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Original Article

Quantitative sensory test for primary restless legs syndrome/Willis–Ekbom disease using the current perception threshold test

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ABSTRACT

Background: Restless legs syndrome/Willis–Ekbom disease (RLS/WED) is a sensorimotor neurological disorder, and it is especially aggravated at night. The purpose of this study was to investigate the diurnal sensory dysfunction in primary RLS/WED using the current perception threshold (CPT) test, compared to healthy controls.

Methods: Thirty primary RLS/WED subjects and 30 healthy controls were enrolled. The severity of RLS/WED and sleep problems were evaluated in all subjects. Peripheral polyneuropathy was excluded through neurological examination and nerve conduction study. We used the Neurometer® system for the CPT test and applied three different parameters (2000 Hz, 250 Hz, and 5 Hz), to stimulate both big toes. The CPT test was performed twice, once during the asymptomatic daytime period and again in the evening, when the patients were symptomatic.

Results: The mean ages of the RLS/WED group and controls were 50.5 ± 11.7 (22; 73.3% female), and 46.3 ± 11.4 (24; 80.0% female), respectively. The mean international RLS/WED study group severity scale score was 28.6 ± 4.25. There was no significant difference in the current perception thresholds between the RLS/WED patients and controls in daytime. However, the RLS/WED patients had lower mean CPT measurements for all three stimulation protocols in the evening (2000 Hz: 393.2 ± 93.7 vs 430.8 ± 79.6, 250 Hz: 172.0 ± 48.4 vs 198.5 ± 38.2, and 5 Hz: 98.0 ± 34.1 vs 124.6 ± 31.3), while the healthy controls showed no difference.

Conclusions: RLS patients showed a lower CPT in the evening. The diurnal variation of hyperalgesia in RLS/WED patients indicates a central (circadian) sensory processing disturbance rather than a peripheral disturbance.

1. Introduction

Restless legs syndrome/Willis–Ekbom disease (RLS/WED) is a sensorimotor neurological disorder that causes an urge to move. It is usually associated with discomfort in the legs, which is especially aggravated at night [1]. Although several mechanisms have been suggested as the cause of disease [2], the pathophysiology of RLS/WED, especially sensory symptoms (ie, pain and dysesthesia), is poorly understood. Previous studies have proposed several mechanisms including disrupted sensory transmission caused by peripheral hypoxia [3], central disinhibition through impaired dopaminergic control [2,4,5], and alteration in pain perception [6,7]. Other studies have investigated the circadian changes of subjective symptoms, dopamine and iron metabolism, and cortical function in RLS/WED [8,9]. A recent review reported disturbed iron metabolism leading to brain hypoxia and impaired dopaminergic control [10]. However, there have been only a few quantitative sensory tests in RLS patients [11].

The current perception threshold (CPT) test, a type of quantitative sensory test, is a method of measuring sensory threshold. Determining the CPT can detect altered cutaneous sensory perception at the peripheral or central nervous systems [12].

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Previous studies have suggested the usefulness of this instrument for the detection, screening, diagnosis, and management of diseases of the peripheral nervous system. Common uses are detection of axonal and demyelinating peripheral neuropathies, quantification of hyperesthetic and hypoesthetic conditions, and measurement and quantification of responses from different sizes of sensory nerves [13–17]. By changing the frequency of current stimulation, this test can measure fiber damage in different types of nerve fibers. The 2000-Hz stimulus specifically evaluates the response of A-β fibers, 250 Hz evaluates A-δ fibers, and 5 Hz is used to evaluate C fibers [12].

The purpose of this study was to investigate the possibility of central dysfunction of sensory perception with circadian variation in patients with primary RLS/WED.

2. Methods

2.1. Subjects

We evaluated 30 primary RLS/WED patients and age- and gender-matched healthy controls. The mean age for the RLS/WED group was 50.5 ± 11.7, and 46.3 ± 11.4 for the healthy controls. There were 22 (73.3%) females in the RLS/WED group and 24 (80.0%) in the controls. All RLS/WED subjects underwent thorough clinical evaluation by a sleep medicine expert based on the diagnostic criteria set by the NIH workshop on RLS, and utilizing the Korean version of the Johns Hopkins Telephone Diagnostic Questionnaire [1] during a face-to-face interview. This diagnostic guideline is also comparable with the updated IRLSSG diagnostic criteria [18]. Only moderate to severe cases of RLS/WED with International RLS rating scale (IRLS) of ≥15 and symptoms occurring on more than five nights per week were recruited. Any treatment such as dopamine agonists, alpha 2 delta drugs, antidepressants, hypnotics, benzodiazepines, and narcotics were stopped at least two weeks prior to the baseline evaluation. Healthy controls were screened using physical examination and, if needed, laboratory tests for any medical conditions. They also had to be free of RLS/WED symptoms, determined by an answer of "no" to the RLS/WED diagnostic questionnaire. All RLS and control subjects had a nerve conduction study to exclude peripheral polyneuropathy. The exclusion criteria included age <18, secondary RLS/WED (due to iron deficiency anemia, polyneuropathy, neurodegenerative diseases, chronic kidney disease, pregnancy, hypothyroidism), and use of medications with potential effect on RLS/WED symptoms that could not be stopped (eg, antipsychotics and antidepressants). Subjects were also excluded for any primary sleep disorder other than RLS/WED (eg, sleep disordered breathing, circadian sleep disorders, and parasomnias as assessed by the validated Korean-language versions of sleep questionnaires) [19–21].

The study was approved by the institutional ethics committee of the Keimyung University Dongsan Medical Center and informed consent was obtained from all participants.

2.2. Sensory evaluation

All RLS/WED patients and healthy controls underwent a CPT test using the Neurometer system (Neurometer®, Baltimore, USA). The normative CPT values obtained through previous clinical trials have been incorporated into the system's data analysis software (Neurotron, Baltimore, MD USA http://www.neurotron.com) [13]. A CPT value of 1 is equal to an output intensity of 0.01 mA with an available maximum of 9.99 mA. A constant alternating current was applied to the big toes bilaterally at a resting supine position. Three distinct frequencies of 2000 Hz (for 1.65 s), 250 Hz (for 1.65 s), and 5 Hz (for 2.88 s), were used to assess large-diameter myelinated, small-diameter myelinated, and unmyelinated sensory nerve fibers, respectively. The stimulation intensity started at 150 CPT units for 2000 Hz, 40 CPT units for 250 Hz, and 15 CPT units for 5-Hz experiments, and was increased until the subjects reported a sensation at which point the intensity was reduced by 0.1 mA. Then the procedure was repeated at a lower intensity until the subject could not detect the stimulus anymore which would be defined as the lowest detection threshold for that frequency [13,15,16]. Each test was performed twice: once at 10:00 h–12:00 h during the asymptomatic daytime period, and once at 20:00 h–22.00 h in the evening during the symptomatic period. The tests were performed in the same temperature-controlled (21–22 °C), room. There were no reports of adverse effects or injury related to the tests. The normative values for CPT are 179–523 at 2000 Hz, 44–208 at 250 Hz, and 18–170 at 5 Hz [13]. A CPT value below the minimum normative range for any particular frequency indicates and quantifies a hyperesthetic state while values above maximum CPT normative range indicate a hypoesthetic state.

2.3. Statistical analysis

Statistical analyses were performed using the SPSS version 18.0. Characteristics of primary RLS/WED group were expressed using descriptive statistics. Continuous variables, age, IRLS score, and other characteristics were compared using the Chi-square test, and independent *t*-test was used to determine differences between RLS/WED patients and healthy controls. We used a paired *t*-test to compare the daytime and evening data for each group. Independent *t*-test was used to compare the two groups. The comparisons between the daytime and evening results were conducted using repeated-measures ANOVA. Statistical significance was defined as $p < 0.05$.

3. Results

There were no statistical differences in age and gender between the two groups. The mean age of onset was 40.4 ± 13.3, and mean disease duration was 10.1 ± 12.3 years. The mean score on the IRLLSG scale was 28.6 ± 4.25 (Table 1).

On the CPT test, all values for both groups were within normal limits [13]. Also, there were no significant differences in the daytime mean CPT between the RLS/WED group and controls at any of the three stimulation frequencies. However, in the evening, RLS/WED patients showed lower mean CPT than the controls at 5 Hz, but the differences failed to reach statistical significance at 2000-Hz and 250-Hz frequencies. There were no differences between daytime and evening results in the controls, the RLS/WED patients had significantly lower mean CPT values at all three frequencies in the evening compared to daytime (2000 Hz, 393.2 ± 93.7 vs 430.8 ± 79.6; 250 Hz, 172.0 ± 48.4 vs 198.5 ± 38.2; 5 Hz, 98.0 ± 34.1

Table 1
Comparison of demographic and clinical characteristics between the restless legs syndrome patients and healthy controls.

	RLS ($N = 30$)	Control ($N = 30$)	t/χ^2	*p*
Age (years)	50.5 ± 11.7	46.3 ± 11.4	1.42	0.16
Gender (% female)	22(73.3)	24(80.0)	0.37	0.54
RLS onset age (years)	40.4 ± 13.3			
RLS symptom duration (years)	10.1 ± 12.3			
International RLS severity scale	28.6 ± 4.25			
Serum ferritin (ng/mL)	72.0 ± 79.0			
Hemoglobin (g/dL)	13.2 ± 1.64			

RLS, restless legs syndrome.