# Small Fiber Neuropathy in Children: Two Case Reports Illustrating the Importance of Recognition

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## abstract

Small fiber neuropathy (SFN) is a debilitating condition that often leads to pain and autonomic dysfunction. In the last few decades, SFN has been gaining more attention, particularly in adults. However, literature about SFN in children remains limited. The present article reports the cases of 2 adolescent girls diagnosed with SFN. The first patient (14 years of age) complained about painful itch and tingling in her legs, as well as dysautonomia symptoms for years. She also reported a red/purple-type discoloration of her legs aggravated by warmth and standing, compatible with erythromelalgia. The diagnosis of SFN was confirmed by a reduced intraepidermal nerve fiber density (IENFD) in skin biopsy sample. No underlying conditions were found. Symptomatic neuropathic pain treatment was started with moderate effect. The second patient (16 years of age) developed painful sensations in both feet and hands 6 weeks after an ICU admission for diabetic ketoacidosis, which included dysautonomia symptoms. She also exhibited some signs of erythromelalgia. The patient was diagnosed with predominant SFN (abnormal IENFD and quantitative sensory testing) as well as minor large nerve fiber involvement. Treatment with duloxetine, combined with a rehabilitation program, resulted in a marked improvement in her daily functioning. Although the SFN diagnosis in these 2 cases could be established according to the definition of SFN used in adults, additional diagnostic tools are needed that may be more appropriate for children. Additional information about the course of SFN in children may result in better treatment options.

Small fiber neuropathy (SFN) is a condition in which predominantly thin myelinated Aδ-fibers and unmyelinated C-fibers are affected. It is characterized by sensory symptoms, particularly neuropathic pain and autonomic dysfunction.[1] Physical examination often reveals no obvious abnormalities because muscle strength, vibration sense, and tendon reflexes are preserved. In pure SFN, results of nerve conduction studies (NCS) are normal because of the absence of large nerve fiber damage. According to international criteria, SFN is based on the clinical picture (≥2 SFN-related symptoms, not otherwise explained) (Table 1), with an abnormal intraepidermal nerve fiber density (IENFD) measurement in the skin biopsy sample[2] and/or abnormal temperature thresholds in quantitative sensory testing (QST).[1,3] After the diagnosis is complete, it is important to search for associated conditions because these may be treatable. These conditions can be categorized into metabolic, immune-mediated, infectious, toxic, and hereditary.[1]

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**DOI:** 10.1542/peds.2016-1215

Accepted for publication Jun 20, 2016

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).



**FINANCIAL DISCLOSURE:** Dr Faber reports grants from the European Union 7th Framework Programme (grant 602273), the Prinses Beatrix Spierfonds (W.OR12-01), and Grifols and Lamepro outside the submitted work. Dr Merkies received funding for research from the Talecris Talents program, the GSB CIDP Foundation International, and from the European Union 7th Framework Programme (grant 602273). In addition, a research

**To cite:** Hoeijmakers JG, Faber CG, Miedema CJ, et al. Small Fiber Neuropathy in Children: Two Case Reports Illustrating the Importance of Recognition. *Pediatrics.* 2016;138(4):e20161215

**TABLE 1** Symptoms of SFN

| Sensory Symptoms | Autonomic Symptoms |
|---|---|
| Pain (burning, shooting, prickling, or itching) | Sicca syndrome (dry eyes and mouth) |
| Paresthesias | Accommodation problems |
| Allodynia | Hyperhidrosis or hypohidrosis |
| Thermal sensory loss | Micturition problems |
| Pinprick loss | Bowel disturbances (eg, constipation, diarrhea, gastroparesis) |
| Sheet or sock intolerance | Hot flashes |
| Restless legs syndrome | Orthostatic dizziness |
| | Cardiac palpitations |
| | Impotence and/or diminished ejaculation or lubrication[a] |

The presence of ≥2 symptoms, not otherwise explained, is suggestive for the diagnosis of SFN.
[a] Sexual dysfunction not applicable in children.

In adults, recent calculations show that SFN has a minimum prevalence of 53 cases in 100 000, which indicates it is not a rare disorder.[4] The impact on quality of life is severe, both physically and mentally.[5] In children, little is known about the epidemiology and the implications for daily life, partly perhaps due to the difficulty in fulfilling the criteria for SFN in children. Especially in young children, a precise description of their symptoms may be difficult. Several types of self-reported pediatric pain measures are available, but all have their own shortcomings and do not cover all SFN-related symptoms.[6] The specific 13-item SFN Symptom Inventory Questionnaire has not yet been validated in children.[7,8] Furthermore, normative values for IENFD in subjects aged <20 years are lacking.[2] Contrary to adults, QST has been implemented much less in children.[3] However, it does seem to be feasible and valid for children aged ≥5 years with their own reference values.[9]

In the present article, we describe 2 cases of children diagnosed with SFN, address the importance of recognition of this diagnosis, and briefly discuss the relevant literature.

## CASE REPORTS

### Patient 1

A 14-year-old girl was referred by the child neurologist (J.V.) because of a 7-year history of tingling and itch in the lower legs after standing for a certain period of time (eg, standing in line for the cash register). Over time, the same symptoms occurred after increasingly shorter periods of standing. One year before presenting, she noticed a red/purple discoloration of her feet, without profound swelling (Fig 1). The redness was then aggravated when taking warm showers; sitting relieved the symptoms. Dysautonomia issues were also present, such as orthostatic dizziness, palpitations, dry eyes, accommodation problems, constipation, and dripping after micturition. The symptoms remained limited to the lower legs. Exercise was painful, and her symptoms interfered with sports and dancing. Medical history was unremarkable other than eczema; except for eczema ointment, no other drugs were used. Family history revealed similar symptoms in the patient's mother and older sister, although was less severe.

Neurologic examination, NCS, and QST revealed no abnormalities (Tables 2, 3, and 4). A skin biopsy specimen taken from the distal part of the leg, 10 cm above the lateral malleolus, demonstrated an IENFD of 7.8/mm. This outcome was decreased compared with normative values for the nearest available age group (5th percentile age 20–29 years, 8.4/mm). Based on clinical symptoms and abnormal IENFD, the patient was diagnosed with having SFN with signs of erythromelalgia (paroxysmal painful red limbs, aggravated by warmth and exercise).

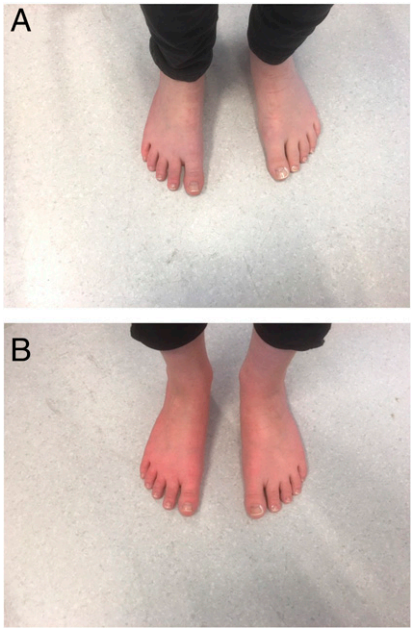


**FIGURE 1**
Red-discolored legs of patient 1. A, Normal color of the feet after resting. B, Redness of the feet after 5 minutes of standing. The redness is induced by exercise and by taking a warm shower, compatible with erythromelalgia.

Chest radiograph and extensive laboratory test results revealed no evidence of the following: diabetes mellitus; impaired glucose tolerance; hyperlipidemia; liver-, kidney-, or thyroid dysfunction; monoclonal gammopathy; connective tissue disorders; sarcoidosis; Sjögren syndrome; Fabry disease; celiac disease; HIV; Lyme disease; and vitamin $B_6$ intoxication or vitamin $B_1$ or $B_{12}$ deficiency. DNA analysis of the SCN9A-, SCN10A-, and SCN11A-gene encoding, respectively, voltage-gated sodium channel (VGSC) $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$, showed no mutations. This approach excludes current stage sodium channelopathy in the examined isoforms as an underlying cause for the SFN and erythromelalgia. Symptomatic treatment with gabapentin was started but with only moderate pain relief.

**TABLE 2** Motor NCS

| Nerve | Record | Patient | Amplitude, mV | Conduction Velocity, m/s | Distal Latency, ms | Distal Distance, cm |
|---|---|---|---|---|---|---|
| Peroneal motor (normal values) | Extensor digitorum brevis | 1 | 6.1 (≥4.0) | 45.1 (≥40.0) | 3.7 (≤4.8) | 7 |
| | | 2 | 2.4[a] (≥4.0) | 40.0 (≥40.0) | 4.1 (≤4.8) | 7 |
| Tibial motor (normal values) | Abductor hallucis brevis | 1 | 11.8 (≥5.0) | 47.1 (≥40.0) | 5.8 (≤6.0) | 9 |
| | | 2 | 3.7[a] (≥4.0) | 35.2[a] (≥40.0) | 4.2 (≤6.0) | 9 |
| Median (normal values) | Abductor pollicis brevis | 1 | 10.3 (≥5.0) | 57.3 (≥50.0) | 3.3 (≤4.2) | 6 |
| | | 2 | 6.9 (≥5.0) | 47.5[a] (≥50.0) | 3.3 (≤4.2) | 6 |

[a] Abnormal. In all recordings, skin temperature was >32°C. All measurements were performed unilaterally.

**TABLE 3** Sensory NCS

| Nerve | Record | Patient | Amplitude, mV | Conduction Velocity, m/s |
|---|---|---|---|---|
| Sural (normal values) | Posterior ankle | 1 | 11.8 (≥6.0) | 47.1 (≥40.0) |
| | | 2 | 4.7[a] (≥6.0) | 41.4 (≥40.0) |
| Median (normal values) | Digitus II | 1 | 50.4 (≥10.0) | 50.0 (≥50.0) |
| | | 2 | 14.4 (≥10.0) | 51.7 (≥50.0) |

[a] Abnormal. In all recordings, skin temperature was >32°C. All measurements were performed unilaterally.

**TABLE 4** QST Results

| Variable | Dorsum Foot Right | | Dorsum Foot Left | | Thenar Right | | Thenar Left | |
|---|---|---|---|---|---|---|---|---|
| | Warmth | Cold | Warmth | Cold | Warmth | Cold | Warmth | Cold |
| Patient 1 (normal value) | 35.0 (<39.4) | 31.1 (>26.6) | 34.8 (<39.4) | 30.5 (>26.6) | 32.5 (<33.2) | 31.6 (>30.1) | 32.5 (<33.2) | 31.5 (>30.1) |
| Patient 2 (normal value) | 42.1[a] (<39.4) | 30.5 (>26.6) | 42.0[a] (<39.4) | 29.5 (>26.6) | NA | NA | NA | NA |

NA, not applicable.

[a] Abnormal. The method of levels was used (per stimulus answering whether a warmer or cooler temperature is sensed). A measurement was classified as abnormal when its *z* value was >2.5. In cases in which an abnormal value was found at the feet, the hands were not tested.

### Patient 2

A 16-year-old girl developed lower back pain without radiation 2 weeks after an ICU admission for diabetic ketoacidosis. Six weeks later, she developed continuous warm and painful burning and tingling sensations in both her feet, accompanied by a red discoloration. Occasionally, the same sensations were present in her hands but to a lesser extent. Due to the pain, the patient's sleep was disturbed. She could not withstand blankets on her feet, and exercise and warm water aggravated the pain. Bathing in cold water provided some relief from these symptoms. Dysautonomia issues consisted of dry eyes, hyperhidrosis, constipation, esophageal motility problems, and palpitations. She was unable to continue her training as a beautician. Except for the recently established diagnosis of maturity-onset diabetes of the young type 3, the patient's medical history was unremarkable. Furthermore, family history revealed a mother and brother with diabetes mellitus but with no neuropathic symptoms.

Neurologic examination showed no signs of large nerve fiber dysfunction or other abnormalities. NCS revealed moderate decreased compound motor action potentials of the peroneal and tibial nerve, decreased sensory nerve action potentials of the sural nerve, and prolonged F waves of the median, peroneal, and tibial nerves, compatible with a mild sensory-motor polyneuropathy (Tables 2 and 3). Because these findings could not explain the entire clinical picture, additional investigations to examine small nerve fiber involvement were performed. QST revealed abnormal temperature thresholds for warm sensation of both feet (Table 4). Skin biopsy results revealed a reduced IENFD of 4.04/mm. In accordance with the clinical symptoms, these results confirmed the diagnosis of SFN with mild involvement of large nerve fibers and signs of erythromelalgia.

Results of similar tests as performed in case 1 revealed no other associated conditions. No VGSC mutations were found. Gabapentin had no effect on the pain, and the patient was switched to duloxetine, which resulted in significant pain relief. In addition, a rehabilitation program was initiated that resulted in a gradual improvement of her daily activities.

## DISCUSSION

These 2 case reports demonstrate that SFN does not exclusively affect adults. In children, the symptoms also interfere with activities of daily living that may hinder normal development. Early recognition is important to start appropriate treatment in time. There was a diagnostic delay of 7 years in patient 1, leading to a delay in proper treatment.

Literature on SFN in children is scarce. In a recent study, SFN was confirmed

in 21 of 41 patients with unexplained widespread pain that started before the age of 21 years.[10] However, the applied diagnostic criteria in this study were questionable and not compatible with the international diagnostic criteria of SFN.[1] One or more abnormal diagnostic test results, including autonomic function testing, sensory nerve biopsy, or IENFD in skin biopsy, were required to establish the diagnosis.[10] Autonomic function tests are useful when autonomic polyneuropathy is suspected. However, the sensitivity and specificity vary per test, and not all tests are easy to perform.[11] The value of sensory nerve biopsy in patients with SFN has never been proven. IENFD is often considered the most important and objective diagnostic tool,[2,12,13] but values for healthy humans aged <20 years are based on very small numbers and are therefore not reliable as normative values.[14] Moreover, regarding the aforementioned study, IENF per square millimeter of skin surface area was used[10,15] instead of IENF per millimeter skin as is recommended.[12]

Because a skin biopsy is an invasive test, there are ethical issues involved in collecting data from healthy children. Corneal confocal microscopy is an emerging noninvasive diagnostic tool that also enables quantification of small nerve fibers, although in the cornea. In adults, corneal confocal microscopy seems to be sensitive and to correlate with a variety of parameters.[16,17] In addition, the method seems reliable and reproducible in children.[18]

Currently, QST is the best noninvasive test to examine the function of the smallest nerve fibers. Normative values are available for children aged ≥5 years.[9] The test has a good sensitivity, but is less specific, because central nervous system dysfunction can also cause abnormal results. For reliable measurements, QST requires the patient to be alert and cooperative.[3] To optimize the results, it is recommended to use the method of levels (per stimulus answering whether a warmer or cooler temperature is sensed) because this approach is reaction time–independent and applicable even in subjects who are difficult to examine (eg, cognitively impaired subjects, children).[3,19]

Induced skin wrinkling tests are easily applicable and could be a potential diagnostic test in children.[20] Immersion of fingertips in water or application of an eutectic mixture of local anesthetic cream stimulates the sympathetic neural supply, resulting in skin wrinkling. This process fails in SFN, and wrinkling is reduced or completely absent. Unfortunately, the currently used method (grading the degree of wrinkling subjectively) lacks reliability and requires further refinement.

More objective tests in which the Aδ- and C-fibers are stimulated selectively are nociceptive evoked potentials.[21,22] Currently, no research has been conducted to examine the applicability of nociceptive evoked potentials in children with neuropathic pain. Their diagnostic value in adults with SFN has also not been systematically investigated.

It is unknown if children diagnosed with SFN have to be screened for the same potentially associated clinical conditions as might be seen in adults. The second case patient developed SFN a short time after experiencing diabetic ketoacidosis. This cause is rare, both in children and adults. Acute painful neuropathy has been described after rapid glycemic control in a 14-year-old boy.[23] He also experienced ketoacidosis but developed symptoms 13 months later.

In both case reports, signs of erythromelalgia were present. This condition is characterized by episodic painful red limbs, induced by warmth and exercise. SFN is associated with erythromelalgia.[24] It has been suggested that both conditions are part of the same spectrum of human pain disorders. VGSC mutations have been found to be responsible for the clinical picture in some of these cases.[25] Despite being considered a partly related genetic entity, patients carrying gain-of-function VGCS mutations develop symptoms at different ages. The combination of a mutated VGSC channel and additional stressors might initiate particular molecular mechanisms leading to SFN symptoms and axonal degeneration.[26,27] It is likely that, particularly in children, these and other genetic factors play a role in the origin of SFN.[28] Although no VGSC mutation could have been demonstrated in patient 1, a genetic origin for her symptoms seems plausible because her mother and sister mentioned similar symptoms.

Unfortunately, because of the lack of research data on SFN in children, no specific treatment regimens are available. Studies regarding general pediatric neuropathic pain treatment are probably the best guidelines to use.[29,30]

## CONCLUSIONS

The diagnosis of SFN should be considered in children with unexplained pain. Other than IENFD and QST, additional diagnostics tools are needed that are more appropriate for children, including age-adjusted normative values. Better diagnostic criteria will facilitate the acquisition of knowledge about associated conditions, underlying pathophysiologic mechanisms, and course of the disease. This approach is also mandatory for the development of more specific treatment in children diagnosed with SFN.

## ABBREVIATIONS

IENFD: intraepidermal nerve fiber density
NCS: nerve conduction studies
QST: quantitative sensory testing
SFN: small fiber neuropathy
VGSC: voltage-gated sodium channel

foundation at the University of Maastricht received honoraria on behalf of Dr Merkies for participation in steering committees of the Talecris ICE Study, LFB, CSL Behring, Novartis, and Octapharma. None of the activities are related to the submitted work. The other authors have indicated they have no financial relationships relevant to this article to disclose.

**FUNDING:** No external funding.

**POTENTIAL CONFLICT OF INTEREST:** The authors have indicated they have no potential conflicts of interest to disclose.

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*Pediatrics* 2016;138;
DOI: 10.1542/peds.2016-1215 originally published online September 22, 2016;

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