Olfactory Testing as an Aid in the Diagnosis of Parkinson's Disease: Development of Optimal Discrimination Criteria

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Since olfactory dysfunction is among the first signs of idiopathic Parkinson's disease (PD), olfactory testing may aid in the early, 'preclinical' diagnosis of this disorder. Indeed, the proportion of early-stage PD patients with olfactory dysfunction appears to be greater than the proportion of early-stage PD patients exhibiting some of the cardinal signs of PD. Because olfactory function varies in the general population and declines with age, empirically-based criteria are needed by the clinician to establish whether the degree of olfactory loss observed in a given patient is concordant with the presence of PD. In this study, we present cutoff criteria for the optimal assessment of olfactory dysfunction in the evaluation of PD. Specifically, we present scores for the University of Pennsylvania Smell Identification Test (UPSIT) that best discriminate between PD patients and age-matched controls. Receiver operating characteristic (ROC) curves, based upon sensitivity and specificity estimates, were computed for three age groups (<60 yrs, 61–70 yrs, and >71 yrs) and scores with highest sensitivity and specificity were determined. Sex- and age-related differences in the test scores were observed, with lower scores occurring for men and for the older patient groups.

Key words: diagnosis, olfaction, Parkinson's disease, Parkinsonism, smell, UPSIT

Idiopathic Parkinson's disease (PD) has been classically considered a motor system disease, its diagnosis being based upon the presence of a set or subset of cardinal motoric signs (e.g. rigidity, bradykinesia, tremor and postural reflex disturbance). Indeed, James Parkinson, in his 1817 monograph on shaking palsy (Parkinson, 1817), succinctly defined this disorder as 'Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured' (italics added).

It is now known that a number of sensory disturbances are present, in varying degrees, in persons with PD. These include changes in olfactory perception (for review, see Doty, 1991), visual contrast sensitivity (Bulens et al., 1986), colour perception (Büttner et al., 1993), perception of the visual vertical (Proctor et al., 1964), and in sensations associated with proprioception and motor control (Snider & Sandyk, 1987). Unfortunately, most such alterations appear to be poor diagnostic markers of early PD, largely because of relatively low prevalence or their heterogeneity in presentation.

An apparent exception to this rule is olfactory dysfunction, which is reliably observed in early PD on a wide range of quantitative olfactory tests, including tests of odour identification, detection and discrimination. Doty, Deems & Stellar (1988), for example, found that 73 of 81 patients studied (90%) had odour identification test scores lower than their matched normal controls. The PD-related loss is bilateral (Doty et al., 1992), present in early hemiparkinsonism (Doty et al., 1988, 1992), stable over time (Doty et al., 1988) and unrelated to disease stage (Doty et al., 1988; Quinn, Rossor and Marsden, 1987; Ward, Hess & Calne, 1983), degree of motoric symptomatology (Doty et al., 1989; Ward et al., 1983) or use of antiparkinson medications (Doty et al., 1988; Quinn et al., 1987; Ward et al., 1983). Importantly, among the
major motor disorders, this alteration in ability to smell is relatively specific to PD. Thus, decreased ability to smell is absent, or present infrequently or only to a minor degree, in progressive supranuclear palsy (a condition which shares a number of signs with PD) (Doty et al., 1993), essential tremor (Busenbark et al., 1992), multiple system atrophy (Wenning et al., 1993), amyotrophic lateral sclerosis (Sajjadian et al., 1994), multiple sclerosis (Doty et al., 1984) and parkinsonism induced by the prionotoxic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Doty et al., 1992). Additionally, subtle differences in olfactory dysfunction exist among subtypes of PD. For example, slightly greater dysfunction is present, on average, in patients with postural instability-gait predominant PD than with tremor-predominant PD (Stem et al., 1994).

In the light of such observations, olfactory testing may aid in the clinical diagnosis of early-stage PD; indeed, decreased olfactory function might even be considered a primary sign or feature of PD. However, since such dysfunction is present to some degree in the general population and age-related declines in the ability to smell are well documented (Deems et al., 1991; Doty et al., 1984), empirically-based standards are needed by the clinician to determine whether the degree of olfactory loss in a given patient is concordant with that expected in PD. To this end, we established scores for the University of Pennsylvania Smell Identification Test (UPSIT; see Methods section) that optimally discriminate between PD patients and age-matched controls. As described in detail below, receiver operating characteristic (ROC) curves, based upon sensitivity and specificity estimates, were computed for three age groups chosen to take into account normal presbyosmia: ≤60 yrs, 61–70 yrs, and ≥71 yrs (Fletcher, Fletcher & Wagner, 1988). Those test scores which fell furthest from the positive diagonal of the ROC curves defined the optimal UPSIT cutoff points.

Methods

Subjects

The overall study group consisted of 180 PD patients and 612 controls, with four controls being matched to each PD patient in the ≤60 and ≥70 year old subject groups. Two or three controls were matched to each PD patient in the 61–69 year age category because fewer appropriate controls were available for such matching in this group. The matches were made on the basis of age and gender and, within the constraints of the matching procedure, were randomly selected from a database of over 2500 subjects maintained at the University of Pennsylvania Smell and Taste Center. This database includes individuals from the community at large who had been administered UPSIT (e.g. persons tested at fairs and public events, employees and students of the University of Pennsylvania, and healthy ambulatory residents of homes for the elderly). The PD patients were outpatients from the Department of Neurosurgery at St. Barnabas Medical Center, Livingston, New Jersey, the Department of Neurology, Graduate Hospital, Philadelphia, Pennsylvania, and the California Parkinson’s Foundation, San Jose, California, and consisted primarily of subjects with early-stage PD [number of subjects at Hoehn and Yahr (1967) stages I–III = 102, 55 and 23, respectively]. At the time of testing, 31 of the patients were unmedicated (most were associated with the DATATOP program; see Parkinson Study Group, 1989), 137 were taking Sinemet or another dopaminergic agent (e.g. Amantadine) either alone or in conjunction with other PD medications (e.g. benztrpine mesylate, deprenyl, trihexyphenidyl) and 23 were taking either deprenyl or trihexyphenidyl alone. The duration of the parkinsonian symptoms ranged from 3 months to 48 years (median = 5.0 yrs). All of the subjects scored 35 or better on the Picture Identification Test (a test analogous to the UPSIT except that pictures, rather than odours, are used as stimuli), precluding the possibility that low UPSIT scores were due to cognitive problems in test taking or to non-olfactory elements of the UPSIT (Vollmecke & Doty, 1985).

Olfactory testing

The UPSIT was the test instrument employed in this study. This standardized test (commercially available as the Smell Identification Test™, Sensonics, Inc., Haddon Heights NJ) is highly reliable (test-retest r’s > 0.90) and correlates strongly with more traditional types of olfactory tests, including odour detection threshold tests (Doty, Shaman & Dann, 1984; Doty, Agrawal, & Frye, 1989). Procedurally, a subject is required to identify, in a 4-alternative multiple choice format, each of 40 odorants presented on microcapsulated ‘scratch and sniff’ labels. For example, one of the test items reads: ‘This odour smells most like: (a) chocolate; (b) banana; (c) onion; or (d) fruit punch’, and the subject is required to provide an answer even if no smell is perceived (i.e. the test is forced-choice). The number of items out of 40 that were answered correctly served as the dependent measure.

Development of receiver operating characteristic (ROC) curves

Sensitivity and specificity estimates were calculated for values at and below 32 of the 40 possible UPSIT scores (0, 5 and 10–40) (chance performance = 10). Sensitivity was defined as the proportion of PD patients falling at or below each of these cut-off scores, where values at or below each score were considered abnormal (sensitivity = true positives/(true positives + false negatives)). Specificity was defined as the percent of control subjects who fell above each UPSIT cut-off score and therefore evidence a
'normal' test result (specificity = true negatives/(true negatives + false positives)). In accord with standard practice, the ROC curves were calculated by plotting the sensitivity estimates vs. 1 minus the specificity estimates (Fletcher et al., 1988). The ROC lines were fitted to the resulting data points using a LOWESS smoothing method (Cleveland, 1979, 1981), a procedure which does not presuppose the shape of the function and incorporates a locally weighted regression algorithm to obtain the best fit (Wilkinson, 1990).

Results

The ROC curves are presented in Fig. 1 for the males and females within each age group. Each data point represents one of the aforementioned UPSIT scores. Those UPSIT scores farthest away from the positive diagonal reflect optimization of the sensitivity and specificity estimates and, thus, test scores which best discriminate between PD and control subjects.

![Figure 1. Receiver Operating Characteristic (ROC) curves relating sensitivity and specificity. (A) Males; (B) Females. Note gender and age group differences in functions. The most discriminative UPSIT scores are found in the upper left corners. Curves fitted using a LOWESS smoothing method (Wilkinson, 1990). ● ≥60 yrs; ▲ 61–70 yrs; ■ ≥71 yrs.](image)

Table 1. Optimal cut-off values and associated sensitivity and specificity estimates determined from Receiver Operator characteristic (ROC) curves. M = Males Only; F = Females Only; Respective sample sizes for the PD and normal subject groups: ≤ 60 yrs: males, 32 & 128; females, 28 & 112; 61–70 yrs: males, 52 & 76; females, 20 & 104; ≥ 71 yrs: males, 25 & 100; females, 23 & 92

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Note: Sensitivity = true positives/(true positives + false negatives)
Specificity = true negatives/(true negatives + false positives)

Discussion

In this study, we provide guidelines for the possible use of the UPSIT as an aid in the early diagnosis of PD; specifically, optimal cut-off values are defined for establishing whether the degree of olfactory dysfunction observed in a given patient is of a magnitude concordant with that expected in PD. The cut-off values listed in Table 1 will help the clinician to minimize his or her error in making this decision.

Since the PD subjects of our study were already identified as having PD, the sensitivity and specificity estimates we obtained cannot be viewed as comparable to classical sensitivity and specificity.
estimates obtained by epidemiologists. To estimate the sensitivity and specificity of UPSIT for detecting either early clinical or 'preclinical' PD in the general population, large numbers of subjects, not yet identified as having or not having PD, would need to be evaluated prospectively and then followed longitudinally to determine what proportion ultimately develop PD.

Olfactory dysfunction, relative to other clinical signs of PD, is unique on several grounds and, thus, may add an important independent dimension to the PD diagnostic process. This uniqueness stems not only from the fact that such dysfunction is sensory, rather than motor, but that it (a) is prevalent to a relatively high degree in the earliest stages of the disease process, (b) does not evidence longitudinal progression, (c) is unrelated to the use of antiparkinsonian medications, (d) does not differ during the 'on' and 'off' states of patients with severe motor fluctuations who are on l-dopa therapy, and (e) is unrelated in magnitude to the degree of motoric or cognitive symptomatology (implying independence from the more dynamic elements of the disease proper) (see opening paragraphs for references).

Although the basis for PD-related olfactory loss is unknown, its early presentation and lack of progression with the disease process are compatible with the hypothesis that it may reflect the adverse effects of an environmental or other agent which enters the brain via the olfactory epithelium (Doty, 1991). Olfactory receptor cells serve as a primary means of entry into the central nervous system for a number of viruses and macromolecules which, in animal models, can damage olfactory neurons (e.g. Barthold, 1988; Lundh, Kristensson & Norry, 1987; Monath, Croop & Harrison, 1983; Moarles et al., 1988; Strop, 1995). Importantly, the blood-brain barrier is largely compromised in this region, although the olfactory mucosa contains very high concentrations of enzymes that metabolize xenobiotics (e.g. cytochromes P-450, flavin containing monooxygenase and aldehyde dehydrogenases, and carboxylesterases) (Dahl, 1985a,b,c, 1988). Interestingly, the metabolic rates for xenobiotics within nasal tissue typically exceed those of other extrahepatic tissues and commonly exceed those of the liver (Dahl, 1984).

Whatever its basis, olfactory dysfunction appears to be an excellent marker for idiopathic PD. Hopefully, the present study will encourage neurologists and others to more fully explore the usefulness of olfactory testing in the early or 'preclinical' diagnosis of PD.

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References


