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ORIGINAL COMMUNICATION

Incidence of Parkinson's disease in a large patient cohort with idiopathic smell and taste loss

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Abstract

Introduction Patients with idiopathic smell loss constitute an at-risk population for the development of Parkinson's disease (PD). The study aimed to follow up a large number of patients with idiopathic smell and/or taste loss to define the incidence of PD in this population and, further, to assess characteristics of both olfactory and gustatory function and their possible association with PD development.

Methods In this prospective case–control study, 833 patients diagnosed with an idiopathic smell disorder at our Smell and Taste Center during the last 15 years were contacted for a telephone interview. In 474 patients, a complete data set containing of demographic data, clinical information, retrospective smell and taste testing results, and telephone assessment was obtained.

Results Out of 474 patients with idiopathic smell loss 45 (9.8%) had been diagnosed with PD, since they received the diagnosis of idiopathic smell and/or taste loss (mean 10.9 years after olfactory loss onset). Thus, with respect to the classification into olfactory/gustatory disorders, 28.6% of the patients with a combined olfactory and gustatory disorder developed PD, whereas in 9.9% of those with a pure olfactory disorder and in 3.8% of those with a pure gustatory disorder, PD was diagnosed. No association emerged between qualitative smell or taste loss and PD development.

Conclusion This large patient cohort study extends the previous literature, indicating that risk stratification might be considerably improved by correct diagnostic allocation and emphasizes the need for an exhaustive olfactory and gustatory assessment in specialized centers.

Keywords Idiopathic smell loss · Idiopathic taste loss · Parkinson's disease

Introduction

Olfactory loss has been reported as one of the major non-motor symptoms in Parkinson's disease (PD) which precedes the occurrence of clinical motor symptoms [1, 2]. It is found in around 90% of patients with PD [3–5] and has been acknowledged as a supportive criterion in clinical PD diagnosis according to the new International Parkinson's Disease and Movement Disorder Society diagnostic criteria [6]. The pronounced olfactory deficit is thought to be, at least in part, related to changes in the olfactory bulb, a region impaired in the first stage of the disease [7], and to be linked to α-synuclein-mediated pathology. The previous results indicate alterations in central olfactory processing [8] without specific changes in olfactory peripheral structures [9].

A number of studies already pointed out the association between unexplained smell loss and later development of PD [10–14], indicating a serious PD at-risk population among patients with olfactory dysfunction. Against this background, a correct and secured "idiopathic" classification according to the current diagnostic ORL criteria for smell disorders, including anterior rhinoscopy, nasal endoscopy, olfactory testing, and MR imaging, should become an essential requirement for a reliable risk stratification.

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While previous prospective studies in patients with unexplained olfactory dysfunction were mainly population-based and merely relied on a combination of patients' history and smell testing without exhaustive clinical assessment, the current study focuses on a large, thoroughly diagnosed patient cohort of a Smell and Taste Clinic.

The aim of this study was to follow up a large number of patients with idiopathic smell and/or taste loss to define the incidence of PD in this population. Furthermore, we assessed characteristics of both quantitative and qualitative olfactory and gustatory function and their possible association with PD development.

Materials and methods

Participants

In this prospective case–control study, 833 patients diagnosed with an idiopathic smell disorder at our Smell and Taste Clinic from 2000 to 2014 were contacted for a telephone interview. The specification of idiopathic olfactory loss required 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/topical treatment with corticosteroids. All aspects of the study were performed in accordance with the Declaration of Helsinki, and the study protocol was approved by the local Ethics Board of the TU Dresden.

Olfactory and gustatory assessment

At the first visit to our clinic, olfactory testing was performed with the "Sniffin' Sticks" [15, 16] a testing battery involving tests for odor threshold, odor discrimination, and odor identification. The sum of the scores from the three subtests resulted in the TDI score (threshold, discrimination, and identification), indicating normosmia, hyposmia, or functional anosmia (further addressed as anosmia). In addition, a basic whole-mouth test (WMT) using taste sprays was applied in all patients for gustatory evaluation. In patients with ageusia or hypogeusia, taste strips (four different concentrations for each taste) were used for further evaluation [17].

Retrospective data collection

Demographic data and clinical information on symptomatology at initial presentation [including age, duration of smell and/or taste loss, olfactory (TDI) and gustatory (WMT/tastes strips) score, qualitative olfactory (parosmia/phantosmia), and gustatory (parageusia, phantogeusia) score] were obtained through retrospective chart review. Furthermore, subtle clinical motor signs at initial presentation (based on a thorough neurological examination) and family history of PD were recorded.

Telephone Interview Questionnaire

Patients ($n = 833$) were followed-up through telephone interview using a standardised questionnaire which included a self-assessment of the patients' current smell and taste function (improvement, decline, and no change). Complete recovery would require exclusion from the study. Furthermore, patients were interviewed about newly developed diseases since the diagnosis of smell loss. Specific questions were asked regarding the possible diagnosis of PD and the use of antiparkinsonian medications (Have you been diagnosed with PD? Who diagnosed the disease? What symptoms do you suffer from? Are you treated by a neurologist? What medications are you taking? Do you respond to dopaminergic therapy?). Only answers clearly indicating a PD diagnosis would justify the classification as a PD patient.

Statistical analysis

Data analysis was performed using SPSS 22 for Windows (SPSS Inc., Chicago, IL, USA). Normal distribution of the data was assessed using the Kolmogorov–Smirnov test. As the majority of the variables did not have normal distribution, statistical analyses were performed by non-parametric Mann–Whitney *U* test. Other variables, such as age of onset of the sensory deficit (in years) and the period from the age of onset to telephone interview, were normally distributed allowing the application of *t* tests. The comparison between categorical variables was performed by Chi-square (χ^2) test (degrees of freedom = 1) and in case of a small sample size (≤ 5) by Fisher's exact test. For all tests, the level of significance was set at $\alpha < 0.05$. Data are presented as mean values ± standard deviation. Furthermore, generalized estimating equation, a general statistical approach to fit a marginal model for longitudinal data analysis, was applied.

Results

Study population

Out of the 833 patients with idiopathic olfactory/gustatory loss 285 (34.2%) could not be contacted because of missing, incorrect, or out-of-date telephone numbers. Fifty-two patients (6.2%) are deceased. Thus, 496 patients were eventually interviewed by telephone. Twenty-two out of these

persons reported a complete recovery of their smell and taste loss, indicating a non-idiopathic cause (e.g., sinunasal or viral) which required exclusion from the study. Finally, data were analysed in 474 patients (Fig. 1) who had been contacted by telephone on average 8.1 years (range 2–17 years; ± SD 3.75) after first presentation to our clinic.

At the time of first presentation, study participants [258 women, 216 men; mean ± SD age: 70.1 ± 11.4 years (range 26–95 years)] had already suffered from smell and/or taste loss for 4.3 ± 5.6 years (mean ± SD). Onset of olfactory disturbances was noticed at the age of 57.9 years ± 12.5 (mean ± SD) and of gustatory disorders at the age of 59.3 ± 13.1 (mean ± SD). No significant difference in sensory loss onset emerged between men and women (olfaction: $p = 0.06$; taste: $p = 0.22$) with, however, male patients being affected on average 2.7 years later.

Olfactory and gustatory function

Out of the 474 participants, 68 (14.3%) presented with normosmia, 192 (40.5%) with hyposmia, and 214 (45.1%) with anosmia (Fig. 2a). Normosmic patients suffered from both gustatory disorder and purely qualitative olfactory disorder.

With regard to taste, 427 patients (90.1%) had normogeusia, 45 (9.5%) hypogeusia, and 2 (0.4%) had ageusia. Patients with normogeusia presented with both olfactory

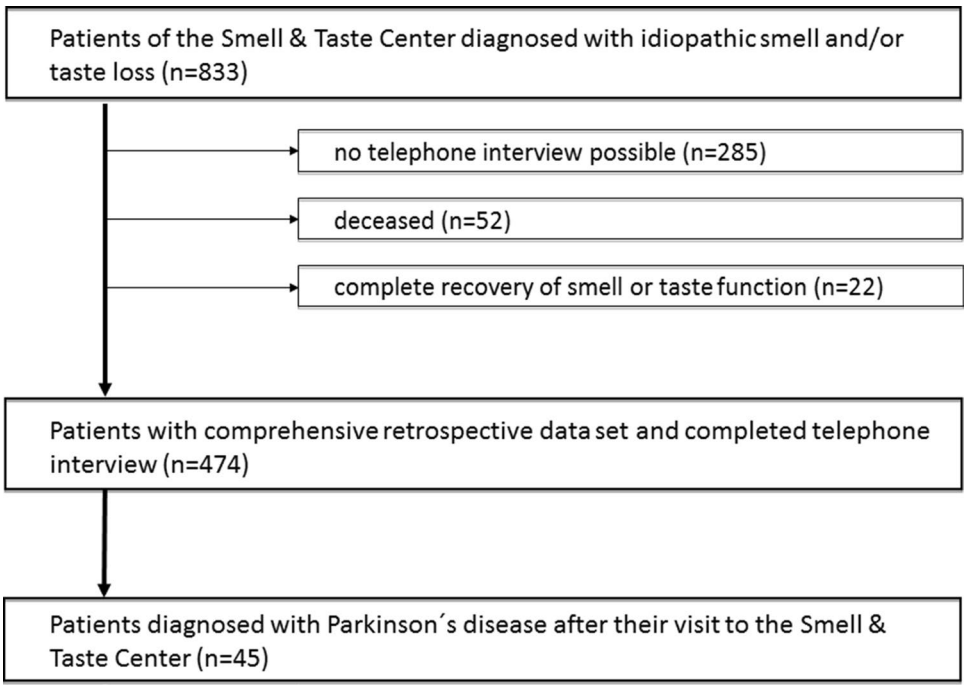

Fig. 1 Analysed patient cohort

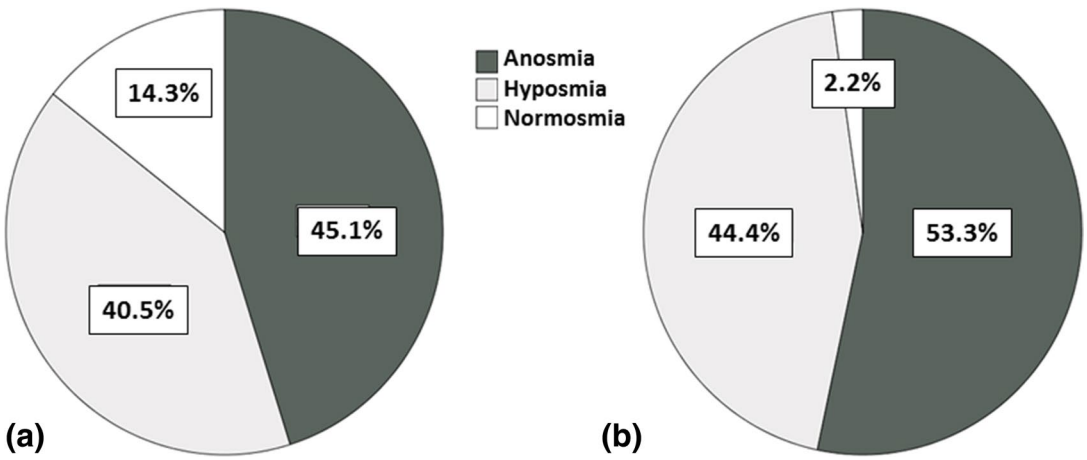

Fig. 2 Degree of smell loss at the first visit to our clinic in the whole cohort (**a**) and in patients who developed PD (**b**)

deficits and purely qualitative gustatory disorders, i.e., parageusia or phantogeusia.

Four hundred and thirty-two (91.1%) of the patients showed quantitative olfactory and gustatory disorders. Among these subjects, 385 (89.1%) had olfactory disorders, while 26 (6%) had been diagnosed with a gustatory disorder and 21 (4.9%) with a combined olfactory and gustatory disorder.

The diagnosis of a qualitative olfactory or gustatory disorder had been made in 242 subjects (51.1%). Parosmia, phantosmia, and parageusia were reported in 21.1% ($n=100$), 32.9% ($n=156$), and 7.6% ($n=36$) of study participants, respectively (also combined qualitative disorders reported). The most common gustatory quality in subjects with parageusia was salty in 13 subjects, followed by putrid, bitter, and metallic taste in 7, 5, and 4 patients, respectively. Five participants reported parageusia with changing qualities, and one person each had salty and sweet phantogeusia.

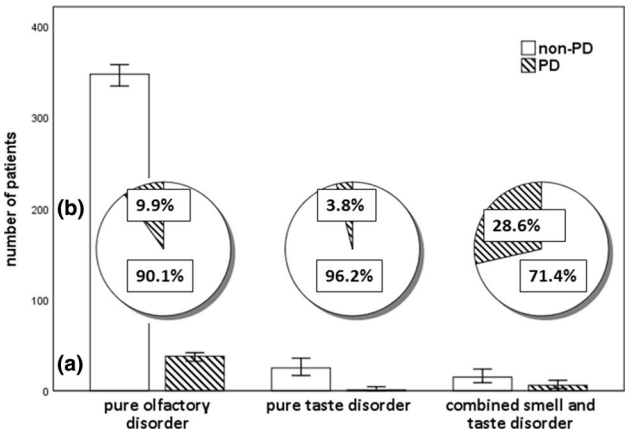

Fig. 3 Frequency of PD in quantitative olfactory and gustatory disorders in absolute numbers (**a**) and relative percentage within the category (**b**)

Diagnosis of PD

Forty-five patients (9.5%; 23 women, 22 men) had been diagnosed with PD, since they received the diagnosis of idiopathic smell and/or taste loss (mean ± SD, years 9.6 ± 3.8, range 2–16). Thus, with respect to the classification into olfactory/gustatory disorders, 28.6% ($n=6$) of the patients with a combined olfactory and gustatory disorder developed PD, whereas in 9.9% ($n=38$) of those with a pure olfactory disorder and in 3.8% ($n=1$) of those with a pure gustatory disorder PD was diagnosed (Fig. 3).

As regards the age of smell loss onset, there were no significant differences (Mann–Whitney U test: $U=8752$, $p=0.91$) between PD patients (58.6 ± 9.6 years) and those who did not develop PD (57.8 ± 12.8 years). The same applies to the age of the onset of gustatory impairment insofar, as no statistical differences [$t(59)=-0.86$, $p=0.39$] were observed between PD patients (63.7 ± 7.8 years) and non-PD subjects (58.8 ± 13.5 years) (Table 1). At the time of the telephone interview, PD patients (M = 74.8 years ± 8.2 SD) were older than those without PD (M = 69.6 years ± 11.6 SD; Mann–Whitney U test: $U=7109$, $p=0.004$; Cohen's $d=0.46$).

Table 1 Clinical characteristics of patients with idiopathic smell and/or taste loss (divided into outcome parameters PD and non-PD)

	PD ($n=45$)	Non-PD ($n=429$)	p value
Female	23 (51.1%)	235 (54.8%)	
Male	22 (48.9%)	194 (45.2%)	
Age of smell loss onset (M ± SD), years	58.6 ± 9.6	57.8 ± 12.8	0.91
Age of taste loss onset (M ± SD), years	63.7 ± 7.8	58.8 ± 13.5	0.39
Pure quantitative olfactory disorder	38 (84.4%)	347 (80.9%)	
Combined quantitative olfactory and gustatory disorder	6 (13.3%)	15 (3.5%)	
Pure quantitative gustatory disorder	1 (2.2%)	25 (5.8%)	
Pure qualitative disorder	0	42 (9.8%)	
Anosmia, *n*	24 (53.3%)	190 (44.3%)	
Hyposmia, *n*	20 (44.4%)	172 (40.1%)	
Normosmia, *n*	1 (2.2%)	67 (15.6%)	
TDI score (M ± SD)	15.62 ± 5.0	17.94 ± 7.8	0.14
Olfactory threshold (M ± SD)	2.2 ± 2.1	2.8 ± 2.9	0.44
Olfactory discrimination (M ± SD)	7.5 ± 2.4	8.2 ± 2.9	0.07
Olfactory identification (M ± SD)	6.0 ± 2.7	7.0 ± 3.5	0.14
Taste stripes score (M ± SD)	12.7 ± 4	15.6 ± 6.1	0.47
Subjective deterioration of smell loss	20 (44.4%)	105 (24.5%)	
Subjective deterioration of taste loss	18 (40%)	93 (21.7%)	

This resulted in a longer period from the smell loss onset to the telephone interview (Mann–Whitney U test: $U = 6028$, $p < 0.001$) in PD patients (16.2 ± 8.7 years) compared to non-PD patients (11.9 ± 6.7 years). This period did not differ, however, in terms of gustatory impairment [$t(59) = -0.64$, $p = 0.53$; PD: M = 11.7 years ± 2.6 SD; non-PD subjects: M = 10.6 years ± 4.2 SD].

PD patients presented for the first time to our Smell and Taste Clinic 6.6 ± 7.6 years (mean ± SD; range 0–20 years) after the onset of olfactory dysfunction and 1.8 ± 1.7 years (mean ± SD; range 0–4 years) after the onset of gustatory dysfunction. PD was diagnosed 10.9 ± 4.6 years (mean ± SD; range 3–20 years) after the onset of olfactory dysfunction. In PD patients, the telephone interview took place on average 9.6 years (range 2–16 years ± 3.8 SD) after first presentation to our clinic.

At the time of presentation to our Smell and Taste Clinic, 5 out of the 45 subjects already showed subtle clinical motor signs when being examined (reduced arm swing: $n = 3$; slight rigidity: $n = 1$; intermittent higher frequency tremor of both hands: $n = 1$). Another four patients reported changes in their gait (instability, decrease in step length) which was not obvious in the neurological examination. In the patients who did not develop PD, no clinical motor signs had been found on examination.

In 15 (3.2%) out of the total 474 patients, a first- or second degree relative with a diagnosed PD was known. Five out of these patients (33.3%) eventually developed PD resulting in a family history of PD in 11.1% of our PD patients and indicating a significant association between family history and PD development ($\phi = 0.15$, $p = 0.009$).

PD patients' olfactory and gustatory characteristics

Quantitative olfactory and gustatory disorders

Among the 45 patients with Parkinson's disease, 38 (84.4%) subjects exhibited a pure olfactory disorder, 1 (2.2%) had a pure gustatory disorder, and 6 (13.3%) showed both olfactory and gustatory disorder. Thus, a significant correlation was observed between the occurrence of PD and the presence of quantitative olfactory deficits ($p = 0.016$, Fisher's exact test) (Cramer-$V = 0.142$, $p = 0.015$).

Twenty-four PD patients (53.3%) presented with anosmia, 20 (44.4%) had hyposmia and only 1 (2.2%) normosmia (patient with a pure gustatory disorder) (Fig. 2b). Subjects with PD showed a higher prevalence of initial anosmia than patients without PD ($p = 0.07$, Mann–Whitney U test, $U = 8195.5$) (Cohen's $d = 0.31$). No significant association was found between anosmia ($\chi^2 = 1.35$, $p = 0.25$, $n = 474$), hyposmia ($\chi^2 = 0.32$, $p = 0.57$, $n = 474$), and the development of PD, whereas normosmia was significantly associated with non-PD ($\chi^2 = 5.95$, $p = 0.015$, $n = 474$). However, when applying the generalized estimating equation approach, an association between the severity of smell loss and PD emerged (Wald $\chi^2 = 214.3$, $p < 0.001$).

No significant differences were found for olfactory scores threshold, identification, discrimination, and TDI (general olfactory function) between subjects with and without PD (Table 1). However, patients with PD showed lower discrimination values (7.5 ± 2.4) than subjects without PD (8.2 ± 2.9) ($p = 0.07$, Mann–Whitney U test, $U = 7591.5$) (Cohen's $d = 0.25$).

In terms of gustatory function, 2.2%, 13.3%, and 84.4% of PD patients presented with ageusia, hypogeusia, and normogeusia. No statistical differences were observed in the frequency of ageusia, hypogeusia, and normogeusia between patients with PD and without PD ($p = > 0.132$, Mann–Whitney U Test, $U = 9034.5$). The same applies to the results of taste strips tasting in these groups (Mann–Whitney U test: $U = 45$, $p = 0.47$), whereby it should be noted that PD patients (M = 12.7 ± 4 SD) on average presented with lower results than non-PD (M = 15.6 ± 6.1 SD).

Qualitative smell and gustatory disorders

Out of the 45 PD subjects, 10 patients (22.2%) showed parosmia and 14 patients presented with phantosmia (31.1%) before the onset of the disease. No association was observed between the incidence of PD and parosmia ($\chi^2 = 0.04$, $p = 0.85$), or phantosmia ($\chi^2 = 0.038$, $p = 0.79$). In addition, parageusia for the salty and metallic qualities had been reported in two subjects (4.4%). None of the patients with a pure qualitative disorder did develop PD.

These results were confirmed by the generalized estimating equation approach, where no effects of qualitative smell disorders on PD development were observed (Wald $\chi^2 = 1.3$, $p = 0.25$).

Subjective assessment

Patients who developed PD reported a decrease in olfactory function (Mann–Whitney U test, $U = 7250$, $p = 0.001$) (Cohen's $d = 0.56$) and gustatory function (Mann–Whitney U test = 7580, $p = 0.003$) (Cohen's $d = 0.45$) more frequently than non-PD patients (Table 1). Among subjects with PD, 20 (44.4%) experienced an aggravation of smell loss, whereas this applies to 105 (22.2%) out of the non-PD patients. In terms of gustatory function, 18 (40%) PD patients reported a decrease in taste function, while 97 (19.6%) of non-PD patients did so (Table 1).

Thus, patients with a decrease in olfactory or gustatory function developed PD with a significantly higher rate compared to patients with a stable smell ($\chi^2 = 8.36$, $p = 0.004$) or taste function ($\chi^2 = 7.62$, $p = 0.006$). A subjective decrease in olfactory or gustatory function indicated an almost 2.5-fold

greater risk of future PD (OR 2.47; 95% confidence interval 1.3–4.6).

Discussion

In this large patient cohort study, we found an almost 10% rate of PD development among patients with diagnosed idiopathic olfactory loss, whereby the PD rate raised to 28.9% in those with a combined olfactory and gustatory loss. We demonstrated that the olfactory dysfunction frequently precedes the PD motor symptoms by more than 10 years and that smell and taste loss are characterized by further deterioration prior to PD diagnosis. Thus, the current study extends the previous literature, indicating a very early start of olfactory symptoms in PD and emphasizing the need for an exhaustive olfactory and gustatory assessment in clinical settings.

Our study was conducted in a large patient cohort of a Smell and Taste Clinic with a comprehensive diagnostic work-up and regular follow-up visits. This ensured a reliable diagnostic allocation and a long observational period. The reported PD rates in olfactory disorders might, therefore, be higher than in the previous population-based reports [13, 14] pointing towards a higher specificity of a clearly diagnosed "idiopathic smell loss" in terms of PD risk stratification. The even higher risk by considering the family history of PD in first- or second-degree relatives is reflected by a percentage of 33% PD development in this patient group in our study. Thus, our findings extend the observation by Ponsen et al. [10, 11] who diagnosed PD in 5 out of 40 first-degree relatives with smell loss and Berg et al. [14] with 8 PD diagnoses out of 468 at-risk persons with hyposmia and/or PD family history.

In previous studies that have investigated the prospective risk for PD in relation with baseline [10–14] follow-up periods ranged from 2 to a maximum of 8 years. The duration of this phase prior to PD diagnosis is still, however, a matter of debate [18]. While Morrish et al. [19] based on [18F]dopa PET data suggested a preclinical period no longer than 7 years, other authors assumed that this period may last up to decades [20]. The latter corresponds to retrospective patients' self-perception, indicating the onset of olfactory loss on average more than 10 years before PD diagnosis [21, 22] and to the results of more recent studies [23, 24] which are in line with our data. This implies that patients with idiopathic smell loss constitute an at-risk population for at least 10 years and should be followed-up on a regular basis over this period.

In contrast to quantitative smell loss, no association between qualitative smell and taste disorders and future PD was found. This corresponds to the results of a follow-up study in 44 patients with idiopathic phantosmia [25]; however, there is currently no literature on qualitative gustatory function and later development of PD.

Compared to smell impairment, taste loss has been less frequently reported in clinical interviews of PD patients [26], and no immunohistochemical and neuroimaging studies on gustatory function in PD currently exist. There is only a small number of cross-sectional studies regarding taste perception in PD [27–32], indicating less pronounced taste impairment in PD compared to smell dysfunction. Taste loss has so far been linked to the advanced stages of the disease [30], whereas reports on prodromal presentation are rare. As one of the few studies on this topic, in the onset PD study [22], estimated time of taste loss onset varied between 2 and 10 years before PD diagnosis. Interestingly, taste loss was present before onset of motor symptoms in more than 70% of those patients reporting them at the time of interview which provides evidence for a very early onset of taste loss similar to the occurrence of olfactory symptoms. Considering the fact that in all patients, taste loss was accompanied by smell dysfunction, testing these two sensory functions together would enhance the predictive value for PD. This was exactly shown in our study by observing an almost three times higher PD frequency in combined smell and taste loss compared to pure olfactory loss. Findings thus imply the need for both olfactory and gustatory testing in a PD at-risk population or, at least, to include simple taste sprays in a screening battery. Furthermore, our observations point towards a pronounced deterioration of smell and taste function during the premotor phase which extends the aggravation in those patients who did not develop PD. Considering the 2.5-fold higher PD risk in patients who experienced olfactory or gustatory deterioration, repeated measurements should be a standard approach.

The strength of this study is its use of a very large patient cohort with a well-defined diagnosis. Limitations may arise from the retrospective data sampling with information based on medical records, the follow-up by telephone interview, and possible selection bias due to loss to follow up. Potential recall errors may have biased data on the onset of smell and taste loss and, finally, the PD onset.

In conclusion, our findings confirm and extend the observations of the previous studies regarding smell loss as a predictor of future PD. Based on the results of this large cohort study, it should be emphasized that risk stratification might be considerably improved by correct diagnostic allocation of smell and taste loss, the use of both olfactory and gustatory testing, and subsequent long-term monitoring of these functions. This in turn emphasizes the importance of a diagnostic work-up in specialized centers.

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Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Hawkes CH, Del Tredici K, Braak H (2010) A timeline for Parkinson's disease. Parkinsonism Relat Disord 16:79–84
2. Berendse HW, Roos DS, Raijmakers P, Doty RL (2011) Motor and non-motor correlates of olfactory dysfunction in Parkinson's disease. J Neurol Sci 310:21–24
3. Doty RL, Deems DA, Stellar S (1988) Olfactory dysfunction in parkinsonism: a general deficit unrelated to neurologic signs, disease stage, or disease duration. Neurology 38:1237–1244
4. Hawkes CH, Shephard BC, Daniel SE (1997) Olfactory dysfunction in Parkinson's disease. J Neurol Neurosurg Psychiatry 62(5):436–446
5. Haehner A, Boesveldt S, Berendse HW, Mackay-Sim A, Fleischmann J, Silburn PA et al (2009) Prevalence of smell loss in Parkinson's disease—a multicenter study. Park Relat Disord 15:490–494
6. Postuma RB, Berg D, Stern M, Poewe W, Olanow CW, Oertel W et al (2015) MDS clinical diagnostic criteria for Parkinson's disease. Mov Disord 30(12):1591–1601
7. Braak H, Del Tredici K, Rub U, de Vos RAI, Jansen Steur ENH, Braak H (2003) Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 24:197–211
8. Iannilli E, Stephan L, Hummel T, Reichmann H, Haehner A (2017) Olfactory impairment in Parkinson's disease is a consequence of central nervous system decline. J Neurol 264(6):1236–1246
9. Witt M, Bormann K, Gudziol V, Pehlke K, Barth K, Minovi A et al (2009) Biopsies of olfactory epithelium in patients with Parkinson's disease. Mov Disord 24(6):906–914
10. Ponsen MM, Stoffers D, Booij J, van Eck-Smit BLF, Wolters EC, Berendse HW (2004) Idiopathic hyposmia as a preclinical sign of Parkinson's disease. Ann Neurol 56:173–181
11. Ponsen MM, Stoffers D, Twisk JW, Wolters ECH, Berendse HW (2009) Hyposmia and executive dysfunction as predictors of future Parkinson's disease: a prospective study. Mov Disord 24(7):1060–1065
12. Haehner A, Hummel T, Hummel C, Sommer U, Junghanns S, Reichmann H (2007) Olfactory loss may be a first sign of idiopathic Parkinson's disease. Mov Disord 22:839–842
13. Ross GW, Petrovitch H, Abbott RD, Tanner CM, Popper J, Masaki K et al (2008) Association of olfactory dysfunction with risk for future Parkinson's disease. Ann Neurol 63:167–173
14. Berg D, Godau J, Seppi K, Behnke S, Liepelt-Scarfone I, Lerche S et al (2013) The PRIPS study: screening battery for subjects at risk for Parkinson's disease. Eur J Neurol 20(1):102–108
15. Hummel T, Sekinger B, Wolf SR, Pauli E, Kobal G (1997) 'Sniffin' Sticks': olfactory performance assessed by the combined testing of odour identification, odour discrimination and olfactory threshold. Chem Senses 22:39–52
16. Hummel T, Kobal G, Gudziol H, Mackay-Sim A (2007) Normative data for the ''Sniffin' Sticks'' including tests of odour identification, odour discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. Eur Arch Otorhinolaryngol 264:237–243
17. Landis BN, Welge-Luessen A, Bramerson A, Bende M, Mueller CA, Nordin S et al (2009) "Taste Strips"—a rapid, lateralized, gustatory bedside identification test based on impregnated filter papers. J Neurol 256:242–248
18. Gaig C, Tolosa E (2009) When does Parkinson's disease begin? Mov Disord 24(Suppl 2):S656–S664
19. Morrish PK, Rakshi JS, Bailey DL, Sawle GV, Brooks DJ (1998) Measuring the rate of progression and estimating the preclinical period of Parkinson's disease with [18F]dopa PET. J Neurol Neurosurg Psychiatry 64:314–319
20. Marek K, Jennings D (2009) Can we image premotor Parkinson disease? Neurology 72(Suppl 7):S21–S26
21. Gaenslen A, Swid I, Liepelt-Scarfone I, Godau J, Berg D (2011) The patients' perception of prodromal symptoms before the initial diagnosis of Parkinson's disease. Mov Disord 26(4):653–658
22. Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R et al (2015) The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). Mov Disord 30(2):229–237
23. Chen H, Shrestha S, Huang X, Jain S, Guo X, Tranah GJ, Garcia ME, Satterfield S, Phillips C, Harris TB, Health ABC Study (2017) Olfaction and incident Parkinson disease in US white and black older adults. Neurology 89(14):1441–1447
24. Mahlknecht P, Kiechl S, Willeit J, Poewe W, Seppi K (2018) Reader response: olfaction and incident Parkinson disease in US white and black older adults. Neurology 90(20):940
25. Landis BN, Reden J, Haehner A (2010) Idiopathic phantosmia: outcome and clinical significance. ORL 72:252–255
26. Kashihara K, Hanaoka A, Imamura T (2011) Frequency and characteristics of taste impairment in patients with Parkinson's disease: results of a clinical interview. Intern Med 50:2311–2315
27. Sienkiewicz-Jarosz H, Scinska A, Kuran W, Ryglewicz D, Rogowski A, Wrobel E et al (2005) Taste responses in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 76:40–46
28. Lang CJG, Leuschner T, Ulrich K, Stössel C, Heckmann JG, Hummel T (2006) Taste in dementing diseases and parkinsonism. J Neurol Sci 248:177–184
29. Shah M, Deeb J, Fernando M, Noyce A, Visentin E, Findley LJ et al (2009) Abnormality of taste and smell in Parkinson's disease. Parkinsonism Relat Disord 15:232–237
30. Deeb J, Shah M, Muhammed N, Gunasekera R, Gannon K, Findley LJ et al (2010) A basic smell test is a sensitive as dopamine transporter scan: comparison of olfaction, taste and DaTSCAN in the diagnosis of Parkinson's disease. QJMed 103:941–952
31. Kim H-J, Jeon BS, Lee J-Y, Cho Y-J, Hong K-S, Cho J-Y (2011) Taste function in patients with Parkinson disease. J Neurol 258:1076–1079
32. Cecchini MP, Osculati F, Ottaviani S, Boschi F, Fasano A, Tinazzi M (2014) Taste performance in Parkinson's disease. J Neural Transm 121:119–122