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A nationwide survey of facial onset sensory and motor neuronopathy in Japan

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ABSTRACT

The epidemiology and etiology of facial onset sensory and motor neuronopathy (FOSMN), a rare syndrome that initiates with facial sensory disturbances followed by bulbar symptoms, remain unknown. To estimate the prevalence of FOSMN in Japan and establish the characteristics of this disease, we conducted a nationwide epidemiological survey. In the primary survey, we received answers from 604 facilities (49.8%), leading to an estimated number of 35.8 (95% confidential interval: 21.5–50.2) FOSMN cases in Japan. The secondary survey collected detailed clinical and laboratory data from 21 cases. Decreased or absent corneal and pharyngeal reflexes were present in over 85% of the cases. Electrophysiological analyses detected blink reflex test abnormalities in 94.1% of the examined cases. Immunotherapy was administered in 81% of cases and all patients received intravenous immunoglobulin. Among them, 35.3% were judged to have temporary beneficial effects evaluated by the physicians in charge. Immunotherapy tended to be effective in the early stage of disease. The spreading pattern of motor and sensory symptoms differed between cases and the characteristics of the motor-dominant and sensory-dominant cases were distinct. Cases with motor-dominant progression appeared to mimic amyotrophic lateral sclerosis. This is the first nationwide epidemiological survey of FOSMN in Japan. The clinical course of FOSMN is highly variable and motor-dominant cases developed a more severe condition than other types of cases. Because clinical interventions tend to be effective in the early phase of the disease, an early diagnosis is desirable.

1. Introduction

Facial onset sensory and motor neuronopathy (FOSMN) is a neurologic syndrome first proposed by Vucic et al. in 2006. They described FOSMN as a syndrome that starts with facial paresthesia and/or sensory

disturbances followed by muscle weakness such as bulbar symptoms. Sensory and motor manifestations spread to the scalp, neck, upper trunk, and upper extremities in a rostral-caudal direction [1]. Atypical cases where manifestations spread to the lower extremities or start from bulbar symptoms have also been reported [1–7]. FOSMN is a rare

Abbreviations: ALS, amyotrophic lateral sclerosis; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Functional Rating Scale; CI, confidence interval; CIDP, chronic inflammatory demyelinating polyneuropathy; CPR, consultation prevalence rate; CSF, cerebrospinal fluid; FOSMN, facial onset sensory and motor neuronopathy; MRI, magnetic resonance imaging; MUPs, motor unit potentials; NCS, nerve conduction study; nEMG, needle electromyography; SNAP, sensory nerve action potential.

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syndrome with only about 100 cases reported worldwide [8] and because of its rarity, the clinical features and pathology of FOSMN are still being discussed. Although several characteristic features, such as decreased or absent corneal reflexes and abnormalities in the blink reflex test, have been proposed to be diagnostic hallmarks of this syndrome [9], there is no consensus on the specific diagnostic criteria of FOSMN.

The first case of FOSMN in Japan was reported by our department in 2008 [10] and we also reported a case series of six Japanese patients with FOSMN in 2018 [11]. Several other case reports have also been reported [12–14]; however, there have been few reported cases of Asian FOSMN and the specific characteristics of FOSMN in Asian patients are unknown. A nationwide epidemiological survey in Japan has been not performed to date; thus, the prevalence of this syndrome in Japan remains unclear.

In this nationwide survey, we determined the prevalence and characteristics of FOSMN in Japan and identified its diagnostic hallmarks. We also revealed the presence of different clinical phenotypes, one of which may often be overlooked when diagnosing FOSMN. Our findings will aid the diagnosis and clinical follow-up of FOSMN in Japan and may identify more undiagnosed patients, especially in Asian countries, which will lead to further insights into this syndrome.

2. Material and methods

This nationwide survey was conducted by the Research Committee of FOSMN and was sponsored by the Ministry of Health, Labour and Welfare, Japan. This study was approved by Kyushu University Ethics Committee (#2022–6).

2.1. Definition of FOSMN

In this survey, FOSMN was defined using the following criteria.

- (1) A case starting with facial and/or intraoral sensory deficits followed by motor symptoms such as bulbar palsy.
- (2) A case starting with bulbar symptoms followed by facial sensory deficits.
- (3) Among (1) or (2), a case, in which symptoms could not be explained by any other diseases, such as amyotrophic lateral sclerosis (ALS), primary lateral sclerosis, spinal muscular atrophy, spinal and bulbar muscular atrophy, Tangier disease, syringomyelia, leprosy, amyloidosis, neurosarcoidosis, Fabry disease, chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barré syndrome, and neuropathy caused by Sjögren syndrome.

Table 1
Summary of primary survey.

Strata	Total number of departments	Sampling rate [%]	Number of departments		Response rate [%]	Number of patients		SE
			Surveyed	Responded		Reported	Estimated	
Special stratum ^a	804	100	804	449	55.9	23	41.2	8.4
University hospital ^b	5	100	5	4	80	0	0	0
≥500 beds	22	100	22	7	31.8	0	0	0
400–499 beds	64	80	51	17	33.3	0	0	0
300–399 beds	152	40	61	22	36.1	0	0	0
200–299 beds	184	20	37	15	40.5	0	0	0
100–199 beds	471	10	47	18	38.3	0	0	0
≤99 beds	3742	5	187	72	38.5	0	0	0
Total	5444	–	1214	604	49.8	23	41.2 ^c	8.4
							95%CI: 24.7–57.7 ^c	

Abbreviations: CI, confidence interval; SE, standard error.

^a Departments accredited by the Japanese Society of Neurology.

^b University hospitals that fulfill the criteria for special stratum ($n = 127$) were categorized in the special stratum.

^c After considering duplicated cases ($n = 2$) and one case who died before 2019, the estimated number of patients with FOSMN was 35.8 (95%CI: 21.5–50.2).

2.2. Study design

A two-stepped postal survey of FOSMN was performed from June 2020 to September 2021.

In the primary survey, to estimate the number of patients with FOSMN in Japan, a questionnaire asking about the number of FOSMN cases experienced in 2019 was sent to neurology departments extracted using the following criteria. Departments were randomly selected from all the neurology departments in Japan according to the number of hospital beds. Sampling rates were 5% for general hospitals with 99 or fewer beds, 10% for those with 100 to 199 beds, 20% for those with 200 to 299 beds, 40% for those with 300 to 399 beds, 80% for those with 400 to 499 beds, and 100% for those with 500 or more beds, with special stratum including departments accredited by the Japanese Society of Neurology and university hospitals (Table 1).

Using a questionnaire sheet, the secondary survey collected detailed clinical information on FOSMN cases reported in the primary survey. The items requested in this questionnaire sheet were as follows: sex, date of birth, onset date, first and last visit dates to the department, initial symptoms, clinical course, clinical signs and symptoms, laboratory findings, magnetic resonance imaging (MRI) findings of the brain and spinal cord, electrophysiologic findings (nerve conduction study (NCS), needle electromyography (nEMG), and blink reflex test), treatment and outcomes, and the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) at the first and the last visit. The actual data of electrophysiologic findings were requested as well. A flow chart of this survey is shown in Fig. 1.

2.3. Grouping for FOSMN

We divided the patients into three groups based on differences in the extension of sensory and motor symptoms: i) sensory disturbances extended wider than muscle weakness (sensory-dominant, $n = 8$); ii) sensory and motor symptoms extended to the same level (simultaneous, $n = 6$); and iii) motor symptoms extended wider than sensory disturbances (motor-dominant, $n = 6$), and then compared their characteristics. One case was excluded from this group because of severe cervical spondylosis.

2.4. Statistical analysis

2.4.1. Calculation of the estimated number of patients with FOSMN

The estimated number of patients was calculated according to “The National Epidemiological Survey Manual to Determine the Number of Patients with Intractable Diseases and Clinical Epidemiology” [15]. Briefly, the estimated number of FOSMN patients (= reported number of patients/(sampling rate × response rate)) in each stratum was

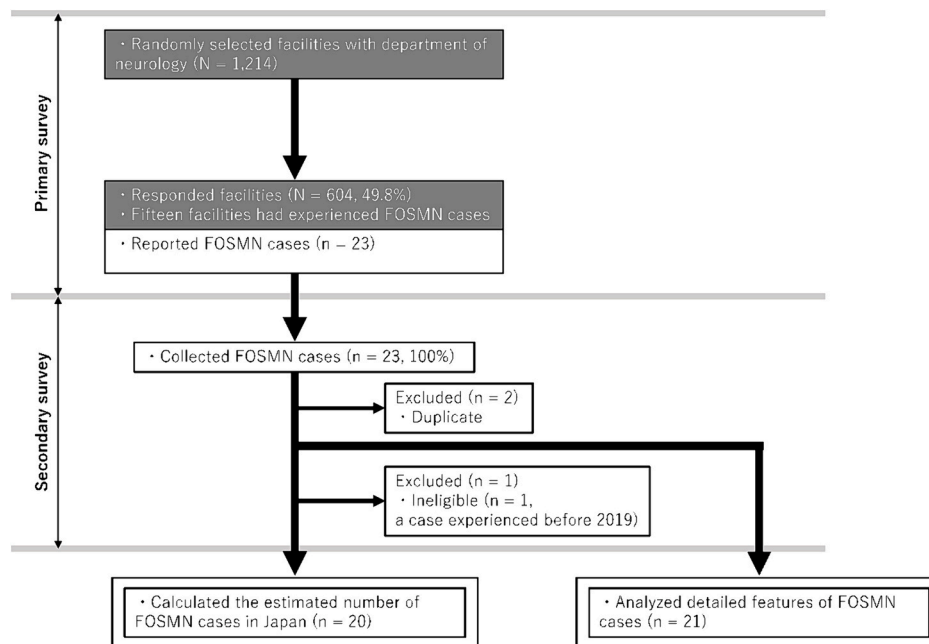


Fig. 1. Flow chart of the survey.

A two-stepped postal survey was performed. In the primary survey, a questionnaire asking about the number of FOSMN cases experienced in 2019 was sent to randomly selected facilities with a department of neurology. In the secondary survey, a questionnaire sheet asking for detailed clinical information on each FOSMN case was sent to the department that experienced the cases. The calculation to estimate the number of FOSMN cases was performed after excluding duplicated or ineligible cases. One case was excluded from the calculation because the patient died before 2019. However, this case also met the definition of FOSMN and was used in the analysis of the characteristics of FOSMN.

FOSMN, facial onset sensory and motor neuronopathy.

calculated. Then, the calculated number in each stratum was totaled to estimate the number of FOSMN patients in Japan. Because there were few reported cases and the response rate of the secondary survey was 100%, the estimated number was revised by the duplication and exclusion rate.

The estimated number of patients with FOSMN per 100,000 population (consultation prevalence rate, CPR) in Japan was calculated using the following formula: estimated CPR = (the estimated number of patients / the total population of Japan in 2019 (126,167,000 [16])) × 100,000.

2.4.2. The clinical features of patients with FOSMN

For the clinical characterization of FOSMN patients in Japan, all cases which fulfilled the diagnostic criteria were included, even if the cases were not experienced in 2019.

Descriptive analysis was performed according to the data from the questionnaire sheet. To determine whether the abnormalities were present throughout their entire disease course, all the data of NCS and nEMG were included if there were several data sources for one patient. Differences between the two groups were tested for significance using the Student's *t*-test for continuous variables and Fisher's exact probability test for categorical variables. The correlation coefficient between cerebrospinal fluid (CSF) protein and disease duration or age at the time of CSF analysis was estimated using Spearman's correlation test.

For the analysis of blink reflex test data, the earliest data of the blink reflex test were used to assess the diagnostic feasibility. Because blink reflex test result data were obtained by side and affected sides were not always limited to one side, data from both sides of each patient were included in the statistical analyses as independent data. To calculate the mean latency of each component, non-evoked components were omitted. The Student's *t*-test was used for comparisons between two groups.

For the comparison of numeric parameters such as disease duration or age at onset between more than two subgroups, the Kruskal-Wallis H-

test was performed. When a significant difference was found, the Mann-Whitney *U* test was used to further assess the difference between subgroups. All statistical analyses were performed with R (version 4.1.3, The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. The estimated number of patients with FOSMN in Japan

The primary survey was sent to 1214 Neurology Departments (Table 1). Among the departments surveyed, 604 responded (response rate: 49.8%), and 23 cases with FOSMN were reported. All cases were reported from departments in the special stratum. In the secondary survey, we collected detailed information on all the cases reported in the primary survey (response rate: 100%). The crude estimation of FOSMN patients in Japan was 41.2 [95% confidence interval (CI) 24.7–57.7]. Finally, considering duplicated cases ($n = 2$) and one case who died before 2019 (Fig. 1), the estimated number of patients with FOSMN in 2019 was calculated as 35.8 cases (95% CI: 21.5–50.2). The estimated CPR was 0.028 cases per 100,000 population.

3.2. Characteristics of FOSMN cases in Japan

3.2.1. Demographic features and clinical findings

The demographic features and clinical findings are summarized in Table 2. The mean age at onset was 56.8 ± 13.0 years (range: 41–83 years old), with a disease duration of 111.1 ± 66.4 months (range: 38–323 months). The female-to-male ratio was 1:2 (7:14). All cases presented with a chronic progressive disease course. Four patients had died by September 2021. Of these, one patient died of aspiration pneumonia and CO₂ narcosis, and one patient died of suffocation from aspiration. The cause of death for the remaining two patients was not reported.

The symptoms started with facial or intraoral paresthesia in 16 cases

Table 2
Summary of demographic features and clinical findings of 21 patients with FOSMN.

<i>Demographics</i>	
Sex ratio [F:M]	7:14
Age at onset [years, mean ± SD]	56.8 ± 13.0
Disease duration [months, mean ± SD]	111.1 ± 66.4
Follow-up period [months, mean ± SD]	42.5 ± 39.6
<i>Clinical course</i>	
Monophasic (%)	0/21 (0.0)
Polyphasic (%)	0/21 (0.0)
Chronic progressive (%)	21/21 (100.0)
<i>Initial symptoms</i>	
Facial paresthesia^a (%)	16/21 (76.2)
Bulbar symptoms (%)	3/21 (14.3)
Facial and bulbar (%)	2/21 (9.5)
Asymmetric (%)	12/20 (60.0)
Death rate (%)	4/21 (19.0)
<i>Cause of death</i>	
Aspiration pneumonia/respiratory failure (%)	2/4 (50.0)
Unknown (%)	2/4 (50.0)
<i>Cranial nerve signs</i>	
Dysosmia (%)	0/21 (0.0)
Abnormal fundus oculi (%)	1/18 (5.6)
Disorder of eye movement (%)	1/21 (4.8)
Ptosis (%)	2/21 (9.5)
Facial sensory disorder (%)	21/21 (100.0)
Decreased/absent corneal reflex (%)	16/18 (88.9)
Facial muscle weakness (%)	17/21 (81.0)
Dysgeusia (%)	11/20 (55.0)
Dysacusia (%)	5/20 (25.0)
Poor elevation of soft palate (%)	8/21 (38.1)
Decreased/absent pharyngeal reflex (%)	18/21 (85.7)
Tongue atrophy (%)	12/21 (57.1)
Poor tongue movement (%)	16/21 (76.2)
Dysarthria (%)	16/21 (76.2)
Dysphagia (%)	20/21 (95.2)
Oral phase (%)	7/13 (53.8)
Pharyngeal phase (%)	2/13 (15.4)
Oral and pharyngeal phases (%)	4/13 (30.8)
Gastrotomy (%)	7/21 (33.3)
Sternocleidomastoid muscle atrophy (%)	14/20 (70.0)
<i>Neurologic signs besides cranial nerve region</i>	
Muscle weakness (%)	17/21 (81.0)^b
Upper extremities (%)	16/21 (76.2)
Lower extremities (%)	10/21 (47.6)
Proximal dominant (%)	10/17 (58.8)
Distal dominant (%)	2/17 (11.8)
Diffuse (%)	5/17 (29.4)
Muscle atrophy (%)	13/21 (61.9)
Upper extremities (%)	11/19 (57.9)
Lower extremities (%)	5/19 (26.3)
Proximal dominant (%)	5/13 (38.5)
Distal dominant (%)	3/13 (23.1)
Diffuse (%)	5/13 (38.5)
Gait disturbance (%)	8/21 (38.1)
Sensory disorder (%)	15/20 (75.0)^c
Upper extremities (%)	15/20 (75.0)
Lower extremities (%)	12/20 (60.0)
Touch sense disorder (%)	11/21 (52.4)
Pain/Temperature sense disorder (%)	11/20 (55.0)
Vibration sense disorder (%)	10/21 (47.6)
Dysesthesia (%)	14/20 (70.0)
Increased tendon reflex (%)	8/20 (40.0) ^c
Pathologic reflex (%)	2/21 (9.5)
Decreased tendon reflex (%)	9/21 (42.9)
Tremor (%)	3/21 (14.3)
Ataxia (%)	2/20 (10.0)
Cerebellar (%)	1/2 (50.0)
Vestibular (%)	1/2 (50.0)
Dysautonomia (%)	3/21 (14.3)
Respiration disorder (%)	4/21 (19.0)
Use of ventilator (%)	2/21 (9.5)

Findings present in over 75% of cases are shown in bold.
Abbreviations: FOSMN, facial onset sensory and motor neuronopathy; SD, standard deviation.

^a Including intraoral paresthesia.
^b One patient only had neck weakness.

^c One patient with cervical spondylosis was excluded.

(76.2%), bulbar symptoms in 3 cases (14.3%), and facial paresthesia and bulbar symptoms within one month in 2 cases (9.5%). Initial symptoms were asymmetric in 60% of the cases. All patients developed facial paresthesia over their disease course, and at least 10 cases had intraoral sensory deficits. Dysphagia was present in 95.2% of cases and dysarthria in 76.2%. Regarding the type of dysphagia, oral phase dysfunction was seen in 11 of 13 cases (84.6%) and pharyngeal phase dysfunction was seen in 6 of 13 cases (46.2%). Decreased or absent corneal reflex, facial muscle weakness, decreased or absent pharyngeal reflex, and tongue movement disorder were present in over 75% of cases. More than half of the cases had a taste disorder and sternocleidomastoid muscle atrophy. Muscle weakness and sensory deficits were extended to the upper extremities in 76.2% and 75.0% of cases, and the lower extremities in 47.6% and 60.0% cases, respectively. Both symptoms seemed to extend from the face to the lower extremities in a rostral-caudal direction (Fig. 2).

Upper motor neuron signs, such as increased tendon reflex and pathologic reflex, were detected in 40.0% of cases. Eight cases met the Awaji criteria (6 cases for possible ALS and 2 cases for probable ALS), although no cases were defined as definite ALS.

3.2.2. Laboratory findings

No remarkable findings were reported in blood tests. Autoantibodies were detected in some cases, but the results were not consistent. The antibodies detected are shown in Table 3.

CSF tests also showed no remarkable abnormalities, although there was a slight increase in CSF protein in the early stage of the disease course (Fig. 3).

3.2.3. Neuroradiology findings

All patients underwent a brain MRI and no abnormalities in the brainstem were reported. Spinal cord MRI was performed in 20 cases: 19 cases at the cervical cord, 9 at the thoracic cord, and 8 at the lumbar cord. A cervical cord lesion related to spondylosis was detected in one patient.

3.2.4. Electrophysiologic findings

An NCS was performed for all cases, and 16 cases (76.2%) had abnormalities. Eleven cases were concluded to have axonopathy and no cases had demyelination. More detailed information on the NCS results was obtained for 15 cases. Of these, a low sensory nerve action potential (SNAP) amplitude was most common (10 cases with median and/or ulnar nerve and 4 cases with sural nerve), followed by a decrease in F-wave frequency (all cases with upper limbs, but no cases with lower limbs) (Fig. 4).

Among 20 cases that underwent nEMG, abnormalities were detected in 80% of cases, and all had neurogenic changes. More detailed information on the nEMG of 18 cases is shown in Table 4. Regarding spontaneous activity, the fasciculation potential was detected in at least five cases and positive sharp wave and fibrillation potential were detected at the same rate. Most abnormal motor unit potentials (MUPs) detected were polyphasic MUPs and/or giant MUPs, and low amplitude MUPs were rare. Neurogenic changes were spread widely from the cranial nerve to the lumbar spinal cord regions (cranial nerve region 64.3%, cervical cord region 80.0%, thoracic cord region 87.5%, lumbar cord region 64.3% among those examined).

Eighteen cases underwent the blink reflex test and the detailed data of 17 cases were obtained. All cases except one had abnormalities over their disease course (Table 3).

Around one-third of each component was not evoked at their initial examination (Fig. 5A). The median latency of each component calculated was delayed, especially in R2 (Fig. 5B). This trend was also seen in the group with facial sensory disorder onset. However, the blink reflex

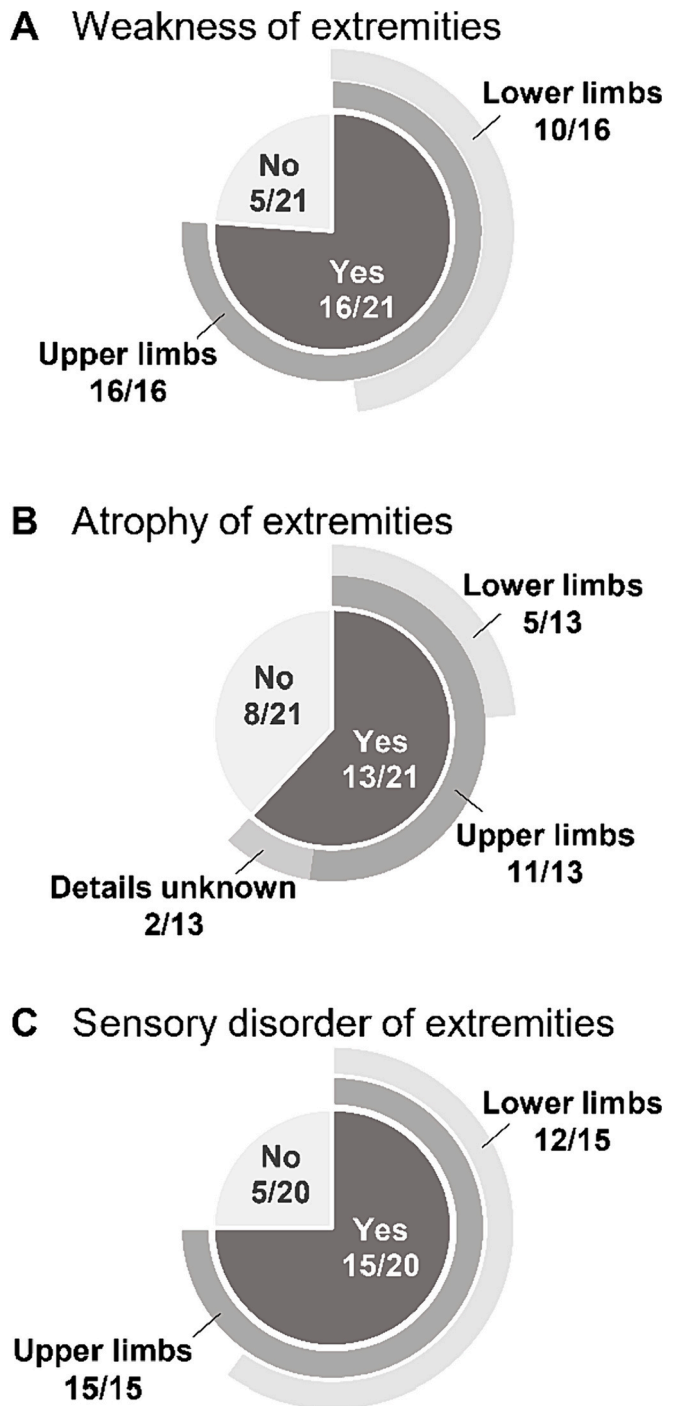


Fig. 2. Spread of motor and sensory symptoms of the extremities in patients with FOSMN. The pie chart shows the distribution of (A) weakness, (B) atrophy, and (C) sensory disorder in the extremities. The center layer represents the presence of each symptom in the extremities. The middle layer represents the number of patients with each symptom in the upper limbs. The outer layer represents that of the lower limbs. No patient had symptoms restricted to the lower limbs and not the upper limbs.

test of patients with bulbar palsy onset was within the normal limits at initial examination (Fig. 5C). One case that started with bulbar palsy did not display an absence or delay of latency, even 5 years after the onset. However, the blink reflex test of this patient indicated an obvious reduction in the amplitude.

Table 3		
Laboratory and electrophysiologic findings of 21 patients with FOSMN.		
Blood test		
HbA1c (NGSP) $\geq 6.5\%$ (%)	0/20 (0.0)	
M-protein (%)	1/15 (6.7)	
ANA (%)	3/20 (15.0)	
Anti-SS-A/SS-B antibody (%)	0/20 (0.0)	
Anti-ganglioside (%)	0/12 (0.0)	
Other antibodies (number of cases)		
Anti-TG, Anti-TPO	2	
Anti-Cardiolipin	1	
Anti-GAD	1	
Anti-Zic4	1	
Anti-PlexinD1	1	
CSF		
Pleocytosis (%)	0/18 (0.0)	
Increased protein (%)	5/18 (27.8)	
Electrophysiologic study		
NCS abnormalities (%)	16/21 (76.2)	
Axonopathy (%)	11/16 (68.8)	
Demyelination (%)	0/16 (0.0)	
Other ^a (%)	5/16 (31.3)	
Blink reflex abnormalities (%)	16/17 (94.1)	
nEMG abnormalities (%)	16/20 (80.0)	
Neurogenic (%)	16/16 (100.0)	
Myogenic (%)	0/16 (0.0)	

Abbreviations: FOSMN, facial onset sensory and motor neuropathy; NGSP, National Glycohemoglobin Standardization Program; ANA, anti-nuclear antibody; SS-A, Sjogren syndrome-antigen A; SS-B, Sjogren syndrome-antigen B; TG, thyroglobulin; TPO, thyroid peroxidase; GAD, glutamic acid decarboxylase; CSF, cerebrospinal fluid; NCS, nerve conduction study; nEMG, needle electromyography.

^a One case with carpal tunnel syndrome, 1 case with cubital tunnel syndrome, and 3 cases only with F-wave abnormalities.

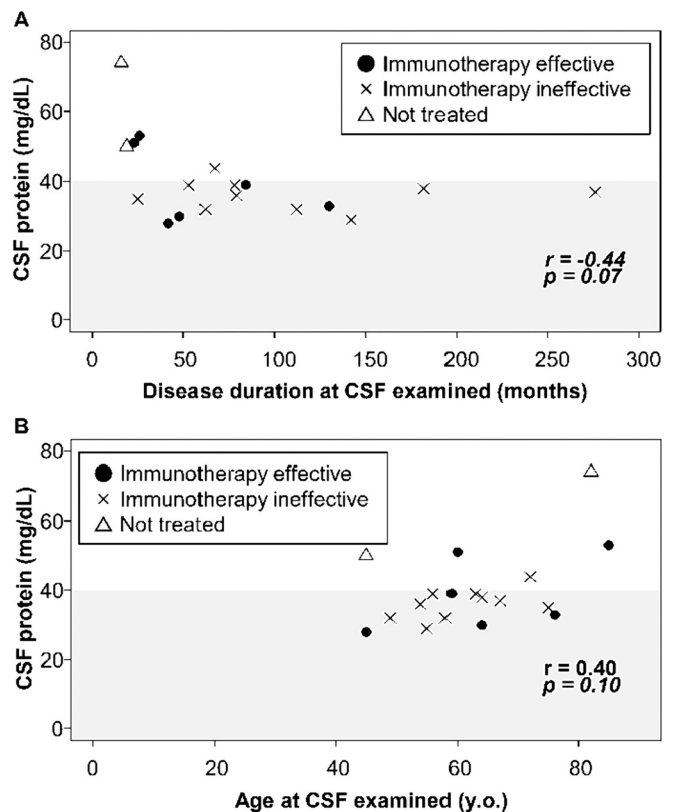


Fig. 3. Distribution of CSF protein levels in patients with FOSMN. (A) Scatterplot of CSF protein levels and disease duration at the time of CSF analysis. (B) Scatterplot of CSF protein levels and age at the time of CSF analysis. The gray area shows CSF protein levels within the normal limits. CSF, cerebrospinal fluid.

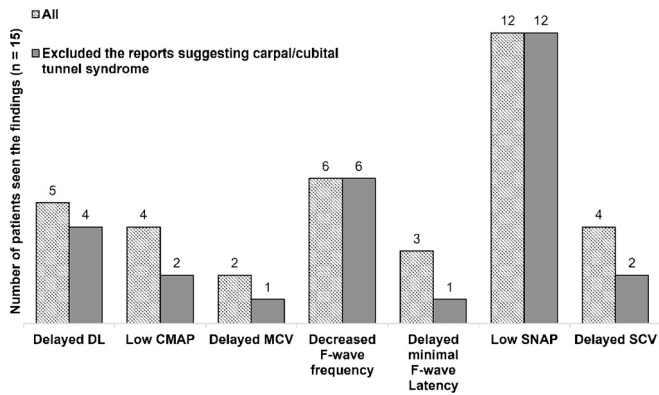


Fig. 4. Details of NCS abnormalities in patients with FOSMN. The number of cases that presented with abnormalities is shown (the number is indicated at the top of each bar). Abbreviations: DL, distal latency; CMAP, compound motor action potential; MCV, motor nerve conduction velocity; SNAP, sensory nerve action potential; SCV, sensory nerve conduction velocity

Table 4
Details of nEMG findings of 18 patients with FOSMN.

Detailed findings	
On-going changes (%)	9/17 (52.9)
Fasciculation potential (%)	5/14 (35.7)
PSW (%)	6/14 (42.9)
Fibrillation potential (%)	5/14 (35.7)
Chronic changes (%)	13/17 (76.5)
Polyphasic MUP (%)	8/14 (57.1)
Giant MUP (%)	9/14 (64.3)
Other findings	
Low amplitude MUP (%)	1/14 (7.1)
Myotonic discharge (%)	2/14 (14.3)
CRD (%)	1/14 (7.1)
Location	
Cranial (%)	9/14 (64.3)
Cervical (%)	12/15 (80.0)
Thoracic (%)	7/8 (87.5)
Lumbar (%)	9/14 (64.3)

Abbreviations: nEMG, needle electromyography; FOSMN, facial onset sensory and motor neuropathy; PSW, positive sharp wave; MUP, motor unit potential; CRD, complex repetitive discharges.

3.2.5. Treatment and outcomes

Immunotherapy was administered to 17 cases. All cases were treated with intravenous immunoglobulin at least once and six cases showed a positive effect. Intravenous methylprednisolone was effective in two of six cases, and an oral corticosteroid was effective in one of two cases. Only one patient received plasma exchange, which was not effective (Table 5).

Among the six immunotherapy-effective cases, complete information was obtained from two cases. In these two cases, sensory and motor symptoms were alleviated, although the effects were temporary, lasting only a few months. The positive effects included subjective improvements such as the alleviation of facial numbness, as well as objective improvements such as the reappearance of the corneal reflex and amelioration of the blink reflex test. The treatment effect seemed to be localized to cranial nerve lesions (Table 6).

There was no statistical difference in the immunotherapy efficacy status except for the presence of dysautonomia (Supplementary Table 1). Fifty percent of the immunotherapy-effective patients had dysautonomia whereas no patients had dysautonomia in the immunotherapy-ineffective group. Although the detailed symptom of dysautonomia was mild pollakiuria in two of three cases, it was not clear whether this symptom was related to FOSMN.

In the immunotherapy-effective group, serum autoantibodies were

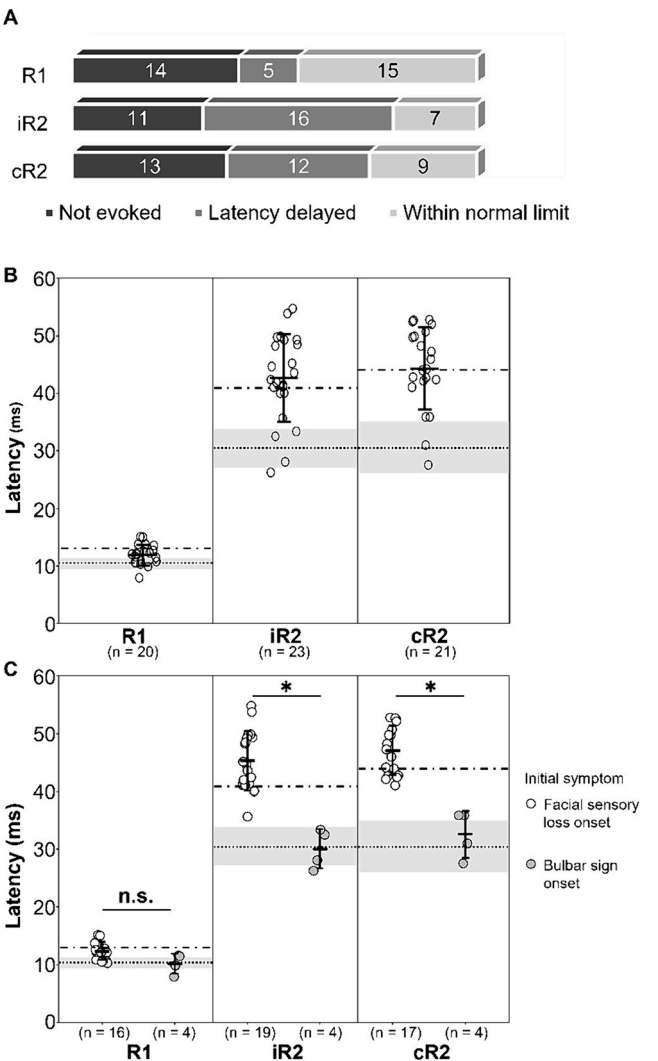


Fig. 5. Details of the blink reflex test results at initial examination in patients with FOSMN. (A) Classification of latency in each component ($n = 34$). Cases in each group are indicated on the bar graph. (B) Scatter plot of latency in each component (non-evoked cases were excluded). (C) Scatter plot of latency in each component compared between those with different initial symptoms. Mean and standard deviations are shown as solid lines. Dotted lines and gray areas represent the normal mean latency and standard deviation. Dashed lines represent the normal upper limits. n.s. = not significant. $*p < 0.05$.

Table 5
Treatment status and its response in 21 patients with FOSMN.

Treatment	Received	Effective	Efficacy rate (%)
Overall	17	6	35.3
IVMP	6	2	33.3
OCS	2	1	50.0
IVIg	17	6	35.3
PE	1	0	0.0

FOSMN, facial onset sensory and motor neuropathy; IVMP, intravenous methylprednisolone; OCS, oral corticosteroid; IVIg, intravenous immunoglobulin; PE, plasma exchange.

positive in four of six cases (Table 6). Two of four cases in which the CSF protein level was >50 mg/dL responded to the immunotherapy. The remaining two cases were not treated (Fig. 3).

Immunotherapy-effective cases tended to visit the hospital more quickly than the immunotherapy-ineffective cases (Supplementary

Table 6
Detailed information of 6 FOSMN patients with treatment efficacy.

Age at onset (years)	Sex	Treatment type	Number of IVIg tried	Effect	Details of effect	Antibodies	Group
41	M	IVIg OCS IVMP PE	1	Effective Effective Effective Ineffective	Only temporary effect Only temporary effect Only temporary effect –	Anti-GAD Anti-Zic4	Simultaneous
52	F	IVIg IVMP	No information	Effective ineffective	No information –	Not detected	Motor-dominant
58	M	IVIg IVMP	2 to 5	Effective Effective	No information No information Alleviation of facial numbness Recovery of corneal reflex and pharyngeal reflex, Improvement of dysarthria and dysgeusia Improvement on blink reflex test Effect lasted 1–2 months (Effective period gradually reduced)	Not detected	Simultaneous Sensory- dominant
60	M	IVIg	over 6	Effective		Anti- Cardiolipin	
65	F	IVIg	2 to 5	Effective	No information Alleviation of facial numbness Improvement of dysarthria and dysphagia Improvement on blink reflex test Effect lasted 1–5 months	ANA 40× ANA 1280× Anti-TG Anti-TPO	Sensory- dominant Unclassifiable
83	F	IVIg	2 to 5	Effective			

FOSMN, facial onset sensory and motor neuronopathy; IVIg, intravenous immunoglobulin; OCS, oral corticosteroid; IVMP, intravenous methylprednisolone; PE, plasma exchange; GAD, glutamic acid decarboxylase; ANA, anti-nuclear antibody; TG, thyroglobulin; TPO, thyroid peroxidase.

Table 1). Of the five patients seen at our department, the initiation of treatment was earlier in the immunotherapy-effective group compared with the immunotherapy-ineffective group (two effective cases vs. three ineffective cases; 39.5 ± 13.4 months vs. 133.7 ± 54.0 months).

3.2.6. Comparison between the sensory-dominant, simultaneous, and motor-dominant groups

The spread of sensory and motor symptoms presented with different

descending patterns in our 21 cases. Patients whose sensory disturbance extended to their lower limbs had a longer disease duration than those with a sensory disturbance localized to the face ($p = 0.00937$, Fig. 6) or extended down to the upper limbs ($p = 0.0703$, Fig. 6), suggesting that sensory disturbances seemed to extend as the disease progressed. However, the extension of muscle weakness was not related to disease duration. Instead, cases in which the motor symptoms extended to their lower extremities had a relatively short disease duration (Fig. 6). This

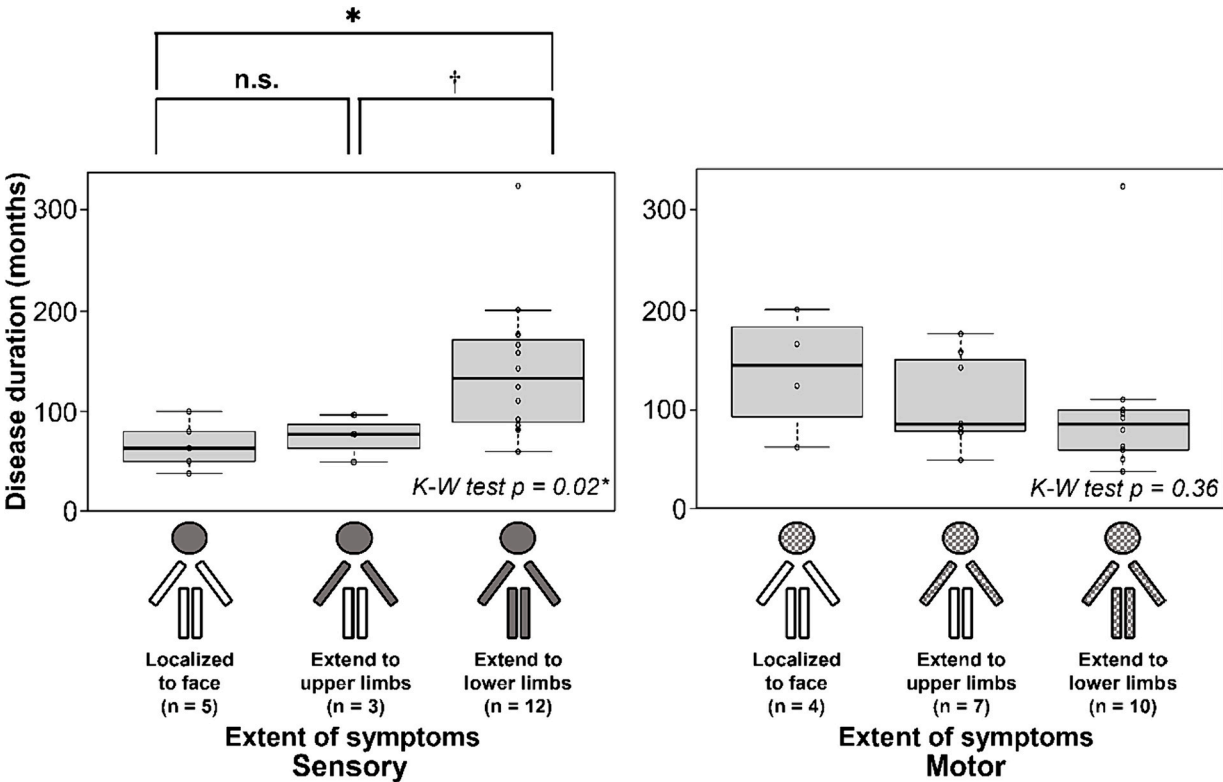


Fig. 6. Relationship between disease duration and extension of symptoms in patients with FOSMN. The boxplots show the disease duration of patients with FOSMN demonstrating distinct extension patterns of sensory or motor symptoms. For the stick figures, the black colored area represents the region to which the sensory symptoms extended and the dotted area represents the region to which the motor symptoms extended. Abbreviations: n.s. = not significant, K-W test = Kruskal-Wallis test. * $p < 0.05$, † $p < 0.1$.

tendency led to a hypothesis that FOSMN can be classified by the descending rate of motor deficits. Thus, we divided our cases into three groups as mentioned in the Methods. The motor-dominant group had worse gait disturbance, higher frequency of receiving gastrostomy, and lower ALSFRS-R than the sensory-dominant group (Table 7). Only patients in the motor-dominant group required ventilation support. Surprisingly, the disease duration until the latest visit of the motor-dominant group was approximately half that of the sensory-dominant group ($p = 0.00799$, Fig. 7 and Table 7). These findings suggest that the motor-dominant group developed severe conditions more rapidly than the sensory-dominant group. Additionally, the motor-dominant group also had a higher proportion of patients with upper motor neuron signs and those who met the Awaji criteria than the sensory-dominant group (Table 7). Although patients in the motor-dominant group shared features similar to ALS, they still had the characteristic features of FOSMN, including evident facial sensory disturbances, decreased or absent corneal and pharyngeal reflexes, and abnormalities in the blink reflex test. In addition, the initial symptoms of all patients in the motor-dominant group were not bulbar symptoms but facial sensory disturbances. Patients in the simultaneous group expressed intermediate characteristics of the sensory and motor dominant groups. Laboratory findings, electrophysiologic findings, and treatment profiles were comparable between the groups (Table 7).

4. Discussion

This is the first nationwide survey of FOSMN in Japan. Apart from the essential symptoms used to enroll patients with FOSMN, decreased or absent corneal and pharyngeal reflexes were observed in over 85% of the cases. Previous studies reported a deficit of the corneal reflex was the main pathognomonic feature of FOSMN [9,17]. Our study confirmed that decreased or absent pharyngeal reflex was another key feature. Another characteristic symptom of FOSMN might be the type of dysphagia observed. In our study, oral-phase dysphagia was more common than pharyngeal-phase dysphagia. We reported the same tendency in a previous report, and we assumed it was related to the early appearance of intraoral sensory deficits during the disease course [11]. Indeed, among six cases reported to have an intraoral sensory deficit with data describing the type of dysphagia, five cases had oral phase dysfunction in this survey.

Abnormalities in the blink reflex test were reported to be distinctive findings in FOSMN [2,5,7,9]. In the present study, the absence or slight delay of each component, especially the R2 component, in the blink reflex test was found in almost all cases. These abnormalities were detected in the early stages of disease in those with the facial sensory onset type, which is the most common type of FOSMN. The same abnormalities were also detected in late-stage ALS patients who cannot blink easily [18]. Abnormalities in the blink reflex test were also reported in CIDP, although an obvious delay in the latency of each component was often seen [19,20]. Thus, FOSMN can easily be distinguished from ALS and CIDP by the blink reflex test, which might be a useful tool for the diagnosis of FOSMN.

To date, neurodegenerative pathology is the most convincing mechanism for FOSMN. Several autopsy cases revealed neurodegenerative changes and, in some cases, intraneuronal TDP-43 inclusions were detected [2,6,12,21]. Additionally, genetic mutations related to ALS were also reported in FOSMN cases [5,8,17], suggesting a similar pathomechanism with ALS. All cases in our study had a chronic progressive disease course, which also supports the involvement of a neurodegenerative mechanism. However, not all the autopsied cases were positive for TDP-43 inclusions, suggesting the disease process is heterogeneous [22].

Several facts support the involvement of autoimmune mechanisms in FOSMN, including being positive for autoantibodies [1,12] and the beneficial effect of immunotherapy [7,10,12,14]. In our study, there was a trend for immunotherapy-effective patients to be positive for

Table 7
Characteristics of FOSMN patients with distinct dominant types.

	Dominant type		
	Sensory (n = 8)	Simultaneous (n = 6)	Motor (n = 6)
Demographics			
Sex ratio [F:M]	2:6	1:5	3:3
Age at onset [years, mean $\pm$ SD]	52.1 $\pm$ 8.1	55.7 $\pm$ 14.0	59.8 $\pm$ 14.4
Disease duration [months, mean $\pm$ SD]	141.8 $\pm$ 42.5*	118.5 $\pm$ 102.5	71.2 $\pm$ 25.1*
Disease duration until first visit [months, mean $\pm$ SD]	93.4 $\pm$ 54.9	62.7 $\pm$ 72.7	42.5 $\pm$ 27.9
Initial symptoms			
Facial/Intraoral paresthesia (%)	6/8 (75.0)	4/6 (66.7)	5/6 (83.3)
Bulbar symptoms (%)	2/8 (25.0)	1/6 (16.7)	0/6 (0.0)
Both (%)	0/8 (0.0)	1/6 (16.7)	1/6 (16.7)
Death rate (%)	3/8 (37.5)	0/6 (0.0)	1/6 (16.7)
Latest ALSFRS-R [points, mean $\pm$ SD]	41.3 $\pm$ 6.4	32.7 $\pm$ 10.6	30.6 $\pm$ 11.1
Neurologic signs			
Decreased corneal reflex (%)	7/7 (100.0)	3/5 (60.0)	5/5 (100.0)
Facial sensory disorder (%)	8/8 (100.0)	6/6 (100.0)	6/6 (100.0)
Facial muscle weakness (%)	6/8 (75.0)	4/6 (66.7)	6/6 (100.0)
Dysgeusia (%)	6/8 (75.0)	3/6 (50.0)	2/5 (40.0)
Decreased pharyngeal reflex (%)	8/8 (100.0)	4/6 (66.7)	5/6 (83.3)
Tongue atrophy (%)	4/8 (50.0)	3/6 (50.0)	5/6 (83.3)
Poor tongue movement (%)	7/8 (87.5)	3/6 (50.0)	5/6 (83.3)
Dysarthria (%)	5/8 (62.5)	4/6 (66.7)	6/6 (100.0)
Dysphagia (%)	8/8 (100.0)	5/6 (83.3)	6/6 (100.0)
Have oral phase dysfunction (%)	5/5 (100.0)	2/3 (66.7)	3/4 (75.0)
Have pharyngeal phase dysfunction (%)	1/5 (20.0)	1/3 (33.3)	4/4 (100.0)
Gastrostoma (%)	1/8 (12.5)	2/6 (33.3)	4/6 (66.7)
Sternocleidomastoid muscle atrophy (%)	4/8 (50.0)	5/6 (83.3)	5/5 (100.0)
Gait disturbance (%)	1/8 (12.5)	3/6 (50.0)	4/6 (66.7)
Upper motor neuron sign (%)	1/8 (12.5)	3/6 (50.0)	4/6 (66.7)
Decreased tendon reflex (%)	5/8 (62.5)	3/6 (50.0)	1/6 (16.7)
Respiration disorder (%)	1/8 (12.5)	1/6 (16.7)	2/6 (33.3)
Use of ventilator (%)	0/8 (0.0)	0/6 (0.0)	2/6 (33.3)
Meeting for Awaji criteria ^a (%)	1/8 (12.5)	3/6 (50.0)	4/6 (66.7)
Laboratory findings			
Blood antibody (%)	3/8 (37.5)	2/6 (33.3)	0/6 (0.0)
Increased CSF protein (%)	0/7 (0.0)	2/4 (50.0)	2/6 (33.3)
NCS axonal changes (%)	6/8 (75.0)	4/6 (66.7)	1/6 (16.7)
Blink reflex abnormalities (%)	6/6 (100.0)	4/5 (80.0)	5/5 (100.0)
nEMG abnormalities (%)	5/7 (71.4)	6/6 (100.0)	5/6 (83.3)
Treatment response			
	2/7 (28.6)	2/5 (40.0)	1/4 (25.0)

Abbreviations: FOSMN, facial onset sensory and motor neuronopathy; SD, standard deviation; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis

Functional Rating Scale; CSF, cerebrospinal fluid; NCS, nerve conduction study; nEMG, needle electromyography.

^a Case meets “possible” or “probable” Awaji criteria. No case was defined as “definite”. * $p < 0.05$.

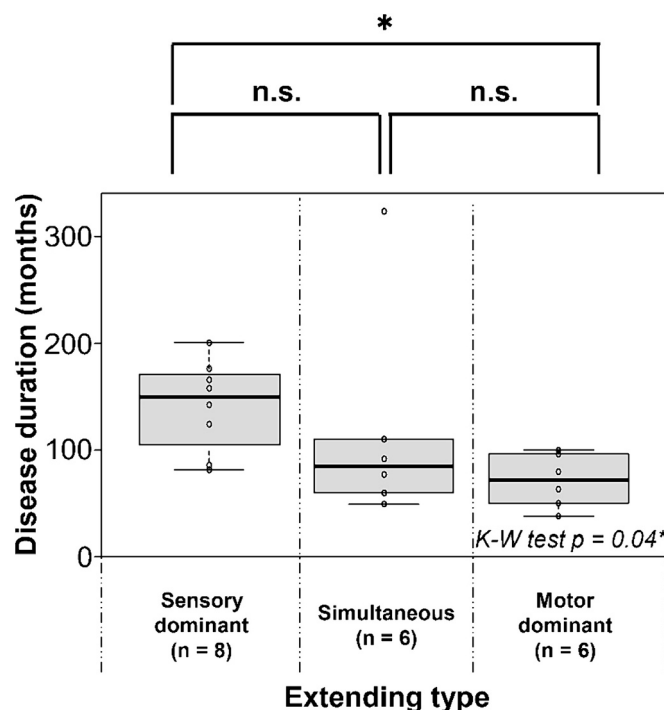


Fig. 7. Comparison of disease duration in patients with FOSMN with distinct dominant symptoms.

Boxplots of disease duration in the sensory-dominant, simultaneous, and motor-dominant groups are shown. Abbreviations: n.s. = not significant, K-W test = Kruskal-Wallis test. * $p < 0.05$.

autoantibodies. Half of the patients who had CSF protein levels increased by >50 mg/dL had a good response to immunotherapy suggesting the involvement of underlying autoimmune mechanisms.

The timing of immunotherapy may also be important. In our study, immunotherapy-effective patients tended to visit the hospital in the early stage of disease, and earlier than the immunotherapy-ineffective patients. Indeed, in our department, immunotherapy was started earlier in the immunotherapy-effective group. The slight elevation of CSF protein in the early stage of disease suggests the involvement of autoimmune mechanisms in the early stage of FOSMN. Thus, at least in some cases, an autoimmune mechanism is assumed to be involved at disease onset. There exists a limitation in that treatment response was judged and reported by the physicians in charge and not by a single criterion due to study design. Whether the autoimmune mechanisms are related to FOSMN requires further investigation.

In our study, cases with affected lower extremities were more frequent than previously reported. Boer et al. reported the frequencies of sensory and motor deficits with affected lower extremities were 11.0% and 23.0%, respectively [8], whereas in our study they were 60.0% and 47.6%. One reason for this difference is that one-third of our cases were atypical, as characterized by the rapid spread of motor symptoms. A FOSMN case with relatively rapid motor spreading was first described in 2011 [23]—symptoms started with right V1 and V2 paresthesia and motor deficits extended to the upper limbs within 6 months. nEMG demonstrated lower motor neuron lesions from bulbar to lumbar levels. Although the patient had low SNAP amplitude in the upper limbs, his sensory symptoms were restricted to the face until he died unexpectedly 7 months after the onset of disease. Upper motor neuron signs were also

detected [23]. The motor-dominant group in our study had a higher proportion of cases with upper motor neuron signs, which resembled ALS as described in this case. Although the overall disease duration was longer than ALS [24,25], these cases had a more severe disease course than other FOSMN cases, especially sensory symptom dominant cases as originally reported [1]. Interestingly, among six autopsied cases in the literature [1–3,6,12,21], motor symptoms were more widespread than sensory symptoms in half of the cases [2,6,21]. Furthermore, all three cases with a motor-dominant phenotype had TDP-43 pathology, suggesting a common pathomechanism between FOSMN and ALS.

Of note, our sensory-dominant cases required a longer time to arrive at the reporting department. This indicates that the diagnosis of these patients took a long time and that potential FOSMN cases might suffer without an appropriate diagnosis. Because FOSMN is not widely recognized and it is difficult to diagnose at symptom onset [26], the number of patients in Japan might be underestimated. Clinical and laboratory findings characteristic of FOSMN should be established to enable its early diagnosis and treatment.

5. Conclusions

In the present study, we confirmed that decreased or absent corneal and pharyngeal reflexes as well as abnormal blink reflex test findings, especially in the R2 component, might be reliable diagnostic hallmarks for FOSMN. We also found that FOSMN cases with relatively rapid motor progression sometimes mimicked ALS and may present with more severe conditions. Finally, because FOSMN may involve an autoimmune mechanism at disease onset, an early diagnosis is recommended to allow the initiation of effective immunotherapy, especially in cases with relatively slow motor progression, which tends to be undiagnosed for a long time.

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CRedit authorship contribution statement

Senri Ko: Writing – review & editing, Writing – original draft, Visualization, Validation, Investigation, Formal analysis, Data curation. **Ryo Yamasaki:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tasuku Okui:** Validation, Supervision, Methodology, Formal analysis, Data curation. **Wataru Shiraishi:** Validation, Supervision, Data curation, Conceptualization. **Mitsuru Watanabe:** Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yu Hashimoto:** Validation, Data curation. **Yuko Kobayakawa:** Validation, Supervision, Data curation, Conceptualization. **Susumu Kusunoki:** Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Jun-ichi Kira:** Validation, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Noriko Isobe:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision.

Declaration of competing interest

RY received honoraria from Teijin Pharma, Ono Pharmaceutical, Takeda Pharmaceutical, Eisai, Novartis, Nihon Pharmaceutical, and CSL Behring. SK received honoraria from CSL Behring, Nihon Pharm, and

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Appendix A. Supplementary data

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