To the Editor:

We read with interest the recent paper by Truini et al. [15,], focused on the relationship between epidermal innervation and neuropathic pain features in 139 peripheral neuropathy patients, 101 of whom complained of pain.

After the availability of cytoplasmatic antibodies able to reliably detect intraepidermal nerve fibers (IENF) [17], pioneering studies demonstrated the usefulness of skin biopsy in diagnosing small-fiber neuropathy in patients with little or no clinical evidence [4,5]. Further observations showed that the decrease of IENF density correlated with negative sensory symptoms and signs (eg, pinprick sensation) [16], supporting experimental skin denervation findings

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However, the most intriguing and challenging question remained as to whether changes in IENF density could correlate with positive sensory symptoms. Some key characteristics of IENF, such as the lack of Schwann cell membrane [7] and the extensive expression of transient receptor potential vanilloid type 1 [9], along with the role of resident epidermal cells in the transduction of somatosensation [10], suggest that the entire skin, rather than nerve fibers alone, is a complex polymodal receptor in which axon-cell networks contribute in the generation of thermal and nociceptive sensation and, possibly, neuropathic pain. The evidence that neuropathy patients with predominantly small nerve fiber loss have a higher probability of experiencing neuropathic pain [1], and that the regeneration of these fibers is associated with recovery from pain [8,14], could not explain the spectrum of phenomena representing neuropathic pain. This remains true in light of the most recent studies in patients with small-fiber neuropathy harboring sodium channel gene mutations, who showed a wide variability in clinical presentation and IENF density [2,3] despite the specific dysfunction of key structures in the generation of nociception. On the other hand, there is clear evidence that epidermal denervation can occur in patients either with excruciating pain [1] or with painless conditions such as congenital insensitivity to pain [11] and Friedrich ataxia [12]. Truini et al’s observations confirm the current understanding that the loss of IENF is a common finding in patients with peripheral neuropathy, irrespective of the presence or absence of pain. Moreover, these investigators also confirmed that the pattern of IENF loss is not related to the underlying etiology. In other words, a blinded morphometric analysis of skin biopsy sections does not allow the inference of any conclusion regarding patient’s clinical picture.

The novel finding reported is that patients with provoked pains (not otherwise specified) and mechanical dynamic allodynia had significantly lower IENF density than those without, suggesting that the degree of epidermal denervation might correlate with a specific pattern of neuropathic pain. The age of the patients belonging to these subgroups ranged approximately between 55 and 70 years. The corresponding 5th percentile of IENF density, adjusted by gender and age decade [6], ranges from 4.3/mm to 2.2/mm in women and from 3.5/mm to 2.1/mm in men. Unfortunately, we do not know whether the authors used these normative values, and therefore whether each patient had an IENF density below the corresponding cut-off value. This would be important when looking both at the sample size and the large standard deviations provided. However, even considering the mean values reported, ranging from 2.3/mm to 3.7/mm as a whole in the 2 subgroups, one should argue on the clinical meaningfulness of a difference of approximately 1 IENF/mm, also at the light of the physiologic decline of approximately 0.9 IENF/mm by age decade from 20 to 80 years [6]. Moreover, it seems likely that provoked/evoked pain was the predominant, but not the exclusive, feature. Indeed, adding these patients to those with ongoing burning pain, the overall number of patients with pain is largely higher than that reported (eg, 101), suggesting an overlap of symptoms in each subgroup. Therefore, the slight difference in terms of IENF density between subgroups should refer to patients with predominant provoked/evoked pains, thus reducing the specificity of the findings.

We agree that the lack of relationship between pain and skin biopsy findings may reflect the heterogeneity of neuropathic pain. However, although the effort to identify a correlation between pain features and IENF density is appreciable, some concerns remain on the interpretation stated by Truini et al. Factors other than simple IENF loss are likely to play key roles in the development of various pain types and future pharmacologic strategies.

Conflict of interest statement

The authors declare no conflict of interest.

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