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Letter to the Editor

Diagnosing small fibre neuropathy requires a golden standard

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With interest we read the article by Galosi *et al*. about 86 patients with suspected small fibre neuropathy (SFN) in whom the diagnostic accuracy of the SFN symptom inventory questionnaire (SFN-SIQ) was assessed [1]. As a reference, a combination of clinical exam, quantitative sensory testing (QST), and skin biopsy was applied [1]. The SFN-SIQ discriminated between patients with and without pure SFN with a sensitivity of 86% and a specificity of 70% [1]. It was concluded that the SFN-SIQ could be useful for screening patients with suspected pure SFN and identifying those requiring instrumental investigations [1]. The study is appealing but raises concerns that require further discussion.

We disagree with the notion that the diagnostic yield of SFN-SIQ is high [1]. According to the presented data, the SFN-SIQ does not detect 14% of SFN patients and provides a false diagnosis in almost one third of the patients [1]. Because the SFN-SIQ is recommended only as a screening test, it is more helpful to apply the clinical exam, QST, and instrumental quantitative tests immediately when SFN is suspected.

A limitation of the SFN-SIQ is that it relies on information provided by the patient and does not apply objective instrumental investigations. It can be used only in alert patients without cognitive impairment and the information provided by the patient cannot be reliably objectified.

A further limitation of the study is that only patients with acral pain, or hyperalgesia, were included [1]. Only one third of the SFN patients present with an acral distribution of sensory abnormalities [2]. However, the spectrum of clinical presentation of SFN patients is much broader [3]. About half of the patients with SFN complain about whole body pain [2]. Furthermore, patients with chronic regional pain syndrome (CRPS), burning mouth syndrome, or restless genital syndrome should be considered.

Generally, SFN can be diagnosed according to the Neurodiab, Devigli (Besta), EFNS, or Blackmore criteria [3]. Irrespective of the criteria applied, the diagnosis of SFN not only relies on a single test but a combination of several of them. In addition to the history, symptoms, and signs, skin biopsy stained with PGB 9.5 or GAP-43, corneal confocal microscopy (CCM), QST, pain-related evoked potentials (PREP), laser speckle contact analysis (LASCA), which relies on axon flare responses, laser Doppler flowmetry, laser Doppler imaging, contact heat-evoked potentials (CHEP), laser-evoked potentials, nerve conduction studies (NCSs), micro-neurography of C-fibers of the superficial peroneal nerve, and sensory stimulation tests can be applied.

In addition to the intra-epidermal nerve fibre density (IENFD), the sweat gland nerve fiber density (SGNFD), and the number of peptidergic fibers (contain substance-P) can be determined on skin biopsy. Additionally, autonomic tests, such as deep breathing, Valsalva manoeuvre, tilt test, cerebral blood flow velocity measurements, heart rate variability, and the quantitative sudomotor axon reflex test (QSART) are warranted if three is obvious autonomic dysfunction Applying several of these test at the same time increases the diagnostic accuracy.

Overall, the study carries obvious limitations that require re-evaluation and discussion. Clarifying these weaknesses would strengthen the conclusions and could improve the study. As long as there is no reliable golden standard for diagnosing SFN, a combination of tests should be applied.

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