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Sleep disorders in Machado–Joseph disease: A dopamine transporter imaging study ☆

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ABSTRACT

Objectives: Sleep disorders, especially restless legs syndrome (RLS) and rapid eye movement sleep behavior disorder (RBD), are common in spinocerebellar ataxia type 3 or Machado–Joseph disease (MJD), and a possible underlying dopaminergic dysfunction is implicated. This study assessed the relationship between sleep disorders in MJD and dopamine transporter (DAT) densities.
Patients and methods: Twenty-two patients with MJD and twenty healthy subjects were enrolled in this study. MJD patients underwent clinical sleep evaluation and polysomnography. SPECT with [^{99m}Tc]-TRODAT-1, was performed in all subjects.
Results: DAT densities were significantly reduced in MJD group when compared to controls. No significant correlation was found between DAT densities and RLS or RBD in MJD.
Conclusion: Our study failed to demonstrate a clear correlation between sleep disorders and DAT densities in MJD patients, hence suggesting that extrastriatal and non-presynaptic dopamine pathways could be implicated in MJD-related sleep disorders.

1. Introduction

Spinocerebellar ataxia type 3 or Machado Joseph Disease (MJD) is a neurodegenerative disease considered the most common autosomal dominant spinocerebellar ataxia worldwide [1]. Its clinical spectrum comprises a wide range of motor and non-motor symptoms [2]. Several studies have focused on non-motor symptoms in MJD, which include cognitive dysfunction, psychiatric disturbances, olfactory dysfunction and sleep disorders [3–5]. However, sleep disorders remain underrecognized despite their significant impact on health-related quality of life in patients with spinocerebellar ataxias (SCA) [6].

The most frequent sleep complaints in MJD are restless legs syndrome (RLS), rapid eye movement (REM) sleep behavior disorder (RBD), excessive daytime sleepiness (EDS), obstructive sleep apnea (OSA) and insomnia [7–9]. Few studies have investigated pathophysiological mechanisms underlying sleep disorders in MJD [10].

Molecular imaging is a useful technique to study in vivo the neurobiological basis for neurodegenerative diseases such as Parkinson's disease [11]. The use of radioligands with high affinity and specificity to dopamine binding sites allows to estimating striatal dopaminergic degeneration. TRODAT-1, a technetium-99m labeled dopamine transporter (DAT) tracer, has become a cost-effective alternative in molecular neuroimaging studies [12]. DAT imaging using [^{99m}Tc]-TRODAT-1 has previously been reported to be decreased in the striatum in MJD [13,14].

Assuming the a priori hypothesis that dopaminergic dysfunction can be involved in the pathophysiology of sleep disorders in MJD, the current study aimed to assess the correlation between sleep disorders in MJD and DAT density, particularly RLS, RBD and periodic limb movements during sleep (PLMS).

2. Patients and methods

2.1. Clinical protocol

We evaluated 22 patients with clinical and molecular-proven MJD, from 15 families, and 20 healthy subjects (non-family members). The following scales were used for clinical assessment in MJD group: RBD Screening Questionnaire (RBDSQ) and International RLS Study Group

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Rating Scale (IRLSRS). The diagnosis and severity of RBD was based on the RBDSQ using a five-point scale. Bed partners described RBD symptoms. Those who met the criteria for the five questions were considered to have clinically-defined RBD [15]. The presence of RLS was determined following recommended procedures [16]. Severity of RLS was measured using IRLSRS [17]. Concerning control group, no subject had RBD or RLS. Therefore, no correlation was performed considering sleep disorders in control group, since those data were irrelevant. We used the Scale for the Assessment and Rating of Ataxia (SARA) in order to measure ataxia severity. The CAG repetition length was also evaluated in all patients.

2.2. Polysomnographic evaluation

MJD patients underwent an all-night polysomnography (PSG). The following were performed using a computerized PSG system (Alice 5, Healthyne): electroencephalogram, electro-oculograms, submental electromyogram (EMG), tibial EMG, electrocardiogram, chest and abdomen movement (plethysmography), nasal–oral air flow (3-way thermistor and nasal cannula pressure transducer) and oxyhemoglobin saturation. Patients were monitored by video camera and observed continuously by experienced technicians. Analysis of sleep, arousals, cardio-respiratory parameters, and loss of atonia during REM sleep (RWA) was performed according to the American Academy of Sleep Medicine standard techniques. Sleep stages and the estimated polysomnographic indices (such as PLMS index) were scored according to standard criteria [18]. PLMS was scored following the scoring rules of the Sleep Disorders Atlas Task Force [19]. Medications that potentially could interfere with sleep, such as benzodiazepines, cholinergic drugs and antidepressants, were discontinued at least one month before PSG. For technical reasons we could not perform polysomnography in the control group.

2.3. Brain imaging and analyses

All MJD patients and 20 healthy subjects underwent brain SPECT imaging using [^{99m}Tc]-TRODAT-1. Images were acquired 4 h after the injection of 740 ± 74 MBq (~20 mCi) of [^{99m}Tc]-TRODAT-1 using a Hawk Eye dual-head gamma camera (GE Infinia, USA), equipped with high-resolution fan beam collimators. For each scan, a total of 128 projections (30 s per frame) were collected in the step-and-shoot mode using circular 360° orbit in a 128 × 128 matrix with mean radius of rotation of 15.5 cm. The image data were reconstructed using standard filtered back projection with a Butterworth filter (cut-off frequency 0.45) with Chang's attenuation correction method. For an accurate determination of volumetric regions of interest (vROIs), all subjects also underwent structural magnetic resonance imaging (MRI). Statistic Parametric Mapping 5 software package (SPM5) (Wellcome Department of Imaging Neuroscience, London, United Kingdom), run in Matlab (Mathworks, Sherborn, Massachusetts), was used for exact coregistration of MRI and SPECT scans. Six spheres representing vROIs were plotted on individually reoriented MRI scans by a researcher (PBN) who was blind to subject identity and diagnosis using a SPM5 toolbox as follows: right caudate (RC), left caudate (LC), right anterior putamen (RAP), left anterior putamen (LAP), right posterior putamen (RPP) and left posterior putamen (LPP) (http://marsbar.sourceforge.net/). The occipital area was used as a reference, representing nonspecific binding of [^{99m}Tc]-TRODAT-1. For each separate vROI, the ratio of specific binding of [^{99m}Tc]-TRODAT-1 was calculated by the following formula: average radioactivity count per voxel per volume of interest minus average radioactivity count per voxel in the occipital/average radioactivity count per voxel in the occipital. The putamen to caudate ratio (P/C) was determined by the following formula: average DAT density at anterior and posterior putamen/DAT density at caudate.

3. Statistical analysis

Means and standard deviations for continuous variables are reported. Differences in means were verified using the Student *t* test (t) for independent samples. Point biserial correlation coefficients (r_{pb}) were calculated to evaluate the strength of correlation between vROIs and sleep disorders. Pearson's correlation coefficient (r) was calculated for the scores of vROIs and the scores on the sleep disorder scales. A p value <0.05 was considered to indicate statistical significance. Ninety-five percent confidence intervals (CI) were calculated for the difference between means. All statistical analyses were performed on a personal computer with the use of Statistical Package for Social Sciences (SPSS) 19 for Windows.

4. Results

There were no differences between controls and MJD patients regarding age (41.7 (±9.1) versus 43.8 (±9.6), $t(40) = -0.71$, 95% CI = −7.9 to 3.8, $p = 0.479$) and sex (45 versus 50% of males, $\chi^2(1) = 0.10$, $p = 0.746$). DAT densities assessed by the SPECT [99mTc]-TRODAT-1 were significantly reduced in patients with MJD when compared to normal controls (Table 1).

In our MJD sample, the mean disease duration was 7.2 (±4.6) years, the mean score on the SARA was 10.8 (±5.9) and the mean CAG repetition length was 70.6 (±3.9), while 54% had RLS, 77% had PLMS, 73% had RWA and 59% had RBD. Although RWA was present in 73% of the patients, only 59% had typical RBD based on RBDSQ and related by bed partners. Only one patient had parkinsonism. Nine patients had both, RBD and RLS. We calculated the correlation coefficients to assess the strength of association between vROIs and the presence of RLS, RLS severity, presence of PLMS, PLMS index, presence of RWA and RBD, and RBD severity, disease duration, ataxia severity (SARA) and CAG repetition length as shown in Table 2. There was no significant correlation between the aforementioned sleep disorders, disease duration, SARA and CAG repetition length, with DAT densities in MJD patients.

As RLS and RLS severity were significantly correlated with LPP, a logistic regression analysis was performed including RLS and RLS severity as the dependent variable and LPP vROI as the independent variable controlling for age. After controlling for age, the relationship between LPP volume and RLS in the [^{99m}Tc]-TRODAT-1 imaging scan was no longer significant.

Table 1
Dopamine transporter (DAT) densities assessed by SPECT [^{99m}Tc]-TRODAT-1 comparing patients with Machado–Joseph disease versus normal controls. A significant DAT reduction is observed.

Group statistics	Controls		MJD group			95%CI (mean difference)		
	Mean	Std. Deviation	Mean	Std. Deviation	t (40)	Lower	Upper	p
RC	2.04	0.49	1.33	0.31	5.68	0.46	0.96	<0.001
LC	2.01	0.54	1.35	0.31	4.88	0.38	0.93	<0.001
RPP	1.45	0.36	0.81	0.34	5.83	0.42	0.86	<0.001
LPP	1.59	0.42	0.80	0.38	6.44	0.54	1.04	<0.001
RAP	1.79	0.41	1.02	0.37	6.44	0.53	1.02	<0.001
LAP	1.90	0.54	1.17	0.33	5.31	0.45	1.01	<0.001

Legends:
MJD: Machado–Joseph disease;
RC: right caudate;
LC: left caudate;
RPP: right posterior putamen;
LPP: left posterior putamen;
RAP: right anterior putamen;
LAP: left anterior putamen.