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REVIEW

Olfactory loss as a supporting feature in the diagnosis of Parkinson's disease: a pragmatic approach

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Abstract There is ample evidence from a large number of clinical and pathological studies of an early involvement of olfactory bulbs and cortex in the Lewy body pathology in idiopathic Parkinson's disease (iPD), the olfactory system being one of the first targets of degeneration in this condition. The olfactory dysfunction may be measurably present at the time of initial presentation and progresses in a proportion of patients as the disease advances. Patients with iPD have a more severe olfactory loss as compared to multisystem atrophy whereas the syndromes of corticobasal degeneration and progressive supranuclear palsy have no olfactory loss. A proportion of drug induced parkinsonism may have olfactory loss indicative of primary pathology of dopaminergic degeneration in these patients. Unlike single photon emission tomography, formal measurement of olfaction would provide a supportive role in diagnosing or excluding iPD depending on the duration of an individual patient's parkinsonian symptoms. Whilst olfaction may be only minimally impaired in early stages and may thus not help to differentiate from other syndromes, an intact olfaction in patients with parkinsonism of few years' duration would indicate a non-iPD pathology. Olfactory measurement is easy, cheap and now easily available in a number of tests, and olfactory assessment at different stages of parkinsonism should be used as a diagnostic aid for idiopathic PD and would enhance the diagnostic accuracy of iPD when used in conjunction with the UK Parkinson's disease society Brain Bank supportive criteria for diagnosis of idiopathic Parkinson's disease.

Keywords Olfaction · Parkinson's disease · Diagnosis

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Parkinson's disease (PD) is a progressive neurodegenerative condition whose aetiology has not yet been fully characterised. Diagnosis is clinical and based on the cardinal motor features of bradykinesia, tremor and rigidity. Imbalance becomes a feature as the disease advances. However, it is now widely accepted that these features are preceded by a prodromal 'pre-motor' phase. This is postulated to commence up to 20 years prior to the development of motor features [1]. The basis for these nonmotor symptoms is that the pathologic process may not start in the substantia nigra pars compacta. Nonmotor symptoms include sleep disturbance, behavioural or emotional changes, autonomic dysfunction, chronic pain and olfactory dysfunction. Patient surveys have found these to be as troublesome, if not more so, as motor symptoms. One of these, olfactory loss has a significant impact on quality of life [2].

Currently, treatment for PD is initiated only once motor symptoms have manifested. Earlier diagnosis whilst patients are in the premotor phase may allow us to understand more about the disease course and implement therapies earlier, perhaps allowing disease management to move from symptomatic treatment to disease modifying or neuroprotective treatment.

This review aims to explore and discuss the prevalence and character of olfactory loss in PD, the underlying pathology and its potential role in clinical diagnosis.

Olfactory loss and its prevalence in Parkinson's Disease

The initial studies of Ansari and Johnson in 1975 [3] were the first to show the increased prevalence of olfactory dysfunction in PD. Interest grew throughout the 1980s, and to date there are a multitude of studies confirming this. Sense of smell declines with age, and studies have shown 62.5 % of 80–97 year olds have olfactory impairment [4]. Furthermore, the likelihood of olfactory dysfunction has been shown to increase twofold per decade after 60 years [5]. However, in PD the prevalence is significantly higher, with some degree of olfactory loss being present in 80–96 % patients [5, 6]. Olfactory loss in PD is not simply due to the ageing process [7]. Total anosmia is rare, and a proportion of the patients are not aware of the deficit until their sense of smell is formally tested. This might be due to mild impairment of olfaction particularly in early stages. In a sample of community-dwelling nondemented elderly persons, those with mild parkinsonian signs had significantly lower olfactory tests as compared to those without parkinsonian signs [8]. As compared to the previous studies [5], more recent studies indicate that in some patients olfaction progressively deteriorates [9, 10]. As per the current knowledge, medications do not influence degree of olfactory loss [11]. Disease duration may [9, 10] or may not influence degree of olfactory loss [11, 12]. Whilst mean olfactory dysfunction has been shown to increase with disease progression, fluctuations occur in individuals, and overall olfactory loss does not predict the course of the disease [13, 14], although it could be postulated that our detection methods are not sensitive enough to identify subtle declines in olfaction [15]. In contrast to clinical results, pathological findings at post-mortem show a strong correlation between neuronal loss in the olfactory bulb and PD duration [16].

Several risk factors have been identified for future development of PD. Individuals with other nonmotor symptoms have been found to have an increased likelihood of developing PD, especially when they occur in combination [17]. One study showed that females outperform males on olfactory tests [18]. Several studies have analysed the future risk in first degree relatives of PD patients. Ponsen et al. [19] used single-photon emission computed tomography (SPECT) to show there was a greater decline in nigrostriatal dopaminergic function in hyposmic relatives compared to normosmic relatives. They found a 10 % increased risk of developing PD in first-degree relatives with idiopathic olfactory impairment. Other studies by these authors have reported the increased risk of 12.5 % over 5 years when combined with executive dysfunction [20, 21].

Thus there is a well defined relationship between olfactory dysfunction and future development of PD, making identification of hyposmia significant in diagnosing PD.

Pathology underlying olfactory dysfunction in Parkinson's Disease

The olfactory system is complex and comprises several components. The olfactory mucosa houses the olfactory receptor cells, whose axons come together to form the olfactory nerve. Nerve fibres synapse in the olfactory bulbs, located above the cribriform plate, one on each side. Here, odour is separated into different components which are passed onto several areas; the anterior olfactory nucleus, lateral olfactory nucleus, amygdala, entorhinal and pirifrom cortices [22]. This system is involved in the early pathological process of PD.

PD is characterised by deposition of eosinophilic inclusion bodies, or Lewy bodies, which contain ubiquitin and alpha-synuclein. The latter has been central to research of PD pathology as mutations in the alpha-synuclein gene are known to cause familial PD. Braak et al. have undertaken studies to further define the 'patho-anatomy' of PD. Their research led to the development of a staging system comprising six separate phases of PD pathology [23]. These are based on both the predictable topographic distribution of Lewy bodies throughout the olfactory system and their absence in nonolfactory cortical regions. Deposition of Lewy bodies in the premotor stages of PD occurs in the olfactory bulb, medulla oblongata and enteric plexuses. This defines stages one and two. Subsequently, in stages three and four, the inclusion body pathology reaches the substantia nigra and midbrain areas in an ascending course [23, 24]. This correlates to the manifestation of motor symptoms. The telencephalic cortex is involved in the final stages, five and six. According to these Braak stages, the olfactory bulb is one of the first areas involved in PD pathologically; therefore, impaired olfaction is one of the earliest indicators of developing PD. Whilst there are limitations to this theory, for instance the heterogenous nature of PD, the observation that the pathology of PD also occurs outside the substantia nigra pars compacta makes it valuable to look for nonmotor features such as olfaction towards an aid to the diagnosis of PD.

Lewy bodies have been found in the olfactory system in several studies, with the primary olfactory cortex being an important site of deposits [25]. The neuronal loss in the olfactory bulb and tracts correlates with disease duration [16]. However one study found increased numbers of dopaminergic neurons in the olfactory bulb, and concluded this may be a compensatory mechanism that may in turn result in damage [26]. There is asymmetry in the depth of right and left olfactory sulcus, the right sulcus being

significantly larger than the left, consistent with the asymmetry of clinical features of PD [27]. This study also revealed a significant negative correlation between olfactory impairment and depth of the right olfactory sulcus. The enlarged right sulcus in these patients with anosmic UPSIT (University of Pennsylvania Smell Identification Test) values would support the notion of increased number of olfactory neurones as a compensatory mechanism [26]. Biopsies of the olfactory epithelium show that it is not involved in the dysfunction of olfaction, providing evidence that the pathology lies in the central nervous system [28].

Imaging studies found olfactory bulb volume to be reduced in PD patients with impaired olfaction, and the amount of volume lost is proportional to the deficit in olfaction [29]. Therefore, the olfactory apparatus appears to undergo atrophic changes as well as being a site for inclusion body deposition [30]. The relationship between olfactory dysfunction and PD medication has been analysed in several studies. Olfactory dysfunction in PD patients is unresponsive to PD pharmacological treatment [5, 31]. There is no difference in the severity of olfactory dysfunction between patients taking dopaminergic agents and those who are not [11]. This implies that underlying dopamine deficiency in PD is not the cause of olfactory loss [32]. In fact, hyposmia may be related to the cholinergic denervation seen in PD [33].

Post-mortem studies found that even in non-PD individuals, the presence of Lewy bodies in the olfactory system correlated with impaired olfaction [34]. Therefore, hyposmia could be an indicator of underlying Lewy body pathology.

The significance of the olfactory system and enteric plexus involvement in early PD has lead to the theory that an external environmental agent may cause or act as a catalyst for the development of PD. This agent may enter the central nervous system through the olfactory system and/or by ingestion, hence the term the 'dual-hit theory' [35].

Olfactory testing methodology

Olfactory testing involves simple, noninvasive measures that could be used routinely in an outpatient clinic. Therefore the inclusion of olfactory tests in the diagnostic work-up of PD is achievable. The University of Pennsylvania Smell Identification Test (UPSIT), developed by Doty et al. [36], involves a card with scratch panels containing different odours. It can be used in all clinical settings, or even posted to the patient at home. Different versions of this product exist, such as the Brief Smell Identification Test (BSIT). Yet these tests are only able to measure smell identification, and not discrimination or threshold, the other aspects of olfactory testing [15]. The 'Sniffin Sticks' which comprises a set of scented pens [37] enables the gaining of information on all three aspects of testing: smell identification, threshold and discrimination. These tests are sensitive enough to identify patients with varying degrees of hyposmia, and can be utilised in clinical settings for the process of accurately diagnosing PD. These studies have shown the disturbance in olfaction occurs equally in both nostrils [38]. Furthermore, there is no relationship between the side of the nose affected and the dominant side of PD motor symptoms.

Imaging studies have played a major role in the research around olfaction in PD. They have been used to improve knowledge of the areas affected by PD and for diagnostic work-up. Functional magnetic resonant imaging (fMRI) can identify the anatomical sites involved in olfaction by using olfactory event related potentials (ERPs) [39]. ERPs are significantly delayed in PD patients when compared to controls [10]. Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) scans have up to 94 % sensitivity and up to 100 % specificity for the identification of the dopaminergic deficit in PD [40]. There is evidence of significant correlation between olfactory dysfunction and neuroimaging measures of dopaminergic denervation, such as SPECT scanning [41].

Many studies found benefit in combining clinic olfactory testing with imaging studies such as diffusion-weighted MRI [21, 42]. It has been proposed that investigations should commence with a detailed history, directed at identifying the presence of nonmotor symptoms. This should be followed by tests of olfaction and subsequently by more invasive and costly imaging studies [43, 44]. Such a screening programme may be designed in the future to identify PD before motor features become apparent.

Olfaction and its association with other non-motor features of Parkinson's Disease

Olfaction is one of several well-documented 'prodromal' nonmotor features of PD. The association between the nonmotor symptoms may be important for future diagnosis, as some may be more likely to indicate a case of developing PD than others, and particular combinations may increase the risk. There is a significant association between odor identification deficit in PD and the motor and nonmotor features [10]. However, their prognostic significance is currently unknown. Constipation, excessive daytime sleepiness and impaired executive function are nonspecific symptoms that are not easily measured, but if identified during focussed history-taking, they may identify patients

at higher risk of developing PD [17]. The Parkinson At Risk Syndrome Study [45] was carried out to determine the relationship between olfactory loss and nonmotor symptoms of PD. This involved posting an olfactory testing kit and questionnaire aimed at identifying the presence of nonmotor symptoms to 4999 non-PD individuals. The study showed an increased prevalence of anxiety, constipation and sleep disturbance in hyposmic individuals. The more nonmotor features reported, the more likely the individual was to be hyposmic. Further studies need to be carried out to decide how accurately the presence of nonmotor features can predict the underlying diagnosis of PD.

Autonomic dysfunction is a well recognised nonmotor manifestation of PD. Hyposmia is associated with degenerative changes in the cardiac sympathetic nervous system. In early PD, these systems begin to degenerate at a similar rate [46]. Furthermore, olfaction is related to vascular sympathetic dysfunction, which manifests as orthostatic hypotension [47].

The patients with the lowest olfactory performance are more at risk of developing clinically significant neuropsychiatric complications such as hallucinations and cognitive decline [33, 48] and more likely to be apathetic [49]. Some areas in the olfactory system are involved in cognition, and a study by Imamura et al. [50] found regional reductions in cerebral blood flow in olfactory areas and areas of cognition, which may explain the association. Altered brain metabolism in the amygdala and piriform cortex in hyposmic patients is associated with memory impairment [51]. Several studies have confirmed findings that severe hyposmia is associated with neuropsychiatric symptoms, but whether we can use the level of severity of hyposmia to predict the development of other non-motor features of PD is not yet known [52].

A greater loss of olfaction is associated with higher risk of weight loss and development of dyskinesia, it has therefore been proposed that the degree of olfactory dysfunction helps to identify different phenotypes for weight loss and dyskinesia [9].

Olfaction and its role in the differential diagnosis of Parkinsonism

Parkinsonism has a vast differential diagnosis. Much research has been carried out to identify methods for discriminating these conditions, and one such way is through olfactory testing. Odor deficit in PD has a significant correlation with striatal dopaminergic deficit on DAT binding as measured with dopamine transporter single-photon emission computed tomography [^{123}I] FP-CIT, (DAT-SPECT) [8]. A basic odor identification test is as sensitive as a dopamine transporter scan for the diagnosis of PD [53].

Olfaction impairment in PD is associated with cognitive dysfunction [33]. Olfaction is also impaired in other degenerative conditions associated with cognitive impairment, i.e., Lewy body disease, vascular dementia and Alzheimer's disease [54, 55]. Olfactory tests thus cannot be used to differentiate PD from other conditions associated with dementia. Moreover, it is not reliable to test odor identification in patients with any degree of cognitive impairment, since the test depends on intact memory.

Important differentials of Parkinsonism include: idiopathic PD (iPD), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), drug-induced parkinsonism (DIP), multiple systems atrophy (MSA) and vascular parkinsonism.

DLB is pathologically indistinguishable from iPD, and clinically patients have features of parkinsonism plus early hallucinations and dementia, the latter distinguishing it from iPD. As expected from the similarities in the underlying pathology, olfaction is disturbed in DLB to a similar extent as in iPD [56]. In contrast, although PSP and iPD can be indistinguishable clinically, PSP patients retain their sense of smell [57]. Therefore, olfactory tests such as the UPSIT can be very useful in the diagnosis of iPD and to exclude PSP. Similarly, studies have found that olfaction is preserved in CBD [58]. Importantly, both PSP and CBD are tauopathies. Furthermore, it has been shown that the tau protein is not deposited in the olfactory bulb [59]. In contrast, a mild olfactory deficit has been found in patients with MSA, making this test less useful for differentiating early idiopathic PD and MSA [56], however the olfactory loss in MSA is mild as compared to iPD. iPD patients have progressive loss of olfaction, one study reporting an UPSIT score of 26 at H&Y stage 1, 17 at stages 2 & 3, and 15 at stage 4 [9]. This has been supported by another study confirming progressive loss of olfaction as the disease progresses [10]. Thus the degree of olfactory dysfunction would help to distinguish MSA from iPD in later stages if not at the time of initial presentation.

Non-neurodegenerative parkinsonism syndromes include vascular parkinsonism and essential tremor. The findings that olfaction is not impaired in these conditions implies the underlying cause of olfactory loss may be related to a degenerative process [60, 61]. Whereas SPECT can distinguish iPD from essential tremor, it cannot distinguish iPD from other conditions, i.e., PSP, CBD and MSA.

Patients with DIP do suffer loss of smell, which is thought to be secondary to dopamine depletion rather than dopamine receptor blockade [62]. The majority of DIP patients have an olfactory score similar to the controls score [63]. However, a subset of patients with DIP may have underlying primary dopaminergic loss and the pathology is merely unmasked by the use of D2 dopamine receptor blocker drugs. It is a frequent clinical observation that a

proportion of DIP patients do not fully recover from parkinsonian features after discontinuing the offending D2 blocker medication. These patients are likely to have iPD, supported by olfactory dysfunction, and should be managed as such. Thus, olfactory testing in this group of patients would help to discriminate between patients with DIP from those who have underlying dopaminergic deficiency unmasked by these drugs. Patients with MPTP-induced PD do not have a significant impairment in olfaction when compared to controls [64]. Within iPD, there are three distinct clinical subgroups; tremor-dominant, akinetic-rigid, and mixed. Olfaction ability differs amongst these subgroups, with the akinetic-rigid subtype having significantly worse olfactory function and it is suggested that measures of olfaction could be useful in determining prognosis [65].

The American Academy of Neurology practice parameter on the diagnosis and prognosis of PD concluded that olfactory testing "should be considered" to differentiate PD from PSP and CBD but not from MSA [66]. Patients with PD score worse than the patients with PSP, CBD and MSA. PSP and CBD have normal olfaction. MSA have some loss of olfaction, but the degree of impairment is much less in MSA, i.e., the MSA patients score much higher than PD [67]. Overall, a patient with a normal sense of smell is unlikely to have iPD. Testing olfaction can potentially rule out the tauopathies, vascular parkinsonism and essential tremor from the differential diagnoses when assessing a patient [67]. Again, this highlights the importance of olfaction in the diagnostic work-up of suspected PD.

A pragmatic approach to the diagnostic value of olfactory loss for idiopathic Parkinson's disease: (Tables 1, 2)

Where does this lead us to in the diagnostic pathway of iPD? A number of diagnostic criteria for PD have been formulated. NICE guidelines in United Kingdom recommend the use of UK PD Brain Bank Criteria in routine clinical practice [68]. This is a three-step approach. The first is to establish the cardinal features of parkinsonism, the second being of a number of exclusion criteria, and the third being of the supportive features. An excellent response to levodopa and the presence of levodopa-induced dyskinesia are supportive features. These criteria were devised prior to the current clinical practice of avoidance of levodopa in the early stages, and thus the levodopa response criteria may not now apply to the majority of patients in early stages; this practice also reduces the risk of levodopa-induced dyskinesia.

On the basis of information described as above olfaction measurement would have a role as a supportive feature in the diagnosis of idiopathic PD. This would also depend on the stage and duration of symptoms of parkinsonism. The atypical features of poor levodopa response, early autonomic impairment, early falls and disproportionate antecollis should alert the clinician to consider alternative diagnosis [65]. Presence of early cognitive impairment or hallucinations would favour the diagnosis of Lewy Body dementia despite a severe impairment of olfaction.

Early stage patients who meet the criteria of cardinal features of parkinsonism should be assessed formally for olfaction. A significant reduction in olfaction would support the diagnosis of iPD, a normal olfaction, however, would not exclude iPD but favour the diagnosis of other disorders, i.e., PSP, CBD and MSA, whereas a mild reduction in olfaction would indicate iPD or MSA.

In more advanced years, i.e., the presence of parkinsonism of a few years' duration, a minimally reduced olfaction would favour the diagnosis of MSA, and a more severe loss of olfaction, i.e,. an arbitrary score of less than 25 on UPSIT, would favour the diagnosis of iPD.

Table 1 Olfactory loss as a supportive diagnostic feature in Parkinson's disease

Early parkinsonism (intact cognition)	
Normal olfaction	Any parkinsonism syndrome
Mild impairment–UPSIT > 30	iPD, MSA, DIP, vascular parkinsonism
Severe impairment–UPSIT < 25	iPD
Later years–duration of 5 years or more (intact cognition)	
Normal olfaction	PSP, CBD, vascular parkinsonism
Mild impairment	MSA, DIP
Severe impairment (expected)	iPD, some cases of DIP with dopaminergic degeneration

iPD idiopathic Parkinson's disease, *MSA* multi-system atrophy, *DIP* drug-induced Parkinsonism, *PSP* progressive supranuclear palsy, *CBD* corticobasal degeneration, *UPSIT* University of Pennsylvania Smell Identification Test

Table 2 Role of SPECT in diagnosing parkinsonian conditions

Conditions with presynaptic dopamine deficiency–(abnormal SPECT scan)	Conditions with preserved presynaptic dopamine function–(normal SPECT)
Idiopathic Parkinson's disease	Essential tremor
Symptomatic parkinsonism	Secondary parkinsonism: Drug-induced
Toxin induced–MPTP	Vascular parkinsonism
Other neurodegenerative conditions	Other conditions with parkinsonian features: Normal pressure hydrocephalus
Progressive supranuclear palsy	
Multiple-system atrophy	
Cortico-basal degeneration	
Dementia with Lewy bodies	

More significantly, the presence of normal olfaction, or olfaction with only a mild impairment, in patients with parkinsonian features of several years' duration would help to exclude the diagnosis of iPD. Dopamine transporter imaging is not helpful in the differential diagnosis of atypical parkinsonism from akinetic-rigid type iPD (Table 2) because all these syndromes, MSA, PSP and CBD, are associated with the presence of presynaptic dopamine deficiency, and as such the scan will be abnormal in all these cases [69, 70]. Olfactory loss assessment provides more discriminative role to arrive at a diagnosis in different parkinsonian conditions than the SPECT scan (Tables 1, 2).

Thus the significance of olfactory loss would have more value in excluding the diagnosis of iPD in patients with several years' of parkinsonism, and some value in diagnosis in early stages, since there is a continuous reduction in olfaction with progressive disease and increasing duration. Presence of impaired olfaction without the cardinal features of parkinsonism would not be of any diagnostic value, but may help as a screening tool. A limitation of our review and recommendations is that we have based our observation on the neuropathology of PD as described in Braak hypothesis, describing PD as a multisystem disease [23, 24].

Conclusion

There is a vast amount of evidence supporting the fact that olfaction is impaired in patients with PD, whatever the underlying mechanism might be, and that this is one of the earliest detectable symptoms. The aetiology of PD is still not fully defined, and treatment is symptomatic rather than neuroprotective. Early diagnosis of PD would allow us to understand more about how the disease progresses and to trial treatments aimed at preventing its development. The identification of olfactory impairment in members of the general population can recognize those at increased risk of developing PD. Testing for olfaction, unlike the SPECT investigation, is noninvasive, cheap and straightforward, and can be carried out easily in clinical settings. This may be used as a screening test for the risk of developing iPD, as has recently been reported [66]. It is, however, debatable what action could be taken after such patients are detected, since there is no neuroprotective medication for intervention. Olfactory testing combined with focussed history-taking to identify other nonmotor symptoms could be the first step of a multi-tiered screening process. Those with hyposmia and, for example, postural hypotension and constipation would be candidates for further investigations.

Olfactory loss is subtle, and patients may not be aware of it. However, it is a significant symptom that could aid early and accurate diagnosis of PD. This in turn can improve our understanding of the course of the disease. Olfactory testing also plays an important role in those patients with established PD. The severity of the hyposmia can predict adverse outcomes, such as motor [9] or neuropsychiatric [33, 48] complications.

Recommendation

Tests for formal assessment of olfaction, such as the UPSIT or other validated tests, should be performed as an essential step in the diagnostic work-up of patients with Parkinsonism (Tables 1, 2), both at the early and the later stages. Significant olfactory loss at the time of initial presentation would support the diagnosis of iPD. The presence of an intact sense of olfaction may rule out iPD particularly in later stages, and increases the likelihood of a nondegenerative cause of parkinsonism or a tauopathy, and the diagnosis of iPD should be revisited. Intact olfaction in patients with atypical features of a few years' duration would support the diagnosis of a non-Parkinson's disease condition. This approach would enhance the supportive diagnostic criteria of the UK Parkinson's disease brain bank diagnostic criteria.

Conflicts of interest None.

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