Combination of ‘idiopathic’ REM sleep behaviour disorder and olfactory dysfunction as possible indicator for α-synucleinopathy demonstrated by dopamine transporter FP-CIT-SPECT

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Summary
REM sleep behaviour disorder (RBD) and olfactory dysfunction are common and very early features of α-synucleinopathies, in particular Parkinson’s disease. To investigate the hypothesis that these two clinical features in combination are an indicator of evolving α-synucleinopathy, olfactory function was assessed in RBD. We studied 30 patients (18 male, 12 female; mean age 48 ± 14 years, range 19–78 years) with clinical (idiopathic, n = 6; symptomatic, n = 13, mostly associated with narcolepsy) or subclinical (n = 11, associated with narcolepsy) RBD according to standard criteria and 30 age- and gender-matched healthy control subjects using standardized ‘Sniffin’ Sticks’. RBD patients had a significantly higher olfactory threshold (P = 0.0001), lower discrimination score (P = 0.003), and lower identification score (P = 0.001). Compared with normative data, 97% of the RBD patients had a pathologically increased olfactory threshold, 63% an impaired odour discrimination score, and 63% a decreased identification score. On neurological examination, signs of parkinsonism were newly found in five patients with clinical RBD (not associated with narcolepsy), who usually had a long history of ‘idiopathic’ RBD. Four of the five patients fulfilled the UK Brain Bank criteria for the clinical diagnosis of Parkinson’s disease. The underlying nigrostriatal degeneration of clinical Parkinson’s disease was confirmed by I-123-FP-CIT SPECT in one patient and early nigrostriatal degeneration was identified by SPECT in a further two patients with ‘idiopathic’ clinical RBD out of 11 RBD patients who agreed to undergo SPECT studies. Our study shows that RBD patients have a profound impairment of olfactory function. Five patients with clinical RBD not associated with narcolepsy had clinical or imaging signs of nigrostriatal degeneration. This new clinical finding correlates with the neuropathological staging of Parkinson’s disease (stages 1–3) as proposed by Braak. In stage 1, the anterior olfactory nucleus or the olfactory bulb is affected (along with the dorsal motor nucleus of the glossopharyngeal and vagal nerves). In stage 2, additional lesions consistently remain confined to the medulla oblongata and pontine tegmentum, which are critical areas for RBD. Midbrain lesions are found only in stage 3, in particular degeneration of dopaminergic neurons in the substantia nigra pars compacta. Thus, ‘idiopathic’ RBD patients with olfactory impairment might present with stage 2 preclinical α-synucleinopathy. Since narcoleptic patients are not known to have an increased risk of developing parkinsonism, the pathophysiology and clinical relevance of hyposmia in RBD/narcolepsy patients requires further research.

Keywords: REM sleep behaviour disorder (RBD); Parkinson’s disease; α-synucleinopathy; olfactory dysfunction; dopamine transporter

Abbreviations: DLB = dementia of the Lewy body type; EMG = electromyography; FP-CIT = N-O-Fluoropropyl-2β-Carbomethoxy-3β-(4-Iodophenyl)-Nortropan; MMSE = Mini-Mental State Examination; MPTP = N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MSA = multiple system atrophy; PSG = polysomnography; PSP = progressive supranuclear palsy; RBD = REM sleep behaviour disorder; REM = rapid eye movement sleep; SPECT = single photon emission computed tomography; TDI = threshold–discrimination–identification; UPDRS = Unified Parkinson’s Disease Rating Scale

Introduction

In 2003 Braak and colleagues proposed a new neuropathological staging of Parkinson’s disease (Braak et al., 2003). Stage 1 frequently affects the anterior olfactory nucleus or the olfactory bulb. In mildly affected cases (stages 1 and 2) lesions are found in the lower brainstem, remaining consistently confined to the medulla oblongata and pontine tegmentum. Only in stage 3 are there additional midbrain lesions, in particular degeneration of dopaminergic neurons in the substantia nigra pars compacta. A clinical correlate to stage 1 may be olfactory dysfunction, and there is convincing evidence that olfactory dysfunction is a common and very early feature in Parkinson’s disease (Ansari and Johnson, 1975; Ward et al., 1983; Quinn et al., 1987; Doty et al., 1988, 1992b; Hawkes et al., 1997; Hawkes and Shepard, 1998; Daum et al., 2000; Tissingh et al., 2001; Müller et al., 2002; Double et al., 2003), and this may make it possible to identify preclinical Parkinson’s disease in relatives of patients with Parkinson’s disease (Markopoulou et al., 1997; Berendsse et al., 2001).

Another associated feature of evolving Parkinson’s disease is rapid eye movement (REM) sleep behaviour disorder (RBD) (Comella et al., 1998; Arnulf et al., 2000; Olson et al., 2000; Gagnon et al., 2002). Schenck and colleagues reported for the first time that 38% of patients with RBD initially considered to be idiopathic developed Parkinson’s disease later in life; this is the commonest form of α-synucleinopathy (Schenck et al., 1996). A further follow-up showed that 65% developed parkinsonism (Schenck et al., 2003). Accordingly, Eisensehr and colleagues reported on a decreased striatal dopamine transporter binding in patients with ‘idiopathic’ RBD (Eisensehr et al., 2000, 2003), and Boeve and colleagues suggested that RBD may predict α-synucleinopathy (Boeve et al., 2001).

RBD is clinically characterized by the intermittent loss of normal skeletal muscle atonia during REM sleep, with the appearance of elaborate motor activity associated with dream mentation (Schenck et al., 1993; Mahowald and Schenk, 1994; Atlas Task Force of the American Sleep Disorders Association, 1997; Olson et al., 2000). Dramatic, often violent behaviours, such as punching or kicking, usually accompanied by vivid dreams, are the most common complaints of RBD patients. Many patients describe a prolonged prodrome, lasting for years, of sleep-related motor behaviour characterized by jerking of the extremities or sleep-talking and yelling. Most patients report that the character of their dreams has changed over the years, dreaming being more vivid, action-packed and violent (for review see Schenck and Mahowald, 2002). Animal studies have shown that brainstem areas, in particular the pontine inhibitory area and medial medulla, are the critical areas for developing RBD.

As stage 2 in the Braak classification affects the key areas for sleep control and eye movements (Hendricks et al., 1982; Schenkkel and Siegel, 1989; Shouse and Siegel, 1992; Sanford et al., 1994), RBD patients may represent patients with stage 2 preclinical α-synucleinopathy. If so, they should have passed stage 1 and therefore possess olfactory dysfunction, and in addition some of them may have reached a preclinical stage 3 with degeneration of the nigrostriatal dopaminergic pathway. To investigate this hypothesis, we selected patients with RBD according to clinically and neurophysiologically accepted consensus criteria and investigated their olfactory function with ‘Sniffin’ Sticks’ and their dopaminergic nigrostriatal system by imaging the presynaptic dopamine transporter, employing I-123-N-o-Fluoropropyl-2B-Carbamethoxy-3B-(4-Iodophenyl)-Nortropan FP-CIT as the ligand in single photon emission computed tomography (SPECT).

Methods

Patients and control subjects

Olfactory testing was performed in 30 patients with clinical or subclinical RBD according to standard criteria (Lapiére and Montplaisir, 1992; Mahowald and Schenk, 1994; Atlas Task Force of the American Sleep Disorders Association, 1997).

Polysomnography

For the diagnosis of RBD, polysomnography was performed. Polysomnography is considered to be essential in establishing the diagnosis of RBD by revealing loss of REM-related muscle atonia, abnormally elevated submental electromyographic (EMG) tone, or excessive phasic submental or limb twitching. In addition, diagnosis requires an abnormal behavioural episode during REM sleep, either during polysomnography (PSG) studies or according to a history of injurious or disruptive sleep behaviours (Atlas Task Force of the American Sleep Disorders Association, 1997; Mahowald and Schenk, 2000; Schenck and Mahowald, 2002). Besides excluding various differential diagnoses for clinical RBD, such as epileptic seizures and non-REM parasomnias, PSG allows the detection of patients with subclinical RBD, which is increasingly considered to be a preclinical form, only presenting with PSG findings typical of RBD (Schenck and Mahowald, 2002).

Polysomnography was performed in each patient according to a standard clinical protocol with recording of EEG (a minimum of C4–A1, C3–A2 and C4–O1 but often with additional derivations to rule out epilepsy), electro-oculography, ECG, oronasal airflow, thoraco-abdominal movements by impedance plethysmography, upper airway sound, and oxyhaemoglobin saturation. All patients had the surface EMG recorded from both mentalis and anterior tibialis muscles. Data were recorded digitally. Split-screen or time-synchronized video recordings were performed. Scoring of sleep stages followed standard methods (Rechtschaffen and Kales, 1968), but was done in a way that allowed identification of the persistence of EMG tone during epochs of otherwise unequivocal REM sleep.

EMG activity of both mentalis and tibialis muscles was scored separately as a percentage of the respective REM sleep episodes. Muscle activity during REM sleep was counted if its amplitude was 50% higher than that of the preceding baseline atonia. We counted activity lasting longer than 1 s or short-lasting activity of less than 0.5 s if more than 10 activities occurred during 10 s (according to a proposal of the task force for motor activity during sleep of the German Sleep Research Society). To allow comparison with previous studies, only EMG activity data of the mentalis muscle are presented. Subclinical or preclinical RBD was defined as PSG evidence of REM sleep without atonia and without violent...
behaviour according to Lapierre and Montplaisir (Lapierre and Montplaisir, 1992).

**Neurological assessment: UPDRS**

All patients underwent a thorough neurological investigation that included Parts II (Activities of Daily Living) and III (motor section) of the Unified Parkinson’s Disease Rating Scale (UPDRS; 31 items; ratings range from 0 to 4, 0 being normal and 4 reflecting maximal dysfunction) (Fahn et al., 1987).

**Control subjects**

Since olfactory function varies in the general population and declines with age (Doty et al., 1984; Deems et al., 1991), we considered it important to measure healthy control subjects in parallel, although normative data are available for the Sniffin’ Sticks (see below). Olfactory testing was therefore performed in 30 age- and sex-matched healthy control subjects. All control subjects were systematically interviewed about their sleep history. Screening polysomnography was not performed in control subjects. Possible subclinical RBD was therefore not excluded. This drawback was accepted as we assumed a rather low probability of undetected subclinical RBD in controls and consequently only marginal interference with our results.

Patients or control subjects with cognitive impairment were excluded. To assess cognitive impairment, the Mini-Mental State Examination (MMSE) was applied to both groups (Folstein et al., 1975). In addition, subjects with depression, asthma, allergic diseases or diseases which affect olfactory ability, e.g. chronic nasal infection or chronic alcoholism, were excluded. Subjects with an infection of the upper respiratory system at the time of investigation were also not allowed to participate. Since there is no clear relationship between smoking and olfactory function (Brämerson et al., 2004), smokers were not excluded from the study. Available information on the concomitant medication of patients and control subjects provided no evidence of their interference with olfactory function.

All patients and control subjects provided written informed consent. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethical committee.

**Olfactory testing**

Olfactory threshold, odour discrimination and odour identification were investigated in three separate subtests using standardized Sniffin’ Sticks (Hummel et al., 1997). The Sniffin’ Sticks are commercially available felt-tip pens. The tampon is filled with liquid odorants or odorants dissolved in polypropylene glycol. For odour presentation, the cap was removed for 3 s and the pen’s tip was placed 2 cm in front of the nostril(s). Patients were asked to sniff vigorously since increasing sniffing vigour is known to improve olfactory scores (Sobel et al., 2001). The interstimulus interval was at least 20 s to prevent olfactory desensitization. During the examination the patients were wearing blindfolds. We routinely investigated the left nostril, the right nostril, and both nostrils together, and generated a subscore for each item (left, right, bilateral) and a total mean score. The investigator only instructed the patient on the sniffing test and had no influence on the scoring of the patient. Therefore, no blinding was performed with respect to the group assignment of the probands.

**Odour thresholds**

The olfactory threshold subtest consists of 16 Sniffin’ Stick triplets with different concentrations of n-butanol. Three sticks were presented to the subject in a randomized order. Two contained only the solvent and the third the odorant at a particular dilution. The task of the subject was to identify the stick with the odorant. Presentation of the sticks occurred until the odorant had been successfully discriminated in two successive trials, which triggered a reversal of the staircase. Threshold was defined as the mean of at least four out of seven staircase reversal points. The sticks are numbered according to decreasing odour concentration. Thus, a low score indicates a high olfactory threshold. Normative values for controls are as follows: 18- to 50-year-old males and females, 9.4 ± 0.9 and 9.5 ± 0.9 respectively; 51- to 80-year-old males and females, 7.1 ± 1.7 and 7.7 ± 2.6 (Hummel et al., 1997).

**Odour discrimination**

In the odour discrimination subtest, 16 Sniffin’ Stick triplets were presented in a randomized order. Two pens contained the same odorant and the third a different odorant. The task was to identify the stick that had a different smell. The higher the score (highest possible score 16), the more the patient is able to discriminate different odours. Normative values for controls are as follows: 18- to 50-year-old males and females, 12.1 ± 1.4 and 12.6 ± 1.6 respectively; 51- to 80-year-old males and females, 10.6 ± 1.8 and 10.6 ± 1.0 (Hummel et al., 1997).

**Odour identification**

The third subtest consisted of 16 single sticks and assessed the ability to identify an odour. Using a multiple-choice task, identification of individual odorants was performed from a list of four descriptors. The sticks contained familiar fragrances, such as orange, leather, cinnamon, peppermint, banana, lemon, liquorice, turpentine, garlic, coffee, apple, clove, pineapple, rose, aniseed and fish. Again, the subjects’ scores ranged from 0 to 16 (the higher the score, the better the patient’s ability to identify an odour). Normative value for controls are as follows: 18- to 50-year-old males and females, 14.9 ± 1.2 and 14.5 ± 1.2 respectively; 51- to 80-year-old males and females, 14.2 ± 1.5 and 13.3 ± 1.5 (Hummel et al., 1997).

Based on an investigation of more than 1000 subjects (Kobal et al., 2000), olfactory function assessed with Sniffin’ Sticks can be categorized into five stages using the bilateral test scores of threshold (T), discrimination (D) and identification (I) testing, which gives a ‘TDI’ sum score. The stages are defined as follows: anosmia (TDI score ≤ 15), severe hyposmia (15 < TDI score ≤ 20), moderate hyposmia (20 < TDI score ≤ 25), mild hyposmia (25 < TDI score ≤ 30) and normosmia (TDI score > 30).

**I-123-FP-CIT SPECT studies**

Eleven out of 30 patients (six males and five females, with a mean age of 46.6 ± 12.6 years) agreed to participate in investigations with I-123-FP-CIT (Amersham, Amersham, UK). I-123-FP-CIT (185 MBq) was administered intravenously after blocking the thyroid gland with sodium perchlorate. All studies were performed with SPECT using a triple-headed gamma-camera (Multi-SPECT 3; Siemens). Images were acquired in 120 projections over a 360° arc using the step-and-shoot mode with an acquisition time of 50 s.
per projection. Transverse slices were created by filtered back-projection using a Butterworth filter with a cut-off frequency of 0.38 and an order of 8.0. The transverse slices were corrected for attenuation and were reangulated, yielding orbitomeatal parallel slices.

The images were evaluated semiquantitatively using a template containing symmetrical pairs of regions of interest adjusted to the nuclei caudati and the putamina by shifting, shrinking or rotation. The shape of the regions was determined empirically from the scintigrams of 10 normal subjects (age 61.1 ± 17.5 years) previously examined with I-123-FP-CIT within the context of phase III multicentre studies (Benamer et al., 2000, 2003). Caudate and putamen to occipital ratios were calculated, and reference values for each striatal region were computed by receiver operating characteristics analysis of the data of the 10 healthy volunteers, five patients with essential tremor and 46 patients with parkinsonian syndromes, as described previously. Thus, the lower limit of the ratio was estimated to be 2.60, indicating that the patient suffered from a parkinsonian syndrome. In all of these patients parkinsonian signs were previously undiagnosed. Patient 2 presented with mild bradykinesia and rigidity of the right arm (UPDRS II score = 1, UPDRS III score = 3). In patient 3 neurological examination revealed discrete hypomimia and generalized bradykinesia (UPDRS II = 1, UPDRS III score = 4). Patient 4 had mild hypomimia, rest tremor of the right hand, and rigidity in both arms (UPDRS II = 2, UPDRS III score = 4). In patient 5 examination revealed mild hypomimia, mild to moderate rest tremor in the right more than in the left arm, rigidity in the left arm, and decreased rapid alternating movements of the extremities (UPDRS II = 10, UPDRS III score = 21). Patient 18 had a history of clumsiness, showed mild hypomimia, rigidity in the left arm, and mild generalized bradykinesia (UPDRS II = 4, UPDRS III score = 5). None of the patients revealed cognitive impairment in the MMSE (mean 29.6 ± 0.49, range 29–30). Eleven RBD patients were smokers. The patients’ clinical characteristics are presented in Tables 1 and 2.

**Statistics**

Differences between RBD patients and control subjects were analysed by means of the Mann–Whitney U test. For correlation analysis, Spearman rank correlation coefficients were calculated. Results are reported as mean ± standard deviation.

**Results**

**Patient characteristics**

Thirty RBD patients (18 male, 12 female; mean age 48.2 ± 13.9 years, range 20–78 years) with a normal neurological examination and a normal MMSE score (mean 29.8 ± 0.50, range 28–30) were investigated. All control subjects (in 87% also their bed-partners) were systematically interviewed about their sleep history. Symptoms of clinical RBD or other sleep disorders could not be found. Nine control subjects were smokers.

**Olfactory testing**

The mean olfactory threshold score of our control subjects was 7.49 ± 2.14, the discrimination score 11.35 ± 3.16 and the identification score 13.78 ± 3.06. The scores of the control subjects were comparable with the published normative data (Hummel et al., 1997). In the control group, two of the 30 subjects (6.7%) reported an impaired sense of smell. The mean olfactory threshold score of RBD patients was 2.85 ± 2.05, the discrimination score 8.61 ± 3.73, and the identification score 11.31 ± 3.33. Compared with normative data, 96.7% of the RBD patients had a pathologically increased olfactory threshold, 63.3% an impaired odour discrimination score, and 63.3% a decreased identification score. Comparison of RBD patients and sex- and age-matched control subjects showed a significantly lower mean olfactory threshold score (P = 0.0001), lower mean discrimination score (P = 0.003) and lower mean identification score (P = 0.001) in RBD patients (Fig. 1). There were no side-to-side differences in both RBD patients (threshold score, left versus right,
Table 1 Clinical characteristics of patients

<table>
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<th>Concomitant sleep disorders</th>
<th>Duration of RBD (years)</th>
<th>UPDRS II</th>
<th>UPDRS III</th>
<th>EMG activity (% REM)</th>
<th>Threshold score</th>
<th>Discrimination score</th>
<th>Identification score</th>
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<th>TDI score</th>
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TDI score = threshold, discrimination and identification sum score of bilateral olfactory testing; UPDRS = Unified Parkinson’s Disease Rating Scale; OSAS = obstructive sleep apnoea syndrome; n.a. = not assessable. *mean score of left, right and bilateral olfactory testing, comparison with normative data; ↓ = decreased compared with normative value.
P = 1.000; discrimination score \(P = 0.350\); identification score \(P = 0.854\) and controls (threshold score, left versus right, \(P = 0.662\); discrimination score \(P = 0.407\); identification score \(P = 0.712\)). The TDI score was significantly lower \((P = 0.0001)\) in RBD patients \((23.0 \pm 7.9)\) compared with controls \((32.3 \pm 7.1)\). In RBD patients, mild hyposmia was present in 30% \((n = 9)\), moderate hyposmia in 23% \((n = 7)\), severe hyposmia in 20% \((n = 6)\) and anosmia in 13% \((n = 4)\). When analysing odour identification separately for the individual odorants, significant differences were observed for banana \((P = 0.004)\), turpentine \((P = 0.008)\), coffee \((P = 0.004)\), apple \((P = 0.001)\), pineapple \((P = 0.001)\) and fish \((P = 0.006)\) as being identified worst by the RBD patients. There was no correlation of the TDI (and single olfactory test scores) with the EMG activity of the mentalis muscle \((P = 0.765)\). Twenty RBD patients \((66.7\%)\) were unaware of an olfactory deficit before testing. The other patients \((33.3\%)\) were aware of an olfactory deficit, reported as an increased threshold of odour perception.

**I-123-FP-CIT SPECT studies**

Compared with the 10 normal subjects \((mean 61.1 \pm 17.5 years)\), the mean striatal-to-frontal ratios were slightly lower in the RBD group, with a mean age of 46.6 \pm 12.6 years (Fig. 2), but the differences were not significant. The RBD group consisted of nine patients with clinical RBD (idiopathic, \(n = 3\); symptomatic, \(n = 6\); associated with narcolepsy in four and obstructive sleep apnoea syndrome in two patients) and two patients with subclinical RBD. According to the reference value of 2.6 for the lower limit of a normal binding ratio, only two patients with idiopathic RBD had abnormal FP-CIT scans, with reduced dopamine transporter binding, at least in both putamina. Patient 6, who had suffered from idiopathic RBD for about 16 years, already presented clinically with pronounced parkinsonian motor signs (UPDRS III, 21 points). Patient 3 had been aware of RBD symptoms for 14 years. He presented with discrete hypomimia and generalized bradykinesia (UPDRS III score, 4 points). In both patients, olfactory testing revealed anosmia. In addition, the marked binding asymmetry in the putamina of patient 18, who had suffered from RBD (without narcolepsy) for 38 years, may support the clinical impression of early parkinsonism (UPDRS III score, 5 points). In the other cases with parkinsonian signs, SPECT either revealed dopamine transporter binding in the low but still normal range (patient 4) or was not performed (patient 2).

**Subgroup analysis**

Of the five patients with RBD and parkinsonian signs, all had clinical RBD not associated with narcolepsy. Of the
11 patients who underwent SPECT studies, nine suffered from clinical RBD and two patients had subclinical RBD (Table 2). Subgroup analysis between patients with clinical (n = 19) and subclinical (n = 11) RBD revealed no significant differences in regard to olfactory threshold (P = 0.767), odour discrimination (P = 0.899) and odour identification (P = 0.582). When comparing test scores with normative data, threshold scores were pathological in 94.7% of patients with clinical RBD and in 100% of patients with subclinical RBD. Discrimination scores were pathological in 63.2% of patients with clinical RBD and in 63.6% of patients with subclinical RBD, while identification scores were pathological in 52.6% of patients with clinical RBD and in 81.8% of patients with subclinical RBD.

Subgroup analysis between clinical and subclinical RBD patients without narcolepsy (n = 11; mean age 59.2 ± 9.7 years) and those with narcolepsy (n = 19; mean age 41.8 ± 12.1 years) also revealed no significant differences in olfactory threshold (P = 0.735), odour discrimination (P = 0.395) and odour identification (P = 0.232). When comparing test scores with normative data, threshold scores were pathological in 94.7% of RBD patients without narcolepsy and in 100% of RBD patients with narcolepsy. Discrimination scores were pathological in 63.2% of RBD patients without narcolepsy and in 63.6% of patients with narcolepsy, while identification scores were pathological in 63.2% of RBD patients without and in 63.6% with narcolepsy. Subgroup analysis between smokers and non-smokers revealed no significant differences in olfactory test scores in either group.

Discussion

**RBD, olfactory dysfunction and parkinsonism**

This study shows for the first time that both ‘idiopathic’ and symptomatic RBD patients possess a profound impairment of olfactory function. In 97% of the RBD patients the olfactory threshold was significantly increased, and in 63% the ability to discriminate and identify odours was additionally impaired. Only four RBD patients were classified as having normosmia according to the TDI scores, but all of them had already presented with an increased olfactory threshold. At the time of olfactory testing, definite Parkinson’s disease was newly diagnosed in one patient with ‘idiopathic’ RBD. In an additional four patients, usually with a long history of ‘idiopathic’ RBD, mild parkinsonian signs were diagnosed clinically. All of the five patients presented with hyposmia or anosmia. Four of these five patients agreed to undergo dopamine transporter imaging by SPECT. In the first ‘idiopathic’ RBD patient with clinically diagnosed Parkinson’s disease the FP-CIT SPECT was markedly reduced in the putamen, with the more extensive deficit on the side contralateral to the clinically more affected side of the body. In two further patients with clinical RBD not associated with narcolepsy, the clinical diagnosis of parkinsonism was supported by an abnormally reduced or asymmetrical FP-CIT signal in the putamina, while in a fourth patient the dopamine transporter SPECT value was in the low normal range. The remaining seven patients in whom RBD was associated either with narcolepsy (n = 6) or obstructive sleep apnoea syndrome (n = 1) revealed a normal image, although with values in the low normal range. The finding of a combination of RBD with...
olfactory dysfunction and in addition with an emerging parkinsonism in a minority (five patients with clinical RBD not associated with narcolepsy) of these RBD patients is in agreement with our working hypothesis, that the combination of impaired olfactory function and ‘idiopathic’ RBD may present the correlates of neuropathological stages 1 and 2 (Braak et al., 2003) of the α-synucleinopathy Parkinson’s disease.

RBD and dopamine transporter imaging

It has already been shown, that patients with ‘idiopathic’ RBD can present with significantly reduced striatal dopamine transporter binding as measured by IPT-SPECT (Eisensehr et al., 2000) and PET studies (Albin et al., 2000) when compared with controls but with greater binding than in patients with Parkinson’s disease. Patients with subclinical RBD also revealed significantly impaired striatal dopamine transporter function, which was less pronounced than in patients with clinical RBD (Eisensehr et al., 2003). Data from these imaging studies provided the first evidence that there is a continuum of striatal presynaptic dopaminergic dysfunction in patients with subclinical RBD, clinical RBD and Parkinson’s disease (Eisensehr et al., 2003). RBD patients with associated narcolepsy, however, were not investigated. In our study, patients with RBD had overall reduced I-123-FP-CIT uptake ratios compared with normal subjects. However, the difference was not significant.

In our 11 (out of 30) RBD patients who agreed to undergo FP-CIT SPECT, only two ‘idiopathic’ RBD patients with severe olfactory dysfunction (anosmia) had degeneration of presynaptic nigrostriatal neurons, as determined by reduced dopamine transporter binding in the I-123-FP-CIT SPECT. The relatively low percentage compared with previous studies is possibly due to the short duration of RBD symptoms in most patients (2–10 years). Accordingly, those patients who had reduced \( n = 2 \) or pathologically asymmetrical \( n = 1 \) mild hyposmia dopamine transporter binding had by far the longest duration of RBD symptoms (14, 16 and 38 years). In addition, the number of patients with nigrostriatal degeneration may have been higher if SPECT studies had been performed in all patients. Notably, none of our patients suffered from dementia.

Olfactory impairment in clinical and subclinical RBD and narcolepsy

The lack of significant differences in olfactory function between patients with clinical and subclinical RBD is interesting but not that surprising since the structures responsible for olfactory function are early affected in α-synucleinopathies.

In addition, no significant differences were assessed in olfactory function between RBD patients with and without an associated disorder, primarily narcolepsy, which is known to be linked to RBD [RBD is present in 18% of narcoleptic patients (Mayer et al., 2002)]. Narcoleptic patients are not known to have an increased risk of developing parkinsonism. We also did not find any parkinsonian signs in RBD patients with narcolepsy. In addition, the two RBD patients in whom nigrostriatal degeneration was proven by I-123-FP-CIT SPECT had ‘idiopathic’ RBD. These observations suggest that hyposmia points to an underlying α-synucleinopathy in ‘idiopathic’ RBD patients only, whereas the olfactory impairment in patients with RBD associated with narcolepsy remains of unclear pathophysiological and clinical relevance. However, narcolepsy is considered a neurodegenerative disease, with selective loss of hypothalamic hypocretin-containing neurons (Peyron et al., 2000; Thannickal et al., 2000). Although these cell bodies are restricted exclusively to the hypothalamus, they have widespread projections throughout the brain, including the substantia nigra, pontine and medullary regions, and the olfactory bulb (Peyron et al., 1998). Alteration of specific axonal projections might explain the association of olfactory dysfunction in narcoleptic RBD patients. In order to assess whether narcolepsy per se is associated with olfactory impairment, we are currently investigating olfactory function in narcoleptic patients with and without RBD.

Olfactory dysfunction in α-synucleinopathies (Parkinson’s disease, multiple system atrophy) and Progressive Supranuclear Palsy (PSP)

Several studies show that patients with Parkinson’s disease have impaired olfactory function (Ansari and Johnson, 1975; Ward et al., 1983; Quinn et al., 1987; Hawkes et al., 1997; Müller et al., 2002; Double et al., 2003). Olfactory dysfunction is present in 80% (Hawkes et al., 1997; Double et al., 2003) to 100% (Müller et al., 2002) of non-demented Parkinson’s disease patients. In Parkinson’s disease, olfactory impairment is reflected by a significantly increased olfactory threshold and less often by impaired odour identification and discrimination (Tissingh et al., 2001; Zucco et al., 1991). Upto 51% of Parkinson’s disease patients are anosmic (Hawkes et al., 1997; Müller et al., 2002), 35% have severe hyposmia and 14% moderate hyposmia (Müller et al., 2002). The olfactory deficit in Parkinson’s disease is bilateral and unrelated to the side of Parkinson’s disease-related motor symptoms, occurs very early in the course of the disease, and is unrelated to the severity or the duration of the disease and the use of antiparkinsonian drugs (Ward et al., 1983; Quinn et al., 1987; Doty et al., 1988; Doty et al., 1992b; Hawkes and Shepard, 1998; Tissingh et al., 2001; Müller et al., 2002; Double et al., 2003). In contrast to Parkinson’s disease, decreased ability to smell is absent in PSP (Bonuccelli et al., 1991; Doty et al., 1993; Wenning et al., 1995) and drug-induced MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) parkinsonism (Doty et al., 1992a) or only present to a minor degree in multiple system atrophy (MSA) (Müller et al., 2002;
Wenning et al., 1995). Thus normal or mildly impaired olfactory function in a patient with parkinsonism is suggestive of atypical parkinsonism, whereas moderately or markedly pronounced olfactory loss is suggestive of Parkinson’s disease. It has also been shown that olfactory dysfunction differentiates tremulous Parkinson’s disease from benign essential tremor (Hawkes, 2003; Hawkes et al., 2004). Recent clinical studies suggest that impaired olfactory function indeed may precede the development of motor symptoms (Daum et al., 2000; Double et al., 2003; Hawkes, 2003). Subjectively, 24% of Parkinson’s disease patients indicated a decrease in olfactory function which preceded diagnosis of Parkinson’s disease (Müller et al., 2002). Another study investigated preclinical signs of Parkinson’s disease in relatives of Parkinson’s disease patients. It demonstrated decreased striatal β-CTI dopamine transporter binding typical of parkinsonism in four out of 25 hyposmic relatives and in none of the normosmic relatives (Berendse et al., 2001). The fact that 41% of at-risk individuals of familial autosomal dominant parkinsonism present with olfactory dysfunction also suggests that olfactory deficits precede the onset of motor signs (Markopoulou et al., 1997).

**RBD in α-synucleinopathies (Parkinson’s disease, multiple system atrophy, dementia of the Lewy body type) and PSP**

RBD is strongly associated with α-synucleinopathies, including Parkinson’s disease (Comella et al., 1998; Arnulf et al., 2000; Olson et al., 2000; Gagnon et al., 2002), MSA (Plazzi et al., 1997; Olson et al., 2000) and dementia of the Lewy body type (DLB) (Uchiyama et al., 1995; Boeve et al., 1998; Ferman et al., 1999) and may be a prodromal feature. Schenck and colleagues have shown for the first time in a longitudinal study that 38% of older patients initially considered to have idiopathic RBD developed a parkinsonian disorder, presumably Parkinson’s disease, on average 12.7 (10–29) years after the onset of RBD symptoms (Schenck et al., 1996). Further long-term follow-up of these ‘idiopathic’ RBD patients 7 years later showed that 65.4% developed parkinsonism with or without dementia (Schenck et al., 2003). Subsequent studies have shown that patients with RBD present with Parkinson’s disease in 27%, MSA in 15% and dementia in 14% (Olson et al., 2000) to 22% (Schenck et al., 1993), most often (92%) DLB (Boeve et al., 1998). On the contrary, studies of Parkinson’s disease patients reveal prevalence of RBD in 15% (Comella et al., 1998) to 33% (Gagnon et al., 2002) and of subclinical RBD in 58% (Gagnon et al., 2002). In MSA patients RBD is found in 90% (Plazzi et al., 1997). In these patient groups RBD symptoms mostly preceded parkinsonian symptoms by many years. A study in 398 patients with neurodegenerative disorders has shown that RBD overall occurs with much greater frequency in α-synucleinopathies (Parkinson’s disease, MSA, DLB) compared with other degenerative parkinsonian or dementing disorders (PSP, corticobasal degeneration, Alzheimer’s disease, Pick’s disease) (Boeve et al., 2001). In this large study, the positive predictive value of the presence of RBD indicating an α-synucleinopathy has been estimated to range between 92 and 100%. Thus, if RBD is present in a patient with a parkinsonian or dementing disorder, there is a high likelihood that an α-synucleinopathy is present (Boeve et al., 2001).

**Neuropathological findings: RBD, olfactory function and α-synucleinopathies**

The high clinical association of parkinsonism and RBD strongly suggests that there might be an anatomical and physiological link between these two disorders (Pompeiano, 1976; Sakai, 1980, 1985; Sakai et al., 1981). Several animal studies have shown that lesions in the pontine inhibitory area (Jouvet and Delorme, 1965; Hendricks et al., 1982; Shouse and Siegel, 1992; Sanford et al., 1994) and inhibitory systems in the medulla (Schenkel and Siegel, 1989) result in REM sleep without atonia and are critical areas for RBD. The ventral midbrain is considered to be the key area for the motor symptoms of parkinsonism (Schneider et al., 1986; German et al., 1988) and, depending on the type of the parkinsonian syndrome (typical or atypical), various areas outside the substantia nigra are known to be involved in the degenerative process (Braak et al., 1996, 2003; Plazzi et al., 1997; Del Tredici et al., 2002). In MSA, by definition multiple CNS areas are involved in the degenerative process, and in particular pontine lesions in MSA have been shown in neuropathological and histochemical studies (Plazzi et al., 1997), making the clinical overlap of MSA and RBD rather plausible.

In the brainstem of Parkinson’s disease patients, Lewy bodies, which contain an aggregated form of the protein α-synuclein (Trojanowski and Lee, 1998) and are considered to be the hallmark of Parkinson’s disease, have been shown not only in the substantia nigra but also, among other areas, in the dopaminergic retrorubral nucleus, ventral tegmental area, dorsal raphe nucleus, the noradrenergic locus coeruleus and subcoeruleus and parabrachial nucleus, the serotonergic median raphe and other systems, such as the pedunculopontine nucleus, pontine inhibitory area, nucleus gigantocellularis and magnocellularis (Ohama and Ikuta, 1976; Forno et al., 1986; Halliday et al., 1990; Wakabayashi et al., 1997; Braak et al., 1999, 2000, 2003). In exactly the same areas, Lewy bodies have been found in ‘idiopathic’ RBD patients (Uchiyama et al., 1995; Turner et al., 2000). Lai and Siegel provided further evidence for an anatomical and physiological link between parkinsonism and RBD via the ventral midbrain. They recently showed in the cat that lesions in the ventral mesopontine junction (VMPJ) elicit RBD-like behaviour and that lesions in the rostroventral midbrain (RVDM) induced Parkinson’s disease-like sleep patterns (Lai and Siegel, 2003). These two areas are anatomically adjacent to each other and have a certain overlap. Lai and Siegel...
hypothesized that neuronal degeneration can start in either part of the ventral brainstem, the VMPI or RVMD, resulting in the respective disease first (Lai and Siegel, 2003).

Derived from post-mortem specimens of individuals with presumed incidental (presymptomatic post-mortem diagnosis) and symptomatic Parkinson’s disease, Braak and colleagues (Braak et al., 2003) proposed the following staging scheme for Parkinson’s disease (stage 1 to stage 6) based on the topographical extent of the lesion. Stage 1 represents the most mildly affected cases, which display lesions frequently in the anterior olfactory nucleus or the olfactory bulb and—with respect to the medulla oblongata—only in the dorsal motor nucleus of the glossopharyngeal and vagal nerves or the intermediate reticular zone. Stage 1–2 represents patients who are still mildly affected but in whom the lesions consistently remain confined to the medulla oblongata (caudal raphe nuclei, gigantocellular reticular nuclei) and pontine tegmentum (coeruleus-subcoeruleus complex). The overlap of the post-mortem findings in stage 2 of Parkinson’s disease and RBD patients is striking. Only in stage 3, i.e. in moderately affected cases, are additional midbrain lesions (in particular in the pars compacta of the substantia nigra) found (Braak et al., 2003).

**Olfactory dysfunction combined with ‘idiopathic’ RBD may represent an early stage of an α-synucleinopathy**

The appearance of smell deficits in early (Müller et al., 2002) and preclinical Parkinson’s disease (Markopoulou et al., 1997; Berendse et al., 2001) and the fact that RBD often precedes Parkinson’s disease, MSA or DLB at the clinical level are well known. This study shows the combination of all three features in the same patient for the first time. In our rather heterogeneous group of RBD patients, almost all patients had impaired olfactory function compared with normative data and with age- and sex-matched controls, and a minority with ‘idiopathic’ RBD clinically revealed parkinsonian signs. The latter features were supported by decreased dopamine transporter ligand binding in SPECT. The staging of Braak et al. (Braak et al., 2003) provides a neuropathological explanation for the clinical features ‘olfactory dysfunction’ and ‘RBD’, because in stages 1 and 2 of the neurodegenerative process structures in the olfactory system and in the medulla/pons considered critical for RBD are affected earlier than the substantia nigra pars compacta. Accordingly, those of our patients who are still mildly affected but in whom lesions consistently remain confined to the medulla oblongata (caudal raphe nuclei, gigantocellular reticular nuclei) and pontine tegmentum (coeruleus-subcoeruleus complex). The overlap of the post-mortem findings in stage 2 of Parkinson’s disease and RBD patients is striking. Only in stage 3, i.e. in moderately affected cases, are additional midbrain lesions (in particular in the pars compacta of the substantia nigra) found (Braak et al., 2003).

**Conclusion**

Our data show for the first time that RBD patients can present with profound impairment of olfactory function. In addition, the combination of the clinical features RBD and olfactory dysfunction with the motor signs of Parkinson’s disease was demonstrated in the same individuals. These clinical findings, together with the proposed neuropathological staging for Parkinson’s disease by Braak, allow us to speculate that ‘idiopathic’ RBD patients with olfactory dysfunction may represent patients with clinical symptoms of stage 2 of the α-synucleinopathy Parkinson’s disease. The pathophysiology of hyposmia in RBD patients with associated narcolepsy requires further research.

**Acknowledgements**

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