Restless Legs Syndrome and Painful Neuropathy—Retrospective Study. A Role for Nociceptive Deafferentation?

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ABSTRACT

Objectives. Restless legs syndrome (RLS) occurs in polyneuropathy with small fiber involvement, possibly as a peculiar form of neuropathic pain; however, the relationship between pain and RLS has been poorly investigated in polyneuropathy.

Design, Setting, and Patients. We evaluated retrospectively the occurrence of RLS in 102 consecutive patients with polyneuropathy manifesting with neuropathic pain or dysesthesia, referred to the Neuromuscular Center, using the National Institutes of Health criteria for RLS. The patients were classified in subgroups characterized respectively by allodynia (hyperphenomena), with reported unpleasant sensations evoked by tactile stimuli, and hypoalgesia (hypophenomena), with absent pain sensation to pinprick, according to putative mechanisms of pain.

Results. RLS was present in 41/102 patients (40.2%). It was significantly more frequent in the “hypoalgesia” (23/37) than in the “allodynia” subgroup (9/31; \( P = 0.008 \)) and in the not classifiable cases (9/34; \( P = 0.004 \)).

Conclusions. RLS is frequent in painful polyneuropathy and is significantly associated with decreased small fiber input, thus nociceptive deafferentation may represent a factor interacting with RLS “generators,” possibly at spinal level. We suggest that overactivity of the spinal structures implicated in RLS may be triggered by nociceptive deafferentation in a subgroup of patients with painful polyneuropathy. Our findings, prompting a mechanistic characterization of RLS associated with painful polyneuropathy, have to be confirmed in a prospective study.

Key Words. Restless Legs Syndrome; Small Fiber Sensory Neuropathy; Neuropathic Pain; Painful Polyneuropathy; A-Delta Fibers

Introduction

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by discomfort of, and urge to move, the legs (primarily during rest or inactivity), partially or totally relieved by movement, with presence or worsening in the evening [1], either as primary, often hereditary disorder, or secondary to other diseases or conditions [2].

Secondary RLS is known to be associated with polyneuropathy, as described in several reports [3–5], although this is still controversial and it has been substantially denied by some studies [6,7]. It is likely that RLS occurrence depends upon the type of polyneuropathy, thus contradictory findings could be partly related to the distribution of neuropathy subtypes in the studied populations [7,8]. Also, in particular, it has been shown that RLS occurs mainly in association with small fiber sensory neuropathy (SFSN) [3–5], possibly representing a peculiar form of neuropathic pain [3,9]. The relationship between pain and RLS, however, has been investigated mainly in primary, non-neuropathic, RLS patients [9,10].

To investigate the relationship between neuropathic pain and RLS, assessing furthermore the prevalence of RLS in a polyneuropathy subgroup characterized by prominent positive sensory
manifestations, we evaluated retrospectively a series of patients with polyneuropathy, and neuropathic pain or dysesthesia as main symptoms, using a tentative mechanism-based classification of neuropathic pain [11,12].

Methods

Medical records of outpatients with painful polyneuropathy referred to the Neuromuscular Center between January 2002 and December 2006 were reviewed retrospectively with regard to the occurrence of RLS. The study was conducted in accordance with the Declaration of Helsinki, with approval from the Review Board of the Department of Neurosciences. Patients with distal symmetrical polyneuropathy were eligible when main symptoms were pain (if the patient himself/herself reported the sensory experience as painful) or dysesthesia (i.e., “an unpleasant abnormal sensation, whether spontaneous or evoked,” according to the International Association for the Study of Pain [13]). Pain and dysesthesia were deemed neuropathic by a clinical judgment based upon the distribution of pain symptoms in the distal legs and volunteered descriptors consistent with neuropathic pain, with exclusion of possible sources of nociceptive pain. When appropriate, neuroimaging studies were performed to exclude a central nature of sensory symptoms and/or RLS. A possible relationship of RLS with current medications was evaluated, considering the temporal relationship between drug assumption and onset of RLS, and when appropriate withdrawal was tested.

The diagnosis of RLS was made in a structured interview, which is part of the evaluation in neuropathy patients at our center since 1996, assessing the presence of all obligated diagnostic criteria, i.e., 1) an urge to move the limbs, 2) exacerbated by rest, 3) relieved by activity, and 4) worse in the evening, in accordance with the National Institutes of Health criteria [1]. The clinical severity of RLS was graded on the Johns Hopkins RLS Severity Scale (JHRLSSS) [14] based on the reported time of usual symptom onset: 1) for mild, defined as usual symptom onset before bedtime; 2) for moderate, defined as after 6 pm but before bedtime; or 3) for severe, defined as before 6 pm. All patients were examined by one of the authors (FG), and medical records were reassessed by FB and FV to substantiate the features for inclusion in the study.

Polyneuropathy was defined on the basis of clinical symptoms and signs consistent with diffuse peripheral nerve involvement in the lower distal extremities to a greater extent than in the hands, and it was classified as sensory, sensorimotor, or mainly motor on the basis of symptoms, as previously described [5]. The definition of polyneuropathy was consistent with the recently published criteria of the American Academy of Neurology [13]. Electrophysiological study with standard methods was performed in all patients, however, normal findings were not considered to exclude polyneuropathy in the presence of prominent symptoms and signs suggesting involvement of the small sensory fibers [16,17]. Although new diagnostic criteria combining clinical and laboratory data have been recently proposed [18], it is generally accepted that the diagnosis of SFSN remains primarily based on the clinical ground, provided that the minimal diagnostic criteria, requiring the presence of painful abnormal sensations with findings of small fiber dysfunction on neurological examination, are satisfied [16]. Accordingly, patients were classified as pure SFSN or small + large fiber neuropathy.

According to previous studies [11,12], the patients were classified on the basis of presumed pathogenic mechanisms in the “allodynia” subgroup (with presumed increased small fiber input or “hyperphenomena”) and in the “hypoalgesia” subgroup (decreased small fiber input or “hypophenomena”). The first subgroup was defined on the basis of reported symptoms suggesting allodynia, when innocuous tactile or thermal stimuli were perceived as painful or disagreeable (more commonly, unpleasant sensations evoked by contact with clothes and sheets), and the second subgroup was defined by absent pain sensation to pinprick with a needle in the distal lower limbs (at least the toes). Pinprick sensitivity was assessed by applying a pressure indenting the skin with a safety pin, asking patients whether the pin felt normally sharp and produced an appropriate pinprick sensation. In the classification of patients, only areas with unequivocal loss of pinprick sensation were taken into consideration. A third subgroup included “not classifiable” patients in whom neither allodynia nor hypoalgesia was seen. Patients with both allodynia and hypoalgesia were classified in the “allodynia” subgroup, assuming that increased fiber input was the prevailing mechanism, as previously suggested [12].

Subgroups of patients were compared using t-test for continuous variables for statistical analysis, and chi-squared test for categorical variables. A two-sided P value of <0.05 was considered
significant, except for comparison of “mechanism-based” subgroups of polyneuropathy in which a Bonferroni adjustment was performed to account for the multiple (3) comparisons performed, and a $P$ value of $<0.15$ was considered significant.

**Results**

We identified 102 patients (43 males, 59 females) with painful/dysesthetic polyneuropathy (Table 1), who were in part (41 cases) also the subject of a previous study [5], in a cohort of 280 consecutive outpatients with polyneuropathy or mononeuropathy multiplex seen at the Neuromuscular Center during the considered period. RLS was present in 41/102 patients (40.2%) and was slightly more frequent in women (42.4%) than in men (37.2%) (25/59 vs 16/43; $P = 0.748$). In the remaining patients with non-painful neuropathy, RLS was by far less frequent than in the considered group (28/178, i.e., 15.7%; $P < 0.001$).

Considering subgroups classified on the basis of presumed pathogenic mechanisms, RLS was significantly more frequent in the “hypoalgesia” subgroup (Table 1). The difference between the “hypoalgesia” and the “allodynia” subgroups was still significant, even if the alldynic patients also showing pinprick sensory loss were excluded from analysis (23/37 vs 3/15; $P = 0.015$) or were located in the hypoalgesia group (29/53 vs 3/15; $P = 0.021$), confirming the correlation of RLS with hypoalgesia. The pain was characterized as burning by the majority of patients in each subgroup (hypoalgesia, 13/37; allodynia, 16/31; and not classifiable, 16/34).

The composition of the subgroups was similar, including mainly diabetic, cryoglobulinemic, and idiopathic neuropathy, but in the “not classifiable” subgroup, cryoglobulinemic neuropathy was scarcely represented.

RLS prevalence did not differ significantly between patients with “pure” small fiber neuropathy (20/55, 36.3%) and patients with additional large fiber involvement (21/47, 44.7%). Most patients (33/41) had RLS graded as mild (usual symptom onset at bedtime) on the JHRLSSS, and only one patient had RLS graded as severe (symptoms before 6 pm). Severity of RLS was not

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**Table 1** Comparison of subgroups of patients with painful polyneuropathy

<table>
<thead>
<tr>
<th>Cause</th>
<th>Hypoalgesia (1)</th>
<th>Allodynia (2)</th>
<th>Not Classified (3)</th>
<th>All</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>37</td>
<td>31</td>
<td>34</td>
<td>102</td>
<td>ns</td>
</tr>
<tr>
<td>Males/females</td>
<td>13/24</td>
<td>13/18</td>
<td>17/17</td>
<td>43/59</td>
<td>ns</td>
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<tr>
<td>Age at observation (years), mean ± SD</td>
<td>64.22 ± 13.86</td>
<td>58.23 ± 14.46</td>
<td>62.65 ± 12.18</td>
<td>61.9 ± 13.6</td>
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<td>Age at onset (years), mean ± SD</td>
<td>61.43 ± 14.16</td>
<td>54.52 ± 15.22</td>
<td>56.76 ± 14.58</td>
<td>57.8 ± 14.8</td>
<td>ns</td>
</tr>
<tr>
<td>Disease duration (years), mean ± SD</td>
<td>2.84 ± 3.66</td>
<td>3.74 ± 4.26</td>
<td>5.96 ± 9.96</td>
<td>3.9 ± 6.5</td>
<td>ns</td>
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<tr>
<td>RLS, N (%)</td>
<td>23 (62.2)</td>
<td>9 (29.0)</td>
<td>9 (26.5)</td>
<td>41 (40.2)</td>
<td>1 vs 2 = 0.008</td>
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<td>Rankin score (1/2/3)</td>
<td>7/27/3</td>
<td>6/23/2</td>
<td>10/24/0</td>
<td>23/74/5</td>
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**CIAP** = chronic idiopathic axonal polyneuropathy; **CIDD** = chronic inflammatory demyelinating polyneuropathy; **CMT1/CMT2** = Charcot-Marie-Tooth disease type 1/2; **GBS** = Guillain-Barré syndrome; **HCV** = hepatitis C virus infection; **HNPP** = hereditary neuropathy with liability to pressure palsy; **MAG** = myelin-associated glycoprotein; **MAPs** = motor action potential; **ns** = not significant; **RLS** = restless legs syndrome; **SAPs** = sensory action potential; **SD** = standard deviation; **SFSN** = small fiber sensory neuropathy; **SLFSN** = small + large fiber sensory neuropathy.
correlated with the extent of pinprick sensory loss. Axonal changes were significantly more frequent in the hypoalgesia group than in the allodynia group (Table 1), but the global prevalence of RLS did not differ significantly between patients with and without axonal degeneration (16/36 vs 25/66; P = 0.664).

Iron and ferritin levels were available in 51 and 52 patients, respectively. Low serum levels of iron were found in 1/21 patients with RLS and in 3/30 patients without RLS; ferritin levels were low in 1/20 patients with RLS and in 1/32 patients without RLS.

Several patients had a symptomatic treatment (69/102), mainly with antiepileptic drugs (more commonly, gabapentin, pregabalin, and oxcarbazepine), without significant differences between subgroups (hypoalgesia, 28/37; allodynia, 18/31; and not classified, 23/34). Given the predominance of painful symptoms, antiepileptic drugs (more commonly, gabapentin, pregabalin, and oxcarbazepine) were preferred in the majority of patients, whereas dopaminergic agents were offered as first-line treatment in only two patients. In most patients, the treatment was not started at the time of examination, or it was temporarily stopped.

Discussion

This study confirmed that RLS is common in neuropathies with small fiber involvement [3,5], providing a possible clue to the pathogenesis of RLS in polyneuropathy. We investigated the relationship between pain and RLS using a putative mechanism-based classification of neuropathic pain [11] that postulates that mechanisms can be basically reascribed to increased small fiber input (hyperphenomena), or decreased small fiber input, i.e., nociceptive deafferentation (hypophenomena). This distinction, as previously postulated for postherpetic neuralgia [11], has been proved valid also for other painful conditions [12], including painful neuropathy [19]. We used a simplified evaluation suitable for a retrospective study, restricted to symptoms of touch allodynia as inferred by interview and findings of pinprick sensory loss on bedside examination, as it has been proposed that simple tools such as a pinprick test may be helpful to address possible mechanisms [12].

Our study had some limitations as a retrospective survey. Our findings were based upon bedside sensory tests, and the presence of allodynia was inferred from patient-reported symptoms, as standardized tests were not available in many patients, whereas other studies, investigating prospectively sensory functions in primary RLS, utilized more accurate laboratory methods [4,10]. Patients with pain or dysesthesia were considered together, as a clear-cut distinction was not allowed by the design of the study, and we assumed that mechanisms operating in both conditions are basically the same, considering dysesthesia a form of attenuated pain probably involving the pathways usually dedicated to the sensation of pain, as it is a constant component of neuropathic pain [20]. Another problem was that several patients could not be classified, as also seen in other studies [19]. As hyperalgesia to pinpricks seems to be frequent in painful conditions, when investigated with specific methods [12], it is likely that “not classifiable” patients can be relocated in part in the “hyperphenomena” group, but this would not presumably influence the substantial result of RLS predominance in the “hypoalgesia” group. Despite these limitations, we think that our study is of interest, as it suggests the association of RLS with nociceptive deafferentation in polyneuropathy, a finding that may deserve further investigation in a prospective study with more sophisticated methods. This would require more stringent criteria for the diagnosis of SFSN, as recently discussed [18], and standardized studies of quantitative sensory testing, in particular, objective tests for allodynia, specific tests for small fiber subtypes, such as capsaicin test [21] and laser-evoked potentials [22], and evaluation of hyperalgesia [10] and thermal thresholds, so as to provide an extensive assessment of hypo- and hyperphenomena, and of the type and degree of deafferentation.

The role of the nociceptive system in RLS has been previously suggested [3,4,10]. In particular, a seemingly contradictory finding was reported in patients with primary RLS by Stiasny-Kolster et al [10], who demonstrated the association of RLS with hyperalgesia, which was ascribed to central sensitization to A-delta fibers as a consequence of impaired dopaminergic inhibition of pain perception. Conversely, our findings may be interpreted assuming that deafferentation of A-delta fibers, mediating pinprick sensation [23], induces disinhibition of dorsal horn neurons and/or reorganization of central connections, as previously postulated [11,12,24,25], and this may represent a factor triggering an overactivity of the spinal circuitry subserving RLS [2]. Deafferentation, as a pain mechanism, is poorly investi-
gated with respect to more popular phenomena of peripheral and central sensitization [24,25], and it is not clear whether it requires a massive deafferentation [11] or a selective involvement of specific fiber subtypes; some studies point to a preferential loss of A-delta fibers in subgroups of patients with neuropathic pain [12,26], consistent with our findings.

A finding in common with the study of Stiasny-Kolster et al. [10] was that RLS did not correlate with allodynia, and this seems to confirm that altered small fiber input of A-delta, rather than of C-fibers implicated in allodynia [27], is important for the occurrence of RLS.

Altogether, these findings point to a remodulation of the nociceptive system as implicated in the pathogenesis of RLS, as a consequence either of dysfunction of descending dopaminergic control in the central nervous system [2,10], likely occurring in primary RLS, and in RLS associated with iron deficiency and Parkinson’s disease [28], or of altered nociceptive inputs in the peripheral nervous system. Recent findings in molecular genetics are consistent with the view that RLS may be generated at different neural levels, as genes implicated in RLS, and in particular the BTBD9 gene [29,30], may be widely expressed in the periphery and in the central nervous system [31]; another involved gene, LBXCOR1 [30], is implicated in a pathway indispensable to the generation of a GABAergic phenotype in a subset of dorsal horn neurons, with possible consequences on the modulation of pain and sensory inputs [31].

The involvement of the sensory nerves and, possibly, of the dorsal horn neurons in RLS may not only account for sensory symptoms, but also contribute to motor manifestations, influencing a remodeling of motor patterns at the spinal level. Presumably, other interplaying factors have to be integrated in this model, considering that RLS also occurs in a minority of neuropathy patients not showing nociceptive sensory loss, a further issue to be addressed in future studies.

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References