Background: Impaired olfaction is a common, nonmotor manifestation of Parkinson disease (PD). However, to our knowledge, qualitative olfactory disturbances, such as odor distortions, have not been extensively reported in this condition.

Objective: To describe 2 patients who reported positive olfactory symptoms preceding typical PD, which were consistent with olfactory hallucinations (phantosmias) in the absence of major smell deficit.

Design: Case series.

Setting: University hospital.

Patients: We describe 2 patients, both seen in 2007, who reported pleasant olfactory hallucinations for several years.

Main Outcome Measures: Iodine 123-labeled ioflupane single-photon emission computed tomography and olfactometric testing results.

Results: The 123I-labeled ioflupane single-photon emission computed tomography showed reduced radiotracer uptake in both striatum more marked in the putamen and on the left side in patient 1 and reduced radiotracer uptake in both putamen more marked on the right side in patient 2. Olfactometric testing showed mild hyposmia in patient 1 and normal function in patient 2. The disappearance of the phantosmias in both patients coincided with the development of typical PD.

Conclusion: We propose phantosmia as a new premotor manifestation of PD and suggest that qualitative abnormalities of olfaction, rather than the typical smell loss demonstrated in this condition, should be more carefully examined in the prodromal phase of PD.

Know for decades, olfactory dysfunction associated with Parkinson disease (PD) has recently attracted considerable attention in view of its high prevalence among patients with PD and its early development in the disease course, usually preceding by several years the motor symptoms of the disorder. Thus, an impaired sense of smell of unknown origin is currently viewed by some authors as a potential premotor biomarker of PD, which may be useful as a diagnostic aid in early or atypical PD and as a premorbid screening tool capable of predicting the future development of PD in at-risk populations. However, this issue remains controversial because not all patients with PD exhibit olfactory disorders and genetically determined forms of PD may even be exempt from smell impairment. Perhaps more important, only half of patients with hyposmia or anosmia perceive their deficit, even when specifically asked. In addition to these measurable quantitative olfactory disorders, smell perception can also be qualitatively altered. Little, however, is known about the occurrence and characteristics of qualitative olfactory dysfunction in PD. We describe 2 patients who complained of positive olfactory symptoms preceding typical PD, which were consistent with olfactory hallucinations (referred to as phantosmias) in the absence of major smell deficit, and we propose them as new premotor symptoms of PD.

Report of Cases

Case 1

A 57-year-old patient had known Crohn disease for several years, which was eventually treated by extensive colectomy in 1998 with no further relapse. Since 2000, she has complained of abnormal olfactory symptoms characterized by the occurrence of brief, repeated, and stereo-
typed episodes of strong smell sensations without substrate. Odorant perceptions were difficult to describe precisely and did not correspond to known odors. When prompted, she compared them to perfumes, to a “rainy day,” or even to a “wet dog,” ascribing them a pleasant aspect. Episodes usually lasted a few seconds up to minutes and could occur many times per day in an unpredictable fashion. Conversely, known odors were perfectly identified, and she denied any subjective smell loss. She never had epileptic seizures, and electroencephalographic results were normal. Brain computed tomography showed to show any structural abnormality in particular in the temporal lobe, olfactory bulbs, or tracts. In 2003, while the frequency of olfactory hallucinations was decreasing, she developed a resting tremor of the right hand that progressively evolved into full-blown, asymmetrical, levodopa-responsive parkinsonism typical of PD. Iodine I 123-labeled ioflupane single-photon emission computed tomography (DaTSCAN; GE Healthcare Biosciences, Little Chalfont, England) showed a severe reduction of radiotracer uptake in both striatum more marked in the putamen and on the left side. In 2005, while the patient was being successfully treated daily with pramipexole, 1.5 mg; amantadine hydrochloride, 200 mg; and a combination of levodopa, 200 mg, carbidopa, 50 mg, and entacapone, 400 mg, abnormal odors disappeared completely and never recurred. The results of a detailed rhinologic examination were unremarkable, and olfactometric testing showed mild hyposmia (normal score, ≥ 31; TDI score, 26.5 points; the TDI test is performed using the Sniffin’ Sticks, which is a validated test battery with normative data available10 that is routinely performed in our institution and assesses the 3 major components of smell, including odor threshold [7-10 items], discrimination [12-16 items], and identification [12-16 items] of common odors; the TDI score is obtained by summing the 3 subscores). Hyposmia detected by the test was subjectively unnoticed by the patient.

CASE 2

A 52-year-old, healthy nurse noticed for approximately 5 years the development of olfactory symptoms initially described as an enhanced capacity to detect odors that allowed her to perceive subtle scents with increased acuity before anyone else around her. She said she had become “a nose,” referring to a French idiom meaning a wine expert who smells wine as much as tastes it. Later, she experienced smelling odors that could not be clearly related to the environment and that she could recognize as fragrances, perfumed candles, or fruits. A more precise identification of the perceived odors could, however, not be proposed (eg, the perfume brand or the type of fruit). These perceptions tended to occur abruptly, mostly in the evening in a quiet and odorless setting, and were felt as pleasant. They lasted for minutes up to half an hour and were occasionally linked to known persons (eg, she said she perceived her mother’s perfume). A rhinologic examination yielded normal results. These symptoms were particularly prominent a year ago but tended to wane and almost disappeared during the last few months. Half a year ago, she complained of clumsiness, slowness, and rigidity of her left hand associated with intermittent resting tremor. The results of a neurologic examination demonstrated asymmetric parkinsonism consistent with PD, and she was prescribed rasagiline, 1 mg/d, with a satisfactory therapeutic response. Brain magnetic resonance imaging and electroencephalographic results were normal, whereas 123I-labeled ioflupane single-photon emission computed tomography showed reduced radiotracer uptake in both putamen more marked on the right side. Thus far, she had not complained of smell loss, and olfactometric testing demonstrated a normal function (TDI score, 34.5 points).

COMMENT

Both patients developed florid and stereotyped distortions of olfactory perception occurring in the absence of any odorant stimulus and corresponding to phantosmias (or olfactory hallucinations). Phantosmia is an uncommon form of smell disturbances that has been reported in a variety of conditions involving the peripheral and central olfactory system, including viral or allergic rhinosinusitis, head trauma, brain tumor, migraine, temporal lobe epilepsy, stroke, or even psychiatric conditions.11,12 All these conditions were thoroughly ruled out in our patients, whose phantosmias differed by many aspects from those reported in these conditions. Indeed, although common phantosmias are usually unpleasant when not frankly repulsive (such as in temporal seizures or after head trauma) and reported as disruptive, our patients considered their phantosmias as pleasant or reminiscent of positive experiences. In our cases, phantosmias occurred in the form of episodes that lasted several minutes, and the entire phenomenon was limited to a few years and spontaneously disappeared, unrelated to any obvious cause. Perhaps more important, discontinuation of phantosmias was concomitant with (patient 2) or superimposed over (patient 1) the development of typical PD, strongly supporting a temporal and causal relationship between both conditions.

Although the phenomenon appears to have been briefly mentioned a long time ago,13 this is a detailed report of phantosmia presenting as a premotor symptom of PD. Indeed, although a quantitative decrease of olfactory function has long been demonstrated in more than 90% of patients with PD, the qualitative aspect of this dysfunction has escaped medical attention; to our knowledge, our report is a first attempt to address this issue. It is possible that phantosmia and perhaps other forms of smell distortion such as parosmia12 are not as rare as the current lack of awareness may suggest, not only in PD but also in other degenerative diseases known to be accompanied by smell loss, such as Alzheimer disease. Indeed, in the general population, qualitative olfactory disorders are seldom spontaneously reported by patients, and recent studies14 exploring their incidence revealed that they may occur in almost one-third of the patients with any type of olfactory impairment. Further observational studies on the topic are, therefore, warranted in the PD population. The phantosmias reported herein seem distinct from olfactory hallucinations described in ad-
Mechanisms underlying the phantosmias reported herein are currently unknown, but hypotheses can be elaborated based on the understanding, however incomplete, of the pathophysiologic basis for olfactory dysfunction in PD. It has now been established that Lewy bodies and Lewy neuritis are present in the olfactory bulb and the anterior olfactory nucleus early in the disease course, long before Lewy pathology has involved the substantia nigra pars compacta. This neuropathologic observation has been considered the anatomical correlate of the defective sense of smell preceding clinically defined PD. However, it has recently been shown, somewhat unexpectedly, that the magnetic resonance imaging–measured volume of olfactory bulbs is not decreased in PD and that the number of periglomerular dopaminergic cells is massively increased, rather than decreased, in the olfactory bulbs of patients with PD, possibly leading to higher dopamine levels and inhibition of olfactory transmission in the olfactory glomeruli. It is, therefore, possible that local increase of dopamine activity may also facilitate the occurrence of olfactory hallucinations, in the same way dopaminergic agents induce visual hallucinations in advanced PD. Another explanation may rely on positive olfactory symptoms, such as phantosmias, resulting from neuronal loss not only in the anterior olfactory nucleus but also in other components of the central olfactory system. Denervation-induced hyperexcitability of mitral cells in the olfactory bulb may then lead to spontaneous olfactory activity in central olfactory systems, perhaps favored by the extensive involvement of these systems by Lewy pathology.

This hypothesis is supported by the recent observation of an abnormal pattern of cortical and subcortical activation in the central processing of olfactory function, as demonstrated by functional magnetic resonance imaging. Altogether, the phantosmias described herein exemplify a virtually unrecognized olfactory manifestation of the premotor stage of PD, which differs completely from hyposmia and may not necessarily be associated with it. The prevalence of this symptom is unknown, but it is possible that qualitative disturbances of olfaction in patients with PD may prove more frequent than currently appreciated.

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REFERENCES