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Characterizing Acute-Onset Small Fiber Neuropathy

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Abstract

Background and Objectives

Immune-mediated small fiber neuropathy (SFN) is increasingly recognized. Acute-onset SFN (AOSFN) remains poorly described. Herein, we report a series of AOSFN cases in which immune origins are debatable.

Methods

We included consecutive patients with probable or definite AOSFN. Diagnosis of SFN was based on the NEURODIAB criteria. Acute onset was considered when the maximum intensity and extension of both symptoms and signs were reached within 28 days. We performed the following investigations: clinical examination, neurophysiologic assessment encompassing a nerve conduction study to rule out large fiber neuropathy, laser-evoked potentials (LEPs), warm detection thresholds (WDTs), electrochemical skin conductance (ESC), epidermal nerve fiber density (ENF), and patient serum reactivity against mouse sciatic nerve teased fibers, mouse dorsal root ganglion (DRG) sections, and cultured DRG. The serum reactivity of healthy subjects (n = 10) and diseased controls (n = 12) was also analyzed. Data on baseline characteristics, biological investigations, and disease course were collected.

Results

Twenty patients presenting AOSFN were identified (60% women; median age: 44.2 years [interquartile range: 35.7–56.2]). SFN was definite in 18 patients (90%) and probable in 2 patients. A precipitating event was present in 16 patients (80%). The median duration of the progression phase was 14 days [5–28]. Pain was present in 17 patients (85%). Twelve patients (60%) reported autonomic involvement. The clinical pattern was predominantly non-length-dependent (85%). Diagnosis was confirmed by abnormal LEPs (60%), ENF (55%), WDT (39%), or ESC (31%). CSF analysis was normal in 5 of 5 patients. Antifibroblast growth factor 3 antibodies were positive in 4 of 18 patients (22%) and anticontactin-associated protein-2 antibodies in one patient. In vitro studies showed IgG immunoreactivity against nerve tissue in 14 patients (70%), but not in healthy subjects or diseased controls. Patient serum antibodies bound to unmyelinated fibers, Schwann cells, juxtaparanodes, paranodes, or DRG. Patients' condition improved after a short course of oral corticosteroids (3/3). Thirteen patients (65%) showed partial or complete recovery. Others displayed relapses or a chronic course.

Discussion

AOSFN primarily presents as an acute, non-length-dependent, symmetric painful neuropathy with a variable disease course. An immune-mediated origin has been suggested based on in vitro immunohistochemical studies.

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Glossary

AOSFN = acute-onset SFN; **DRG** = dorsal root ganglion; **ENF** = epidermal nerve fiber density; **ESC** = electrochemical skin conductance; **LEP** = laser-evoked potential; **NCS** = nerve conduction study; **QST** = quantitative Sensory Testing; **SFN** = small fiber neuropathy; **WDT** = warm detection threshold.

Introduction

Small fiber neuropathies (SFNs) are characterized by preferential involvement of thinly myelinated A δ -fibers and unmyelinated C-fibers.¹ Immune-mediated SFNs are increasingly recognized²⁻⁵ and might be immunotherapy responsive.^{6,7}

Diagnosis of SFN is challenging. Indeed, SFN diagnostic criteria regularly evolve⁸⁻¹⁰ but remain controversial.¹¹ Among the NEURODIAB criteria, SFN is typically chronic length-dependent polyneuropathy.^{1,9} However, several phenotypes have been described, such as non-length-dependent SFN¹² and acute-onset SFN (AOSFN).¹³

The clinical presentation of AOSFN may be initially misleading, characterized by isolated acute neuropathic pain or pure sensory symptoms, and normal nerve conduction studies.^{6,13-16} Descriptions of AOSFN are rare, mainly reported as single cases or small series without systematic investigations.^{6,13-20} Some AOSFNs are associated with the transient presence of antibodies of unknown specificity.¹⁵ We report a series of AOSFN cases with clinical, neurophysiologic, pathologic, and experimental assessment.

Methods

Patient Population

Between April 2017 and April 2022, we included all consecutive inpatients and outpatients referred to our tertiary neuromuscular center for AOSFN that is probable or definite SFN according to the NEURODIAB criteria,⁹ with a maximal 4-week onset.

All patients underwent a complete clinical examination, including evoked pain and thermal sensory assessment, by 2 neurologists (TG and AC). The diagnosis of probable SFN was based on the NEURODIAB criteria according to the presence of symptoms and clinical signs of small fiber damage in an anatomical distribution compatible with peripheral neuropathy and without any clinical or neurophysiologic signs of large fiber involvement.⁹ Indeed, patients were excluded if they presented any clinical signs of large fiber involvement (including ataxia, muscle weakness, proprioceptive impairment, or vibration sensation alteration) or abnormal nerve conduction study (NCS) at the time of the first investigation. Positive symptoms (neuropathic pain or paresthesia), negative symptoms (reduced or absent sensitivity to cold, heat, or noxious stimuli), positive signs of mechanical or thermal

stimuli (allodynia or hyperalgesia), and negative signs (thermal or pain hypoesthesia) were considered compatible with small fiber involvement.

Acute onset was defined as the extension and maximal intensity of both symptoms and signs reached within 28 days.

A length-dependent pattern, based on patient history and clinical examination, was defined as predominant distal symmetric neuropathy, beginning at the feet and involving the fingers when it ascends up to the knees.²¹ Other patterns were considered non-length-dependent.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by an Independent Ethics Committee (CO-15-006; Bicêtre, December 18, 2015). All patients provided a written informed consent before participation.

Neurophysiologic Assessment

Large Fiber Assessment

Conventional electrodiagnostic studies, including NCS and needle EMG, were performed before inclusion and were normal for all patients.

Small Fiber Assessment

The laser-evoked potentials (LEPs) were used to assess the function of A δ -fibers. LEPs were recorded by laser stimulation of the dorsum of the hands (radial nerve territory) and feet (superficial fibular nerve territory) on both sides using an ND:YAP laser (Stimul 1,340 laser, Electronic Engineering, Florence, Italy). Each stimulus consisted of a brief radiant heat pulse (laser beam diameter 4 mm, pulse duration 5 ms, energy progressively increased from 1.5 to 2.5J by steps of 0.25J, resulting in energy density between 120 and 200 mJ/mm²).²² Habituation, sensitization, and nociceptor fatigue were minimized by slightly moving the laser beam between stimuli. LEPs were recorded using a scalp electrode placed at Cz, according to the International 10–20 EEG System, referenced to the linked earlobes. A Velcro bracelet strapped around the left forearm was used as the ground electrode. The electrooculogram was recorded using pregelled surface adhesive electrodes placed at the right infraorbital lateral margin. Two blocks of 10–12 trials were performed, and the results were averaged offline. The signal was filtered (bandpass: 0.5–30 Hz), and trials contaminated by eye blinks, ocular movements (saccades), or any raw signal exceeding 70 μ V were excluded from averaging. The N2-P2 complex was studied by

measuring N2-P2 peak-to-peak amplitude and N2 latency. The LEPs were abnormal if latencies were above 170 ms at upper limbs (UL) or 237 ms at lower limbs (LL) or the amplitude was below 15 μ V at UL or 13 μ V at LL.

Quantitative sensory testing (QST) was performed on the dorsum of the hands and feet (the same territories used for LEPs). The detection thresholds for warm stimuli (WDT) were used to assess the function of the sensory C-fibers. We measured WDT using a 16 cm² Peltier probe connected to a Thermal Sensory Analyzer TSA 2001 (Medoc, Ramat Yishai, Israel)²³ and the method of limits.²⁴ After an adaptation period at a neutral temperature of 32°C, the temperature increased (heating up to 50°C) at a linear rate of 1°C/s, until the patient pressed a signal button when they began to feel warm ('first perception' or 'detection' threshold). The detection thresholds (in °C) were determined as the average value from 3 trials and the absolute difference between the measured threshold and the neutral baseline temperature of 32°C. The WDT were abnormal if they were above 5.8°C at UL or 10.5°C at LL. These normative values have been established in a large number of healthy subjects and are evenly distributed for age and sex.²⁵

Electrochemical skin conductance (ESC) was used to assess autonomic C-fibers. ESC was performed with Sudoscan® (Impeto Medical, Paris, France).^{26,27} The patient stood placing both palms and soles on large nickel electrode plates through which low-voltage direct current (less than 4 V) was delivered for 2 minutes. The electrodes were alternately used as anode and cathode, and the current between the electrodes was generated by reverse iontophoresis. The local conductance (in microsiemens, μ S) was measured simultaneously at the 4 extremities from the electrochemical reaction between sweat chloride ions released by the sweat glands and the nickel electrode plates delivering the direct current. The ESC was considered abnormal if it was below 64 μ S at the UL or 67 μ S at the LL.

Pathologic Investigation

Epidermal innervation was assessed using 3-mm punch skin biopsies taken from the right calf (10 cm above the lateral malleolus) and the proximal lateral right thigh (20 cm below the anterosuperior iliac spine).²⁸ The skin biopsies were fixed, cryoprotected, sectioned, and immunostained with polyclonal antibodies against panaxonal marker, protein gene product 9.5. Observers assessed the linear density/mm of ENF from 3 to 6 50- μ m thick sections selected at random from each biopsy specimen. ENF was considered abnormal in the calf if it was below the fifth percentile values of previously published age-normative and sex-normative data.²⁹ There were no normative data for ENF in the thigh. However, normal ENF in the thigh is reported to be 130% higher than the ENF in the calf.³⁰ Therefore, we considered abnormal ENF in the thigh if it was below the fifth percentile values of previously published age-normative and sex-normative data for the calf or if it was

below the value of ENF in the calf in the same patient (i.e., ENF_{thigh}/ENF_{calf} ratio <1).

Amyloid staining was ruled out with a minor salivary gland biopsy in 9 patients.

Biological Investigation

The following tests were performed: complete blood count (20 patients), renal (20), liver (20) and thyroid (20) function tests, lipid screen (20), C-reactive protein (20), fasting blood glucose (20), glycosylated hemoglobin (20), antinuclear antibody (20), anti-SSA and SSB antibodies (19), antineutrophil cytoplasmic antibodies (14), serum immunofixation (19), cryoglobulin (7), hepatitis B and C titers (18), Lyme titer (15), HIV titer (18), vitamin B12 and folate levels (18), anti-transglutaminase and antiendomysium antibodies (13), antithyroperoxidase (anti-TPO) and antithyroglobulin antibodies (anti-Tg) (7), antiganglioside antibodies (10), onconeural antibodies such as antiHu antibodies (13), anticontactin-associated protein-2 antibodies (anti-CASPR2, 20), antibodies targeting the node and the paranode of Ranvier [anticontactin-associated protein (anti-CASPR1), anticontactin (anti-CNTN1), antineurofascin 155 (anti-Nfasc155) antibodies, 20], antifibroblast growth factor 3 antibodies (anti-FGFR3, 18), genetic testing for *TTR* (5), genetic testing for *SCN9A*, *SCN10A*, and *SCN11A* (4), and CSF analyses (5).

Other Investigations

Spinal cord MRI was performed on 10 patients. Several patients underwent chest radiography and chest and abdominal tomography. History ruled out neurotoxic drugs, heavy metal intoxication, or occupational exposure.

Nerve and DRG

Immunohistochemical Labeling

Sciatic nerve teased fibers and dorsal root ganglion (DRG) sections were prepared from adult C57BL/6J mice, as previously described.³¹ Tissues were postfixed with acetone for 10 minutes at -20°C, washed, blocked for 1 hour with blocking solution (5% fish skin gelatin, 0.1% Triton X-100 in phosphate-buffered saline), and then incubated overnight at 4°C with the patients' sera diluted at 1:200 and goat anticontactin-1 antibodies (1:2000; R&D Systems) to label paranodes or chicken antiperipherin antibodies (1:500; Aves Labs) to stain unmyelinated axons. The next day, the slides were washed 3 times and incubated for 1 hour with donkey anti-human IgG conjugated to Alexa 488, donkey anti-human IgM conjugated to Alexa 594, and donkey anti-goat IgG conjugated to Alexa 647 (1:500; Jackson ImmunoResearch). The slides were mounted and counterstained with 4',6-diamidino-2-phenylindole (DAPI) to stain the nuclei. Sera from healthy subjects (n = 10), patients with *PMP22* duplication (n = 7), and patients with amyotrophic lateral sclerosis (n = 5) were also analyzed.

Table 1 Clinical Features of the Patients

Patient	Age (decade)	Relevant medical history	Precipitating event	Progression phase duration (d)	Symptoms			Clinical signs					Disease course	Treatment
					Pain	Paresthesia	Dysautonomia	Pinprick alteration		Thermal alteration		Length-dependent pattern		
								Hypo	Hyper	Hypo	Hyper			
1	50s	GSD II	α-glucosidase	14	Burning	—	Faintness	—	+	—	+	—	Chronic	
2	50s	None	FLS	5	Burning, stretching, allodynia	—	Flush, tachycardia	+	—	+	—	—	Partial recovery	
3	20s	Endometriosis	DTP vaccination	28	Allodynia	Tingling	Tachycardia	—	+	—	+	—	Recovery	
4	30s	Treated HCV	No	28	Burning, cramping, deep pain	—	Extremity discoloration, faintness	—	+	—	+	—	Partial recovery	
5	50s	None	FLS	3	—	Contact dysesthesia	Faintness	—	+	—	+	—	Relapses then chronic	IVIg (1 at 2 g/kg): no effect
6	40s	AS during follow-up	Hepatitis B virus vaccination	28	Electric-like	—	Vertigo, bloat, erectile dysfunction	—	—	+	—	—	Recovery	
7	50s	None	Syphilis	28	Burning	Tingling	Tachycardia	+	—	+	—	+	Partial recovery	
8	20s	None	FLS	15	Allodynia, electric-like	Tingling, internal tremor	—	—	+	—	+	—	Partial recovery	
9	30s	Psoriasis	Anti-TNFα	15	Cramping	Numbness	Vertigo	+	—	+	—	—	Relapses, then partial recovery	
10	60s	None	FLS	7	Burning	Tingling	—	+	—	—	—	+	Chronic	IVIg (3 at 2 g/kg), PLEX (4 in 2 wk): no effect
11	30s	None	No	15	Burning, tightness	Warmth	—	+	—	+	—	—	Relapsing then chronic	
12	40s	None	No	5	—	Tingling, numbness	—	—	—	+	—	—	Relapsing then recovery	
13	30s	None	Ciprofloxacin	3	Burning	Tingling	Tachycardia, faintness, bloat, urinary frequency	+	—	+	—	—	Chronic	
14	30s	TRAPS	Diarrhea	21	Burning	—	—	+	—	+	—	—	Recovery	Oral CS (1 mg/kg for 1 mo): efficacy
15	50s	None	COVID-19	28	Cramps, electric-like	Tingling	—	+	—	+	—	—	Partial recovery	
16	70s	None	None	21	Burning	Tingling	—	+	—	—	—	—	Partial recovery	Oral CS (1 mg/kg for 1 wk): efficacy
17	50s	None	Flu vaccination	28	Electric-like, prickling	Contact dysesthesia	—	+	+	+	—	+	Partial recovery	Oral CS (1 mg/kg for 1 mo): efficacy

Continued

Table 1 Clinical Features of the Patients (continued)

Patient	Age (decade)	Relevant medical history	Precipitating event	Progression phase duration (d)	Symptoms		Clinical signs				Disease course	Treatment		
					Pain	Paresthesia	Dysautonomia	Pinprick alteration		Thermal alteration			Length-dependent pattern	
								Hypo	Hyper	Hypo				Hyper
18	20s	None	FLS	7	—	Numbness	POTS; urinary frequency, accommodation disorders	+	—	+	—	—	Chronic	
19	30s	EMC	B6 vitamin	1	Electric-like, prickling	Tingling	Tachycardia	+	+	+	—	—	Chronic	
20	40s	Sarcoidosis	Metronidazole and tetracycline	3	Burning	—	Xerophthalmia, urinary frequency	+	—	+	—	—	Partial recovery	

Abbreviations: AS = ankylosing spondylitis; Anti-TNF α = antitumor necrosis factor α ; COVID-19 = coronavirus disease 2019; CS = corticosteroids; EMC = erythema migrans chronica; DTP = diphtheria, tetanus, poliomyelitis; F = female; FLS = flu-like syndrome; GSD II = glycogen storage disease type II; HCV = hepatitis C virus; Hyper = hyperalgesia; Hypo = hypoalgesia; IVg = IV immunoglobulin; M = male; PLEX = plasma exchange; POTS = postural orthostatic tachycardia syndrome; TRAPS = TNF receptor-associated periodic syndrome.

Neuron-Based Assay

Cultured DRG were prepared from 1-month-old C57Bl/6J mice on 12-mm coverslips and maintained for 3 days in vitro. Live neurons were incubated with patients' sera diluted 1:50 in DMEM (Thermo Fisher) for 1 hour at 37°C, washed several times, and fixed for 20 minutes with 2% paraformaldehyde. The cells were permeabilized with blocking solution, incubated for 1 hour at room temperature with chicken antibodies against neurofilament heavy (1:2,000; Ab5539; Merck Millipore), and incubated with secondary antibodies. Sera from healthy subjects and diseased controls were also analyzed.

Statistical Analyses

We performed the descriptive analyses with *Microsoft Excel*. We calculated percentages for qualitative data and medians and interquartile ranges for quantitative data.

Data Availability

Data are available on request to the corresponding author.

Results

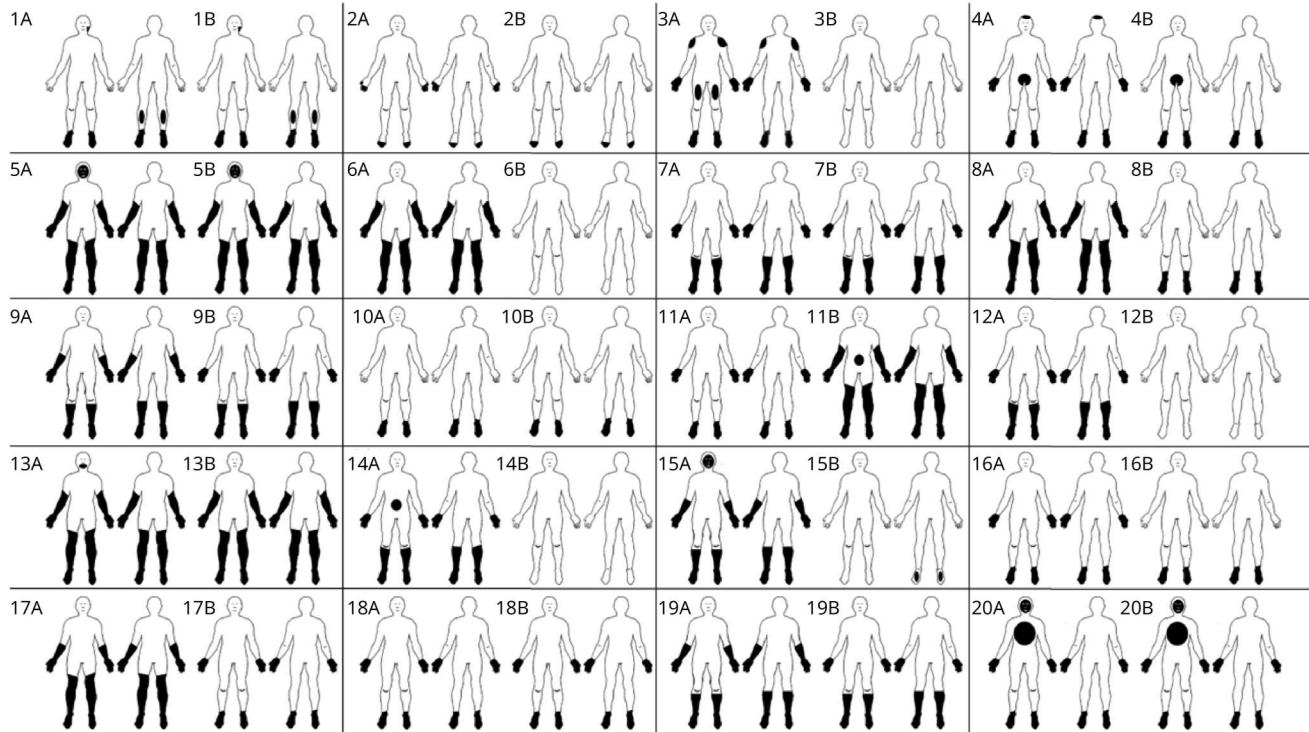
Clinical Features

Twenty patients were included (60% women, median age [interquartile range] 44.2 years [35.7–56.2]). The clinical features of the patients are shown in Table 1. A precipitating event was present in 16 patients (80%): an infectious event in 8 [flu-like syndrome with negative Sars-Cov2 testing (5), syphilis (1), diarrhea (1), and COVID-19 (1)], a recently introduced treatment in 5 (antibiotics in 2, antitumor necrosis factor α , vitamin, enzyme replacement therapy), and vaccination (flu, hepatitis B virus, and diphtheria-tetanus-poliomyelitis) in 3. The median duration of the progression phase was 14 days [5–28]. Seventeen patients reported pain (85%). Paresthesia was observed in 14 patients (70%). The symptom distributions at onset and last follow-up are presented individually in Figure 1. Autonomic involvement was reported in 12 patients (60%), mainly faintness and tachycardia. Pinprick alteration was present in 18 patients (90%), including hypoalgesia in 11 patients, hyperalgesia in 5, or both in different sites in 2 patients. Responses to heat and cold were altered in 18 patients (90%), including hypoalgesia in 13 patients and hyperalgesia or allodynia in 5. The clinical pattern was not length-dependent in 17 patients (85%).

Diagnostic Evaluation

The neurophysiologic and pathologic features are presented in Table 2. All the patients underwent at least one neurophysiologic test. These tests showed evidence of small fiber involvement in 15 patients (75%). The recording of LEPs was the most sensitive test (60%). The sensitivities of WDT and ESC were lower (39% and 31%). Among the 5 patients with normal neurophysiologic findings, patient 3 was assessed after spontaneous complete recovery of symptoms. Eleven patients underwent skin biopsies. ENF was reduced in 6 patients

Figure 1 Individual Distribution of Sensory Symptoms at the Peak and the Last Follow-Up



Body diagrams representing the regional distribution of sensory symptoms at the peak (A) and last follow-up (B) for the front (left) and back (right) of 20 patients with acute-onset small fiber neuropathy. The numbers on the top left of each figure correspond to the patient numbers in Tables 1–3.

(55%). Five patients had normal ENF in the calf but exclusively reduced in the thigh. Therefore, considering both neurophysiologic studies and ENF, SFN was definite in 18 patients (90%) and remained probable in 2 patients.

Immunologic Studies

CSF analyses revealed normal white cell counts and protein levels in all 5 tested patients. Oligoclonal bands were absent in one patient. One patient tested negative for CSF onconeural and neural surface antibodies.

Abnormal laboratory results and immunologic features of the patients are presented in Table 3. Anti-CASPR2 IgG antibodies were present in 1 of 20 patients, as we previously reported.³² Anti-FGFR3 IgG antibodies were positive for 4 of 18 patients. Two of the 7 tested patients had antithyroid antibodies.

In vitro studies revealed mouse sciatic nerve fiber or DRG immunostaining with the sera from 14 patients (70%). Immunostaining was not observed with sera from either healthy subjects or diseased controls. Immunostaining was obtained only with anti-IgG, but not with anti-IgM antibodies. Different immunostaining patterns in sciatic nerve fibers and DRG are shown in Figures 2 and 3, respectively. The sera from 3 patients contained antibodies that lead to paranodal immunostaining of Schwann cells (No. 6) or axons (Nos. 11 and 13). The serum from patient No. 10 had antibodies that

caused juxtaparanode immunostaining, consistent with not only circulating anti-CASPR2 antibodies but also unmyelinated fiber immunostaining.³² The sera from 5 patients lead to unmyelinated fiber immunostaining. The sera from a total of 5 of the tested patients contained antibodies for DRG.

Disease Course and Treatment Response

The disease course varied (Table 1). Thirteen patients (65%) reported recovery of symptoms, complete in 4 patients, or partial in 9. Five patients (25%) experienced a steady and chronic course after an acute onset. Four patients (20%) reported relapses, followed by a chronic clinical condition in 2, complete recovery in one, and partial recovery in one. Three patients received a 1-month course of oral corticosteroids at 1 mg/kg during the acute phase and presented with complete or partial recovery. Two patients received IV immunoglobulin (IVIg) after the acute phase, without any efficacy. Patient No. 10, with anti-CASPR2 antibodies, also underwent plasma exchange without any efficacy. None of the 20 patients had developed large fiber involvement at the last follow-up (median 4.8 years [3.2–8.0]).

Discussion

We report a series of AOSFN cases with 20 patients collected over 5 years from a tertiary center, suggesting that it is a rare condition. To date, only a few small series have been reported

Table 2 Neurophysiologic and Pathologic Features of the Patients

Patient	Neurophysiologic assessment							ENF		SFN diagnosis (definite or probable)
	Ab test ≥ 1	LL LEP	UL LEP	LL ESC	UL ESC	LL WDT	UL WDT	Calf	Thigh	
Ab testing	15/20 (75%)	12/20 (60%)		7/18 (39%)		5/16 (31%)		6/11 (55%)		Definite: 18/20 (90%)
		10/20 (50%)	11/19 (58%)	5/18 (28%)	6/18 (33%)	4/15 (27%)	3/16 (19%)	1/11 (9%)	6/9 (67%)	
1	Y	Ab	Ab	Ab	Ab	N	N	ND	ND	Definite
2	Y	N	N	N	Ab	N	N	N	N	Definite
3	No	N	N	ND	ND	ND	ND	ND	ND	Probable
4	Y	Ab	Ab	N	N	Ab	N	N	Ab	Definite
5	Y	Ab	Ab	N	N	Ab	Ab	N	Ab	Definite
6	Y	N	N	N	N	Ab	Ab	ND	ND	Definite
7	Y	Ab	Ab	N	N	N	Ab	N	N	Definite
8	Y	N	N	Ab	Ab	N	N	Ab	Ab	Definite
9	Y	Ab	Ab	N	N	N	N	ND	ND	Definite
10	Y	Ab	Ab	ND	ND	ND	ND	N	ND	Definite
11	Y	Ab	Ab	N	N	N	N	ND	ND	Definite
12	Y	Ab	Ab	Ab	N	N	N	ND	ND	Definite
13	No	N	N	N	N	N	N	N	Ab	Definite
14	No	N	ND	N	N	ND	N	ND	ND	Probable
15	Y	N	Ab	N	N	N	N	N	N	Definite
16	Y	Ab	Ab	Ab	Ab	ND	ND	ND	ND	Definite
17	No	N	N	N	N	N	N	N	Ab	Definite
18	Y	N	Ab	N	Ab	ND	ND	N	ND	Definite
19	Y	Ab	N	Ab	Ab	Ab	N	ND	ND	Definite
20	No	N	N	N	N	N	N	N	Ab	Definite

Abbreviations: Ab = abnormal; ENF = epidermal nerve fiber density; ESC = electrochemical skin conductance; LEP = laser-evoked potential; LL = lower limb; m = mean; N = normal; ND = not done; UL = upper limb; SFN = small fiber neuropathy; WDT = warm detection threshold; Y = yes.

ranging from one to 6 patients, some of which are them restricted to postvaccinal or postinfectious contexts (eTable 1, [links.lww.com/NXI/A972](https://www.lww.com/NXI/A972)).^{6,13-20} In the present series, we draw a picture of AOSFN, including clinical, neurophysiologic, pathologic, and experimental features. Patients with AOSFN have variable disease courses, and one-third of patients have unfavorable outcomes. In vitro analyses provided arguments for a possible immune-mediated process.

The diagnosis of AOSFN may be challenging in clinical practice. Patients usually present with acute symmetric non-length-dependent neuropathic pain, frequently preceded by a particular event, such as infection or vaccination. In a previous cohort of non-length-dependent SFN, one-third of patients had an acute onset.¹² However, patients may be painless, as in other SFN presentations.³³ During the acute phase, the absence of large fiber involvement on clinical

examination and NCS study ruled out acute inflammatory demyelinating polyneuropathy.³⁴ In addition, we found normal CSF while results were more discrepant in previous studies.^{6,13-15} Functional neurologic disorders should be considered in the context of a predominantly painful presentation with normal investigations. Indeed, patients with functional neurologic disorders frequently present subjective symptoms potentially mimicking SFN.³⁵ However, this was not the case in our series of patients who presented clinical signs of sensory disorders and abnormal neurophysiologic or neuropathologic findings, leading to the diagnosis of definite SFN in 90% of patients. Two patients were diagnosed with probable SFN because their neurophysiologic findings were normal, but a skin biopsy was unfortunately not performed. In this study, we used a battery of neurophysiologic tests to assess $A\delta$ and C sensory fibers and C autonomic fibers. In previously published series, neurophysiologic assessment was

Table 3 Laboratory and In Vitro Studies of the Patients

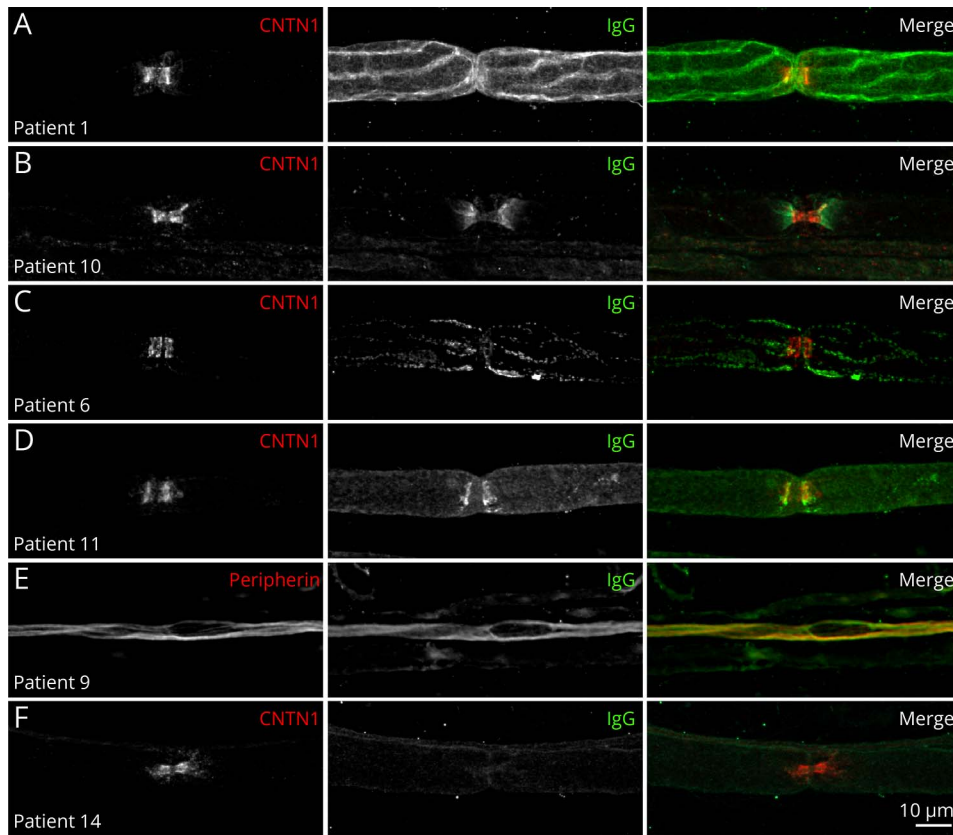
Patient	Delay between the onset and laboratory assessment (d)	Abnormal laboratory studies	IF sciatic nerve IgG staining	DRG culture IgG staining	DRG section IgG staining	Interpretation of immunostaining reactivity
1	22	N	Schwann cells	—	—	Myelin
2	888	N	—	+	—	DRG
3	485	N	—	—	+	DRG (probably)
4	1,213	N	—	—	—	Negative
5	3,613	Anti-FGFR3 +	Unmyelinated fibers	+	+	Small fibers
6	1,370	B12 deficiency	Schwann cells at paranodes	—	+	Paranodes
7	282	Anti-FGFR3 +	Schwann cells	—	—	Myelin
8	228	Folate deficiency	—	+	+	DRG
9	1877	Anti-FGFR3 +	Unmyelinated fibers	—	—	Small fibers
10	308	Anti-CASPR2 +	Juxtaparanodes and unmyelinated fibers	+	+	Juxtaparanodes and small fibers
11	1,572	N	Paranodes	—	—	Paranodes
12	74	N	—	+	—	DRG
13	995	Iron-deficiency anemia	Unmyelinated fibers and paranodes	—	—	Paranodes and small fibers
14	34	Anti-Tg +	—	+	—	DRG
15	170	N	Unmyelinated fibers	+	—	Small fiber
16	54	Anti-TPO and anti-Tg +	—	—	—	Negative
17	26	N	—	—	—	Negative
18	962	Thrombocytopenia	—	—	—	Negative
19	1,529	High B6 level	—	—	—	Negative
20	354	Anti-FGFR3 +	—	—	—	Negative

Abbreviations: + = staining; CASPR2 = contactin-associated protein-2; DRG = dorsal root ganglion; FGFR3 = fibroblast growth factor receptor 3; IF = immunofluorescence; N = normal; TG = thyroglobulin; TPO = thyroperoxidase.

rarely performed or limited to a single test. Interestingly, LEPs have been the most sensitive indicator of SFN. By contrast, thermal QST and ESC exhibited poor sensitivity, below 40%. This is consistent with our previously published data on the sensitivity of neurophysiologic tests for diagnosing SFN.²⁵ By contrast, ENF was reduced more often in the thigh than in the calf, which is consistent with non-length-dependent neuropathy. In this context, other laboratory tests investigating small nerve fibers would have been useful to perform, such as corneal confocal microscopy.³⁶ Symptoms associated with small nerve fibers involvement, such as pain, can be explained not only by lesions of these fibers but also by their dysfunction (leading to nerve hyperexcitability³⁷) or a combination of these phenomena.³⁸ Thus, the normality of neuropathologic and neurophysiologic investigations cannot rule out the involvement of small fibers in a clinical picture characterized by only positive sensory symptoms. In this series, the patients

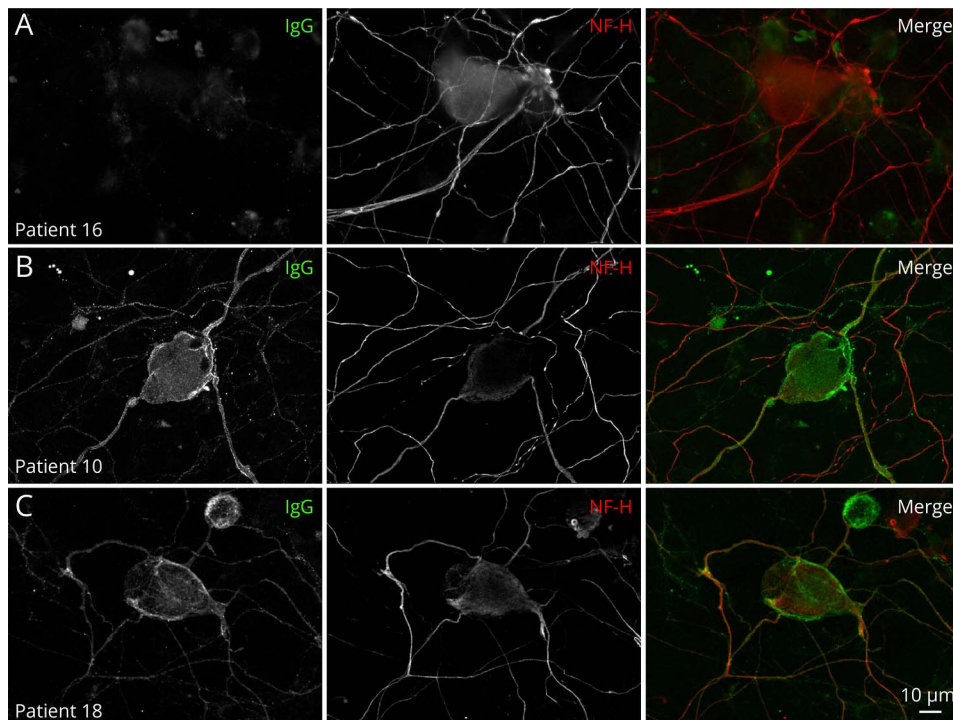
had variable disease courses which require caution to differentiate relapses from functional neurologic fluctuations. The heterogeneity of the disease course is usual in acute-onset inflammatory neuropathies affecting large-diameter fibers. AOSFN may have complete recovery or sequelae, such as Guillain-Barré syndrome,³⁹ or may be the onset of chronic neuropathy, such as acute-onset chronic inflammatory demyelinating polyneuropathy.⁴⁰ One cannot exclude that patients may later develop an associated large-fiber involvement, although the median follow-up was 4.8 years in this study. The proportion of patients with an unfavorable course may be overestimated because our hospital is a tertiary neuromuscular center. Therefore, patients with AOSFN whose symptoms had complete and rapid resolution may not have benefited from neurologic evaluation at our center, which may have been requested for patients with a more prolonged course of the disease.

Figure 2 Patterns of Nerve Fiber Staining



This figure shows teased fibers from mouse sciatic nerves immunostained with patient IgG (green), goat anti-contactin-1 IgG (CNTN1; red) to localize to the node of Ranvier (A, B, C, D, F), or chicken antiperipherin IgG (red) to localize unmyelinated axons (E). IgG deposition was observed on Schwann cells (A), at the juxtapanodes in patients with circulating anti-CASPR2 antibodies (B), on the surface of Schwann cells near the paranodal region (C), at paranodes (D), or on unmyelinated fibers (E). IgG deposition was not observed in some patients (F). Scale bar: 10 µm.

Figure 3 Patterns of Cultured Dorsal Root Ganglion Staining



Live dorsal root ganglia (DRG) were incubated with patient sera, fixed, and immunostained for human IgG (green) and antibodies against neurofilament heavy (NF-H; red) to stain DRG. Some patients did not show reactivity toward the DRG (A). Other patients showed strong IgG reactivity against surface antigens expressed by both large and small cells in DRG (B-C). Patient No. 10, who presented with circulating anti-CASPR2 antibodies, showed strong reactivity against the soma and axons of the DRG (B). Patient No. 8, without any identified antibody target, also showed strong reactivity against the DRG soma and axons (C). Scale bar: 10 µm.

This investigation suggests that immune dysfunction is probably the cause of AOSFN. A precipitating event was frequently found, either infection or vaccination, as in previous series of AOSFN,^{13-16,19,20} as well as other types of immune neuropathies, such as Guillain-Barré syndrome³⁹ or post-COVID neuropathy.^{41,42} In 3 patients with AOSFN, their sera showed transient immunoreactivity to murine small fibers during the acute phase.¹⁵ The present in vitro studies are also compatible with antibody-associated pathophysiology. Indeed, in vitro studies demonstrated IgG immunostaining by the sera of most patients with AOSFN. Although heterogeneous binding sites suggest nonspecific findings, the absence of immunostaining from the sera of healthy subjects or diseased controls supports an immune-mediated process in AOSFN. Patient sera contained antibodies to unmyelinated or thinly myelinated fibers, including the paranodal region, and DRGs. IgG deposits on nerves have also been found in other types of chronic inflammatory neuropathy.⁴³ However, one cannot exclude the possibility that these immunoreactions were a consequence of peripheral nervous system lesions and not the cause of these lesions. Indeed, an antibody probably responsible for the occurrence of AOSFN was identified in only one previously reported patient with CASPR2-related juxtapanodopathy, which exclusively involved small nerve fibers.^{32,44} The number of autoantibodies associated with SFN has increased in recent years, including anti-TS-HDS and anti-FGFR-3 antibodies which have been associated with AOSFN in some cases.^{3,45} However, their pathogenicity in SFN remains uncertain.⁴⁶ Moreover, we observed IgG cell membrane immunostaining. This contrasts with the reported anti-TS-HDS antibodies which are IgM.³ It also contrasts with anti-FGFR-3 IgG antibodies which usually target the intracellular portion of FGFR-3.⁴⁷ Thus, the extracellular immunostaining pattern in this study is not consistent with anti-FGFR-3 antibody reactivity, despite circulating anti-FGFR-3 antibodies being identified in 20% of our patients. Anti-plexin D1 IgG antibodies seem to be frequently found in painful neuropathies in Japanese patients^{2,48} and induce hyperexcitability of DRG sensory neurons.⁴⁹ It would be interesting to look for the presence of anti-plexin D1 antibodies, notably in patients with immunostaining involving DRG. Our in vitro studies did not reveal signs of autoimmunity in some patients. However, patients' sera were collected several months after the disease onset, and this may have led to missing a transient immune process.¹⁵ Finally, although paraneoplastic neuropathies were excluded from our series on the basis of the negativity of onconeural antibodies and clinical follow-up, such a cause could be possibly encountered in a context of AOSFN, even if we lack data to make this assumption.

In conclusion, the present cohort supports the concept of AOSFN and refines its clinical description. The typical clinical pattern is associated with acute non-length-dependent symmetric painful neuropathy with a monophasic or relapsing chronic course. In vitro studies have provided clues regarding immune pathogenesis. Regarding treatment, corticosteroids in the acute phase could have a beneficial effect, whereas IVIg

infusions were ineffective in 2 patients who were treated for chronic symptoms long after the acute phase.

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Appendix (continued)

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