International Journal of Psychophysiology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

International Journal of Psychophysiology

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

Neurocognitive function in patients with idiopathic Restless Legs Syndrome before and after treatment with dopamine-agonist

Andrea Galbiati [a,b,1], Sara Marelli [a,1], Enrico Giora [a,b], Marco Zucconi [a], Alessandro Oldani [a], Luigi Ferini-Strambi [a,b,*]

[a] San Raffaele Scientific Institute, Dept of Clinical Neurosciences, Sleep Disorders Center, Milan, Italy
[b] Vita-Salute San Raffaele University, Faculty of Psychology, Milan, Italy

ARTICLE INFO

Article history:
Received 24 June 2014
Received in revised form 5 December 2014
Accepted 7 December 2014
Available online xxxx

Keywords:
Vortioxetine
Antidepressant
Memory
LTP
Novel object recognition
Neurogenesis

ABSTRACT

Although a huge amount of clinical evidence for Restless Legs Syndrome (RLS) is present in literature, an exhaustive account of cognitive profile in RLS patients is still lacking. In this study we evaluated the neurocognitive function in RLS patients and the effects of a three-month treatment with a dopamine agonist (pramipexole) at low doses.
Clinical and polysomnographic characteristics, cognitive abilities, quality of life and psychological clinical indices were assessed in 20 RLS patients and 15 age-matched controls. The neurocognitive results, obtained by untreated RLS patients (baseline), were firstly compared to those of controls and then to those of the same RLS group after treatment (follow-up). Increased Total Sleep Time, Slow Wave Sleep, Sleep Efficiency and decreased Sleep Latency, Wake After Sleep Onset and periodic leg movement index were found by polysomnographic recording after a three-month treatment.
Results showed that cognitive functions, impaired at baseline when compared to control subjects, improved after the pharmacological treatment, reaching the scores of healthy subjects. Decision making, problem solving and categorizing abilities, investigated by the Iowa Gambling Task (IGT) and the Wisconsin Card Sorting Test (WCST), resulted lower in RLS patients at baseline than in controls. All these functions improved after pharmacological treatment, as well as quality of life, depressive and anxiety symptoms, and daytime sleepiness.

1. Introduction

Restless Legs Syndrome (RLS) is a sensory–motor neurological disorder characterized by paresthesia/dysesthesia with uncomfortable and unpleasant sensations in the legs, which are urged to move (Montplaisir et al., 2011). The RLS usually affects the legs but can also affect other parts of the body. The symptoms begin or worsen during periods of rest or inactivity such as lying down and sitting. Patients usually describe exacerbation of symptoms in situations such as watching television, driving, flying long distance or attending business meetings. The urge to move and the unpleasant leg sensations are typically relieved by activity and patients may use different motor strategies to mitigate the discomfort (Montplaisir et al., 2011).

This disorder has a circadian peak in the evening or at night, and it can severely disrupt sleep. Patients frequently report insomnia as the main sleep symptom, finding it difficult to get to sleep or stay asleep (typical nocturnal awakenings). Daytime consequences such as fatigue, irritability, drowsiness, impaired concentration, and depressed mood are frequently reported. Patients affected by a severe RLS syndrome may obtain a degree of chronic sleep loss rarely seen in other sleep conditions (Allen and Earley, 2000). Disorders such as anxiety, chronic pain and depression have been associated to chronic sleep loss and appear to be more prevalent in RLS patients than in healthy subjects (Bassetti et al., 2001). However, a recent study (Gupta et al., 2013) suggested that depression is independent from RLS symptoms and sleep disturbance and it should be regarded as a co-morbid condition. Despite the fact that daytime sleepiness is not reported as a severe complaint in RLS patients (American Academy of Sleep Medicine, 2014), it might produce cognitive deficits similar to those found in sleep deprivation studies. Pearson et al. (2006) evaluated RLS patients while off medications for at least 14 days prior to the cognitive assessment. The therapy interruption determined an accumulating sleep deficit. The authors pointed out that this withdrawal effect generally did not last more than the first 4–7 days and it should not have affected the tests. Data indicated that untreated RLS patients showed specific cognitive deficits, in particular when performing tasks that specifically stressed the pre-frontal cortical (PFC) functioning (Choi et al., 2012). This decreased performance was similar to that seen in 36 h total sleep deprivation. In general, polysomnography (PSG) recordings indicated that untreated RLS

* Corresponding author at: Sleep Disorders Center, Università Vita-Salute San Raffaele, Milan, Italy. Tel.: +39 02 2643 3363; fax: +39 02 2643 3394.
E-mail address: ferinistrambi.luigi@hsr.it (L. Ferini-Strambi).
[1] First authors.

http://dx.doi.org/10.1016/j.ijpsycho.2014.12.005
0167-8760/

patients have chronically reduced sleep time (Montplaisir et al., 2011). This reduced sleep time was observed throughout all the 14 days without treatment that preceded the cognitive testing. The cognitive deficits in the RLS patients could then result from the chronic sleep disruption rather than being a direct effect of the RLS pathology itself, reinforcing the clinical significance of the sleep disruption in this disorder.

Gamaldo et al. (2008) compared the cognitive function of untreated RLS patients to sleep-restricted control subjects. A 14-day sleep restriction protocol was employed to simulate the chronic sleep loss routinely experienced by the RLS patients. Interestingly, RLS patients performed better than sleep restricted controls on tasks sensitive to sleep deprivation, such as phonemic and semantic fluency. Those data suggested that RLS subjects may show a relative degree of sleep loss adaptation and this can be explained with an enhanced level of alertness that compensates for significant sleep loss. It is possible that this potential compensatory alertness may not only reduce the cognitive deficits from sleep deprivation but also the actual physiological sleepiness. This would be in accordance to the evidence that RLS patients, despite the severe chronic sleep loss, do not commonly report falling asleep at inappropriate times.

Even though the pathophysiology of RLS is not yet clear, iron status, genetic factors and dopaminergic system are supposed to play a role in this disorder (Clemens et al., 2006). Dopaminergic drugs, especially D3 receptor agonists, are particularly effective in RLS. On the contrary, neuroleptics (dopamine antagonists) trigger or aggravate RLS symptoms (Ferini-Strambi and Marelli, 2014). Dopaminergic system is involved in decision making, particularly in a context of risk or ambiguity (Bechara and Damasio, 2005; Rogers, 2011). The pharmacological treatment of RLS provides therefore the opportunity to test the effect of dopamine agonist drugs on decision making.

Bayard et al. (2010) found that drug-free RLS patients exhibited reduced efficiency in decision making under ambiguity. Recently, Bayard et al. (2013) investigated impulse control disorders, impulsivity, and substance addictions, showing that they were infrequent in drug-free patients with RLS or in those treated with a low dose of dopamine agonists. Preferences towards risky choices were instead found on the Iowa Gambling Task (IGT) for both drug-free and dopamine agonist treated RLS patients. That should lead to negative long term consequences, such as the development of impulse control disorders (Bayard et al., 2013).

Furthermore, the negative effects on daily life caused by RLS have been already described. Symptoms of anxiety and depression in RLS patients have been observed. Winkelmann et al. (2005) assessed 238 RLS patients with a standardized diagnostic interview and found an increased risk of having a 12-month anxiety and depressive disorder with a particularly strong association with panic disorder, generalized anxiety disorder and major depression. Lee et al. (2014) compared both cognitive performances and depressive symptoms in three groups (No RLS, untreated RLS, treated RLS). Minimal group differences were observed in cognitive performance, but the untreated RLS group had significantly higher depressive symptoms than the treated RLS and No RLS groups. In this study, RLS therefore did not seem to affect cognition, whereas a strong association between untreated RLS and depression appeared. Other studies showed no cognitive dysfunctions in mild RLS patients (Driver-Dunckley et al., 2009; Chen et al., 2013), but reported the absence of depression symptoms (Driver-Dunckley et al., 2009).

Although there is a significant amount of clinical evidence, a clear account of the effects of RLS on cognitive function is still lacking. In addition, the effect of dopamine agonist treatment on patients' cognitive abilities, quality of life and psychological clinical indices deserves further investigation. The aims of our study therefore are: (1) to describe clinic and polysomnographic (PSG) characteristics of idiopathic RLS patients (iRLS) sample, de novo, (2) to assess cognitive functions, quality of life, sleep quality, and anxiety and depressive symptoms in patients with iRLS at baseline compared to age matched controls (No RLS), and (3) to assess changes after a three-month treatment (follow-up) with a dopamine agonist drug (pramipexole) at low doses.

2. Subjects and methods

2.1. Subjects

Twenty never-treated iRLS patients (M = 8, F = 12, mean age 46.80 ± 10.10, mean education level 14.80 ± 3.19) and 15 age- and education-matched healthy controls (M = 6, F = 9, mean age 46.40 ± 9.10, mean education level 15.00 ± 1.41) were recruited. All participants were right-handed, monolingual native Italian speakers, had normal or corrected-to-normal visual acuity and a Mini Mental State Examination (MMSE) score >24 in order to exclude subjects with cognitive deterioration. All participants provided written informed consent to the experimental procedure, which was previously approved by the local ethical committee.

Inclusion criteria for patients enrolled were a mean frequency of symptoms during the last six months greater than two times per week and a score of at least 20 (corresponding to severe RLS) on the International RLS Study Group Rating Scale (Walters et al., 2003). Only iRLS patients never-treated with dopaminergic agents, benzodiazepines, opioids and anticonvulsants at the time of the evaluation, were included. Additional inclusion criteria were an age between 18 and 70 years and periodic leg movement (PLMs) index >10 at the PSG baseline. Patients with an apnea/hypopnea index >5 were excluded. All participants, including healthy controls, reported regular sleep–wake schedules, based on daily sleep diaries, with an average Total Sleep Time (TST hours) of 6.5 ± 1.4 h in four days prior to the study.

Neurological examination was unremarkable for all patients. Routine blood tests (including serum iron and ferritin, B12 vitamin and folate), as well as electromyography (EMG) and electroneurography of the lower limbs, were also normal. Patients suffering from known causes of secondary RLS (e.g., renal failure, anemia with iron-deficiency, pregnancy, rheumatoid arthritis, or clinical peripheral neuropathy), other sleep disorders (e.g., narcolepsy, parasomnia and sleep breathing disorder), other movement disorders, or any medical conditions that would affect the assessment of RLS (e.g., fibromyalgia syndrome) were also excluded.

2.2. Polysomnography

Only iRLS subjects underwent an adaptation night in the laboratory, followed by baseline nocturnal PSG recordings. No medication was administered before the recording night (baseline). After three months (iRLS follow-up), 18 out of 20 treated patients performed the second night of recording (two out of 20 patients dropped out because of low compliance to pharmacological treatment). During the three months' time, subjects received a treatment with a single oral dose of 0.25 mg pramipexole at 9:00 p.m.

Lights-out time was based on the individual's usual bedtime and ranged between 11.00 and 11:30 p.m. The following signals were recorded: electroencephalogram (EEG) (six channels, including C3 or C4 and O1 or O2, referred to the controlateral mastoid); electrooculogram (EOG); EMG of the submentalis muscle; EMG of the right and left tibialis anterior muscles; and electrocardiogram (ECG; one derivation) according to the American Sleep Disorders Association (ASDA) scoring criteria (Berry et al., 2012). The sleep respiratory pattern of each patient was monitored using oral and nasal airflow thermistors and/or nasal pressure cannula, thoracic and abdominal respiratory effort strain gauge and by monitoring oxygen saturation (pulse-oximetry). Sleep stages were scored following standard criteria (Rechtschaffen and Kales, 1968) on 30-s epochs using the sleep analysis software Hypnolab 1.2 (SWS Soft, Italy). Leg movements (LM) during sleep were first detected by the same software, which allows for computer-assisted detection. With this software, detection of LM is performed using a human-

Please cite this article as: Galbiati, A., et al., Neurocognitive function in patients with idiopathic Restless Legs Syndrome before and after treatment with dopamine-agonist, Int. J. Psychophysiol. (2014), http://dx.doi.org/10.1016/j.ijpsycho.2014.12.005