Regional cerebral blood flow changes in patients with idiopathic REM sleep behavior disorder

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Background: Recent studies have shown an association between rapid eye movement sleep behavior disorder (RBD) and neurodegenerative disorders, especially alpha-synucleinopathies.
Objective: We investigated regional cerebral blood flow (rCBF) changes using single photon emission computed tomography (SPECT) in patients with idiopathic RBD (iRBD), to determine functional brain alterations associated with the disorder.
Methods: The SPECT data of 24 patients with iRBD were compared with those of 18 age-matched normal controls using statistical parametric mapping 2.
Results: We found decreased rCBF in the parietooccipital lobe (precuneus), limbic lobe, and cerebellar hemispheres in patients with iRBD, which is commonly seen in patients with Lewy body disease (Parkinson's disease and dementia with Lewy bodies) or multiple system atrophy.
Conclusion: Our SPECT study suggests that iRBD can be a presymptomatic stage of alpha-synucleinopathies.

Introduction

Rapid eye movement (REM) sleep behavior disorder (RBD) is a parasomnia characterized by a loss of normal skeletal muscle atonia during REM sleep and prominent motor activity whilst dreaming. RBD occurs either as an idiopathic disease or in association with neurodegenerative diseases, particularly alpha-synucleinopathies [1]. Recent studies have demonstrated several neuropsychological impairments, such as visuospatial construction dysfunction, executive dysfunction, and memory disturbance [2,3], smell testing abnormalities [4–6], and a reduction of striatal presynaptic dopamine transporters [4,7] in idiopathic RBD (iRBD). Another study has also shown reduced cardiac ^{123}I-metaiodobenzylguanidine uptake in patients with iRBD, indicating the presence of sympathetic cardiac denervation [8]. Because these findings are characteristic features of alpha-synucleinopathies, including Parkinson's disease (PD) and dementia with Lewy bodies (DLB), iRBD may be a prodromal stage of alpha-synucleinopathies.

In this study, we investigated regional cerebral blood flow (rCBF) changes using single photon emission computed tomography (SPECT) in patients with iRBD to determine whether there may be a unique feature of functional brain abnormalities which is associated with alpha-synucleinopathies.

Methods

We studied 24 consecutive patients (21 men and 3 women; mean age ± SD: 68 ± 7 years) with iRBD, which was diagnosed based on thorough clinical interviews and polysomnography (PSG) findings by sleep disorder expert physicians, according to the criteria of the International Classification of Sleep Disorders, Second Edition [9]. PSG and videotape recordings were made simultaneously as the patients slept.

Exclusion criteria were as follows: (i) abnormal neurologic findings on examination by geriatric neurological specialists, including Parkinsonism, cerebellar ataxia, and autonomic dysfunction, (ii) alcohol or psychotropic drug use, (iii) psychiatric disorders, (iv) obstructive sleep apnea-hypopnea syndrome or

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(v) abnormalities on brain MRI except for minimal white matter hyperintensity lesions. We also excluded patients with poor performance on neuropsychological tests, including the Mini-Mental State Examination (MMSE) score [10], Wechsler Memory Scale-revised (WMS-R) logical memory-I and -II [11], memory factors (word recall, orientation, word recognition, and instruction recall), language factors (spoken language ability, comprehension, word-finding difficulty, command, and naming), and praxis (constructional praxis and ideational praxis) factors on the Alzheimer's Disease Assessment Scale – cognitive subscale Japanese version (ADAS-Jcog) [12], Frontal assessment battery (FAB) Test [13], Digit symbol test (DST) [14], and Visual Perception Test for Agnosia (VPTA) [15]. The cutoff scores of each neuropsychological test were ≥24 on the MMSE, ≥13 and ≥10 on the WMS-R logical memory-I and -II, respectively, <10 on the total ADAS-Jcog, ≥13 on the FAB Test, ≥30 on the DST, and $=0$ on the VPTA.

Eighteen age- and education-matched healthy control subjects consisted of nine men and nine women (age range 51–79, mean age 70 ± 8 years). They were cognitively normal, with no history of sleep disorders, no neurologic or psychiatric illnesses, and had no or minimal white matter changes on brain computed tomography or magnetic resonance imaging (MRI). Written informed consent was obtained from each subject.

This study was approved by the ethics committee of our institute.

Polysomnography

Polysomnography monitoring included electroencephalography (C3, C4, 1, and O2), electrooculography, chin muscle electromyography, electrocardiography, airflow detection by a thermistor, plethysmography for ribcage and abdominal wall motion, oximetry for measurement of arterial oxyhemoglobin saturation, detection of changes in sleeping position, and bilateral electromyography of the tibialis anterior muscles. Sleep stages were manually scored according to the criteria of Rechtschaffen and Kales [16]. REM sleep was scored without the chin EMG criterion, thereby allowing for maintenance of muscle tone during REM sleep [17]. None of the patients with iRBD were taking any medication affecting the central nervous system at the time of PSG and SPECT examinations.

Single photon emission computed tomography study

All SPECT studies were performed using a triple-head rotating gamma camera (PRISM 3000 XP; Philips Medical Systems, Cleveland, OH, USA) with a fan-beam collimator permitting a spatial resolution of 6.8 mm full-width at half-maximum. The imaging was begun 15 min after an intravenous injection of 222 MBq of *N*-isopropyl-p- [^{123}I] iodoamphetamine. The SPECT acquisition was undertaken in 24 steps (72 projections), and each step collected counts for 40 s. Reconstruction of the images was performed by filtered backprojection using Butterworth and Ramp filters (order 8; cutoff 0.40/cm) with attenuation correction (Chang 0.09/cm). The matrix size and slice thickness of the SPECT images were 128×128 mm and 4.3 mm, respectively.

Images were analyzed with a statistical parametric mapping system (SPM 2; Wellcome Department of Cognitive Neurology, London, UK) in Matlab 7.1 (Mathworks Inv., Sherborn, MA, USA). Image data were transferred to a personal computer and converted to the ANALYZE format. All studies were then registered and normalized to the SPM template provided by the Montreal Neurological Institute (MNI). A standard *t* test was performed for comparison between the patients and control groups. The statistical thresholds were set at $P < 0.01$, uncorrected for multiple comparisons, for groups of at least 50 contiguous voxels. Coordinates presented here have been converted from MNI to Talairach space. The Talairach Daemon was used to assign anatomical labels to voxel coordinates. Threshold SPM results were overlaid onto an MRI scan in MNI space.

Results

Clinical, neuropsychological, and PSG data for patients with iRBD are shown in Table 1. Significantly decreased rCBF in patients with iRBD compared with controls was found in the right cerebellum (posterior and anterior lobes), left cerebellum (posterior lobe), right and left parietal lobes (precuneus), left occipital lobe (precuneus), and right limbic lobe (uncus) (Table 2, Fig. 1). We found no brain areas with significantly increased rCBF in patients with iRBD compared with controls. No significant correlation was found amongst rCBF changes and PSG variables or RBD duration.

Discussion

We found decreased rCBF in the parietooccipital and limbic lobes and in the cerebellar hemispheres in patients with iRBD. To the best of our knowledge, there are two SPECT studies which examined cerebral perfusion changes in patients with iRBD [18,19]. However, the results are inconsistent. Shirakawa *et al.* [18] showed decreased perfusion in the upper portion of the frontal lobe and the pons, whilst Mazza *et al.* [19]

Table 1 Clinical, neuropsychological, and polysomnography data of patients with idiopathic rapid eye movement sleep behavior disorder

Age (years)	68 ± 7 (59–80)
Gender (men/women)	21/3
Duration of symptoms (years)	6 ± 5 (1–20)
Education (years)	13 ± 2 (9–16)
Neuropsychological function	
MMSE	28 ± 2 (24–30)
WMS-R	
Logical memory-I	20 ± 6 (13–32)
Logical memory-II	17 ± 5 (10–29)
ADAS-Jcog	5.1 ± 2.2 (1.3–9.3)
Memory	4.6 ± 1.9 (1.3–8.3)
Language	0.4 ± 0.5 (0–1)
Praxis	0.1 ± 0.2 (0–1)
Frontal assessment battery	15 ± 2 (13–17)
Verbal fluency (animals/min)	15 ± 4 (11–22)
Digit symbol test	45 ± 10 (30–60)
Visual preception test for agnosis	0 ± 0 (0)
Geriatric depression scale – 15	3 ± 2 (0–6)
Polysomnography variables	
Total sleep time (min)	415.3 ± 74.4 (229.5–513.5)
Sleep efficiency (%)	78.7 ± 14.0 (42.2–95.0)
Stage 1 NREM (%)	16.4 ± 12.4 (5.1–58.8)
Stage 2 NREM (%)	44.3 ± 13.7 (0–60.7)
Stage 3 + 4 NREM (%)	4.0 ± 0.9 (0–11.4)
REM sleep (%)	12.6 ± 5.8 (3–25.6)
REM without atonia (%) (/REM)	27.4 ± 19.4 (0–68.8)
Arousal index	18.4 ± 7.1 (5.8– 31.3)
Apnea-hypopnea index	6.5 ± 6.0 (0–14.3)

Values are presented as means ± SD. MMSE, Mini-Mental State Examination; WMS-R, Weschler Memory Scale-revised; ADAS-Jcog, Alzheimer's Disease Assessment Scale-cognitive subscale Japanese version; NREM, non-REM sleep. REM, rapid eye movement. Parentheses indicate a value range (min. – max.)

found decreased perfusion in the frontal, temporal, and parietal lobes and increased perfusion in the hippocampus, putamen, and pons in patients with iRBD. The inconsistent results may be mainly derived from differences in assessment of cerebral perfusion (manual selection of regions of interest versus statistical imaging analysis), as well as patient characteristics.

Structural lesions in the dorsolateral tegmental portion of the pons, especially the subcoeruleus region and laterodorsal tegmental nuclei, have been proposed as the regions responsible for the occurrence of RBD [1]. However, as reported above, two perfusion studies have reported contradictory results concerning the perfusion of this region of interest. We also failed to identify significant rCBF change in the mesencephalus and pontine tegmentum. One possible reason is that spatial resolution was too low to depict perfusion alterations in some small nuclei in the tegmental portion of the pons using SPECT. We also did not find decreased perfusion in the frontal lobe, concordantly reported by the previous two studies. Some studies reported perfusion impairment in the frontal lobes of patients with PD [20,21], which could correspond to their executive dysfunction. However, no subjects in the present study had frontal executive dysfunction as shown on the FAB Test and DST. This may be the main reason why the patients in the current study showed no frontal rCBF changes. In addition, we found no perfusion impairment in the striatum or thalamus, which has been shown in some patients with PD and DLB possibly because of an upregulation of postsynaptic dopamine receptors [20,21]. However, the decreased rCBF levels in the parietooccipital lobe (precuneus) and cerebellum found in the present study are known to be characteristic perfusion deficits in patients with PD [20], DLB [22,23], and multiple system atrophy [24], respectively. Thus, our data indicate the existence of rCBF changes in patients with iRBD which are very similar to those seen in alpha-synucleinopathies. However, because rCBF changes in the precuneus and cerebellum are also seen during normal human REM sleep or during nightmares [25], further studies are required to determine the exact functional correlation between these regions and RBD.

Several studies have shown that patients with iRBD exhibit subclinical abnormalities in several domains, such as visuospatial constructional and executive impairment [2,3], olfactory deficit [4–6], reduced nigrostriatal dopaminergic innervation [4,7], and cardiac sympathetic denervation [8,26]. All are common

Table 2 Brain areas with significant reduced regional cerebral blood flow of patients with idiopathic RBD, compared with controls

Regions		BA	*t*-value	Coordinates		
				x	*y*	*z*
Cerebellum	Rt-posterior lobe	–	3.7	36	−70	−34
	Rt-anterior lobe	–	2.51	36	−52	−28
	Lt-posterior lobe	–	2.97	−40	−58	−26
Parietal lobe	Rt-precuneus	7	2.61	18	−76	39
	Lt-precuneus	7	3.65	−17	−63	29
Occipital lobe	Lt-precuneus	31	3.3	−18	−63	20
Limbic lobe	Rt-uncus	20	3.01	32	−5	−30

Rt, right side; Lt, left side; BA, Broadmann area.

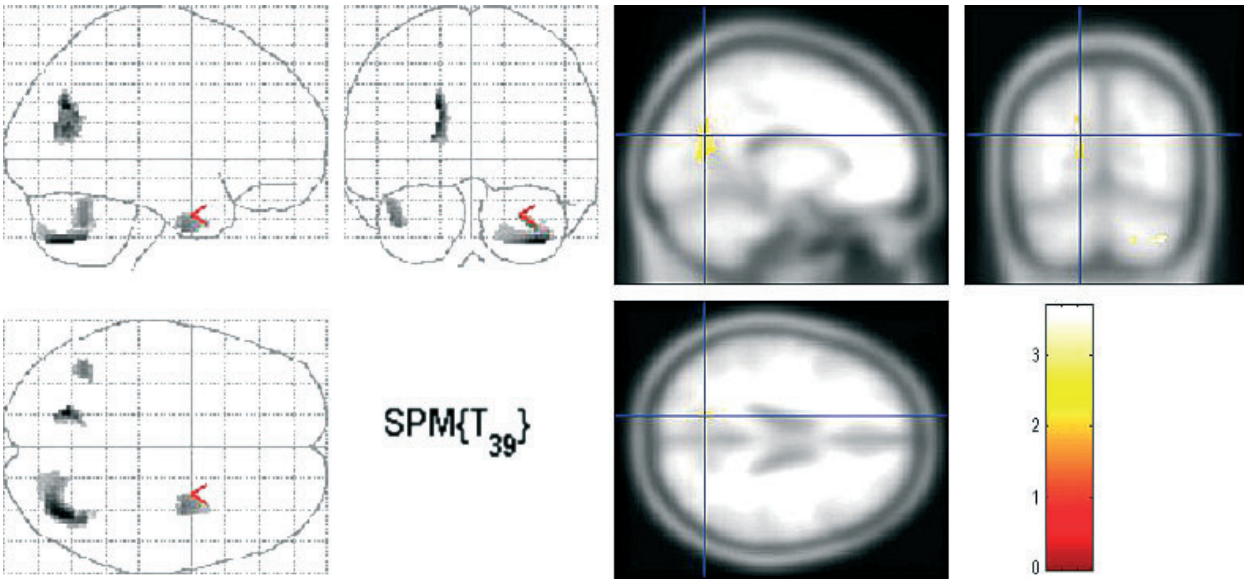

Figure 1 Statistical parametric mapping projections showing areas with significantly decreased regional cerebral blood flow in patients with idiopathic sleep behavior disorder, compared with controls.

characteristics of Lewy body disease. Recently, Unger *et al*. [27] described diffusion tensor imaging changes in patients with iRBD. They found important microstructural abnormalities in the white matter of the brain stem, as well as in the right substantia nigra, olfactory region, left temporal lobe, fornix, and the right visual stream of patients with iRBD, which are known to be involved in REM sleep regulation and/or to indicate neurodegenerative pathology in early PD. Because in the present study none of the iRBD patients showed signs of Parkinsonism or cerebellar ataxia, our results suggest that iRBD can be a preclinical stage of alpha-synucleinopathies. Therefore, careful follow-up of patients with iRBD may result in the early detection of alpha-synucleinopathies.

This study has some limitations. First, the men to women ratio was not matched in the iRBD and control subjects. Although in healthy adults subtle differences in rCBF and metabolism between sexes have been shown, the differences have been less consistent with respect to regional brain areas [28]. Second, we did not quantify absolute rCBF. Because our purpose was to determine the characteristic features of functional brain abnormalities associated with alpha-synucleinopathies, we analyzed SPECT data using statistical parametric mapping. Third, the control subjects did not undergo detailed neuropsychological tests and PSG. Fourth, although carefully examined by geriatric neurologists, the iRBD patients and the controls did not undergo a standardized exam, e.g. the motor part of the Unified Parkinson's disease rating scale. Thus very subtle Parkinsonian signs may have been missed.

In conclusion, we found decreased rCBF in the parietooccipital lobe (precuneus), limbic lobe, and cerebellar hemispheres in patients with iRBD. Such perfusion abnormalities are also common in patients with confirmed alpha-synucleinopathies. Thus, based on these findings, the present SPECT study suggests that iRBD can be a presymptomatic stage of alpha-synucleinopathies.

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