



Functional and histological improvements of small nerve neuropathy after high-concentration capsaicin patch application: A case study

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Abstract

Introduction: Small fiber neuropathy has been found to occur in a large variety of pathological conditions, and the gold standard for diagnosis of small fiber neuropathy is skin biopsy. Sudorimetry is now considered an accurate technique to evaluate small fiber function with a good sensitivity and specificity for the diagnosis of small fiber neuropathy. Capsaicin high-concentration patch is approved for the treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for pain.

Methods: We describe the case of a 50-year-old woman diagnosed with small fiber neuropathy. After 2 previous treatment failures, she was proposed a treatment with high-dose capsaicin patches on the sole of her foot. The patient experienced an important diminution of her neuropathic pain. There was a 50% decrease in the pain numeric scale. Electrochemical skin conductance and skin biopsy were repeated 3 months after patch application.

Results: At 3 months, the patient then experienced an important diminution of her neuropathic pain, electrochemical skin conductance had normalized both in the hands and feet and intraepidermal nerve fiber density at distal leg increased almost reaching normal range.

Conclusion: This case report shows the correlation between clinical improvement, electrochemical skin conductance normalization, and intraepidermal nerve fiber density improvement after a high-dose capsaicin patch in a patient with small fiber neuropathy.

Keywords: Capsaicin, Sudorimetry, Small fiber neuropathy, Intraepidermal nerve fiber density

1. Introduction

Small fiber neuropathy has been found to occur in a large variety of pathological conditions (eg, diabetes mellitus, infectious diseases, toxic causes, and dysimmune disease). The gold standard for diagnosis of small fiber neuropathy is skin biopsy.⁵ Skin biopsy is followed by indirect immunofluorescence or immunohistochemical analysis to assess the density of small

nerve fibers in the epidermis of the skin.⁵ In the European guidelines, an epidermal nerve fiber density lower than 7.6/mm at the leg has a diagnostic value of 88% to 90% with 90% to 95% specificity and 70% to 83% sensitivity for small fiber neuropathy.¹⁰ A more recent study published new intraepidermal nerve fiber (IEFN) density normative values for clinical use for each year of age and patients' sex.⁶

Sudorimetry is a quick noninvasive technique that measures sudomotor function based on reverse iontophoresis and chronoamperometry. By measuring electrochemical skin conductance, sudorimetry serves as a biomarker for sweat gland function, which is related to sweat gland innervation by sympathetic unmyelinated nerve fibers of small diameter. Sudorimetry is now considered an accurate technique to evaluate small fiber function.¹⁵ To date, sudorimetry displays, in many studies, a good sensitivity and specificity for the diagnosis of small fiber neuropathy.^{3,11}

The link between impaired electrochemical skin conductance and low IEFN density has been highlighted in 2 studies.^{13,14} Novak showed a significant correlation between impaired electrochemical skin conductance and abnormally low epidermal nerve fiber density and abnormally low sweat gland nerve fiber density.¹³ These results support the previous results of Smith

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et al.,¹⁴ which showed that electrochemical skin conductance has the same diagnostic efficiency with similar area under curve.

Capsaicin is derived from chili peppers and is a natural ligand of the transient receptor potential vanilloid 1 channel. In 2009, a high-concentration transdermal capsaicin 8% patch (Qutenza; Acorda Therapeutics, Inc, Ardsley, NY; Astellas Pharma Europe Ltd, Chertsey, Surrey, United Kingdom) was approved. To date, in Europe, the capsaicin high-concentration patch is approved for the treatment of peripheral neuropathic pain in adults either alone or in combination with other medicinal products for pain.

The high-concentration capsaicin patch is proven to be effective in neuropathic pain. The effect of the patch remains for a mean 5 months before return of the symptoms.¹² Trials were originally designed for postherpetic neuralgia and HIV-associated neuropathy. Recent data suggest it is also effective in peripheral diabetic neuropathy.¹⁶ The Cochrane review in 2017 concluded that high-concentration topical capsaicin used in neuropathic pain in postherpetic neuralgia, HIV neuropathy, and painful diabetic neuropathy was shown to produce moderate or substantial levels of pain relief compared with control treatment using a much lower concentration of capsaicin. Yet, the quality of evidence was moderate to very low.⁷ Thus, the 2015 NeuPSIG gave only a weak recommendation for high-concentration capsaicin for use and proposal as second-line treatment.⁸

We report here a first case of both electrochemical skin conductance and IENF density improvement after high-concentration capsaicin patches for an idiopathic small nerve neuropathy.

2. Methods

2.1. Case Report

We report the clinical case of a 50-year-old woman who was seen as an outpatient for bilateral pain of the soles of her feet. Moreover, she presented with dysautonomic symptoms such as tachycardia, nausea, and constipation. Neuropathic pain was suspected; the DN4 questionnaire yielded a positive score of

5/10. The clinical neurological examination confirmed this suspicion of neuropathic pain. A small fiber neuropathy was suspected. Sudorimetry with Sudoscan (Impeto Medical, Paris, France). Sudoscan provides a quantitative measure of chloride conductance (measured in microsiemens). The sudorimetry for this patient revealed an impaired electrochemical skin conductance (**Fig. 1**) in both hands and feet. A skin biopsy was performed at distal leg with 3-mm punch biopsy, and it was processed in a standard fashion as recommended.¹⁰ IENF density was assessed with bright-field immunohistochemistry. In this patient, a reduced IENF density was shown at distal leg 3.03 IENF/mm (lower fifth percentile normal IENF density for the age and gender, as defined by Collongues et al.⁶, is 4.9 IENF/mm). Extensive explorations were made to find the origin, although none was found, and she was diagnosed with idiopathic small fiber neuropathy. Laboratory test showed normal blood count, normal renal function, normal hepatic function, normal fasting glucose and glucose tolerance test, normal vitamin B6 and B12 level, no antinuclear antibodies, no anti-ENA, and no anti-DNA. Serological tests were negative for HVB, HVC, and HIV. Electro-neuromyogram of the legs was normal.

As treatment, she responded insufficiently to gabapentin up to 1800 mg/d and did not tolerate further increase in dosage. She did not tolerate amitriptyline nor clomipramine. Lidocaine patches were poorly efficient; the decrease in pain numeric scale was only 10%. Hence, she was prescribed high-concentration capsaicin patches on the sole. Patches were applied, simultaneously, during half an hour on both entire soles. Immediate tolerance was good with moderate burning sensations during the patches application; this was relieved by icing the soles. She received only one application on both soles and was reevaluated 3 months afterwards.

3. Results

At 3 months after capsaicin application, the patient then experienced an important diminution of her neuropathic pain. Decrease in the pain numeric scale was 50% with a pain rating of

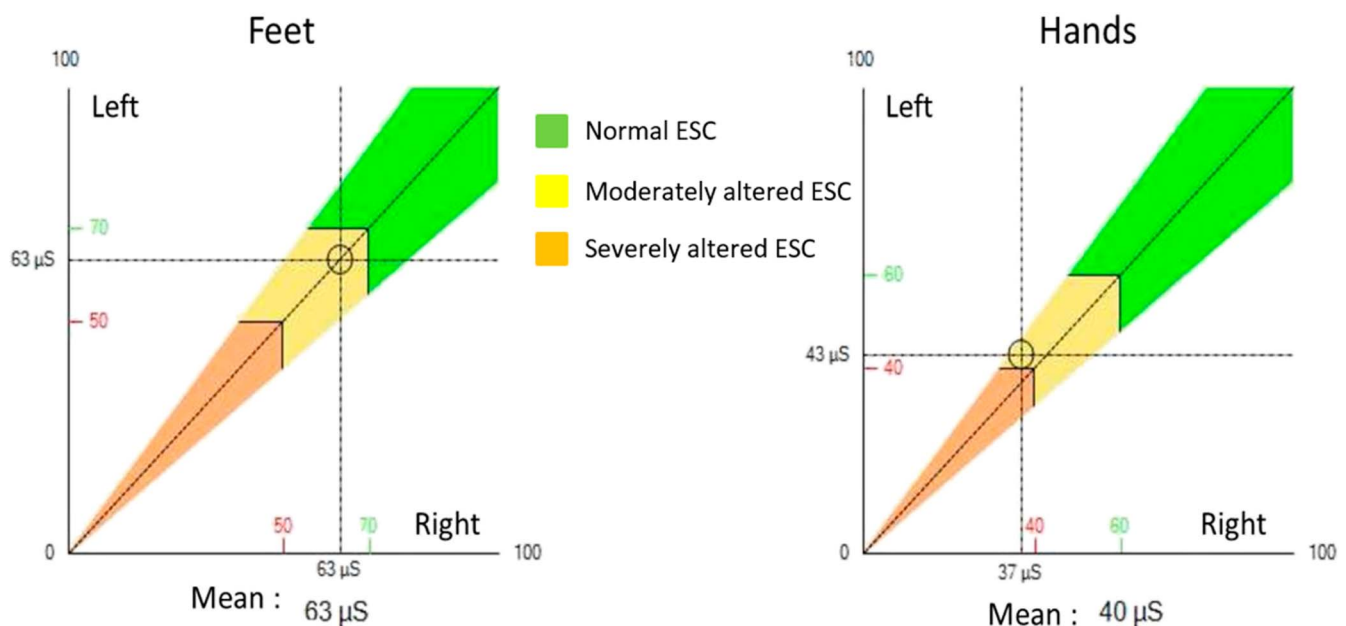


Figure 1. Electrochemical skin conductance by sudorimetry of the patient at diagnosis of her small fiber neuropathy. μ S, microsiemens; ESC, electrochemical skin conductance.

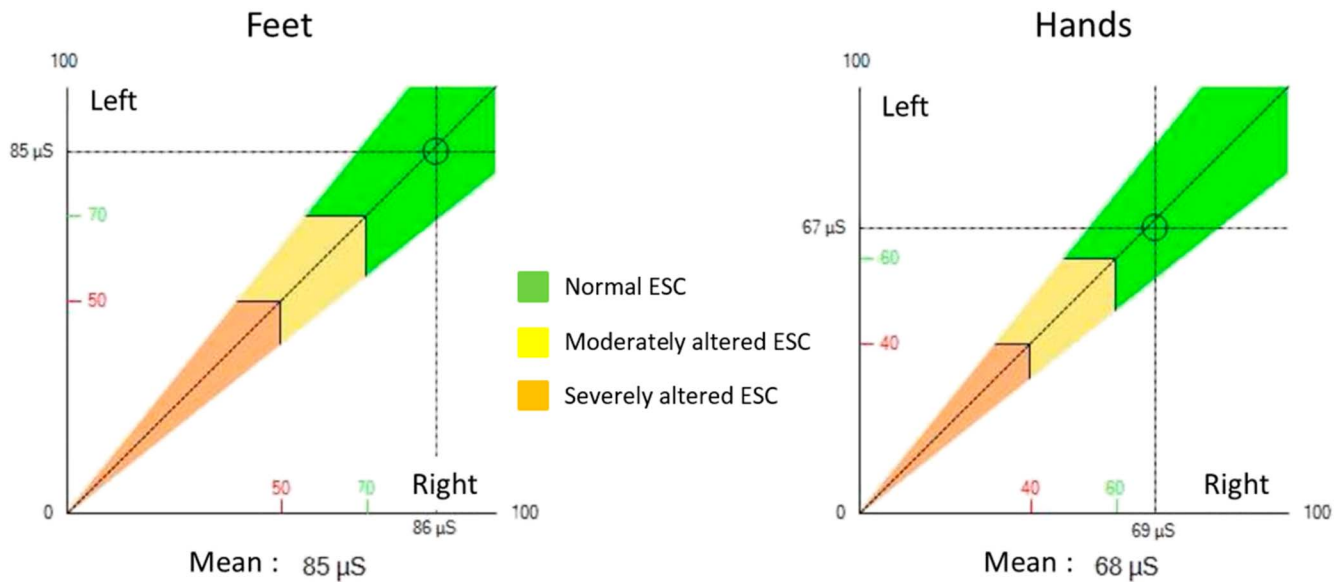


Figure 2. Electrochemical skin conductance by sudorimetry of the patient 3 months after high-concentration capsaicin patch application. μ S, microsiemens; ESC, electrochemical skin conductance.

3/10. Also, 3 months after capsaicin application, sudorimetry showed a normalization of the electrochemical skin conductance at the feet and a normalization of skin conductance at the hands (Fig. 2).

Given this normalization of sudorimetry, the patient agreed to a new skin biopsy (3 months after the capsaicin patch). The biopsy showed an increase in IEFN density at distal leg, almost reaching normal range: 4.17 IENF/mm.

4. Discussion

To the best of our knowledge, this is the first report of both functional and histological improvement after active high-concentration capsaicin patch treatment for neuropathic pain. This case leads to 2 discussions, first, the histological and functional improvements and, second, the potential interest of sudorimetry as a marker of treatment efficacy.

The potential action of capsaicin on small nerve fibers is shown in many immune-histochemical studies. They provide evidence that capsaicin can produce highly localized diminution of nociceptive nerve fiber terminals in the epidermis and dermis.^{1,9} However, after capsaicin application, there is a regrowth and intraepidermal nerve density returns to baseline level. In Gibbons et al.⁹, comparing the effects of topical capsaicin on cutaneous autonomic nerves, baseline intraepidermal nerve density returned to baseline level by day 100. The same pattern of decrease and return to baseline was seen in sudomotor function measured by quantitative sudomotor axon reflex testing and in sweat gland nerve fiber density.⁹ Here, after 90 days, the patient's intraepidermal nerve density has neither decreased nor is back to baseline level but has increased, almost reaching normal density. Moreover, this unexpected regrowth with a higher density than baseline level seems to have been of more functional small fiber since it is correlated with sudorimetry normalization for this patient.

Sudorimetry is now being assessed as a tool to measure progression and regression of disease. In this case, sudorimetry improvement is correlated with histological improvement and clinical efficacy. In one study, it was demonstrated that

electrochemical skin conductance improved with intensified insulin treatment in patients with diabetes.² Yet, larger studies are still needed in diabetes with strict glycemic control but also in other etiologies with other neuropathic treatment. In another recent study, electrochemical skin conductance improved at 12 weeks and continued to improve at 24 weeks after bariatric surgery in obese patients with type 2 diabetes.⁴

To date, no study has shown improved electrochemical skin conductance after a high-concentration capsaicin patch, and we report here the first case with improvement of pain intensity, electrochemical skin conductance, and IEFN density (although IEFN density of the patient remained under healthy control).

Larger cohorts are needed to demonstrate the good correlation between sudorimetry variation and clinical improvement to use sudorimetry as a monitoring tool for treatment efficacy.

Disclosures

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