

## Facial Onset Sensory and Motor Neuronopathy: A Case Series and Literature Review

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### ABSTRACT

**Introduction:** Facial Onset Sensory and Motor Neuronopathy (FOSMN) typically presents with paresthesias in the trigeminal nerve distribution and weakness that progresses rostro-caudally.

**Objective:** To present two new cases of FOSMN, summarize the current literature, and address areas for future study.

**Methods:** Observational data was collected from two patients with FOSMN from our institution. A literature review of FOSMN was completed using PubMed.

**Results:** We reviewed 100 cases of FOSMN, including our two new cases. 93% presented with facial paresthesias. 97% had bulbar symptoms. Five had family history of ALS. Abnormal Blink reflex was most common on EMG/NCS. CSF was typically normal, but a rare severe case showed elevated protein. Mutations included: TARDBP, OPMD, D90A-SOD1, CHCHD10, VCP, and SQSTM1. Neuropathological studies showed neurodegenerative changes without inflammation. Some cases have reported transient stabilization or improvement to immunomodulatory therapy.

**Case Reports:** A 72-year-old man presented with right-sided trigeminal paresthesias that progressed in a rostro-caudal fashion, dysphagia, and hand weakness. He died 4-5 years after symptom onset. A 69-year-old man presented

with left-sided jaw paresthesias, dysphagia and dysarthria. He was trialed on IVIG for 1.5 years without improvement and died 2.6 years after symptom onset.

**Conclusion:** FOSMN is a rare disorder with a unique clinical and electrophysiological phenotype. The pathophysiology has been associated with neurodegeneration and multiple gene mutations have correlated to FOSMN. Some reports suggest transient response to immunomodulatory therapy, though prospective studies are lacking. CSF protein elevation may be seen in severe disease. Future studies will help further elucidate the approach to diagnosis, treatment, and prognostic counseling (biomarkers).

**Keywords:** FOSMN, Facial Onset Sensory and Motor Neuronopathy, Neurodegenerative disorders

### Introduction

In 2006, Vucic et al. were the first to report a "syringomyelia-like syndrome" that involved facial sensory loss and progressive motor deficits seen in four adult male patients.<sup>1</sup> Later this disease was coined Facial Onset Sensory and Motor Neuronopathy (FOSMN), which manifests as a mild asymmetric facial sensory deficit commonly in the trigeminal nerve distribution that advances caudally to include the scalp, neck, upper trunk, and upper extremities. Progressive motor symptoms such as weakness in the bulbar, neck, upper limbs, and later the lower limbs can develop months to years following the initial onset of sensory symptoms and can lead to functional impairments such as dysphagia and dysarthria.

There have subsequently been at least 98 cases of FOSMN described in the literature. It is a rare syndrome with unknown incidence. FOSMN affects both males and females, with a male predominance.<sup>2</sup> Onset of disease is typically between the fourth to seventh decade with one case onset reported at seven years old.<sup>3</sup> FOSMN duration can span from months to decades.<sup>4</sup> The diagnosis is mostly made based on clinical features but absent or latent corneal blink reflex is a hallmark of electrodiagnostic testing in many cases.<sup>5</sup>

The pathogenesis of this heterogeneous disease remains a topic of debate. An immunologic process has been suggested due to transient clinical response to intravenous immunoglobulin (IVIg) and the presence of autoantibodies at low concentrations observed in some patients.<sup>6</sup> However, it is this same transient or absent response to immunomodulatory therapy along with a stereotyped clinical picture of a chronically progressive disease that suggests a primary neurodegenerative mechanism. In many cases, it is a diagnosis of exclusion. Many of the diseases to be

excluded have a neurodegenerative pathology, one of which is amyotrophic lateral sclerosis (ALS). Recent literature has suggested a link between ALS and FOSMN, which would further confirm a neurodegenerative pathway. For example, corneal confocal microscopy has revealed a reduction of corneal small fiber sensory nerves in ALS patients, which may suggest a link with FOSMN as patients with FOSMN typically have early trigeminal nerve distribution sensory symptoms.<sup>7</sup> Cervical cord atrophy can be seen in both ALS and FOSMN.<sup>6,8,9</sup> Similar genetic variants have also been found in FOSMN including SOD1.<sup>10</sup>

Our objective is to characterize the key clinical findings, diagnosis, treatment, and outcomes of patients with FOSMN while adding two additional cases to the literature. Our study will not only review the current literature, but also address gaps that future studies must consider to advance our understanding of FOSMN in order to optimize management of those with the condition.

## Methods

This is a case series presenting observational data collected from two patients at The Ohio State University, Wexner Medical Center with a diagnosis of FOSMN. Verbal consent was obtained from the patients prior to publication. Furthermore, a comprehensive literature review was performed through PubMed. The following MeSH terms were used: “FOSMN” and “Facial Onset Sensory Motor Neuronopathy.” Articles included all previously reported cases with the diagnosis of FOSMN.

We evaluated patient characteristics, clinical features, physical examination findings, comorbidities, laboratory, electromyogram/nerve conduction study (EMG/NCS) and magnetic resonance imaging (MRI) findings, genetic testing, disease course, autopsy, requirements for tracheostomy or percutaneous endoscopic gastrostomy (PEG) tube, and treatments.

## Case Summary

### Case Presentation 1

A 72-year-old male with past medical history of monoclonal gammopathy of undetermined significance (MGUS) complicated by distal small fiber neuropathy, gastro-esophageal reflux disease (GERD), and esophageal stricture post balloon dilatation, presented to our hospital with an acute choking episode in the setting of a progressive three-year history of recurrent choking episodes, sensory loss in the face, mouth, and limbs, and reduced hand dexterity.

His symptoms initially started with paresthesias in the trigeminal (V2) distribution on the right side of his face

that slowly spread to involve all trigeminal nerve sensory areas and then later progressed in a rostro-caudal fashion to involve his scalp, neck, trunk and arms. Within three months, he developed dysphagia (to both solids and liquids), throat numbness, and loss of taste. Two years after symptom onset, he noticed trouble with hand dexterity and sensory loss in the lower extremities. He reported no changes in cognition, fluctuation of his symptoms or visual complaints. There was no family history of motor neuron disease.

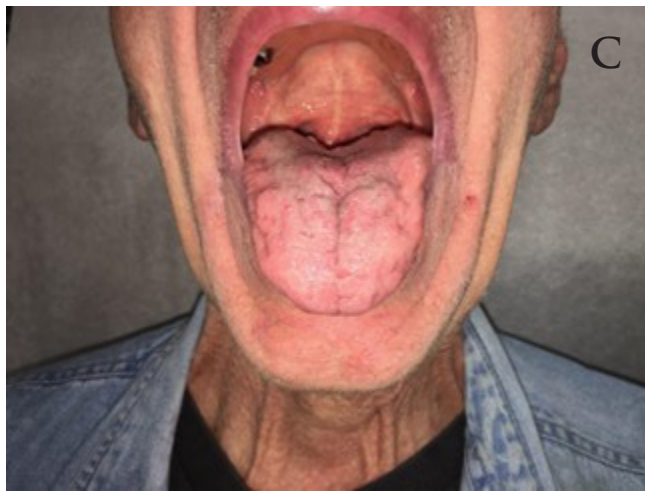
On exam, he had loss of sensation to sharp involving the face, head, neck, arms and trunk above a suspended T4 level. There was atrophy of the tongue and thenar muscles in the hand, similar to the split hand sign seen in ALS (Figure 1), along with moderate intrinsic hand muscle weakness. Tongue fasciculations were prominent. Lower extremities had absent reflexes and loss of vibratory sensation (attributed to MGUS).

Work up included unremarkable laboratory studies, including basic metabolic, autoimmune testing and vitamin levels. CK was 120 U/L. MRI of the brain without contrast showed no atrophy or focal abnormalities. MRI of the cervical spine without contrast showed an atrophic spinal cord, measuring 0.43 cm in antero-posterior diameter (Figure 2). NCS was suggestive of a non-length-dependent sensorimotor polyneuropathy or neuronopathy with decreased sensory conduction amplitudes in the upper extremity and normal amplitudes in the lower extremity. Blink reflexes were absent. EMG showed active and chronic denervation in cranio-bulbar, cervical, and lumbosacral regions. Given the clinical symptoms, exam findings, cervical cord atrophy, and EMG/NCS findings, FOSMN syndrome was considered the most likely diagnosis. During his hospital stay, he was treated for aspiration pneumonitis, had his diet modified, and he was discharged. He was not trialed on any immunotherapies for FOSMN.

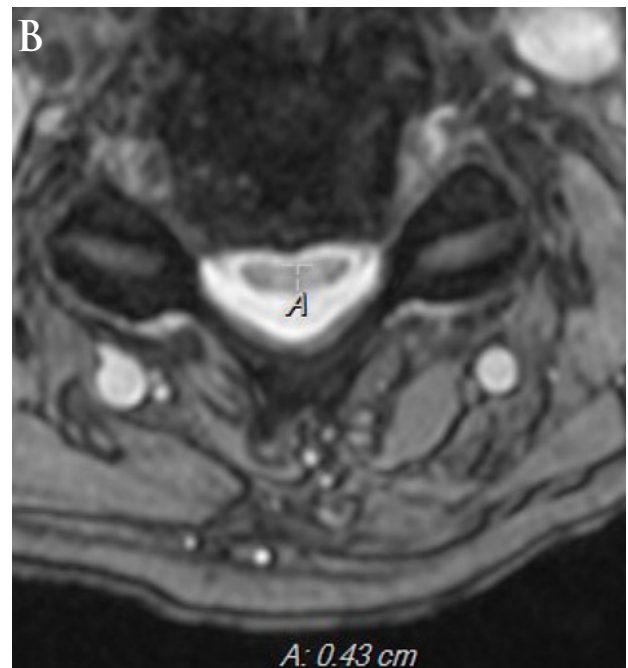
He was followed in neuromuscular clinic and underwent speech therapy with clinical stability for approximately one year at follow up, or four years after symptom onset. Subsequently he required admissions for aspiration pneumonia and eventually died after a hospitalization for a hernia causing small bowel obstruction which was complicated by a cardiac arrest event secondary to respiratory failure.

### Case Presentation 2

A 69-year-old male with no past medical history presented to our neurology clinic with left sided jaw paresthesias, difficulty chewing, and dysarthria. His symptoms started seven months prior to presentation with initial symptoms of left jaw and tongue numbness. A few months later, his facial paresthesias progressed to involve his



**Figure 1:** Case 1 with A) left greater than right first dorsal interossei (FDI) atrophy, B) left greater than right thenar atrophy, and C) prominent tongue atrophy



**Figure 2:** Case 1's MRI of the cervical spine  
A: Sagittal T2-weighted image showing cervical cord atrophy  
B: Axial T2-weighted image showing cervical cord anterior-posterior diameter of 0.43 cm

entire face and he developed dysarthria, difficulty chewing foods, and neck muscle weakness. He ultimately also had an unintentional 40lb weight loss over the preceding months. He denied any cognitive or visual changes. There was no family history of motor neuron disease.

On exam, he had sensory loss to light touch and pin prick in the left V1-V3 trigeminal nerve region, bilateral orbicularis oris and tongue weakness, bitemporal wasting, and tongue fasciculations. He had generalized decreased muscle bulk. On initial strength testing, he had slight infrapinatus weakness on the left, but all other muscles of the upper and lower extremities were 5/5 on the Medical Research Council Manual Muscle Testing scale.

Lab and imaging tests were negative for autoimmune disorders, myasthenia gravis, leptomenigeal disease and Kennedy's disease. Anti-NRI antibody was initially positive in serum paraneoplastic panel testing but later became negative twice on repeat testing. CT chest, abdomen and pelvis were negative for malignancy. CK was 140 U/L. CSF protein was mildly elevated at 48 mg/dL and all other basic CSF labs were unremarkable. MRI brain showed an incidental meningioma over the right cavernous sinus. Nerve conduction studies, including upper and lower limb sensory and motor studies, were normal. EMG revealed active and chronic denervation in his cranio-bulbar, cervical, and lumbar regions. Blink reflex testing showed absent ipsilateral and contralateral R1 and R2 potentials when stimulating the left side. When stimulating the right side, the ipsilateral R1 and R2 and contralateral R2 potentials were mildly prolonged. 3-hz repetitive nerve stimulation (RNS) of both the left orbicularis oris and right trapezius showed a CMAP decrement of >10% at rest with evidence of partial improvement in decrement immediately post-exercise. This may have been secondary to denervation and reinnervation changes.

He had a significant choking event nine months from symptom onset. Around this same time, his weakness progressed to involve his upper and lower extremities, left worse than right. He regressed from being able to tolerate a thick pureed diet to only broth and had to wear a jaw brace to combat his jaw drop. Given the degree of involvement of his bulbar musculature, he was trialed on IVIg monthly for three months. He reported improvement in his swallowing and had improvement in his Dysphagia Scoring Scale as well. His IVIg frequency was increased to weekly, and he was started on prednisone 30 mg daily. He was on this regimen for about a year and a half. However, his swallowing and weakness progressed, and he eventually required a PEG tube 22 months after symptom onset. He ultimately died due to respiratory failure 31 months after symptom onset.

## Results

We reviewed 100 total cases, including our two new cases. Table 1 outlines a summary of the characteristics of patients with FOSMN. The mean age of onset is 54.5 years old. The male to female ratio is about 2:1. Initial symptoms typically include sensory loss in the trigeminal nerve distribution. When previous literature mentioned initial symptoms, 93% had facial sensory loss at onset. This typically advances rostro-caudally into the scalp, neck, upper back and arms. Lower motor neuron findings, including fasciculations, muscle atrophy and weakness, are present in almost all cases and progress in a rostro-caudal manner. Upper motor neuron findings have been mentioned in at least 23 patients. 97% of patients have bulbar symptoms. 27% of patients required percutaneous endoscopic gastrostomy (PEG) placement. The average time from symptom onset to PEG placement was 2.3 years. Taste disturbance has been reported as an initial symptom in two case reports<sup>11,12</sup> and loss of taste was seen in three out of four of the originally described FOSMN patients.<sup>1</sup> Five patients had a family history of ALS.<sup>13,14</sup> Five patients were also diagnosed with behavioral variant frontotemporal dementia (bvFTD) and met Rascovsky criteria.<sup>5,15</sup> There are no known social risk factors for FOSMN.

Common clinical examination findings include absent to decreased corneal reflex, decreased sensation in the trigeminal nerve distribution, dysarthria, weak cough and gag reflex, decreased upper extremity reflexes, fasciculations and atrophy. There can be facial, tongue and upper extremity weakness.

Cervical cord atrophy has been found in seven patients<sup>6,9,14,16</sup> and one of our patients had cervical cord atrophy as well (Figure 2). Frontotemporal atrophy has been seen in at least one patient with FOSMN.<sup>17</sup> The "bright tongue sign" has been reported in three cases, which can also be seen in ALS.<sup>14</sup> This sign is found on brain MRI and consists of hyperintense signaling in tongue muscles.

Blink reflex abnormalities on EMG/NCS are seen in almost all patients with FOSMN.<sup>15</sup> The most common abnormality is seen in the R2 response. All but one patient had either a unilateral or bilateral R2 abnormality. 82% had bilateral R2 abnormalities. If an article mentioned an R1 response, it was abnormal 77% of the time. Other common findings on EMG include decreased SNAPs and neurogenic findings in bulbar or cervical muscles.<sup>14,18</sup> One of our patients had a >10% CMAP decrement on RNS with immediate post-exercise repair.

Cerebrospinal fluid (CSF) is typically normal in most patients. There have been rare, reported cases of elevated protein and IgG. The patient with elevated CSF protein

had a more rapid disease course and died within 18 months of symptom onset.<sup>5</sup> CK can be mildly elevated, with the highest reported CK being 894.<sup>5</sup> Antibodies have been found in some cases and include anti-sulfatide antibodies (five patients; two titers reported at 10,350 IU/L and 4,521 IU/L), anti-GD1b antibodies (three patients), anti-myelin-associated glycoprotein (anti-MAG) IgG (one patient), anti-sulfo-glucuronyl paragloboside (SGPG) IgG (one patient), antinuclear antibodies (two patients; one titer reported at 1:100), and anti-Ro antibodies (one patient).<sup>1,6,9,19,20</sup>

Four patients have been found to have TAR-DNA binding protein (TDP-43) inclusions on autopsy.<sup>4,12,20,21</sup> There are two cases with autopsy showing no inclusions.<sup>19</sup> TDP-43 inclusions have been found at various locations, but all have included the cervical spinal cord motor neurons. Genetic variants that have been found in FOSMN patients include: TARDBP (three patients), OPMD (one patient), D90A-SOD1 (one patient), CHCHD10 (one patient), VCP (one patient), and SQSTM1 (one patient).<sup>9,10,17,22,23</sup>

Sural nerve biopsy has revealed loss of myelinated fibers and Wallerian degeneration without inflammatory cell infiltrates, evidence of vasculitis, or amyloid deposition.<sup>1,10,24</sup> Skin biopsy has shown decreased intraepidermal nerve fiber density with severe myelinated fiber involvement but sparing of unmyelinated fibers.<sup>10,13,25</sup>

For treatment of patients with FOSMN, there are no FDA-approved therapies. However, clinicians have trialed IVIg and other immunomodulatory therapies. Knopp et al. presented a case of a patient with FOSMN and positive low titer ANA (1:100) and anti-Ro antibodies who had improvement in swallowing, speech, and lower extremity strength with IVIg.<sup>6</sup> Fluchere et al. described a case of FOSMN who had transient improvement in bulbar symptoms. However, her symptoms eventually deteriorated, and she died of aspiration pneumonia before being able to have a PEG placed.<sup>18</sup> Hokonohara et al. described a patient with FOSMN who received IVIg and had resultant improvement in paresthesias of his face and fingers, masticatory and tongue strength, swallowing, and increased SNAP amplitudes of the median and ulnar nerves. He had improvement for two weeks after treatment but worsened after this.<sup>16</sup> Sonoda et al. described a FOSMN case with anti-sulfoglucuronyl paragloboside (SGPG) IgG and anti-myelin-associated glycoprotein (MAG) IgG antibodies who received IVIg and had transient improvement in facial strength and paresthesias.<sup>20</sup> Cruccu et al. trialed IVIg on four patients with FOSMN and two had subjective improvement but no improvement in clinical or neurophysiological status.<sup>24</sup> Watanabe et al. reported three additional cases with partial improvement from IVIg, with all three cases having improvement in their sensory symptoms.<sup>26</sup>

## Discussion

### Clinical Presentation

FOSMN is a rare disorder that presents with initial sensory loss in the trigeminal nerve distribution that progresses rostro-caudally, along with weakness that progresses in a similar manner and involves the bulbar, neck and upper extremities. There is typically an absent corneal reflex and lower motor neuron findings on exam, however, upper motor neuron findings can be present as well. Taste can be affected and neuronal loss and reactive astrocytes with TDP-43 inclusions have been revealed in the solitary nucleus, potentially explaining this.<sup>1</sup> FOSMN can lead to severe dysphagia requiring PEG tube placement, and potentially lead to severe weight loss, aspiration pneumonia, and/or death.

### Pathogenesis

The pathogenesis of FOSMN is an area of debate with neurodegeneration and autoimmunity at the forefront of potential hypotheses. However, over the years, evidence continues to build towards a primary neurodegenerative process. Previous neuropathological studies by Vucic et al. have shown neurodegenerative changes without inflammation.<sup>19</sup> There have been few cases with response to immunomodulatory therapy, and these have not generally been sustained responses. The progressive disease course is also more typical of a neurodegenerative disorder. Furthermore, similarities between FOSMN and ALS patients have been described. Both conditions have a male predominance. Although FOSMN starts with sensory symptoms, motor symptoms become most prominent. Corneal confocal microscopy has interestingly revealed a corneal small fiber sensory neuropathy in ALS patients as well, and anatomical damage was related to bulbar function disability scores.<sup>7</sup> The progression of worsening dysphagia leading to PEG tube placement and death from aspiration pneumonia or respiratory failure can be a very similar progression between the disorders. Although upper motor neuron signs are rare, they can occur in FOSMN. Our patient had thenar atrophy, similar to the split hand sign seen in ALS. Cervical cord atrophy, frontotemporal atrophy, and the “bright tongue sign” are radiographic findings that can be seen in both FOSMN and ALS. CK can be normal to moderately elevated. Furthermore, at least five patients with FOSMN have been diagnosed with behavioral variant frontotemporal dementia and met Rascovsky criteria, suggesting that there may be a continuum with FTD.<sup>5,15</sup> TARDBP and SQSTM1 variants, which have been previously reported as causal in ALS and FTD and encode

Table 1: Characteristics of patients with FOSMN

	n (%)	n tested out of
Patients	<b>100</b>	
Male	<b>75 (75%)</b>	<b>100</b>
Mean age of onset (years)	<b>54.5</b>	
Onset with facial sensory symptoms	<b>83 (93%)</b>	<b>89</b>
Onset with loss of taste	<b>5</b>	
Bulbar symptoms	<b>97 (97%)</b>	<b>100</b>
Family history of ALS	<b>5</b>	
Patients diagnosed with bvFTD	<b>5</b>	
Upper motor neuron findings	<b>23</b>	
PEG placement	<b>17 (27%)</b>	<b>62</b>
Average time of symptom onset to PEG (years)	<b>2.3</b>	
Tracheostomy placement	<b>1</b>	
Time of symptom onset to tracheostomy (years)	<b>3</b>	
Patients with positive antibodies	<b>13</b>	
Patients with negative genetic testing for Kennedy's disease	<b>23</b>	
Neuroimaging findings		
Cervical cord atrophy	<b>8</b>	
Frontotemporal atrophy	<b>1</b>	
Bright tongue sign	<b>3</b>	
EMG/NCS		
R1 abnormality	<b>43 (77%)</b>	<b>56</b>
R2 abnormality	<b>56</b>	<b>57</b>
Bilateral R2 abnormality	<b>47 (82%)</b>	<b>57</b>
SNAPs reduced	<b>26</b>	
Neurogenic changes in bulbar or cervical muscles	<b>23</b>	
Patients trialed on IVIg	<b>42</b>	
Patients with partial or transient improvement from IVIg	<b>11 (26%)</b>	<b>42</b>
Causes of death		
Respiratory failure	<b>11</b>	
Bulbar weakness/ aspiration pneumonia	<b>7</b>	
Pulmonary embolus	<b>1</b>	
Lung cancer	<b>1</b>	
Sepsis	<b>1</b>	
Traumatic head injury	<b>1</b>	
Average symptom onset to death (years)	<b>7</b>	

The last column represents the total amount of cases where reports mentioned either a positive or negative finding (not all reports mentioned what we were evaluating). If there is not a value in the last column, this means the number in the middle column is the total number that was mentioned, and other reports did not mention a positive or negative finding.

for TDP-43 proteins, have been reported in one patient with FOSMN.<sup>17</sup> A D90A-SOD1 variant has been reported in FOSMN as well.<sup>10</sup> Four FOSMN patients have been found to have TDP-43 inclusions on autopsy and all involved the cervical spinal motor neurons.<sup>21</sup>

Despite evidence to suggest that FOSMN is a neurodegenerative disorder similar to ALS, there is further hesitancy to classify this disease within the ALS-FTD spectrum. TMS studies have not shown cortical hyperexcitability in FOSMN, as they have in ALS.<sup>9</sup> There are no Bunina bodies on neuropathological examination in patients with FOSMN, which are classically seen in ALS.<sup>19</sup> The blink reflex is almost always abnormal in FOSMN, whereas it is not typically abnormal in ALS.

### EMG/NCS

Almost all patients have an abnormal blink reflex. In previous studies that have mentioned the R2 value, almost all patients had a delayed or absent R2 response and a large proportion had bilateral R2 abnormalities. R1 abnormalities were found less frequently than R2 abnormalities, but still at a very high rate. This indicates that there may be an abnormality within the spinal trigeminal tract or nucleus in the medulla. Previous pathological studies have correlated with this as well and have found neuronal loss with reactive gliosis in the spinal trigeminal nucleus and tract.<sup>19</sup> Of note, this is near the solitary nucleus of the medulla, which as previously mentioned, may be involved in patients' loss of taste. This is also in line with nearby cervical cord atrophy findings that can be seen on MRI. Other common findings on EMG include decreased SNAPs and neurogenic changes in bulbar or cervical muscles. One of our patients had abnormal decrement on RNS, and this has been reported before.<sup>27</sup> This may be due to denervation and reinnervation changes, but further studies could be done to further elucidate these findings.

### Treatment

IVIg has been trialed as a treatment approach due to a potential inflammatory component to the disease. There are 11 reported cases with transient or partial response to IVIg. In these cases, at least five patients had some improvement in facial sensory symptoms. IVIg has generally not been shown to prevent progression of weakness or bulbar symptoms. Of note, autoimmune disorders, such as Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis and mixed connective tissue disease can be associated with bilateral trigeminal neuropathy and other cranial neuropathies.<sup>28,29</sup> As there are alternative, treatable conditions, it is crucial to rule these disorders out. Other differential diagnoses include Kennedy's disease, Tangier

disease, neurosarcoidosis, amyloidosis, syringomyelia, and Fabry's disease.

There are currently no FDA-approved treatments for FOSMN. Based on the current literature, it may be reasonable to have a discussion with the patient about trialing IVIg if the sensory symptoms are burdensome, but with the knowledge that it will not likely stop disease progression or alleviate bulbar, neck or upper extremity weakness. Since FOSMN appears to have some clinical and pathological similarities to ALS, use of medications known to slow ALS progression could also be trialed in FOSMN patients. As FOSMN patients share similar variants with ALS patients, similar treatments such as antisense oligonucleotide therapies could be targeted at these.

### Conclusion

FOSMN is a diagnosis that was first described in 2006 and at least 100 cases have since been reported. We have been able to identify patients with this disease clinically and through exam, but there are currently no standardized criteria for diagnosis. Further clarifying the pathogenesis, social risk factors, behavioral and cognitive changes, abnormalities in diagnostic tests, and associated genetic variations can help lead to better treatment targets and our ability to identify potential biomarkers to predict prognosis.

### Acknowledgements

The authors would like to express their gratitude to the patients who contributed to this study. There was no funding for this project.

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### Disclosures

Jonathan Morena, Hera Kamdar, Rabia Yasin, J. Chad Hoyle, Adam Quick, and Stephen Kolb report no conflicts of interest. There was no funding received for this work.

This work has been formally presented at the AANEM conference on September 22, 2022, in Nashville, TN.

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