

Olfactory Loss May Be a First Sign of Idiopathic Parkinson's Disease

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Abstract: Recent studies support the idea of olfactory dysfunction as a very early sign of idiopathic Parkinson's disease (IPD). Aim of the present study was to clinically follow-up patients with idiopathic hyposmia to find out the percentage of patients developing IPD after 4 years time. At baseline, olfactory tests had been combined with transcranial sonography of the substantia nigra and ¹²³I-FP-CIT SPECT imaging. At the

present neurological examination, 7% of the individuals with idiopathic hyposmia had developed clinical IPD. Altogether, 13% presented with abnormalities of the motor system. Our data suggest that a combination of olfactory testing and other tests may constitute a screening tool for the risk to develop IPD.
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Idiopathic Parkinson's disease (IPD) is closely associated with olfactory loss.^{1–6} Deficits in the sense of smell may precede clinical motor symptoms by years. Although there is evidence from recent studies to support this view,^{7–9} the use of olfactory testing as a screening tool for IPD is discussed controversially. In one study, 10% of first-degree relatives of IPD patients with olfactory loss developed clinical IPD.⁸ In contrast, authors of a twin study¹⁰ concluded that smell identification ability may not be a sensitive indicator of future IPD, even in a theoretically at-risk population. This was based on the fact that their patients who subsequently developed IPD had no evidence of significant smell loss when they were tested initially. Thus, the question arises whether a combination of olfactory loss together with pathological results from diagnostic tools assessing other than motor parameters would reliably predict the early onset of IPD.

The present study was designed as a clinical follow-up of a previous investigation,¹¹ in which 30 patients diagnosed with idiopathic olfactory loss had participated. In the preceding study, olfactory tests were combined with transcranial sonography (TCS) of the substantia nigra (SN),^{12–14} SPECT imaging, and baseline assessment of motor symptoms related to IPD. The follow-up after 4 years time aimed at the clinical re-evaluation of motor symptoms with respect to IPD, the objective being to determine diagnostic landmarks on the way to develop IPD screening strategies.

METHODS

In the baseline study, thirty patients with idiopathic olfactory loss participated, who were either referred, or presented themselves to the Smell and Taste Clinic of the Department of Otorhinolaryngology. Following a thorough clinical work-up, olfactory loss was ascertained by means of the validated "Sniffin' Sticks" test kit (Burghart instruments, Wedel, Germany),^{15,16} which is composed of three tests of olfactory function: phenyl ethyl alcohol odor threshold, "T", odor discrimination, "D", and odor identification, "I". Its result is reported as the "TDI score," which is the sum of scores from the three subtests. TDI scores below 16 indicate anosmia.

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The specification of “idiopathic” olfactory loss was based on negative MR/CT scans, no history of an association between olfactory loss and head trauma, or infections of the upper respiratory tract, gradual onset of olfactory loss over months or years, absence of signs of sino-nasal disease as established through a detailed nasal endoscopy, and lack of response to short-term systemic treatment with corticosteroids (see also Ref. 11).

Eleven of the 30 patients exhibited an increased echogenicity of the SN in the TCS (Elegra, Siemens, Issaquah, WA), which was performed by two neurologists experienced in this procedure (US, SJ). In 10 of these 11 patients, SPECT scans with ¹²³I-FP-CIT were performed (one patient declined to undergo this procedure). Median uptake ratios in the basal ganglia were pathologic (>1.5 standard deviations [SD] below mean normal values) in five patients, two patients exhibited borderline findings (>2.0 standard deviations [SD] below mean normal values), and three patients had normal results. Thus, seven of 30 patients were identified as having abnormal SPECT scans of the crucial brain structures, which indicated potential risk to develop IPD.

Clinical follow-up was performed 4 years after baseline procedures. Of the total group of 30 patients with olfactory loss, six could not be followed up (one patient deceased, two patients had moved to unknown addresses, three patients declined to participate in the follow-up test but reported their conditions to be unchanged), leaving a group of 24 patients (8 women, 16 men; mean age 59 ± 10 years [mean ± standard deviation, SD]; range 39–80 years).

Patients were seen by an experienced neurologist (AH) who examined them with special focus on early motor signs of IPD. This investigator was blinded with regard to the specific olfactory status of the patients. The “Unified Parkinson’s Disease Rating Scale III” (UPDRS III)¹⁷ was used to evaluate bradykinesia, tremor, or rigidity. Arbitrary cut-off criteria were defined in relation to the baseline examination.¹¹ UPDRS scores were classified as normal (0–2 points), borderline (3–5 points), or pathological (above 5 points).

RESULTS

A graphical summary of the patients’ results is presented in Table 1.

Unified Parkinson’s Disease Rating Scale

On neurological follow-up examination, in the UPDRS motor score (III), 20 patients had 0–2 points (clinically irrelevant), two patients had 3–5 points (borderline cases), and two patients presented with 9 and 12 points (pathological findings). The patient with UPDRS score 9

TABLE 1. Comparison of follow-up UPDRS results (right) and baseline UPDRS, TCS, and SPECT findings (left) from 30 subjects with olfactory loss

No.	Baseline			4-Year follow-up UPDRS
	UPDRS	TCS	SPECT	
1	Light Gray	White	White	Light Gray
2	Light Gray	White	White	Light Gray
3	Light Gray	White	White	Light Gray
4	Light Gray	White	White	Light Gray
5	Light Gray	White	White	Light Gray
6	Light Gray	White	White	Light Gray
7	Light Gray	White	White	Light Gray
8	Light Gray	White	White	Light Gray
9	Light Gray	White	White	Light Gray
10	Light Gray	White	White	Light Gray
11	Light Gray	White	White	Light Gray
12	Light Gray	White	White	Light Gray
13	Light Gray	White	White	Light Gray
14	Light Gray	White	White	Light Gray
15	Light Gray	White	White	Light Gray
16	Light Gray	White	White	Light Gray
17	Light Gray	White	White	Light Gray
18	Light Gray	White	White	Light Gray
19	Light Gray	White	White	Light Gray
20	Light Gray	Dark Gray	Light Gray	Dark Gray (IPD)
21	Light Gray	Dark Gray	Light Gray	Light Gray
22	Light Gray	Dark Gray	Light Gray	Light Gray
23	Light Gray	Dark Gray	Light Gray	Light Gray
24	Light Gray	Dark Gray	Light Gray	Light Gray
25	Light Gray	Dark Gray	Light Gray	Light Gray
26	Light Gray	Dark Gray	Light Gray	Light Gray
27	Light Gray	Dark Gray	Light Gray	Light Gray
28	Light Gray	Dark Gray	Light Gray	Light Gray
29	Light Gray	Dark Gray	Light Gray	Light Gray
30	Light Gray	Dark Gray	Light Gray	Light Gray

Columns represent results of a diagnostic tool each: UPDRS III, neurological examination; TCS, transcranial sonography; ¹²³I-FP-CIT SPECT, Single Photon Emission Computed Tomography with ¹²³I-FP-CIT. Rows represent subjects; cells represent individual results.

Test results are indicated by the shading/patterns of cells: light gray = normal, dotted = borderline (UPDRS III: 3 to 5 points; SPECT: >1.5 standard deviations [SD] below mean normal values), dark = pathological (UPDRS III: >5 points; TCS: hyperechogenicity; SPECT: >2 SD below mean normal values). White areas indicate that the test had not been performed. IPD = patient who developed IPD. Please see text for details on individual patients.

was known to have subtle motor signs at the first investigation (initial score: 4), as well as the patient who scored 12 in the UPDRS (initial score: 5); moreover, this patient was clinically identified to have developed IPD.

Of the two patients with borderline findings at the follow-up examination, one patient also had borderline UPDRS scores at baseline, while the other one did not exhibit relevant motor abnormalities at the initial visit.

TCS comparisons

Initially, 14 of the 30 patients had neither abnormal findings in TCS nor in the UPDRS. After 4 years time, none of these 14 patients developed clinically relevant

motor abnormalities. In contrast, three out of 11 patients with pathological TCS results (hyperechogenic SN of 0.2 cm² or more on one or both sides) presented with clinically relevant findings in the follow-up UPDRS motor score. However, the TCS result of the single patient who had positively developed IPD at follow-up, and had presented with a borderline UPDRS score at baseline, was normal.

SPECT comparisons

In SPECT imaging, five patients presented with pathological uptake ratios of the striatum, (caudate nucleus and putamen), two of whom showed unilateral, three bilateral abnormalities. Only one out of these five patients presented with IPD relevant motor symptoms at the follow-up visit. This patient had a UPDRS score of 4 at baseline, and 9 at follow-up (duration of smell loss 4.5 years); he had been found to have pathological ratios in the caudate nucleus on both sides. Out of the three patients with *bilateral* pathological ratios, he presented with the most pronounced abnormality. At baseline, the side with the most reduced signal of dopamine transporters did correspond to the side with the higher SN echogenicity in the TCS.

Two additional patients showed borderline uptake ratios in ¹²³I-FP-CIT SPECT imaging. One of these patients had a normal UPDRS baseline score, and did not attend the follow-up session; the other one presented with borderline UPDRS findings in both assessments.

The patient who later developed IPD did not consent to an additional investigation with the SPECT scan.

TDI

Olfactory function did not change significantly between baseline and follow-up procedures ($P = 0.88$; mean TDI-score at baseline 18.4 ± 8.8 ; at follow-up visit 17.3 ± 8.6). In particular, TDI scores did not change significantly¹⁸ in the four patients who subsequently developed motor symptoms.

DISCUSSION

Four years from baseline, 7% of the individuals with idiopathic olfactory loss had newly developed clinical IPD symptoms, and altogether, 13% of the patients presented with IPD relevant abnormalities of the motor system. As compared to an IPD prevalence of 1.6‰ in the general European population,¹⁹ and of 1.8 to 2.6‰ in the elderly,²⁰ our results support previous data⁸ indicating that olfactory loss is indeed of prognostic value with respect to IPD symptoms.

Agreement with pathological UPDRS scores was observed in two of seven abnormal SPECT results, and in

three of 11 abnormal TCS findings, whereas the numbers of “false negatives”—normal results as opposed to pathological UPDRS scores—were two among SPECT, and one among TCS data. The incomplete matrix of procedures performed in this study has to be taken into account, limiting the range of conclusions. However, our data obtained so far suggest that a combination of olfactory testing and an additional TCS or SPECT examination may constitute a promising screening tool.

Another aspect of SPECT scans with regard to presymptomatic IPD concerns the time course of decline of activation indicated by dopaminergic markers. This has been estimated to approximate an annual rate of 7 to 9%.^{21–23} Thus, it relates to the thresholds at which deficits become detectable by SPECT and motor symptoms become clinically significant. Possibly, olfactory dysfunction antedates the reaching of both, as Braak et al.²⁴ observed the neuropathological alterations associated with IPD to occur earliest in the anterior olfactory nucleus (and dorsal motor nuclei of cranial nerves IX and X).

Why was olfactory loss not identified in the careful study by Marras et al.¹⁰ as an early marker of IPD? As mentioned in the Introduction, they observed that none of their patients developing IPD over a 7-year period had initially exhibited olfactory loss. However, as pointed out by the authors themselves, the reason for this negative finding might lie in the very long observation period of 7 years, which may have been too early for their subjects to have yet developed signs of smell dysfunction.

In conclusion, the present results indicate that unexplained olfactory loss may be associated with an increased risk of developing IPD relevant motor symptoms. Although further work, preferably with larger samples and more sophisticated study designs will be needed to assess in detail feasible and effective ways of IPD screening, olfactory loss should be considered a promising contribution to the diagnosis of early IPD.

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