Olfactory Disturbances in Parkinson's Disease

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Abstract
Olfaction is not a leading sense in humans, but it plays an important role for the quality of life. The classical observations of Dr. J. Parkinson may state that senses and intellect remain intact, but it has been proven recently that 70% to 100% of patients with Parkinson's disease have olfactory disturbances. Complete loss of olfaction can be seen in half of the patients. The disturbances worsen significantly after Hoehn-Yahr stage II. Olfactory dysfunction is considered attractive as a potential biomarker for Parkinson's disease because of its high prevalence and easy assessment. It can also be useful for the differential diagnosis with other extrapyramidal disorders. Studies give evidence of normal olfaction in patients with essential tremor, progressive supranuclear palsy and corticobasal degeneration, and normal or mildly impaired function in multiple system atrophy, unlike the moderate to severe impairment in Parkinson's disease.

Keywords: Parkinson's disease, olfactory disturbances, anosmia, neurodegeneration

The classical observations of Dr. J. Parkinson may state that senses and intellect remain intact, but it has been proven recently that almost all patients with Parkinson's disease have olfactory disturbances (5, 7).

Olfaction is not a leading sense in humans, but it plays an important role for the quality of life: it determines the aromas of foods and beverages and protects from close contact with dangerous substances. Impairments may influence body weight, as the pleasure that comes with food is a factor for appetite. That said, doctors may not pay enough attention to olfactory problems, while patients often don't realize or neglect them (25).

The first publication on the topic of olfactory disturbances in Parkinson's disease dates back to 1975 (Ansari and Johnson). Later, other authors confirm olfactory dysfunction in 70% to 100% of patients: prevalence close to that of rest tremor, the most popular cardinal symptom of Parkinson's disease (2, 3, 12).

The identification of olfactory stimuli is a complex task requiring detection, pre-learned answer, and sensory processing in the piriform cortex, the hippocampus, the prefrontal cortex, the amygdala, and in some language areas (2). Impairment in Parkinson's disease encompasses perception and semantic processing. Discrimination, identification, and smell perception threshold are impaired to such extent that they can be demonstrated using standard qualitative methods. Olfactory disturbances appear long before motor symptoms and progress with time (20). Olfactory impairment is seen in virtually all patients with Parkinson's disease. Over 50% suf-

fer from anosmia, 35% have severe hyposmia, and in over 14% it is moderate (22). Impaired olfaction precedes the development of motor symptoms by at least one to five years. After five years the risk for healthy persons with olfactory disturbances to develop Parkinson's disease significantly decreases. Because of its high prevalence, olfactory dysfunction may even be regarded as a cardinal symptom of the disease (11).

A recent large multicenter study provided evidence of hyposmia in over 96% of patients with Parkinson's disease and in about 25% of the common population aged over 52 years (9). According to some authors the tremor form of the disease goes together with a relatively more preserved olfactory function (11, 12).

The symptoms of impaired olfaction are not specific but can be seen frequently in neurodegenerative disorders. Etiology and neuropathology are though specific, with the formation of Lewy bodies in Parkinson's disease and of amyloid plaques and neurofibrillary tangles in Alzheimer's disease. According to the model of Braak the olfactory bulb and the anterior olfactory nucleus are among the first structures affected by the pathologic process. The olfactory pathway enters the skull without additional synapsing, thus creating prerequisites for entry of toxic or infectious agents in the central nervous system. Different assumptions exist: for a prion-like or viral agent, spreading through nervous pathways, impairing olfaction first, and later the central nervous system, or for patients with primary hypo- or anosmia which doesn't allow them to exit an area with dangerous chemical substances. Unfortunately, proofs supporting such theories are not yet available.

Degeneration affects cortical structures as well: the olfactory tubercle, the frontal and temporal piriform cortex, the periamygdaloid and entorhinal cortex (4, 13, 14, 17).

Complete loss of olfaction can be seen in half of the patients with Parkinson's disease. It has been speculated that impairment of the cognitive appraisal of olfactory stimuli is also involved, but presently no options exist for in vivo differentiation of patients with impairment of the olfactory bulb from those with cortical olfactory deficit (8, 20).

The olfactory epithelium and the nasal mucosa do not differ from those in healthy persons. The olfactory bulb is reduced in size and in cell number according to some authors, but others state that it is intact. An increased number of dopaminergic inhibitory neurons has been found there, possibly as a compensatory response to the cellular loss in the basal ganglia. Such increase may also explain the lack of efficacy of dopaminergic treatment on olfaction (1, 21).

Functional MRI assessment of olfactory processing in Parkinson's disease shows decreased neuronal activity in the amygdala and hippocampus. Alpha sinuclein can be found predominantly in the central rhinencephalon on pathologic assessment. These results support the thesis for selective impairment of the identification, memory and discrimination of olfactory stimuli with impairment of the cognitive processing, and not for ordinary threshold impairment, reflecting peripheral damage (11, 12).

Neurodegeneration and the formation of Lewy bodies play an important role for olfactory dysfunction, a proof for this being the confirmed olfactory disturbances in dementia with Lewy bodies and the normal olfaction in vascular Parkinsonian syndrome, MPTP-induced parkinsonism, or parkin-positive parkinsonism (20, 23).

When pleasant aromas are used as stimuli, decreased neuronal activity is observed in the thalamus and the amygdala in Parkinson's disease. Dysregulation of dopaminergic response to pleasant aromas also leads to the activation of ventral striatum and prefrontal lateral areas. The decreased perception of intensity most probably reflects the decreased activation of primary central olfactory structures such as the amygdala, while changes of perception for valence are due to impaired activation of ventral striatum and left prefrontal areas (16, 18).

Cholinergic denervation of the limbic archicortex is also a factor for anosmia. Degeneration of the cholinergic system develops early in untreated patients with Parkinson's disease and progresses with the appearance of dementia. Limbic denervation and cognitive deficit correlate with an increase of olfactory disturbances (3).

Atrophy of the limbic and paralymbic cortex, areas related to olfaction, has been found by means of MRI morphometry. Olfactory disturbances correlate significantly with atrophy of the right piriform cortex (primary olfactory area) in early Parkinson's disease and of the right amygdala (secondary olfactory area) in moderately advanced Parkinson's disease. Volume loss is not related to generalized brain atrophy, but represents a selective regional process. Piriform cortex plays an important role

for normal olfaction, not only in unimodal sensory processing, but also in learning, memorizing, and identifying olfactory stimuli. The amygdala takes part in olfactory perception also with the emotional appraisal of stimuli, which is significantly reduced in Parkinson's disease (26).

Regardless of the fact that impairment is due to damage of dopaminergic neurons in the olfactory bulb and the olfactory nuclei, they do not correlate with the severity of motor symptoms which also have dopaminergic mediation, and do not benefit from antiarkinsonian drugs. Most probably the lack of efficacy of dopaminergic treatment is due to the fact that olfactory disturbances develop in the beginning of the disease and progress irreversibly, long before the appearance of movement disorders, when the diagnosis can be established and treatment can be initiated (22).

Olfactory disturbances have initially been considered static, unrelated to the evolution of the disease, but it has been found later that they progress with the development of the pathologic process and correlate with the severity of Parkinson's disease. Even in patients de novo, assessed three times during a one-year period, progressive worsening of olfactory function has been demonstrated (20). Olfactory disturbances worsen significantly after Hoehn-Yahr stage II (15, 19).

It has been known that olfactory disturbances are selective. American studies have discovered that the greatest differences between patients and healthy persons are for the aromas of pizza, wintergreen, banana, petrol, pineapple, smoke and cinnamon from the short form of UPSIT, while in a German study banana and pineapple, but not cinnamon, are the most sensitive. Differences are possibly due to population and cultural specifics, which suggests the need for creation of different forms of the common tests (11, 12).

Correlation has been observed between anosmia and autonomic disturbances in Parkinson's disease with cardio-vagal and efferent sympathetic baroreflectory disturbance, postganglionic cardiac and selective extracardiac noradrenergic denervation. All these changes are independent of dopamine deficit in the striatum and are most probably due to a central and peripheral loss of noradrenergic neurons (10).

Despite the presence of hypo- or anosmia, olfactory hallucinations are seen rarely, and most often present with the feeling of a smell of burning rubber, grass, or rotting fish (6).

In order to diagnose hyposmia in Parkinson's disease, neuroimaging should be negative, trauma and local disorders should be excluded. Smoking significantly alters olfaction, but a significant part of patients with Parkinson's disease are non-smokers. A problem of retrospective studies is that patients tend to miss or neglect olfactory disturbances. An important number of them do not remember since when the changes have been present, and they may even recognize them for the first time during the interview (11, 12, 24).

Olfactory dysfunction is attractive as a potential biomarker for Parkinson's disease because of its high prevalence and easy assessment. One of the most widely used diagnostic tests is UPSIT (University of Pennsylvania Smell Identification Test) and its short version which can be used in persons outside the Western world. Another option is the Sniffin' sticks test (with aroma sticks for assessment of threshold, discrimination and identification).

Some authors discover preferential disturbance of the identification of olfactory stimuli, and not of their perception, a fact that again leads to olfactory memory. Dysfunction of the identification of olfactory stimuli correlates with the dopaminergic loss in the striatum (TRODAT SPECT) and with the sympathetic cardiac denervation (MIBG SPECT). In another study, 10% of close relatives with hyposmia and abnormal SPECT have developed Parkinson's disease in two years. This motivates some researchers, in order to increase specificity and sensitivity of the diagnosis, to recommend the combination of assessment of olfaction, functional assessment of the brain, and sonography of the s. nigra. Still, PET and SPECT are way too expensive to be used as screening methods.

Olfactory disturbances help a lot for the differential diagnosis with other extrapyramidal disorders. Some authors even recommend the diagnosis of Parkinson's disease to be revised in patients with Parkinsonian syndrome but with normal olfaction. In qualitative assessment difficulties can be found only in patients with multiple system atrophy, but quantitative assessment provides an immediate answer, because in multiple system atrophy the impairment is significantly milder. Nevertheless, in the instruction given by the American Academy of neurology it has been stated that assessment of olfaction may differentiate Parkinson's disease from progressive supranuclear palsy and cortico-

basal degeneration, but not from multiple system atrophy (20).

Olfactory disturbances have long been considered a potential premotor marker (Ansary and Johnson, 1975), and observations have discovered impairment in 41% of close relatives of patients with sporadic or inherited Parkinson's disease. The risk in such relatives for developing sporadic Parkinson's disease is also increased. Though olfactory dysfunction with different etiology can be seen in a large part of the common population, this symptom may aid the diagnosis of Parkinson's disease. Moreover, studies give evidence of normal olfaction in patients with essential tremor, progressive supranuclear palsy and corticobasal degeneration, and normal or mildly impaired function in multiple system atrophy, unlike the moderate to severe impairment in Parkinson's disease (22).

When theoretically determining the risk in relatives of patients with Parkinson's disease or in the common population, ethical issues should not be disregarded, despite the positive expectations (20).

The presence of olfactory disturbnces is well-known in Parkinson’s disease. They have been studied extensively and are frequent and easy to assess. These facts support the application of their assessment as one of the markers for establishing the diagnosis even in the early stages of the disease.

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