Olfactory testing differentiates between progressive supranuclear palsy and idiopathic Parkinson’s disease

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Article abstract—Olfactory dysfunction occurs in most patients with idiopathic Parkinson’s disease (PD). In this study, we sought to determine whether such dysfunction is also present in progressive supranuclear palsy (PSP), a condition which shares a number of motor symptoms with PD and is commonly misdiagnosed as PD. We administered the University of Pennsylvania Smell Identification Test, a standardized test of odor identification ability, to 21 PSP patients; 17 also received a forced-choice odor detection threshold test. We compared the olfactory test scores to those obtained from PD patients and normal controls matched to the PSP patients on the basis of age, sex, and smoking habits. Overall, the olfactory function of the PSP patients was markedly superior to that of the PD patients and did not differ significantly from that of the normal controls. There was no association in either the PSP or PD patient groups between (1) the olfactory test scores and (2) measures of motor symptom severity, disease stage, and medication usage. These findings demonstrate that patients with PSP and PD differ markedly in their ability to smell and suggest that olfactory testing may be useful in their differential diagnosis.

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Progressive supranuclear palsy (PSP) accounts for nearly 5% of patients who manifest parkinsonian symptoms. Although this syndrome is frequently characterized by bradykinesia and rigidity early in its progression, tremor is rarely present. The distinguishing feature of this disorder is vertical-gaze paresis (especially downgaze paresis) which can be overcome by the oculocephalic maneuver. Another prominent feature of PSP is a slowing of thought processes. Because this disorder shares a number of motor symptoms with idiopathic Parkinson’s disease (PD), it is commonly misdiagnosed as PD. Unlike PD, however, its parkinsonian features are less responsive to anti-PD medications. Furthermore, PSP differs from PD in additional neuronal loss within the basal ganglia, cerebellum, and the upper brainstem and more severe frontal lobe dysfunction. A considerable body of evidence...
suggests that the mesolimbic and mesocortical dopamine systems degenerate to a lesser degree in PSP than in PD.6,7

Most patients with PD evidence major olfactory dysfunction, as measured by tests of odor identification, discrimination, and detection threshold.8-10 Importantly, the olfactory deficits are bilateral, uninfluenced by antiparkinsonian medications, and statistically unrelated to disease stage, disease duration, magnitude of motoric symptoms (as determined from clinical ratings), or measures of cognitive and perceptual-motor function.9-14 The severity of olfactory deficit observed in PD is similar to that of Alzheimer’s disease (AD)15 and the parkinsonism-dementia complex of Guam (PDC),16 suggesting the possibility that the olfactory dysfunction of these three disorders depends on a common neuropathologic substrate.

The present study sought to determine whether olfactory dysfunction is present in PSP and, if so, whether it is as severe as that observed in PD. We hypothesized that if the olfactory deficit of PD is related to damage to dopaminergic cells within the mesolimbic and mesocortical pathways, then the olfactory function of PSP patients would be normal, since comparatively little damage occurs to these pathways in PSP.

Methods. Subjects. Twelve men and nine women with well-characterized PSP served as the primary study group (respective mean ages [SD] = 68.2 [8.0] and 67.1 [6.7] years). Eighteen were outpatients from the Department of Neurology, Robert Wood Johnson Medical School, New Brunswick, New Jersey, and the remainder were outpatients from Graduate Hospital, Philadelphia, Pennsylvania. The duration of the PSP symptoms ranged from 3 months to 10.5 years (mean [SD] = 4.4 [2.9] years). Overall, the motor symptoms were advanced, with five patients at stage III, six at stage IV, and 10 at stage V of the Hoehn and Yahr scale.17 At the time of testing, 14 of these patients were taking carbidopa-levodopa, either alone (five patients) or in combination with an antidepressant (eg, amitriptyline, six patients), a monoamine oxidase inhibitor (deprenyl, one patient), or two other drugs (amantadine and amitriptyline, one patient; fluoxetine and nortriptyline, one patient). One patient was taking amitriptyline alone, and another imipramine alone. Five were unmedicated.

Twenty-one patients with PD (12 men and nine women; respective mean ages [SD] = 68.3 [8.2] and 66.8 [6.0] years) and 21 persons with no apparent neurologic abnormalities (12 men and nine women; respective mean ages [SD] = 67.4 [6.8] and 67.0 [7.0] years) served as comparison groups. These individuals were matched exactly to the PSP subjects on the basis of sex and current smoking habits. All but three of the individuals were matched in age within 2 years of their respective PSP cohorts; two were matched within 3 years and one within 4 years. No statistical difference was present among the ages of the three groups [F(2,60) = 0.26, p > 0.20]. The PD patients had less advanced motor pathology than did the PSP patients, with 13 at stage I and eight at stage II of the Hoehn and Yahr scale. However, this difference was unlikely to have influenced the results of the study since (1) the PSP patients evidenced less olfactory dysfunction than the PD patients (contrary to what would be expected if the magnitude of motor pathology was associated with the degree of olfactory dysfunction) and (2) no statistical association was observed between measures of motor pathology and the olfactory test measures in either the PSP or PD groups (see below). The latter observation in PD patients has been noted previously.9,11,14

At the time of testing, 18 of the PD patients were taking carbidopa-levodopa, either alone (six patients) or in combination with a monoamine oxidase inhibitor (deprenyl, three patients), a dopamine receptor agonist (bromocriptine mesylate, four patients), or a combination of deprenyl and a dopamine receptor agonist (five patients—four were taking the agonist bromocriptine mesylate and one the agonist pergolide mesylate). One patient was taking only deprenyl and bromocriptine mesylate, whereas another was taking only pergolide mesylate. One patient was unmedicated at the time of testing.

All subjects performed 35 or better on the Picture Identification Test, a 40-item test specifically designed to screen individuals unable to perform the nonolfactory components of the odor identification test used in this study.12 Therefore, none of the subjects evidenced cognitive dysfunction that would confound the interpretation of their olfactory test results.

Olfactory tests. Two tests of olfactory function were administered. The first, the University of Pennsylvania Smell Identification Test (UPSIT; commercially known as the “Smell Identification Test,” Sensonics, Inc., Haddon Heights, NJ), was administered to all 21 subjects. This forced-choice standardized test uses 40 microencapsulated odorants and is sensitive to a wide variety of olfactory deficits, including those due to cigarette smoking,18 AD,15 idiopathic PD,11,12 head injury,19 and many other common disorders.20,23 Details of the test and its development are presented elsewhere.21,22 The second test, a single staircase forced-choice odor detection threshold test incorporating the rose-like odorant phenyl ethyl alcohol (PEA) dissolved in propylene glycol, was administered to 17 of the 21 PSP patients and their respective matched PD and normal controls. The procedural details of this test, which is also sensitive to the disorders mentioned above, are presented elsewhere.20

Ratings of motor dysfunction. All of the PSP and PD patients were administered the motor section of the Unified Parkinson’s Disease Rating Scale (UPDRS; 31 items—ratings range from 0 to 4, with 0 being normal and 4 being maximal dysfunction).24 Seventeen of the PSP patients received a five-point downgaze paresis scale, where 0 = normal; 1 = normal range, but other supranuclear defects present; 2 = downgaze present but limited; 3 = downgaze absent but other useful eye movement present; and 4 = no useful eye movement elicitable on command.

Results. As shown in the figure, the PSP patients performed significantly better than the PD patients on the UPSIT and on the odor detection threshold test. The magnitude of these effects was large. Thus, the PSP patients scored, on average, over 12 points higher on the UPSIT than did the PD patients, and evidenced an average threshold difference of nearly two log concentration units. The average test scores of the PSP patients appeared to
be slightly inferior to those of the normal controls, although these effects were not statistically significant at the 0.05 alpha level. A summary of the statistical analyses is as follows: one-way analyses of variance applied to the UPSIT and PEA threshold data sets separately revealed highly significant group effects [UPSIT group effect F(2,60) = 33.39, p < 0.0001; PEA group effect F(2,48) = 13.93, p < 0.0001]. Orthogonal contrasts among the groups revealed the following: UPSIT data—control versus PSP F(1,60) = 1.67, p = 0.201; control versus PD F(1,60) = 58.28, p < 0.0001; PSP versus PD F(1,60) = 40.20, p < 0.0001; PEA threshold data—control versus PSP F(1,48) = 3.09, p = 0.085; control versus PD F(1,48) = 26.92, p < 0.0001; PSP versus PD F(1,48) = 11.77, p = 0.001.

Pearson correlation coefficients computed between the olfactory test scores and (1) Hoehn and Yahr stage, (2) the UPDRS, and, in the case of the PSP patients, (3) the ratings on the downgaze paresis scale did not reveal any meaningful relationships (all ps > 0.20; Bonferroni correction for inflated alpha level). No apparent associations between medication usage and olfactory test scores were present in either the PD or PSP groups, although the relatively small sample sizes within the different medication groups precludes, in this study, a definitive evaluation of this point.

**Discussion.** The present study clearly indicates that the olfactory function of patients with PSP is markedly superior to that of patients with idiopathic PD. Such superiority is present for tests of both odor identification and detection threshold, which suggests that quantitative measures of olfactory function may aid in the clinical differentiation of these two disorders. Thus, in addition to poor responsiveness to levodopa therapy and other signs and symptoms which are not typically present in PD (eg, blurred vision, diplopia, eye discomfort, photophobia, oscillopsia, downgaze palsy, hypomet-
In addition to helping to differentiate PSP from PD, olfactory tests may also be useful in the differential diagnosis of PSP from a number of other neurologic disorders. Thus, UPSIT scores are severely depressed in AD and PDC, moderately to severely depressed in Huntington's chorea (R.L. Doty, unpublished), mildly depressed in schizophrenia, and normal or nearly normal in MPTP-induced parkinsonism. A challenge for the future will be not only to determine the usefulness of olfactory testing in such differential diagnosis, but to determine whether such differences in function represent differing degrees of damage to a common neurologic substrate.

References