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Original Article

Chronic dopaminergic treatment in restless legs syndrome: does it affect the autonomic nervous system?

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ABSTRACT

Objective: The link between the autonomic nervous system and restless legs syndrome (RLS) has been recently postulated. Since dopaminergic agents are used as first-line treatment for RLS, the purpose of our study is to verify whether chronic pramipexole treatment could influence the autonomic control of cardiovascular reflexes and heart rate variability (HRV) in RLS during wakefulness.
Methods: Consecutive drug naive RLS patients underwent polysomnography (PSG), subjective scales, and cardiovascular function tests including head-up tilt test (HUTT), Valsalva maneuver, deep breathing, handgrip and cold face before and after 3-month pramipexole therapy. HRV analysis was performed in the frequency domain using both autoregressive and fast Fourier transform algorithms in rest supine condition and during HUTT.
Results: Twenty RLS patients reported a significant reduction of RLS symptoms after pramipexole treatment, while PSG did not show significant improvements except for periodic limb movement index. Pramipexole induced a trend to a lower systolic blood pressure and a significant higher variation of systolic and diastolic blood pressure at HUTT. Cardiovascular responses to the other tests were unchanged. No significant differences in HRV spectral analysis between drug naive and treated patients were observed. Moreover, the within-group analysis of HRV between orthostatic and supine position did not show any significant change in sympathetic and parasympathetic components both in the drug naive and pramipexole groups.
Conclusions: Chronic pramipexole treatment does not seem to affect autonomic balance during wakefulness. Considering that neither PSG data nor autonomic parameters are significantly modified by pramipexole, we hypothesize a non-dopaminergic autonomic dysfunction in RLS.

1. Introduction

Restless leg syndrome (RLS) is a common sleep-related movement disorder characterized by five essential criteria established by the International Restless Legs Syndrome Study Group (IRLSSG) [1]. About 10%–15% of RLS patients have symptoms severe enough to require medical treatment aimed at relieving sensory and motor symptoms, improving sleep and quality of life, and preventing cardiovascular complications [2,3].

Currently, dopaminergic agents are used as first-line treatment for moderate to severe RLS. The European Federation of Neurological Societies has recommended non-ergot dopaminergic agents such as ropinirole and pramipexole as tablets, or rotigotine as patches [4], because of their tolerability and efficacy even at very low doses and since the first night of administration [5].

More than 80% of RLS patients present with periodic limb movements during sleep (PLMS) that are associated with cortical arousals and autonomic activation [6]. The link between RLS and the autonomic nervous system (ANS) may rest in the neurological circuits that are supposed to be involved in the pathophysiology of RLS, given that inhibitory dopaminergic neurons of the hypothalamic A11 nucleus project to the dorsal and ventral horns and to the intermediate-lateral nucleus, which acts as the final common pathway of the sympathetic system [7].

The involvement of the ANS in RLS has been evaluated during sleep by means of heart rate variability (HRV) spectral analysis [8–11]. In a recent study, we examined the potential involvement of ANS in RLS during wakefulness through cardiovascular reflexes

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and HRV, and we observed that untreated RLS patients exhibited a reduced amplitude of both sympathetic and parasympathetic responses at HUTT and a tendency toward hypertension, supporting the hypothesis of diurnal ANS involvement and of enhanced cardiovascular risk in RLS [12].

The impact of chronic treatment with dopamine agonists on ANS in RLS has not been investigated so far. It should be noted, however, that studies on acute pramipexole treatment in RLS on HRV during sleep demonstrated a reduction of the number of PLMs and of the amplitude of the autonomic response to residual PLMs without affecting tonic vegetative regulation [11].

The purpose of our study is to clarify whether chronic pramipexole treatment could influence the autonomic control of cardiovascular reflexes and HRV during wakefulness in RLS patients.

2. Methods

2.1. Subjects and study design

Consecutive drug-naive adult patients affected by idiopathic RLS, diagnosed in accordance with the five essential criteria established by the IRLSSG [1] and referred to the Sleep Medicine Centre of University of Rome Tor Vergata, were prospectively enrolled. All patients underwent neurological examination, routine blood tests (including serum iron, transferrin and ferritin, B_{12} vitamin, and folate), electromyography (EMG), and electroneurography of the lower limbs to exclude peripheral nervous system diseases and secondary RLS. Diabetes mellitus, hypertension, and cardiac, endocrine, metabolic, and renal diseases, as well as smoking habit, were excluded by history taking. Concomitant use of antidepressants, benzodiazepine or other active drugs able to interfere with the central nervous system, and any other drugs known to affect the ANS, was also considered as exclusion criterion. Patients with apnea–hypopnea index (AHI) greater than 5 per hour were also excluded.

At the time of enrollment, all eligible patients underwent clinical evaluation, including the International Restless Legs Syndrome Study Group rating scale (IRLS) [13], commonly used to assess the severity of the disease, and the Epworth Sleepiness Scale (ESS) [14,15], to subjectively evaluate daytime somnolence.

Subjects underwent polysomnographic evaluation (PSG) to assess their nocturnal sleep, and on the following morning they performed the first session of autonomic function tests (AFTs). Thereafter they started pramipexole treatment, which was administered at a daily dose of 0.25 mg pramipexole dihydrochloride monohydrate (equivalent to 0.18 mg pramipexole) at 9 p.m. and kept constant for 12 weeks, when PSG, AFTs, and clinical evaluations were repeated. The use of concomitant RLS medications was not allowed. All subjects gave their informed consent to the procedures, and the study was approved by the local ethical committee.

2.2. Polysomnography

All patients underwent two 48-hour PSG monitoring sessions to evaluate diurnal and nocturnal sleep. The first 24-hour period of each monitoring session was considered as adaptation, and the remaining 24-hour period was used for sleep analysis. PSG monitorings were performed through an ambulatory dynamic 32-channel system polygraph (Somnoscreen; Somnomedics, Randersacker, Germany). The signal was stored on a flash card using a common average reference and a time constant of 0.3 seconds. Electrodes were positioned according to the 10–20 International System. More in detail, the montage consisted of two oculographic channels, three electromyographic channels (mental and anterior tibialis muscles), and eight referential EEG channels (F4, C4, T4, O2, A2, F3, C3, T3, O1, A1). Respiration was assessed using recordings of oronasal flow, thoracic and abdominal movements (plethysmography), and pulsoximetry. Sleep stage analysis was performed according to the American Academy of Sleep Medicine (AASM) criteria [16]. Hypopneas, apneas, and respiratory effort-related arousals were scored using the standard AASM criteria [17]. Episodes of periodic limb movements during sleep (PLMS) were defined as leg movements with amplitude increase of 8 μV above the baseline value, duration of 0.5–10 seconds, a period length between two consecutive movements of 5–90 seconds, and a minimum of four consecutive movements [18]. The periodic limb movement index (PLMI) was considered pathological if >15 per hour. The periodic limb movement arousal index (PLMAI) was defined as the number of PLMs per hour of sleep associated with an arousal on polysomnography. Finally, the isolated limb movement index (LMI) referred to isolated leg movements (leg movements with onset–onset intervals >90 seconds or PLM in sequences formed by <4) per hour of sleep [18].

2.3. Cardiovascular reflexes

The patients were tested in the morning between 8 a.m. and 10 a.m. in a clinical investigation room (23 ± 1 °C) with a continuous polygraphic recording of systolic blood pressure (SBP) and diastolic blood pressure (DBP) (Finometer, Model-1, TNO Biomedical Instrumentation, Amsterdam, The Netherlands), heart rate (HR), oronasal breathing, and EMG of the right and left tibialis anterior muscles (Grass model 15-LT).

None of the subjects were under medication known to affect autonomic function, and they were asked to abstain from alcohol and caffeine for at least 24 hours before the investigations. AFTs were performed using standard procedures [19]. The tests were performed in the order outlined below, allowing a period of rest aimed at restoring basal blood pressure (BP) and heart rate (HR) values between investigations. The results of each test were automatically obtained by means of Light-SNV software. All subjects performed the following tests: HUTT, Valsalva maneuver, deep breathing, handgrip test, and cold face.

After 30 minutes of supine rest, the subject was tilted up at 65° on HUTT for 10 minutes. At each minute of HUTT, the changes in SBP, DBP, and HR were calculated with respect to basal values. Pre-HUTT supine values (baseline) for SBP, DBP, and HR were set at 0, and changes were expressed as Δ (raw data) from baseline. The Valsalva maneuver was performed by blowing through a mouthpiece attached to a manometer and maintaining a pressure of 40 mm Hg for 15 seconds. The maneuver has four phases. Phases I and III are purely mechanical, reflecting intrathoracic pressure changes. Phase II is an important determinant of adrenergic function, as the most reliable index of systemic peripheral resistance, and phase IV seems to be more dependent on cardiac adrenergic tone [20].

We have considered as indices of autonomic activity the ratio between HR in phases II and IV (VR) and the BP variations during phases II and IV. At the deep breathing test, the sinus arrhythmia calculated in beats per minute was evaluated. The difference between the maximum HR during inspiration and minimum HR during expiration (I–E difference) in an individual respiratory cycle was calculated and expressed as the mean of the differences in 10 respiratory cycles. At the handgrip test, subjects were asked to exert 30% of maximal voluntary contraction of the dominant hand for 5 minutes on a dynamometer. BP was measured in the nonexercising arm at rest and at the third minute of the test. At the cold face test were compared changes in SBP, DBP, and HR compared to baseline values after 60 seconds of synthetic ice (0–1 °C) applied to the forehead.

2.4. Heart rate variability analysis

Heart rate variability (HRV) analysis was performed on each patient in the frequency domain using dedicated software (Light-SNV software). Stable HR epochs of 5 minutes' duration were chosen