

Original Article

Idiopathic olfactory dysfunction

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ABSTRACT

INTRODUCTION. Idiopathic olfactory dysfunction (IOD) is a frequent diagnosis in specialised smell clinics and represents a diagnostic challenge. Olfactory dysfunction is a well-recognised early feature of Parkinson's disease (PD) and dementia, but the prognostic significance of isolated IOD remains unclear.

METHODS. We conducted a retrospective clinical cohort study with prospective follow-up of patients diagnosed with IOD at a tertiary smell-and-taste clinic between 2017 and 2020. Assessment included clinical examination, medical history and standardised olfactory testing using the Sniffin' Sticks test battery (TDI score: threshold, discrimination, identification). Follow-up information was obtained through repeat clinical evaluation, structured telephone interviews and review of medical records.

RESULTS. A total of 153 patients with IOD were included. During follow-up, 132 patients (86%) remained classified as idiopathic. Seven patients (5%) were diagnosed with PD and five patients (3%) with dementia, while an additional nine patients (6%) developed neurological symptoms suggestive of neurodegenerative disease without a confirmed diagnosis.

CONCLUSIONS. Most patients remained without clinically manifest neurodegenerative disease during follow-up. Although a minority later developed PD or dementia, IOD alone had limited predictive value at the individual patient level. These findings support a conservative clinical approach and suggest that routine extensive neurological investigation may not be warranted in patients with isolated idiopathic olfactory loss.

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The sense of smell plays an important role in everyday functioning, contributing to flavour perception, hazard detection and overall quality of life [1]. Olfactory dysfunction is a common clinical complaint and may arise from a wide range of well-recognised causes, including sinonasal disease, upper respiratory tract infections, head trauma, congenital disorders, toxic exposure and neurodegenerative disease. Most patients can be assigned an aetiological diagnosis following systematic evaluation [2-4].

However, a substantial proportion of patients presenting with olfactory dysfunction remain without an identifiable cause despite thorough clinical assessment. These patients are commonly classified as having idiopathic olfactory dysfunction (IOD). In tertiary smell clinics, idiopathic cases may account for approximately one quarter of all referrals, underscoring both the frequency of the condition and the diagnostic uncertainty IOD entails [2, 4, 5].

IOD has attracted growing attention because olfactory impairment is a well-established early feature of Parkinson's disease (PD) and dementia [6]. This has triggered the hypothesis that isolated olfactory loss of unknown cause may represent a premorbid manifestation of neurodegenerative disease [4, 7-12]. While this

notion is biologically plausible, existing evidence is limited and inconsistent, and most available studies are small, cross-sectional or based on selected populations. Importantly, it remains unclear to what extent patients diagnosed with IOD in routine clinical practice subsequently develop neurodegenerative disease.

From a clinical perspective, this uncertainty poses a dilemma. On one hand, clinicians are cautious not to overlook early signs of neurodegenerative disease; on the other, overinterpretation of isolated olfactory dysfunction may lead to unnecessary investigations and patient anxiety.

The primary aim of this study was to describe the clinical course of patients diagnosed with IOD in a tertiary referral setting. Specifically, we examined whether olfactory function remained stable over time and whether patients subsequently developed PD, dementia or neurological symptoms suggestive of neurodegenerative disease. A secondary aim was to explore whether baseline clinical characteristics, including olfactory test performance, symptom duration and imaging findings, differed between patients who remained idiopathic and those who later developed neurological disease.

Methods

Study design and setting

This study was conducted as a retrospective clinical cohort with prospective follow-up. Patients were identified from the Flavour REDCap database, which contains systematically collected clinical data from patients evaluated at the Flavour Clinic, Department of Otorhinolaryngology, Head & Neck Surgery, Gødstrup Hospital, Denmark. All patients had provided informed consent for registration and follow-up.

Study population

Patients were eligible for inclusion if they had been classified as having IOD at their first clinical assessment between 2017 and 2020.

Patients were excluded if an identifiable cause of olfactory dysfunction was present at baseline.

Baseline assessment

Baseline assessment comprised clinical examination, detailed medical history and standardised olfactory testing using the Sniffin' Sticks test battery, expressed as the composite TDI (threshold, discrimination, identification) score. Patients completed the Sino-Nasal Outcome Test (SNOT-22) and the Major Depression Inventory questionnaires and underwent cognitive screening with the Mini-Mental State Examination (MMSE).

Information on allergy status was obtained from referral letters based on prior skin prick testing or specific IgE blood tests. Smoking status was self-reported and categorised as current, former or never smoking. Comorbidity was quantified using the Charlson Comorbidity Index (CCI) based on active diagnoses registered in the electronic medical record at the time of the baseline visit.

When available, MRI of the olfactory bulb was reviewed and categorised as not performed, normal or abnormal based on the radiological report.

Follow-up and outcome classification

Follow-up information was obtained through repeat clinical assessments, structured telephone interviews and review of electronic medical records. Follow-up intervals and assessment modalities varied.

Based on all available follow-up information, patients were classified into one of four mutually exclusive outcome groups: persistent IOD, PD, dementia or clinically suspected neurodegenerative disease.

Confirmed PD and dementia diagnoses were based on documentation from specialist neurological assessment. Patients without a confirmed diagnosis but with neurological symptoms suggestive of PD or dementia were classified as clinically suspected. Suspicion of PD was defined as the presence of at least three compatible symptoms or two core motor symptoms. Suspicion of dementia was defined as an MMSE score below 25 in combination with clinical features suggestive of cognitive impairment. This category reflected diagnostic uncertainty and did not represent a formal diagnosis.

Statistical analysis

Analyses were descriptive. Continuous variables are presented as means with standard deviations; categorical variables, as numbers and percentages. Baseline characteristics were described overall and stratified by neurological outcome group. No formal hypothesis testing was performed.

Trial registration: not relevant.

Results

Study population

A total of 153 patients diagnosed with IOD were included (Table 1). The mean age at baseline was 61.9 years (SD: 12.8 years), and 61.4% were women. Baseline demographic and clinical characteristics were comparable between sexes. However, olfactory test results are presented stratified by sex because of known sex-related differences in olfactory performance [13].

TABLE 1 Study population at baseline.

	Women (N _w = 94 (61.4%))	Men (N _m = 59 (38.6%))	Total (N _{tot} = 153 (100.0%))
Age, mean (SD), yrs	63.0 (12.5)	60.2 (13.2)	61.9 (12.8)
<i>Allergy, n (%)</i>			
Known allergies	9 (9.6)	9 (15.3)	18 (11.8)
No known allergy	73 (77.7)	44 (74.6)	117 (76.5)
Allergy status unknown	12 (12.8)	6 (10.2)	18 (11.8)
<i>Smoking, n (%)</i>			
Present smoker	6 (6.4)	1 (1.7)	7 (4.6)
Never	54 (57.5)	37 (62.7)	91 (59.5)
Former smoker	34 (36.2)	21 (35.6)	55 (36.0)
CCI score, mean (SD)	2.0 (1.2)	1.7 (1.4)	1.9 (1.3)
<i>Duration of IOD</i>			
< 10 yrs, n (%)	66 (70.2)	43 (72.9)	109 (71.2)
≥ 10 yrs, n (%)	28 (29.8)	16 (27.1)	44 (28.8)
Mean (SD), yrs	6.8 (6.1)	6.3 (5.8)	6.6 (6.0)

CCI = Charlson Comorbidity Index; IOD = idiopathic olfactory dysfunction.

The mean duration of olfactory dysfunction at baseline was 6.6 years (SD: 6.0 years), and 28.8% of patients reported a symptom duration of ten years or longer. The overall comorbidity burden was low, with a mean CCI score of 1.9 (SD: 1.3).

The median follow-up time was 6.25 years (range: 5.08-7.75 years).

Loss to follow-up was limited to six patients: four who died and two who withdrew consent.

Neurological outcomes during follow-up

During follow-up, 132 patients (86.3%) remained classified as idiopathic (Table 2). Seven patients (4.6%) were diagnosed with PD; five (3.3%), with dementia. An additional nine patients (5.9%) developed neurological symptoms suggestive of PD or dementia without a confirmed diagnosis and were classified as clinically suspected.

TABLE 2 Neurological outcomes during follow-up.

	Idiopathic (N _{id} = 132 (86.3%))	Dementia (N _{de} = 5 (3.3%))	PD (N _{pd} = 7 (4.6%))	Suspected PD/dementia (N _{pd/dem} = 9 (5.9%))
<i>Demographics</i>				
Age at baseline, mean (SD), yrs	61.3 (12.9)	75.8 (1.3)	62.7 (13.2)	64.2 (11.3)
Gender: female/male, n	81/51	4/1	4/3	5/4
<i>Olfaction and duration of disease</i>				
Baseline TDI score, mean (SD)	15.5 (5.9)	12.3 (4.3)	13.5 (5.1)	14.6 (6.4)
Duration of OD < 10 yrs, n (%)	95 (72.0)	4 (80.0)	5 (71.4)	5 (55.6)
Duration of OD, mean (SD)	6.6 (6.2)	5.8 (5.1)	7.9 (4.0)	6.6 (7.0)
<i>Clinical characteristics</i>				
CCI score, mean (SD)	1.8 (1.2)	3.4 (0.5)	2.1 (2.4)	2.0 (1.1)
Allergy status, n (%):				
Known	16 (12.1)	1 (20.0)	-	-
No known allergy	101 (76.5)	3 (60.0)	-	-
Unknown	15 (11.4)	1 (20.0)	-	-
Smoking status, n (%):				
Current	7 (5.3)	0	0	0
Former	49 (37.1)	1 (20.0)	2 (28.6)	3 (33.3)
Never	76 (57.6)	4 (80.0)	5 (71.4)	6 (66.6)
MRI: abnormal	17 (12.9)	0	0	0

CCI = Charlson Comorbidity Index; OD = olfactory dysfunction; PD = Parkinson's disease; TDI = threshold, discrimination and identification.

Among patients who developed PD, the median interval from anosmia onset to diagnosis was eight years (range: 5-20 years). Among patients who developed dementia, the median interval from anosmia onset to diagnosis was nine years (range: 7-19 years).

Patients diagnosed with dementia were older at baseline than patients in the other outcome groups. Sex distribution was similar across patients who remained idiopathic, those diagnosed with PD or dementia, and those classified as clinically suspected.

Baseline olfactory function and symptom duration

Baseline olfactory performance differed across outcome groups. Mean baseline TDI scores were lowest among patients later diagnosed with PD or dementia, intermediate among patients classified as clinically suspected and highest among patients who remained idiopathic. However, substantial overlap in TDI scores was observed between all groups.

The duration of olfactory dysfunction at baseline was comparable across outcome groups, in both mean duration and the proportion of patients with symptoms lasting ten years or longer.

Comorbidity and imaging

CCI scores were highest among patients diagnosed with dementia, whereas scores were similar among idiopathic patients, patients diagnosed with PD and clinically suspected patients.

MRI of the olfactory bulb was available for a subset of patients. Abnormal findings were observed in 12.9% of the patients who remained idiopathic but were not observed among patients diagnosed with PD, dementia or classified as clinically suspected.

Discussion

In this clinical follow-up study of patients diagnosed with IOD in a tertiary referral setting, most patients remained without an identifiable neurological diagnosis during follow-up. Although a minority subsequently developed PD or dementia, most patients did not progress to clinically manifest neurodegenerative disease. These findings highlight the heterogeneous nature of IOD.

Olfactory dysfunction is a well-established early feature of PD and dementia. Therefore, impaired olfaction has been proposed as a potential biomarker of prodromal neurodegeneration [7, 8, 14]. However, our data demonstrate that isolated IOD, even among patients with severe olfactory impairment and long symptom duration, rarely progresses to clinically manifest neurological disease. This underscores the importance of distinguishing between population-level associations and individual-level clinical prediction.

A clinically important finding was the identification of a subgroup of patients with neurological symptoms suggestive of PD or dementia but without a confirmed diagnosis at the time of follow-up. It should be emphasised that this subgroup is heterogeneous and not a formally validated patient group. However, this subgroup represents the true clinical challenge, requiring heightened clinical vigilance and thoughtful clinical judgement. This group likely reflects the gradual and often nonspecific onset of neurodegenerative disease, where diagnostic thresholds may not yet be met. By analysing these patients separately rather than merging them with confirmed cases, the study reflects real-world diagnostic uncertainty and avoids premature attribution of neurodegenerative disease.

Baseline olfactory test performance differed across outcome groups, with lower mean TDI scores observed among patients who later developed PD or dementia. However, the substantial overlap in olfactory performance between groups limits the clinical utility of olfactory testing alone for individual risk prediction. Similarly, symptom duration at baseline did not distinguish patients who remained idiopathic from those who developed neurological disease. Many patients had experienced olfactory dysfunction for several years, and in some cases for several decades, without progression to neurodegenerative disease. This argues against symptom duration as a reliable prognostic marker.

MRI of the olfactory bulb did not contribute meaningfully to risk stratification in this cohort. Abnormal findings were observed only among patients who remained idiopathic, and no consistent pattern was identified among patients with confirmed or suspected neurodegenerative disease. Together, these findings suggest that currently available routine ENT data, including olfactory test scores, symptom duration and imaging findings, cannot be combined into a clinically useful prediction algorithm for future neurodegenerative disease. At the same time, it is important to bear in mind that our study was designed to provide a descriptive characterisation of the cohort and its clinical outcomes rather than to identify prognostic markers.

From a clinical perspective, the study provides reassurance. While vigilance is warranted, IOD alone should not prompt extensive neurological investigation in the absence of other suggestive symptoms. Rather, IOD should remain a diagnosis of exclusion, with emphasis on patient information, symptom monitoring and re-evaluation if neurological features emerge over time (Table 3).

TABLE 3 Clinical management of idiopathic olfactory dysfunction.

Step	Description
Initial assessment	ENT evaluation to exclude common causes of olfactory dysfunction, including sinonasal disease, infection, trauma and congenital conditions Document olfactory function using standardised testing Focused medical history, including neurological symptoms, medication use, and relevant comorbidities
Diagnosis	IOD should be regarded as a diagnosis of exclusion based on the clinical information available at the time of assessment Patients should be informed that IOD is common and often remains stable over time
Neurological evaluation	Routine neurological referral or neuroimaging is not indicated in patients with IOD and no other neurological symptoms Neurological assessment should be considered if patients develop motor symptoms, cognitive decline, behavioural changes, or other features suggestive of neurodegenerative disease
Follow-up	Systematic follow-up is not mandatory for all patients but may be considered in older patients or in those with evolving symptoms Patients should be advised to seek re-evaluation if new neurological symptoms arise
Patient information	Providing balanced information to avoid unnecessary anxiety, emphasising that most patients with IOD do not develop neurodegenerative disease

ENT = ear, nose, throat; IOD = idiopathic olfactory dysfunction.

Strengths and limitations

The strengths of this study include a well-characterised clinical cohort, systematic baseline assessment, senior validation of the idiopathic diagnosis, long-term follow-up with access to clinical records and minimal loss to follow-up, ensuring a high degree of outcome ascertainment.

Several limitations should be acknowledged. The cohort was recruited from a tertiary referral centre, which may limit generalisability. The reported onset of olfactory dysfunction was based on patient recall at the baseline assessment. Because symptom onset may have occurred many years before study inclusion, these estimates are subject to recall bias. Follow-up assessments were affected by the COVID-19 pandemic, resulting in variable follow-up intervals and incomplete quantitative data for some patients. Neurological diagnoses were based on available clinical documentation, and diagnostic delay is well recognised in both PD and dementia. It is therefore possible that additional patients may develop neurodegenerative disease with longer follow-up.

Clinical implications

Based on these findings, patients presenting with IOD can generally be reassured that the risk of subsequent neurodegenerative disease appears to be low. Routine neurological referral is unlikely to be necessary in the absence of other neurological symptoms.

Conclusions

In this tertiary referral cohort, most patients diagnosed with IOD remained without clinically manifest neurodegenerative disease during follow-up. Although a small proportion later developed PD or dementia, these

findings suggest that isolated IOD may have limited utility for predicting subsequent neurodegenerative disease at the individual patient level. The study supports a conservative clinical approach, emphasising careful initial evaluation, patient reassurance and longitudinal clinical vigilance rather than routine extensive neurological investigation.

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