

1 **TITLE**

2 **Characterizing acute-onset small fiber neuropathy**

3

4 **AUTHORS AND AFFILIATIONS**

5 Thierry Gendre<sup>1,2\*</sup>, Jean-Pascal Lefaucheur<sup>2,3,4</sup>, Tarik Nordine<sup>2,3,4</sup>, Yasmine Baba-Amer<sup>5</sup>,  
6 François-Jérôme Authier<sup>2,5,6</sup>, Jérôme Devaux<sup>7</sup>, Alain Créange<sup>1,2,4</sup>

7 1. Service de Neurologie, CHU Henri Mondor APHP, Créteil, France

8 2. Centre de Référence des Maladies Neuromusculaires Nord/Est/Ile-de-France

9 3. Unité de Neurophysiologie Clinique, CHU Henri Mondor APHP, Créteil, France

10 4. Unité de Recherche EA 4391, Faculté de Santé, Université Paris Est Créteil, Créteil, France

11 5. IMRB INSERM U955-Equipe 10, Université Paris Est Créteil, Créteil, France

12 6. Service d'Anatomo-Pathologie, CHU Henri Mondor APHP, Créteil, France

13 7. Institut de Génomique Fonctionnelle, Université de Montpellier, CNRS, INSERM,  
14 Montpellier, France

15

16 **\*Corresponding author**

17 Thierry Gendre

18 16-digit ORCID: 0000-0003-2514-6148

19 Service de Neurologie

20 CHU Henri Mondor – APHP

21 1 rue Gustave Eiffel 94010 CRETEIL CEDEX (France)

22 Phone: +33 (0)1 49 81 23 03

23 Mail: [thierry.gendre@aphp.fr](mailto:thierry.gendre@aphp.fr)

24

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## 34 ABSTRACT

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

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

49 **Results:** Twenty patients presenting AOSFN were identified (60% women; median age: 44.2  
50 years [IQR: 35.7–56.2]). SFN was definite in 18 patients (90%) and probable in two patients.  
51 A precipitating event was present in 16 patients (80%). The median duration of the  
52 progression phase was 14 days [5–28]. Pain was present in 17 patients (85%). Twelve patients  
53 (60%) reported autonomic involvement. The clinical pattern was predominantly non-length-  
54 dependent (85%). Diagnosis was confirmed by abnormal LEPs (60%), ENF (55%), WDT  
55 (39%), or ESC (31%). CSF analysis was normal in 5/5 patients. Anti-fibroblast growth factor  
56 3 antibodies were positive in 4/18 patients (22%) and anti-contactin-associated protein-2  
57 antibodies in one patient. *In vitro* studies showed IgG immunoreactivity against nerve tissue  
58 in 14 patients (70%), but not in healthy subjects or diseased controls. Patient serum antibodies  
59 bound to unmyelinated fibers, Schwann cells, juxtaparanodes, paranodes, or DRG. The  
60 patients' condition improved after a short course of oral corticosteroids (3/3). Thirteen  
61 patients (65%) showed partial or complete recovery. Others displayed relapses or a chronic  
62 course.

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

66

67 **KEYWORDS (5)**

68 Small fiber neuropathy; acute inflammatory polyneuropathy; neuralgia; sensory neuropathy;  
69 peripheral neuropathy

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## 71 **MAIN TEXT**

### 72 **INTRODUCTION**

73 Small fiber neuropathies (SFN) are characterized by preferential involvement of thinly  
74 myelinated A $\delta$ -fibers and unmyelinated C-fibers.<sup>1</sup> Immune-mediated SFN are increasingly  
75 recognized,<sup>2-5</sup> and might be immunotherapy-responsive.<sup>6,7</sup>

76 Diagnosis of SFN is challenging. Indeed, SFN diagnostic criteria regularly evolve<sup>8-10</sup> but  
77 remain controversial.<sup>11</sup> Among the NEURODIAB criteria, SFN is typically chronic length-  
78 dependent polyneuropathy.<sup>1,9</sup> However, several phenotypes have been described, such as non-  
79 length dependent SFN<sup>12</sup> and acute-onset SFN (AOSFN).<sup>13</sup>

80 The clinical presentation of AOSFN may be initially misleading, characterized by isolated  
81 acute neuropathic pain or pure sensory symptoms, and normal nerve conduction studies.<sup>6,13-16</sup>

82 Descriptions of AOSFN are rare, mainly reported as single cases or small series without  
83 systematic investigations<sup>6,13-19</sup>. Some AOSFN are associated with the transient presence of  
84 antibodies of unknown specificity.<sup>15</sup> We report a series of AOSFN cases with clinical,  
85 neurophysiological, pathological, and experimental assessment.

86

## 87 **METHODS**

### 88 **Patient population**

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

92 All patients underwent a complete clinical examination, including evoked pain and thermal  
93 sensory assessment, by two neurologists (TG and AC). The diagnosis of probable SFN was  
94 based on the NEURODIAB criteria according to the presence of symptoms and clinical signs  
95 of small fiber damage in an anatomical distribution compatible with peripheral neuropathy  
96 and without any clinical or neurophysiological signs of large fiber involvement.<sup>9</sup> Indeed,  
97 patients were excluded if they presented any clinical signs of large fiber involvement  
98 (including ataxia, muscle weakness, proprioceptive impairment, or vibration sensation  
99 alteration) or abnormal nerve conduction study (NCS) at the time of the first investigation.  
100 Positive symptoms (neuropathic pain or paresthesia), negative symptoms (reduced or absent  
101 sensitivity to cold, heat, or noxious stimuli), positive signs of mechanical or thermal stimuli  
102 (allodynia or hyperalgesia), and negative signs (thermal or pain hypoesthesia) were  
103 considered compatible with small fiber involvement.

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

106 A length-dependent pattern, based on patient history and clinical examination, was defined as  
107 predominant distal symmetric neuropathy, beginning at the feet and involving the fingers  
108 when it ascends up to the knees.<sup>20</sup> Other patterns were considered non-length dependent.

109

### 110 **Standard Protocol Approvals, Registrations, and Patient Consents**

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

113

### 114 **Neurophysiological assessment**

115 *Large fiber assessment*

116 Conventional electrodiagnostic studies, including NCS and needle electromyography (EMG),  
117 were performed before inclusion and were normal for all patients.

#### 118 *Small fiber assessment*

119 The laser-evoked potentials (LEPs) were used to assess the function of A $\delta$ -fibers. LEPs were  
120 recorded by laser stimulation of the dorsum of the hands (radial nerve territory) and feet  
121 (superficial fibular nerve territory) on both sides, using an ND:YAP laser (Stimul 1340 laser,  
122 Electronic Engineering, Florence, Italy). Each stimulus consisted of a brief radiant heat pulse  
123 (laser beam diameter 4mm, pulse duration 5ms, energy progressively increased from 1.5 to  
124 2.5J by steps of 0.25J, resulting in energy density between 120 and 200mJ/mm<sup>2</sup>).<sup>21</sup>  
125 Habituation, sensitization, and nociceptor fatigue were minimized by slightly moving the laser  
126 beam between stimuli. LEPs were recorded using a scalp electrode placed at Cz, according to  
127 the International 10-20 EEG System, referenced to the linked earlobes. A Velcro bracelet  
128 strapped around the left forearm was used as the ground electrode. The electrooculogram was  
129 recorded using pre-gelled surface adhesive electrodes placed at the right infra-orbital lateral  
130 margin. Two blocks of 10-12 trials were performed, and the results were averaged offline.  
131 The signal was filtered (bandpass: 0.5-30 Hz) and trials contaminated by eye blinks, ocular  
132 movements (saccades), or any raw signal exceeding 70  $\mu$ V were excluded from averaging.  
133 The N2-P2 complex was studied by measuring N2-P2 peak-to-peak amplitude and N2  
134 latency. The LEPs were abnormal if latencies were above 170 ms at upper limbs (UL) or 237  
135 ms at lower limbs (LL), or the amplitude was below 15  $\mu$ V at UL or 13  $\mu$ V at LL.

136 Quantitative Sensory Testing (QST) was performed on the dorsum of the hands and feet (the  
137 same territories used for LEPs). The detection thresholds for warm stimuli (WDT) were used  
138 to assess the function of the sensory C-fibers. We measured WDT using a 16cm<sup>2</sup> Peltier probe  
139 connected to a Thermal Sensory Analyzer TSA 2001 (Medoc, Ramat Yishai, Israel)<sup>22</sup> and the  
140 method of limits.<sup>23</sup> After an adaptation period at a neutral temperature of 32 °C, the  
141 temperature increased (heating up to 50 °C) at a linear rate of 1 °C/s, until the patient pressed  
142 a signal button when they began to feel warm ('first perception' or 'detection' threshold). The  
143 detection thresholds (in °C) were determined as the average value from three trials and the  
144 absolute difference between the measured threshold and the neutral baseline temperature of  
145 32 °C. The WDT were abnormal if they were above 5.8 °C at UL or 10.5 °C at LL. These  
146 normative values have been established in a large number of healthy subjects and are evenly  
147 distributed in terms of age and sex.<sup>24</sup>

148 Electrochemical Skin Conductance (ESC) was used to assess autonomic C-fibers. ESC was  
149 performed with Sudoscan® (Impeto Medical, Paris, France).<sup>25,26</sup> The patient stood, placing  
150 both palms and soles on large nickel electrode plates, through which low-voltage direct  
151 current (less than 4 V) was delivered for 2 minutes. The electrodes were alternately used as  
152 anode and cathode, and the current between the electrodes was generated by reverse  
153 iontophoresis. The local conductance (in microsiemens,  $\mu\text{S}$ ) was measured simultaneously at  
154 the four extremities from the electrochemical reaction between sweat chloride ions released  
155 by the sweat glands and the nickel electrode plates delivering the direct current. The ESC was  
156 considered abnormal if it was below 64  $\mu\text{S}$  at the UL or 67  $\mu\text{S}$  at the LL.

157

## 158 **Pathological investigation**

159 Epidermal innervation was assessed using 3 mm punch skin biopsies taken from the right calf  
160 (10 cm above the lateral malleolus) and the proximal lateral right thigh (20 cm below the  
161 anterosuperior iliac spine).<sup>27</sup> The skin biopsies were fixed, cryoprotected, sectioned, and  
162 immunostained with polyclonal antibodies against panaxonal marker, protein gene product  
163 9.5 (PGP9.5). Observers assessed the linear density/mm of ENF from three to six 50  $\mu\text{m}$  thick  
164 sections selected at random from each biopsy specimen. ENF was considered abnormal in the  
165 calf if it was below the 5<sup>th</sup> percentile values of previously published age- and sex-normative  
166 data.<sup>28</sup> There were no normative data for ENF in the thigh. However, normal ENF in the thigh  
167 is reported to be 130% higher than the ENF in the calf.<sup>29</sup> Therefore, we considered abnormal  
168 ENF in the thigh if it was below the 5<sup>th</sup> percentile values of previously published age- and  
169 sex-normative data for the calf, or if it was below the value of ENF in the calf in the same  
170 patient (i.e.,  $\text{ENF}_{\text{thigh}}/\text{ENF}_{\text{calf}}$  ratio < 1).

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

172

## 173 **Biological investigation**

174 The following tests were performed: complete blood count (20 patients), renal (20), liver (20)  
175 and thyroid (20) function tests, lipid screen (20), C-reactive protein (20), fasting blood  
176 glucose (20), glycosylated hemoglobin (20), antinuclear antibody (20), anti-SSA and SSB  
177 antibodies (19), antineutrophil cytoplasmic antibodies (14), serum immunofixation (19),  
178 cryoglobulin (7), hepatitis B and C titers (18), Lyme titer (15), HIV titer (18), vitamin B12

179 and folate levels (18), anti-transglutaminase and anti-endomysium antibodies (13), anti-  
180 thyroperoxydase (anti-TPO) and anti-thyroglobulin antibodies (anti-Tg) (7), antiganglioside  
181 antibodies (10), onconeural antibodies such as antiHu antibodies (13), anti-contactin-  
182 associated protein-2 antibodies (anti-CASPR2, 20), antibodies targeting the node and the  
183 paranode of Ranvier [anti-contactin-associated protein (anti-CASPR1), anti-contactin (anti-  
184 CNTN1), anti-neurofascin 155 (anti-Nfasc155) antibodies, 20], anti-fibroblast growth factor 3  
185 antibodies (anti-FGFR3, 18), genetic testing for *TTR* (5), genetic testing for *SCN9A*, *SCN10A*,  
186 and *SCN11A* (4), and CSF analyses (5).

187

## 188 **Other investigations**

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

192

## 193 **Nerve and dorsal root ganglion (DRG) immunohistochemical labeling**

194 Sciatic nerve teased fibers and dorsal root ganglion (DRG) sections were prepared from adult  
195 C57BL/6J mice as previously described.<sup>30</sup> Tissues were post-fixed with acetone for 10 min at  
196 -20°C, washed, blocked for 1 h with blocking solution (5% fish skin gelatin, 0.1% Triton X-  
197 100 in phosphate-buffered saline), then incubated overnight at 4°C with the patients' sera  
198 diluted at 1:200 and goat anti-contactin-1 antibodies (1:2000; R&D Systems) to label  
199 paranodes or chicken anti-peripherin antibodies (1:500; Aves Labs) to stain unmyelinated  
200 axons. The next day, the slides were washed three times and incubated for 1 h with donkey  
201 anti-human IgG conjugated to Alexa 488, donkey anti-human IgM conjugated to Alexa 594,  
202 and donkey anti-goat IgG conjugated to Alexa 647 (1:500; Jackson Immunoresearch). The  
203 slides were mounted and counterstained with 4',6-diamidino-2-phenylindole (DAPI) to stain  
204 the nuclei. Sera from healthy subjects (n=10), patients with *PMP22* duplication (n=7), and  
205 patients with amyotrophic lateral sclerosis (n=5) were also analyzed.

206

207

208 **Neuron-based assay**

209 Cultured DRG were prepared from 1-month-old C57Bl/6J mice on 12 mm coverslips and  
210 maintained for 3 days *in vitro*. Live neurons were incubated with patients' sera diluted 1:50 in  
211 DMEM (Thermo Fisher) for 1 h at 37°C, washed several times, and fixed for 20 min with 2%  
212 paraformaldehyde. The cells were permeabilized with blocking solution, incubated for 1 h at  
213 room temperature with chicken antibodies against neurofilament heavy (1:2000; Ab5539;  
214 Merck Millipore), and incubated with secondary antibodies. Sera from healthy subjects and  
215 diseased controls were also analyzed.

216

217 **Statistical analyses**

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

220

221 **Data availability**

222 Data are available on request to the corresponding author.

223

224

## 225 **RESULTS**

### 226 **Clinical features**

227 Twenty patients were included (60% women, median age [IQR] 44.2 years [35.7–56.2]). The  
228 clinical features of the patients are shown in *Table 1*. A precipitating event was present in 16  
229 patients (80%): an infectious event in eight, a recently introduced treatment in five (antibiotics  
230 in two, anti-tumor necrosis factor  $\alpha$ , vitamin, enzyme replacement therapy), and vaccination  
231 in three. The median duration of the progression phase was 14 days [5–28]. Seventeen  
232 patients reported pain (85%). Paresthesia was observed in 14 patients (70%). The symptom  
233 distributions at onset and last follow-up are presented individually in *Figure 1*. Autonomic  
234 involvement was reported in 12 patients (60%), mainly faintness and tachycardia. Pinprick  
235 alteration was present in 18 patients (90%), including hypoalgesia in 11 patients, hyperalgesia  
236 in five, or both in different sites in two patients. Responses to heat and cold were altered in 18  
237 patients (90%), including hypoalgesia in 13 patients and hyperalgesia or allodynia in five. The  
238 clinical pattern was not length-dependent in 17 patients (85%).

239

### 240 **Diagnostic evaluation**

241 The neurophysiological and pathological features are presented in *Table 2*. All the patients  
242 underwent at least one neurophysiological test. These tests showed evidence of small fiber  
243 involvement in 15 patients (75%). The recording of LEPs was the most sensitive test (60%).  
244 The sensitivities of WDT and ESC were lower (39% and 31%). Among the five patients with  
245 normal neurophysiological findings, patient 3 was assessed after spontaneous complete  
246 recovery of symptoms. Eleven patients underwent skin biopsies. ENF was reduced in six  
247 patients (55%). Five patients had normal ENF in the calf but exclusively reduced in the thigh.  
248 Therefore, considering both neurophysiological studies and ENF, SFN was definite in 18  
249 patients (90%) and remained probable in two patients.

250

### 251 **Immunological studies**

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

255 Abnormal laboratory results and immunological features of the patients are presented in *Table*  
256 *3*. Anti-CASPR2 IgG antibodies were present in 1/20 of the patients, as we previously  
257 reported.<sup>31</sup> Anti-FGFR3 IgG antibodies were positive for 4/18 patients. Two of the seven  
258 tested patients had anti-thyroid antibodies.

259 *In vitro* studies revealed mouse sciatic nerve fiber or DRG immunostaining with the sera from  
260 14 patients (70%). Immunostaining was not observed with sera from either healthy subjects or  
261 diseased controls. Immunostaining was obtained only with anti-IgG, but not with anti-IgM  
262 antibodies. Different immunostaining patterns in sciatic nerve fibers and DRG are shown in  
263 *Figures 2* and *3* respectively. The sera from three patients contained antibodies that lead to  
264 paranodal immunostaining of Schwann cells (No. 6) or axons (Nos. 11 and 13). The serum  
265 from patient No. 10 had antibodies that caused juxtapanode immunostaining, consistent  
266 with circulating anti-CASPR2 antibodies, but also unmyelinated fiber immunostaining.<sup>31</sup> The  
267 sera from five patients lead to unmyelinated fiber immunostaining. The sera from a total of  
268 five of the tested patients contained antibodies for DRG.

269

## 270 **Disease course and treatment response**

271 The disease course varied (*Table 1*). Thirteen patients (65%) reported recovery of symptoms,  
272 complete in four patients or partial in nine. Five patients (25%) experienced a steady and  
273 chronic course after an acute onset. Four patients (20%) reported relapses, followed by a  
274 chronic clinical condition in two, complete recovery in one, and partial recovery in one. Three  
275 patients received a one-month course of oral corticosteroids at 1mg/kg during the acute phase  
276 and presented with complete or partial recovery. Two patients received intravenous  
277 immunoglobulin (IVIg) after the acute phase, without any efficacy. Patient 10, with anti-  
278 CASPR2 antibodies, also underwent plasma exchange without any efficacy. None of the 20  
279 patients had developed large fiber involvement at the last follow-up (median 4.8 years [3.2–  
280 8.0]).

281

282



## 283 DISCUSSION

284 We report a series of AOSFN cases, with 20 patients collected over five years from a tertiary  
285 center, suggesting that it is a rare condition. To date, only a few small series have been  
286 reported ranging from one to six patients, some of which are them restricted to post-vaccinal  
287 or post-infectious contexts (*Table 4*).<sup>13,6,32,14,17,18,15,19,16</sup> In the present series, we draw a picture  
288 of AOSFN, including clinical, neurophysiological, pathological, and experimental features.  
289 Patients with AOSFN have variable disease courses, and one-third of patients have  
290 unfavorable outcomes. *In vitro* analyses provided arguments for a possible immune-mediated  
291 process.

292

293 The diagnosis of AOSFN may be challenging in clinical practice. Patients usually present  
294 with acute symmetric non-length-dependent neuropathic pain, frequently preceded by a  
295 particular event, such as infection or vaccination. In a previous cohort of non-length-  
296 dependent SFN, one-third of patients had an acute onset.<sup>12</sup> However, patients may be painless,  
297 as in other SFN presentations.<sup>33</sup> During the acute phase, the absence of large fiber  
298 involvement on clinical examination and NCS study ruled out acute inflammatory  
299 demyelinating polyneuropathy.<sup>34</sup> In addition, we found normal CSF, while results were more  
300 discrepant in previous studies.<sup>6,13-15</sup> Functional neurological disorders should be considered  
301 in the context of a predominantly painful presentation with normal investigations. However,  
302 this was not the case in our series of patients who presented clinical signs of sensory disorders  
303 and abnormal neurophysiological or neuropathological findings, leading to the diagnosis of  
304 definite SFN in 90% of patients. Two patients were diagnosed with probable SFN because  
305 their neurophysiological findings were normal, but a skin biopsy was unfortunately not  
306 performed. In the present study, we used a battery of neurophysiological tests to assess A $\delta$   
307 and C sensory fibers and C autonomic fibers. In previously published series,  
308 neurophysiological assessment was rarely performed or limited to a single test. Interestingly,  
309 LEPs have been the most sensitive indicator of SFN. In contrast, thermal QST and ESC  
310 exhibited poor sensitivity, below 40%. This is consistent with our previously published data  
311 on the sensitivity of neurophysiological tests for diagnosing SFN.<sup>24</sup> In contrast, ENF was  
312 reduced more often in the thigh than in the calf, which is consistent with non-length-  
313 dependent neuropathy. In this context, other laboratory tests investigating small nerve fibers  
314 would have been useful to perform, such as corneal confocal microscopy.<sup>35</sup> Symptoms

315 associated with small nerve fibers involvement, such as pain, can be explained by lesions of  
316 these fibers, but also by their dysfunction (leading to nerve hyperexcitability<sup>36</sup>), or a  
317 combination of these phenomena.<sup>37</sup> Thus, the normality of neuropathological and  
318 neurophysiological investigations cannot rule out the involvement of small fibers in a clinical  
319 picture characterized by only positive sensory symptoms.. In the present series, the patients  
320 had variable disease courses, as was also the case for acute-onset inflammatory neuropathies  
321 affecting large-diameter fibers. AOSFN may have complete recovery or sequelae, such as  
322 Guillain-Barré syndrome,<sup>38</sup> or may be the onset of chronic neuropathy, such as acute-onset  
323 chronic inflammatory demyelinating polyneuropathy.<sup>39</sup> One cannot exclude that patients may  
324 later develop an associated large-fiber involvement, although the median follow-up was 4.8  
325 years in this study. The proportion of patients with an unfavorable course may be  
326 overestimated because our hospital is a tertiary neuromuscular center. Therefore, patients with  
327 AOSFN whose symptoms had complete and rapid resolution may not have benefited from  
328 neurological evaluation at our center, which may have been requested for patients with a more  
329 prolonged course of the disease.

330

331 The present investigation suggests that immune dysfunction is the cause of AOSFN. A  
332 precipitating event was frequently found, either infection or vaccination, as in previous series  
333 of AOSFN<sup>13-16,18,19</sup>, as well as other types of neuropathies, such as Guillain-Barré syndrome<sup>38</sup>  
334 or post-COVID neuropathy.<sup>40</sup> In three patients with AOSFN, their sera showed transient  
335 immunoreactivity to murine small fibers during the acute phase.<sup>15</sup> The present *in vitro* studies  
336 are also compatible with antibody-associated pathophysiology. Indeed, *in vitro* studies  
337 demonstrated IgG immunostaining by the sera of most patients with AOSFN. Although  
338 heterogeneous binding sites suggest non-specific findings, the absence of immunostaining  
339 from the sera of healthy subjects or diseased controls supports an immune-mediated process  
340 in AOSFN. Patient sera contained antibodies to unmyelinated or thinly myelinated fibers,  
341 including the paranodal region, and DRGs. IgG deposits on nerves have also been found in  
342 other types of chronic inflammatory neuropathy.<sup>41</sup> However, one cannot exclude the  
343 possibility that these immunoreactions were a consequence of peripheral nervous system  
344 lesions and not the cause of these lesions. Indeed, an antibody probably responsible for the  
345 occurrence of AOSFN was identified in only one previously reported patient with CASPR2-  
346 related juxtapanodopathy, which exclusively involved small nerve fibers.<sup>31,42</sup> The number of  
347 autoantibodies associated with SFN has increased in recent years, including anti-TS-HDS and

348 anti-FGFR-3 antibodies which have been associated with AOSFN in some cases.<sup>3,43</sup> However,  
349 their pathogenicity in SFN remains uncertain.<sup>44</sup> Moreover, we observed IgG cell membrane  
350 immunostaining. This contrasts with the reported anti-TS-HDS antibodies which are IgM.<sup>3</sup> It  
351 also contrasts with anti-FGFR-3 IgG antibodies which usually target the intracellular portion  
352 of FGFR-3.<sup>45</sup> Thus, the extracellular immunostaining pattern in the present study is not  
353 consistent with anti-FGFR-3 antibody reactivity, despite circulating anti-FGFR-3 antibodies  
354 being identified in 20% of our patients. Anti-plexin D1 IgG antibodies seem to be frequently  
355 found in painful neuropathies in Japanese patients,<sup>2,46</sup> and induce hyperexcitability of DRG  
356 sensory neurons.<sup>47</sup> It would be interesting to look for the presence of anti-plexin D1  
357 antibodies, notably in patients with immunostaining involving DRG. Our *in vitro* studies did  
358 not reveal signs of autoimmunity in some patients. However, patients' sera were collected  
359 several months after the disease onset and this may have led to missing a transient immune  
360 process.<sup>15</sup> Finally, although paraneoplastic neuropathies were excluded from our series on the  
361 basis of the negativity of onconeural antibodies and clinical follow-up, such a cause could be  
362 possibly encountered in a context of AOSFN, even if we lack data to make this assumption.

363

364 In conclusion, the present cohort supports the concept of AOSFN and refines its clinical  
365 description. The typical clinical pattern is associated with acute non-length-dependent  
366 symmetric painful neuropathy with a monophasic or relapsing chronic course. *In vitro* studies  
367 have provided clues regarding immune pathogenesis. Regarding treatment, corticosteroids in  
368 the acute phase could have a beneficial effect, whereas IVIg infusions were ineffective in two  
369 patients who were treated for chronic symptoms long after the acute phase.

370

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373

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376

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388

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500 **TABLES**501 **Table 1. Clinical features of the patients**

502

Patient	Age (y) / sex	Relevant medical history	Precipitating event	Progression phase duration (days)	Symptoms			Clinical signs				Disease Course	Treatment	
					Pain	Paresthesia	Dysautonomia	Pinprick alteration		Thermal alteration				Length dependent pattern
								hypo	hyper	hypo	hyper			
1	59/F	GSD II	$\alpha$ -alglucosidase	14	Burning	-	Faintness	-	+	-	+	-	Chronic	
2	52/F	None	FLS	5	Burning, stretching, allodynia	-	Flush, tachycardia	+	-	+	-	-	Partial recovery	
3	28/F	Endometriosis	Vaccination	28	Allodynia	Tingling	Tachycardia	-	+	-	+	-	Recovery	
4	33/M	Treated HCV	No	28	Burning, cramping, deep pain	-	Extremity discoloration, faintness	-	+	-	+	-	Partial recovery	
5	57/M	None	FLS	3	-	Contact dysesthesia	Faintness	-	+	-	+	-	Relapses then chronic	IVIg (1 at 2g/kg): no effect
6	43/M	AS during follow-up	Vaccination	28	Electric-like	-	Vertigo, bloat, erectile dysfunction	-	-	+	-	-	Recovery	
7	52/M	None	Syphilis	28	Burning	Tingling	Tachycardia	+	-	+	-	+	Partial recovery	
8	23/M	None	FLS	15	Allodynia, electric-like	Tingling, internal tremor	-	-	+	-	+	-	Partial recovery	
9	35/F	Psoriasis	Anti-TNF $\alpha$	15	Cramping	Numbness	Vertigo	+	-	+	-	-	Relapses, then partial recovery	
10	69/M	None	FLS	7	Burning	Tingling	-	+	-	-	-	+	Chronic	IVIg (3 at 2g/kg), PLEX (4



														in 2 weeks): no effect
11	38/F	None	No	15	Burning, tightness	Warmth	-	+	-	+	-	-	Relapsing then chronic	
12	44/F	None	No	5	-	Tingling, numbness	-	-	-	+	-	-	Relapsing then recovery	
13	34/F	None	Ciprofloxacin	3	Burning	Tingling	Tachycardia, faintness, bloat, urinary frequency	+	-	+	-	-	Chronic	
14	37/F	TRAPS	Diarrhoea	21	Burning	-	-	+	-	+	-	-	Recovery	Oral CS (1mg/kg for 1 month): efficacy
15	59/F	None	COVID-19	28	Cramps, electric-like	Tingling	-	+	-	+	-	-	Partial recovery	
16	72/F	None	None	21	Burning	Tingling	-	+	-	-	-	-	Partial recovery	Oral CS (1mg/kg for 1 week): efficacy
17	55/F	None	Vaccination	28	Electric-like, prickling	Contact dysesthesia	-	+	+	+	-	+	Partial recovery	Oral CS (1mg/kg for 1 month): efficacy
18	22/H	None	FLS	7	-	Numbness	POTS, urinary frequency, accommodation disorders	+	-	+	-	-	Chronic	
19	39/F	EMC	B6 vitamin	1	Electric-like, prickling	Tingling	Tachycardia	+	+	+	-	-	Chronic	

20	46/H	Sarcoidosis	Metronidazole & tetracycline	3	Burning	-	Xerophthalmia, urinary frequency	+	-	+	-	-	Partial recovery	
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503 AS: ankylosing spondylitis. Anti-TNF $\alpha$ : anti-tumor necrosis factor  $\alpha$ . COVID-19: coronavirus disease 2019. CS: corticosteroids. EMC: erythema  
504 migrans chronica. F: female. FLS: flu-like syndrome. GSD II: glycogen storage disease type II. HCV: hepatitis C virus. Hyper: hyperalgesia.  
505 Hypo: hypoalgesia. IVIg: intravenous immunoglobulin. M: male. PLEX: plasma exchange. POTS: postural orthostatic tachycardia syndrome.  
506 TRAPS: TNF receptor-associated periodic syndrome.

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507 **Table 2. Neurophysiological and pathological features of the patients**

508

Patient	Neurophysiological Assessment							ENF		SFN Diagnosis (Definite or probable)
	Ab test ≥1	LL LEP	UL LEP	LL ESC	UL ESC	LL WDT	UL WDT	Calf	Thigh	
<b>Ab testing</b>	<b>15/20 (75%)</b>	<b>12/20 (60%)</b>		<b>7/18 (39%)</b>		<b>5/16 (31%)</b>		<b>6/11 (55%)</b>		<b>Definite: 18/20 (90%)</b>
		<b>10/20 (50%)</b>	<b>11/19 (58%)</b>	<b>5/18 (28%)</b>	<b>6/18 (33%)</b>	<b>4/15 (27%)</b>	<b>3/16 (19%)</b>	<b>1/11 (9%)</b>	<b>6/9 (67%)</b>	
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

509

510 Ab: abnormal. ENF: epidermal nerve fiber density. ESC: electrochemical skin conductance.  
 511 LEP: Laser-evoked potential. LL: lower limbs. m: mean. N: normal. ND: not done. UL: upper  
 512 limbs. SFN: small fiber neuropathy. WDT: warm detection threshold. Y: Yes.

513

514

515 **Table 3. Laboratory and *in vitro* studies of the patients**

516

Patient	Delay between the onset and laboratory assessment (days)	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	1213	N	-	-	-	Negative
5	3613	Anti-FGFR3 +	Unmyelinated fibers	+	+	Small fibers
6	1370	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	1572	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	1529	High B6 level	-	-	-	Negative
20	354	Anti-FGFR3 +	-	-	-	Negative

517

518 CASPR2: contactin-associated protein-2. DRG: Dorsal root ganglion. FGFR3: fibroblast growth factor receptor 3. IF: Immunofluorescence. N:  
519 normal. TG: thyroglobulin. TPO: thyroperoxidase. +: staining.

520 **Table 4. Literature synthesis of acute-onset small fiber neuropathy**

521

Authors/year	Number of cases	Median Age (years) / Women	Precipitating event	Clinical features	Neurophysiology / ENF	CSF / Immunology	Treatment	Disease Course
Seneviratne 2002 <sup>13</sup>	6	31 / 33%	Infection: 67%	Numbness: 100% Burning pain: 67%	Normal NCS: 100% Abnormal SSR: 20% ENF: not performed	CSF protein elevation (100%)	Oral CS: 1 patient with partial recovery.	Complete recovery in 33% Partial recovery in 67%
Dabby 2006 <sup>6</sup>	4	21 / 50%	No	Burning pain: 100%	Normal NCS: 100% Abnormal thermal QST: 100% Reduced ENF: 100%	CSF: normal in 1 patient	IVIg: inefficacy in 1 patient Oral CS: all patients with efficacy.	Complete recovery in 75% Relapse in 25%
Paticoff 2007 <sup>32</sup>	1	20	No	Erythralgia, sensory loss	Normal NCS Reduced ENF	CSF: normal	IV and oral CS: efficacy	Complete recovery
Souayah 2009 <sup>14</sup>	5	46 / 60%	Vaccination: 100%	Numbness: 60% Burning pain: 60%	Normal NCS: 100% Reduced ENF: 100%	CSF: normal in 1 patient	IVIg: inefficacy in 1 patient Oral CS: inefficacy in 1 patient	Partial recovery in 40% Chronic course in 40% Not available in 20%
Miyazaki 2011 <sup>17</sup>	1	53 / 100%	0	Thermal anesthesia, anhidrosis, anosmia and ageusia	Normal NCS ENF: not performed	Anti-GalNAc-GD1a antibodies	IVIg: efficacy	Partial recovery
Kafaie 2016 <sup>18</sup>	1	14 / 100%	Vaccination	Generalized pain and paresthesia	Normal NCS Reduced ENF	-	-	Chronic course
Yuki 2018 <sup>15</sup>	3	26 / 0%	Infection: 100%	Neuropathic pain: 100% Autonomic involvement: 100%	Normal NCS: 100% Reduced ENF: 100%	CSF protein elevation (100%) Transient presence of IgG antibodies in the acute phase with murine small nerve fibers	IVIg: 2 patients. Oral CS: 1 patient	Partial recovery in 100%

						immunostaining.		
Faignart 2020 <sup>19</sup>	5	9 / 40%	Infection: 60%	Acute monophasic erythromelalgia	Abnormal ESC in 1/1 patient Abnormal SSR in 1/2 patients Abnormal ENF: 3/4 patients	Elevated AAN in 1 patient	IVIg: 1 patient IV and oral CS: 1 patient	Complete recovery in 100%
Abbott 2022 <sup>16</sup>	3	60 / 67%	Vaccination: 100%	Neuropathic pain: 33% Altered temperature sensation: 67%	Normal NCS: 100% Abnormal thermal QST: 100% Reduced ENF: 100%	-	-	Complete recovery in 33% Chronic course in 67%

522 AAN: antinuclear antibody. CS: corticosteroids. ENF: epidermal nerve fiber density. ESC: electrochemical skin conductance. GalNAc-GD1a: N-  
523 acetylgalactosaminyl-GD1a. IVIg: intravenous immunoglobulins. NCS: nerve conduction study. QST: quantitative sensory testing. SSR:  
524 sympathetic skin response.

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## 526 **FIGURE LEGENDS**

### 527 **Figure 1. Individual distribution of sensory symptoms at the peak and the last follow-up.**

528 Body diagrams representing the regional distribution of sensory symptoms at the peak (A)  
529 and last follow-up (B) for the front (left) and back (right) of 20 patients with acute-onset small  
530 fiber neuropathy. The numbers on the top left of each figure correspond to the patient  
531 numbers in Tables 1, 2, and 3.

532

### 533 **Figure 2. Patterns of nerve fiber staining.**

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

541

### 542 **Figure 3. Patterns of cultured dorsal root ganglion staining**

543 Live dorsal root ganglia (DRG) were incubated with patient sera, fixed, and immunostained  
544 for human IgG (green) and antibodies against neurofilament heavy (NF-H; red) to stain DRG.  
545 Some patients did not show reactivity toward the DRG (A). Other patients showed strong IgG  
546 reactivity against surface antigens expressed by both large and small cells in DRG (B-C).  
547 Patient 10, who presented with circulating anti-CASPR2 antibodies, showed strong reactivity  
548 against the soma and axons of the DRG (B). Patient 8, without any identified antibody target,  
549 also showed strong reactivity against the DRG soma and axons (C). Scale bar: 10  $\mu$ m.







