Olfactory Dysfunction in Parkinson's Disease

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Key Words

Olfaction • Parkinson's disease • Neuropathology • Smell • Olfactory bulb • Parkinsonian disorders • Dopaminergic functional imaging

Abstract

Prior to the onset of the cardinal motor features of idiopathic Parkinson's disease (PD), other manifestations of neurodegeneration such as olfactory dysfunction are often apparent. Characterizing these potential biomarkers of preclinical PD is particularly important in identifying individuals who will go on to develop disabling symptoms, and thus be good candidates for new neuroprotective strategies. As shown by the Braak neuropathologic staging of PD, the olfactory system is among the first neuronal populations to display Lewy body pathology. Clinically, loss of smell can be easily tested in the office using several validated techniques and is often helpful to the physician in distinguishing idiopathic PD from other forms of parkinsonism. Recent findings have indicated that a decline in olfaction may be observed in selected at-risk patients, which has significant implications for identifying potential study populations. Ongoing studies of olfactory dysfunction may also reveal potential for use as a medication-independent biomarker of disease progression in addition to use as a biomarker for the diagnosis of PD.

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Introduction

While first reported by Ansari and Johnson [1] in 1975, the phenomenon of olfactory dysfunction in idiopathic Parkinson's disease (PD) has been an area of active research at the University of Pennsylvania since Doty et al. [2] first confirmed the Ansari observation in 1988. With a prevalence between 70 and 90%, olfactory dysfunction is at least as common among PD patients as one of the cardinal motor features, resting tremor [2–4]. Smell loss in PD is robust enough to be easily measured by standard quantitative tools, with deficits in all areas of olfaction: odor discrimination, odor identification and odor detection threshold [5]. This impairment has been shown to appear early in the neurodegenerative process, prior to the onset of motor symptoms, which is congruent with the early involvement of the olfactory system in the evolution of Lewy pathology demonstrated by Braak et al. [6]. While olfactory dysfunction was thought for years to be a static process, not correlating with disease duration or stage, recent studies have shown that careful sample selection with close follow-up intervals may reveal progression of olfactory dysfunction over time. Demonstrating the time course of olfactory loss in PD is important for better understanding of the premotor phase of PD, and for identifying a population of at-risk patients during a stage of the illness when intervention with neuroprotective therapeutics may prove most beneficial.

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Fig. 1. Lewy pathology of the olfactory bulb and tract. Immunostaining with antibodies to α -synuclein reveals Lewy pathology in the olfactory bulb and tract in patients with PD and incidental Lewy body disease. **a** In a patient with incidental Lewy body disease, Lewy neurites are demonstrated in the external plexiform layer (EPL) and rarely in the glomerular layer (GL). **b** In the same patient, Lewy neurites and rare Lewy bodies are demonstrated in the anterior olfactory nucleus (AON) and Lewy neurites in the olfactory tract (OT). **c** In a patient with PD, higher burdens of Lewy pathology are demonstrated in the AON and OT. **d** Higher-power magnification of the AON in another patient with PD reveals large numbers of Lewy bodies as well as a Lewy neurites. **a, b, d** Original magnification $\times 200$. **c** Original magnification $\times 100$.

Neuropathology of PD: Why Olfaction?

While olfactory dysfunction has been found in association with multiple neurodegenerative disorders, the pathology of the olfactory system appears to be disease specific. Olfactory impairment occurs in both Alzheimer's disease (AD) and PD, but the etiology appears distinct as the olfactory bulb reveals the hallmark pathologic features typical of each disorder – neurofibrillary tangles and amyloid plaques in AD and Lewy bodies and Lewy neurites in PD (fig. 1) [7]. Lewy bodies and Lewy neurites are protein aggregates formed from insoluble α -synuclein and other proteins that occur in the cell soma and cell processes, respectively. These aggregates of insoluble proteins, collectively referred to as Lewy pathology, displace other intracellular structures and may lead to an interruption of axonal transport, axonal degeneration and eventual demise of the affected neuron [8]. Braak et al. [6] examined the distribution of Lewy pathology in a large cohort of patients with PD as well as many patients with Lewy pathology but no clinical history of PD, commonly referred to as incidental Lewy body disease (ILBD), and described a topographical progression of Lewy pathology throughout the brain. From this pattern, a neuropathological staging system was proposed, in which pathologic changes in the anterior olfactory nucleus and olfactory bulb are among the first to occur, implicating

the olfactory system as an 'induction' site of Lewy pathology [9]. Interestingly, no evidence of Lewy pathology was seen in the short-lived olfactory receptor neurons of the olfactory epithelium [10]. As the genetic and environmental interplay responsible for aggregating α -synuclein into Lewy pathology remains unclear, the olfactory system, with its unique neuronal privilege of entering the brain from the outside world without intervening synapse, seems remarkably poised for the delivery of external pathogens to the central nervous system [11]. Indeed, the olfactory bulb and tract are ideally suited for neuropathological investigation into the pathophysiology of Lewy neurodegeneration in that it is one of the few easily dissectible preparations that include the dendritic arborization, cell soma, axon and axon terminal of neurons selectively vulnerable to Lewy pathology.

Beyond the anterior olfactory nucleus and olfactory bulb, olfaction-related cortical structures have also been found to be susceptible to formation of Lewy pathology in PD and ILBD. Silveira-Moriyama et al. [12] examined the primary olfactory cortices including the olfactory tubercle, the frontal piriform cortex and the temporal piriform cortex in 7 cases of ILBD, 10 cases of PD and 4 healthy controls. They observed Lewy pathology in each area in all cases of ILBD and PD, but none of the controls [12]. Similarly, Braak et al. [6] recognized that while Lewy pathology aggregated within periamygdaloid, piriform

and entorhinal cortices, they did not immediately spread to adjacent cortex unrelated to olfactory processing.

It would seem that the neuropathological spread of Lewy pathology to the olfactory cortex may underlie the spectrum of olfactory deficits present, in the same way that cortical Lewy pathology correlates with dementia in PD [13]. True anosmia is somewhat rare in PD; even those patients most impaired in odor identification are still able to detect some strong odors, indicating that impairment in identification may involve cognitive processes beyond that of detection threshold. Indeed, major deficits in the cognitive judgment regarding different odors have been observed in patients with PD [14]. Differentiating cortically-mediated olfactory impairment from olfactory dysfunction due to olfactory bulb involvement may be impossible until a biomarker of Lewy pathology arises, allowing the selection of subjects with isolated olfactory bulb pathology.

The mechanism by which Lewy pathology in the olfactory bulb and anterior olfactory nucleus leads to impaired odor detection has not yet been elucidated. The depletion of dopaminergic neurons in nigral pathways in PD is evident on imaging with dopamine transporter PET and SPECT as well as clinically in the response of motor symptoms to dopaminergic medications. Olfactory dysfunction, however, does not respond to dopaminergic medication, which might imply a neuronal population that was damaged early enough that no response would be possible by the time antiparkinsonian medications are typically prescribed or, alternatively, dysfunction in nondopaminergic cell populations [15]. Interestingly, one study has shown a doubling of tyrosine hydroxylase-positive periglomerular neurons in the olfactory bulb in PD cases compared to healthy controls [16]. As dopamine is known to inhibit transmission between axons of olfactory receptor neurons and dendrites of mitral cells in the olfactory bulb in animal models, it is possible that a tonic inhibition of olfactory neurotransmission occurs, related to a compensatory increase in dopamine receptors in extranigral sites [17, 18]. However, since all of the patients examined in this study had PD for at least 4 years, the relationship between early olfactory dysfunction and dopaminergic cell populations in the olfactory bulb remains to be determined. It is indeed possible that the increase in dopaminergic periglomerular cells observed represents a compensatory response to the primary cause of olfactory dysfunction in PD.

Many studies have sought to find changes in cognitive, sensory or motor processing that, while subtle, may be predictors of development of future PD. Possible indica-

tors have included neurocognitive tests, behavioral or mood changes, sensory complaints, REM sleep behavior disorders, or nonspecific musculoskeletal pain [19–21]. The observation of Braak et al. [6] that lower brainstem and olfactory pathways are involved before the nigrostriatal pathway suggests that extranigral degeneration is the cause of these early nonmotor symptoms and offers hope that a panel of nonmotor symptoms may become a useful screening tool for patients with early PD.

Assessing Smell Loss in PD

Olfactory dysfunction is an attractive potential biomarker for PD because of its high prevalence among PD patients as well as its ease of testing. Olfactory identification has been the most widely used assessment of olfaction. The University of Pennsylvania Smell Identification Test (UPSIT), developed by Doty et al. [22], has been validated as a reliable method of quantifying olfactory identification. In this 40-item test, the patient is asked to scratch the surface of the testing card and identify the odor released from 4 possible choices. The UPSIT was formally modified to include only 12 items as the Cross-Cultural Smell Identification Test (CC-SIT, also known as the Brief Smell Identification Test), addressing some concerns that certain of the 40 odors were unlikely to be recognized by non-Western populations [3, 22]. One recent study identified 3 of the UPSIT odors that seemed to select those PD patients with significant dopaminergic nigrostriatal loss in their study population as evidenced by dopamine transporter PET, even more robustly than the full 40-item test [23], but this observation has yet to be confirmed. Another olfactory testing method, Sniffin' Sticks, developed by Hummel et al. [24], uses a pen-like device to test odor threshold, discrimination and identification. The patient sniffs the pen, which delivers successive concentrations of n-butanol for threshold testing, 16 pairs of odorants for discrimination and 16 single odorants for identification from 4 stated choices.

While the olfactory impairment in PD has been described in odor identification, odor discrimination, threshold detection and odor recognition memory, recent studies have shown that different domains may be affected disproportionately [5]. Potagas et al. [25] used unique tests of odor discrimination and identification to demonstrate a preferential decline in odor identification rather than odor detection, invoking impairment in odor memory. The novel methods of determining these deficits make this study difficult to validate against others,

but it has been reiterated that designing tests of multiple olfactory domains is more effective for screening assessments [26, 27].

It has been noted that decreased sniffing amplitude as a function of motor symptoms in PD may confound our ability to test olfaction. With decreased sniffing ability alone, 2–3 points out of 40 can be lost on the UPSIT [28]. Olfactory event-related potentials (OERPs) can be obtained in response to olfactory stimulants, offering a method of quantifying olfaction independent of sniff volume or memory. The P1 response is thought to correlate with activity at the olfactory bulb and P3 with the olfactory cortex. The time to these intervals in PD has been shown to be clearly slowed without reduction in amplitude [4, 29, 30]. Limiting the use of OERPs is electroencephalography contamination by slow wave activity, patient compliance required by long (30–40 s) interstimulus intervals and the difficulty of interpreting a negative OERP in the setting of functional anosmia [31].

Using multiple psychometric tests together or in combination with imaging studies invariably increases the ability to detect early PD. Montgomery et al. [32] found that specificity for early PD could be increased to 92%, with 68% sensitivity, when combining tests of motor function, mood and olfaction. Interestingly, cardiac SPECT has been shown to be useful in differentiating between idiopathic PD and other parkinsonian syndromes, and thus correlates closely with olfactory dysfunction in PD, independent of motor symptoms [33–35]. Recently, Siderowf et al. [36] demonstrated a correlation between striatal dopaminergic loss seen with TRODAT-SPECT imaging and odor identification impairment in early PD. While advanced neuroimaging studies such as PET and SPECT are able to selectively portray dopaminergic loss in the brain, these are currently too expensive to be widely implemented in screening. Transcranial sonography, more readily available and less invasive than PET or SPECT, can identify hyperechogenicity in the substantia nigra of PD thought to be due to increased iron deposition. Imaging in combination with olfactory testing has been used in several studies, successfully identifying patients who would develop other signs or symptoms of PD [37–39]. Sommer et al. [39] used nigral hyperechogenicity on transcranial sonography to target which patients of those presenting with idiopathic olfactory loss should receive SPECT scans, with 50% of these patients also demonstrating dopaminergic loss on SPECT. Ponsen et al. [37] showed that in their cohort of asymptomatic relatives of PD patients, 10% of those with idiopathic hyposmia and SPECT abnormalities at baseline and none of the

normosmic relatives went on to develop clinical PD at a 2-year follow-up. These data indicate that olfactory dysfunction may be used in the future to select those individuals at risk for developing PD who warrant further investigation.

Olfactory Loss as a Biomarker of PD

In assessing the clinical utility of any marker of early PD, it is important to consider how such a test would not only indicate the presence of PD, but also discriminate against other causes of parkinsonism. Olfactory dysfunction has been shown to help in the differentiation of PD from other causes of parkinsonism, to the extent that in evaluating a patient with parkinsonian signs but preserved olfaction, the diagnosis of early PD should be reconsidered. Olfaction is less impaired in multiple system atrophy compared to idiopathic PD [27], while patients with progressive supranuclear palsy and corticobasal degeneration appear to have preserved olfaction [27, 40]. Based on these observations, a recent evidence-based practice parameter from the American Academy of Neurology stated that olfactory testing should be considered to differentiate PD from progressive supranuclear palsy and corticobasal degeneration, but not from multiple system atrophy [41].

While olfactory dysfunction has been demonstrated in AD, patients with Lewy body dementia have even greater impairments in olfaction, lending significance to the role of Lewy pathology in olfactory dysfunction [42–44]. Based on this assumption, it would be expected that nondegenerative causes of parkinsonism have intact olfaction, as is the case in vascular parkinsonism [45] and MPTP-induced parkinsonism [46]. In addition, Khan et al. [47] found that a cohort of parkin-positive PD patients had better olfaction than idiopathic PD patients, supporting the concept of parkin-associated PD as a separate entity without Lewy bodies. In one study of patients with neuroleptic-induced parkinsonism published in abstract form, low UPSIT scores identified those patients who did not recover after cessation of the offending drug; the mechanism by which neuroleptic medication would cause an ‘unmasking’ of an underlying idiopathic PD remains unknown [48].

The utility of olfactory testing in identifying a population at risk of developing PD is perhaps best demonstrated by studies of relatives of PD patients. As shown by Berendse et al. [49] and Ponsen et al. [37] in multiple studies of their cohort of asymptomatic first-degree relatives

of PD patients, hyposmia was frequently the only finding in relatives who would go on to develop PD. One powerful conclusion of these studies was that normosmic relatives of PD patients demonstrated a risk of developing PD lower than that of the general population. If olfactory testing continues to prove to be an efficient method of stratifying risk in relatives of PD patients, physicians will likely need to consider the ethical issues surrounding making such definitive preclinical assessments.

In one study of unaffected twins of idiopathic PD patients, olfactory testing was not sensitive enough to detect those that would develop PD at a 7-year follow-up evaluation [50]. In studies that showed olfactory dysfunction to be predictive of development of PD, the follow-up time was 1, 2 or 4 years, suggesting that olfactory dysfunction may only occur a short time prior to the onset of other PD symptoms [37–39, 49]. The possible rapid degeneration of the olfactory system early in the course of PD may provide one explanation for why olfactory dysfunction has traditionally been observed to be a static phenomenon in PD, although significant questions remain surrounding this issue. While initially described as unrelated to the progression of disease in PD [2], olfactory dysfunction was found to correlate with PD subtype by Stern et al. [51]: olfaction was more impaired in those with Hoehn and Yahr stage III or greater ('malignant') PD than in those with Hoehn and Yahr stage II or less for 4 or more years ('benign'). Recent studies have suggested that an even closer link may be found between PD progression and olfactory dysfunction. Tissingh et al. [26] found that odor discrimination loss was related to disease

severity, while Hummel [52] showed that OERPs correlated with Webster scores of disability due to PD. In one study with 5 de novo PD patients published by Muller et al. [27], olfaction was tested 3 times in the first year after diagnosis. Each of the 3 patients that demonstrated hyposmia on initial testing also showed a decline in olfactory function with these repeated tests [27]. While this finding necessitates further evaluation with larger sample sizes, it highlights the possibility that progression of olfactory dysfunction has previously been missed in PD studies due to inclusion of many patients with advanced disease, possibly contributing to a ceiling effect.

Conclusion

Olfactory testing offers an inexpensive, reliable method for screening those patients already known to be at risk (such as family members of PD patients), and discriminating between PD and other parkinsonian syndromes. Siderowf and Stern [53] have described olfaction and other early nonmotor signs as part of the 'Parkinson's disease at risk syndrome (PARS)'. Characterizing the features of PARS will take on even greater importance as neuroprotective or disease-modifying agents are developed for clinical trials. Thus, markers are needed for premotor disease, in which some signs of disease are present but intervention is still possible. Due to its high prevalence early in the course of PD, olfactory dysfunction serves as such a marker of the premotor state, and will hopefully help in identifying future treatments.

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