Visual Hallucinations in Posterior Cortical Atrophy

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Background: Visual hallucinations have been reported to occur in up to 25% of patients who meet the criteria for posterior cortical atrophy (PCA). It is not known, however, whether patients who meet the criteria for PCA and have hallucinations are different from those who meet the criteria and do not have hallucinations.

Objective: To compare the clinical and imaging features of patients with PCA with and without well-formed visual hallucinations.

Design: Case-control study.

Setting: Tertiary care medical center.

Patients: Fifty-nine patients fulfilling the criteria for PCA were retrospectively identified and divided into 2 groups based on the presence (n=13) or absence (n=46) of visual hallucinations.

Main Outcome Measures: Statistically significant clinical differences and imaging differences using voxel-based morphometry between the 2 groups.

Results: In patients with PCA and hallucinations, parkinsonism and rapid eye movement sleep behavior disorder occurred more frequently, as did myoclonic jerks (P<.001 for both). Voxel-based morphometry showed greater atrophy in a network of structures, including the primary visual cortex, lentiform nuclei, thalamus, basal forebrain, and midbrain, in patients with hallucinations.

Conclusions: Hallucinations in patients with PCA are associated with parkinsonism, rapid eye movement sleep behavior disorder, and myoclonic jerks. The voxel-based morphometry results suggest that hallucinations in PCA cannot be exclusively attributed to atrophy of the posterior association cortices and may involve a circuit of thalamocortical connections.

Arch Neurol. 2006;63:1427-1432

POSTERIOR CORTICAL ATROPHY (PCA) is a clinical syndrome characterized by visuospatial and visuoperceptual impairment, visual agnosia, and features of Balint syndrome and Gerstmann syndrome. Case studies in PCA demonstrate atrophy of the bilateral occipital, parietal, and posterotemporal lobes on magnetic resonance imaging (MRI). Similarly, functional imaging studies in PCA reveal a pattern of decreased perfusion affecting these same regions. Many pathologic studies demonstrate that the predominant underlying histologic feature of PCA is the presence of neurofibrillary tangles and senile plaques. However, the distribution of abnormalities differs from that of typical Alzheimer disease, affecting predominantly the occipital and parietal lobes.

Although there are cardinal features of PCA, studies have described additional features not originally reported in PCA. One such feature is visual hallucinations, which have been reported to occur in up to 23% of patients who meet the criteria for PCA. It is not known, however, whether patients who meet the criteria for PCA and have hallucinations are different from those who meet the criteria and do not have hallucinations. We therefore set out to compare the clinical and imaging features of patients with PCA with and without visual hallucinations.

METHODS

PATIENTS

The Mayo Clinic medical records database was used to identify all patients with a clinical diagnosis of PCA who had been evaluated between January 1, 1995, and December 31, 2005. Seventy patients were identified. The medical records of these 70 patients were reviewed independently by 1 behavioral neurologist (K.A.J.) to ensure that they fulfilled the proposed diagnostic criteria for PCA. Inclusion criteria were as follows: (1) an insidious onset of symptoms; (2) a chief com-
plaint of at least 2 prominent symptoms referable to the occipital, parietal, or postero temporal lobes that have been linked to PCA; (3) no primary ocular disease accounting for the complaint after ophthalmologic evaluation by an ophthalmologist; (4) an evaluation by at least 1 behavioral neurologist; (5) progression of symptoms; and (6) MRI or computed tomography of the head showing a predominantly posterior pattern of atrophy on visual inspection. The list of prominent symptoms linked to PCA included visuospatial deficit, visuoperceptual deficit, visual agnosia, color agnosia, environmental disorientation, dressing apraxia, ideomotor apraxia, alexia, hemianopia, transcortical sensory aphasia, anomia, prosopagnosia, body schema distortion, and any feature suggestive of Balint syndrome or Gerstmann syndrome. Patients were excluded if there were any findings of a hemispheric infarct in the occipital, parietal, or temporal lobes on head MRI or computed tomography (reviewed by J.L.W. and C.R.J.) that could have contributed to the presenting syndrome.

Eleven patients did not meet the inclusion and exclusion criteria. The remaining 59 patients were divided into 2 groups: those with visual hallucinations and those without. Visual hallucinations were defined as false visual perceptions not associated with real external stimuli and not associated with falling or awakening from sleep. A patient was placed into the hallucinations group if the hallucinations were well formed, recurring, documented, nonfleeting, and spontaneous.

**VOLUMETRIC MRI**

Voxel-based morphometry (VBM) was used to assess the pattern of gray matter (GM) atrophy in all the patients with hallucinations who had an available volumetric MRI (n = 7) with that in a group of age- and sex-matched patients without hallucinations (n = 7) and controls (n = 38).

The T1-weighted volumetric MRIs were acquired at 1.5 T (field of view, 22 × 16.5 cm; flip angle, 25°; and 124 contiguous 1.6-mm-thick coronal slices). An optimized method of VBM was applied, implemented using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm). To reduce any potential normalization bias across the disease groups, customized templates and prior probability maps were created from all the study patients. To create the customized templates and priors, all the images were registered to the Montreal Neurological Institute (MNI) template using a 12-df affine transformation and were segmented into GM, white matter, and cerebrospinal fluid using MNI priors. The GM images were normalized to the MNI GM before using a nonlinear discrete cosine transformation. The normalization variables were applied to the original whole head, and the images were segmented using the MNI priors. Average images created of the whole head, GM, white matter, and cerebrospinal fluid were smoothed using an 8-mm full-width at half-maximum smoothing kernel. All the images were then registered to the customized whole-brain template using a 12-df affine transformation and were segmented using the customized priors. The GM images were normalized to the custom GM prior using a nonlinear discrete cosine transformation. The normalization variables were then applied to the original whole head, and the images were segmented once again using the customized priors. All the images were modulated and smoothed using an 8-mm full-width at half-maximum smoothing kernel.

**STATISTICS**

Statistical analyses were performed using a software program (JMP version 5.1.2; SAS Institute Inc, Cary, NC), with statistical significance set at P < .05. The Mann-Whitney test was used to compare mean age at disease onset between the 2 clinical groups. Sex ratios and the presence or absence of clinical signs were compared using the χ2 test. The Fisher exact test was used in any comparison with small numbers (n < 6).

Two-sided t tests were used to analyze the smoothed modulated images from the PCA group with hallucinations vs controls and from the PCA group without hallucinations vs controls. In addition, 2 direct comparisons were performed between the 2 PCA groups, first to identify regions that showed greater loss in PCA with vs without hallucinations and second to identify regions that showed greater loss in PCA without vs with hallucinations. Regions of GM loss identified by means of VBM were also visually rated: 0 indicates no loss; +, mild loss; and ++, moderate or severe loss (P < .001, uncorrected).

**RESULTS**

The demographic and clinical features of the 59 study patients are given in Table 1. Twenty-two of the 59 patients have been described previously. Thirty-six pa-

<p>| Table 1. Comparison of Patients With PCA With and Without Visual Hallucinations |
|-----------------------------|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>With Hallucinations (n = 13)</th>
<th>Without Hallucinations (n = 46)</th>
<th>Total (N = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M/F, No.</td>
<td>6 (46)</td>
<td>17 (29)</td>
</tr>
<tr>
<td>Age at disease onset, median (range), y</td>
<td>63 (49-86)</td>
<td>57 (40-74)</td>
</tr>
<tr>
<td>Right-handed, No. (%)</td>
<td>13 (100)</td>
<td>45 (98)</td>
</tr>
<tr>
<td>Educational level, median (range), y</td>
<td>12 (12-17)</td>
<td>14 (8-20)</td>
</tr>
<tr>
<td>RBD present, No. (%)</td>
<td>8 (62)</td>
<td>0</td>
</tr>
<tr>
<td>Parkinsonism present, No. (%)</td>
<td>10 (77)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Myoclonic jerks present, No. (%)</td>
<td>6 (46)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Difference between onset of hallucinations and onset of PCA, median (range), y</td>
<td>4 (1-12)</td>
<td>NA</td>
</tr>
<tr>
<td>Difference between onset of RBD and onset of PCA, median (range), y</td>
<td>3 (1-7)</td>
<td>NA</td>
</tr>
<tr>
<td>Difference between onset of Parkinsonism and onset of PCA, median (range), y</td>
<td>4 (2-10)</td>
<td>3 (2-7)</td>
</tr>
<tr>
<td>Difference between onset of myoclonic jerks and onset of PCA, median (range), y</td>
<td>2 (1-11)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not applicable; PCA, posterior cortical atrophy; RBD, rapid eye movement sleep behavior disorder.

*P < .001.
patients (61%) were women, and 58 (98%) were right-handed. All the patients had been evaluated by at least 1 behavioral neurologist and on average had been evaluated 2.6 times throughout their disease course. Fifteen patients had 1 evaluation, 39 patients had 2 to 5 yearly evaluations, and 5 patients had more than 5 evaluations. All the patients had typical early signs and symptoms of PCA and across time developed a variety of additional features (Figure 1). During their disease course, 5 patients had 2 to 3 of the cardinal signs and symptoms of PCA, 16 patients had 4 to 5, 36 patients had 6 to 10, and 2 patients had more than 10. In addition to the typical features of PCA, cerebellar ataxia was noted to have occurred in 10% of the patients. Syncopal attacks were also described in 3 patients, and 2 patients were found to have temporal lobe epileptic spikes on electroencephalograms. Episodic memory loss was not the dominant initial symptom in any of the 59 patients.

Thirteen patients with PCA had well-formed visual hallucinations (Table 1 and Table 2). These 13 patients did not differ from those without hallucinations in terms of sex or age at disease onset, although there was a trend for them to be older. Patients with PCA and hallucinations had a greater frequency of rapid eye movement sleep behavior disorder (RBD), parkinsonism, and myoclonic jerks (P<.001 for all). Rapid eye movement sleep behavior disorder was confirmed by a board-certified sleep specialist (B.F.B.) and met the new diagnostic criteria B for RBD, defined as wild flailing movements occurring during sleep, with either sleep-related injuries, potentially injurious movements, or a history of sleep disruptions.11 Parkinsonism was defined by the presence of 2 or more of the following: cogwheel rigidity, stooped posture, shuffling gait, bradykinetic alternating motor rates, facial masking, and resting tremor and was scored based on the modified Hoehn and Yahr stage.12 Only spontaneous, well-documented parkinsonism was included. Postural tremor and drug-induced parkinsonism were excluded. All 13 patients eventually met the diagnostic criteria for probable dementia with Lewy bodies (DLB).13

but none would have met the criteria at baseline evaluation or in the first 2 years of follow-up. None of the 46 patients without hallucinations would have fulfilled the criteria.

The onset of hallucinations occurred a mean of 4 years after the onset of typical symptoms of PCA, similar to the onset of parkinsonism (4 years), RBD (3 years), and myoclonic jerks (2 years), in patients with hallucina-
Patients with PCA and hallucinations showed bilateral GM atrophy involving the occipital, parietal, and posterior temporal lobes compared with controls (P < .001, uncorrected) (Figure 2). However, the regions of loss focused on the posterior cingulate and retrosplenial cortex, the temporal and parietal association cortices, and the mediotemporal lobe. The patterns of loss were bilateral but with a slight right-sided predominance. There was also mild involvement of the midbrain, primary visual cortex, and cerebellum (P < .001, uncorrected).

Table 3 summarizes the patterns of loss observed in both groups compared with controls and indicates the severity of loss in each region based on a visual assessment of the VBM results (P < .001, uncorrected). It demonstrates that patients with hallucinations showed relatively more loss in the primary visual cortex, midbrain, and basal ganglia regions than patients without hallucinations and, conversely, that patients without hallucinations showed greater loss in the posterior cingulate, temporoparietal association cortices, and right temporal lobe. A direct statistical comparison between the groups using VBM revealed that patients with hallucinations had greater atrophy bilaterally in the thalamus, although greater on the left, and globus pallidus than patients without hallucinations (P < .005, uncorrected) (Figure 3). The only region found to be significantly more atrophied in patients without hallucinations on direct comparison was a small region in the cingulate gyrus (P < .005, uncorrected; data not shown).

**COMMENT**

This large group study of patients with PCA reveals clinical and imaging differences between those with and without visual hallucinations. Each of the 59 patients with PCA in this study satisfied published criteria for the diagnosis of PCA. In all the patients, additional features of PCA also developed later in the disease course, sometimes with as many as 11 typical features being present. The most frequent presenting symptoms were visuospatial and visuoperceptual deficits, including features of...
Balint syndrome, and visual disorientation, with initial complaints such as “difficulty climbing stairs,” “difficulty finding the handle of a car door,” and “difficulty following the lines of text while reading.” Approximately 50% of the patients with PCA eventually complained of episodic memory loss; however, in none was the memory loss the most prominent initial feature, and in most the memory loss developed later in the disease course. In this series, women were overrepresented. This higher frequency of women with PCA is similar to the higher frequency of women reported in studies of typical Alzheimer disease and is not necessarily surprising because the most common pathologic mechanisms underlying PCA are neurofibrillary tangles and senile plaques.

Almost a quarter of the patients with PCA (n=13) were found to have visual hallucinations, similar to 2 other series of PCA. The visual hallucinations were well formed, recurrent, spontaneous, and nonfleeting and, in many cases, were present for many years. The hallucinations were also similar to the type of hallucinations encountered in patients with DLB and occurred at least 1 year after PCA symptom onset, as previously reported. All the patients with visual hallucinations met the clinical research criteria for probable DLB, although not at baseline evaluation, as all had coexisting RBD or spontaneous parkinsonism. None of the 46 patients without hallucinations met the criteria for probable DLB. None of the 13 patients with hallucinations were ever diagnosed as having DBL by their treating physicians, suggesting that it is not generally recognized that isolated prominent visuospatial deficits, classic features of PCA, may later progress into a DLB-like phenotype. This should be of no surprise because many different abnormalities underlie the PCA syndrome. We therefore suggest that when patients meet the criteria for PCA and develop well-formed visual hallucinations, a diagnosis of DLB be rendered given that DLB is a well-recognized clinicopathologic entity for which treatment approaches differ from those for “typical” PCA and Alzheimer disease.

The finding of increased myoclonic jerks in patients with hallucinations is interesting, but the cause of the association is unknown. We speculate that both phenomena may occur as a result of atrophy or damage to a common network of cortical and subcortical structures. Although both groups of patients with PCA showed a posterior pattern of atrophy on VBM, confirming previous studies of PCA and correlating with the clinical features, there were some striking differences between patients with and without hallucinations. Patients with hallucinations showed greater atrophy in a network of structures, including the primary visual cortex, thalamus, hypothalamus, basal ganglia, midbrain, and basal forebrain, than patients without hallucinations. In contrast, patients without hallucinations showed greater loss in the posterior cingulate (including the retrosplenial cortex), temporal and parietal association cortices, and medial temporal lobe than patients with hallucinations. These findings suggest that visual hallucinations in PCA are not occurring as a result of atrophy of the posterior cortical association regions, as the posterior association regions were more affected in patients without hallucinations.

Of the structures most affected in patients with PCA and hallucinations (thalamus, hypothalamus, basal ganglia, midbrain, and primary visual cortex), the most likely regions accounting for the hallucinations are the primary visual cortex, midbrain, and thalamus. However, atrophy of one of these regions is unlikely to be the sole cause. More likely would be destruction of a network of interconnecting anatomical structures, specifically, thalamocortical and ascending midbrain pathways.

Of the other structures most affected in patients with hallucinations, atrophy of the midbrain and basal ganglia regions would explain why more than three quarters of the patients with hallucinations also had parkinsonism. Furthermore, the midbrain has been linked to RBD.

A major strength of this study was the large number of well-defined cases. All the patients in this study were initially assessed by a behavioral neurologist with expertise in neurodegenerative diseases. The average follow-up of the patients was more than 2 years, suggesting that most patients had at least 2 evaluations, with some patients being followed up for as long as 9 years. More than a third of the patients were also initially enrolled in the Mayo Alzheimer’s Disease Research Center and Alzheimer’s Disease Patient Registry, which are longitudinal studies using standardized clinical, imaging, and genetic protocols. A major limitation of this study is the relatively small number of patients with hallucinations who had a volumetric MRI available for VBM; however, PCA is a relatively rare syndrome.

Multiple different abnormalities can underlie the PCA syndrome. The late occurrence of hallucinations in patients who meet the criteria for PCA suggests progressive damage to thalamocortical connections and should prompt the physician to consider the diagnosis of DLB.
Acquisition of data: Josephs and Tang-Wai.

Author Contributions: Study concept and design: Josephs and Tang-Wai. Acquisition of data: Josephs, Whitwell, Boeve, Drubach, and Jack. Analysis and interpretation of data: Josephs, Whitwell, Boeve, Knopman, Jack, and Petersen. Drafting of the manuscript: Josephs, Whitwell, Tang-Wai, and Petersen. Critical revision of the manuscript for important intellectual content: Whitwell, Boeve, Knopman, Jack, and Petersen. Obtained funding: Petersen. Administrative, technical, and material support: Boeve and Drubach. Study supervision: Jack.

Funding/Support: This study was supported by Roadmap Multidisciplinary Clinical Research Career Development Award grant K12/NICHD-HD49078 from the National Institutes of Health; by grants P50 AG16574, U01 AG06786, and R01 AG11378 from the National Institutes of Health; by grants P50 AG16574, U01 AG06786, and R01 AG11378 from the National Institute on Aging; and by the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Program of the Mayo Foundation.

REFERENCES


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