Generalized chronic itch induced by small-fibre neuropathy: clinical profile and proposed diagnostic criteria

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Abstract

Background Small-fibre neuropathy (SFN) is a known cause for pain, however, it may be also associated with chronic itch. The clinical profile of chronic itch due to SFN is poorly defined and accordingly under-diagnosed in clinical care.

Objectives To establish the clinical profile of patients with SFN and to propose diagnostic criteria for this patient population.

Methods Clinical data from patients diagnosed with SFN [chronic generalized itch and reduced intraepidermal nerve fibre density (IENFD)] were analysed retrospectively.

Results A total of 142 patients (60 females, median age: 62.5 years) were included. Patients reported daily, moderate to severe itch intensity scores occurring mostly in attacks (62.5%). Only 11 patients experienced exclusively itch, while the remaining patients (92%) reported pruralgia (itch along with painful sensations). Burning (50%), a sensation like needle pricks (46%) and tingling (45%) were the sensory symptoms reported by most patients. Cold or ice application led to an alleviation of the symptoms. The IENFD did not correlate with itch intensity; however, patients with a severely reduced IENFD (<30% of the normative cut-off value) reported more frequently sharp, spiky and drilling sensations compared to the remaining patients. The quality of life was moderately impaired and correlated with itch intensity, whereas anxiety and depression scores were low.

Conclusions Onset of pruralgia on normal appearing skin, occurrence in attacks and symptomatic alleviation with cold/ice application should alert physicians for a possible neuropathic SFN-related origin of itch. A reduced IENFD can confirm the diagnosis of SFN.

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Conflicts of interest

SST is an investigator for Dermasence, Galderma, Kiniksa, Menlo Therapeutics, Trevi Therapeutics, Novartis, Sanofi, and Vanda Therapeutics and a consultant for Almirall, Bayer, Beiersdorf, Bionorica, Cara Therapeutics, Celgene, DS Biopharma, Galderma, Kiniksa, Kneip, Maruho, Menlo Therapeutics, Marz, NeRRe Therapeutics, Novartis, Nuformix, Perrigo, Sienna Therapeutics, ACO HUD Nordic, Toray, Trevi Therapeutics and Bellus Health. MPP, LD, GMZH and KA declare no conflicts of interest.

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Introduction

Peripheral small-fibre neuropathy (SFN), which results from damage of unmyelinated C-fibres and thinly myelinated Aδ-fibres,1 is associated with chronic pain. A variety of conditions may lead to SFN, and metabolic disorders such as diabetes mellitus or vitamin B12 deficiency are a common cause. Also autoimmune, infectious, malignant and genetic diseases have been linked to SFN, as well as the intake of certain medications, as e.g. chemotherapeutic and antiretroviral agents.2 Clinically, pain arising from SFN is often accompanied by paraesthesias such as burning, pricking or tingling and may be associated with damage of large nerves.2 SFN may occur isolated or as a feature of a polyneuropathy.

Remarkably, one possible symptom of SFN is itch.3,4 When assessing a patient presenting with chronic itch on normal
appearing skin, SFN should be considered as a potential origin of the itch. However, the clinical profile of patients with chronic generalized itch arising from SFN is still widely unknown and diagnostic criteria are missing.

Upon clinical suspicion, the diagnosis of SFN can be confirmed by detecting a reduced intraepidermal nerve fibre density (IENFD). The IENFD is quantified in skin obtained from a 4-mm punch biopsy after staining with an antibody against an axonal marker (protein gene product 9.5) and is analysed using light or fluorescence microscopy. The intraepidermal nerve fibres crossing the dermo-epidermal junction are counted manually and divided by the length of the epidermis (Fig. 1). Normative values are available for the distal leg at the innervation site of the sural nerve.

In the present study, we retrospectively analysed patients with generalized chronic itch associated with a decreased IENFD and thus signs of SFN. Aims of this study were (i) to establish the clinical profile of this patient population and (ii) to propose diagnostic criteria for chronic generalized itch due to SFN in order to facilitate the clinical management of these patients.

Methods

Patients

Consecutive adult patients diagnosed with a SFN and chronic generalized itch (≥6 weeks duration) showing a decreased IENFD according to normative values, presenting from January 2012 to May 2018 at the Center for Chronic Pruritus, Department of Dermatology of the University Hospital Münster (Germany) were included in this retrospective analysis. Upon diagnostic work-up according to the German guideline for chronic itch, other aetiologies for the itch (e.g. dermatological or systemic origins such as cholestatic itch) were excluded by history (no relation between comorbidity and itch) or work-up and thus the SFN confirmed by a reduced IENFD was considered to be the cause for the itch as per physician’s assessment. The study was performed according to the Helsinki Declaration and later revisions and was approved by the local Ethics Committee (2007-413-f-S).

Study outcomes

Using the centre’s own database, data on demographic features, comorbidities, atopy [IgE, Erlangen Atopy Score (EAS)], itch (onset, frequency, dynamic, accompanying sensory symptoms, trigger and alleviating factors), scratching behaviour and skin status (none, single or multiple scratch lesions according to the physician’s assessment) were collected, as well as the IENFD assessed at the distal lower leg 10 cm above the lateral malleolus. Additionally, standardized questionnaires and scales were completed by patients in order to assess the itch intensity [numeric rating scale (NRS, range: 0–10)] and visual analogue scale (VAS, range: 0–10), to screen for psychiatric comorbidities [Hospital Anxiety and Depression Scale (HADS, range for subscale anxiety and depression: 0–21)] and to evaluate the impairment of the quality of life owing to the chronic itch (ItchyQol). ItchyQol scores are presented as the mean of all items scores (range 1–5), as previously performed.

Statistics

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0 (Armonk, NY, USA). Data are shown as median [interquartile range (IQR)] and as number of cases/total number of assessments (percentage of cases). Correlation analyses were performed with Spearman’s rho. The Mann–Whitney U-test and the Kruskal–Wallis test were used for comparisons of continuous variables between groups as appropriate, while the chi-square test and the Fisher’s exact test were performed for group comparisons of categorical variables. The level of statistical significance was set at \( P < 0.05 \).

Results

Subjects

One hundred and forty-two patients (male: 82, female: 60) were included in this analysis. There was no difference in age between males and females (\( P = 0.16 \)). In this retrospective clinical observational study, at the time patients were treated at the centre not all parameters were assessed in each case. For transparency, the number of patients that were assessed for each
Itch induced by small-fiber neuropathy

| Table 1 | Demographic data and comorbidities of patients with chronic itch associated with small-fibre neuropathy |
|---------|-----------------------------------------------------------------------------------------------|
| **Demographics** | | |
| Sex | All | Male | Female |
| Age (years) | 62.5 [51.4; 72.6], n = 142 | 64.2 [54.2; 73.3], n = 82 | 61.5 [48.8; 68.7], n = 60 |
| Height (m) | 1.75 [1.67; 1.80], n = 114 | 1.80 [1.75; 1.85], n = 66 | 1.66 [1.60; 1.72], n = 48*** |
| Weight (kg) | 80 [68; 95], n = 114 | 90 [78; 98], n = 66 | 66 [60; 79], n = 48*** |
| Body mass index (kg/m²) | 26.4 [23.8; 29.5], n = 114 | 27.5 [24.7; 29.4], n = 66 | 24.2 [21.6; 29.9], n = 48** |
| **Comorbidities** | | |
| Lumbar spinal disc herniation/spinal canal stenosis | 30/121 (25%) | 17/70 (24%) | 13/51 (25%) |
| Diabetes | 25/140 (18%) | 17/82 (21%) | 8/58 (14%) |
| Depression | 21/121 (17%) | 6/70 (9%) | 15/51 (29%)** |
| Hypothyroidism | 23/140 (16%) | 9/82 (11%) | 14/58 (24%)* |
| Cervical spinal disc herniation/spinal canal stenosis | 15/121 (12%) | 7/70 (10%) | 8/51 (16%) |
| Coronary artery disease | 13/122 (11%) | 10/71 (14%) | 3/51 (6%) |
| Previous chemotherapy | 12/140 (9%) | 5/60 (6%) | 7/58 (12%) |
| Previous stroke | 12/139 (9%) | 6/70 (9%) | 6/58 (10%) |
| Renal insufficiency | 11/140 (8%) | 7/70 (9%) | 4/51 (8%) |
| Hepatic insufficiency | 7/140 (5%) | 5/60 (6%) | 2/58 (3%) |
| Vitamin B12 deficiency | 5/140 (4%) | 2/60 (3%) | 3/58 (5%) |
| Lupus erythematosus | 1/140 (0.8%) | 0/56 (0%) | 1/58 (2%) |
| IgE > 100 IU/mL | 32/140 (33%) | 21/56 (36%) | 11/58 (30%) |
| Patients without comorbidities | 5/142 (3.5%) | 2/80 (2.5%) | 3/62 (5.3%) |

*P < 0.05, **P < 0.01, ***P < 0.001.

Data are shown as median [interquartile range] or number of cases/total number of assessments (percentage of cases). Group comparisons between male and female patients were performed with Mann–Whitney U-test (age, height, weight and body mass index) and with chi-square test or Fischer’s exact test, as appropriate (comorbidities).

According to the EAS, 20/122 (16.4%) had an atopic disposition (EAS ≥ 10), while in the remaining cases an atopic disposition was unclear [22/122 (18.0%), EAS = 8–9] or unlikely [80/ 122 (65.6%), EAS < 8]. Patients with atopic disposition had higher IgE scores (IgE: 147 kU/L [86; 494], n = 13) compared to patients, in which atopic disposition was unclear (IgE: 63 kU/L [14; 242], n = 16; P = 0.02) or unlikely (IgE: 55 kU/L [18; 127], n = 54; P = 0.002).

**Itch characteristics**

The majority of patients (63%) reported itch lasting over 1 year. Moderate average itch and severe worst itch intensities were recorded at presentation to our centre (Table 2). In most patients, itch occurred in attacks (70/112, 63%) and on a daily basis (83/106, 78%). Eleven patients (3 female and 8 male) experienced exclusively itch, while all others reported itch and painful sensations. The most common painful qualities reported were burning (56/111, 50%), a sensation like needle pricks (50/109, 46%) and tingling (50/111, 45%). Most commonly reported trigger factors were warmth (59/112, 53%) and calmness (47/108, 44%). Application of emollients (57/108, 53%) and of cold water (57/109, 52%) alleviated the itch (Table 2).

**Scratching behaviour**

The majority of patients reported only scratching when they experienced itch (77/108, 71%). Scratching alleviated itch in 72% (76/106) of the cases, while 43% (46/108) considered scratching to be also a trigger factor. 19/108 (18%) of the patients reported that scratching was an automatic behaviour and 2/108 (2%) admitted scratching also when not perceiving itch. In the physical examination, 47% (65/138) of the patients showed no scratch lesions, while 48/138 (35%) had some and 25/138 (18%) multiple scratch lesions as per physician’s assessment. No difference was recorded between males and females with regard to the amount of scratch lesions (P = 0.67). Age (P = 0.85) and itch intensity assessed with the NRS (average 24 h) and the VAS (average 24 h, worst 4 weeks, average 4 weeks; P > 0.05) did not differ between patients with no, some or multiple scratch lesions.

**IENFD**

In accordance with the inclusion criteria of the study, all patients had a decreased IENFD (3.4 [1.8; 5.8] fibres/mm, n = 142).
Table 2 Itch characteristics

| Itch characteristics | | |
|----------------------|------------------|------------------|
| **Duration**         | >6 weeks to 6 months: 8/108 (7%) | 6–12 months: 32/108 (30%) |
|                      | >1–10 years: 54/108 (50%) | >10 years: 14/108 (13%) |
| **Itch intensity**   | NRS 24 h average itch: 5.0 [3.0; 7.0], n = 114 | VAS 24 h average itch: 6.0 [4.0; 8.0], n = 114 |
|                      | VAS 4 weeks worst itch: 8.0 [6.0; 8.9], n = 114 | VAS 4 weeks average itch: 6.0 [3.5; 8.0], n = 114 |
| **Sensory qualities**| Burning: 56/111 (50%); needle pricks: 50/109 (46%); tingling: 50/111 (45%); stinging: 41/111 (37%); painful: 28/108 (26%); biting: 27/108 (25%); sensation like crawling ants: 26/109 (24%); warmth sensation: 23/108 (21%); superficially localized: 22/108 (20%); localized deep inside: 17/108 (16%); spiky: 14/108 (13%); electric shocks: 12/108 (11%); sharp: 7/108 (6%); caressing: 7/108 (6%); cold sensation: 6/108 (6%); drilling: 4/108 (4%) |
| **Dynamic**          | Itch attacks: 76/112 (69.0%) | Continuous itch: 42/112 (38.0%) |
| **Frequency**        | At least once daily: 83/106 (78%) | Multiple times in the week: 18/106 (17%) |
|                      | Multiple times in the month: 5/106 (5%) |
| **Trigger factors**  | Warmth: 59/112 (53%); calmness: 47/108 (44%); scratching: 46/108 (43%); skin rubbing: 36/108 (34%); sweating: 35/108 (32%); touch: 27/108 (25%); feeling strained: 27/108 (25%); tight clothes: 26/106 (25%); physical strain: 24/108 (22%); emotional strain: 23/108 (21%); pressure: 19/108 (18%) |
| **Alleviating measures** | Scratching: 76/110 (72%); applying ointment: 57/108 (53%); cold water: 57/109 (52%); skin rubbing: 45/108 (42%); using objects: 28/108 (26%); warm water: 24/105 (23%); using finger nails: 24/108 (22%); scrubbing: 22/108 (20%); cold/ice packs: 21/110 (19%); skin pinching: 17/108 (16%); being alone: 16/108 (15%); socializing: 14/108 (13%); warmth: 11/108 (10%); skin kneading: 5/108 (5%) |

Data are shown as median [interquartile range] or number of cases/total number of assessments (percentage of cases). NRS, numerical rating scale; VAS, visual analogue scale.

Females showed a higher IENFD (4.2 [2.3; 6.2] fibres/mm) compared to males (2.9 [1.5; 4.9] fibres/mm; P = 0.04), while the IENFD decreased with age (r = −0.25, P = 0.002, n = 142). Patients with diabetes mellitus (n = 25/140 (18%), P = 0.004), chronic renal insufficiency (n = 11/140 (8%), P = 0.03) and coronary artery disease (n = 13/122 (11%), P < 0.001) showed a significantly reduced IENFD compared to patients not affected by these conditions. The IENFD did not correlate with itch intensity assessed by NRS and VAS (r = 0.28, P = 0.017, n = 74) and with the worst itch intensity of the previous 4 weeks assessed by the VAS (r = 0.31, P = 0.009, n = 71), but not with the remaining parameters.

Patients with severely reduced IENFD (<30% of the normative cut-off value) did not differ in terms of itch intensity, amount of scratch lesions or impairment of the quality of life compared to those with a moderate or small reduction of the IENFD (≥30% of the normative cut-off value, Table 3). However, patients with severely reduced IENFD reported more frequently a sharp (14% vs. 2%, P = 0.02), spiky (23% vs. 6%, P = 0.01) and drilling sensation (9% vs. 0%, P = 0.02) compared to the remaining patients.

Disease burden

Patients reported a moderate impairment of the quality of life as assessed by the ItchyQol (Fig. 3a), while HADS scores were low both for the anxiety and the depression subscale (Fig. 3b). Correlation coefficients between itch intensity and scores for ItchyQol and HADS are shown in Table 4. Owing to the itch, patients slept a median of 2.0 h [1.0; 4.0] (n = 79) less than their normal amount of sleeping hours, as per patient’s own assessment. Sleep deprivation correlated with the ItchyQol function subscale (r = 0.28, P = 0.017, n = 74) and with the worst itch intensity of the previous 4 weeks assessed by the VAS (r = 0.31, P = 0.009, n = 71), but not with the remaining parameters.

Fig. 2 Intraepidermal nerve fibre density across patients with no, some and multiple scratch lesions. Middle line: median, bottom/top of box: 1st/3rd quartile; whiskers: lowest/highest case within 1.5 times interquartile range; n = 138.
Table 3  Demographic, morphological and clinical characteristics of patients with a severely reduced IENFD (<30% of the normative cut-off) and with moderately to slightly reduced IENFD (>30% of the normative cut-off)

|                                | Reduced intraepidermal nerve fibre density: <30% of cut-off value | Reduced intraepidermal nerve fibre density: >30% of cut-off value | P-value |
|--------------------------------|------------------------------------------------------------------|------------------------------------------------------------------|---------|
| n                              | 59                                                               | 83                                                               | n.s.    |
| Sex (m : w)                    | 37 : 22                                                          | 45 : 38                                                          |         |
| Age (years)                    | 65.5 [58.5; 73.2], n = 59                                       | 59.7 [48.7; 68.8], n = 83                                       | 0.02    |
| Height (m)                     | 1.78 [1.70; 1.80], n = 51                                       | 1.74 [1.64; 1.82], n = 63                                       | n.s.    |
| Weight (kg)                    | 90 [78; 101], n = 51                                            | 74 [64; 88], n = 63                                             | <0.001  |
| Body mass index (kg/m²)        | 29.1 [24.7; 32.6], n = 51                                       | 24.9 [22.7; 27.6], n = 63                                       | <0.001  |
| IENFD (fibre/mm)               | 1.5 [0.6; 3.3], 59                                              | 5.3 [4.0; 6.8], 83                                              | <0.001  |
| Scratch lesions                | None: 27 (47%)                                                  | None: 38 (47%)                                                  | n.s.    |
|                               | Some: 16 (28%)                                                  | Some: 32 (40%)                                                  |         |
|                               | Multiple: 14 (25%)                                              | Multiple: 11 (13%)                                              |         |
| NRS 24 h average itch (0–10)   | 6.0 [4.0; 8.0], n = 47                                          | 5.0 [3.0; 7.0], n = 67                                          | n.s.    |
| VAS 24 h average itch (0–10)   | 6.5 [3.5; 8.0], n = 48                                          | 6.0 [4.5; 7.5], n = 66                                          | n.s.    |
| VAS 4 weeks worst itch (0-10)  | 8.0 [5.9; 9.0], n = 48                                          | 8.0 [6.5; 8.5], n = 66                                          | n.s.    |
| ItchyQol (1–5)                 | 2.9 [2.3; 3.4], n = 47                                          | 2.9 [2.3; 3.4], n = 48                                          | n.s.    |
| HADS-A (0–21)                  | 5.0 [3.0; 8.0], n = 50                                          | 7.0 [5.0; 10.0], n = 69                                         | 0.04    |
| HADS-D (0–21)                  | 4.0 [2.5; 9.0], n = 51                                          | 6.5 [3.0; 10.0], n = 70                                         | n.s.    |

Significant differences between the two groups are shown. HADS-A, Hospital Anxiety and Depression Scale – Subscale Anxiety; HADS-D, Hospital Anxiety and Depression Scale – Subscale Depression; IENFD, intraepidermal nerve fibre density; NRS, numerical rating scale; n.s., non-significant; VAS: visual analogue scale.

Patients with more scratch lesions showed a higher impairment of the quality of life assessed by the ItchyQol (P = 0.001, n = 114, Fig. 4), a finding also observed for the symptom (P < 0.001, n = 111) and function subscales (P = 0.02, n = 111), but not for the emotion subscale or for the HADS score (P > 0.05).

![Fig. 3](https://example.com/fig3.png)  
**Fig. 3**  Disease burden. Scores of the ItchyQol (range 1–5; panel (a) and of the Hospital Anxiety and Depression Scale (range for each subscale: 0–21; panel (b) are shown. Data are shown as median [interquartile range]. Middle line: median, bottom/top of box: 1st/3rd quartile; whiskers: lowest/highest case within 1.5 times interquartile range; circle: outlier.

**Discussion**

In this study, we analysed a large sample of patients with a SFN associated with chronic generalized itch and decreased IENFD. The aim was to describe typical clinical characteristics in this entity.

Based on the findings of this study, we propose clinical criteria for the diagnosis of SFN associated with chronic generalized itch (Table 5). The presence of chronic itch (≥6 weeks), beginning of the itch on normal appearing skin and pathological number of intraepidermal nerves, as assessed by the determination of the IENFD, constitute mandatory criteria for diagnosing SFN associated with chronic generalized itch. Facultative criteria include the presence of a daily, moderate to severe itch, pruritus, i.e. additional painful sensations such as burning, tingling or a sensation like needle pricks (92%) next to the presence of itch, occurrence of itch in attacks (63%), alleviation of itch with cold/ice application (54%) and worsening with warmth (53%). These criteria should be considered as a suggestion to aid physicians identify patients with chronic itch arising from a SFN, while other possible origins of the itch (e.g. dermatoses or systemic diseases) should be excluded.

SFN is a neuropathic type of itch as peripheral nerves are damaged. Itch arising from a neuropathic condition begins typically on normal appearing skin, or if a scratching behaviour has ensued, excoriations may be observed. This is in agreement with our data, since 47% of the patients showed no scratch lesions, 53% had some or multiple scratch lesions and none had a primary skin disease. Consistent with previous reports, the
Correlation analyses were performed with Spearman’s rho. Significances are highlighted in bold. HADS: Hospital Anxiety and Depression Scale; NRS: numerical rating scale; VAS: visual analogue scale.

**Table 4** Correlation analysis between scores assessing humanistic burden (quality of life and psychological burden) and itch intensity

| Parameters          | NRS 24 h average | VAS 24 h average | VAS 4 weeks worst | VAS 4 weeks average |
|---------------------|------------------|------------------|-------------------|---------------------|
| ItchyQol (total score) | $r = 0.33$ | $r = 0.29$ | $r = 0.25$ | $r = 0.35$ |
|                     | $P < 0.001^{***}$ | $P = 0.003^{**}$ | $P = 0.01^{*}$ | $P < 0.001^{***}$ |
|                     | $n = 108$ | $n = 108$ | $n = 108$ | $n = 108$ |
| ItchyQol (symptom subscale) | $r = 0.36$ | $r = 0.27$ | $r = 0.26$ | $r = 0.37$ |
|                     | $P < 0.001^{***}$ | $P = 0.006^{**}$ | $P = 0.008^{**}$ | $P < 0.001^{***}$ |
|                     | $n = 105$ | $n = 105$ | $n = 105$ | $n = 105$ |
| ItchyQol (function subscale) | $r = 0.29$ | $r = 0.25$ | $r = 0.25$ | $r = 0.32$ |
|                     | $P = 0.003^{**}$ | $P = 0.009^{**}$ | $P = 0.01^{*}$ | $P = 0.001^{**}$ |
|                     | $n = 105$ | $n = 105$ | $n = 105$ | $n = 105$ |
| ItchyQol (emotion subscale) | $r = 0.18$ | $r = 0.17$ | $r = 0.09$ | $r = 0.20$ |
|                     | $P = 0.07$ | $P = 0.09$ | $P = 0.34$ | $P = 0.045^{*}$ |
|                     | $n = 105$ | $n = 105$ | $n = 105$ | $n = 105$ |
| HADS (anxiety subscale) | $r = 0.11$ | $r = 0.10$ | $r = 0.03$ | $r = 0.12$ |
|                     | $P = 0.23$ | $P = 0.30$ | $P = 0.73$ | $P = 0.21$ |
|                     | $n = 112$ | $n = 113$ | $n = 113$ | $n = 112$ |
| HADS (depression subscale) | $r = 0.09$ | $r = 0.12$ | $r = 0.09$ | $r = 0.17$ |
|                     | $P = 0.36$ | $P = 0.21$ | $P = 0.35$ | $P = 0.07$ |
|                     | $n = 113$ | $n = 113$ | $n = 113$ | $n = 113$ |

*P < 0.05, **P < 0.01, ***P < 0.001.

Correlation analyses were performed with Spearman’s rho. Significances are highlighted in bold. HADS: Hospital Anxiety and Depression Scale; NRS: numerical rating scale; VAS: visual analogue scale.
suggest that sensory perception is altered in patients with highly reduced IENFD, as this patients reported more frequently experiencing sharp, spiky and drilling sensations compared to the remaining patients. Future functional studies should analyse possible diverging qualities of sensory symptoms according to the magnitude of IENFD reduction. Interestingly patients with a highly reduced IENFD showed a higher bodyweight and body mass index compared to the remaining patients. Possibly due to overweight, these patients may be more affected by comorbidities leading to a SFN (e.g. diabetes). Future studies should confirm this observation.

Regarding the aetiology of the SFN, some patients had comorbidities that typically lead to a SFN, as diabetes mellitus (18%), exposure to chemotherapy (9%) or vitamin B12 deficiency (4%). However, in the majority of the cases no clear cause for a SFN was identified, which is in agreement with previous studies reporting an unknown origin for SFN in up to 50% of cases.20 One third of the patients had augmented IgE serum levels. Atoxic disposition was however not systematically assessed in our cohort. Possibly, atopic disposition may be a contributing factor to the development of itch when a SFN is present. Future studies investigating this issue are needed.

History of depression was observed in females more frequently than in males (29% vs. 9%). Previous studies have shown that women with chronic pruritus have more frequently accompanying psychosomatic disorders and report more often a worsening of the pruritus by emotional and psychosomatic factors compared to men.21 Using the HADS, higher anxiety but not depression scores was recorded in women with CP.22 In the present study although women had more often a diagnosis of depression compared to men, HADS scores for depression did not differ between sexes ($P = 0.76$), which is in accordance with previous studies.22 The retrospective nature of this study constitutes its main limitation. However, at our centre history taking, physical examination and follow-up visits are performed in a standardized fashion for all patients. Additionally, patients are asked to fill out standardized assessment instruments at every visit. This contributes to high-quality data even when analysed in a retrospective approach.

### Conclusion

SFN should be considered as a possible origin for chronic generalized itch in routine care. Although there is no unique clinical pattern, characteristics such as beginning of the itch on normal appearing skin, association with additional painful symptoms, alleviation with cold/ice application and itch occurring in attacks should alert attending physicians to a possible neuropathic origin of the itch. Morphological examinations such as the determination of the IENFD should then be performed in order to confirm the diagnosis of SFN. Future prospective trials should investigate the clinical utility of the diagnostic criteria proposed in this study.

### References

1. Oaklander AL. Neuropathic itch. In Carstens E, Akiyama T, eds. Itch: Mechanisms and Treatment. CRC Press/Taylor & Francis Group, LLC., Boca Raton, FL, 2014: 89–118.

2. Lauria G, Merkies IS, Faber CG. Small fibre neuropathy. Curr Opin Neurol 2012; 25: 542–549.

3. Stander S, Weisshaar E, Mettang T et al. [Clinical classification of chronic pruritus Interdisciplinary consensus proposal for a diagnostic algorithm]. Hautarzt 2006; 57: 390–394.

4. Stander S, Weisshaar E, Mettang T et al. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. Acta Derm Venereol 2007; 87: 291–294.

5. Lauria G, Hsieh ST, Johansson O et al. European Federation of neurological societies/peripheral nerve society guideline on the use of skin biopsy in the diagnosis of small fibre neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the peripheral nerve society. Eur J Neurol 2010; 17: 903–912, e44-9.

6. Provitera V, Gibbons CH, Wendelschafer-Crabb G et al. A multi-center, multinational age- and gender-adjusted normative dataset for immuno-fluorescent intraepidermal nerve fibre density at the distal leg. Eur J Neurol 2016; 23: 333–338.

7. Lauria G, Bakkers M, Schmitz C et al. Intraepidermal nerve fiber density at the distal leg: a worldwide normative reference study. J Peripher Nerv Syst 2010; 15: 202–207.

8. Stander S, Zeidler C, Augustin M et al. S2k-leitlinie zur diagnostik und therapie des chronischen pruritus - update - kurzversion. J Dtsch Dermatol Ges 2017: 15: 860–873.

9. Uter W, Schwanitz HJ, Pfaflenberg A, Gefeller O. Atopic signs and symptoms: assessing the ‘atopy score’ concept. Dermatology 2001; 202: 4–8.
10 Phan NQ, Blome C, Fritz F et al. Assessment of pruritus intensity: prospective study on validity and reliability of the visual analogue scale, numerical rating scale and verbal rating scale in 471 patients with chronic pruritus. Acta Derm Venereol 2012; 92: 502–507.

11 Reich A, Heisig M, Phan NQ et al. Visual analogue scale: evaluation of the instrument for the assessment of pruritus. Acta Derm Venereol 2012; 92: 497–501.

12 Snaith RP. The hospital anxiety and depression scale. Health Qual Life Outcomes 2003; 1: 29.

13 Krause K, Kessler B, Weller K et al. German version of ItchyQoL: validation and initial clinical findings. Acta Derm Venereol 2013; 93: 562–568.

14 Pereira MP, Kremer AE, Mettang T, Stander S. Chronic pruritus in the absence of skin disease: pathophysiology, diagnosis and treatment. Am J Clin Dermatol 2016; 17: 337–348.

15 Pereira MP, Luling H, Dieckhofer A et al. Application of an 8% capsaicin patch normalizes epidermal TRPV1 expression but not the decreased intraepidermal nerve fibre density in patients with brachioradial pruritus. J Eur Acad Dermatol Venereol 2018; 32: 1535–1541.

16 Stander S, Richter L, Osada N, Metze D. Hydroxyethyl starch-induced pruritus: clinical characteristics and influence of dose, molecular weight and substitution. Acta Derm Venereol 2014; 94: 282–287.

17 Misery L, Brenaut E, Le Garrec R et al. Neuropathic pruritus. Nat Rev Neurol 2014; 10: 408–416.

18 Ward L, Wright E, McMahon SB. A comparison of the effects of noxious and innocuous counterstimuli on experimentally induced itch and pain. Pain 1996; 64: 129–138.

19 Andersen HH, Akiyama T, Nattkemper LA et al. Alloknesis and hyperknesis-mechanisms, assessment methodology, and clinical implications of itch sensitization. Pain 2018; 159: 1185–1197.

20 Terkelsen AJ, Karlsson P, Lauria G et al. The diagnostic challenge of small fibre neuropathy: clinical presentations, evaluations, and causes. Lancet Neurol 2017; 16: 934–944.

21 Stander S, Stumpf A, Osada N et al. Gender differences in chronic pruritus: women present different morbidity, more scratch lesions and higher burden. Br J Dermatol 2013; 168: 1273–1280.

22 Stumpf A, Stander S, Warlich B et al. Relations between the characteristics and psychological comorbidities of chronic pruritus differ between men and women: women are more anxious than men. Br J Dermatol 2015; 172: 1323–1328.