

Categorising visual hallucinations in early Parkinson's disease

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Running Title: Visual hallucinations in Parkinson's disease

Key Words: Parkinson's disease, Visual hallucinations, Cognition, Quality of life

Abstract

Background

Visual hallucinations (VHs) are common in Parkinson's disease (PD), with prevalence ranging from 27-50% in cross-sectional cohorts of patients with well established disease. However, minor hallucinations may occur earlier in the disease process than previously reported and so we sought to categorise VHs in a cohort of newly diagnosed PD patients and their relationship to other clinical features.

Methods

Newly diagnosed PD participants (n=154) were recruited as part of the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in PD (ICICLE-PD) study. Participants completed the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS III), Montreal Cognitive Assessment (MoCA), and Parkinson's Disease Questionnaire (PDQ-39) to assess motor severity, cognition and quality of life (QoL), respectively. VHs were classified using the North East Visual Hallucinations Inventory. Hierarchical regression was used to build predictive models of motor severity, QoL and cognition.

Results

22% (n=34) of participants experienced recurrent VHs with minor VHs being most frequently reported (64.7% of hallucinators). Complex VHs were present in 32.4% of hallucinating participants. Linear regression showed VHs predicted poorer PDQ-39 and MoCA scores ($\beta=0.201$, $p=0.006$ and $\beta=-0.167$, $p=0.01$, respectively) but not motor severity ($p>0.05$).

Conclusions

Over a fifth of people with newly diagnosed PD reported recurrent VHs; minor hallucinations were the most common, although a small proportion reported complex VHs. Recurrent VHs were found to be a significant independent predictor of cognitive function and QoL but not motor severity. Our findings highlight the importance of screening for VHs at diagnosis.

Introduction

Visual hallucinations (VHs) are common in Parkinson's disease (PD) with prevalence rates ranging from 27-50% in patients with well-established disease [1]. Their presence can be distressing and has been associated with poorer quality of life (QoL) in both patients [2] and caregivers [3] as well as cognitive impairment [4] with progression to dementia (PDD) and motor severity [1, 8][5]. Risk factors associated with VHs in PD are disease severity and depression [1, 8, 9], although this association appears to be less pronounced in early PD participants with some such studies finding no association at all [10, 11].

Fully formed complex VHs are usually seen at later stages of PD and in PDD [12]. In contrast minor hallucinations, which have previously been defined as a feeling of presence or passing of an entity [1] and typically last a few seconds, have been said to occur in as many as 42% of PD patients, including those in early stage disease [11]. Furthermore, minor VHs have been found to be less malignant than complex VHs in terms of associated risk of cognitive impairment [13], but this is unresolved and may be a more significant predictor of cognitive problems in patients in early stage disease. We therefore sought to address this question of the characteristics of hallucinations in newly diagnosed incident PD and their relationship to motor severity, cognitive function and QoL.

Methods

Participants

Subjects participated in the Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation in PD (ICICLE-PD) study [15]. Newly diagnosed idiopathic PD patients from Newcastle upon Tyne and Gateshead (UK) were invited to participate between June 2009 and December 2011 from community and outpatient clinics. Patients were diagnosed by a movement disorder specialist and met Queen's Square Brain Bank criteria for idiopathic PD [16]. Patients were excluded if they had significant cognitive impairment defined as a Mini Mental State Examination (MMSE) score <24 or a diagnosis of dementia [17]. Patients with insufficient English to be assessed, PD diagnosis before the onset of the study, drug-induced parkinsonism, vascular parkinsonism and atypical forms of parkinsonism such as progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration were also excluded. This study was approved by the Newcastle and North Tyneside Research Ethics Committee and performed according to the Declaration of Helsinki. All subjects provided written informed consent.

Assessments

Participants completed a schedule of assessments. Participants were assessed when "on" their normal anti-PD medication. Demographic data included age, gender, disease duration and number of years in education. PD medications were recorded and levodopa equivalent daily dose (LEDD) was calculated [18]. Disease severity was assessed using the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part II and III [19] and Hoehn and Yahr stage [20]. Motor phenotypes were defined using the MDS-UPDRS scale as Postural Instability/Gait difficulty (PIGD), Tremor Dominant (TD) or Indeterminate phenotype [21].

The Geriatric Depression Scale (GDS-15) [22] was used to assess depression. Excessive daytime sleepiness was assessed using the Epworth Sleepiness Scale (ESS) [23]; the Pittsburgh Sleep Quality

Index (PSQI) [24] was used to assess sleep quality and disturbance. Quality of life was assessed using the Parkinson's Disease Questionnaire (PDQ-39, with higher scores representing poorer QoL) [25].

The MMSE [26] and Montreal Cognitive Assessment (MoCA) [27] were used to assess global cognition. We used modified PD-MCI criteria to determine whether a patient had MCI – namely scores that were 1.5 standard deviations (SD) below normative means [15, 28] in two tests, either within one cognitive domain or in two different domains, as described previously [29].

An assessment of VHs was conducted using the North East Visual Hallucination Inventory (NEVHI) [30]. This semi-structured interview identifies and assesses VHs by category (complex, illusions, simple and minor (Supplementary Table 1)), and by frequency. For the purposes of this study, floaters and hallucinations occurring in the context of a migraine were excluded and analyses focused on recurrent hallucinations in the last month. Recurrent was defined as more than one separate episode of hallucination, as per the NEVHI. This criteria was used to classify VHs in the analysis to exclude those who had had hallucinations in a non PD context such as, for example, from an episode of delirium.

Statistical analysis

Statistical analyses were performed using SPSS (Version 21.0. Armonk, NY: IBM Corp). The normality distribution of the data was assessed using the Kolmogorov-Smirnov test and visual histograms.

Differences between two groups were assessed using either independent t-tests or Mann–Whitney U tests as appropriate. Comparisons between more than two groups were conducted with Kruskal-Wallis tests. Chi-squared tests were used to compare differences between categorical variables. Significance was set at $p < 0.05$ for all analyses. Bonferroni's correction was applied for multiple comparisons.

Hierarchical regression was used to determine predictors of QoL, cognition and motor severity.

Backwards stepwise regression was used and non-significant predictors were excluded to produce a

basic model for each dependent variable. Predictors of PDQ-39 scores included GDS-15 scores, gender, years of education, age and MDS-UPDRS part III scores [31, 32]. Predictors of cognition using MoCA scores included in the initial model comprised ESS scores, MDS-UPDRS part III scores, age and years of education [15]. Predictors of MDS-UPDRS part III scores included in the initial model included gender, GDS-15 scores, PD-MCI and age [33]. To determine whether VHs were an independent predictor of each outcome, occurrence of recurrent VHs or not was subsequently added as a binary variable to the basic model.

Results

Of the 158 individuals enrolled [34], 154 participants completed the NEVHI and were therefore included in this study (Table 1). Application of the NEVHI identified 38.3% (n=59) of the participants as having any previous VHs. Of these, 22.1% (n=34) reported having recurrent VHs in the last month. Of the participants reporting recurrent VHs, 41.2% (n=14) reported more than one type of VH. The most frequently reported classification of VHs were minor hallucinations (64.7%, n=22), 38.2% (n=13) of participants with recurrent VHs reported recurrent simple VHs and 20.6% (n=7) recurrent illusions. Cumulatively, 11 participants (32.4%) reported recurrent complex VHs comprising of animals and people, including familiar and deceased individuals.

Clinical features of patients with and without VHs

The clinical characteristics of those patients with and without recurrent VHs were compared (Table 2). There was no difference in age, but those with recurrent VHs were more likely to be male. Participants with recurrent VHs had significantly poorer QoL, (PDQ-39 26.7 ± 17.0 vs. 16.4 ± 12.7 , respectively, $p=0.001$), higher daytime somnolence scores (ESS 8.8 ± 5.0 vs. 5.4 ± 4.1 , respectively, $p<0.001$) and more depressive symptoms (GDS-15 3.9 ± 3.1 vs. 2.5 ± 2.3 , respectively, $p=0.015$) compared to those without VHs. Lower global cognition scores were found in participants with VHs compared to those without using both the MoCA and the MMSE scores (Table 2).

A trend towards a difference in motor phenotypes was found between those with and without recurrent VHS (Table 2, $p=0.063$). Within the recurrent VH group, there was a significantly higher proportion of participants identified as PIGD compared to indeterminate or tremor dominant phenotypes (61.8% vs. 14.7% vs. 23.5%, respectively; $\chi^2=21.05$, $p<0.001$).

Participants with recurrent VHS were categorised according to the most severe classification of hallucinations reported to create distinct groups of participants with VHS, such that complex VHS > illusions > simple VHS > minor VHS (Table 3). No significant differences in any clinical characteristic were found between groups. Post hoc analysis did not reveal significant differences when using two group comparisons after Bonferroni corrections were applied ($p>0.008$).

The effects of VH on quality of life, cognition and motor severity

We next investigated whether recurrent VHS were predictive of clinical features. Backwards stepwise linear regression was used to determine predictors of PDQ-39, MDS-UPDRS part III and MoCA scores. Occurrence of VHS were then added to the model. Covariates are listed in Table 4. Recurrent VHS were a significant predictor of poorer QoL scores, accounting for 2.3% of the variance ($\Delta R^2 = 0.023$, $p=0.006$) and poorer cognition, accounting for 3.7% of the variance ($\Delta R^2 = 0.037$, $p<0.001$, Table 4). However, recurrent VHS were not a significant predictor of MDS-UPDRS part III scores ($p>0.05$).

Discussion

This study found recurrent VHS were reported in 22% of newly diagnosed PD participants. The most prevalent form was minor hallucinations, although 32% reported complex VHS, and their presence was associated with both poorer cognition and QoL.

Our finding of 1 on 5 incident PD patients reporting VH is similar to that reported by Pagonabarraga *et al.* [11], where they found that 24% of drug-naïve early PD patients experienced VHS more than

once per week, albeit in a smaller sample (n=50). Our study also found, in line with this study of Pagonabarraga et al, that minor VHS were the most frequently reported VH, occurring in 65% of recurrent hallucinators. However we also uniquely found that 32% of recurrent hallucinators reported complex VHS, which is surprising given their association with later stages of PD and PDD [4] and the fact that we found no differences in the clinical characteristics of patients with these different forms of VHS. This may have been due to the small numbers in each VH classification group.

However, we did find that recurrent VHS were significantly associated with worse global cognition scores using the MoCA, independent of age and years of education- although what happens over time is still being investigated as we follow up this cohort. In particular, understanding the relationship over time between cognition and VHS could be useful in identifying those at risk of developing PDD in the future [6, 35].

Consistent with previous findings in newly diagnosed patients [11], there was no significant difference in motor phenotype classification or in motor severity and the presence or not of VHS. It has been previously reported that VHS are found in patients with greater motor severity of disease [1, 9], although this was generally in participants with more advanced PD than in our cohort.

We found that QoL was significantly poorer in participants reporting VHS, in line with earlier studies [2, 36]. It has previously been suggested that reduced QoL in hallucinators may be due to depression [8] and reduced independence through nursing home placement [37]. However, our participants were newly diagnosed in early stages of PD, with none were living in nursing or residential care and only a few meeting a diagnostic criteria for depression, as measured by the GDS-15.

The main strengths of this study include a large well characterised representative incident cohort of patients, which by virtue of being a longitudinal study, means that misdiagnosis rates are minimised. The majority of participants in the present study were on dopaminergic medication (87.7%) at the time of recruitment (even though the mean disease duration was only 6 months) which is

representative of patients in real life clinical practice. Limitations included the small subgroup sizes, which limited statistical power to detect subtle differences between groups, as well as our analysis being cross-sectional, which means we cannot draw conclusions regarding the relationship between VHs and disease progression or cognitive decline. Finally, this study used global measures of cognition, which may have missed important findings regarding which specific cognitive modalities are associated with VHs early in PD.

In summary, we have found that VHs are common even in newly diagnosed PD patients, with minor hallucinations being the most frequently reported. Recurrent VHs in early PD were associated with poorer global cognition and QoL, but not with motor severity and as such may be an early harbinger of the development of PD dementia. However the longitudinal follow up of our cohort is needed to answer this question

Conflicts of interest:

The authors have no conflicts of interest to report.

Funding sources:

ICICLE-PD was funded by Parkinson's UK (J-0802, G-1301, G-1507). The research was supported by the Lockhart Parkinson's Disease Research Fund, the National Institute for Health Research (NIHR) Newcastle Biomedical Research Unit based at Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University and a NIHR Biomedical Research Centre award to the University of Cambridge/Addenbrooke's Hospital.

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Table 1. Demographic and clinical data

	Participant characteristics (n=154)
	n (%)
Sex: male	100 (64.9)
Dopaminergic medication	135 (87.7)
PD-MCI	68 (41.2)
	Mean \pm SD
Age	66.4 \pm 10.4
Years of education	12.8 \pm 3.8
Duration of PD (months)	6.0 \pm 4.6
LEDD	178.1 \pm 148.2
Hoehn and Yahr	2.0 \pm 0.7
MoCA	25.2 \pm 3.7
MMSE	28.6 \pm 13.1
GDS-15	2.8 \pm 2.5
MDS-UPDRS part III	26.9 \pm 12.1
ESS	6.2 \pm 4.5
PDQ-39	18.7 \pm 14.4
PSQI	6.3 \pm 3.9

MoCA = Montreal Cognitive Assessment, MMSE = Mini-Mental State Examination, MDS-UPDRS = Movement Disorder Society - Unified Parkinson's disease rating scale, LEDD = Levodopa equivalent daily dose, GDS-15 = 15 item Geriatric Depression Scale, PSQI - Pittsburgh Sleep Quality Index global score, ESS = Epworth Sleepiness Scale, PDQ-39 = Parkinson's Disease Questionnaire summary index.

N = 15 did not complete the MoCA

Table 2: Clinical characteristics of newly diagnosed participants with Parkinson’s disease with and without recurrent visual hallucinations

	Participants with recurrent visual hallucinations (n=34)	Participants without recurrent visual hallucinations (n=120)	t/ χ^2 /Z	P
Age (years)	65.7 ± 9.2	66.6 ± 10.7	0.39	0.696 ^t
Sex: male n(%)	27 (79.4)	73 (60.8)	4.02	0.045^x
PD-MCI n(%)	16 (47.1)	49 (40.8)	0.42	0.516 ^x
Education (years)	12.2 ± 3.6	12.9 ± 3.9	-1.28	0.199
Disease duration (months)	6.2 ± 4.5	6.0 ± 4.6	-0.49	0.623
Motor Phenotype n (%)			5.53	0.063 ^x
PIGD	21 (61.8)	48 (40.0)		
Indeterminate	5 (14.7)	20 (16.7)		
Tremor dominant	8 (23.5)	52 (43.3)		
MoCA	23.8 ± 3.9	25.5 ± 3.5	-2.24	0.025
MMSE	28.2 ± 1.4	28.8 ± 1.3	-2.26	0.024
MDS-UPDRS Part II	12.3 ± 5.4	10.4 ± 5.8	-1.75	0.081
MDS-UPDRS Part III	28.3 ± 12.0	26.5 ± 12.1	-0.74	0.459 ^t
Hoehn and Yahr	2.0 ± 0.7	2.0 ± 0.7	-0.24	0.815
LEDD (mg/day)	186.9 ± 149.1	175.5 ± 148.4	-0.70	0.485
GDS-15	3.9 ± 3.1	2.5 ± 2.3	-2.43	0.015
PSQI	7.2 ± 4.7	6.0 ± 3.7	-1.13	0.260
ESS	8.8 ± 5.0	5.4 ± 4.1	-3.52	<0.001
PDQ-39	26.7 ± 17.0	16.4 ± 12.7	-3.28	0.001

Data presented as mean ± SD unless otherwise stated X= chi squared, t= independent samples t test, remainder of tests were Mann-Whitney U test. Significant results highlighted in bold (p<0.05)

PD-MCI = Mild Cognitive Impairment at 1.5SD, PIGD = Postural Instability Gait Difficulty, MoCA = Montreal Cognitive Assessment, MMSE = Mini-Mental State Examination, MDS-UPDRS = Movement Disorder Society - Unified Parkinson's disease rating scale, LEDD = Levodopa equivalent daily dose, GDS-15 = 15 item Geriatric Depression Scale , PSQI - Pittsburgh Sleep Quality Index global score , ESS = Epworth Sleepiness Scale , PDQ-39 = Parkinson's Disease Questionnaire summary index.

N = 15 did not complete the MoCA

Table 3. Clinical characteristics of newly diagnosed participants with Parkinson’s disease and differing severities of visual hallucinations experienced

	Minor VHs (N=10)	Simple VHs (N=9)	Illusions (N=4)	Complex VHs (N=11)	X ²	P
Age (years)	66.7 ± 11.4	66.9 ± 9.0	69.1 ± 11.9	67.4 ± 5.5	2.2	0.537
Sex: male n (%)	7 (70.0)	7 (77.8)	3 (75.0)	10 (90.9)	5.1	0.278 ^x
PD-MCI n (%)	6 (60.0)	4 (44.4)	2 (50.0)	4 (36.4)	1.7	0.797 ^x
Education (years)	11.3 ± 3.3	13.7 ± 3.7	11.0 ± 0.8	12.2 ± 4.2	2.7	0.448
Disease duration (months)	4.8 ± 3.3	6.6 ± 7.4	7.9 ± 4.2	6.8 ± 2.1	3.7	0.291
Motor phenotype n (%)					11.2	0.191 ^x
PIGD	9 (90.0)	4 (44.4)	2 (50.0)	6 (54.5)		
Indeterminate	1 (10.0)	2 (22.2)	1 (25.0)	1 (9.1)		
Tremor Dominant	0 (0.0)	3 (33.3)	1 (25.0)	4 (36.4)		
MoCA	24.1 ± 4.1	23.4 ± 4.5	23.3 ± 2.1	24.0 ± 4.1	0.3	0.953
MMSE	28.1 ± 1.5	28.3 ± 1.3	28.5 ± 1.0	28.1 ± 1.6	0.3	0.968
MDS-UPDRS Part II	14.3 ± 6.2	10.2 ± 4.3	12.5 ± 5.9	12.2 ± 5.3	1.4	0.696
MDS-UPDRS Part III	27.2 ± 12.2	26.8 ± 12.0	34.0 ± 11.0	28.4 ± 13.2	1.5	0.686
Hoehn and Yahr	2.2 ± 0.8	1.8 ± 0.7	2.5 ± 0.6	1.8 ± 0.6	4.6	0.208
LEDD (mg/day)	173.0 ± 74.5	206.7 ± 186.5	130.0 ± 124.9	204.1 ± 183.6	0.8	0.826
GDS-15	4.2 ± 3.4	3.8 ± 4.1	4.5 ± 1.0	3.4 ± 2.7	1.8	0.610
PSQI	6.9 ± 5.1	6.7 ± 5.4	7.3 ± 3.6	7.8 ± 4.6	0.7	0.883
ESS	9.3 ± 6.7	7.8 ± 4.2	6.8 ± 3.7	9.8 ± 4.5	2.2	0.542
PDQ-39	28.0 ± 18.6	23.7 ± 17.0	31.8 ± 18.3	26.1 ± 17.2	0.9	0.832

Data presented as mean ± SD unless otherwise stated X= chi squared, t= independent samples t test, remainder of tests were Mann–Whitney U test. Post hoc Bonferroni correction for group comparison at p < 0.008.

PD-MCI = Mild cognitive impairment at 1.5 SD, PIGD = Postural Instability Gait Difficulty, MoCA = Montreal Cognitive Assessment, MMSE = Mini-Mental State Examination, MDS-UPDRS = Movement Disorder Society - Unified Parkinson's disease rating scale, LEDD = Levodopa equivalent daily dose, GDS-15 = 15 item Geriatric Depression Scale , PSQI - Pittsburgh Sleep Quality Index global score , ESS = Epworth Sleepiness Scale , PDQ-39 = Parkinson's Disease Questionnaire summary index, VHs = visual hallucinations. Data presented as mean ± SD unless otherwise stated. N=4 did not complete the MoCA.

Table 2: Regression coefficients and model fit of predictors of MoCA, PDQ-39 and MDS-UPDRS part III scores.

		t	p	β	95% CI for β	
					Lower Bound	Upper Bound
MoCA	Initial model ^a					
	Age	-4.1	<0.001	-0.3	-0.2	-0.1
	Education	3.0	0.003	0.2	0.1	0.4
	Initial model + Recurrent VHS ^b	-2.6	0.010	-0.2	-3.0	-0.4
PDQ-39	Initial model ^c					
	GDS-15	9.0	<0.001	0.5	2.3	3.6
	MDS-UPDRS part III	4.5	<0.001	0.3	0.2	0.5
	Age	-3.6	<0.001	-0.2	-0.5	-0.1
	Education	-2.4	0.020	-0.1	-1.0	-0.1
	Initial model + Recurrent VHS ^d	2.8	0.006	0.2	1.5	9.3
MDS-UPDRS Part III	Initial model ^e					
	GDS-15	3.5	0.001	0.3	0.6	2.0
	PD-MCI	2.5	0.012	0.2	1.0	8.5
	Initial model + Recurrent VHS ^f	-0.1	0.906	0.0	-4.8	4.2

a: $R = 0.477$, $R^2 = 0.227$, adjusted $R^2 = 0.216$, $F = 20.0$, $p < 0.001$, $SE = 3.2$

b: $R = 0.514$, $R^2 = 0.264$, adjusted $R^2 = 0.248$, $F = 16.2$, $p < 0.001$, $SE = 3.2$, $\Delta R^2 = 0.037$

c: $R = 0.725$, $R^2 = 0.526$, adjusted $R^2 = 0.514$, $F = 41.4$, $p < 0.001$, $SE = 10.0$

d: $R = 0.741$, $R^2 = 0.549$, adjusted $R^2 = 0.534$, $F = 36.1$, $p < 0.001$, $SE = 9.8$, $\Delta R^2 = 0.023$

e: $R = 0.358$, $R^2 = 0.128$, adjusted $R^2 = 0.116$, $F = 11.1$, $p < 0.001$, $SE = 11.4$

f: $R = 0.358$, $R^2 = 0.128$, adjusted $R^2 = 0.111$, $F = 7.3$, $p < 0.001$, $SE = 11.4$, $\Delta R^2 = 0.000$

CI = confidence intervals, MoCA = Montreal Cognitive Assessment, VHS = visual hallucinations, MDS-UPDRS = Movement Disorder Society - Unified Parkinson's disease rating scale, GDS-15 = 15 item Geriatric Depression Scale, PDQ-39 = Parkinson's Disease Questionnaire summary index, PD-MCI = Mild Cognitive Impairment applying cut-off of 1.5SD below normative values, Significant results highlighted in bold.

Supplementary Table 3. Summary of visual hallucination classification

Classification of Visual Hallucination	Description
Complex Hallucination	Formed visual hallucination such as people, animals, objects, devils etc.
Illusion	A misperception in vision e.g. wallpaper patterns move, perceiving clothing as an animal or person.
Simple Hallucination – without migraine	Unformed visual hallucinations such as lights, spots, colours, shadows.
Simple Hallucination – in context of migraine	Unformed visual hallucinations as described above that occur during a migraine.
Minor Hallucination - Presence	The feeling of a person, being or thing nearby or out of view.
Minor Hallucination - Passage	The feeling or vision of an animal, shadow or person passing by.
Floater	Generally spots which move with the individuals eyes.