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Original Article

Alterations in pain responses in treated and untreated patients with restless legs syndrome: Associations with sleep disruption

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ABSTRACT

Objective: There has been recent interest in characterizing potential abnormalities of pain processing in patients with sleep disorders such as Restless Legs Syndrome (RLS). The aim of this study was to evaluate psychophysical responses to noxious heat and pressure stimuli in both treated and untreated RLS patients, compared to matched controls.
Methods: This study is a cross-sectional group comparison of RLS patients with matched controls. A total of 31 patients (15 treated, 16 untreated) with a confirmed diagnosis of RLS were compared to 18 controls with no history of RLS or related sleep disorders.
Results: RLS patients (both treated and untreated) demonstrated reduced pain thresholds and reported greater clinical pain relative to controls. Moreover, RLS patients demonstrated enhanced temporal summation of heat pain ($p < .05$), which may reflect aberrant central nervous system facilitation of pain transmission. Both treated and untreated RLS patients reported disrupted sleep relative to controls, and mediation analyses suggested that the reduced pain thresholds in RLS were attributable to sleep disturbance. However, the effect of RLS on the magnitude of temporal summation of heat pain was independent of sleep disturbance.
Conclusions: These findings suggest that central nervous system pain processing may be amplified in RLS, perhaps partially as a consequence of sleep disruption. RLS patients, even those whose symptoms are managed pharmacologically, may be at elevated long-term risk for the development or maintenance of persistent pain conditions. Further studies in larger samples could help to improve the prospects for pain management in RLS patients.

1. Introduction

Restless Legs Syndrome (RLS) is a neurologic disorder that affects up to 10% of the population [1]. Its symptoms show circadian variability, with a worsening in the evening, and include dysesthetic sensations in the legs along with an urge to move [2]. Although the pathophysiology of RLS remains incompletely characterized, strong evidence suggests a central role for dopaminergic [3] and opioidergic systems [4]. Given that opioids and dopamine play leading roles in central pain-modulatory processes [5–7], it is natural to inquire whether the symptomatology of RLS may include alterations in the perception and experience of pain.

There appears to be significant comorbidity among RLS, fibromyalgia [8], and headache [9], and recent surveys of RLS patients have revealed high rates of moderate to severe pain [10–13]. Other work has indicated that the severity of core RLS symptoms correlates with pain severity [12,14], suggesting overlap between manifestations of the disease and pain. Moreover, effective treatment with dopaminergic agonists reduces daily pain complaints among RLS patients [15]. While these clinical findings hint that the perception of pain may be amplified in RLS, few laboratory studies have examined responses to standardized stimuli in a controlled environment.

In one such report, RLS patients exhibited profound mechanical hyperalgesia at multiple body sites, which normalized after long-term treatment with dopamine agonists [16]. The study's authors noted that RLS should perhaps be categorized as a disorder of central pain processing as well as a motor and sleep disorder [16], a suggestion echoed by other RLS researchers [3,10,17]. In addition, one functional neuroimaging study revealed a dysfunctional

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pattern of cerebral endogenous opioid binding in RLS patients. These findings, in concert with indications of enhanced spinal reflexes in RLS [18], indicate that RLS may be associated with central sensitisation of spinal neurons or reduction in supraspinally-generated pain-inhibition.

In the present investigation, we used quantitative sensory testing [19] to evaluate the pain responses of both treated and untreated RLS patients to a variety of noxious stimuli, compared to matched controls. Prior studies of pain responses in RLS patients have not generally evaluated both treated and untreated participants in order to assess the putative effects of pharmacologic management of RLS symptoms on pain perception. In addition, we assessed whether the qualitative severity of sleep disruption, which is often severe in RLS patients [1,12,20], accounted for any observed group differences in pain responses. Since previous studies have suggested that naturally-occurring sleep disturbance [21,22], or experimental sleep disruption [23,24], results in enhanced pain perception and pain report, this constitutes one apparent mechanism by which RLS may impact the perception of pain.

2. Materials and methods

2.1. Subject recruitment and screening

All subjects provided verbal and written informed consent, and all procedures were approved by the Institutional Review Board. All subjects were screened using medical history and RLS diagnostic questionnaires as well as the validated Hopkins diagnostic interview for RLS [25] performed by an RLS specialist (RPA). Controls subject had to have no positive responses to any of the four defining RLS features in order to have a definite NOT-RLS diagnosis. RLS subjects had to have all four defining features of RLS [20] and not have other symptoms or conditions that might mimic RLS in order to have a "definite" RLS diagnosis [25]. Any subjects who had chronically painful conditions such as arthritis, neuropathy, or muscle pain were excluded, as were subjects who reported being on analgesic medications (e.g., opiates).

For RLS subjects who were off medication for this study, all centrally active medications, including RLS medications, were withdrawn at least 11 days or 6 drug half-lives (whichever length of time was greater) prior to the study. All but three of the subjects in this group were on dopaminergic agonists for at least 3 months prior to withdrawal. The other three subjects were taking clonazepam (one subject) and gabapentin (two subjects). For RLS subjects who remained on medications, the individual had to have been on the current dose of medication at least 3 months and report satisfaction with treatment of their RLS of 85% or better. The two RLS groups did not differ in their RLS severity based on the Johns Hopkins RLS Severity Scale [26] (see Table 1). This scale queries respondents about RLS symptoms at the time of onset/diagnosis; the fact that no group differences were observed suggests that the treated and untreated patients experienced approximately equivalent levels of initial RLS symptomatology. Control subjects were age-, and gender-matched to RLS cohort and were not on any centrally acting medications.

2.2. Session protocol

The setting for the study was a Clinical Research Center based within a university hospital. Participants arrived between 12:00 and 12:30 pm. Standardized questionnaires included a medical history form, the Beck Depression Inventory (BDI) [27], the Pittsburgh Sleep Quality Index (PSQI) [28], and the SF-36 [29]. After a 15-min period of rest, participants underwent the psychophysical pain testing procedures described below.

Table 1
Laboratory pain and questionnaire response data by participant group.

Variable	Controls	RLS-treated	RLS-untreated
Age	60.5 ± 8.8	63.3 ± 9.4	58.0 ± 9.5
% Female	44%	53%	50%
% White	89%	93%	94%
HPTh (arm) (°C)	46.5 ± 3.9[a]	43.7 ± 4.4[b]	45.0 ± 2.9[ab]
PPTh-leg (kPa)	898.6 ± 326.9[a]	687.3 ± 274.5[b]	670.0 ± 257.0[b]
PPTh-thumb (kPa)	444.0 ± 150.9	374.7 ± 164.2	358.7 ± 113.8
PPTh-trapezius (kPa)	608.4 ± 252.1[a]	442.0 ± 149.6[b]	468.9 ± 164.7[b]
Cold pain ratings (0–100)	65.4 ± 21.3	77.1 ± 17.1	70.7 ± 14.8
DNIC index	134.4 ± 44.3	121.8 ± 20.2	123.3 ± 30.2
JHRLSSS	0.0 ± 0[a]	2.1 ± 0.6[b]	2.0 ± 0.8[b]
SF-36 BP	89.7 ± 12.0[a]	65.5 ± 21.1[b]	73.6 ± 19.8[b]
PSQI	6.0 ± 3.0[a]	12.7 ± 3.9[b]	12.9 ± 4.5[b]
BDI	2.6 ± 3.0[a]	9.7 ± 11.1[b]	6.5 ± 6.3[ab]

Note: HPTh = heat pain threshold; PPTh = pressure pain threshold, in Kilopascales; DNIC = diffuse noxious inhibitory controls; JHRLSSS = Johns Hopkins restless legs syndrome severity scale; SF-36 BP = short form 36, bodily pain; PSQI = Pittsburgh Sleep Quality Index; BDI = Beck Depression Inventory.
[ab] Groups with like letters do not differ; groups with differing letters differ at $p < .05$.

2.3. Psychophysical pain testing

Mechanical pain thresholds were assessed first using a digital pressure algometer (Somedic; Sollentuna, Sweden). Pressure pain thresholds (PPThs) were determined twice, bilaterally: the trapezius muscle, the metacarpophalangeal joint of the thumb, and the quadriceps muscle, near the insertion of the proximal patellar tendon. At each site, mechanical force was applied using a 0.5-cm^2 probe covered with polypropylene pressure-transducing material; pressure was increased at a steady rate of 30 kPA/s until the subject indicated that the pressure was "first perceived as painful".

Next, contact heat stimuli were delivered using a Medoc Thermal Sensory Analyzer (TSA-II, Ramat Yishai, Israel) with a 9 cm^2 thermode. We first tested heat pain thresholds (HPTh) on the ventral forearm using an ascending method of limits paradigm with a rate of rise of 0.5 °C/Sec. Three trials of HPTh were performed, followed by several trials of suprathreshold heat stimulation to assess temporal summation of heat pain. Temporal summation of pain (i.e., the human analog to "wind-up") is a frequently-used index of central pain facilitation [30–32] which involves rapidly applying a series of identical noxious stimuli and determining the increase in pain across trials. In brief, sequences of 10 rapid heat pulses were applied to the forearm, as in prior studies [33]. Within each sequence, the procedure was as follows: from a 38 °C baseline temperature, 10 successive heat pulses were delivered. The rate of rise and fall of the thermode temperature was 10 °C/s, and target temperatures were delivered for approximately 0.5 s each. The thermode remained in a fixed position during administration of the 10 pulses and was then repositioned between sequences, with inter-sequence intervals of 2 min. Two different target temperatures (49 and 51 °C) were used. Subjects verbally rated the painfulness of each heat pulse on a 0–100 (0 = "no pain", 100 = "most intense pain imaginable") numeric rating scale, and then verbally rated the painfulness of after-sensations 15 s after the stimuli had ceased [34].

Finally, responses to noxious cold were evaluated using a repeated cold pressor task (CPT) involving immersion of the right hand in a circulating cold water bath maintained at 4 °C. The CPT is the most commonly-used method of pain induction in the laboratory and has demonstrated clinical relevance [19]. In the present protocol, participants underwent a series of five cold pressor tasks, with the first 4 consisting of serial immersions of the right hand for 30 s, with 2 min between immersions. The 5th and final CPT involved an immersion of the right hand lasting until a participant reached pain tolerance (or a 3 min maximum). Participants rated