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Microneurographic evaluation of sympathetic activity in small fiber neuropathy ☆

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HIGHLIGHTS

- SSR and SVR could help to disclose autonomic involvement in small fiber neuropathy.
- First study reporting microneurography, SSR and SVR in small fiber neuropathy.
- Microneurography showed different involvements of the sympathetic branches in SFN.

ABSTRACT

Objective: Small fiber neuropathy (SFN) may involve somatic and autonomic fibers. Assessment of somatic epidermal nerve fiber density (ENFs) is considered the gold standard test in the diagnosis of SFN. By contrast, autonomic involvement in SFN is more difficult to ascertain. Here we investigate peripheral sympathetic outflow by microneurography in patients with selective small nerve fiber involvement of different origin with and without autonomic symptoms to ascertain the ability of microneurography and the corresponding skin organ effector responses (sympathetic skin activity-SSR and skin vasomotor reflex-SVR) to disclose autonomic involvement.

Methods: We studied 59 patients with SFN because of reduced leg ENFs and normal conduction studies. Thirty patients reported only burning paresthesia (somatic SFN) whereas 29 patients complained of additional autonomic dysfunctions (autonomic SFN). They underwent microneurography from peroneal nerve with the recording of muscle sympathetic nerve activity (MSNA), skin sympathetic nerve activity (SSNA) and the corresponding SSR and SVR in the same innervation field. Thirty age and sex-matched healthy subjects served as controls.

Results: Patients with autonomic SFN mainly complained of loss of sweating. They showed a significant absence of indirect (SSR and SVR) and direct (MSNA and SSNA) sympathetic tests compared to somatic SFN patients and controls. SSNA, SSR and SVR were more often absent than MSNA. In addition, SSR and SVR were absent in all patients with no recordable SSNA but no significant relationship was found with MSNA recording.

Conclusions: SSR and SVR, simple indirect tests of sympathetic activity, could help to disclose autonomic involvement in SFN with a good sensitivity mainly in patients with sweating dysfunctions although they expressed autonomic failure in only one sympathetic branch.

Significance: Microneurographic evaluation of sympathetic activity, technically more difficult than indirect tests, was a useful functional tool contributing to the diagnosis and extension of autonomic involvement in SFN. Our data showed that the skin sympathetic branch is more often involved than the muscle sympathetic branch in SFN.

1. Introduction

Small fiber neuropathy (SFN) is a well-characterized peripheral neuropathy with the underlying involvement of small-diameter myelinated and unmyelinated peripheral nerve fibers (Lacomis, 2002; Lauria, 2005). SFN may involve somatic and autonomic fibers. Affected patients typically complain of neuropathic pain including burning paresthesia, allodynia and reduced thermal sensation (Lauria, 2005) when somatic fiber abnormalities are preva-

☆ This paper is devoted to the memory of Prof. Pasquale Montagna who passed away prematurely on 9 December 2010.

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lent, or skin sudomotor and vasomotor dysfunctions associated with erectile and pupils abnormalities, orthostatic hypotension or gastrointestinal dysmobility when autonomic fibers are mainly involved (Lacomis, 2002; Hoitsma et al., 2004; Freeman, 2005).

Assessment of somatic epidermal nerve fiber density (ENFs) using the pan-neuronal marker against protein gene product (PGP) 9.5 is considered the gold standard test in the diagnosis of SFN (Kennedy, 2004). By contrast, autonomic involvement in SFN is more difficult to ascertain usually requiring specialized analysis or procedures. Autonomic innervation of skin annexes has been investigated in several types of SFN using PGP (Dabby et al., 2007; Gibbons et al., 2009) and more specific autonomic markers such as vasoactive intestinal peptide (VIP) and dopamine beta hydroxylase (DβH) (Donadio et al., 2006; Nolano et al., 2010), but an important limitation of this analysis is the lack of a reliable quantitative method (Lauria et al., 2010). Peripheral sympathetic activity may also be analyzed by several indirect tests exploring effector organ responses namely sudomotor activity tests such as quantitative sudomotor axon reflex (QSART) and sympathetic skin activity (SSR) or skin vasomotor reflex (SVR). QSART may reveal sudomotor involvement in the majority of patients with SFN although it is a specialized technique requiring specific skills and instrumentation and is performed in relatively few centers (Low et al., 2006). SSR and SVR are simple tests which can be readily performed in most electromyography laboratories but they can be affected by several neural (i.e. suprabulbar, medullary and spinal) or non-neural (i.e. sweat gland) mechanisms and do not reflect a selective postganglionic dysfunction (Low, 1984; Maselli et al., 1989; Herbaut et al., 1990; Kolev et al., 1995; Donadio et al., 2005).

Microneurography is a technique for direct recording of sympathetic action potentials from unmyelinated postganglionic fibers in alert man (Wallin, 1994). Compared to the majority of autonomic tests used in SFN that analyze sympathetic activity to the skin, microneurography allows a broader analysis of peripheral sympathetic outflow exploring additional muscle sympathetic nerve activity (MSNA). Microneurography also allows the measurement of sympathetic reflex latencies that can be used as a sympathetic velocity index since sympathetic latency is mainly due to conduction in postganglionic sympathetic fibers (Fagius and Wallin, 1980a). Sympathetic activity has been studied by microneurography in patients with polyneuropathy characterized by large nerve fiber involvement (Fagius and Wallin, 1980b) but no data are available in neuropathy with selective small fiber involvement.

The main aim of this study was to analyze peripheral sympathetic outflow by microneurography in patients with selective somatic SFN of different origin with and without autonomic symptoms to ascertain the ability of microneurography and the corresponding effector organ responses (i.e. SSR and SVR) to disclose autonomic involvement.

2. Materials and methods

Fifty-nine patients (34 men and 25 women; mean age 53 ± 15 years) with suspected SFN because of distal leg burning paresthesia were prospectively enrolled for this study. The SFN was confirmed by skin biopsy showing reduced leg ENFs in all patients. Thirty patients reported only burning paresthesia (i.e. somatic SFN group) whereas 29 patients complained of additional autonomic dysfunctions (i.e. autonomic SFN group) including sweating dysfunctions (21 patients), gastrointestinal dysmotility (6), orthostatic hypotension (4), erectile impotence and/or bladder paresis (3), and skin hyperemia (1). They underwent an extensive laboratory evaluation including motor including F wave (ulnar, median and tibial bilaterally) and sensory (ulnar, median and sural bilaterally) nerve conduction studies, lumbar puncture and screening for autoimmune, inflammatory, microbiologic, metabolic and neuroendocrinological disorders. The SFN etiology included diabetes mellitus (15 patients), Fabry disease (6), Sjogren disease (6), immune-mediated (five patients with cerebrospinal fluid albumino-cytologic dissociation) disorders, C hepatitis (4), primary amyloidosis (2), or was undetermined (21).

Thirty age and sex-matched healthy subjects without clinical signs of neurological dysfunctions served as controls (Table 1).

The procedures used followed the Helsinki Declaration regarding international clinical research on human beings and all subjects gave their written informed consent to the study.

2.1. Measurements

Patients lay reclining in an ambient temperature of 20–25 °C and relative humidity of 20–30% in a semi-dark sound-proof room. *ECG* was recorded via Ag–AgCl electrodes on the chest and *respiratory movements* were monitored by a strain gauge belt around the lower part of the chest. *Arterial finger blood pressure* was measured non-invasively by the volume-clamp method (Finometer model, Arnhem, The Netherlands), with the cuffs around the middle phalanx of the third finger on the same side as the microneurography recording. *SVR* and *SSR* were recorded by an infrared photoelectric transducer placed on the toe (model PPS, Grass Instruments) and Ag–AgCl surface electrodes on the sole respectively (filter setting 0.2–100 Hz for both). SVR and SSR were recorded in the same corresponding innervation field of peroneal nerve studied by microneurography.

Multiunit efferent post-ganglionic sympathetic nerve activity was recorded with an insulated tungsten microelectrode with a tip diameter of a few microns inserted into the left peroneal nerve, posterior to the fibular head. A low-impedance reference electrode was inserted subcutaneously a few centimeters away.

The nerve signal was amplified (×50,000), filtered (band pass 700–2000 Hz) and fed through a discriminator for further noise reduction and audio-monitoring. A mean voltage (integrated) display was obtained by passing the original signal through a resistance–capacitance circuit (time constant 0.1 s). During the experiment, neural activity, arterial pressure and skin sympathetic effector responses were monitored on a storage oscilloscope. When a muscle or skin nerve fascicles was identified, small electrode adjustments were made until a site was found in which sympathetic impulses with a good signal-to-noise ratio could be recorded.

A recording of *MSNA* was considered acceptable when it revealed spontaneous, pulse-synchronous bursts of neural activity that fulfilled the criteria for MSNA, previously described (Sundlöf and Wallin, 1977). After acquiring a stable recording site, resting MSNA was recorded for 15 min.

A burst of skin sympathetic nerve activity (*SSNA*) was considered if it: (1) showed irregular occurrence varying in strength and duration, unrelated to heart beats; (2) at rest was followed

Table 1
Demographic data.

	sSFN	aSFN	Control	*p*
Number of subjects	30	29	30	0.83
Age (years; mean years ± SD)	54 ± 14	52 ± 16	53 ± 17	0.66
Sex (male:female)	17:13	19:10	18:12	0.78
Duration (years; mean years ± SD)	5 ± 3	6 ± 3	–	0.53
Height (cm; mean ± SD)	168 ± 0.1	170 ± 0.1	170 ± 0.1	0.81

sSFN = somatic small fiber neuropathy; aSFN = autonomic small fiber neuropathy.