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The diagnostic accuracy of *Sudoscan* in transthyretin familial amyloid polyneuropathy

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HIGHLIGHTS

- Assessment of autonomic function is critical in the diagnosis of transthyretin familial amyloid polyneuropathy (TTR-FAP).
- Feet electrochemical skin conductance was a significant independent predictor for the presence of symptoms and autonomic dysfunction in TTR-FAP.
- *Sudoscan* showed a good sensitivity and specificity in the early diagnosis of TTR-FAP.

ABSTRACT

Objective: Transthyretin familial amyloid polyneuropathy (TTR-FAP) is an axonal sensory-motor and autonomic neuropathy. Reliable quantification of sudomotor function could prove essential in the diagnosis and early treatment management. We aim to assess the diagnostic value of a new sudomotor test (*Sudoscan*) in TTR-FAP.
Methods: One hundred and thirty-three TTR-FAP Val30Met carriers, divided in asymptomatic and symptomatic stage 1, were compared with 37 healthy controls. We analyzed the right sural sensory nerve action potential (SNAP), the plantar sympathetic skin response (SSR) and the electrochemical skin conductance (ESC) measured by *Sudoscan* in both hands and feet.
Results: All neurophysiological measures were significantly worse in the symptomatic group. However, feet ESC was the only test distinguishing symptomatic patients with autonomic dysfunction from those without autonomic dysfunction, and both groups from asymptomatic subjects and healthy controls. Feet ESC was a significant independent predictor for the presence of symptoms and autonomic failure, after adjusting for demographic characteristics, sural SNAP and SSR amplitudes ($p < 0.05$). Feet ESC showed 76% sensitivity and 85% specificity for detection of dysautonomia.
Conclusion: Feet ESC is a sensitive test to assess early autonomic dysfunction in TTR-FAP subjects. This investigation should be considered for routine assessment in this population.
Significance: Abnormal feet responses on *Sudoscan* support early diagnosis in TTR-FAP.

1. Introduction

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, adult-onset, hereditary disorder characterized by the primary extracellular deposition of amyloid fibrils in unmyelinated and small myelinated fibers, with later involvement of the large fibers (Said et al., 1984).

TTR-FAP is an heterogeneous disease associated with a wide range of clinical manifestations, which leads to the phenotypic heterogeneity that characterizes the disease (Conceição et al., 2015; Sekijima, 2015). If untreated, the disease progresses rapidly and death usually occurs within the first decade after the onset of symptoms (Planté-Bordeneuve and Said, 2011).

The clinical presentation more often includes progressive peripheral sensory-motor polyneuropathy, typically with an early autonomic dysfunction. Nonetheless, cardiac involvement,

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gastrointestinal manifestations (diarrhea, constipation, alternating episodes of constipation and diarrhea), weight loss, carpal tunnel syndrome, renal insufficiency, proteinuria and vitreous opacity can be also observed (Conceição et al., 2015; Sekijima, 2015).

Making an accurate early diagnosis is important because tissue damage is largely irreversible and the available treatment options are most beneficial in early stages of the disease (Coelho et al., 2013; Plante-Bordeneuve, 2014).

The function of large fibers is easily evaluated by conventional nerve conduction studies. In TTR-FAP, sensory fibers dysfunction generally antedates motor fibers changes (Montagna et al., 1996). Although the assessment of small nerve fibers in TTR-FAP is of paramount importance due to its early involvement, it has been difficult to define a test with high diagnostic accuracy. Intraepidermal nerve fiber density is considered the current gold standard for small fiber neuropathies assessment (Hoeijmakers et al., 2012). However, its value in TTR-FAP is still largely unknown. Most neurophysiological techniques assessing small fiber function in TTR-FAP have low sensitivity and specificity, hence their limited use. The quantitative sudomotor axonal reflex test (QSART) (Low et al., 1983) is a well-established technique to quantify sudomotor function, which is considered useful in the evaluation of distal symmetric polyneuropathies (England et al., 2009); nonetheless, it is a time consuming and challenging method to attain routine application. Another relevant technique is the heart rate variability evaluation, which has been used as an outcome measure in recent clinical trials for TTR-FAP (Coelho et al., 2012; Suanprasert et al., 2014). However, this test reflects mainly the parasympathetic function, thus its adequacy in TTR-FAP has been controversial (Suanprasert et al., 2014). Finally, the sympathetic skin response (SSR) is a fairly simple, quick and innocuous test that has been proven useful in the diagnosis of small fiber damage in TTR-FAP (Montagna et al., 1988; Conceição et al., 2008), but its limited reproducibility hinders its use as a reliable technique (Vetrugno et al., 2003).

Sudoscan is a fairly recent technique that provides a quick, non-invasive and quantitative assessment of the sudomotor function (Mayaudon et al., 2010). It combines low direct current (DC) stimulation ($\leqslant$4 V) and reverse iontophoresis, as a way of measuring the local conductance derived from the electrochemical reaction between the sweat chloride and the nickel electrodes (Mayaudon et al., 2010). At these low voltages, the *stratum corneum* acts as a capacitor, making the current measured only dependent on the chloride production by the sweat glands. The electrochemical skin conductance (ESC) is then expressed in microSiemens (μS) (Ayoub et al., 2012). Recently, *Sudoscan* has been described as a promising tool in the assessment of sudomotor dysfunction in diabetic small-fiber neuropathy (Mayaudon et al., 2010; Yajnik et al., 2012).

In the present study, we aimed to assess the diagnostic accuracy of the ESC measurements by *Sudoscan* in TTR-FAP subjects.

2. Methods

2.1. Population

One hundred and thirty-three carriers of Val30Met mutation, confirmed by molecular analysis and regularly followed at our department were included. Sixty-nine subjects were Val30Met carriers without signs or symptoms related to TTR-FAP; sixty-four subjects were symptomatic patients with sensory or autonomic symptoms in stage 1 of the disease (Coutinho et al., 1980) and with a modified Polyneuropathy Disability Score (PNDs) $\leqslant$1 (Yamamoto et al., 2007). Patients with paresthesias, neuropathic pain, tingling, numbness or with temperature and/or pain insensitivity were categorized as patients with sensory symptoms; patients with postural hypotension, nauseas and vomiting, diarrhea or diarrhea/constipation, sphincter abnormalities or sexual dysfunction were classified as patients with autonomic dysfunction. For the assessment of the autonomic symptoms in this population, the Compound Autonomic Dysfunction Test (CADT) (Denier et al., 2007) was applied. The score of at least one point was considered indicative of autonomic dysfunction and categorized patients in the group of those with autonomic manifestations. Subjects with walking disability (PNDs > 1), taking anticholinergic drugs or with other medical or neurological disorders were excluded.

Thirty-seven healthy volunteers, matched for age and sex, with no signs or symptoms of neuropathy were selected as a control group.

All subjects gave written informed consent. Protocol was approved by the local Ethics' committee.

2.2. Neurophysiological studies

The neurophysiological tests were performed on the same day for all subjects. Skin temperature was above 32 °C and room temperature was kept at about 25 °C.

2.2.1. Conventional tests

These tests were only performed in subjects with the mutation.

2.2.1.1. Sympathetic skin response. SSR was recorded from the right sole using surface electrodes (reference on the *dorsum* region). The patient was kept relaxed in a quiet room. Responses were elicited by a single electrical stimulus to the contralateral median nerve at the wrist (stimulus intensity, 70 mA; duration, 0.2 ms). The responses were amplified using a band pass of 0.5 Hz to 2 kHz and displayed at a sweep speed of 1 s/division, with a gain of 0.2 mV/division (Conceição et al., 2008). Two responses were obtained with a variable interval gap of a few minutes and the largest one was selected. Peak-to-peak amplitude was measured. This test was performed before all the other neurophysiological studies.

2.2.1.2. Nerve conduction studies. Right sural sensory nerve action potential (SNAP) was recorded using surface electrodes located behind the lateral malleolus, 10 cm distal to the stimulator electrode placed on the sural region. Signal was filtered (20 Hz to 2 kHz) and averaged (gain of 20 μV/division) for analysis. Latency was defined at the initial deflection from the baseline. Peak-to-peak SNAP amplitude and sensory conduction velocity (SCV) were considered.

2.2.2. Sudoscan

This test was performed in carriers and controls.

Subjects were asked to place their hands and feet on the electrodes and to stand still for 3 min. Individual right and left hands and feet were studied, but a final mean score of both hands (hands ESC) and both feet (feet ESC) was given automatically and considered for analysis (Yajnik et al., 2012). The test was repeated 10 min after to ensure reliability.

2.3. Body mass index

As body fat can alter autonomic tests (Peterson et al., 1988) body mass index was calculated by the formula $\mathrm{BMI} = \frac{\mathrm{Weight\ (in\ kg)}}{\mathrm{Height}^2\ \mathrm{(in\ m)}}$ to compare it between groups.

2.4. Statistical analysis

Data analysis was performed using MATLAB R2014b (The MathWorks Inc., USA). For the significance level α = 0.05 was considered.