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Characterisation of patients with idiopathic olfactory dysfunction and plan for clinical follow-up

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ABSTRACT

Introduction: Characterisation and management of olfactory dysfunction (OD) can be challenging, especially in patients diagnosed with idiopathic OD. This group of patients is at risk of developing neurodegenerative diseases such as Parkinson's disease, wherefore appropriate guidelines for management of OD are needed. We aimed to identify and characterise patients suffering from idiopathic hyposmia/anosmia.

Methods: This prospective study included 515 consecutive patients referred to the Flavour Clinic, Holstebro, Denmark. Patients with idiopathic, sino-nasal or post-infectious OD were compared with regards to symptoms and clinical findings including endoscopy of the upper airways, sino-nasal CT, allergy testing, and olfactory and gustatory assessment.

Results: Patients with idiopathic OD were older and a preponderance of females was observed compared with the sino-nasal group ($p = 0.0302$, and $p = 0.0549$, respectively). The idiopathic OD group had a lower prevalence of allergy and longer symptom duration than both the sino-nasal and the post-infectious groups ($p < 0.0001$ and $p = 0.0014$; $p < 0.0001$ and $p < 0.0001$, respectively).

Conclusions: Patients suffering from idiopathic OD were predominantly females with a long symptom duration. Only few of these patients suffered from allergies or sino-nasal pathologies. Patient history, the Sino-Nasal Outcome Test and threshold discrimination identification scores from the Extended Sniffin Sticks test are the most valuable clinical tools for diagnosing the aetiology behind OD. An ideal workup for idiopathic OD is presented.

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Complete loss of smell (anosmia) and reduced sense of smell (hyposmia) are common disorders worldwide, occurring in 1% and 15% of populations, respectively [1]. Olfactory disorders (OD) are currently gaining increasing awareness, partly due to the reported associated decrease in quality of life [2].

The main causes of OD include head traumas, chronic rhinosinusitis (CRS), viral upper-airway infections, neurodegenerative diseases and congenital olfactory loss [3]. However, the underlying cause of OD is not always identifiable. Idiopathic OD is of particular interest and challenging. When diagnosing patients at a smell and taste centre, 16% are classified as suffering from idiopathic OD [3]. In Parkinson's disease (PD) and Alzheimer's disease, idiopathic OD often precedes motor symptoms, meaning that patients with idiopathic OD are at risk of

developing PD. More specifically, a 10% risk of PD development in patients with idiopathic OD has been reported [4]. Therefore, physicians must consider idiopathic OD as a potential prodromal symptom of a neurodegenerative condition.

Techniques have evolved to quantify OD, and treatment modalities have emerged [3]. A thorough patient history is valuable [3]. Subjective assessment comprises part of the workup for OD patients. A common tool is the Sino-Nasal Outcome Test (SNOT-22), a validated patient-reported outcome for CRS that assesses the overall disease burden [3]. This tool is helpful when monitoring the effect of clinical intervention. However, a previous study has shown that self-assessment is not sufficient, and additional testing is necessary for accurate assessment of olfactory function [5].

The utility of imaging techniques for assessing olfactory dysfunction remains debated. A previous study justified the cost of screening patients with idiopathic OD by magnetic resonance imaging (MRI) [6], whereas a study by Hoekman et al concluded that patients with idiopathic OD should not undergo routine MRI because the costs were not justified by the rate of detectable abnormalities [7].

In the present study, we aimed to describe an unselected group of patients suffering from idiopathic OD in order to identify possible parameters that could differentiate these patients from those with the most common causes of OD: CRS and previous infection.

METHODS

Participants

From 2017 to 2019, 515 consecutive patients were included at the only smell and taste clinic in Denmark: the Flavour Clinic, ENT Department, Region Hospital West Jutland. Idiopathic OD was diagnosed in 118 patients (23%) using the following criteria: no endoscopic pathology in the nasal cavity, no response to systemic or topical corticosteroids, and no timely association between OD and infections of the upper airway or head trauma [4]. To distinguish between idiopathic OD and congenital OD, a history of previously normal olfactory function was required. Patients with traumatic OD were not included for comparison due to their limited number.

All patients had a CT scan of the nose and sinuses, endoscopic examination of the upper airways, and allergy test by serum immoglobulin E or skin test before referral to the clinic. CRS and allergic conditions needed to be optimally treated by the referring ear, nose and throat specialist.
A thorough patient history was taken. A questionnaire of taste and smell symptoms including allergies, smoking and alcohol status, occupational exposure and family history was completed. Furthermore, patients filled in the SNOT-22 and the Major Depression Inventory (MDI).

Physical examination was performed including rhinoscopy and flexible endoscopy focusing on the olfactory cleft, inspection of the oral cavity, neurological screening, and the Mini-mental State Examination (MMSE). If neurological pathology was suspected based on these examinations, the patient was referred for 1.5T MRI of the brain.

Olfactory and gustatory assessment

Olfactory and gustatory testing was performed by trained nurses or medical students. According to the TDI scores from the Extended Sniffin Sticks test (**t**hreshold, **d**iscrimination, and **i**dentification), patients were categorised with normosmia, hyposmia or functional anosmia [8]. Hyposmia was defined as scoring below the tenth percentile, corresponding to a TDI score below 29.8 [8]. Anosmia has been defined as a TDI score below 16 [9]. Assessment of gustatory function changed during the inclusion period: Initially, the taste strip test was used.

This test was replaced by the more reliable Taste Drop Test [10]. After this replacement, all patients were screened by the Taste Spray Test [11]; and in case the patient failed to recognise one or more of the four basic tastes, the Taste Drop Test was applied.

Statistics

All data were registered in a database [12] and analysed. As included variables were non-parametric, Kruskal-Wallis test was used to compare age across all three groups, whereas the Mann- Whitney test was used between groups. Pearson's χ^2-test was used for evaluating differences in categorical variables between all groups, while Fisher's exact test was used for 2 × 2 contingency tables.

$p < 0.05$ were considered significant. However, as this study is exploratory by nature, multiple comparisons were made between groups. To avoid Type I error, correction for multiple comparisons was made using the Bonferroni correction, yielding a corrected p-value significance of 0.005.

Trial registration: not relevant.

RESULTS

A group of patients with idiopathic OD (n = 118) was compared with patients with sino-nasal OD (n = 129) and post-infectious OD (n = 152) (**Table 1**). Across all aetiologies, we observed no significant difference according to age (p = 0.067, Kruskal-Wallis). Patients with idiopathic OD were older than patients in the sino-nasal group (p = 0.0302, Mann-Whitney test). However, this difference was not statistically significant after correction for multiple comparisons.

TABLE 1 / Patient characteristics.

	Idiopathic (N = 118)	Sino-nasal (N = 129	Post-infectious (N = 152)
Gender male, n (%)	46 (39.0)*	67 (51.9)**	49 (32.2)*
Age, yrs, median (IQR)	61.5 (53.8-72)*	59 (47.5-68)**	60 (50.25-67)
Subjective sense of smell, n (%)			
Normal	1 (0.8)	1 (0.8)	1 (0.7)
Reduced	40 (33.9)	46 (38.0)	71 (46.7)
Absent	77 (65.3)*	73 (60.3)	80 (52.6)**
Subjective sense of taste, n (%)			
Normal	22 (18.6)	22 (17.6)	23 (15.1)
Reduced	68 (57.6)	73 (58.4)	85 (55.9)
Absent	25 (21.2)	28 (22.4)	41 (27.0)
Symptom duration, mo.s, median (IQR)	69 (36-120)*	72 (36-132)*	48 (18-120)**
Smoking status, n (%)			
Current	5 (4.2)	11 (8.9)	9 (5.9)
Previous	39 (33.0)	45 (36.6)	37 (24.3)
Non	74 (62.7)	67 (54.5)	106 (69.7)
Allergies, n (%)			
Allergy	18 (15.4)*	46 (37.7)**	48 (31.6)**
No allergies	95 (81.2)	57 (46.7)	93 (61.2)
Unknown	4 (3.4)	19 (15.6)	11 (7.2)
CT, normal, n (%)	85 (72.0)*	34 (26.4)**	107 (70.4)*

IQR = interquartile range.
*, **) Significant groups differences are indicated with */** to show which groups differ.

The gender distribution differed between groups ($\chi^2 = 11.398$, $p = 0.0033$), as the idiopathic and post-infectious group had more women than the sino-nasal group ($p = 0.0549$ and $p = 0.0010$, respectively, Fisher's exact test). The prevalence of allergy differed between groups ($\chi^2 = 20.585$, $p < 0.0001$) and was significantly lower in the idiopathic group than in the sino-nasal group and the post-infectious group ($p < 0.0001$ and $p = 0.0014$, respectively, Fisher's exact test).

Self-reported anosmia was significantly more frequent among idiopathic OD patients than among patients with post-infectious smell loss ($\chi^2 = 4.710$, $p = 0.0300$), which is linked to the finding that patients with post-infectious smell loss had significantly better TDI scores ($p < 0.0001$, Kruskal-Wallis) than patients in both the idiopathic OD and the sino-nasal OD group (**Table 2**).

TABLE 2 / Test results. The values are median (interquartile range).

	Idiopathic	Sino-nasal	Post-infectious
TDI score			
Threshold	1 (1-2.25)	1 (1-1.88)	1.25 (1-3.25)
Discrimination	6 (5-9)	7 (5-9)	9 (6-11)
Identification	7 (5-9)	7 (4-11)	10 (6-13)
Total	14 (11.0-20.1)*	16 (10.5-22.0)*	20 (14.0-25.3)**
SNOT 22 score	13 (7-25)*	24 (14.75-38)**	18 (12-29.25)*
MDI score	3.5 (1-7.25)	4 (2-10)	5 (2-12)
MMSE score	29 (28-30)	28 (27-29)	29 (28-29)
Gustatory scores			
Taste Spray	4 (4-4)	4 (4-4)	4 (4-4)
Taste Strips	12 (10.5-14)	13 (9-15)	12 (10-15)
Taste Drop Test	22 (18.25-24.75)	26 (15.75-28)	25 (19-29.5)

MDI = Major Depression Inventory; MMSE = Mini-mental State Examination; SNOT 22 = The Sino-Nasal Outcome Test; TDI = threshold discrimination identification.
*, **) Significant groups differences are indicated with */** to show which groups differ.

Fewer patients with sino-nasal OD had a normal CT ($\chi^2 = 139{,}212$, $p < 0.0001$).

The SNOT-22 yielded significantly higher scores in the sino-nasal group than in the idiopathic group ($p < 0.0001$, Mann-Whitney) and the post-infectious group ($p = 0.0111$, Mann-Whitney).

Independent of aetiologies, MDI and MMSE scores were indistinguishable between groups ($p = 0.1059$, Kruskal-Wallis) ($p = 0.0903$, Kruskal-Wallis).

Symptom duration was significantly shorter for post-infectious OD than for idiopathic OD ($p < 0.0001$, Mann-Whitney) and sino-nasal OD ($p < 0.0001$, Mann-Whitney).

DISCUSSION

We found that the patients with idiopathic OD were older than the patients in the sino-nasal group. This may reflect a general age-related neuronal degeneration as in the case of presbyacusis. But it may also be the first manifestation of PD, which usually is diagnosed at the age of 65 to 70 years [13]. Previous studies have shown that olfactory symptoms on average precede the PD diagnosis by more than ten years [4].

Among patients with idiopathic OD and post-infectious OD, we recorded more women than men compared with the sino-nasal group. Haehner et al [4] also found a majority of women among patients with idiopathic OD. This is not surprising as women are generally more frequently referred to taste and smell clinics due to various OD-types than men [14].

Complete absence of smell was more often reported in idiopathic OD than in post-infectious OD. In addition, patients with post-infectious OD had higher TDI scores than patients with idiopathic OD. As such, an idiopathic aetiology seems to be associated with a more severe OD. This may be due to the regeneration known to occur in

post-infectious OD and the effects of treatment in sino-nasal OD [3]. In line with our findings, Migneault-Bouchard et al [15] also found higher TDI scores in the post-infectious and sino-nasal groups than in the idiopathic group, which supports the findings that idiopathic OD causes a more pronounced olfactory impairment. Furthermore, this is supported by our finding that subjective and objective loss of smell were associated [16], which emphasises the importance of combining the self-reported questionnaires and objective testing when diagnosing OD.

We found no significant differences related to MDI and MMSE scores. Despite a previously reported correlation between OD and depression [17], none of the groups in our study had high MDI scores. It deserves mention, though, that MDI is not an accurate test, and we did not take use of anti-depressants at the time of diagnosis into account.

Patients with manifest PD show subnormal MMSE scores [18]. Even so, we did not expect to find a difference between the groups, as cognitive deficits is not a typical prodromal symptom in PD [19]. The use of these psychometric tests can be informative, but in the present study they did not inform the process of diagnosing the underlying aetiology.

We found that symptom duration was longer in idiopathic OD and sino-nasal OD than in the post-infectious group, which may indicate that some of the patients with idiopathic OD may have forgotten that the olfactory loss began after an infection, which is one of the most common causes of OD.

Analysis of SNOT-22 questionnaires, allergy status and CT yielded significant information about group differences. These findings are in line with the criteria of CRS from the European Position Paper on Rhinosinusitis and Nasal Polyps, where symptoms of CRS are included in the SNOT-22, and CTs are supportive of the CRS diagnosis [20]. CRS can be a manifestation of allergies the prevalence of which was significantly higher in the sino-nasal and post-infectious groups than in the idiopathic OD group. Gustatory testing yielded no significant difference between the three patient groups. Similarly, the study from Migneault-Bouchard et al [15] showed no difference between aetiology and the results of taste strips. We were unable to identify any significant findings, which is likely due to the small percentage of patients with concomitant olfactory and gustatory dysfunction. Additional studies with larger study populations are needed to establish whether patients suffering from idiopathic OD also have gustatory disorders more often than patients suffering from OD of other aetiologies.

A strength of our study is the comprehensive number and completeness of questionnaires, patient history, examinations and paraclinical tests for all the consecutively included patients. Furthermore, the questionnaires and tests have been validated for use in Denmark [8, 10].

Although differences were found on a group level, the application of each of the clinical parameters cannot be used to differentiate at the individual patient level. In a clinical setting, this means that it is still not possible to differentiate between the causes of OD based on single details in the patient history, objective findings or paraclinical tests. It is up to the physician to take all these factors into account.

Recommendations

When conducting a diagnostic workup of a patient suffering from OD, our study shows that especially a thorough patient history, SNOT-22 and TDI testing are crucial in making the right diagnosis. Psychometric tests such as the MMSE and the MDI may be helpful in ruling out alternative aetiologies, but not in differentiating between post-infectious, sino-nasal and idiopathic OD. Patients with low MDI scores are referred to a psychiatrist, psychologist or general practitioner, whereas low MMSE scores trigger referral to a neurologist (**Table 3**). Patients in whom the medical history or objective neurological findings raise suspicion of cerebral

causes are referred for cerebral MRI. In case of clinical and/or MRI-based suspicion of cerebral pathology, the patients are referred to a neurologist.

TABLE 3 / Clinical workup.

Almost 25% of all olfactory disorders (OD) are idiopathic
Idiopathic olfactory disorders may be a prodrome of Parkinson's disease, identification is important
Work-up includes clinical examination, sino-nasal CT, allergy testing, olfactory and gustatory assessment
Referral to a neurologist if two or more risk markers are present: 1st-degree relative with Parkinson's disease Rapid eye movement sleep disorder Constipation Clear signs of autonomic dysfunction: Orthostatic hypotension, erectile dysfunction, urinary incontinence or retention A Mini-mental State Examination score < 27 Age > 75 years Motor symptoms (objective): tremor, rigidity, bradykinesia or postural instability[a] Motor symptoms (subjective): handwriting changes, lack of manual dexterity in repetitive tasks, feeling of imbalance.

a) All patients should be referred even in the absence of other symptoms.

If underlying prodromal PD is suspected, a more elaborate approach is required. We suggest to use a questionnaire about risk factors such as those presented by Heinzel et al [19]. These risk factors include gender, possible rapid eye movement, sleep behaviour disorder, smoking, pesticides, clear signs of autonomic dysfunction and constipation, etc. It is important, however, to point out that such a questionnaire cannot disclose a diagnosis of prodromal PD on its own.

Patients who have been diagnosed with idiopathic OD for less than three years are recommended daily olfactory training with different odorants [3] and follow up 12-18 months later. Those with an unchanged or worsened status are referred to a neurologist.

CONCLUSIONS

We found that patients with idiopathic OD were predominantly female with a both subjectively and objectively severely reduced sense of smell as well as a long symptom duration. Only few of these patients suffered from allergies or sino-nasal pathologies. No significant differences in MMSE or MDI scores were found. However, we found that patient history, the SNOT-22 and TDI testing are the most valuable tools in the clinic for diagnosing the aetiology behind OD. Finally, we presented an ideal workup for patients with idiopathic OD.

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* The article has been updated due to som minor corrections in the text. A new Table 3 has been inserted. Primary corrections are; the old table mentions random eye movements, correct is rapid eye movements, orthostatic hypertension is now changed to orthostatic hypotension.

LITERATURE

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