16 ms; and first dorsal interosseous (FDI) 25.5 ms. Latencies of ipsilateral MEPs (iMEPs): biceps 49 ms; EDC 75 ms; FDS 73 ms; and FDI 85 ms. (B) A figure-of-eight TMS coil was discharged over the hand area of the left primary motor cortex. Latencies of contralateral MEPs (cMEPs): Biceps 12.5 ms; EDC 16.8 ms; FDS 15.3 ms; and FDI 28.4 ms. cMEPs are plotted on the left in A and on the right in B; iMEPs are plotted on the right in A and on the left in B. TMS intensity is expressed relative to resting motor threshold (RMT). (C) Two of the newly reported patients were available for ttTMS studies (Patients 7 and 10) and compared with four previously reported patients (historical patients) with facial onset sensory and motor neuronopathy (FOSMN) and 30 healthy controls. The average short interval intra-cortical inhibition (SICI) was not significantly different between the healthy controls and historical patients as previously reported (Vucic et al., 2012). The new patients demonstrated cortical hyperexcitability, implying the presence of TDP43 proteinopathy.
increased latencies for both R1 and R2 responses, the most common observation was that reliable R1 and R2 responses could only be obtained with very high stimulation strengths. Because stimulation strength is not typically documented, normative data is lacking (Meincke et al., 1999). These data should be collected in future studies, particularly given the variation in R1/R2 threshold observed in controls (Sanes et al., 1982).

EMG identified neurogenic change in all patients reported in the literature, with the prevalence of such changes displaying a rostral to caudal distribution (Fig. 3C and 3D). The observation of both acute and chronic neurogenic change in bulbar muscles of most cases, progressing to cervical and thoracic muscles, is reminiscent of the findings in bulbar MND/ALS with contiguous progression of EMG changes (Liao et al., 2020). Moreover, of the eight patients who underwent EMG in our series, one patient fulfilled the Awaji-Shima Criteria (de Carvalho et al., 2008) for the diagnosis of ALS (Patient 6 had fibrillation potentials, positive sharp waves and polyphasic unstable motor units in cervical, thoracic and lumbar myotomes, and high amplitude voluntary motor units discharging at high frequency together with spontaneous complex repetitive discharges in genioglossus) and four (Patients 1, 4, 6, and 9) fulfilled the more recent Gold Coast Criteria (Sheffner et al., 2020) (Supplementary Table 4).

Although MEP CMCTs were normal in all patients tested (n = 4), iMEPs were identified in one patient, tTMS was abnormal in two patients and BIMC was abnormal in three out of four patients, implying the presence of upper motor neuron (UMN) dysfunction in a subgroup of FOSMN syndrome patients. Whilst iMEPs, when identified, are indicative of UMN disease in ALS, iMEP CMCTs can vary significantly, with CMCTs of up to 45.6 ms in one study (Krampfl et al., 2004). The shortest iMEP CMCT we observed was 43 ms (Biceps), consistent with previous reports. However, we also observed very prolonged iMEP CMCTs (e.g., 67.8 ms; first dorsal interosseus). These have not previously been described in ALS. One explanation might be that the long latency iMEPs are evidence of very early and evolving adaptive changes in compensatory ipsilateral/bilateral descending motor pathways; with time therefore iMEP latencies and thus iMEP CMCTs would be predicted to reduce as these connections strengthen.

Reassuringly, in the patient in whom the presence of iMEPs indicated disease in the primary motor cortex of the right hemisphere (Patient 1), BIMC was absent in the left upper limb (i.e., innervated by crossed corticospinal input from the right primary motor cortex) but not in the right upper limb. Given there was very little evidence of peripheral nerve dysfunction on upper limb sensory nerve conduction studies (and the borderline abnormalities on SEPs were symmetrical), the results of BIMC analysis are likely to be attributable to corticospinal tract degeneration and not to loss of sensory afferents (Baker et al., 2006; Klíner et al., 2004).

Historically, it has been recognised that UMN signs can be masked by the presence of significant lower motor neuron (LMN) disease or a sensory neuropathy, perhaps explaining the underreporting of signs indicative of UMN disease in FOSMN. The potential masking of UMN signs by LMN disease is discussed in the most recent incarnation of the MND/ALS diagnostic criteria, the Gold Coast Criteria (Sheffner et al., 2020), which also acknowledges the utility of ancillary investigations to probe the integrity of the corticospinal tracts and cortical function. Our novel observations therefore suggest that UMN disease is more widespread than previously appreciated in FOSMN. Moreover, our electrophysiologic observations, particularly the description of progressive, contiguous spreading disease affecting both LMNs and UMs, provide further support for the contention that FOSMN syndrome is a TDP43 proteinopathy (De Boer et al., 2021; Gromicho et al., 2020).

The results of sensory and motor NCS together with the findings on needle EMG therefore exhibit a characteristic and recognisable pattern of abnormalities in FOSMN syndrome. As most published data on the neurophysiology of FOSMN syndrome are cross-sectional, it is difficult to comment on the time course of progression of these abnormalities with any precision. In our series, electrophysiological measurements were acquired at more than one time point in a subgroup of patients, enabling limited inference on the evolution of electrophysiological changes in FOSMN syndrome. This was particularly the case for SEPs, which were obtained at two time points in three of our patients (Table 2) and showed that CSCTs increased in all individuals with time from symptom onset (Fig. 2E). Furthermore, given the contrasting observation that neither SNAPs nor SNCVs showed significant change in our cohort over time (Fig. 2A-D), SEPs would appear to be a more sensitive electrophysiological parameter for documenting progressive sensory changes in FOSMN.

In ALS, the early SEP components do not appear to be affected by disease progression (Cascino et al., 1988; Chiappa, 1997; Machii et al., 2003; Zanette et al., 1990). Where abnormalities or progressive changes in SEPs have been identified in ALS (de Carvalho et al., 1995; Cosi et al., 1984; Dasheiff et al., 1985; Georgesco et al., 1997; Hamada et al., 2007; Iglesias et al., 2015; Khalili-Ardali et al., 2021; Matheson et al., 1986; Radtke et al., 1986; Sangari et al., 2018; Subramaniam and Yannikas, 1990; Zanette et al., 1996), these affect the later cortical SEP components and are thought to be a consequence of adaptive or secondary degenerative processes related to the loss of cortical layer V pyramidal neurons as disease progresses.

It is perhaps not surprising that SNAPs/SNCVs are not a sensitive method of monitoring neuropathic processes in the short-term, given the variability inherent in measuring responses over short segments of peripheral nerve (see Supplementary Fig. 1), with susceptibility to temperature change, local trauma and entrapment, as well as problems of consistent electrode placement and impedance amongst other technical variations, as demonstrated by various studies in controls (Kong et al., 2009; Lanza et al., 2017). In FOSMN syndrome, a disorder characterised by progressive degeneration of dorsal root ganglion neurons (Rossor et al., 2019), where the fastest conducting, large diameter axons are initially affected (Supplementary Fig. 1A), only a very minimal increase in SNAP latency will be measured over a short distal nerve segment with an indiscernible drop in amplitude, resulting in inconsistent changes in SNAP amplitude over time (Fig. 2B).

By contrast, the SEP measures latency changes that include almost the entire length of the axon, from the site of peripheral nerve stimulation to the dorsal column nucleus, and by calculating the CSCT, this takes account of differences in height/arm length, peripheral nerve entrapment and test-to-test variation in stimulation site (Supplementary Fig. 1B). By minimising measurement error and thus variability, the SEP CSCT therefore offers a reasonably accurate and reliable means of detecting the loss of the initial component of the sensory potential mediated by the largest diameter axons (Supplementary Fig. 1C-E). It is not surprising that upper limb SEP CSCTs were at the upper limit of normal or delayed in all four patients tested (Fig. 2E), whilst upper limb SNAPs were only reduced in one patient (Fig. 2A).

One further intriguing observation was that the rate of change of CSCT (ΔCSCT/month) correlated with disease duration (Fig. 2F), suggesting that the rate of SEP-CSCT change may be a reliable biomarker of disease progression. This preliminary observation requires confirmation, particularly given sensory symptoms are common in FOSMN syndrome and are accompanied by TDP43 aggregation in dorsal root ganglion neurons (Rossor et al., 2019). It can therefore be argued that progressive dorsal root ganglion degeneration, occurring secondary to a similar pathophysiological process that causes motor neuron degeneration, leads to central sensory nerve degeneration and thereby progressive delays
Electrodiagnostic findings in FOSMN

**Blink Reflexes**
- Abnormal in all patients 21 months from onset of facial sensory symptoms

**NCS & Needle EMG**
- UL SNAPs abnormal as disease progresses in ~20% of patients
- Neurogenic MEPs documented in rostro-caudal distribution without motor signs or symptoms in ~50% of patients

**SEPs**
- UL SEPs are more sensitive than SNAPs at detecting monitoring subclinical sensory changes
- Rate of change of SEP CSCT may provide prognostic information
- Consider referring for SEPs at first presentation and repeating at 6-12 months

**Testing for Subclinical UMN Dysfunction**
- 1 of 4 patients tested had ipsilateral MEPs (iMEPs)
- Pathological cortical hyperexcitability in 2 of 6 patients tested
- BIMC abnormal in 3 of 4 patients tested

Fig. 6. Summary of electrodiagnostic findings in facial onset sensory and motor neuronopathy (FOSMN). The neurophysiological examination is useful in identifying pathognomonic signs of FOSMN such as abnormal blink reflexes, in addition to identifying subclinical lower motor neuron and upper motor neuron involvement, as described in other phenotypes of motor neuron disease (MND)/amyotrophic lateral sclerosis (ALS). Somatosensory evoked potentials (SEPs) are not commonly performed in MND/ALS or FOSMN. Original data presented in this article suggest that SEP central sensory conduction time (CSCT) may correlate with disease progression and therefore should be performed longitudinally in patients diagnosed with FOSMN.

in SEP CSCT. SEPs might thus be of utility not only in diagnosis but also as a biomarker for disease monitoring. Collection of such data should be encouraged in all cases of suspected FOSMN to further clarify this point.

The findings from the present study provide further evidence for the notion that FOSMN syndrome is a neurodegenerative process affecting sensory and motor neurons. Additionally, our findings should provoke a re-appraisal of the involvement of sensory neurons in MND/ALS, an understudied area despite existing evidence for sensory dysfunction in MND/ALS (Ferrari et al., 2014; Hammad et al., 2007; Isak et al., 2017). Understanding precisely what factors determine the susceptibility of dorsal root ganglia degeneration in a small subset of patients with MND/ALS could provide significant insights into the underlying pathobiology.

**4.1. Conclusion**

We have reviewed the existing literature describing the neurophysiology of FOSMN and reported novel findings, including the identification of iMEPs, changes in ttTMS and absence of BIMC, indicating that subclinical UMN dysfunction is more prevalent in FOSMN than previously reported. We suggest that SEPs, specifically SEP CSCTs, rather than SNAPs/SNCVs, are a more sensitive method for assessing sensory dysfunction in FOSMN.

This study is not without limitations, not least of which is the inconsistency of data collection across geographically separated sites. Moreover, clinical data collection was retrospective and thus susceptible to ascertainment bias. Finally, given the rarity of the syndrome, case numbers are small and thus these findings require confirmation in a larger cohort of patients with FOSMN from multiple centres. Fig. 6 summarises the electrodiagnostic findings in FOSMN from which a framework for diagnostic investigations and collection of neurophysiological data can be inferred.

Importantly, our observation that patients have subclinical evidence of UMN disease and evidence of subclinical progression of LMN disease, supports the concept that FOSMN is a rare neurodegenerative disorder with pathophysiological overlap with MND/ALS. In our opinion, patients with FOSMN should therefore be given the opportunity to benefit from care in a specialist multidisciplinary MND/ALS clinic.

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**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Appendix A. Supplementary material**

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2022.04.020.

**References**

American Clinical Neurophysiology Society. Guideline 9D: Guidelines on short-latency somatosensory evoked potentials. J Clin Neurophysiol 2006;23:168–79. https://doi.org/10.1097/00004691-200604000-00013.

Baker SN, Chiu M, Feté EE. Afferent encoding of central oscillations in the monkey arm. J Neurophysiol 2006;95(6):3904–10. https://doi.org/10.1152/jn.01165.2005.

Barca E, Russo M, Mazzeo A, Terranova C, Giarlanda P. Facial onset sensory motor neuronopathy: A case report. J Peripher Nerv Syst 2012;17:54–5.

Bélénotti P, Benyamine A, Bensahia H, Ene N, Sevy A, Attarian S, Serratrice J, Pouget J, Weiller P-J, Krolak-Salmon P. Tout est dans la chronologie. Rev Med Interne 2010;31(11):784–7. https://doi.org/10.1016/j.revmed.2010.08.014.
sensitive inversion recovery (PSIR) imaging in motor neuron disease. PLoS ONE 2018;13(11):e0208255. https://doi.org/10.1371/journal.pone.0208255

Paganoni S, Macklin EA, Lee A, Murphy A, Chang J, Zifp A, Cudkowicz M, Atassi N. Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler Frontotemporal Degener 2014;15(5-6):453–6. https://doi.org/10.3109/21678421.2014.903924.

Pinto WBVR, Naylor FGM, de Souza PVS, Oliveira ASB. New findings in facial-onset sensory and motor neuronopathy (FOSMN) syndrome. Rev Neurol (Paris) 2019;175(4):238–46. https://doi.org/10.1111/revn.12030.

Raddie RA, Erwin A, Erwin CW. Abnormal sensory evoked potentials in amyotrophic lateral sclerosis. Electromyogr Clin Neurophysiol 1986;36(6):796.

Rong P, Pattey GL. A potential upper motor neuron measure of bulbar involvement in amyotrophic lateral sclerosis using jaw muscle coherence. Amyotroph Lateral Scler Frontotemporal Degener 2021;22(3-6):368–79. https://doi.org/10.1080/21678421.2021.1874993.

Rossor AM, Jaunmuktane Z, Rossor MN, Hoti G, Reilly MM. TDP43 pathology in the brain, spinal cord, and dorsal root ganglia of a patient with FOSMN. Neurology 2019;92:E951–6. https://doi.org/10.1212/WNL.0000000000007298.

Sanes JN, Foss JA, Ison JR. Conditions that affect the thresholds of the components of the blink reflex in humans. J Neurol Neurosurg Psychiatry 1982;45(6):543–9. https://doi.org/10.1136/jnnp.45.6.543.

Sangari S, Giron A, Mareelee G, Pradat-Pauvert V. Abnormal cortical brain integration of somatosensory afferents in ALS. Clin Neurophysiol 2018;129(4):874–84. https://doi.org/10.1016/j.clinph.2017.12.008.

Shefner JM, Al-Chalabi A, Baker MR, Cui L-Y, de Carvalho M, Parker MR, Simon N, Swash M, Talbot K, Turner MR, Ugawa Y, van den Berg LH, Vucic S, Zhang Q, Cao B, Chen Y, Liang Y, Wei Q, Zhou D, Shang H. Facial onset motor and sensory neuronopathy syndrome with a novel TARDBP mutation. Neurologist 2014;20(5-6):453–6. https://doi.org/10.1002/mus.20481.

Sonoda K, Sasaki K, Tateishi T, Yamashita R, Hayashi S, Sakae N, Ohyagi Y, Iwaki T, Kira J-I. TAR DNA-binding protein 43 pathology in a case clinically diagnosed with facial-onset sensory and motor neuronopathy syndrome: An autopsied case report and a review of the literature. J Neurol Sci 2013;322(1-2):148–53. https://doi.org/10.1016/j.jns.2013.06.027.

Subramaniam JS, Yiannikas C. Multimodality Evoked Potentials in Motor Neuron Disease. Arch Neurol 1990;47(9):989–94. https://doi.org/10.1001/archneur.1990.0390090003015.

Tankisi H, Burke D, Cui L, de Carvalho M, Kuwabara S, Nandedkar SD, Rutkove S, Stålberg E, van Putten MJAM, Fuglsang-Frederiksen A. Standards of instrumentation of EMG. Clin Neurophysiol 2020;131(1):243–58. https://doi.org/10.1016/j.clinph.2019.07.073.

Truini A, Provitera V, Bassotta A, Stancaneli A, Antonini G, Santoro L, Cruccu G, Molteno A. Differential trigeminal myelinated and unmyelinated nerve fiber involvement in FOSMN syndrome. Neurology 2015;84(5):540–2.

Vázquez-Costa JF, Pedrola Vidal L, Moreau-Le Lan S, Teresi-Copovi I, Frasquet M, Chumillas MJ, Sevilla T. Facial onset sensory and motor neuronopathy: a motor neuron disease with an oligogenic origin? Amyotroph Lateral Scler Frontotemporal Degener 2019;20(3-4):172–5. https://doi.org/10.1080/21678421.2019.1562671.

Vucic S, Howells J, Trevislton L, Kienan MC. Assessment of cortical excitability using threshold tracking techniques. Muscle Nerve 2006a;33(4):477–86. https://doi.org/10.1002/mus.20481.

Vucic S, Steen TD, Hedley-Whyte ET, Reddel SR, Tisch S, Kotschet K, Cros D, Kiernan MC. FOSMN syndrome: Novel insight into disease pathophysiology. Neurology 2012;79(1):73–9. https://doi.org/10.1212/WNL.0b013e31825dce13.

Vucic S, Tian D, Chong PST, Cudkowicz ME, Hedley-Whyte ET, Cros D. Facial onset sensory and motor neuronopathy (FOSMN syndrome): a novel syndrome in neurology. Brain 2006b;129:3384–90. https://doi.org/10.1093/brain/awl255.

Vucic S. Facial onset sensory motor neuronopathy (FOSMN) syndrome: An unusual amyotrophic lateral sclerosis phenotype? J Neurol Neurosurg Psychiatry 2014;85(9):951. https://doi.org/10.1136/jnnp-2014-307756.

Watanabe M, Shiraishi W, Yamashita R, Isobe N, Sawatubashi M, Yasumatsu R, Nakagawa T, Kira J-I. Oral phase dysphagia in facial onset sensory and motor neuronopathy. Brain Behav 2018;8(6):e00999. https://doi.org/10.1002/brb3.999.

Zanette G, Polo A, Gasperini M, Bertolasi L, De Grandis D. Far-field and cortical somatosensory evoked potentials in motor neuron disease. Muscle Nerve 1990;13(1):47–55. https://doi.org/10.1002/mus.880130110.

Zanette G, Tinazzi M, Polo A, Razzuto N. Motor neuron disease with pyramidal tract dysfunction involves the cortical generators of the early somatosensory evoked potential to tibial nerve stimulation. Neurology 1996;47(4):932–8. https://doi.org/10.1212/br.47.4.932.

Zhang Q, Cao B, Chen Y, Liang Y, Wei Q, Zhou D, Shang H. Facial onset motor and sensory neuronopathy syndrome with a novel TARDBP mutation. Neurologist 2019;24(1):22–5. https://doi.org/10.1002/mus.20901.

Zuo B, Williams TL, Walters RJL, Jauser SK, Attems J, Wieschna UC, Lainer AJ, Jacob A. Facial onset sensory and motor neuronopathy: Further evidence for a TDP-43 proteinopathy. Case Rep Neurol 2015;7(1):95–100. https://doi.org/10.1159/000381944.