Impaired Visual Acuity as a Risk Factor for Visual Hallucinations in Parkinson’s Disease

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ABSTRACT

Pathophysiology of hallucinations in Parkinson's disease is poorly understood. This study investigated relationships between visual hallucinations and visual acuity. Twenty-six consecutive patients with Parkinson's disease participated in this study. Patients were divided into two groups: patients with visual hallucinations (VH group) and those without visual hallucinations (no-VH group). Unaided and corrected eyesight was evaluated in all patients, and if frequent use of prescription glasses or contact lenses was involved, eyesight using these lenses was also measured as the patient's own best eyesight. If a patient did not use prescription glasses or contact lenses, the patient's own best eyesight was defined as the unaided eyesight. Multivariate regression analysis demonstrated that agonist use and best eyesight were different after the backward elimination method. Visual hallucinations were closely related not to uncorrected eyesight or unaided eyesight but to the patient’s best eyesight. It is suggested that impaired visual acuity is a risk factor for visual hallucinations. (J Geriatr Psychiatry Neurol 2006;19:36-40)

Keywords: Parkinson's disease; visual hallucination; visual acuity; Charles-Bonnet syndrome

Neuropsychological, psychiatric symptoms in Parkinson's disease and side effects during treatment of the disease have long been reported and continue to be a topic of increasing interest.\(^1,2\) Hallucinations are common symptoms or side effects, and many studies have reported hallucinations in Parkinson's disease.\(^3-6\) These studies showed that hallucinations, mainly visual, affected as many as one fourth of outpatients with Parkinson's disease. However, pathophysiology of these hallucinations is poorly understood. Dopaminergic, serotonergic, or cholinergic systems may play a role in hallucinations. There are almost no histopathological studies on hallucinations in Parkinson's disease. One autopsy study documented an association between the presence of visual hallucinations and Lewy bodies in the temporal lobe and specifically in the amygdala and the parahippocampus.\(^7\) To date, there have been few neuroimaging studies on Parkinson's disease with hallucinations.

Visual hallucinations in Parkinson's disease are similar to those in Charles Bonnet syndrome.\(^8\) In Charles Bonnet syndrome, visual impairment is a risk factor for hallucinations. We recently reported 2 patients with Parkinson's disease whose visual hallucinations disappeared after cataract surgery.\(^9\) We hypothesized that impaired visual acuity might be one of the risk factors for visual hallucinations in Parkinson's disease.

Here, we report a prospective and pilot study establishing a relationship between visual hallucinations and visual acuity and show that impaired visual acuity was one of the risk factors for visual hallucinations in Parkinson's disease.

METHODS

Patients
Twenty-six consecutive patients with Parkinson's disease who were admitted to our department participated in this study. All patients fulfilled the UK Parkinson's Disease Society Brain Bank criteria for idiopathic Parkinson's disease.\(^10\) None of the patients had been prescribed with either anticholinergic agents or antihallucinatory medications. None of the patients had other central nervous diseases. Patients suspected of other forms of parkinsonism such as multiple system atrophy or diffuse Lewy body disease were not enrolled. The clinical diagnosis of multiple system atrophy was based on probable multiple system...
atrophy diagnostic criteria proposed by Gilman et al.\textsuperscript{11} We differentiated patients with diffuse Lewy body disease from those with Parkinson's disease with dementia using the 1-year rule.\textsuperscript{12} Fully informed consent was received from all patients. We divided patients into 2 groups: patients with visual hallucinations (VH group) and those without visual hallucinations (No-VH group). The VH group included patients with visual hallucinations occurring at least once a week, and the No-VH group included patients who did not have any experience of visual hallucinations. Frequency of hallucinations was assessed via a self-report.

**Visual Acuity**

Ophthalmologists performed ophthalmologic examinations including individual interviews, eyesight tests, screening for cataracts, and fundoscopy. No patients showed any ophthalmologic disease other than cataracts. Unaided eyesight was evaluated at 5-m distances using Landolt circle and was assessed using decimal notations. Corrected eyesight was also evaluated in all patients, and if a patient frequently used prescription glasses or contact lenses, eyesight using these lenses was also measured as the patient's best eyesight. If a patient did not use prescription glasses or contact lenses, we defined the patient's best eyesight as the unaided eyesight.

**Statistical Analysis**

To compare profiles between the two groups, a Mann-Whitney U test was used for analysis of nonparametric data, and an unpaired one-tailed t test was used for parametric data. Significance was accepted at \( P < .05 \).

First, for comparison of visual acuity between the 2 groups, an unpaired t test was used. Because we hypothesized that visual hallucinations occurred more likely if patients had bad eyesight, we used a one-tailed t test but not a two-tailed test. Results were expressed as mean ± standard deviation.

Second, we performed a multivariate logistic regression analysis using age, sex, disease duration, levodopa dosage, agonist use, Hoehn-Yahr stage, Mini-Mental State Examination (MMSE) score, and best eyesight as variables, and the backward elimination method (cutoff: \( P < .05 \)) was performed. Presence of visual hallucinations was a dependent variable, and other factors were predictors. Because there was a close correlation between disease duration and levodopa duration, we selected disease duration as the only variable on subsequent analysis.

Statistical analysis was performed using the JMP version 5.1 software package (SAS Institute Inc, Cary, NC).

**RESULTS**

Details of patient profiles are shown in Table 1. Distribution of age, sex, agonist use, and MMSE scores did not show significant differences. Hoehn-Yahr stage, disease duration, levodopa dosage, and duration of levodopa therapy differed significantly between the two groups.

Unpaired \( t \) test results are shown in Table 2. There was a significant difference only between best eyesight. Unaided eyesight and corrected eyesight did not differ significantly between the two groups. Distribution of best eyesight is shown in Fig. 1.

Using multivariate regression analysis, we selected agonist use (odds ratio \( 36.1, P = .0278 \)) and best eyesight (odds ratio \( 0.0017, P = .0124 \)) and found them to be sig-

### Table 1. Summary of Clinical Findings

<table>
<thead>
<tr>
<th></th>
<th>VH</th>
<th>No-VH</th>
<th>( P ) Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>16</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>68.6 ± 5.6</td>
<td>69.1 ± 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>6/10</td>
<td>1/9</td>
<td></td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>12.0 ± 9.7</td>
<td>5.1 ± 5.2</td>
<td>.0137</td>
</tr>
<tr>
<td>Levodopa dosage (mg)</td>
<td>315.6 ± 76.9</td>
<td>170.0 ± 156.7</td>
<td>.0091</td>
</tr>
<tr>
<td>Levodopa dosage (years)</td>
<td>9.8 ± 7.5</td>
<td>3.7 ± 4.9</td>
<td>.0095</td>
</tr>
<tr>
<td>Agonist (user/non-user)</td>
<td>13/3</td>
<td>6/4</td>
<td></td>
</tr>
<tr>
<td>Hoehn-Yahr stage</td>
<td>3.3 ± 0.6</td>
<td>2.9 ± 0.7</td>
<td>NS</td>
</tr>
<tr>
<td>MMSE score</td>
<td>24.9 ± 4.2</td>
<td>25.1 ± 4.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Note: VH = visual hallucinations; NS = not significant; MMSE = Mini-Mental State Examination. A Mann-Whitney U test was used for analysis of nonparametric data, and unpaired and one-tailed \( t \) tests were used for analysis of parametric data. Data are shown as mean ± standard deviation.*

### Table 2. Summary of Eyesight Examinations

<table>
<thead>
<tr>
<th></th>
<th>VH</th>
<th>No-VH</th>
<th>( P ) Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaided eyesight</td>
<td>0.29 ± 0.14</td>
<td>0.42 ± 0.37</td>
<td>NS</td>
</tr>
<tr>
<td>Best eyesight</td>
<td>0.40 ± 0.18</td>
<td>0.63 ± 0.31</td>
<td>.0277</td>
</tr>
<tr>
<td>Corrected eyesight</td>
<td>0.89 ± 0.22</td>
<td>0.90 ± 0.38</td>
<td>NS</td>
</tr>
<tr>
<td>Glasses or contact lenses (user/non-user)</td>
<td>6/10</td>
<td>3/7</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Note: VH = visual hallucinations; NS = not significant. Unpaired and one-tailed \( t \) tests were used. Data are shown as mean ± standard deviation.*
nificant after the backward elimination method. $R^2$ value was .4169 and $P$ value was .0007 in this multivariate logistic regression model.

**DISCUSSION**

Despite the small number of patients used, we demonstrated that best eyeglass and agonist use were closely related to the presence of visual hallucinations in Parkinson's disease.

Hallucinations in Parkinson's disease are commonly considered to be a side effect of dopaminergic therapy. However, in some studies, hallucinations were not associated with dosage of dopaminergic medications (levodopa or dopamine agonists). Furthermore, with patients treated with dopamine agonists for pituitary tumors, hallucinations only occurred in a few patients and hallucinations were reported in Parkinson's disease before the use of levodopa. Hence, visual hallucinations do not simply relate to high levels of dopaminergic stimulation, but clearly dopaminergic drugs interact with Parkinson's disease in some ways to produce visual hallucinations. Other risk factors include increased age, disease duration, cognitive impairment, and disease severity.

Pathophysiology of hallucinations is poorly understood. Dopaminergic, serotonergic, or cholinergic systems have been suggested to play a role in hallucinations. Cholinergic deficits occur in Parkinson's disease, and therefore cholinergic systems may play an important role in hallucinations, but there are almost no studies on cholinergic systems and hallucinations in Parkinson's disease. In addition, there are only few histopathological studies on Parkinson's disease and hallucinations. One autopsy study documented an association between the presence of visual hallucinations and Lewy bodies in the temporal lobe and specifically in the amygdala and parahippocampus.

Very few imaging studies on Parkinson's disease are available. Recently, a functional magnetic resonance imaging study of Parkinson's disease showed greater activation in frontal and subcortical areas and less activation in the visual cortex after visual stimuli in patients with hallucinations. A study using resting blood flow single photon emission computed tomography reported a low cerebral blood flow in the left temporal lobes in patients with hallucinations compared with patients without hallucinations. A fluorodeoxyglucose positron-emission tomography study showed that relative regional cerebral glucose metabolic rate was greater in frontal areas in Parkinson's disease patients with visual hallucinations compared with patients without hallucinations. These imaging studies are controversial, but we hypothesize that frontal hyperfunction and temporal–occipital hypofunction may lead to visual hallucinations.

Recently, Charles Bonnet syndrome has attracted particular attention. Indeed, a number of cases with visual hallucinations have been reported in elderly, sane subjects with visual impairments attributable to diseases of the eye or optic nerve. The syndrome is defined as visual hallucinations in elderly patients with preserved intellectual function, and impaired visual function is a risk factor. Visual hallucinations may occur in as many as 12% of cognitively normal people with poor visual acuity. In the past, it was commonly believed that visual hallucinations were caused by abnormal stimulation of the visual pathway. Cogan reported that hallucinations were caused by disruption of the normal flow of visual impulses to the occipital cortex, resulting in initiation of endogenous cerebral activity of the visual system. This model might also apply to visual hallucinations in Parkinson's disease.

Interestingly, visual hallucinations in Charles Bonnet syndrome share some features with those occurring in Parkinson's disease. These features include the wide variety of images and patient awareness of the unreal nature of hallucinations, with most patients not being distressed by hallucinations. In addition, visual hallucinations in Charles Bonnet syndrome and Parkinson's disease frequently occur in the evening or at night, suggesting that both sensory deprivation and low level of arousal are facilitating factors.

Some reports previously showed that decreased visual acuity is a risk factor for visual hallucinations in patients with Alzheimer's disease. As an example, report that impaired visual acuity was a risk factor for visual hallucinations in Alzheimer's disease, and ophthalmologic treatment prevented hallucinations.

Moreover, our study also demonstrated a close relationship between impaired visual acuity and visual hallucinations in Parkinson's disease. Although there have been many reports about hallucinations in Parkinson's disease, there are only a few studies on their association with visual acuity. reported that disease severity, dementia, depression, and worse visual acuity were significantly related to visual hallucinations. Similar to our study, also used "best vision." Our findings matched those in their study. Visual hallucinations were closely related to uncorrected eyesight or unaided eyesight but to patient's best eyesight. This supports the hypothesis that impaired visual acuity is a risk factor for visual hallucinations rather than the theory that impaired visual acuity and visual hallucinations involve similar pathological processes, because glasses and contact lenses are apparently unrelated to the disease process itself.

We emphasize that it is necessary to perform eye examinations in patients with visual hallucinations and make appropriate corrections. Such eyesight corrections can treat visual hallucinations in Parkinson's disease.

It is known that patients with Parkinson's disease have subtle visual disturbances related to the disease, including abnormalities in spatiotemporal contrast sen-
sitivity and in color discrimination.\textsuperscript{40,41} In patients with normal visual acuity, people with visual hallucinations showed significantly worse performances in tests assessing color vision and contrast discrimination.\textsuperscript{42} Another study has suggested an association between distorted chromatic contour perception and the presence of visual hallucinations in patients with Parkinson's disease.\textsuperscript{43} Therefore, visual factors other than impaired visual acuity may contribute to visual hallucinations in Parkinson's disease, and this requires further investigations.

References
