



Original Article

Topography of sensory symptoms in patients with drug-naïve restless legs syndrome

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ABSTRACT

Objectives: We aimed to describe the sensory topography of restless legs syndrome (RLS) sensory symptoms and to identify the relationship between topography and clinical variables.**Methods:** Eighty adult patients with drug-naïve RLS who had symptoms for more than 1 year were consecutively recruited. During face-to-face interviews using a structured paper and pencil questionnaire with all participants, we obtained clinical information and also marked the topography of RLS sensory symptoms on a specified body template, all of which were subsequently inputted into our in-house software. The RLS sensory topography patterns were classified according to localization, lateralization, and symmetry. We investigated if these sensory topography patterns differed according to various clinical variables.**Results:** The lower extremities only (LE) were the most common location (72.5%), and 76.3% of participants exhibited symmetric sensory topography. Late-onset RLS showed more asymmetric sensory distribution compared with early-onset RLS ($P = .024$). Patients whose sensory symptoms involved the lower extremities in addition to other body parts (LE-PLUS) showed more severe RLS compared with those involving the LE ($P = .037$).**Conclusion:** RLS sensory symptoms typically were symmetrically located in the lower extremities. LE-PLUS or an asymmetric distribution more often occurred in patients with more severe RLS symptoms or late-onset RLS.

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1. Introduction

Most patients with restless legs syndrome (RLS) report abnormal and unpleasant sensations in both legs, usually with a symmetrical distribution. However, other body parts also can be involved, such as the arms [1–11], the abdomen [12], and even the genital area [13–19]. Furthermore, either an asymmetric or a strictly unilateral (UNI) distribution of sensory symptoms is not uncommon in patients with RLS [5,20–22]. Because the diagnosis of RLS almost entirely relies on subjective reports of symptoms that match the defining features of RLS without any detectable abnormality in the extremities [23], the characteristic topography

of the RLS sensation may be helpful for both an accurate diagnosis and the differential diagnosis of RLS.

Karroum et al. [22] systematically evaluated the topography of the sensations in patients with RLS. The study was meaningful in that it informed clinicians about the typical distribution of RLS and other possible rare presentations. In particular, the authors proposed that the unique distribution of RLS may suggest some points for its differential diagnosis by providing “a major clinical difference with polyneuropathy sensations” [22]. However, their study population was treated with dopaminergic agents or other agents for several years. Although the authors tried to eliminate “the possible impact of augmentation on the natural variation of the topography” [22], they did not avoid other effects of drugs on the topography of RLS sensations including reducing the symptoms. Hence a study of the topography of the sensation in drug-naïve patients with RLS should be conducted, as RLS medication might contribute to the topography of the sensory symptoms.

Here we report the topography of RLS sensory distribution prospectively collected from patients who had never been treated for RLS. Our objectives were to describe the topography of RLS sensory symptoms and to identify the relationships between the

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topography and clinical variables, which may help discriminate the various subtypes of RLS.

2. Methods

2.1. Participants and study design

Patients with RLS who visited the sleep clinics of Korea University Medical Center (KUMC) and Keimyung University Dongsan Medical Center (DSMC) were consecutively recruited from each hospital. Informed consent was obtained from all participants in accordance with the guidelines issued by the Institutional Review Board of each institute.

All participants underwent a standardized interview using a structured sleep questionnaire and clinical neurologic examinations by 2 sleep medicine neurology experts. The diagnosis of RLS was established by a neurologist, based on the diagnostic criteria set by the National Institutes of Health workshop on RLS, utilizing the validated Korean-language version of the John Hopkins telephone diagnostic questionnaire during a face-to-face interview [24,25]. The diagnostic questionnaire has questions that help exclude conditions that may mimic RLS. Nerve conduction studies and appropriate neuroimaging studies were performed in selected patients, such as participants with UNI or asymmetric distribution. In these cases, we also confirmed the RLS diagnosis using supportive criteria, including family history, positive response to dopamine therapy, and presence of periodic limb movements during sleep as revealed by polysomnography.

The inclusion criteria were participants aged 18–70 years, symptom duration for more than 1 year, and no prior treatment for RLS. The exclusion criteria were: (1) those patients with notable comorbidities likely to be associated with secondary RLS, such as pregnancy, chronic kidney disease, or peripheral neuropathy; (2) presence of a cognitive disorder that prevented participants from describing their symptom distribution; and (3) the presence of disorders with symptoms similar to RLS, such as attention-deficit/hyperactivity disorder, essential tremor, Parkinson disease, neuroleptic-induced akathisia, congestive heart failure, vascular claudication, neurogenic claudication, myelopathy, or arthritis. We were careful to exclude such patients, though we understand that true RLS occurs with one or more of these pathologies.

2.2. Clinical variables

The sleep questionnaire contained current age; gender; the Pittsburgh Sleep Quality Index (PSQI) scores [26]; and RLS-related variables, including age at onset, duration of RLS history, family history of RLS, and the International RLS Severity rating scale (IRLS) [27]. Family history was considered positive if the patient reported any first-degree relative with RLS. Participants were classified into early-onset (≤ 45 y) or late-onset (> 45 y) RLS [28]. Blood glucose, serum creatinine, iron and ferritin levels, and thyroid hormone levels also were checked. Participants who had ferritin levels < 45 $\mu\text{g/L}$ (reference range, 15–180 $\mu\text{g/L}$) were considered to have a low serum ferritin levels [24,29,30].

2.3. Topographic measure of RLS sensation

During patient interviews, the topography of RLS sensory symptoms was initially manually drawn on a human body template by 2 research nurses who asked about the presence of sensory symptoms. The drawings were approved by the patients. The research nurses were trained about clinical manifestations of RLS by one of the study authors (KJ). The body template was categorized into 14 anatomically defined regions (i.e., head, neck, arms and shoulders,

forearms, hands, chest, abdomen, back, anterior thighs, posterior thighs, shins, calves, feet, and genital area) along with 5 body parts (i.e., head and neck, upper extremities, trunk, lower extremities, and the genital area).

After inspecting all figures, 3 RLS sensory topography patterns were identified according to localization, lateralization, and symmetry of the body. The topography of RLS symptoms was classified according to the localization into 2 groups of participants with RLS sensory symptoms involving lower extremities only (LE) and involving the lower extremities in addition to other body parts (LE-PLUS). The LE group included participants with sensory symptoms confined only to the lower extremities. The LE-PLUS group was comprised of participants with sensory symptoms in other body parts in addition to the lower extremities, such as upper extremities, head, neck, chest, abdomen, back and genital area, regardless if RLS symptoms involved their lower extremities.

RLS symptom distribution also was classified according to lateralization as two groups of participants with UNI and bilateral (BI) RLS sensory topography. In other words, patients in the BI group had symptoms on both sides, whereas patients in the UNI group had symptoms located only on one side. The BI group was further classified into those with symmetric (BI-SYM) and asymmetric (BI-ASYM) RLS sensory topography. For example, participants in the BI-SYM group had sensory symptoms with almost complete symmetry. However, participants in the BI-ASYM group showed markedly asymmetric topography.

2.4. Development of a software application

We developed an in-house software application to plot the topography of RLS sensory symptoms using C# programming language. The RLS sensory distribution for each patient was drawn on the body template in the software using the mouse as an input device according to the figures manually drawn during each interview, and all electronically drawn pixels were saved.

RLS-related clinical variables obtained from a sleep questionnaire and other clinical parameters and laboratory findings were entered into the program, along with the patient's sensory topographic map.

Therefore, we extracted common sensory distribution patterns according to the above-mentioned variables, which allowed us to create an overlay sensory topography map using any combination of clinical variables. Body areas with a high frequency of involvement were distinguished as thicker by using colored bars. Furthermore, we counted the pixels drawn for all participants, which were divided by the number of pixels of the entire body area, resulting in the percentage of surface area affected by the RLS sensation for each individual [22].

2.5. Statistical analysis

We identified significant differences in the topography of the participants' RLS sensory symptoms according to various clinical variables. We used the χ^2 test or the Fisher exact test for discrete variables. Linear-by-linear association tests were used for the semiquantitative IRLS groups (mild, moderate, severe, very severe). We employed Student *t* test and the Mann-Whitney test for continuous variables when appropriate. We used either Pearson product moment correlation coefficients (*r*) or Spearman rank correlation coefficient (ρ) for the correlation analysis. The Statistical Package for the Social Sciences (SPSS) ver. 17.0 was used (SPSS Inc., Chicago, IL, USA) for all statistical analyses.

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