Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD

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ABSTRACT

Objective: The aim of the present study was to determine the predictive value of olfactory dysfunction for the early development of a synuclein-mediated neurodegenerative disease in subjects with idiopathic REM sleep behavior disorder (iRBD) over an observational period of 5 years.

Methods: Thirty-four patients with polysomnography-confirmed iRBD underwent olfactory testing using the entire Sniffin' Sticks test assessing odor identification, odor discrimination, and olfactory threshold. Patients with iRBD were prospectively followed up over a period of 4.9 ± 0.3 years (mean ± SD). The diagnosis of neurodegenerative diseases was based on current clinical diagnostic criteria.

Results: After 2.4 ± 1.7 years (mean ± SD), 9 patients (26.5%) with iRBD developed a Lewy body disease (6 Parkinson disease and 3 dementia with Lewy bodies). The entire Sniffin' Sticks test and the identification subtest had the same overall diagnostic accuracy of 82.4% (95% confidence interval: 66.1%–92.0%) in predicting conversion. The relative risk for a Lewy body disease in the lowest tertile of olfactory function was 7.3 (95% confidence interval: 1.8–29.6) compared with the top 2 tertiles.

Conclusions: Assessment of olfactory function, particularly odor identification, may help to predict the development of a Lewy body disease in patients with iRBD over a relatively short time period and thus to identify patients suitable for future disease modification trials. ***Neurology*®** **2015;84:654–658**

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GLOSSARY

AUC = area under the curve; **DAT-SPECT** = dopamine transporter–SPECT; **DLB** = dementia with Lewy bodies; **HC** = healthy control; **iRBD** = idiopathic REM sleep behavior disorder; **PD** = Parkinson disease; **ROC** = receiver operating characteristic; **UPDRS-III** = Unified Parkinson's Disease Rating Scale, Part III.

Idiopathic REM sleep behavior disorder (iRBD) is increasingly recognized as a harbinger of neurodegenerative diseases because the majority of patients with iRBD will develop such a disorder, most frequently Parkinson disease (PD) and dementia with Lewy bodies (DLB).[1,2] However, median intervals to conversion range between 12 and 14 years[1,2] and markers for early conversion are needed. iRBD is also associated with nonmotor symptoms frequently observed in patients with PD, in particular hyposmia.[3] Previous studies showed that reduced smell identification displays an increased risk to develop PD among community-dwelling elderly[4] and even patients with iRBD.[5] These observations broadly fit the postulated stage-wise progression of PD pathology where synuclein pathology in the olfactory system and lower brainstem would both represent sites of initiation of disease in the brain.[6]

We hypothesized that patients with iRBD that will go on to clinically develop a Lewy body disease within a period of less than 5 years would represent Braak stage 1/2[6] and would thus be likely to also have olfactory dysfunction. The aim of our study was to accurately describe all dimensions of smell function (i.e., odor identification, odor discrimination, and olfactory

Supplemental data at Neurology.org

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Table 1 Baseline characteristics of subjects

	Healthy controls (n = 41)	iRBD (n = 34)	PD (n = 49)	Overall *p*
Age at baseline,[a] y	66.8 ± 3.8	67.6 ± 5.4	66.4 ± 8.9	0.71
Sex,[b] M/F	23/18, $p = 0.018$	29/5	32/17, $p = 0.084$	0.024
Disease duration since diagnosis,[a] y	NA	2.4 ± 3.4	6.1 ± 4.2	NA
UPDRS-III[c] (range 0–108; 108 = greater severity)	1.5 (0.0–3.6), $p = 0.99$	2.4 (0.0–4.8)	25.7 (23.8–27.6), $p < 0.001$	<0.001
Odor identification[c] (range 0–16; 0 = greater severity)	12.9 (11.9–14.0), $p < 0.001$	9.1 (7.9–10.2)	6.5 (5.5–7.4), $p = 0.003$	<0.001
Odor discrimination[c] (range 0–16; 0 = greater severity)	12.1 (11.2–13.1), $p < 0.001$	9.1 (8.0–10.1)	7.6 (6.7–8.5), $p = 0.12$	<0.001
Olfactory threshold[c] (range 0–16; 0 = greater severity)	6.8 (6.1–7.6), $p = 0.001$	4.7 (3.8–5.5)	3.4 (2.7–4.1), $p = 0.073$	<0.001
Sniffin' Sticks sum[c] (range 0–48; 0 = greater severity)	31.9 (29.6–34.2), $p < 0.001$	22.8 (20.2–25.4)	17.5 (15.4–19.6), $p = 0.007$	<0.001

Abbreviations: iRBD = idiopathic REM sleep behavior disorder; NA = not applicable; PD = Parkinson disease; UPDRS-III = motor section of Unified Parkinson's Disease Rating Scale.
The *p* values in the last column report significances of overall differences between groups. The *p* values in the second column (controls) and fourth column (PD) refer to comparison of patients with iRBD to healthy controls and to patients with PD and are post hoc Bonferroni-corrected.
[a] Results represent means ± SD; *p* values calculated using analysis of variance.
[b] The *p* value calculated using χ^2 test.
[c] Results represent means (95% confidence intervals) adjusted for age and sex; *p* values calculated using analysis of covariance with age as factor and sex as covariate.

threshold) in patients with iRBD compared to patients with PD and healthy controls (HCs) and to determine the predictive value of olfactory dysfunction for conversion to PD or other neurodegenerative diseases in subjects with iRBD over an observational period of 5 years.

METHODS

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committees. All patients gave written informed consent according to the Declaration of Helsinki.

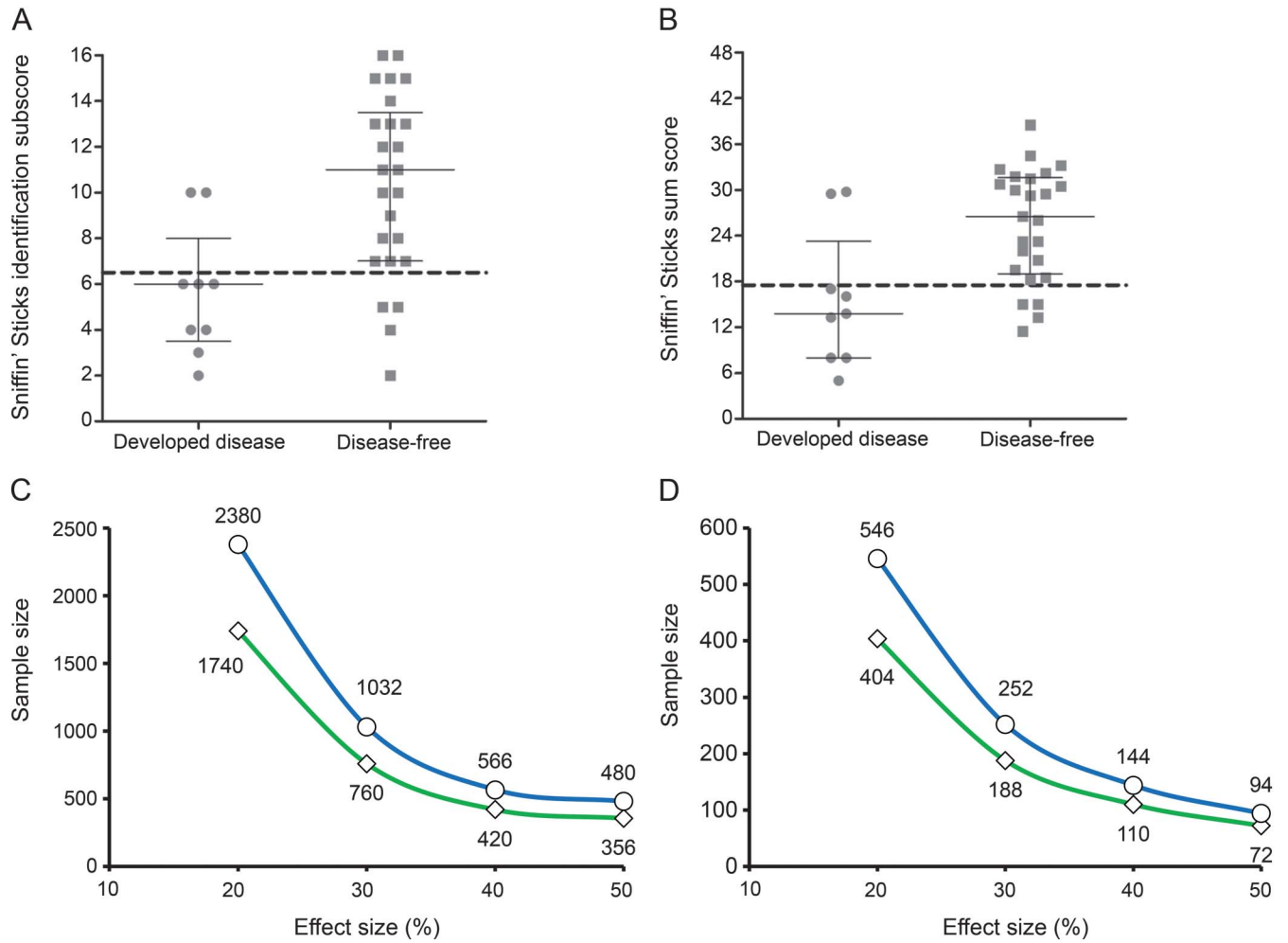
Subjects and procedures. Thirty-four patients with polysomnography-confirmed iRBD were consecutively recruited from referrals or follow-up visits at the Sleep Disorders Clinics at the Department of Neurology at Innsbruck Medical University, Austria (n = 24), and the Hospital Clinic de Barcelona, Spain (n = 10), as previously described.[7] At baseline, none of the patients with iRBD fulfilled current clinical diagnostic criteria for dementia or parkinsonian disorders.[e1–e5] Baseline assessments were performed at the Innsbruck site in 2008/2009 in all participants, who underwent a standardized neurologic evaluation including the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS-III) and olfactory testing with the entire Sniffin' Sticks test (Burghart Medizintechnik, Germany)[e6] assessing odor identification, odor discrimination, and olfactory threshold. Patients with iRBD underwent regular follow-up visits at their sleep disorder clinics over a period of 4.9 ± 0.3 years (mean ± SD). Diagnosis of PD and other neurodegenerative diseases were made according to the UK Brain Bank and current clinical diagnostic criteria.[e1–e5] Subjects with iRBD meeting such criteria underwent dopamine transporter–SPECT (DAT-SPECT) to assess nigrostriatal function as part of our routine clinical procedure. The Sniffin' Sticks results of patients with iRBD at

Table 2 Baseline evaluations in patients with iRBD who developed disease or remained disease-free

	Disease-free (n = 25)	Developed disease (n = 9)	*p*	AUC values (95% CI)
Age at baseline,[a] y	67.4 ± 4.9	68.2 ± 6.7	0.65	
Sex,[b] M/F	21/4	8/1	0.72	
RBD duration since diagnosis,[a] y	2.1 ± 3.2	3.1 ± 3.7	0.55	
UPDRS-III[c] (range 0–108; 108 = greater severity)	2.3 (1.1–3.4)	4.2 (2.7–5.8)	0.032	0.75 (0.55–0.95)
Odor identification[c] (range 0–16; 0 = greater severity)	10.2 (8.8–11.6)	5.9 (3.5–8.3)	0.004	0.83 (0.69–0.97)
Odor discrimination[c] (range 0–16; 0 = greater severity)	9.9 (8.7–11.1)	6.6 (4.6–8.3)	0.007	0.76 (0.56–0.97)
Olfactory threshold[c] (range 0–16; 0 = greater severity)	5.1 (4.0–6.2)	3.7 (1.9–5.6)	0.21	0.64 (0.39–0.89)
Sniffin' Sticks sum[c] (range 0–48; 0 = greater severity)	25.2 (22.3–28.2)	16.3 (11.3–21.2)	0.004	0.82 (0.65–0.99)

Abbreviations: AUC = area under the curve; CI = confidence interval; iRBD = idiopathic REM sleep behavior disorder; RBD = REM sleep behavior disorder; UPDRS-III = motor section of Unified Parkinson's Disease Rating Scale.
The AUC values give an estimate of the diagnostic accuracy of the motor examination and olfactory testing for predicting the transition to a Lewy body disease.
[a] Results represent means ± SD; *p* values calculated with an unpaired *t* test.
[b] The *p* value calculated with a χ^2 test.
[c] Results represent means (95% CIs) adjusted for age and sex; *p* values calculated with an analysis of covariance with age as factor and sex as covariate.

Figure Diagnostic accuracy of olfactory assessment and its value for potential interventional trials in patients with iRBD



Scatterplots of the identification subscore (A) and the Sniffin' Sticks total score (B) in subjects with iRBD developing a Lewy body disease and in those remaining disease-free. Single values are given with the respective group median and the 25th and 75th percentiles. The dotted lines represent the receiver operating characteristic–based cutoff values (<7/16 for the identification subscore [A] and <18/48 for the Sniffin' Sticks sum score [B]) and correspond also to the cutoff between the lowest and the middle tertile of olfactory function in the entire iRBD group. At these cutoffs, both tests yielded the same diagnostic accuracy of 82.4% (95% CI: 66.1%–92.0%) with a sensitivity of 77.8% (95% CI: 44.3%–94.7%), a specificity of 84.0% (95% CI: 64.7%–94.2%), a positive predicate value of 63.6% (95% CI: 35.2%–85.0%), and a negative predictive value of 91.3% (95% CI: 72.0%–98.8%) in predicting the development of a Lewy body disease in patients with iRBD. The relative risk for a Lewy body disease in the lowest tertile of olfactory function was 7.3 (95% CI: 1.8–29.6) compared with the top 2 tertiles. Required sample sizes for randomized, placebo-controlled, 5-year follow-up interventional trials with effect sizes ranging from 20% to 50% were estimated based on the conversion rate to a Lewy body disease obtained in the total iRBD cohort (C) vs the iRBD subcohort with olfactory dysfunction (D). The green lines represent calculations at 80%, the blue lines at 90% power. For example, a total of 760 patients with iRBD vs 188 patients with iRBD and olfactory dysfunction would be required to have an 80% chance to detect a 30% decrease in the primary outcome measure of conversion to a Lewy body disease. CI = confidence interval; iRBD = idiopathic REM sleep behavior disorder.

baseline were additionally compared to 41 age-matched HCs from a population-based sample[8] without history suggestive of REM sleep behavior disorder and to 49 consecutive age-matched patients with PD. None of the participants had potential causes of symptomatic olfactory loss (e.g., head trauma, nasal fracture or surgery, recent or chronic upper airway infection).

Statistics. Categorical variables were compared using the χ^2 test. For comparison of quantitative dependent variables across groups, appropriate parametric tests were used (see table legends). Adjustments for age, sex, and post hoc testing (Bonferroni) were applied if appropriate. Residual checks for nonnormality and outliers were performed using Q-Q plots and boxplots. Receiver operating characteristic (ROC) curve analyses were used to estimate the potential of baseline olfactory performance to predict conversion into a neurodegenerative disorder reported as area under the curve (AUC) and to determine cutoff values. The performance of the best predictors (AUC > 0.8) is given by conventional measures of diagnostic accuracy and the relative risk. Sample size calculations for interventional trials were performed accepting a 1-sided type I error of 5% for 80% and 90% power. SPSS 22.0 (IBM Corp., Armonk, NY) was used for all statistical analyses.

RESULTS Characteristics of the 3 groups are depicted in table 1. Olfactory scores of patients with iRBD were similar between the 2 centers (table e-1 on the *Neurology*® Web site at Neurology.org) and were significantly lower compared to HCs and

significantly higher compared to patients with PD. Over the follow-up period, 9 patients (26.5%) with iRBD developed a Lewy body disease (6 PD and 3 DLB; table e-2) after an interval of 2.4 ± 1.7 years (mean ± SD) from baseline and 5.5 ± 4.7 years from iRBD diagnosis. All but one of them underwent DAT-SPECT. There was nigrostriatal dysfunction in 7, and one subject with a clinical diagnosis of DLB had a normal DAT-SPECT result. Compared with patients who remained disease-free, patients who went on to develop disease had significantly lower olfactory scores at baseline (table 2). Baseline olfactory function of patients developing disease was in the PD range with no differences in any of the olfactory domains between these 2 groups (all p values >0.3).

ROC curve analysis revealed that baseline olfactory testing was predictive for the development of a Lewy body disease (table 2). The best predictors (AUC $>$ 0.8) were the entire Sniffin' Sticks test and the identification subtest. The figure shows respective diagnostic accuracies (A and B) and estimated sample sizes for interventional trials with conversion as primary endpoint (C and D). Pretesting for olfaction reduces illustrated sample sizes by 73.8% to 80.4%.

DISCUSSION In this prospective study of patients with polysomnography-confirmed iRBD, olfactory dysfunction was associated with a 7.3-fold risk of developing a Lewy body disease within 5 years of follow-up. Although iRBD in itself is a major risk factor for the development of a Lewy body disease with highest specificity and predictive value among all currently identified risk markers, median time to conversion ranges between 12 and 14 years.[1,2] This limits the feasibility of designing future preventive trials in such cohorts, and markers for those at risk of early conversion are needed. In one study, the combination of abnormalities in transcranial sonography and DAT-SPECT identified those subjects who developed the classic features of PD and DLB after 2.5 years with a sensitivity of 100% and a specificity of 55%.[9] However, DAT-SPECT is time-consuming, expensive, and involves exposure to a radioactive substance. In this study, baseline olfactory performance of subjects with iRBD who converted to a synucleinopathy in less than 5 years was already in the range of performance of patients with PD, whereas nonconverters had significantly better smell function. This is in line with a study showing a 5-year cumulative disease-free survival of 35% in those subjects with iRBD with impaired odor identification, compared to 86% of those with normal olfaction.[5] However, because of the variable and short follow-up duration, diagnostic accuracy was not formally assessed.[5] In our study, diagnostic accuracy for future conversion was 82.4% within 5 years as assessed by the entire Sniffin' Sticks test and the identification subtest, such that olfactory testing, particularly odor identification, may have the potential to identify at an individual level those subjects with iRBD who are likely to convert to a Lewy body disease over a relatively short time period. In accordance with a previous study,[10] in our iRBD cohort, higher baseline UPDRS-III scores were associated with conversion. However, the AUC value was lower compared with the values achieved with olfactory testing.

Our study has limitations. Although 5-year follow-up was complete, the primary outcome was based on clinical diagnoses without pathologic confirmation. Furthermore, we did not serially assess olfactory function in patients with iRBD. However, a recent study suggests that olfactory deficits in iRBD do not worsen over a 4-year period[3] and olfactory testing may therefore not serve as an outcome measure in future disease modification trials.

Recently, a task force of the International Parkinson and Movement Disorder Society proposed a framework for a redefinition of PD in which probable prodromal PD refers to a high likelihood for the disease (e.g., >80%, sufficiently certain for neuroprotective trials).[11] Our results suggest that the combination of iRBD status and olfactory dysfunction might meet such criteria, defining a potential cohort for future disease modification trials.

AUTHOR CONTRIBUTIONS

P.M. and K.S.: study concept, recruitment of subjects and acquisition of data, statistical analysis and interpretation of data, drafting of the manuscript, and manuscript revision. A.I., B.H., B.F., E.T., J.S., M.S., C.S., and W.P.: study concept, recruitment of subjects and acquisition of data, interpretation of data, and manuscript revision. G.G.: statistical analysis, interpretation of data, and manuscript revision. C.M., T.M., V.G., and F.B.: recruitment of subjects, acquisition of data, and manuscript revision.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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Olfactory dysfunction predicts early transition to a Lewy body disease in idiopathic RBD (see p. 654)

This podcast begins and closes with Dr. Robert Gross, Editor-in-Chief, briefly discussing highlighted articles from the February 17, 2015, issue of *Neurology*. In the second segment, Dr. Binit Shah talks with Dr. Werner Poewe about his paper on olfactory dysfunction predicting early transition to Lewy body disease in idiopathic RBD. Dr. Adam Numis then reads the e-Pearl of the week about fragile X tremor/ataxia syndrome. In the next part of the podcast, Dr. Stacey Clardy focuses her interview with Dr. Josep Dalmau on other recently described antibodies associated with autoimmune encephalitis.

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