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Eur J Paediatr Neurol. Author manuscript; available in PMC 2023 March 17.

Published in final edited form as:

Eur J Paediatr Neurol. 2020 September ; 28: 198–204. doi:10.1016/j.ejpn.2020.06.004.

Acute monophasic erythromelalgia pain in five children diagnosed as small-fiber neuropathy

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Abstract

The small-fiber polyneuropathies (SFN) are a class of diseases in which the small thin myelinated (Aδ) and/or unmyelinated (C) fibers within peripheral nerves malfunction and can degenerate. SFN usually begins in the farthest, most-vulnerable axons, so distal neuropathic pain and symptoms from micro-vascular dysregulation are common. It is well known in adults, e.g. from diabetes, human immunodeficiency virus, or neurotoxins, but considered extremely rare in children, linked mostly with pathogenic genetic variants in voltage-gated sodium channels. However, increasing evidence suggests that pediatric SFN is not rare, and that dysimmunity is the most common cause. Because most pediatric neurologists are unfamiliar with SFN, we report the diagnosis and management of 5 Swiss children, aged 6–11y, who presented with severe paroxysmal burning pain in the hands and feet temporarily relieved by cooling—the erythromelalgia presentation. Medical evaluations revealed autoimmune diseases in 3 families and 3/5 had preceding or concomitant infections. The standard diagnostic test (PGP9.5-immunolabeled lower-leg skin biopsy) confirmed SFN diagnoses in 3/4, and autonomic function testing (AFT) was abnormal in 2/3. Blood testing for etiology was unrevealing, including genetic testing in 3. Paracetamol and ibuprofen were ineffective. Two children responded to gabapentin plus mexiletine, one to carbamazepine, two to mexiletine plus immunotherapy (methylprednisolone/

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Financial disclosure

The authors have indicated they have no financial relationships relevant to this article to disclose.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article to disclose.

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IVIg). All recovered within 6 months, remaining well for years. These monophasic tempos and therapeutic responses are most consistent with acute post-infectious immune-mediated causality akin to Guillain-Barré large-fiber polyneuropathy. Skin biopsy and AFT for SFN, neuropathic-pain medications and immunotherapy should be considered for acute sporadic pediatric erythromelalgia.

Keywords

Erythromelalgia; Small-fiber neuropathy; Child; Monophasic; Dysimmune; Acute

1. Introduction

In healthy children, sudden onset of episodic burning pain in hands and feet without prior trauma or skin lesions is puzzling. It may be considered psychogenic or labeled erythromelalgia (red painful extremities in Greek), a syndrome characterized by bilateral, often paroxysmal and burning distal extremity pain, hyperemia and hyperthermia [1], first described in 1878 by S. Weir Mitchell [2]. Not all patients present fully and symptoms are worsened by external heat, or internal heat from exercise or fever. Most use cooling for temporary relief [1,3–5]. Anti-inflammatory and opioid analgesics are generally ineffective [1].

Most erythromelalgia presentations are caused by small-fiber polyneuropathy (SFN) [3,6–12]. SFN's classic sensory symptoms are pain and itch beginning distally in 3/4 patients. Internal symptoms include tachycardia, abnormal blood pressure, and abdominal distress from gastrointestinal dysmotility and microcirculatory insufficiency. SFN symptoms reflect spontaneous and/or excess firing of the small C-fiber neurons that sense pain and innervate small blood vessels. If prolonged, the excess potentials raise energy demands, permitting entry of excess ions and fluids that lead to distal degeneration of peripheral small-fibers and sensory loss [13,14]. In turn, distal axonal degeneration initiates trans-synaptic downregulation of inhibitory circuits in the dorsal horn and rostrally to compensate for reduced presynaptic input. In SFN, this can amplify or initiate spontaneous pain. In addition, peripheral axonal degeneration may cause sodium channels to accumulate more proximally rendering C-fibers hyperexcitable and spontaneously active [15].

In mature adults, common causes are chronic medical conditions (e.g. diabetes, monoclonal gammopathies) toxic (e.g. some cancer chemotherapies, arsenic, vitamin B6, anti-infectives) and immune-mediated, (e.g. Sjögren's [16], paraneoplastic). Blood-test screening identifies potentially treatable causes or contributors in 1/3–1/2 of patients [17,18]. Actual adult population prevalence is unknown. The only estimate – 52,95/100 000 – yields a global prevalence of 4 077 150, which is probably too low because ascertainment required specialist documentation of >2 symptoms, confirmatory skin biopsies or thermal thresholds and normal electrodiagnosis [19].

Pre-pubertal SFN is only recently recognized, hence there is no case definition and no epidemiologic prevalence is available [12]. Sensory and internal symptoms are similar to those in adults and erythromelalgia is a well-recognized presentation [1,9,12,20], It has been

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associated with pathogenic variants in genes coding for alpha subunits of the 3 voltage-gated sodium channels preferentially expressed in small-fiber sensory and sympathetic neurons, that are identifiable by sequencing [21,22]. Among 1139 Dutch adults with objectively confirmed pure SFN 5.1% had *SCN9A* variants, 3.7% had *SCN10A*, and 2.9% had *SCN11A* variants, although a U.S. study did not find elevated prevalence of *SCN* variants in neuropathy patients suggesting regional variability [23,24].

A few single case observations and 2 larger series link early acute SFN to dysimmunity analogous to Guillain-Barré syndrome (GBS). Additional evidence of dysimmune causality comes from reports, mainly in adolescents and young adults, showing beneficial effects of corticosteroids and intravenous immunoglobulins (IVIg), the primary treatments for immune large-fiber neuropathies [8–10,12,20,25–28] even in some patients with *SCN9A* variants [29]. Furthermore reports of associated autoantibodies [30,31] and a patient serum transfer study that replicated painful SFN in mice [32] strengthen this hypothesis.

We report five children with sudden onset of episodic burning or stinging pain in their distal extremities and no other illness or interictal abnormalities. All had objective evidence of SFN from lower-leg skin biopsy or physiological testing. Their non-familial, post-infectious, monophasic courses and rapid responses to IVIg and steroids in 2/5 are consistent with dysimmune rather than genetic causality. This case series characterizes among the youngest patients with an erythromelagia presentation of SFN and supports the hypothesis that most cases reflect dysimmune causality, and are thus treatable. Table 1 summarizes other published cases with acute monophasic non-genetic erythromelalgia/SFN under 21 years.

2. Methods

Patients:

These were 5 consecutive children, admitted to the Centre Universitaire Hospitalier Vaudois, or for whom an opinion was requested, between January 2011 to January 2018 for new-onset, unexplained distal pain. The 2 girls and 3 boys were aged 6–11 years. All were unrelated Caucasians of European origin, three from the nearby Swiss Neuchâtel region. We obtained written parental consent for medical record review and extraction for publication.

Neurodiagnostic Evaluations:

As summarized in Table 2, all had undergone 2–3 mm punch skin biopsies immunolabeled against pan-neuronal marker PGP9.5 to permit morphometric quantitation of epidermal nerve fiber density (END) [33,34]. However, only 4 were removed from the site 5–10 cm above the lateral malleolus for which data are available to permit pathological analysis. Biopsies had been fixed in Zamboni's fixative solution and mailed to the Massachusetts General Hospital (MGH) Nerve Unit clinical diagnostic laboratory, which has pediatric norms for comparison. Measured ENDs less than the 5th centile of the predicted normal distribution confirmed SFN in suspected patients. Age-matched norms and statistical modeling are essential to reduce false-negative interpretations if children's biopsies are compared to adult norms. Normal children have 3–4 times higher END that progressively declines until the mid-20's [35].

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Other testing included nerve-conduction study (1/5) and measuring sympathetic skin responses (SSR) on the soles and palms (3/5), although not tolerated in one 6-year-old. One child had electrochemical skin conductance measured by Sudoscan® (Impeto Medical, Paris, France) [36].

3. Representative case

This healthy 6-year-old girl (Table 2, case 1, Fig. 1) complained of sudden severe burning pain in one foot developing a few minutes after skiing. There had been no recent trauma, fever or illness. During the next few days, she had several daily recurrences in the soles and toes of both feet and in the palms and fingertips; each lasting 2–10 min and preventing walking and playing. No redness or swelling were visible during or between attacks. On day 9, pain severity prompted community hospital admission. Between episodes she was symptom free with normal vital signs and general and neurological examination. Attempted analgesia (Fig. 1) was ineffective except for hand and foot immersion in cold water. On day 22 continued worsening prompted University Hospital transfer; pain episodes were occurring every 60–90min and lasting ≥30 min. Continual immersion of hands and feet in cold water interfered with activities and sleep (Fig. 1). Examination revealed only persistent tachycardia (100–110bpm) and hypertension (99th percentile for age and height) [37]. Normal results were obtained from lumbar puncture, electroencephalography, nerve conduction study, capillary microscopy of the nail-beds, blood tests for auto-immunity and infection (HIV, hepatitis and Lyme borreliosis), Fabry disease, thyroid dysfunction, and *SCN9A* sequencing. The only abnormal result was anti-nuclear antibody (ANA titer 1:80). Initiating gabapentin (36mg/kgBW/d) plus mexiletine (27mg/kgBW/d) provided pain relief, and chloral hydrate and chlorpromazine improved sleep. At hospital discharge 2 months post-onset she had only 1–2 painful episodes/day relieved by cold pack-applications. A lower leg skin biopsy on Day 79 was interpreted as diagnostic for SFN (Fig. 2). At 3 months post-onset, pain attacks ceased but were followed by total-body itching, on hands and feet for 2 weeks, perhaps to indicate small-fiber regeneration. All medications were slowly weaned and discontinued during recovery and she remains symptom-free for 9 years.

4. Discussion

These five children were ultimately diagnosed with early-onset SFN. The characteristic tachycardia and elevated blood pressure in three patients persisted between episodes in two. Although initially attributed to pain, these specific abnormalities are common in pediatric SFN, providing clues to diagnosis (Table 1) [9,12] whereas adults more often have orthostatic hypotension or blood pressure swings [3,13,38]. None of our patients had distal redness or heat, typically part of adult erythromelalgia, but cold relieved their pain as expected. We hypothesize that their absence of distal flushing and edema reflects children's shorter stature, which reduces the orthostatic pressure that potentiates neuropathic capillary and venous congestion [13,39,40].

Because of pain's subjective nature, objective confirmation of SFN using lower leg skin biopsies and/or autonomic nerve function testing (AFT) is preferred in clinical care and required for research [1,3,12,13,41–43].Skin biopsies have the advantage of not requiring

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patient cooperation, special equipment or expertise. However, in two large skin biopsy studies of adults with erythromelalgia, only 10% of lower-leg biopsies were diagnostic, whereas 81% had reduces finger and toe END, showing that a biopsy taken above the ankle can miss far distal abnormalities [41,43]. In addition, as axonal degeneration is typically later and longer-lasting than excess C-fiber firing, skin biopsies performed early in the disease course can be less sensitive than AFT, such as quantitative sudomotor axon reflex testing (QSART). Multiple large studies indeed report impaired far-distal small-fiber control of sweating in 60–94% of erythromelalgia patients and a smaller proportion (34%) have additional cardiovascular abnormalities [14,40,41,43].

Objective confirmation of SFN is however difficult in children because pediatric norms for skin biopsies and sudomotor function testing such as QSART are scant [35,44,45]. SSR tends to provide an “all-none” rather than graded response, like in our cases 2 and 3. Both QSART and SSR are obtained via electrical stimuli and thus require the child’s cooperation [45]. Although diagnostic in one child here, with published pediatric normative values from a little cohort [36], preliminary data suggest that Sudoscan® measurements of sweating have low specificity and sensitivity for detecting SFN in children (Klein et al. unpublished data).

The disease course in all patients was acute and monophasic, peaking within days or a few weeks, and then plateauing for weeks and recovery within 6 months without relapse. Patients’ prior and subsequent normal health, essentially discards genetic, metabolic, paraneoplastic or rheumatological causes. Although GBS is predominantly a large-fiber demyelinating, dysimmune neuropathy, the time course is similar to our young SFN patients and overlap cases are increasingly recognized [3,26,32,38,46]. This continuum between erythromelalgia/SFN and GBS is also supported by albuminocytologic dissociations found in the cerebrospinal fluid in one series of 6 adults [27], even if most patients have bland lumbar punctures.

Inflammatory or dysimmune causality is the most commonly reported cause in children and adolescents with acute early-onset SFN with and without erythromelalgia (Table 1) [8,12,20,26]. The simultaneous or recent mild infections in 3 of our patients are indeed consistent with autoreactive immunity, reported in other acute-onset cases (Table 1) [7,8,10,20,26,32,38,47–52]. In 4/8 pediatric SFN patients, Epstein-Barr virus was implicated [30] and immunization against human papilloma virus is strongly linked to onset of SFN symptoms worldwide [53–55]. In Oaklander et al.’s large cohort, of 41 patients below 21 years with unexplained pain syndromes, almost all with evidence of SFN, 89% had blood-test markers of disordered immunity including 45% with ANA titer ≥ 1:80 and 25% with shortly preceding infections [12]. In our series, 2 children had ANA titers ≥ 1:80, 3 had preceding or concomitant infections and 3/5 families had autoimmune histories, consistent with the 52% family history prevalence of Oaklander’s cohort. Anti-fibroblast growth factor receptor 3 (FGFR3) is linked to SFN in adults, but was unrevealing in one of our patients (Case 5) [56,57].

SFN-treatment is two-pronged: symptom relief plus disease modification. Cooling, gabapentin and sodium-channel blockers best relieved symptoms in our patients. Regarding immunotherapies, a few children with erythromelalgia presentations of SFN received

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steroids and improved (Table 1). Typical for hospitalized patients is the intravenous methylprednisolone dose of 500mg/1,73m^2/day during 3 days used here, with prednisone 1–2 mg/kg/day given in outpatients [8,10,26]. One study of 15 corticosteroid-treated children and adolescents with biopsy-confirmed SFN reported 67% sustained improvement [12]. IVIg is the primary treatment overall for autoimmune neuropathy, and the evidence, also uncontrolled, is even stronger in adults [12,25,58], A randomized clinical trial of IVIg for idiopathic SFN is underway in the Netherlands [59]. In our 2 patients, IVIg was administered once at standard adult and pediatric doses of 2g/kgBW over 1–5 consecutive days. In the largest uncontrolled study, of 55 adults and children treated with ≥1g/kgBW/4 weeks for ≥3 months, 74% of patients rated themselves “improved”, their neurologist labeled 77% as IVIg responders, and 16% remained in remission after IVIg withdrawal. Their proportion of abnormal autonomic testing dropped from 89% at baseline to 55% ($p \leq 0{,}001$) [25]. Although both of our immunotherapy-treated patients improved quickly, benefits were difficult to measure with mexiletine given concomitantly.

5. Conclusion

We describe 5 children with acute onset, episodic erythromelalgia pain in the extremities without other illness, shown to be SFN. Their monophasic courses are consistent with immune, perhaps post-infectious etiology akin to GBS. Lower-leg skin biopsy and sweating quantitation provide best diagnostic confirmation, although better norms from healthy children would improve accuracy. Identification of specific autoantibodies remains scarce, especially in children.

Acknowledgements

We warmly thank our colleagues D. Mercati, M. Hofer, I. El Faleh, T. Kuntzer and graphic designer E. Alibrandi for their contributions to our manuscript.

Funding

NIH 1-NS093653, 2-NS093653 (Oaklander), U.S. DoD GW140169 (Oaklander).

Abbreviations:

SFN	Small-fiber polyneuropathy
GBS	Guillain-Barré syndrome
NSAIDs	non-steroidal anti-inflammatory drugs
IVIg	intravenous immunoglobulins
AFT	autonomic nerve function testing
END	epidermal nerve fiber density
FGFR3	fibroblast growth-factor 3
kgBW	kilograms body-weight

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PGP9.5	protein gene product 9.5
ESC	electrochemical skin conductance
SSR	sympathetic skin response
QSART	quantitative sudomotor axon reflex testing

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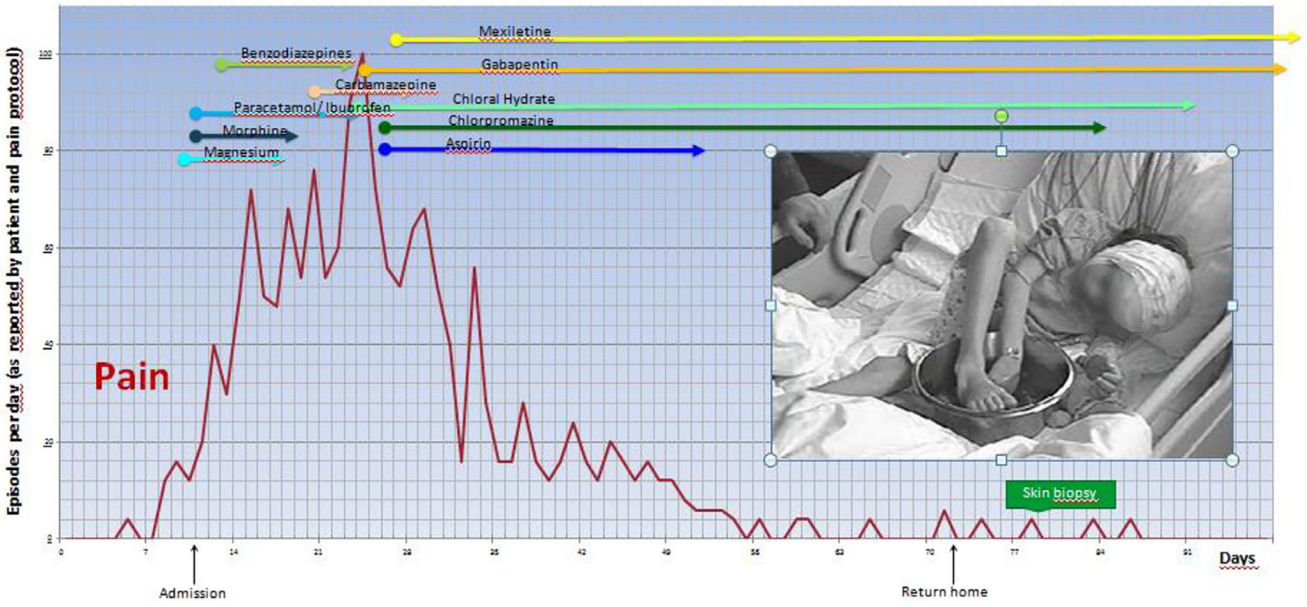

Fig. 1. Case 1: Clinical presentation and time course.

The graph illustrates the painful episodes (up to 100) reported per day and the numerous medications tried within 90 days. The cold-water immersion depicted was replaced by wrapped dry icepacks to prevent skin maceration.

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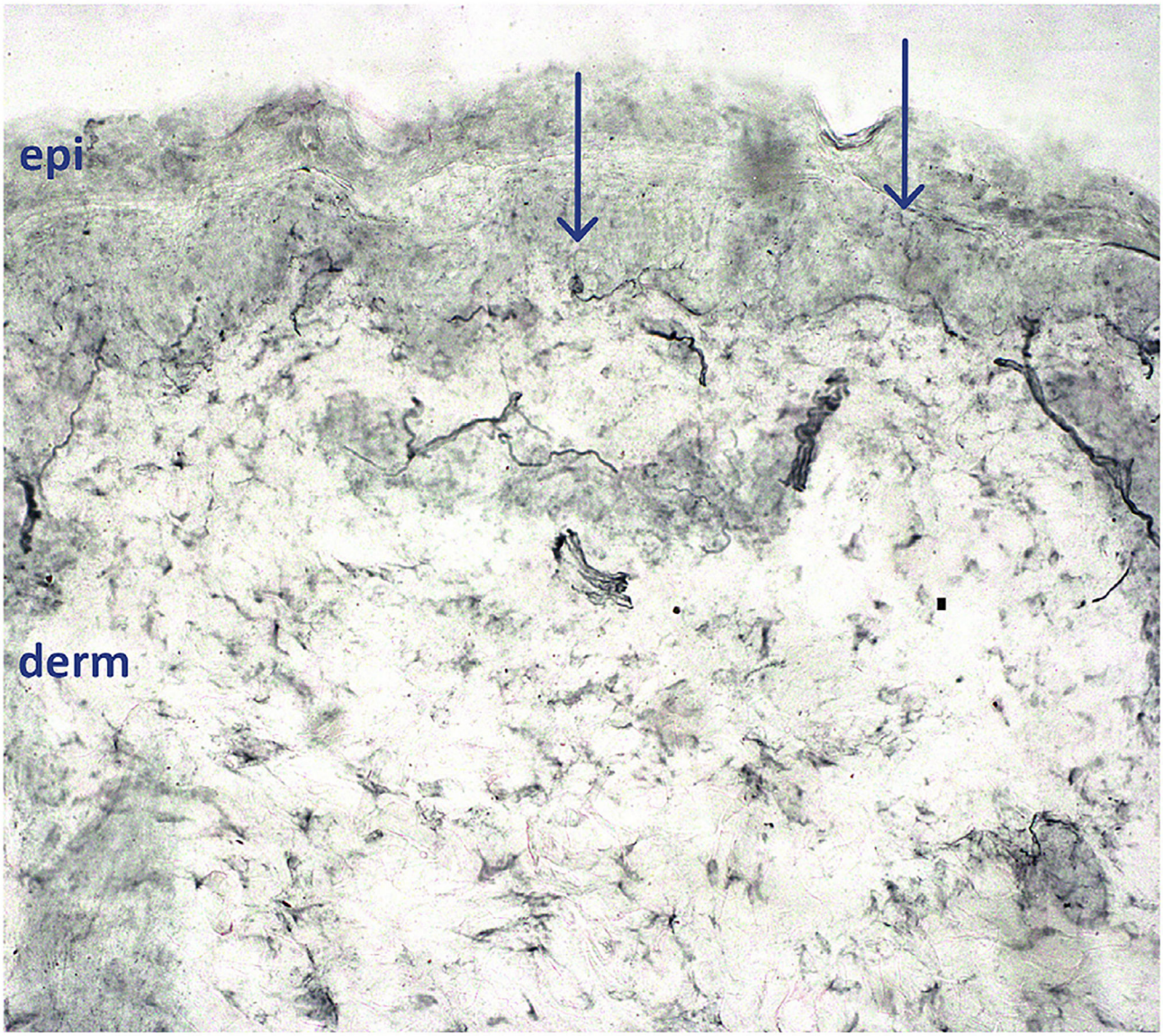

Fig. 2. Case 1: lower leg PGP9.5-immunolabeled skin biopsy.

epi = epidermal layer, derm = dermal layer. All neurites crossing the dermalepidermal junction (arrows) are counted by a blinded morphometrist, and measurements compared to those from age-matched healthy volunteers. Virtually all epidermal innervation is sensory small-fiber. The arrow at left demonstrates an epidermal neurite with intraaxonal swelling, a potential pre-degenerative sign. Small-fiber epidermal innervation was nearly depleted, with END of 68 epidermal neurites/mm^2 skin surface area, below the 1st centile of the predicted normal distribution, calculated from END of 76 healthy children aged 8–20y. END ≤5th centile are interpreted as confirming suspected clinical cases of SFN. 40x magnification.

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Table 1

Cases of acute monophasic pediatric erythromelalgia/SFN with onset before age 21 years (published since 1997 in chronological order).

First author, publication year	No	Age (y)	Sex M/ F	Major somatic symptoms	Dysautonomia signs and symptoms	Illness, vaccination in preceding weeks	Trauma shortly preceding	Pathological confirmation	Autonomic function testing	SFN objectively confirmed	Nerve conduction study	Cerebrospinal fluid	Outcome of immunotherapy
Confino, 1997	1	4.5	F	acute burning pain, erythema, edema, palms and soles	elevated blood pressure	Influenza vaccination	No data	No biopsies	No testing	No	No data	No data	None administered
Wakamoto, 1999	1	12	F	acute burning pain, loss of pinprick and temperature sensation, vomiting	hypertension, gastroparesis	Acute febrile illness	No data	Yes (SB) No (NB)	Not standard	Yes,	normal	normal	None administered
Zenz, 1999	1	5	M	acute burning pain, erythema hands and feet	hypertension	Gastroenteritis	No	No biopsies	No testing	No	normal	Normal	CR (IVIg)
Dabby, 2006	1	17	M	acute burning pain, edema hands and feet	No data	No data	No	Yes (SB)	diagnostic AFT	Yes	normal	Normal	NR (IVIg) CR (corticosteroids)
Paticoff, 2007	1	20	M	acute severe pain hands and feet	hypertension, tachycardia	No	Yes	Yes (SB)	diagnostic AFT	Yes	normal	normal	CR (corticosteroids)
Iqbal, 2009	2	12/8	M	acute burning pain, erythema hands and feet	No data	No	No	No biopsies	No testing	No data	No testing	No data	None administered
Pfund, 2009	1	12	F	acute burning pain palms and soles, motor weakness	No data	No	No	No biopsies	No testing	No	abnormal	No data	CR (corticosteroids)
Cook-Norris, 2011	32	5–18	10 M/ 22F	consecutive chronic or acute erythromelalgia,	No data	No data	No data	No neurolabelling of skin biopsies	4/6 abnormal QSART, 6/14 abnormal TST	Yes (10/32)	12/12 normal	No data	None administered
Morales, 2012	1	9	M	acute burning pain, limbs	hypertension	No data	No data	No biopsies	No testing	No data	No testing	No data	CR (corticosteroids)
Jakob, 2012	1	12	M	acute pain, edema, feet and hands	hypertension	Yes	No	No (SB)	No testing	No	No testing	No data	None administered
Elgueta, 2013	1	9	M	acute burning pain, edema,	No data	No data	No data	No biopsies	No testing	No data	No testing	No data-	NR (corticosteroids)

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First author, publication year	No	Age (y)	Sex M/ F	Major somatic symptoms	Dysautonomia signs and symptoms	Illness, vaccination in preceding weeks	Trauma shortly preceding	Pathological confirmation	Autonomic function testing	SFN objectively confirmed	Nerve conduction study	Cerebrospinal fluid	Outcome of immunotherapy
				erythema, warmth in hands and feet									
Oaklander, 2013	41	12.3 ± 5.7	11 M 30F	consecutive acute and chronic unexplained distal-limb pain, 23% had erythromelalgia	40/41 with dysautonomic symptoms	10/41 infections, 14/41 autoimmune diseases	11/41	11/37 SB, 2/2 NB	18/34 diagnostic AFT	24/41 definite 7/41 probable 9/41 possible	2/24 abnormal	Normal 11/41	10/15 PR (corticosteroids) 5/8 PR (IVIg)
Huh, 2015	1	12	F	acute burning pain, erythema with linear pattern	hypertension	Seronegative vasculitis	No data	No biopsies	No testing	No data	No testing	No data	PR (corticosteroids)
Hoeijmakers, 2016	2	14/16	F	1 chronic/1 acute burning pain, tingling legs and feet, minor large-fiber involvement	Palpitations, dry eyes, hyperhidrosis, gastrointestinal dysmotility	No/diabetes ketoacidosis 6wks prior	No data	Yes (SB) 2/2	1/2 abnormal QST	Yes(2/2)	1/2 abnormal	No data	None administered
Gorlach, 2019	26	14,2 ± 3,9	11 M 15F	5 acute, 21 chronic distal pain	18/26	2/26 acute 11/26 chronic illness	No data	Yes (SB) 13/26 diagnostic, 9/26 borderline	No testing	Yes (13/26)	2/11 abnormal	No data	None administered

Table 1 abbreviations:: y = years, M = male, F = female, SFN = small-fiber polyneuropathy, AFT = autonomic function testing, QST = quantitative sensory testing, SB = skin biopsy, NB = nerve biopsy, IVIg = intravenous immunoglobulins, NR = not responding, CR = complete remission, PR = partial remission.

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Table 2

Patient clinical presentation and results.

	Case 1, girl, 6 years	**Case 2, boy, 9 years**	**Case 3, boy, 10 years**	**Case 4, girl, 7 years**	**Case 5, boy, 11 years**
Chief complaint	Burning pain in one foot, spread to hands and feet	Needles and pins in both fingertips and toe tips	Burning pain in palms and soles	Needles and pins, burning pain in one foot, rapidly spreading to hands and feet	Needles and pins, burning pain, initially palms and soles, later palms only
Circumstances at onset	After a day of skiing No trauma	None	Concomitant streptococcal infection	Diarrhea 2 weeks before onset (sister with rotavirus)	Concomitant streptococcal infection
- *frequency*	↑, all 10–15min, also night	↑, several times/d also night	↑, up to continuous pain	↑, up to continuous pain	↑, >30 episodes/d
- *duration*	10–30min	30min	20 min, later constant	Minutes, later constant	10–15min
Patients self-treatment	Cold water immersion	Activity in the cold (ice hockey)	Rubbing limbs, contact with cold (tiles)	Cold water immersion	Cold water immersion
Autonomic signs	↑, blood pressure (persistent)	None	↑ blood pressure, tachycardia (during symptomatic episodes only)	Persistent ↑ blood pressure, tachycardia, unexplained hyperthermia	↑ blood pressure and ↑ body temperature (during symptomatic episodes only)
Sleep disturbance	Yes	Yes	Yes	Yes	Yes
Local skin lesions	Maceration due to cold water	None	None	Maceration due to cold water	None
Attempted treatment (chronological order, helpful drugs in bold italics)	paracetamol/ibuprofen tramadol/morphine ASA/ carbamazepine ***chloral hydrate chlorpromazine gabapentin mexiletine***	gabapentin ***carbamazepine***	paracetamol/ibuprofen ASA/ cetirizine gabapentin/***pregabalin*** lidocaine patch ***morphine/fentanyl iv*** ketamine/clonidine lidocaine iv/ ***mexiletine + methylprednisolone/ prednisone***	carbamazepine ASA ***gabapentin mexiletine***	paracetamol/ibuprofen tramadol/morphine gabapentin carbamazepine ***chlorpromazine lorazepam mexiletine IVIg***
Time to symptom resolution	3 months	6 months	3 months	24 days	44 days
Relapse	No	No	No	No	No
Duration of follow up	8 years	6 years	4 years	3,5 years	1 year
Family history	Multiple sclerosis (aunt)	Negative	Negative	Diabetes mellitus type 1 (father)	lupus (grandfather) rheumatoid arthritis (grandmother)
Other investigations (only pathologic results)	ANA 1/80 Low IgG *	ANA 1/320	Thrombocytosis (450 G/l) *	–	*
Skin biopsy END (neurites/ mm^2 skin surface area) and centile on predicted normal distribution	Day 79 Two from distal leg 68 ENF/mm^2 each <1st centile **2/2 diagnostic**	6 months after onset Distal leg skin biopsy with 269 ENF/mm^2 3.8th centile **diagnostic**	Day 35 Palm of hand and sole of foot Sites not valid for interpretation	Day 30 Two from distal leg 444 ENF/mm^2 and 352 ENF/mm [2], 4.68th and 0.9th centile **2/2 diagnostic**	Day 40 460 ENF/mm2 41st centile normal
*Electrochemical skin conductance***	Not performed	Not performed	Not performed	Not performed	**No response, suggestive of SFN**

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	Case 1, girl, 6 years	Case 2, boy, 9 years	Case 3, boy, 10 years	Case 4, girl, 7 years	Case 5, boy, 11 years
Sympathetic skin response	Not tolerated	Normal	**No response, suggestive of SFN**	Not performed	Not performed

Patients 1, 3 and 5 had negative genetic testing for *SCN9A* (cases 1, 3, 5), *SCN10A*, *SCN11A* and *TRPA1* (cases 3 and 5),

** Sudoscan®,

SLE = systemic Lupus Erythematosus, ANA = antinuclear antibody (elevated if 1/80, significant if > 1/320). ASA = acetylsalicylic acid; IVIg = intravenous immunoglobulin.