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Computerized movement analysis and beta-CIT-SPECT in patients with restless legs syndrome

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Summary. Considering the positive effect of dopaminergic treatment on Restless Legs Syndrome (RLS), it has been suggested that the cause of RLS may be linked to central dopaminergic dysfunction. As problems of alternating movements can result from a failure in the dopaminergic system, we used a movement analysis system to analyse this and in-parallel, performed [^{123}I]β-CIT-SPECT to investigate signs of dopaminergic dysfunction in patients with RLS. In 10 patients with idiopathic RLS, we conducted a three-dimensional computerized ultrasound-based movement analysis before a single dose of levodopa (L-dopa) was given and 90 minutes after the L-dopa challenge. In 6 of the 10 RLS patients, the striatal dopamine transporter system was studied with [^{123}I]β-CIT-SPECT. We did not observe any significant change in the movement pattern with the computerized movement analysis and no significant effect of L-dopa on the movement. We did not detect any significant differences between patients and normal controls regarding β-CIT-signals in putamen or caudate nucleus, respectively. There was, however, a slight but significant change regarding the relative [^{123}I]β-CIT-SPECT binding in the putamen vs. the caudate nucleus. We conclude that the methods used could not detect any definite signs of changed central dopaminergic function in patients with RLS.

Keywords: Restless legs, RLS, computerized movement analysis, movement patterns, alternating movements, [^{123}I]β-SPECT, L-dopa.

Introduction

The Restless Legs Syndrome (RLS) is a common illness with a prevalence between 5% and 10% (Ekbom, 1945; Strang, 1967; Lavigne et al., 1994; Phillips et al., 2000; Rothdach et al., 2000; Machtey, 2001). Still the etiology and

pathophysiology of RLS is unknown and thus far, the treatment has only been directed at symptomatic relief. A majority of RLS patients has been observed to benefit from dopaminergic agents or to worsen after taking antidopaminergic medications (Akpinar, 1987; Collado-Seidel et al., 1999; Paik et al., 1989; Walters and Hennig, 1987; Henning et al., 1999; Stiasny, 2001; Winkelmann et al., 2001). Therefore, it has been suggested that the cause of RLS may be linked to central dopaminergic dysfunction. Since patients with central dopaminergic dysfunction have typically exhibited difficulties performing alternating movements (for example hand pronation–supination, hand tapping, finger tapping and foot tapping), we used a newly-developed computerized movement analysis test to investigate whether there were signs of dopaminergic dysfunction during such movements. In addition, we studied the striatal dopamine transporters in a subgroup of the idiopathic RLS patients with single photon emission computed tomography (SPECT), using the radiotracer, [^{123}I]2β-carbomethoxy-3β-4-iodophenyl-tropane ([^{123}I]β-CIT) (van Dyck et al., 1995). The aim of the study was to investigate the movement pattern in patients with RLS with an ''easy-to-use'', objective method in order to illustrate, whether the assumed dopaminergic dysfunction in RLS has an influence on movement characteristics.

Material and methods

Patients

Ten patients (8 women and 2 men) with idiopathic restless legs syndrome were selected for the study (Table 1). The RLS patients had to fulfill the clinical criteria for the diagnosis of restless legs syndrome according to the guidelines of the International RLS Study Group (Walters, 1995). The diagnosis was confirmed with a questionnaire based on the criteria for RLS and a clinical neurological examination. In six of the ten patients (Numbers 3, 4, 6, 7, 8 and 9) there was a positive family history of RLS. Causes for secondary RLS were excluded with electroneurography (no signs of polyneuropathy) and blood tests (including complete blood count, renal parameters, glucose, iron, ferritin and transferrin). There were no signs of other neurological diseases in the patients, and in particular, they did not fulfill the United Kingdom Parkinson's disease (PD) Society Brain Research Center (UKPDSBRC) criteria for PD (Hughes et al., 1992).

Table 1. Patient characteristics

	Patient number									
	1	2	3	4	5	6	7	8	9	10
Sex	f	f	f	f	f	f	f	f	m	m
Age (yrs)[a]	57	61	57	26	61	29	59	57	66	58
Duration of RLS symptoms (yrs)[a]	35	20	20	13	17	14	36	6	40	30
Daily L-dopa dose (mg)[a]	100	100	0	0	0	0	200	200	100	0

[a] At the time of the investigation. *f* female, *m* male

Single dose L-dopa test and computerized movement analysis

In patients treated with dopaminergic medications, the last dopaminergic dose was given at least 12 hours before the computerized movement analysis test, which started at 8 a.m. The patients then received a single dose of levodopa (L-dopa; 100 mg Madopar LT^{TM} with 200 ml water). The L-dopa test involved performing the movement analysis testing before the L-dopa dose, and 90 minutes after the L-dopa, to evaluate the dopaminergic responsiveness, such as in ''defined off'' and ''defined on'' conditions in clinical studies with PD patients. One L-dopa test was performed for each patient.

The movements were recorded using an ultrasonic device that continuously calculated the three-dimensional spatial position of small markers (10 mm × 8 mm, weight 3 g) attached via flexible cables to moving body parts (CMS 50-4, Zebris, Isny, Germany). Ultrasound impulses were emitted by the small, active acoustic markers placed on two points of the subject's investigated limb, and received by four sensors mounted in a square panel (55 × 55 cm). We analyzed pronation–supination, hand-tapping, index finger-tapping, and leg tapping movements (Hermsdörfer et al., 1999).

The computerized movement analysis was performed for three upper limb alternating movements and one lower limb movement, on each side of the body: alternate forearm pronation and supination (FPS), whole hand tapping (HT), index finger tapping (FT), and the lower limb movement, flexion and extension in the hip joint (HFE). The upper limb movements were measured and recorded according to the protocol as previously described by Hermsdörfer et al. (1999). For the lower limb measurement, HFE, the subject sat comfortably in a chair and was asked to flex the lower limb at the hip joint, until a distance of 10 cm to 15 cm was reached between the heel and the ground, and then to extend the joint again. HFE was recorded with one marker at the upper margin of the patella and the second one on the upper thigh, 10 cm proximal to the 1st marker. HFE appeared as a line connecting the two markers and the horizontal plane.

Before measurements began, the examiner demonstrated each of the requested movements. Subjects were instructed to perform the movement as fast as possible with a maximum movement amplitude. Initially, the patients were given three short practice trials; then the next three trials were recorded and stored on computer disk for off-line analysis.

The positional data of the two markers were analysed using a specially-designed software system (Marquardt et al., 1999). First, raw joint angles were calculated; then, data points were smoothened and time derivatives were obtained by means of kernel estimates (cut-off frequency 12 Hz), which provided a non-parametric estimation of regression functions by moving weighted averages (Marquardt and Mai, 1994). Data analysis was performed on approximately five movement cycles in each trial, excluding the first two to three cycles at the start of the movement. The following parameters were then calculated for each trial and averaged across the three trials available for each task:

- Frequency (FREQ) determined from the number of full cycles within a trial divided by the corresponding duration,
- Smoothness of the velocity profiles expressed as the number of inversions of the velocity profiles per movement segment (NIV), only inversions with amplitudes higher than 3% of maximal velocity were counted,
- Maximum angular velocity (VMAX) averaged across the movement cycles,
- Time to reach VMAX (VTIME) defined for each cycle as the time from the beginning of the movement segment to the VMAX.

[^{123}I]β-CIT-SPECT

[^{123}I]2β-Carbomethoxy-3β-(4-iodophenyl)-tropane ([^{123}I]β-CIT) was prepared according to Carroll et al. (1991) and Bettin et al. (1997) with minor modifications. For each SPECT study 185 MBq [^{123}I]β-CIT was injected intravenously after thyroid blockade with perchlorate. SPECT acquisition was performed 24 hours post-injection using a Multispect 3 three-headed-camera (Siemens, Erlangen, Germany) equipped with medium energy collimators. The spatial resolution

of the system was 14 mm to 15 mm full width at half maximum (FWHM) in the reconstructed transaxial tomograms. For image acquisition, the subject's head was fixed using a head-holder, which assured the canthomeatal line to be perpendicular to the rotational axis. 180 frames of 40 seconds duration each and with a matrix size of 128×128 (pixel-size 3.3 mm) were obtained over 360°. Transaxial tomograms were reconstructed using filtered backprojection (Butterworth filter: cut-off 0.55 Nyquist, order 20). Attenuation correction was performed according to Chang with a coefficient of $\mu = 0.12/\text{cm}$. Specific uptake in the striatal region was assessed semiquantitatively based on region of interest (ROI) analysis. For this, three consecutive transaxial slices showing the highest uptake in the striatal region were added. In the resulting image, ROIs of standardized size and shape were positioned over caudate and putamen on either side (Seibyl et al., 1995). In the same image, a reference region was placed over the cortex. This region was obtained by drawing an elliptical outline at the external boarder of the cortex and a second, smaller ellipse within the first, with a distance of 3 pixels (approximately 1 cm) in all directions between them. All pixels defined by the two ellipses and the space between them were used as a reference region, which encompassed parts of the frontal, temporal and occipital cortex. Ratios of count density between striatal regions and the reference region were calculated. Furthermore, a quotient of caudate- to putamen-ratio was calculated for each side. SPECT investigations were performed in 6 of the 10 RLS patients (numbers: 1, 5, 7–10; 4 female, 2 male; mean age 60 ± 4 years) and 7 healthy control subjects (5 female, 2 male; mean age 55 ± 10 years). There was no significant difference between the RLS patients and healthy controls with regard to age ($p = 0.108$).

Statistics

The Mann-Whitney Rank Sum test and the t-test for unpaired samples were employed to detect significant differences in clinical scores, results of movement analysis and ratios obtained in [^{123}I]β-CIT-SPECT between the control group and the RLS patient group. The t-test for paired samples was used to assess differences between caudate and putamen and side-comparisons in [^{123}I]β-CIT-SPECT ratios. The threshold of significance was set to $p = 0.05$.

Results

Table 1 shows the demographic data of the patients. At the time of the investigation, the average patient age was 53 years with a standard deviation (SD) of 13.8 years, and the average duration of the RLS symptoms was 11.4 years with an SD of 23.1 years. Two male and 8 female RLS patients were included in the study.

Computerized movement analysis

The computerized movement analysis results revealed no significant differences observed between the RLS patients without L-dopa and a group of age- and sex-matched normal control persons (7 female and 3 male; the average age was 54.6 years with a standard deviation (SD) of 13.7 years) in any of the computerized movement tests performed (data not shown). Only non-significant changes in movement parameters were detected after administration of L-dopa: the movement frequency was slightly faster; the number of inversions of velocity were a bit lower; the maximum velocity was comparable or slightly higher; and the time to reach maximum velocity slightly shorter than without L-dopa (Fig. 1a–d).

[^{123}I]β-CIT-SPECT

[^{123}I]β-CIT did not reveal significant reductions of caudate-to-cortex ratios or putamen-to-cortex ratios in RLS patients compared to controls for both the left

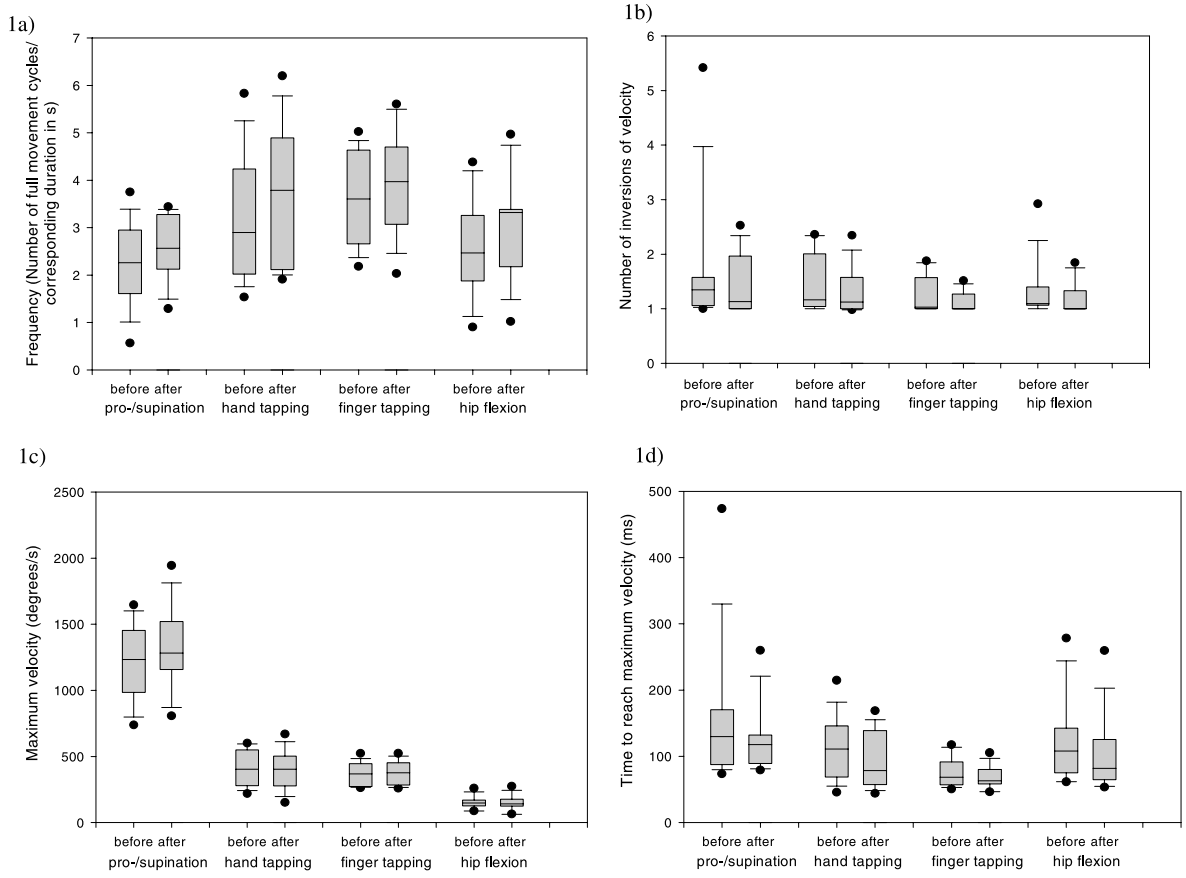

Fig. 1. a–d Frequency, number of inversions of velocity, maximum velocity and time to reach maximum velocity in RLS patients before (before) and 90 minutes after (after) 100 mg of peroral L-dopa, regarding alternating forearm pronation and supination, whole hand tapping, index finger tapping and hip tapping. 5th, 10th, 25th, median, 75th, 90th, and 95th percentiles are shown

Table 2. Results of [^{123}I]β-CIT SPECT: striatum to cortex ratios and quotient of ratios from putamen to caudate for right and left side – significance of differences between patients and controls and differences between as caudate and putamen in either group (t-test)

	Right caudate to cortex	Left caudate to cortex	Right putamen to cortex	Left putamen to cortex	Putamen to caudate right side	Putamen to caudate left side
Controls mean ± SD	$9.1 \pm 1.7^{*}$	$9.0 \pm 1.7^{\#}$	$8.7 \pm 1.4^{*}$	$8.5 \pm 1.4^{\#}$	0.96 ± 0.07	0.95 ± 0.07
Patients mean ± SD	$10.2 \pm 1.3^{\dagger}$	$10.4 \pm 1.4^{\ddagger}$	$8.6 \pm 1.1^{\dagger}$	$8.6 \pm 1.1^{\ddagger}$	0.85 ± 0.05	0.83 ± 0.07
t-test	$p = 0.215$	$p = 0.149$	$p = 0.966$	$p = 0.915$	$p = 0.007$	$p = 0.012$

t-test: $^{*}p = 0.102$, $^{\#}p = 0.121$, $^{\dagger}p = 0.002$, $^{\ddagger}p = 0.003$

and the right sides (Table 2). Moreover, no significant side differences were detected in both groups. Of interest, however, in the RLS patients, the putamen ratios (right: 8.6, left: 8.6) were significantly lower than the caudate ratios

(right: 10.2, $p = 0.002$; left: 10.4, $p = 0.003$). In the healthy controls, no significant difference between putamen ratios and caudate ratios could be detected. The quotient of ratios from putamen and caudate was significantly lower in the RLS patients (right: 0.85, left: 0.83) compared to the healthy controls (right: 0.96, $p = 0.007$; left: 0.95, $p = 0.012$).

Discussion

Thus far, the pathophysiology of RLS has not been well understood. Neurophysiological, pharmacological, and imaging studies have indicated a complex interaction between central and peripheral structures (Odin et al., 2002; Winkelmann and Trenkwalder, 2001; Allen and Earley, 2001). In this study, we present data from objective, computerized movement analyses and [^{123}I]β-CIT-SPECT, in order to illustrate, whether the assumed dopaminergic dysfunction has an infuence on the movement patterns.

The three-dimensional computerized movement analysis here used has been a suitable method for a more detailed, objective and quantitative examination of alternating movements in Parkinson's disease patients (Hermsdörfer et al., 1999; Schimke et al., 2000; Jöbges et al., 2003). A main advantage with this type of analysis is that it is largely observer-independent, thereby being suitable for mono as well as multicenter studies. In a parallel study, Joebges and co-workers have shown that computerized movement parameters which reflect the smoothness of alternating movements, namely the number of inversions of velocity and the time to reach the maximum velocity, correlated particularly well to the degree of illness, as reflected by the Unified Parkinson's Disease Rating Scale (UPDRS) total score and UPDRS III score, and thus, likely correlating with the degree of dopaminergic denervation (Joebges et al., 2003).

In our investigations of the RLS patients, we could not observe any statistically significant pathology between the measurements without L-dopa and 90 minutes after the L-dopa dose, regarding the 4 measured motor parameters. There were no signs that dopaminergic imbalance significantly influenced the alternating movements of the RLS patients. To further investigate the dopaminergic system, we performed [^{123}I]β-CIT SPECT investigations in 6 of the 10 RLS patients. There was no significant reduction of binding to striatal dopamine transporters as assessed by caudate-to-cortex or putamen-to-cortex ratios and no significant differences between patients and normal controls regarding signals in putamen or caudate nucleus. These results correspond with the investigation from Michaud and co-workers, which found no significant difference in the presynaptic dopamine transporter binding in 10 RLS patients with beta-CIT (Michaud et al., 2002).

The quotient of ratios, however, between the putamen and caudate was slightly – but significantly lower in RLS patients. This result could, in principle, be within the scope of a decrease in putamen or an increase of caudate nucleus or both at the same time, but the actual values in the respective structure were within normal limits.

Reductions of presynaptic dopaminergic function have been found in two studies in RLS patients using [^{18}F]F-dopa. Ruottinen and co-workers reported

decreases of uptake of 12% in the caudate and 11% in the putamen, and Turjanski et al. reported a significant decrease in the putamen ($p = 0.04$), but not in the caudate (Routinen et al., 2000; Turjanski et al., 1999). On the other hand, Trenkwalder and co-workers could not confirm impaired [^{18}F]F-dopa uptake in the striatum, but concluded that they could not detect subtle changes in a small group of 4 patients (1999). In the meantime, Eisensehr and co-workers observed that with IPT SPECT and IBZM-SPECT, there were no pre- or postsynaptic differences in 14 drug-naïve and 11 levodopa-treated RLS patients when compared to age-matched normal controls (Eisensehr et al., 2001). Furthermore, pathological examination of the substantia nigra pars compacta in 2 patients did not show dopaminergic cell depletion (Boyer et al., 2000).

Considering our data from [^{123}I]β-CIT, we can not rule out that increased binding in the caudatus nucleus of the RLS patients, although not statistically significant, when compared to healthy controls, might contribute to the finding of relatively impaired binding in the putamen. However, together with the previously reported results of reduced presynaptic dopaminergic function in the striatum, as measured by [^{18}F]F-dopa, transporter dysfunction in the putamen would more likely be the cause of our findings. But altogether, and in the context of the aforementioned studies, we could not firmly demonstrate a significantly decreased binding to dopamine transporters in the putamen when comparing to healthy controls.

The reason for the different results of neuroimaging could be due to multiple factors, such as a significant age difference between RLS patients and healthy controls in some studies, with the concentration of D2 receptors showed an age dependence with decline in age. Moreover, the study groups were sometimes too small for a statistical evaluation, which makes a comparison between the studies more difficult. In addition, all studies ignored the fact that the clinical symptoms of RLS patients are at their maximum (worst) in the evening or at night, and to explore the possibility of a dysfunction of another dopaminergic system, such as the diencephalospinal or the mesolimbic system. Therefore, further imaging studies performed at other times of the day and perhaps focusing on other central nervous system regions would be highly warranted.

The primary pathophysiologic mechanism of Restless Legs Syndrome thus remains unclear. It is possible that other dopaminergic pathways or that a dopamine deficit on the spinal level plays an important role in the pathophysiology. Animal studies have revealed spinal dopamine receptors (D1, D2, D3) that might be involved (van Dijken et al., 1996; Levant and McCarson, 2001; Scatton et al., 1984; Yokoyama et al., 1994; Gladwell et al., 1999). In conclusion, the present study does not demonstrate, that the dopaminergic imbalance significantly influenced the alternating movements of the RLS patients, so there was no firm evidence for involvement of the nigrostriatal dopaminergic system in the pathophysiology of RLS. Further studies involving clinical investigations on larger groups of patients, over longer periods of time, as well as histopathological and genetics analyses, will be necessary to shed more light on the pathophysiology of this challenging disease.

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