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The value of electrochemical skin conductance measurement using Sudoscan® in the assessment of patients with familial amyloid polyneuropathy

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HIGHLIGHTS

- Distal involvement of small autonomic fibers is predominant in familial amyloid polyneuropathy (FAP).
- Electrochemical skin conductance, assessing sympathetic innervation, is easily measured by Sudoscan.
- FAP severity well correlated with Sudoscan measures, able to reveal early autonomic dysfunction.

ABSTRACT

Objective: To reappraise the value of electrochemical skin conductance (ESC) measurement by Sudoscan® to assess the distal involvement of small autonomic fibers in familial amyloid polyneuropathy (FAP) due to various transthyretin (TTR) mutations.
Methods: ESC was measured at both hands and feet in 126 patients with either Val30Met (n = 65) or non-Val30Met (n = 61) TTR mutation. This series included clinically asymptomatic (n = 21) and paucisymptomatic (n = 30) patients, as well as patients with moderate (n = 37) or advanced (n = 38) TTR-FAP.
Results: ESC measures did not differ between patients according to the type of TTR variant and were reduced in 24% of clinically asymptomatic patients, 40% of paucisymptomatic patients, 65% of patients with moderate TTR-FAP, and 92% of patients with advanced TTR-FAP. ESC measures were found to correlate with patients' clinical status, especially assessed by the Neuropathy Impairment Score and Karnofsky Performance Status.
Conclusion: ESC measures well correlate with the severity of TTR-FAP and could provide early marker of the disease.
Significance: ESC measures appear to be relevant to evaluate distal autonomic involvement in the context of amyloidosis.

1. Introduction

Familial amyloid polyneuropathy (FAP) due to transthyretin (TTR) mutation results from an irreversible extracellular fibril protein deposits caused by mutated TTR and is a length-dependent

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small-fiber predominant neuropathy (Planté-Bordeneuve and Said, 2011). Because of this characteristic, the evaluation of the autonomic cutaneous innervation of the extremities by unmyelinated C fibers is particularly relevant in this disease. A few studies addressed this issue. At distal limb level, sudomotor innervation was assessed in patients with TTR-FAP by sympathetic skin reflex recording (Montagna et al., 1996; Alves et al., 1997; Shivji and Ashby, 1999; Conceição et al., 2008, 2014; Lefaucheur et al., 2013, 2015; Castro et al., 2016), quantitative sudomotor axon reflex testing (QSART) (Wang et al., 2008; Kim et al., 2009), and sweat gland quantitation in skin biopsy (Chao et al., 2015). More recently, a new device, called Sudoscan® (Impeto Medical, Paris, France), was introduced in clinical practice to evaluate peripheral neuropathies affecting small-diameter fibers, e.g., in diabetes (Mayaudon et al., 2010; Gin et al., 2011; Yajnik et al., 2012; Calvet et al., 2013; Casellini et al., 2013; Selvarajah et al., 2015). The Sudoscan® technique is based on reverse iontophoresis and chronoamperometry. It measures electrochemical skin conductance (ESC) changes secondary to chloride ion flux in the skin in response to a locally applied very low direct current (less than 4 V). This measurement, expressed in microSiemens (μS), reflects sudomotor skin reactivity triggered by C-type unmyelinated nerve fibers (Smith et al., 2014; Novak, 2017).

In the context of TTR-FAP, ESC results have been reported in only two studies (Castro et al., 2016; Planté-Bordeneuve et al., 2017). In the first study (Castro et al., 2016), 133 TTR-FAP carriers, all with Val30Met mutation and asymptomatic or paucisymptomatic clinical presentation, were compared with 37 healthy controls: the authors found that ESC measured at the feet was able to differentiate symptomatic patients from asymptomatic subjects and healthy controls. In the second study (Planté-Bordeneuve et al., 2017), ESC results were included in a small-fiber neurophysiological score used to follow the treatment of TTR-FAP patients by Tafamidis, a drug that aims at stabilizing the structure of TTR to avoid amyloid deposits. However, ESC results were not detailed in this latter study.

In the present study, we report our experience of ESC measurement for the diagnosis of TTR-FAP in a large series of 126 patients with TTR mutation, including various variants (not only Val30Met) and variable clinical severity ranging from asymptomatic to very advanced neuropathy.

2. Methods

Electrochemical skin conductance (ESC) measurements of 126 consecutive patients investigated in our centre for TTR mutation were retrieved. These measurements were made using Sudoscan®, between February 2012 and October 2017, in patients referred to the Clinical Neurophysiology lab of University Hospital Henri Mondor, Creteil, France for the diagnosis or follow-up of TTR-FAP as a standard medical management. No patients with diabetes or possible cause of neuropathy other than amyloidosis were included. This study was approved by a local Institutional Review Board as a routine care study

2.1. Investigated variables

The investigated clinical parameters were: (i) type of TTR mutation; (ii) gender; (iii) age; (iv) body mass index (BMI, in kg/m2); (v) the Neuropathy Impairment Score (NIS) (Dyck et al., 1997), which is a composite clinical score combining motor function (79% of total score), sensory function (13% of total score), and tendon reflexes (8% of total score), ranging from 0 [normal] to 244 [total impairment]; (vi) the Karnofsky Performance Status (KPS) (Yates et al., 1980), which reflects the global health of the patient, ranging from 100 [normal] to 0 [dead]; (vii) the modified Polyneuropathy Disability Score (mPND) (Steen and Ek, 1983), which is a score evaluating walking capacity as follows: 0: normal; 1: sensory disturbances in the lower limbs but normal walking capacity; 2: impaired walking but no need of aid or stick; 3: walking with one or two sticks; 4: wheelchair or bed confinement.

For performing Sudoscan® test, the patients, in standing position, were asked to place both palms and soles on large-area stainless-steel electrodes. After a scan lasting only 2 min, the ESC values are immediately provided by the system for both palms and soles, and the average scores were calculated for the two upper limbs (ESC-UL), the two lower limbs (ESC-LL), and the four extremities (ESC-TOT). In our laboratory, the limits of normal ESC values are 64 μS at the palms and 67 μS at the soles, as previously published (Lefaucheur et al., 2015).

2.2. Statistical analyses

InStat and Prism softwares (GraphPad Software, Inc., La Jolla, CA, USA) were used to perform statistical analyses, which were based on nonparametric tests, since not all data showed normal distribution according to Kolmogorov-Smirnov test. In all cases, a p value less than 0.05 was considered significant.

The following analyses were performed: (i) comparison analyses of ESC-UL, ESC-LL, or ESC-TOT values at baseline according to the type of TTR mutation (Val30Met vs. non-Val30Met), the gender (women vs. men), or the mPND (<2 vs. ≥2) using the Mann-Whitney test; (ii) comparisons between patients with Val30Met vs. non-Val30Met mutation using the Mann-Whitney test for continuous variables and the Fisher's exact test for categorical variable (gender and mPND); (iii) correlation analyses between ESC-UL, ESC-LL, or ESC-TOT values and patients' age, BMI, NIS, or KPS using the Spearman test in the entire series of patients and in the subgroups of patients with either Val30Met or non-Val30Met mutation.

3. Results

The investigated patients were 52 women and 74 men, aged from 25 to 81 years (mean ± SEM: 59.2 ± 1.2). Among these patients, 21 patients were clinically asymptomatic (mPND = 0, NIS = 0, and KPS = 100), 30 patients were paucisymptomatic (mPND ≤ 1, NIS ≤ 10, and KPS ≥ 90), 37 patients had a moderate TTR-FAP (mPND ≤ 1, associated with NIS > 10 and/or KPS < 90), and 38 patients had an advanced TTR-FAP (mPND > 1, NIS > 10, and KPS < 90). Regarding the 105 patients paucisymptomatic or with overt TTR-FAP, the age at disease onset ranged between 22 and 79 years (mean ± SEM: 56.2 ± 1.4) and disease duration between 1 and 22 years (mean ± SEM: 4.8 ± 0.4).

Among the 126 investigated patients, 61 patients (48%) had non-Val30Met TTR variants including Ala19Asp (n = 1), Arg21Gln (n = 1), Val28Met (n = 2), Thr49Ile (n = 4), Ser50Arg (n = 1), Glu61Lys (n = 2), Ile68Leu (n = 1), Val71Ala (n = 1), Ser77Phe (n = 3), Ser77Tyr (n = 12), Glu89Lys (n = 1), Val94Ala (n = 1), Ile107Val (n = 8), Tyr116Ser (n = 2), and Val122Ile (n = 21) variants. The demographic and clinical data in patients with Val30Met and non-Val30Met mutation are presented in Table 1. No statistical difference was found between the two subgroups, except for age, the patients with Val30Met being younger than those with non-Val30Met mutation (Table 1).

The NIS ranged between 0 and 126 (mean ± SEM: 25.2 ± 2.7), the KPS between 50 and 100 (mean ± SEM: 84.0 ± 1.2), and the BMI between 16.2 and 41.7 kg/m^2 (mean ± SEM: 24.2 ± 0.4). The mPND was 0 in 38 patients; 1 in 50 patients, 2 in 16 patients and 3 in 19 patients, and 4 in 3 patients.