LETTER TO THE EDITOR

Sensory profile in primary restless legs syndrome and restless legs syndrome associated with small fibre neuropathy

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Sir, The association of restless legs syndrome with polyneuropathy, especially with involvement of small sensory fibres, is suggested by several observations (Iannaccone et al., 1995; Polydefkis et al., 2000; Gemignani et al., 2006); however, it is still controversial (Hattan et al., 2009). Bachmann et al. (2010) investigated 34 consecutive outpatients with restless legs syndrome from their Movement Disorders Clinic and identified 13 patients (38%) with small fibre neuropathy. The main scope of the study was to compare the sensory profile—according to a validated, comprehensive quantitative sensory test protocol—in primary restless legs syndrome versus secondary restless legs syndrome associated with small fibre neuropathy, and the conclusion was that thermal hypoaesthesia characterizes the latter.

We have several concerns regarding the methodology of this study. Differential diagnosis of secondary restless legs syndrome associated with small fibre neuropathy was based on clinical symptoms, i.e. patients with small fibre neuropathy were identified as having persistent plus symptoms, mainly painful, whereas patients with primary restless legs syndrome had tingling and dragging paraesthesias; however, even these latter symptoms may be features of small fibre neuropathy (Lacomis, 2002; Hoitsma et al., 2004). The diagnosis of small fibre neuropathy was confirmed by skin biopsy, which was, however, not performed in any of the patients with putative primary restless legs syndrome. In addition, not all patients with small fibre neuropathy had skin biopsy findings consistent with definite abnormalities (<5 intraepidermal nerve fibres per mm), but values were between 5 and 7 in some patients (‘possible’ small fibre neuropathy).

Some features of the patient subgroups were perplexing. Mean age of restless legs syndrome onset was not significantly different between the two groups (41 years in primary restless legs syndrome and 46.7 in secondary restless legs syndrome), in contrast with the observation that primary and secondary restless legs syndrome segregate in different ranges of onset age (Allen and Earley, 2000; Whittom et al., 2007). On the other hand, the age at onset in patients with small fibre neuropathy is usually older, in the 6–7th decade (Devigili et al., 2008; Gemignani et al., 2010); thus, it may be that patients with restless legs syndrome–small fibre neuropathy in this series represented a peculiar subpopulation of small fibre neuropathy. A positive family history was present in 38% of patients with secondary restless legs syndrome, and this again is in contrast with the notion that genetic factors play a specific role in primary restless legs syndrome (Paulus et al., 2007; Whittom et al., 2007). The argument that Hattan et al. (2009) identified 37% of patients with restless legs syndrome and neuropathy reporting a positive family history is not pertinent as their series included many patients with genetic neuropathy. It is also puzzling that in the primary restless legs syndrome group there were patients with an elevated glycated haemoglobin (7/19, if we consider normal range ≤6.1%, as indicated in the article), implicating a possible diabetic aetiology, rather than primary restless legs syndrome. In summary, some patients classified with secondary restless legs syndrome displayed features usually associated with primary restless legs syndrome, whereas in the primary group there were patients who could be suspected to have small fibre neuropathy, and this could even suggest that in some patients, restless legs syndrome was generated by interacting central and peripheral factors (Polydefkis et al., 2000; Gemignani, 2010).

In the comparison of the sensory profiles, there were similarities between the two groups that were almost as impressive as differences. Pinprick and pressure hyperalgasia were of identical degree, whereas dynamic mechanic allodynia was absent in both groups; this latter finding is in contrast with the current view that...
touch alldynia represents a characteristic feature of small fibre neuropathy (Devigili et al., 2008). On the other hand, if we assume that the two identified groups actually represented primary restless legs syndrome and restless legs syndrome associated with small fibre neuropathy, respectively, the conclusion that thermal hypoesthesia characterizes the latter seems rather tautological, as abnormal thermal sensation is typical of small fibre neuropathy and is part of the proposed diagnostic criteria (Lacomis, 2002; Devigili et al., 2008). We would regard this as an incorporation bias, in that a difference in the studied quantitative sensory test is implicated in the definition of the subgroups. Further, one can suspect that sensory findings have been conditioned by the treatment. It is said that ‘restless legs syndrome medication was paused... prior to quantitative sensory testing’, but this presumably does not apply to pregabalin and tildine, thus a possible influence of these drugs on thermal hypoesthesia is not excluded.

An interesting point in this study was that in consecutive, non-selected patients with restless legs syndrome, symptoms and signs of small fibre involvement were frequently present, in contrast with the quite diffuse view that disregards a relationship between neuropathy and restless legs syndrome, as a casual association or ‘mimics’ originating from diagnostic inaccuracy due to symptom overlap between neuropathy and restless legs syndrome (Hattan et al., 2009; Hening et al., 2009).

The authors have to be commended for proposing, for the first time, a comparison of the sensory profile between ‘central’ and ‘peripheral’ restless legs syndrome. This should not only support the differential diagnosis of primary and secondary nature of restless legs syndrome but could also provide a pathogenetic clue, as it has been proposed that different sensory features may reflect the transduction of variable pathomechanisms (Jensen and Baron, 2003; Baron, 2006). For instance, the same authors have previously demonstrated the presence of static mechanic hyperalgesia in primary restless legs syndrome, which was reversed by dopaminergic treatment (Stiasny-Kolster et al., 2004). This suggests that a central sensitization of spinal neurons (translating into static mechanic hyperalgesia) is implicated in restless legs syndrome mechanisms, which could be elicited by altered descending dopaminergic pain modulation. Is this also the case of secondary restless legs syndrome, as a consequence of abnormal peripheral sensory inputs? The presence of static mechanic hyperalgesia in secondary restless legs syndrome associated with small fibre neuropathy would suggest it is, but methodological limitations may have produced misleading findings. Hypothesizing that abnormal central and peripheral inputs operate through different mechanisms to generate restless legs syndrome, it is expected that comparing sensory phenotypes would sort out different mechanistic biomarkers, but the comparison should be made on the basis of a clear-cut differentiation between primary and secondary forms. In addition, we think that further parameters should be evaluated as comparison measures, as thermal hypoesthesia is an almost obligate feature of small fibre neuropathy, and it should rather be incorporated into the small fibre neuropathy diagnostic criteria. A detailed analysis of various features of sensory symptoms (‘descriptors’) could be of interest, in the perspective that different alterations in the somatosensory system, possibly implicated in restless legs syndrome subtypes, are translated into specific sensory phenotypes.

References


