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Case Report: Headache-associated phantosmia as a harbinger of Lewy body dementia

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Abstract

Olfactory hallucinations, or phantosmias, can occur in many neurological, psychiatric, and medical conditions, but no widely used standardized approach exists to comprehensively assess qualitative olfactory dysfunction in the clinical setting. Additionally, medical professionals, patients, and their family members may not recognize phantosmia as a potentially neurological problem. Given the many possible etiologies for symptomatic phantosmia, it is important to recognize this unusual presentation and elicit a meaningful history to explore the potential underlying cause. We describe a 77-year-old gentleman with a two-year history of headaches accompanied by smelling a foul odor and discuss the differential diagnosis for new onset and persistent phantosmia. This unusual case ultimately manifested features consistent with Lewy body dementia, highlighting the varied clinical presentations that are possible with this neurodegenerative disorder. We discuss the possible pathophysiology of phantosmia in Lewy body disorders, including a proposed mechanism for olfactory hallucinations arising prior to the typical well-formed hallucinations in Lewy body dementia.

Keywords

Cognitive Disorders; Dementia; Hallucinations; Headache and Facial Pain

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CASE REPORT

A 77-year-old left-handed gentleman with Factor V Leiden, hyperlipidemia, and sensorineural hearing loss presented to the Headache Clinic with dull and vice-like daily headaches typically followed by smelling a foul odor within the hour. The headache was predominantly located posteriorly with intermittent frontal involvement and extension above both ears. The headache would often awaken him from sleep and then lessen during the daytime. During an episode, he would appear distraught but not confused.

He endorsed headache episodes without olfactory symptoms starting two years ago and onset of accompanying smell in the last 14 months. He was initially managed by Otolaryngology for abnormal smell sensation. He also reported recurrent falls starting about five years prior. His initial fall was with head strike and loss-of-consciousness (LOC) without presentation for medical care, but he had overall improvement in ambulation over the last 18 months without additional falls.

His evaluation prompted concern for phantosmia representing aura of a primary headache disorder versus epilepsy. Posttraumatic headache was also considered, although the temporal correlation of falls to initial headaches was not consistent given onset years after his fall with traumatic brain injury (TBI). Lamotrigine was initiated as preventative treatment for both headache and potentially underlying epilepsy. The plan of care included admission to the Epilepsy Monitoring Unit (EMU) for spell capture and referral to the Behavioral Neurology Clinic after his family reported cognitive changes.

In the Behavioral Neurology Clinic, he endorsed worsening short-term memory, difficulty with name recall, slowed responses, and vision changes. His family noticed additional word-finding problems, worsening handwriting and spelling, and misplacing items. These changes were present for at least three years resulting in inability to manage his business but had worsened significantly over the last six months. Multiple mistakes were made in personal finances including inappropriately sharing sensitive information. There were increasing concerns about driving safely based on out-of-character incidents of aggressive driving and attempts to take the wheel as a passenger. He recently misidentified a stranger as a close relative and misinterpreted his hotel as a clinic.

Notably, behavior changes were observed prior to his falls, headaches, and cognitive changes. New marital discord started about six years before his evaluation driven by suspicions that his wife was unfaithful. He later became increasingly concerned about strangers trespassing onto his property, leading to him regularly carrying a firearm.

Current medications included those for vascular risk factors and lamotrigine 75 mg twice daily. He was a remote former smoker, but he had no recent alcohol use and no prior illicit drug use. Family history was unremarkable. His neurologic examination disclosed mild parkinsonism including bradykinesia with decrementing and a slowed, stooped walk with reduced arm swing, but no tremor. Cognitive evaluation with the Montreal Cognitive Assessment yielded a score of 14/30 with most profound deficits in visuospatial/executive function, language, abstraction, delayed recall, and orientation. Serum tests (e.g., thyroid stimulating hormone, rapid plasma reagin, and vitamin B12) were unremarkable. Brain MRI

performed a year prior showed old left lentiform nucleus and external capsule lacunes, prominent vascular spaces in the basal ganglia, and atrophy with predominance in the posterior regions. A routine EEG disclosed no epileptiform activity or other abnormalities. His EMU stay revealed two events of mild phantosmia without electrographic correlate.

He met clinical criteria for dementia given his progressive cognitive decline that interfered with daily activities. The additional clinical history and exam were most concerning for Lewy body dementia (LBD) and more specifically dementia with Lewy bodies (DLB). Despite multiple vascular risk factors, his imaging was not consistent with vascular dementia. The differential diagnosis also included cognitive impairment due to ongoing subclinical seizures as an unrevealing EMU stay does not conclusively rule out epilepsy. Other neurodegenerative disorders were considered, but he did not clearly meet the clinical criteria for behavioral variant frontotemporal dementia despite the early marital discord[1] and there were no other features to suggest other Parkinson-plus syndromes such as supranuclear palsy[2] or corticobasal syndrome.[3] He initially met criteria for probable Alzheimer's disease (AD) except for the exclusionary criteria of DLB core features.[4]

The DLB clinical criteria requires dementia,[5] which is often with initial deficits most notable in executive function, visuospatial abilities, and attention/processing speed and in some cases involvement of language and memory.[6] Core clinical features include prominent cognitive fluctuations, well-formed visual hallucinations (VH), rapid eye movement (REM) sleep behavior disorder, and parkinsonism (Table 1).[5] DLB is distinguished from Parkinson's disease (PD) dementia (PDD) by the "one year rule" such that PDD must have a clear PD diagnosis for at least one year before the onset of dementia.[5] Notably, LBD is an umbrella term that includes both DLB and PDD. An unusual feature of this case is the appearance of early paranoid delusions about infidelity, as delusions typically arise later in the course of LBD.[6]

The most novel feature of this case is that the inaugural and most prominent hallucination was olfactory. Only a year after he was first seen in the Behavioral Neurology Clinic did he describe well-formed VH of "gentlemen" sharing his room that he could physically guide with touch, consistent with tactile hallucinations previously described in DLB.[7] Given dementia, fluctuations, VH, and parkinsonism, he met the clinical criteria for probable DLB without biomarkers over time (Table 1).[5] Over time, our patient's Lewy Body Composite Risk Score (LBCRS)[8] was five (Table 2). A LBCRS of three or more assists in distinguishing DLB from AD with a sensitivity of 94.2% and specificity of 78.2% and any other dementia with a sensitivity of 97.9% and specificity of 86.1%.[8] His TBI was thought to be unrelated to his later diagnosis of DLB as the current literature does not support a strong association,[9–12] but his falls likely represented unrecognized parkinsonism during his early disease course.

His headaches were initially prominent despite uptitration of lamotrigine, but became less frequent and then ceased over months at which time lamotrigine was titrated off without headache recurrence. His phantosmia remained persistent. He additionally developed features consistent with olfactory reference syndrome (ORS), which is categorized under other specific obsessive-compulsive and related disorders,[13] as he would wake up perceiving

a foul odor emanating from his own body that prompted nightly showers. ORS is rare, generally with early age of onset (average 21 years), and is often associated with other comorbid psychiatric diagnoses.[14] ORS has been described previously in PD,[15] but the prevalence of ORS in Lewy body disease is unknown.

DISCUSSION

Olfaction requires a functional olfactory neuroepithelium, olfactory bulb, and olfactory nerve.[16] The primary olfactory regions (e.g., anterior olfactory nucleus, tenia tecta, olfactory tubercle, entorhinal cortex, piriform cortex, and amygdala) and secondary olfactory regions (i.e., thalamus, hypothalamus, and orbitofrontal cortex) with additional connections to the hippocampus and insular cortex are all required for the perception, identification, discrimination, emotional response, and modality-specific memory consolidation of olfactory inputs.[16] Olfactory function is localized to both cerebral hemispheres based on lesional and functional brain imaging studies, but some authorities have hypothesized a dominant role for the right temporal lobe in light of epilepsy cases that underwent unilateral temporal lobectomy.[16]

Olfactory hallucinations (OHs) are a type of qualitative olfactory dysfunction that involves a perception of a smell in the absence of an odor stimulant.[16] This phenomenon, also known as phantosmia, contrasts with parosmia (also called troposmia, or “twist/turn the sense of smell”), another qualitative olfactory dysfunction that refers to a distorted smell perception in the presence of an odor stimulant.[16, 17] Hyposmia (reduced smell) and anosmia (lost smell) are quantitative olfactory dysfunctions.[16]

Many non-neurological and neurological conditions are associated with qualitative and/or quantitative olfactory dysfunction, however less is known about qualitative olfactory dysfunction.[16, 18] Phantosmia is associated with a wide-range of conditions, therefore the differential for new onset phantosmia is broad (Table 3).[19] Phantosmia has been described in primary headache disorders,[20–22] focal epilepsy,[16, 23] multiple sclerosis,[24] PD,[16, 19, 25] and following TBI.[19, 26] Phantosmia has also been described in multiple non-neurologic medical conditions including psychiatric disorders,[27–29] post-upper respiratory tract infections,[19] sino-nasal disease,[19, 30, 31] and gastroesophageal reflux disease.[32] Phantosmia is also correlated with some prescription medications.[32] Idiopathic phantosmia is not uncommon, but does not clearly predict the development of serious health conditions or neurodegenerative disorders when followed longitudinally.[33]

Unlike quantitative olfactory dysfunction (i.e., hyposmia and anosmia) for which there are standardized clinical assessments for smell identification, no standardized approach exists for clinical assessment of qualitative olfactory dysfunction. A detailed clinical interview performed by an experienced clinician is the most frequent approach,[17] but standardized questionnaires have been proposed.[26, 31, 32] Given the absence of standardized assessments, phantosmia is predicted to be under-assessed and under-identified despite an estimated prevalence of 4.9%[34] to 6.5%[26] in older adults. However, only a small portion (11.1%) of individuals with phantosmia discuss alterations in smell with a medical provider.[26] Additionally, the current literature regarding the duration, quality (e.g., pleasant, unpleasant,

neutral), and other features (e.g., vague versus precise; intrinsic versus extrinsic) of the perceived odors associated with qualitative olfactory dysfunction and possible specific associations with the various etiologies are unclear beyond select case reports and case series.[20, 25, 28, 35] Phantosmia is associated with parosmia,[34] female sex,[26, 34] younger age,[26] low socioeconomic status,[26] vascular risk factors,[34] fair/poor health status,[26] and *brain derived neurotrophic factor* (*BDNF*) allele 10status.[34] Given the association with COVID-19 infections,[36] phantosmia prevalence is likely to increase.

There are multiple proposed mechanisms for phantosmia depending on the clinical context (Table 3),[20, 23] including both peripheral and central etiologies.[37] Regarding phantosmia in synucleinopathies, olfactory bulb α-synuclein has a high specificity and sensitivity for multiple Lewy body disorders including LBD and PD,[38] but there is actually increased dopaminergic signaling within the olfactory bulb and anterior olfactory nucleus in PD.[25] As such, it has been proposed that hyperexcitable dopaminergic activity in the setting of olfactory pathway denervation may be responsible for phantosmia in PD.[25] However, reduced thalamocortical cholinergic signaling resulting in enhanced cortico-thalamocortical and cortico-cortical signaling has been implicated in VH pathogenesis in DLB,[39] and therefore it is appealing to hypothesize that disrupted cholinergic signaling to the piriformis[23] may play a role in OH in DLB. Regardless of the neurotransmitter system(s) involved, it has been proposed that incomplete loss of olfactory sensory neurons, or the disproportionate loss of inhibitory neurons, may be responsible for overactivity leading to parosmia and phantosmia.[17]

The type and frequency of hallucinations in DLB include the more common VH that are followed by auditory hallucinations, OH, and finally tactile hallucinations; notably, OH are present in only 6.63% of patients.[40] Indeed, OHs are rare in neurodegenerative disorders and most often accompanied by other types of hallucinations or delusions.[41] Isolated OHs have been described in a subset of patients with PD without cognitive impairment.[42] However, VHs are more commonly the initial hallucination in PD, but often followed by the addition of nonvisual hallucinations over time.[43] To our knowledge, there are no reported cases of isolated OH in DLB. Additionally, there is no literature on the prevalence of OH at the time of DLB diagnosis, suggesting OH as either being rare or an under-assessed symptom in early DLB.

If the inaugural phantosmia in our patient is secondary to DLB neurodegeneration, it is intriguing to hypothesize why the olfactory system was affected first followed by the visual and ultimately sensory systems. Differences in temporal symptom onset in PD versus DLB may be related to the differential and sequential anatomy affected by synuclein pathology.[44] Specifically, it has been proposed that DLB synuclein pathology begins in the olfactory bulb and propagates to nearby limbic regions followed by higher associative neocortices in a rostro-caudal fashion as opposed to the caudo-rostral Braak staging model for PD.[44] With a rostro-caudal model in mind, the piriform cortex would be affected early in DLB.[44] Given the well-known gradient of inhibitory interneurons conferring a smaller population of inhibitory interneurons in the anterior piriformis,[45] the rostro-caudal spread of synuclein pathology may lead to an even more disproportionate loss of inhibitory neurons in the anterior piriformis leading to overactivity and ultimately phantosmia. Along this line, the

later spread of synuclein to the thalamus[44] may be responsible for later onset VH via alteration of thalamocortical connections with the temporo-occipital visual areas.[39]

Given the unusual presentation and wide differential for phantosmia, there was some delay in diagnosis even after he received specialized care in the Behavioral Neurology Clinic. Incorrect initial diagnoses are frequently made in patients with LBD, such that some reports document an 18-month delay for diagnosis of this disease on average.[46] However, recognizing OHs as a potential early symptom of DLB may help earlier diagnosis in future cases.

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Table 1:

Diagnostic Criteria for Dementia with Lewy Bodies

Level of Certainty	Criteria
Possible	a. One core clinical feature[a] with no indicative biomarker[b]
	b. No core clinical features[a] with one or more indicative biomarkers[b]
Probable	a. Two or more core clinical features[a] with or without indicative biomarkers[b]
	b. One core clinical feature[a] with one or more indicative biomarkers[b]

[a]Core clinical features includes prominent cognitive fluctuations, well-formed visual hallucinations, rapid eye movement sleep behavior disorder, and parkinsonism.

[b]Indicative biomarkers includes reduced dopamine transporter uptake in basal ganglia by single-photon emission computed tomography or positron emission tomography scans, low cardiac uptake by ^{123}iodine-metaiodobenzylguanidine myocardial scintigraphy, and confirmation of rapid eye movement sleep without atonia by polysomnography.

Table 2:

Lewy Body Composite Risk Score

Does the patient...	**Yes**	**No**
Have slowness in initiating and maintaining movement or have frequent hesitations or pauses during movement?	X	
Have rigidity (with or without cogwheeling) on passive range of motion in any of the 4 extremities?	X	
Have a loss of postural stability (balance) with or without frequent falls?	X	
Have a tremor at rest in any of the 4 extremities or head?		X
Have excessive daytime sleepiness and/or seem drowsy and lethargic when awake?		X
Have episodes of illogical thinking or incoherent, random thoughts?	X	
Have frequent staring spells or periods of blank looks?		X
Have visual hallucinations (see things not really there)?	X	
Appear to act out his/her dreams (kick, punch, thrash, shout or scream)?		X
Have orthostatic hypotension or other signs of autonomic insufficiency?		X

The Lewy Body Composite Risk Score is comprised of ten dichotomous history and exam features present at least three times over the prior six months that can easily be assessed in the clinical setting.

Table 3:

Differential Diagnosis, Positive Clinical and/or Diagnostic Findings, and Proposed Mechanism(s) of Various Phantosmia Presentations

Associated Diagnosis	Positive Clinical and/or Diagnostic Findings	Proposed Mechanism(s)
Neurologic		
Trauma	Evidence of trauma (hemorrhage or volume loss) on imaging[16]	Damage to olfactory neurons, olfactory bulb, or primary olfactory regions[26]
Epilepsy	EEG epileptiform activity; focal lesions on imaging[16]	Seizure focus within mesial temporal lobe structure (e.g., amydala)[16] or piriform cortex[23]
Multiple sclerosis	Demyelination on imaging[24]	Gray matter atrophy and/or demyelination of central olfactory system[24]
Primary headache disorders	Meets ICHD-3 criteria for aura[47]	Cortical spreading depression affecting primary, secondary, or association olfactory areas[20]
Parkinson's disease	Reduced striatum uptake on SPECT[25]	Multiple[a]
Psychiatric		
Schizophrenia spectrum disorders	Most often associated with other sensory hallucinations[48]	Dopamine dysregulation in the olfactory tubercle[29] and multiple structural and functional abnormalities of olfactory system[49]
Depression	Depression severity correlates with severity of olfactory dysfunction[28]	Reduced volumes of olfactory bulb, primary/secondary olfactory regions, and association cortices[27, 28]
Eating disorders	Additional gustatory dysfunction common[50]	Alteration in olfactory microbiome[b] or disrupted cell regeneration of olfactory epithelium[50]
Medical		
Sino-nasal disease		Microbial associated odor stimulus,31,[b] conductive olfactory loss,[30] inflammatory damage to olfactory receptor neurons,[51] or olfactory bulb atrophy[51]
Post-upper respiratory infection	Close temporal relationship to URI[52]	Viral damage to neuroepithelium and central olfactory pathways[52]
Gastroesophageal reflux disease		Reflux associated odor stimulus32,[b]
Medications		Medication associated odor stimulus32,[b]
Radiation therapy	Temporal correlation to radiation therapy[35]	X-ray induced odor stimulus[b] versus activation of olfactory pathway[35]

[a] See text discussion for proposed mechanisms of phantosmia in synucleinopathies.

[b] This phenomenon may not represent true phantosmia given potential odor stimulus, therefore may be closer to parosmia.

Abbreviations: ICHD-3 = The International Classification of Headache Disorders, 3rd Edition; SPECT = single-photon emission computed tomography; URI = upper respiratory infection.