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Odor Identification Deficits are Associated with Increased Risk of Neuropsychiatric Complications in Patients with Parkinson's Disease

Randolph Stephenson, MD¹, David Houghton, MD, MPH², Sri Sundararajan, BA¹, Richard L. Doty, PhD³, Matthew Stern, MD¹, Sharon X. Xie, PhD^{4,5}, and Andrew Siderowf, MD, MSCE^{1,5,*}

¹ Department of Neurology University of Pennsylvania, School of Medicine, Philadelphia, Pennsylvania, USA

² Department of Neurology, University of Louisville School of Medicine, Louisville, Kentucky, USA

³ Smell and Taste Center and Department of Otorhinolaryngology: Head and Neck Surgery, University of Pennsylvania, Philadelphia, Pennsylvania, USA

⁴ Department of Biostatistics and Epidemiology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

⁵ Morris K. Udall Center of Excellence in Parkinson's Disease Research, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania, USA

Abstract

Olfactory deficits appear early in the course of Parkinson's disease (PD) but their prognostic significance is not known. The goal of this study was to determine whether the severity of olfactory impairment is associated with subsequent risk of developing complications of PD. One hundred patients with PD self-administered the University of Pennsylvania Smell Identification Test (UPSIT). Testing was done, on average, 3.6 years from the time of initial diagnosis. The incidence of neuropsychiatric features of PD, including cognitive decline and visual hallucinations, was ascertained through chart review after an average of 6.8 years of follow-up. Incidence of motor outcomes including falls and dyskinesias was also obtained. There was a significant trend for increased risk of neuropsychiatric complications across declining quartiles of olfactory test scores. In addition, subjects in the lowest quartile of olfactory performance had a significantly higher adjusted risk of hallucinations (HR = 4.70, 95% CI 1.64, 13.42) and cognitive decline (HR = 3.10, 95% CI 1.05, 9.21) than those in the reference quartile. There was no

*Correspondence to: Dr. Andrew Siderowf, Department of Neurology, 330 South 9th Street, Philadelphia, PA 19107, siderowa@pahosp.com.

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association between olfactory dysfunction and dyskinesias, and a very modest association with risk of falls. These findings suggest that severity of olfactory impairment early in the disease course may be a useful marker for the risk of neuropsychiatric complications of PD.

Keywords

Parkinson's disease; olfaction; dementia; visual hallucinations

Olfactory impairment is common in patients with Parkinson's disease (PD). It occurs early in the disease course, is unrelated to treatment, and changes little once motor features are evident.¹ Recent pathological studies suggest that changes in the olfactory system may be among the earliest abnormalities that occur in PD.^{2,3} These findings support the hypothesis that pathological changes spread from the lower brainstem and olfactory pathways to the midbrain and the cortex.⁴

The degree of olfactory impairment in early PD is highly variable.¹ Some cross-sectional studies have shown a modest relationship between motor features of PD and olfactory performance.^{5–7} Results of studies of the relationship between olfactory performance and physiologic measures such as dopamine transporter (DAT) imaging have been inconsistent, with several studies in recently diagnosed patients showing an association between olfactory performance and imaging.^{8,9} It remains unknown whether the variability in olfactory performance has prognostic significance for the later course of the disease. The means for providing more accurate prognostic information in PD is needed. In particular, greater ability to predict disabling nonmotor features of PD, such as cognitive impairment and hallucinations, would be highly desirable.

The purpose of this study was to determine if an association exists between performance on an odor identification task and subsequent risk of reaching milestones of clinically meaningful disease progression, particularly nonmotor complications including cognitive impairment and visual hallucinations.

METHODS

Design

This was a longitudinal cohort study. Study subjects initially participated in two cross-sectional studies of olfactory performance, one conducted between 1988 and 19925 and the other in 2000.⁸ In these studies, subjects were evaluated with the University of Pennsylvania Smell Identification Test (UPSIT), a test described in detail below. For the longitudinal assessment, patient charts were abstracted to identify the first incidence of the motor and nonmotor outcomes of interest. All procedures were approved by the University of Pennsylvania Institutional Review Board.

Subjects

Subjects were PD patients treated at the University of Pennsylvania's Parkinson's Disease and Movement Disorders Center (PDMDC) from 1984 to the present. The diagnosis of idiopathic PD was made in all cases by a movement disorders specialist. Subjects had to be at least 40 years of age or older at the time of diagnosis. Patients who met the diagnostic criteria for any other parkinsonian syndrome including diffuse Lewy body disease, progressive supranuclear palsy, cortico-basal degeneration, or multiple system atrophy at any point in their disease course were excluded. To be included, a patient had to be followed for at least 1 year at the PDMDC. Patients who had a baseline score of 1 or higher on the "Thought Disorder" or "Intellectual Impairment" item in part I of the Unified Parkinson

Disease Rating Scale (UPDRS)10 at the time of smell testing were excluded from the current analysis.

Evaluations

Demographic features including age, gender, date of symptom onset, and date of diagnosis were all recorded. Motor performance was rated using the UPDRS and Hoehn and Yahr (HY) scale.¹¹ Odor identification was assessed using the University of Pennsylvania Smell Identification Test (UPSIT).¹² The UPSIT is a standardized forced-choice test comprised of four booklets containing 10 odorants apiece, 1 odorant per page. The stimuli are embedded in “scratch and sniff” microcapsules fixed and positioned on strips at the bottom of each page. A multiple-choice question with four response alternatives for each item is located above each odorant strip. The specific stimuli, basis for their selection, and reliability and sensitivity of this test have been described in detail previously.^{12,13} Scores are calculated as the number of items correctly identified. Respondents can be placed into percentiles based on gender- and age-standardized norms for the number of correctly identified odorants. The UPSITs are packaged in envelopes and come with easy-to-follow instructions. A subset of subjects in this study (n = 46) also completed the picture identification test (PIT), a test analogous to the UPSIT that assesses picture recognition of the stimulus items contained in the UPSIT. The purpose of the PIT was to test whether nonolfactory deficits, such as impaired cognition, account for variations in UPSIT performance. As with the UPSIT, the maximum score on the PIT is 40.

Charts were abstracted to determine the onset of each clinical complication including cognitive problems, visual hallucinations, dyskinesias, and falls. A subject was deemed to have reached an endpoint if he or she satisfied one of three requirements: scored a 2 or higher on that item on the UPDRS, scored a 1 or 1.5 and had corroborating documentation in the chart for the corresponding visit, or had a clear description of that particular endpoint in the chart. Chart review was performed by a trained neurologist (R.S.) who was blinded to the subject’s baseline olfactory performance.

Analysis

Descriptive statistics were calculated for the predictor and outcome variables. Patients were divided into quartiles based on UPSIT performance. Those in quartile one had the highest UPSIT scores (i.e., least smell deficit) and those in the fourth quartile had the lowest scores (i.e., the greatest smell deficit). The ranges for each quartile were as follows: quartile 1: 30 to 40, quartile 2: 23 to 29, quartile 3: 17 to 22, and quartile 4: 0 to 16. The risk period began at the time of smell testing and ended when an outcome was reached or when the patient was last evaluated, whichever came first.

To test whether baseline olfactory performance was associated with increased risk of developing a complication, hazard ratios were calculated for the total UPSIT score, and by quartile using Cox proportional hazards regression with quartile 1 as the reference group. The proportional hazard model approach is a type of survival analysis that allows adjustment for covariates. Analyses were conducted for the presence of a trend in risk across quartiles using a likelihood ratio test. Risk associated with individual quartiles of olfactory performance was compared to the reference quartile of best olfactory performance.

Both adjusted and unadjusted analyses were performed. Covariates including age, sex, baseline HY stage, and disease duration at the time of olfactory testing were controlled for by inclusion as covariates within the proportional hazards model. These specific covariates were chosen based on their potential relationships with either olfactory performance or

disease progression. All comparisons were made at the nominal $P = 0.05$ level. Analyses were conducted using STATA 10.0, College Station, TX.

RESULTS

Two hundred twenty four (224) patients were administered smell tests between 1988 and 2000. One hundred of these patients qualified for the final analysis. Of the 124 patients who were excluded, 81 had missing charts that were archived and could not be recovered, 14 patients had a baseline score of 1 or higher on either the Intellectual Impairment or Thought Disorder sections of the UPDRS at the time of smell testing, 13 patients had their diagnoses revised to something other than idiopathic PD after the baseline evaluation, 12 patients were followed for less than 1 year, and 4 patients did not have ratings of motor performance recorded at the time of smell testing. Because some subjects had already experienced either falls or dyskinesias at baseline evaluation, the number of eligible subjects for these outcomes (falls = 92; dyskinesias = 76) was somewhat smaller.

Of the 100 eligible participants 37 were female. The mean ($\pm$ SD) age was 61.5 (11.3) years. Motor symptoms were mild to moderate. About 44% were in HY stage 1, 5% were in stage 1.5, 46% were in stage 2, 1% were stage 2.5, and 3% were in stage 3. The mean (SD) duration of time since diagnosis was 3.6 (3.8) years. The mean (SD) UPSIT score for all patients was 23.2 (8.2). The mean (SD) UPSIT score was 34.1 (2.6) for the best quartile, 26.3 (2.1) for those in the second quartile; 18.8 (1.8) in the third quartile; and 13.4 (3.4) for those in the lowest quartile. One subject scored below 38 on the PIT. Results were not affected by excluding this subject.

The mean duration of follow-up ($\pm$ SD) was 6.8 (4.6) years. About 37% of the sample developed visual hallucinations over the course of follow-up; 38% had cognitive symptoms; 65% had falls; and 66% developed dyskinesias.

Visual Hallucinations

Impairments in olfactory performance were consistently associated with a higher risk of developing visual hallucinations. The increased hazard associated with each one-point increase in the UPSIT score was 1.11 (95% CI 1.05, 1.16; $P = <0.001$). This effect was still highly significant after adjustment for covariates (HR = 1.10, 95% CI 1.03, 1.15; $P = 0.003$). There was a dose-effect with each successive quartile having a higher odds of visual hallucination than the prior quartile (1.0 [reference], 1.57 [second quartile], 2.09 [third quartile], and 6.71 [lowest quartile]), with a statistically significant test for trend ($\chi^2 = 15.82$; $df = 3$; $P = 0.0006$). Analysis adjusted for age, gender, disease duration at the time of olfactory testing, and baseline Hoehn and Yahr stage yielded similar results (Table 1). The greatest effect was for subjects in the lowest quartile of olfactory performance. These individuals have significantly higher risk of visual hallucinations compared to those in the three other quartiles, combined (HR, 3.53; 95% CI, 1.64–7.61, Fig. 1).

Cognitive Impairment

There was also a significant association between olfaction and risk of subsequent cognitive impairment. The increased hazard associated with each one-point increase in the UPSIT score was 1.10 (95% CI 1.04, 1.16; $P = <0.001$). This effect was also significant after adjustment for covariates (HR = 1.06, 95% CI 1.01, 1.12; $P = 0.024$). There was a trend for increasing risk of cognitive decline across quartiles of baseline olfactory impairment, although the effect is somewhat smaller in magnitude than for hallucinations. This trend remained significant after adjustment for covariates.

Motor Features

After adjustment for covariates, there was no significant overall effect of olfactory performance on the two motor outcomes, falls and dyskinesias. There was no association between UPSIT scores, either as a continuous measure or when divided by quartiles, on risk of dyskinesias in either adjusted or unadjusted analyses. In unadjusted analysis, there was an increased risk of falls based on UPSIT score as a continuous variable (HR = 1.04, 95% CI 1.00, 1.08, $P = 0.031$). However, this association was not significant after adjustment for covariates (HR = 1.03, 95% CI 0.99, 1.06, $P = 0.25$). Likewise, in unadjusted analysis there was a modest, but significant, trend for higher risk of falls across worsening quartiles of olfaction, as well as a significant difference in risk between quartile 1 and 4. However, after correction for covariates, these associations were no longer significant. These data are shown in Table 1.

DISCUSSION

Patients with the greatest olfactory impairment at baseline were at higher risk for developing visual hallucinations and cognitive decline over the course of clinical follow-up. After adjustment for covariates, there was no significant relationship between baseline olfactory performance and risk of motor progression indicated by incident dyskinesias and falls. Our results suggest that olfactory testing can provide useful prognostic information regarding neuropsychiatric features of PD. In addition, the observed clinical associations suggest that olfactory performance may be a marker for extranigral pathology to a greater extent than for nigrostriatal dysfunction.

There was a pattern of increasing risk of neuropsychiatric complications with each quartile drop in olfactory performance. The greatest risk was for patients in the lowest quartile of smell loss, with UPSIT scores of 16 or lower. This level of smell loss represents nearly complete anosmia, since a score of ~10 of 40 is expected simply by guessing. Although there was no association between impaired olfaction and motor performance in adjusted analysis, subjects in the lowest quartile of olfactory performance were more likely to develop falls in the data of the unadjusted analysis. In previous research, axial symptoms have been more associated with neuropsychiatric features of PD than other motor aspects of the disease.¹⁴ The present data suggest that the risk of dyskinesias is unrelated to olfactory impairment. Our results do not entirely exclude a modest association between impaired olfaction and subsequent risk of falls.

Prior studies have investigated the relationship between olfaction and motor features of PD, and to a lesser extent, olfaction and cognition in Lewy Body disorders. Several studies have shown that odor identification deficits appear early in the course of PD¹ and are modestly related to severity of motor disability.¹⁵ One study showed that olfactory deficits and cognitive impairment are independent factors in PD patients.¹⁶ However, severe odor identification deficits are present in patients with dementia with Lewy Bodies (DLB),¹⁷⁻¹⁸ and they may be more common and pronounced in the Lewy Body variant of Alzheimer's disease (AD) than in typical AD.¹⁹ These studies show that olfactory deficits occur in cognitive disorders associated with extranigral LB pathology.

Our findings are consistent with the pathological staging system proposed by Braak et al.²⁰ in which the olfactory bulb and anterior olfactory nucleus are among the first sites of Lewy body pathology, while nigral pathways are affected later. In this context, it is possible that lower brainstem pathology leads more directly to nigral disease, whereas olfactory system pathology is more related to extranigral degeneration.

The results of this study have clinically relevant implications. Nonmotor features of PD are increasingly recognized as important determinants of impaired function and reduced health-related quality of life (HRQL) in PD.^{21,22} Patients with visual hallucinations are at higher risk for institutionalization and mortality²³ than patients without visual hallucinations. Cognitive impairment in PD has been associated with greater disability,^{24,25} reduced HRQL,²⁶ higher caregiver burden,²⁷ and increased mortality.²⁸ If PD patients at increased risk for developing these problems could be identified earlier, it is possible that they could be managed more appropriately. In the future, these at-risk individuals could be targeted to receive disease-modifying therapies that might delay or mitigate the devastating effects of dementia and psychosis in PD.

Several limitations of this study should be noted. Inclusion criteria were based in part on UPDRS, part I items which is not as accurate as formal neuropsychological testing. As a result, some subjects with mild dementia or psychosis that would have been detected with more sensitive measures may have been included in this cohort. Furthermore, it is possible that subjects with mildly impaired cognition at baseline may have had worse olfactory performance due to impaired attention or memory. While this potential source of bias can not be excluded, the uniformly high scores on the PIT in the subset to whom this test was administered suggest that it was not a major problem in this cohort. Outcome data were collected retrospectively by review of clinical charts, and a number of the clinical charts were not available for review. In addition, outcomes may not always be accurately recorded in medical charts. Although these problems are a potential source of bias, there are several reasons why it is unlikely that they would lead to finding false associations. First, assessment of outcomes was performed blinded to baseline olfactory status. Second, it is unlikely that subjects would be lost to follow-up based on performance on their olfactory testing. Thus, while both of these limitations are important, and we can not completely exclude the possibility that low baseline olfaction is associated with a greater probability of remaining in the cohort and developing psychosis, neither would be likely to produce “false positive” results. The more likely problem is that our study underestimates the magnitude of the relationship between olfaction and nonmotor outcomes, and may have failed to detect smaller associations between olfactory deficits and motor features. This may have occurred in the case of falls. However, our data do not support any association between olfaction and risk of dyskinesias. Another limitation is that a treatment history was not included in the analysis. Treatment with dopaminergic medications is clearly associated with visual hallucinations in PD patients. However, it is unlikely that treatment would be related to baseline olfactory performance, and therefore, it is unlikely that the relationship between baseline olfactory performance and subsequent emergence of visual hallucinations would be confounded by dopaminergic treatment.

To address these limitations, our results should be confirmed in prospective longitudinal studies. Particularly in the setting of effective medical and surgical treatments for the cardinal motor features of PD, non-motor problems are major determinants of disability and mortality. Accurate prediction of these problems would have substantial research and clinical impact. Olfactory testing, perhaps combined with other tests, could be used to identify at-risk patients. With better prognostic information, these patients could be managed more effectively and potentially enrolled in research to better understand the evolution and treatments of neuropsychiatric complications of PD.

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FIG. 1.

Kaplan-Meier plot showing the risk of developing visual hallucinations for subjects in the lowest quartile of baseline olfactory performance compared to subjects in the top 3 quartiles (HR = 3.53; 95% CI, 1.64–7.61).

TABLE 1

Risk of neuropsychiatric and motor outcomes based on baseline UPSIT performance

	Unadjusted hazard ratio	Adjusted hazard ratio
Hallucinations		
Highest quartile	Reference	Reference
Second quartile	1.56 (0.55, 4.43)	1.41 (0.49, 4.05)
Third quartile	2.09 (0.73, 5.90)	1.63 (0.53, 5.08)
Lowest quartile	6.71 (2.40, 18.71) ^a	4.70 (1.64, 13.42) ^a
<i>p</i> -Value for trend	0.006	0.008
Cognitive decline		
Highest quartile	Reference	Reference
Second quartile	1.04 (0.37, 2.94)	0.86 (0.30, 2.46)
Third quartile	2.61 (0.94, 7.27)	1.73 (0.57, 5.23)
Lowest quartile	5.59 (1.94, 16.17) ^b	3.10 (1.05, 9.21) ^c
<i>p</i> -Value for trend	0.002	0.03
Falls		
Highest quartile	Reference	Reference
Second quartile	0.92 (0.43, 1.95)	0.91 (0.42, 1.96)
Third quartile	1.58 (0.78, 3.22)	1.26 (0.57, 2.77)
Lowest quartile	2.56 (1.18, 5.52) ^c	1.93 (0.85, 4.34)
<i>p</i> -Value for trend	0.04	0.16
Dyskinesias		
Highest quartile	Reference	Reference
Second quartile	1.31 (0.59, 2.90)	1.67 (0.73, 3.85)
Third quartile	1.02 (0.44, 2.37)	1.67 (0.67, 4.19)
Lowest quartile	1.04 (0.41, 2.69)	2.42 (0.76, 7.65)
<i>p</i> -Value for trend	0.90	0.22

^a $p < 0.001$.^b $p < 0.01$.^c $p < 0.05$.

Numbers in parentheses are 95% confidence limits. Adjusted analysis accounts for age, gender, disease duration and HY Stage at the time of smell testing. *P*-values marked with symbols are for comparisons of individual quartiles to the reference quartile.