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Original Article

Prevalence and clinical characteristics of restless legs syndrome in diabetic peripheral neuropathy: comparison with chronic osteoarthritis

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ABSTRACT

Background: The prevalence of restless legs syndrome (RLS) in patients with peripheral neuropathy has been reported to be higher than that of the general population in some studies, which suggests an association between neuropathy and RLS, but not all studies show increased RLS with neuropathy. These differences may reflect adequacy of the diagnosis, effects of chronic pain complicating the diagnosis, or population differences. Moreover, if there is increased risk for RLS with neuropathy, it may reflect consequences of the chronic pain rather than other aspects of diabetes mellitus (DM). Therefore, we investigated the effects of diagnosis rigor on the estimated prevalence of RLS in patients with diabetic peripheral neuropathy (DPN) and those with chronic leg pain from osteoarthritis (OA), and then we compared the RLS prevalence in these two populations with each other and with population prevalence for Korea.

Methods: Our study is a prospective case-control study of 199 patients with DPN and 220 patients with OA. After evaluating the presence of RLS in these subjects using the diagnostic criteria of the International RLS Study Group, we confirmed the diagnosis of RLS through face-to-face interviews using the 18-item Hopkins Diagnostic Questionnaire, which removes RLS mimics; and through independent examinations by two neurologists.

Results: Of the 199 subjects with DPN, 44 (22%) appeared to have RLS from their answers on the 4-item RLS diagnostic questionnaire compared to 8 (3.6%) of 220 subjects with OA. However, the prevalence of RLS in the DPN group dropped to 16 (8%) subjects but stayed at 8 (3.6%) OA subjects when using the Hopkins Telephone Diagnostic Interview (HTDI) adapted for clinical interview. The RLS prevalence determined by HTDI remained significantly higher ($P = .042$) in the DPN group compared to the OA group and was twice that reported for the general Korean population (8% vs 3.9%). Among subjects with DPN, those with RLS were older (68.06 ± 8.43 years vs 62.46 ± 11.05 years; $P = .049$) and had higher pain scores (visual analog scale [VAS], 4.69 ± 2.52 vs 2.72 ± 2.12; $P = .002$). The quality of sleep (MOS [Medical Outcomes Study] sleep scale) and health-related quality of life (QoL) (total score on the 36-Item Short-Form Health Survey [SF-36]) showed no significant difference between the two groups.

Conclusions: The prevalence of RLS in patients with DPN cannot be accurately assessed with only the four diagnostic criteria interview, but the prevalence was higher than expected for Koreans from the general population prevalence and also was higher than occurred with OA patients with chronic leg pains when accurately assessed with a structured interview. Chronic leg pain from OA does not significantly complicate RLS diagnosis, and chronic pain itself does not explain the increased RLS prevalence in diabetic neuropathy.

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1. Introduction

Restless legs syndrome (RLS), also called Willis-Ekbom disease, is a neurologic disease that is characterized by unpleasant and at times painful sensations in the legs associated with an overwhelming urge to move the legs (i.e., akathisia) [1]. Like RLS, peripheral neuropathy causes pain in the legs and is associated with an increased prevalence of RLS in some studies [2–8]. This finding is indicative of a correlation between peripheral neuropathy and RLS. However, there are two significant issues of putative relations between RLS and peripheral neuropathy. First, the differential diagnosis can be difficult. The prevalence of RLS in patients with peripheral neuropathy ranges from 5.2% to 30% [2–4,7,8]. Although this wide variation may reflect population differences, it also could result from differing degrees of care in making this somewhat difficult diagnosis of RLS with peripheral neuropathy. Second, leg pain itself may engender or exacerbate RLS; that is, the association between peripheral neuropathy may be related to leg pains and not to the neuropathy. The presence of leg pain also may complicate the diagnosis and may be the primary reason for problems regarding the reliability of RLS diagnosis. Our study sought to address both of these questions. First, we compared a clinical face-to-face diagnosis of RLS based on the four essential criteria to a structured interview diagnosis (the Hopkins Telephone Diagnosis Interview [HTDI]), which emphasizes differential diagnoses [9,10]. Second, we aimed to assess the effects of leg pains. Our study used this same diagnostic procedure to evaluate RLS prevalence in patients with other conditions that produced leg pains with minimal systemic neurologic or immunologic complications (i.e., osteoarthritis [OA]).

Our study has three primary a priori hypotheses: (1) prevalence of RLS with peripheral neuropathy will be significantly less when the diagnosis is determined by a validated structured diagnostic interview than by the usual clinical interview evaluating only the four RLS diagnostic criteria; (2) the difference between RLS diagnosis by clinical ascertainment of the four essential criteria vs the validated structured interview will be greater for DPN than OA patients; and (3) prevalence of RLS when diagnosed using the structured interview will be greater for patients with peripheral neuropathy than those with leg pains from OA controlling for effects of gender and age. Sleep, pain, and quality of life (QoL) scales also were used to explore the status of these clinical features for RLS patients with peripheral neuropathy vs those with leg pains from OA.

2. Methods

Our study was a prospective case-control study, which was approved by the institutional ethics committee of a local hospital. For our study, evaluations were limited to peripheral neuropathy occurring with diabetes mellitus (DM) and of OA primarily involving the knee. Between June 2009 and August 2011, a consecutive series of consenting patients with diabetic peripheral neuropathy (DPN) or with OA of the knees were identified through the University Hospital Endocrinology and Rheumatology Outpatient clinics in Korea.

DPN was diagnosed based on clinical symptoms and neurologic examinations and was confirmed by nerve conduction studies in all patients with type 2 DM. OA of the knee was diagnosed in accordance with the American College of Rheumatology criteria [11]. DPN subjects could not have notable OA, and OA subjects could not have DM or symptoms of peripheral neuropathy. We excluded patients from both groups if they had other significant medical issues (i.e., renal or hepatic failure, pulmonary dysfunction, active or unstable cardiac disease, neurodegenerative diseases, stroke, multiple sclerosis, spinal myelopathy, radiculopathy, neuropathy not clearly attributable to DM). We also excluded those with notable comorbidities likely to be associated with secondary RLS (i.e., pregnancy- and iron-deficiency anemia). Diagnostic criteria of iron deficiency anemia were anemia (hemoglobin <12 g/dL for women and <13 g/dL for men [reference range, 14.0–17.5 g/dL]) with serum ferritin <15 ng/mL (reference range, 15–200 ng/mL), total iron-binding capacity >400 μg/dL (reference range, 250–450 μg/dL), or serum iron <30 μg/dL (reference range, 60–150 μg/dL).

All of the subjects who entered into our study first had a face-to-face interview by trained study coordinators. Each subject was asked if they had symptoms meeting the four essential diagnostic criteria for RLS, as specified by the National Institutes of Health workshop on RLS [1]. Only subjects who answered yes to all four diagnostic criteria questions were further interviewed by two neurologists. All of these subjects were interviewed by the neurologists. They used the validated Korean version of the HTDI [9] adapted for the clinical rather than telephone interaction to make the final RLS diagnosis. The HTDI contains multiple questions to ensure accurate assessment of the four primary diagnostic criteria for RLS and also multiple questions that help exclude conditions which may mimic RLS. The neurologists' interviews were made independent of each other, without knowledge of the results from each one. The diagnosis was only confirmed when both neurologists agreed on the final diagnosis. In our study there was a 96.2% agreement on the independently made diagnoses. The Medical Outcome Study (MOS) sleep scale and the McGill pain inventory with a visual analog scale (VAS) also were part of the initial assessment and were used to establish the degree of sleep disruption and level of pain, respectively. The 36-Item Short-Form Health Survey (SF-36), a QoL questionnaire, also was completed during the initial evaluation.

2.1. Statistical analysis

Statistical analysis was performed using the SPSS 19.0 program. The first primary hypothesis is descriptive. The second and third hypotheses compare the two RLS groups (DPN and OA). Qualitative data were analyzed using the χ^2 test or the Fisher exact test. The independent t test and the Mann–Whitney U test were used to compare the differences in mean scores between the two groups. The analysis of covariance also was used to compare the differences between the two groups using control covariates (e.g., age, gender). To analyze the independent variables affecting the diagnosis of RLS, binary logistic regression analysis was used. The SF-36 was used as part of a secondary analysis on general QoL. The subscores were only analyzed if the overall SF-36 score was significant.

If the P value was less than .05 it was considered to be statistically significant for the second and third primary hypotheses as well as for all exploratory analyses, recognizing the need to replicate any significant findings from the exploratory analyses.

3. Results

3.1. Overall DPN and OA population characteristics

Table 1 presents the comparison of the clinical characteristics and questionnaire results for the DPN and OA population surveyed. The mean age of the DPN patients was significantly younger than the OA group (mean ± standard deviation [SD], 62.91 ± 10.95 years and 67.67 ± 8.67 years; $P < .001$) and consisted of fewer women (53.8% vs 83.6%; $P < .001$). The reported level of pain in the OA group as indicated by all the components of the McGill Pain inventory and VAS was significantly higher than in the DPN group