Sleep Medicine 15 (2014) 808–815

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Working memory deficit in patients with restless legs syndrome: an event-related potential study

Sung Min Kim [a], Jeong Woo Choi [b], Chany Lee [c], Byeong Uk Lee [c], Yong Seo Koo [a], Kyung Hwan Kim [b,1], Ki-Young Jung [c,*]

[a] Department of Neurology, Korea University Medical Center Anam Hospital, Korea University College of Medicine, Seoul, South Korea
[b] Department of Biomedical Engineering, College of Health Science, Yonsei University, Wonju, South Korea
[c] Department of Neurology, Seoul National University College of Medicine, Seoul, South Korea

ARTICLE INFO

Article history:
Received 17 November 2013
Received in revised form 5 March 2014
Accepted 9 March 2014
Available online 20 April 2014

Keywords:
Restless legs syndrome
Working memory
Cognition disorders
Event-related potential
P300
Frontal lobe

ABSTRACT

Objective: The aim of this study was to investigate whether there is a working memory (WM) deficit in restless legs syndrome (RLS) patients, by studying the Sternberg WM task of event-related potential (ERP).
Methods: Thirteen drug-naive RLS patients and 13 healthy age-matched controls with no sleep disturbances participated in the present study. P300 ERP was recorded during Sternberg WM task using digits as mnemonic items. P300 amplitudes and reaction times were compared between groups (RLS vs control) considering brain regions (frontal, central, and parietal) and memory load sizes (two, three, and four) as within-subject factors. Clinical and sleep-related variables were correlated with P300 amplitude.
Results: The reaction time in RLS patients was significantly longer than controls over all memory load sizes. The P300 amplitude at parietal regions in RLS patients was significantly lower than in controls regardless of memory load sizes, which was significantly negatively correlated with duration of RLS history in RLS patients.
Conclusion: Our study suggests that patients with severe RLS have WM deficits. Furthermore, negative correlation of P300 amplitudes with the duration of RLS illness suggests that cerebral cortical dysfunction in RLS patients results from repeated RLS symptom attacks.

1. Introduction

Restless legs syndrome (RLS) is a sensorimotor network disorder characterized by an irresistible urge to move the legs during rest [1]. Neuropsychological evaluations in RLS patients have reported that patients show cognitive deficits, particularly in relation to frontal function, such as a decline in stroop task performance, short-term attention, verbal fluency, and trail-making tests [2–4]. Electrophysiologic studies also support the existence of cognitive deficit in RLS patients. For example, a recent event-related potential (ERP) study showed longer latency and lower amplitude of P300 in RLS patients compared with control subjects [5]. Inattention due to bothersomeness during the ERP study was significantly correlated with P300 latency in which the lower P300 amplitude observed in RLS patients appears to be due to the increase in demands of attentional and processing resources. Decreased gamma-band phase synchrony in RLS further supports cortical dysfunction in RLS [6], since gamma rhythm has an important role in attention, working memory (WM), and long-term memory [7]. Clinically, RLS patients frequently experience hyperactivity and inattention, and it has been suggested that RLS symptoms mimic those of attention deficit/hyperactivity disorder (ADHD), and even that RLS might be associated with ADHD [8]. Both disorders share a common pathophysiology of dopamine dysfunction [8,9]. These findings seem to suggest that RLS patients have attention deficit, considering neuropsychological tests and ERP study as well as clinical evidence.

The WM may be defined as the system for the temporary maintenance and manipulation of information, which is necessary for the performance of complex cognitive activities such as comprehension, learning, and reasoning. WM is closely associated with attention function, and consists of memory buffers and a central executive function [10]. The function of memory buffers is to reactivate information by refreshing and rehearsing. A central

* Corresponding author. Address: Department of Neurology, Seoul National University College of Medicine, 101 Daehak-Ro, Jongno-Gu, Seoul 110-744, South Korea. Tel.: +82 2 2072 4988.

E-mail addresses: khkim0604@yonsei.ac.kr (K.H. Kim), jungky10@gmail.com (K.-Y. Jung).

1 Co-corresponding author. Address: Department of Biomedical Engineering, College of Health Science, Yonsei University, 234 Maeji-ri, Heungup-myun, Wonju, Gangwon-do, South Korea. Tel.: +82 33 760 2364.

http://dx.doi.org/10.1016/j.sleep.2014.03.010
1389-9457/

executive function is assumed to allocate attention resources to the memory buffers and to perform manipulation [11]. WM deficits might be caused by depression, insomnia, or sleep deprivation, which are widespread in RLS [12–16]. Therefore, we would expect impairment of WM in RLS patients. However, only a few studies have evaluated WM function with neuropsychological evaluation in RLS patients, and these have shown no difference in either block span backward or digit span backward test compared with control subjects [4,17,18].

An ERP study provides useful information for exploring cognitive function and non-invasive monitoring of brain processes with excellent temporal resolution and modest spatial resolution covering the whole brain. Therefore, we used ERP to evaluate WM function in RLS patients. The Sternberg task is widely used for observing cortical activity associated with memory load variation with ERP study. The P300 ERP component during the retrieval phase in the Sternberg WM test is a key marker of cognitive demands in WM. As memory load size increases, the P300 component has been found to decrease [19]. It is suggested that P300 amplitude reflects demands on the same pool of perceptual–central resources, which are depleted by both target identification and memory search processes [20]. A reduction in P300 amplitude during WM tasks is observed in many neuropsychiatric diseases, such as schizophrenia [21], post-traumatic stress disorder [22], and depression [23,24]. The aim of this study was to investigate whether there is a WM deficit in RLS patients using Sternberg WM task of ERP study.

2. Methods

2.1. Participants

Patients with RLS who visited the sleep clinic of Korea University Medical Center were recruited. Healthy controls were recruited on a voluntary basis by local advertisement. All participants underwent a standardized interview using a structured sleep questionnaire and clinical neurological examinations by a neurology expert in sleep medicine. 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 for a face-to-face interview [25]. The diagnostic questionnaire has questions that help exclude conditions that may mimic RLS.

The inclusion criteria for patients were as follows: (i) aged 18–70 years; (ii) RLS symptom duration longer than one year; (iii) International RLS Severity Scale (IRLS) score >19; and (iv) no prior treatment for RLS. The exclusion criteria were as follows: (i) those with significant comorbidities likely to be associated with secondary RLS: pregnancy, chronic kidney disease, or peripheral neuropathy; (ii) presence of sleep disorders other than RLS such as sleep apnea, rapid eye movement sleep behavior disorder, parasomnia and so on, which was identified by the polysomnography (PSG) after enrollment of patients; (iii) presence of cognitive disorders that prevented participants from describing their symptom distributions; and (iv) presence of disorders with symptoms similar to RLS, such as ADHD, essential tremor, Parkinson disease, neuroleptic-induced akathisia, congestive heart failure, vascular claudication, neurogenic claudication, myelopathy, and arthritis.

The sleep questionnaire included the Global Sleep Assessment Questionnaire (GSAQ) [26], the Pittsburgh Sleep Quality Index (PSQI) [27], the Epworth Sleepiness Scale (ESS) [28], the Insomnia Severity Index (ISI) [29] and the Korean version of the Beck Depression Inventory II (BDI-II) [30]. It also included questions about sleep habits and medication history. RLS severity was determined using the IRLS [31]. Hemoglobin, iron/ferritin, blood glucose, and serum levels of creatinine and thyroid hormones were checked in all patients.

Subjects were included as healthy controls in the present study only if they were in the normal range based on their in a sleep questionnaire and not identified as having RLS according to the validated Korean-language version of the John Hopkins Telephone diagnostic questionnaire for a face-to-face interview. Control subjects were excluded when PSG showed sleep disorders or significant poor sleep quality (total sleep time <6 h, sleep efficiency <80%, arousal index >30/h, and significant sleep fragmentation) after initial inclusion. All subjects signed written informed consents. The experimental protocol was approved by the Institutional Review Board of Korea University Medical Center.

2.2. Polysomnographic recordings

All participants (both control and RLS) underwent one night of PSG recording in our sleep laboratory. Overnight PSG was recorded using 19 electrodes placed on the scalp in accordance with the international 10–20 system, a two-channel electro-oculogram (EOG), an electromyogram of submental and anterior tibialis muscles, and an electrocardiogram with surface electrodes. The electroencephalographic (EEG) signals were sampled at 200 Hz. A thermistor (for monitoring nasal and mouth breathing), a cannula (for monitoring nasal air pressure), an oximeter (for measuring oxygen saturation), piezoelectric bands (for determining thoracic and abdominal wall motion), a body position sensor, and a snoring sensor were also attached. Patients were recorded on videotape using an infrared video camera and were continuously observed by a PSG technician. Sleep stage was scored in 30 s epochs according to the standard criteria described by American Academy of Sleep Medicine manual for scoring sleep [32]. Periodic leg movements (PLMs) were defined using World Association of Sleep Medicine/International RLS Study Group criteria as a series of four consecutive leg movements lasting 0.5–10 s, separated by intervals of 5–90 s [33]. The periodicity index was computed as the number of intervals belonging to sequences of at least three inter-leg movement (LM) intervals >10 and ⩽90 s divided by the total number of inter-LM intervals. The distribution of number of PLMS per hour of sleep duration was also computed [34].

2.3. Sternberg WM paradigm

Fig. 1 shows the paradigm of the Sternberg WM task (standard 'yes'/'no' version). A modified Sternberg WM task using digits as mnemonic items was applied. Each trial started with the word 'blink', encouraging the subjects to blink in order to reduce artifacts later in the trial. After presenting a small black cross for 2000 ms, we sequentially presented memory lists of two to four digits which reflected the number of digits and memory load size. Each item was presented for 1200 ms with 200 ms intervals between the digits. Following a 2000 ms delay period, a probe item was presented for 3000 ms. The subjects were instructed to indicate as quickly and as accurately as possible whether or not the probe matched an item on the memory list. Reaction times (RTs) and the accuracy of task performance (hit rates, HRs) were also measured for the behavioral response. The responses were given by pressing one of two buttons, one by the right thumb and the other by the left thumb. Feedback on correct and incorrect responses was presented at the end of the trial. The experiment consisted of randomly presented trials per item (200 trials in total).

2.4. ERP recording

Following overnight PSG recording, all subjects performed Sternberg WM task at 09:00 when RLS symptoms were nadir. ERPs