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REVIEW

Visual hallucinations in the differential diagnosis of parkinsonism

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ABSTRACT

Visual hallucinations (VH) occur commonly in Parkinson's disease (PD) and dementia with Lewy bodies (DLB) but are reported much less frequently in other neurodegenerative causes of parkinsonism, such as progressive supranuclear palsy, multiple system atrophy and corticobasal degeneration syndrome. This clinical sign may be helpful when considering the differential diagnosis of patients with parkinsonism. The observation that VH may be specific to Lewy body pathology probably reflects a greater vulnerability of the visual systems to PD and DLB neurodegeneration compared with other diseases. Topographic differences in pathology are probably the major factor producing VH in Lewy body diseases, rather than neurophysiological changes that are specific to α-synuclein protein accumulation. VH correlate with pathology in the limbic system and more specifically the amygdale that is frequently affected in PD and DLB but relatively preserved in other forms of parkinsonism often misdiagnosed as PD. In this review, the published frequencies of VH in these different conditions are compared to put into context the notion of VH as a clinical clue to underlying Lewy body pathology.

INTRODUCTION

Parkinsonism is a clinical syndrome defined by the presence of bradykinesia with tremor, extrapyramidal rigidity and postural instability. Progressive neurodegenerative parkinsonism is most commonly associated with idiopathic Parkinson's disease (PD) but is also a clinical feature in progressive supranuclear palsy (PSP), multiple system atrophy (MSA) and vascular parkinsonism among other nosological entities. Over the past 2 decades, operational diagnostic criteria have been developed for these conditions which appears to have improved diagnostic accuracy.[1] Even so, it is common for patients to partially satisfy several different diagnostic criteria forcing clinicians to consider other factors outside these criteria when reaching a clinical diagnosis. In specialist movement disorder clinics the clinical diagnosis may be incorrect in up to 15% of patients compared with pathological diagnosis post mortem.[2] This inaccuracy is even more apparent early in disease when clinical signs have yet to fully evolve and parkinsonian features are mild.[3–5] Accurate diagnosis is important for informing the patient about their disease and prognosis, planning treatment strategies and, in the future, for testing possible neuroprotective treatments.

While parkinsonian motor features are commonly the instigator for a patient to attend medical services, non-motor features may be present which assist in the differential diagnosis. Visual hallucinations (VH) are a common finding in patients with underlying Lewy body pathology (PD and dementia with Lewy bodies (DLB)) but are not frequently associated with other parkinsonian diseases. This observation has prompted the consideration that VH be included among the clinical factors predictive of Lewy body pathology.

In this context, VH may provide a clinical clue that assists in the diagnosis of patients presenting with inconclusive clinical signs and atypical parkinsonism, or may help predict the underlying pathology or anatomical distribution of that pathology.

CLINICAL PHENOMENOLOGY AND DIFFERENTIAL DIAGNOSIS

Hallucinations are sensory perceptions in the absence of an external stimulus and may manifest as visual, auditory, olfactory or tactile phenomena. In comparison, illusions are distortions of perception in the presence of an external stimulus.

Hallucinations occur in 15–75% of patients with PD.[6–10] The variability in reported prevalence depends in part on study methodology. Most published reports included patients referred to specialist movement disorders clinics and report hallucinations in between 25% and 50% of all PD patients.[6 7] In contrast, a community survey of a geographically defined cohort in Norway with case ascertainment of 96% revealed a much lower rate of reported hallucinations of 16%.[8] Longitudinal studies have reported a higher prevalence than cross sectional studies, increasing over the course of the disease.[10 11]

PD was originally described in terms of motor disturbance but non-motor features, including cognitive and mood disturbances, sleep disturbance, constipation and anosmia, are prominent and may predate the onset of motor symptoms by up to 10 years.[12] Other parkinsonian diseases often present with the same motor features and clues to alternative diagnoses may remain obscured for some months or years. PSP, MSA and corticobasal degeneration (CBD) are often misdiagnosed as PD or DLB early in their course because of this.

The clinical signs of PD are usually asymmetric in onset, often with rest tremor, and a good response to dopaminergic medications is expected. The pathology is characterised by nigrostriatal deficiency with neuronal loss predominantly in the substantia nigra pars compacta, among other brainstem nuclei,

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with accumulation of α-synuclein in Lewy bodies and neurites. DLB is used to designate patients with dementia and parkinsonism that occur together.[13] The pathological difference between DLB and PD can be subtle and relates to the distribution of synuclein pathology and the extent of neuronal loss.[14]

In contrast, PSP is characterised by prominent akinesia, impaired postural reflexes, falls and vertical supranuclear gaze palsy or slowing of vertical saccades. These symptoms do not improve with dopaminergic medications. PSP is a primary tauopathy with neurofibrillary degeneration most severe in the globus pallidus, subthalamic nucleus, substantia nigra and pons. Up to a third of patients with PSP tau pathology have other clinical presentations, including: PSP—parkinsonism (PSP-P) with dominant early features of asymmetry, tremor, bradykinesia, dystonia and levodopa responsiveness; and pure akinesia with gait freezing characterised by early gait freezing without rigidity, tremor, dementia or supranuclear gaze palsy, which is somewhat less common.[15 16]

The 'motor presentation' of CBD manifests as unilateral limb rigidity, dystonia and bradykinesia with myoclonus and cortical sensory loss emerging later. This non-levodopa responsive parkinsonism may coexist with frontal and parietal cognitive disturbance with features that include apathy, agitation, personality change, depression, apraxia and a non-fluent aphasia. Pathologically there are diffuse cortical neuronal and glial tau deposits in addition to swollen or 'ballooned' neurons.[17]

Patients with MSA experience symptomatic dysautonomia, cerebellar ataxia, pyramidal signs and parkinsonism that is usually poorly responsive to levodopa. Neuropsychiatric features are seen in many cases, predominantly depression in more than 40%, but dementia is uncommon. Neuronal loss, reactive gliosis and iron deposition are seen in the basal ganglia, pons, medulla, cerebellum, inferior olivary nucleus and spinal cord.[18]

HALLUCINATIONS IN PARKINSON'S DISEASE

Visual experiences account for the majority of hallucinations in PD and DLB, and only a small proportion of patients report auditory, tactile or olfactory hallucinations.[6] Most authors have focused on the appearance of formed VH which are predominantly of people, animals or objects. These are generally described as solid images which may be still or moving, and may be miniaturised in up to 35% of cases.[19] One-third of patients report hallucinations lasting for hours at a time.[19]

A prodromal syndrome of minor hallucinations probably precedes the emergence of formed VH. These brief experiences include visual illusions, extracampine hallucinations (or 'presence' hallucinations, the sense of a presence in the room, often behind or beside the patient) or passage hallucinations (sense of movement in the periphery).[6] These experiences are often not reported by patients as hallucinations, and must be sought on direct questioning.[20] The majority of patients report that hallucinations appear when they have their eyes open, particularly in dim lighting or at the end of the day.

Most patients are aware of the hallucinatory nature of their experiences, with insight maintained in all non-demented and 64% of demented patients in one series.[6] They are often not perceived as frightening, although when they do become so the behavioural disturbance that may ensue is likely to have significant impact on care needs and are likely the explanation for the significant contribution of hallucinations to the rate of nursing home placement.[21] The presence of hallucinations correlates with the incidence of major depression,[22] and are associated with increasing age,[7] sleep disturbance,[7] depression[19] and cognitive disturbance.[7]

The relationship between VH and dopaminergic medications in PD is complex. VH were occasionally reported in PD before the availability of dopaminergic medication.[23] Conflicting reports have shown both a positive[24] and no association between dopaminergic medication dose and the appearance of VH.[6 7] Most medications used in the treatment of PD, including dopaminergic, anticholinergic and monoamine oxidase inhibitors, may also induce delirium.[24]

In one retrospective series, eight patients developed hallucinations in the setting of dopamine agonist use for pituitary tumours which translated to a rate of 1% in that series of 600 patients.[25] The hallucinations reported were predominantly auditory and associated with paranoid delusions and all patients had resolution of their psychotic symptoms with reduction or withdrawal of the medication. This suggests that while dopaminergic medication may have some inherent hallucinatory potential, the much higher rate of hallucinations seen in parkinsonian patients implies hallucinations develop as part of the disease process.[9]

VISUAL HALLUCINATIONS AS A MARKER OF DISEASE PROGRESSION

In contrast to DLB, VH are uncommon early in PD and appear to be the most important risk factor for permanent placement in a nursing home and associated increased mortality.[21]

The proposed pathological staging of PD by Braak[26] suggests synuclein pathology begins in the brainstem and progresses in a caudal-rostral pattern to the pons and mesencephalon. Non-motor symptoms such as REM sleep behaviour disorder and hyposmia have been suggested to relate to the involvement of these brainstem structures rather than dopaminergic cell loss and commonly predate motor features.[12] Motor dysfunction progresses in parallel to nigrostriatal dopaminergic deficiency, as assessed by functional imaging over the course of the disease.[27] Lewy body density correlates directly with disease duration[28] and with dementia[29] and is therefore predicted to evolve throughout the disease, with inevitable involvement of the cortex. Longitudinal studies show a progressive increase in cumulative prevalence of dementia over the course of the disease[10 11] and coincident development of hallucinations.[6]

VH have been suggested as a marker of disease severity and a measure of disease progression, which corresponds to standard clinical measures of disease severity.[7] Duration of disease appears to correlate most closely with the development of hallucinations,[6] and time to first hallucination is reported to be about 12 years after diagnosis.[9]

DOES THE APPEARANCE OF VISUAL HALLUCINATIONS SUGGEST ANATOMICOPATHOLOGICAL CORRELATES?

VH probably emerge as the result of disruptions in several different brain regions important in visual perception, processing and interpretation. They have been shown to emerge due to lesions along the whole of the visual axis, from cortical lesions, including occipital, temporal, parietal and frontal lobes, as well as following disruption to deep nuclei and brainstem structures. The complex relationships between the different pathophysiological factors involved in VH are incompletely understood but have been nicely integrated in a single model reviewed by Diederich *et al*.[30]

In the context of PD, where brainstem pathology probably develops before cortical pathology, the concept of 'peduncular hallucinosis' is of interest. It has been postulated that structural lesions in the brainstem and its connections (including the

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thalamus and temporal cortex) may cause hallucinations from disruption of serotonergic inhibitory neurons originating in the raphe nucleus.[31] These connections are important for regulation of REM sleep cycles and the resultant loss of inhibition in the lateral geniculate nucleus could lead to brief dream-like periods emerging during wakefulness.[32]

Sleep disturbance is common in PD and has been related to the development of hallucinations[7] but the underlying mechanism for this association is unclear. Patients with PD and hallucinations have reduced sleep efficiency and decreased REM sleep compared with those without.[33] One model of hallucinations that appears relevant to PD is narcolepsy associated hypnogogic hallucinations which are potentiated by drowsiness and may be induced by lesions of the brainstem or hypothalamus.[34] In PD, brainstem pathology may lead to both sleep disturbance and hallucinatory phenomena through disruption of the balance between serotonergic and cholinergic inputs to the lateral geniculate nucleus of the thalamus, involved in both arousal and modulation of inputs to the visual cortex.[34] VH occur earlier and more frequently in patients with DLB compared with PD, which may be related to the greater cholinergic deficit in DLB. Cholinergic neuronal loss is prominent in the temporal cortex, striatum and pedunculopontine projections to the thalamus and is also a feature of PD with dementia.[35]

Disruption to the visual pathway is a well documented mechanism for producing VH without psychosis, the classic description of the Charles Bonnet syndrome. This syndrome describes complex VH with retained insight to the hallucinatory nature of the visual phenomena in the context of decreased visual input. VH may emerge following lesions causing loss of function in the occipital cortex,[36] optic chiasm, optic radiation and retina.[37] This has been postulated as a central release phenomena, in which lack of sensory stimulus, or deafferentation, leads to neuronal hyperexcitability.[38] Evidence to support this theory includes the demonstration of spontaneous electrical activity in neurally isolated cortex on EEG and pathological studies of deafferented neural tissue.[38]

Visual disturbance and problems with visual processing deficiency occur at several different levels in PD so there are several disease factors that could allow hallucinations to emerge. For example, disruption of retinal dopamine function in PD underlies altered spatial contrast sensitivity which reduces the ability to undertake visuospatial tasks.[39] Delays in visual evoked responses and disturbances of visuospatial processing, suggesting involvement of the visual pathway beyond the retina, have also been demonstrated in PD.[40] Visual event related potentials are slower in patients with PD who have reported VH, consistent with a role for visual processing pathways in their onset.[41] Interestingly, visuospatial functions appear to be relatively spared in MSA and PSP, where hallucinations are rare.[42]

The theoretical models of VH are, to some extent, supported by imaging and pathological examination. Using MRI voxel based morphometry, reduced brain volume in the lingual gyrus and superior parietal cortex in non-demented PD hallucinators compared with PD non-hallucinators has been reported.[43] These brain regions contribute to the processing of colour perception and visuospatial working memory, with dysfunction postulated to effect visuoperceptive impairments.[43] Although atrophic changes such as these are indicative of neuronal cell loss, neuronal dysfunction is likely to be present years before demonstrable tissue loss occurs. Functional imaging has the potential to demonstrate in vivo dysfunction and several authors have used functional imaging in an attempt to identify the pathological substrate that contributes to hallucinations. Some of the functional imaging studies have been contradictory[44 45] but some correlate with anatomical predictions.[46] For example, reduced glucose metabolism shown on fluorodeoxyglucose–positron emission tomography in the ventral right temporal lobe and the right lateral visual cortex in PD suggests a functional deficit.[46] Pathological investigation of these regions studying Lewy body density identified a strong correlation between VH and pathological severity, particularly medial temporal lobe Lewy body density.[47] In addition, there is an association between α-synuclein pathology in the amygdala and hallucinations in demented PD patients.[48]

The limbic system is progressively affected by PD pathology throughout the course of the disease[28] but is affected early in DLB. Lewy body pathology preferentially affects the central, accessory cortical and basolateral nuclei in the amygdala.[48] The cortical nucleus is involved in olfactory perception and interruption promotes anosmia, well documented in PD.[12] The central nucleus projects to brainstem structures and the basal forebrain, consistent with a role in autonomic functions. The basolateral nucleus projects to the hippocampus and prefrontal association cortex, and has a role in modulating consolidation of emotional memory.[49] Increased Lewy bodies in the basolateral nucleus has been correlated with the presence of VH in those with PD.[48] The amygdala has a pivotal role in the recognition of facial expressions[50] and integration of the ventral visual system subserving conscious visual identification.[51] In non-demented PD patients increased Lewy body density in the amygdala predicted the development of hallucinations, with the highest correlation occurring with basolateral nucleus pathology.[47 48]

Models of the visual systems propose that the amygdala is responsible for integrating emotional responses to visual stimuli in the extrageniculostriate or 'ventral' visual system.[50] The amygdala receives sensory inputs from temporal and thalamic regions, and projects to temporal, occipital and brainstem structures that are important in the control of behavioural responses. It is proposed that the amygdala modulates behaviour through adjustments of neuronal activity in the extrastriate cortex in response to the emotional content of visual input. Interruption of amygdalar function from progressive α-synuclein neurodegeneration may lead to a central release phenomenon producing abnormal visual experiences, similar to that seen with lesions elsewhere in the visual pathways.[31] The limbic structures that appear important in the genesis of VH in PD and DLB appear to be much less vulnerable to PSP tau and MSA synuclein pathology than Lewy body pathology.[52 53] Unlike in advancing PD, temporal lobe pathology is less common in PSP.[54] Although low density nuclear inclusions are found in the subiculum and dentate gyrus in MSA, there is little or no cell loss in the amygdala and hippocampus.[53 55] It is worth noting, however, that up to 10% of patients with pathological MSA may also have Lewy bodies[5] and there are rare reports of temporal lobe atrophy in patients with slow disease progression and long disease duration.[55] These factors may be relevant in the emergence of VH in the few reported cases of MSA.

WHAT IS THE ROLE OF VISUAL HALLUCINATIONS IN THE DIFFERENTIAL DIAGNOSIS OF PARKINSONISM?

Given the high prevalence of VH in patients with Lewy body pathologies, it is tempting to consider that their emergence and development might, in some way, be due to neuronal dysfunction that is specific to α-synuclein protein accumulation. VH are established as a diagnostic feature of DLB.[13] The prevalence of

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Table 1 Rates of primary visual hallucinations reported in parkinsonian syndromes (not due to delirium)

		VH rate (%) (mean disease duration, years)					
Reference	**Referral source**	**DLB**	**PD**	**PSP**	**MSA**	**CBD**	**VP**
Klatka[56]	Brain bank series	60.7 (9.5) n=28					
Aarsland[8]	Community		16 (9.1) n=253				
Fenelon[6]	Specialist clinic		40 (9.5) n=216				
Hely[11]	Longitudinal cohort		50 (15) n=52				
Hely[10]	Longitudinal cohort		74 (20) n=30				
Holroyd[19]	Specialist clinic		26 (9.7) n=102				
Sanchez-Ramos[7]	Specialist clinic		26 (6.9) n=214				
Aarsland[57]	Specialist clinic		25 (2.8) n=103	3 (4.2) n=61			
Williams[20]	Specialist clinic		75 (10) n=115	5 (4.8) n=22	0 (6.7) n=9		20 (6.6) n=5
Williams[9]	Brain bank series	73 (4.6)† n=44	50 (11.9)† n=445	7 (4.5)† n=120	9 (6.9)† n=86	0 (6.8) n=9	4 (10.5)† n=25
Stefanova[18]	European MSA registry				6 n= 437		
Papapetropoulos[58]	Specialist clinic		57 (13.1) n=21		10 (8.5) n=21		
Cooper[59]	Specialist clinic			5 n=10		0 n=11	
Papapetropoulos[60]	Brain bank series			9 n =22			
Diederich[61]	Specialist clinic			13 n=30		21 n=14*	
Litvan[62]	Specialist clinic			0 (4.3) n=34		0 (3.8) n=15	

*Diagnosis possible, probable or suspected.
†Latency to onset of hallucinations reported (years).
CBD, corticobasal degeneration; DLB, dementia with Lewy bodies; MSA, multiple system atrophy; PD, Parkinson's disease; PSP, progressive supranuclear palsy; VH, visual hallucinations; VP, vascular parkinsonism.

VH in PD compared with other forms of parkinsonism argues they should form part of the diagnostic criteria for PD also.[9]

Although both DLB and PD are characterised by Lewy body pathology, VH are significantly more common and tend to present earlier in DLB.[13] Of course, the major difference between these conditions under the microscope is the distribution of the Lewy body pathology. In both, Lewy body neurodegeneration occurs in the brainstem and limbic structures but clinical dementia correlates with neocortical Lewy body density regardless of other clinical features.[29] It is in these patients that VH are more likely to occur.

Therefore, as a clinical marker, VH are much more likely to reflect the topographic distribution of pathology than characteristics inherent to specific insoluble protein accumulations, such as α-synuclein, or even β-amyloid or tau. In this light, VH as a diagnostic feature of Lewy body pathology is limited by the extent to which other pathologies affect the brain regions important in the genesis of VH. Fortunately, most clinical and pathological studies report a low frequency of VH in non-Lewy body forms of Parkinsonism (see table 1), which we would interpret as a low likelihood of these conditions affecting the visual cortex, temporal cortex and other visual pathways. This assumption is supported by the pathological data.

VH are reported in only 7% of patients with non-PD parkinsonism with confirmed pathological diagnosis.[9] PSP is associated with high rates of apathy and disinhibition but low rates of hallucinations, even in the context of dopaminergic medication use.[9 57] Hallucinations have been reported to occur in 5–9% of patients with MSA but rarely in CBD.[18 58] The presence of VH at any stage over the course of the disease is strongly predictive of Lewy body pathology and suggests this symptom may be useful in determining diagnosis.[63]

As an illustrative case, Compta *et al* described a patient with clinical features of PD who was responsive to levodopa for some years, and developed visual hallucinations late in the disease course. Although the clinical diagnosis remained consistent with PD, at autopsy she was found to have no synuclein or ubiquitin staining, but widespread phosphorylated tau deposits consistent with PSP, including severe pathology in the hippocampus and amygdala.[64]

Therefore, while the development of VH is very suggestive of Lewy body pathology, it appears more likely that the location of that pathology in the brain is the most important factor. The specificity of VH for Lewy body pathology likely relates to the higher frequency of involvement of the amygdala, visual and temporal cortices in PD and DLB compared with the other parkinsonian syndromes.

CONCLUSION

VH frequently occur later in the course of PD but are rarely spontaneously reported by patients when mild. Direct questioning is often needed to identify VH, and they are more likely to occur in patients who have cognitive disturbance, depression, visual pathology and REM sleep behaviour disorder. Although patients often maintain insight into the abnormal visual experiences, hallucinations are not benign phenomena as they are often not responsive to medical treatments and represent a risk factor for nursing home placement and increased mortality. The development of VH is the result of complex mechanisms integrating visual input, processing and interpretation through limbic and temporal regions. The differential expression of hallucinations is likely related to the increased predilection for Lewy body pathology to affect these brain regions and therefore, in the appropriate clinical setting, the presence of VH should be considered strongly suggestive of underlying Lewy body pathology.

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