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Prodromal Posterior Cortical Atrophy: Clinical, Neuropsychological and Radiological Correlation

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Abstract

We present longitudinal clinical, cognitive and neuroimaging data from a 63-year-old woman who enrolled in research as a normal control and evolved posterior cortical atrophy (PCA) over five year follow-up. At baseline she reported only subtle difficulty driving and performed normally on cognitive tests, but already demonstrated atrophy in left visual association cortex. With follow-up she developed insidiously progressive visuospatial and visuoperceptual deficits, correlating with progressive atrophy in bilateral visual areas. Amyloid PET was positive. This case tracks the evolution of PCA from the prodromal stage, and illustrates challenges to early diagnosis as well as the utility of imaging biomarkers.

Introduction

Posterior cortical atrophy (PCA) is an insidiously progressive disorder that presents with deficits in visuospatial and visuoperceptual processing (Benson et al. 1988). Patients may exhibit elements of Balint's syndrome (optic ataxia, oculomotor apraxia, simultanagnosia) or Gerstmann's syndrome (right-left disorientation, finger agnosia, acalculia, agraphia). Other features include: environmental disorientation, dressing apraxia, transcortical sensory aphasia, alexia and apraxia. Insight, verbal memory and verbal fluency are usually preserved in the early stages (Mendez et al. 2002, Renner et al. 2004, Tang-Wai et al. 2004, McMonagle et al. 2006, Lehmann et al. 2011). PCA can involve both the dorsal and ventral visual processing pathways (Galton et al. 2000, Lehmann et al. 2011, Crutch et al. 2012), with dorsal stream symptoms predominating in the majority of patients (McMonagle et al. 2006). Primary visual deficits and visual neglect can be detected by employing sensitive measures and are occasionally the presenting features (Galton et al. 2000, Lee and Martin 2004, Lehmann et al. 2011). Despite the preservation of episodic memory, the underlying

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histopathology at autopsy is most commonly Alzheimer's disease (AD), although PCA is infrequently associated with dementia with Lewy bodies, corticobasal degeneration, Pick's disease and prion disease (Renner et al. 2004, Tang-Wai et al. 2004, Alladi et al. 2007). As the disease progresses, clinical features begin to overlap with more classical AD (Migliaccio et al. 2009, Lehmann et al. 2012).

In the last decade, the anatomy of PCA has been described using structural and functional neuroimaging. On MRI, PCA patients show bilateral occipitoparietal and occipitotemporal atrophy, often with right-sided predominance (Migliaccio et al. 2009, Ridgway et al. 2012). Compared to patients with amnesic AD, PCA patients show greater atrophy in right occipitotemporal cortex, while amnesic AD patients show greater atrophy in the left hippocampus (Whitwell et al. 2007, Lehmann et al. 2011). Similar patterns have been reported with FDG-PET and SPECT (Nestor et al. 2003, Kas et al. 2011, Rosenbloom et al. 2011). This anatomy is reflected at autopsy in a posterior shift of AD pathology, with very high counts of neurofibrillary tangles (NFTs) in primary and association visual areas and relatively lower NFT counts in medial temporal cortex compared to "typical" amnesic AD (Hof et al. 1997, Renner et al. 2004, Tang-Wai et al. 2004). The numbers of amyloid plaques have been reported to be 3–5 higher in visual cortex compared to amnesic AD in some studies (Hof et al. 1997), though other studies have not found no difference in plaque distribution (Renner et al. 2004, Tang-Wai et al. 2004).

Recent studies have suggested that PCA accounts for ~5% of AD cases seen in dementia referral centers (Snowden et al. 2007, Koedam et al. 2010). Accordingly, PCA is included as a clinical variant of AD in new research criteria (Dubois et al. 2010, McKhann et al. 2011). While the AD field is moving towards early diagnosis by combining clinical features with imaging and other biomarkers (Dubois et al. 2010, Jack et al. 2011), little is known about the earliest symptoms and biomarker changes associated with PCA. Patients in prodromal or early clinical stages of PCA are rarely evaluated in dementia clinics, because the symptoms are often initially perceived to be ophthalmologic in origin (Crutch et al. 2012). Kennedy and colleagues recently reported clinical and imaging data from a patient who evolved PCA while enrolled in a study of subjective memory impairment, though molecular biomarker evidence of underlying AD (in the form of amyloid PET or CSF biomarker profile) was not available (Kennedy et al. 2012). Here we report serial clinical, cognitive and imaging data from a woman who developed PCA while enrolled in a research study of normal aging at our center. At the time of diagnosis, the patient met National Institute on Aging-Alzheimer's Association (NIA-AA) criteria for high likelihood underlying AD pathophysiology based on a positive amyloid (PIB) PET scan and evidence of posterior neurodegeneration on MRI and FDG-PET (McKhann et al. 2011). Demographic information has been altered to protect the patient's identity.

Clinical Description

A 63 year-old right-handed woman enrolled as a cognitively normal volunteer in a study of aging at the University of California San Francisco Memory & Aging Center. At enrollment, both the subject and her daughter (interviewed separately) reported normal cognition and function. On detailed questioning, she denied difficulties with memory, language, executive

or visuospatial functions and she had no motor, sensory, behavioral or systemic symptoms. She had noticed a subtle change in her driving but this had not led to traffic accidents or “close calls” on the road. She reported no problems with daily function.

Past medical history included hypothyroidism, hypertension and hypercholesterolemia. Her only prescription medication was thyroxine. Her mother had been diagnosed with Alzheimer’s disease at age 76. She never smoked and drank alcohol occasionally. She had a high school education and had retired two years prior. On examination, she was alert, cooperative and socially appropriate. Physical neurological examination, which included assessments of praxis, spatial attention, visual fields, oculomotor function and performance of movements under visual guidance, was normal. Apolipoprotein E genotype, tested as part of the research study, was $\epsilon 4/\epsilon 4$.

One year later (Year 2), she complained of deterioration in her vision, though she continued to drive. She had no difficulty recognizing faces or objects, could find her way in a familiar environment and dressed without difficulty. She complained of mild anomia and had developed difficulty reading, describing that words seemed to move or “smudge” on the page. She complained of difficulty with peripheral vision and was tripping over objects. Her day-to-day function was unimpaired. Her neurological examination remained normal except for mild deviations from a straight line on tandem walking.

The patient’s next scheduled research visit occurred two years later (Year 4). Reading was considerably worse and she had difficulty following lines of text. She had trouble going up and down stairs. She described mild word-finding difficulties and very mild forgetfulness. She had difficulty following conversations, making decisions and performing complex tasks. She was aware of her deficits and became tearful during the interview. On neurological examination, her speech was tangential. She made occasional paraphasic errors. She did not have overt hemispatial neglect. Her physical neurological examination was normal. She was clinically diagnosed with mild cognitive impairment (MCI) (Winblad et al. 2004).

Over the next year the patient’s visual symptoms progressed to the point that she sought ophthalmological evaluation. Her visual acuity was 20/30 in each eye with best correction. She was found to have early cataracts bilaterally. A semi-congruous right homonymous hemianopia was detected clinically and confirmed by Humphrey field testing (Figure 1). Her pupils were equal and reactive. Extraocular eye movements were full and the ocular alignment was orthotropic. Intraocular pressure was normal. Fundus examination revealed posterior vitreous detachments in both eyes. The cup/disc ratio was normal. Nothing on her primary ocular examination was felt to explain her symptoms or visual field loss.

At this point, now over four years since her initial research visit, the patient was referred by her primary care physician for formal neurologic evaluation in our cognitive clinic. Her primary complaints remained visual. She had the sense that she was “missing things” that other people saw and a feeling that her depth perception was “off”. She found reading tiring, bright lights were uncomfortable and the motion of driving was disconcerting. Her daughter reported that her memory had declined. She misplaced objects, needed to write down all appointments and refer to grocery lists. She had difficulty orienting diapers when caring for

her grandchildren, and felt disoriented at a familiar shopping mall. She had mild word-finding difficulty. Her executive functions remained relatively intact. She lived alone and managed her own affairs. She complained of depression and anxiety. On examination, she was intermittently tearful and seemed overwhelmed. Speech was fluent with no word finding or grammatical difficulties. There was no ideomotor apraxia. Visual field examination revealed decreased vision in the right hemi-field. On oculomotor examination she now showed saccadic breakdown of smooth pursuit. Tone was slightly increased in the upper extremities with activation, and she had mild difficulty with tandem walking. At this visit she was diagnosed with PCA due to presumed AD pathology.

Her last visit occurred six months later, at age 67. She reported seeing “spots” in both visual fields. Her reading and spelling abilities had declined. She reported an altered depth perception and colors appeared to be brighter than before. Her memory had declined further. Her daughter moved in to live with her in order to assist her in daily activities. Treatment with an acetylcholinesterase inhibitor was initiated.

Methods

All research protocols were approved by the University of California San Francisco Committee on Human Research.

General Neuropsychological and Functional Evaluation

The patient underwent four neuropsychological and functional evaluations over four years. The battery of cognitive tests has been previously described (Kramer et al. 2003) and includes an assessment of general cognitive functioning, episodic memory, language, attention and working memory, executive functions, behavioral symptoms and general functioning. Specifically, assessment of visuospatial skills included copying a picture of two intersecting pentagons (as part of the Mini Mental State Examination (MMSE)) and copying a simplified version of the Rey-Osterreith figure (Modified Rey). Spatial perception was assessed by the Number Location test from the Visual Object Space Perception (VOSP) Battery (Warrington and James 1991). Reading was assessed at various time points using subtests of the Wide Range Achievement Test-Fourth Edition (WRAT-4) or the Psycholinguistic Assessments of Language Processing in Aphasia (PALPA) (Kay et al. 1992).

Magnetic Resonance Imaging (MRI) and Voxel-based Morphometry (VBM)

The patient underwent three volumetric MRI scans (years 1, 2 and 4) at the San Francisco Veterans Affairs Medical Center on a 1.5-T Magnetom VISION system (Siemens Inc., Iselin, NJ, USA). Magnetization prepared rapid gradient echo (MPRAGE) T1-weighted images of the entire brain were obtained as previously described (Rosen et al. 2002). MRI was performed within one week of clinical and cognitive evaluations.

Optimized voxel-based morphometry (VBM) (Ashburner and Friston 2000, Good et al. 2002) was applied to assess differences in gray matter volume between each of the patient's MRI scans and a single cohort of 23 age-matched cognitively normal female controls (mean age 65.8 ± 2.8 years, mean education 16.5 ± 2.2 years). Image preprocessing and analysis

were performed using SPM5 (Wellcome Department of Imaging Neuroscience, London; <http://www.fil.ion.ucl.ac.uk/spm>). Gray matter images were smoothed with a 12-mm FWHM isotropic Gaussian kernel. Differences in gray matter volumes were assessed with analysis of covariance (ANCOVA) with age and total intracranial volume included as nuisance variables. Given the single-subject nature of the analysis, we accepted a statistical threshold of $p < 0.001$ uncorrected for multiple comparisons for imaging analyses.

Positron Emission Tomography (PET)

Following her Year 5 evaluation, the patient underwent positron emission tomography (PET) with the beta-amyloid specific tracer [^{11}C]PIB and with [^{18}F]FDG at Lawrence Berkeley National Laboratory. The imaging acquisition and analysis protocols have been previously described (Rabinovici et al. 2007).

Results

General Neuropsychological and Functional Evaluation

The results of the patient's four neuropsychological evaluations are summarized in Table 1. When she first presented as a normal research subject, she performed within normal limits across all tests. On visuospatial testing, she received a perfect score on copy of the Modified Rey-Osterreith figure, correctly copied the intersecting pentagons on the MMSE, and scored within normal limits on the VOSP Number Location test. Tests of executive function were normal, though phonemic fluency (D-words) was in the low average range and performance on Modified Trails-B and Stroop-interference were below average. Verbal episodic memory was above average, while visual memory was in the low average range. She performed within normal limits on language testing, including on tests of reading.

At Year 2, despite subjective visual complaints, she obtained perfect scores on formal tests of visuospatial function. Semantic word fluency dropped just below normal limits while phonemic fluency remained at the lower limit of normal. Performance on Modified Trails-B slightly declined. There were no significant changes in verbal memory and performance on the visual memory task actually improved.

At Year 4, MMSE had declined to 27. For the first time she demonstrated impaired performance on copy of the modified Rey-Osterreith (score dropped from 17/17 to 14/17) and her performance on VOSP Number Location dropped from 10/10 to 4/10. She missed one point on a calculation task. In the executive functioning domain, set-shifting abilities remained relatively stable while her performance on both the color naming and inhibition portions of the Stroop task and design fluency declined. The examiner noted that her ability to perform these tasks was clearly limited by her visual dysfunction. There was now a notable discrepancy between visual and verbal memory scores, with verbal memory remaining above average whereas visual memory declined and fell to the low average range. During the evaluation, her speech was at times tangential and she made several paraphasic errors, though she continued to score in the normal range on formal language tests. She reported feeling frustrated by her cognitive symptoms and her Geriatric Depression Scale score increased to 15/30.

At Year 5, MMSE was 29, losing one point for poor copy of intersecting pentagons. Despite her obvious functional limitations which now met criteria for dementia, her Clinical Dementia Rating (CDR) remained 0. Visuospatial scores were unchanged from her previous visit. She performed poorly on a reading task (WRAT-4). Performance on most executive functioning tasks remained unchanged, with non-verbal fluency, processing speed, and inhibition scores falling slightly below average and verbal fluency scores in the low average range. Working memory declined from 4 to 3 digits backwards. There was a slight decline in verbal episodic memory, although performance still fell within normal limits. Visual memory remained in the low average range.

MRI and VBM

Representative slices from the patient's MRI scans are shown in Figure 2, and VBM comparisons to matched controls are shown in Figure 3. Compared to controls, the patient showed an evolving pattern of atrophy in left greater than right occipital, temporal and to a lesser degree parietal cortex (Figure 3, Supplemental Table). In Year 1, in the absence of deficits on cognitive testing and with minimal visual complaints, gray matter loss was already detectable in left visual association cortex (Brodmann's areas (BA) 18 and 19), involving left superior and middle occipital gyri and lingual gyrus. A small cluster was also identified in the right superior parietal lobule (BA 7). At Year 2, atrophy extended into left primary visual cortex (BA 17) and bilateral inferior occipital gyri (BA 18, 19). By Year 4, when neuropsychometric impairment became evident, atrophy was more extensive in all these regions in the left hemisphere, left inferior temporal gyrus was now involved, and atrophy of right visual association cortex (BA 18 and 19) and right superior parietal lobule was apparent.

PET

PET imaging with [¹¹C] PIB revealed diffuse tracer binding throughout occipital, temporoparietal and frontal cortex and striatum suggestive of underlying beta-amyloid deposition (Figure 4). [¹⁸F]FDG-PET revealed hypometabolism in occipital and inferior temporal cortex, left greater than right, and left parietal cortex (Figure 4).

Table 2 summarizes the patient's longitudinal clinical, cognitive and structural neuroimaging data.

Discussion

In this report we describe longitudinal clinical, cognitive and radiological findings from a single patient who evolved the PCA syndrome while followed in a study of normal cognitive aging. Understanding the evolution of PCA in its prodromal and early symptomatic stages is important given the current shift towards early diagnosis and intervention in AD, yet data about the initial stages of PCA are lacking. This case demonstrates the slow and insidious evolution of PCA, and the challenges to early diagnosis using common clinical tools. Though atrophy in left visual association areas could already be detected at enrollment (Figure 3), the patient complained only of subtle changes in driving, a non-specific and common symptom in older individuals. At Year 2 the patient's complaints (difficulty

reading and decreased peripheral vision) were misattributed to primary ocular disease, and she was again classified as “cognitively normal.” In Years 1–2 the main finding on cognitive testing was below expected performance on executive tests (though still within normative values), a non-specific finding in older individuals, which in retrospect was likely related to limitations in visuospatial abilities. The clinical diagnosis of MCI was not made until Year 4, when her visual loss had already caused significant functional problems and her cognitive testing showed a clear trend for decline. The diagnosis of PCA was made one year later, when functional impairment was considerable, other cognitive domains were declining and clear-cut neurologic signs (e.g. hemianopia) were present.

In clinical practice, the diagnosis of PCA is often delayed. While patients with amnesic, aphasic or dysexecutive presentations of AD are likely to seek a neurological evaluation, patients with PCA are often seen initially by ophthalmologists, and a primary neurodegenerative disorder is not appreciated until additional cognitive domains are affected or until the neurologic nature of visual dysfunction is recognized. We were able to capture the early evolution of PCA in this patient because she happened to be enrolled in a study of normal aging at our center. Kennedy and colleagues recently reported a similar case of a 61 year-old man who developed PCA while followed in a study of subjective memory complaints (Kennedy et al. 2012). These patients provide preliminary insight into the prodromal changes associated with PCA. In both cases, some of the earliest neuropsychological changes were noted on a trail making task, generally considered a test of executive function, though test performance also relies heavily on visual search and attention faculties. This underscores the need to interpret cognitive tests in the context of a patient’s strengths and weaknesses, and to be careful to not rigidly ascribe performance on a test to dysfunction in a single cognitive domain. Both our patient and the patient reported by Kennedy performed below average on visual memory tasks at their baseline visit, though interestingly in both cases visual memory fluctuated early in the course, and actually improved from baseline on subsequent visits (Table 1), perhaps due to practice effects that can occur even in the prodromal stages of disease (Duff et al. 2011). Interestingly, later testing sessions showed a clear-cut declining course, and there was no improvement on visuospatial tests once impairment was evident.

Our patient complained of subtle problems with peripheral vision at Year 2, and by Year 5 developed a semi-congruous right homonymous hemianopia which was apparent on confrontation testing and confirmed by Humphrey visual field testing (Figure 1). Estimates of the prevalence of homonymous visual field deficits in PCA have varied considerably in the literature. McMonagle et al. reported visual field defects at presentation in only 1/19 patients (McMonagle et al. 2006), while Tang-Wai and colleagues detected field deficits in 19/40 patients at first evaluation (Tang-Wai et al. 2004). Pelak et al. found abnormalities in all 9 PCA patients screened with threshold computerized visual field perimetry (Pelak et al. 2011), suggesting that field defects may be highly prevalent when ascertained with sensitive tools. Visual field defects in PCA most often consist of homonymous hemianopia or quadrantanopia, a pattern that is clearly distinct from the bilateral inferior constriction pattern described in amnesic AD (Trick et al. 1995). Visual field deficits have profound implications for patient safety and function – since confrontation testing may not be

sensitive to subtle defects, we recommend early ophthalmological referral and formal visual field testing for all patients.

While molecular biomarker confirmation of AD pathophysiology was not available in the patient reported by Kennedy et al., the patient presented in this report was confirmed to have underlying neuritic plaques on the basis of a positive PIB-PET scan. New diagnostic criteria set forth by the National Institute on Aging–Alzheimer’s Association (NIA-AA) and the International Working Group (IWG) recognize PCA as a non-amnestic variant of AD, and integrate biomarkers to increase confidence in the presence of AD pathophysiology (Dubois et al. 2010, McKhann et al. 2011). Early data from our group and others support the utility of amyloid imaging and CSF AD biomarkers for detecting AD pathology in patients presenting with PCA (Formaglio et al. 2011, Rabinovici et al. 2011, Rosenbloom et al. 2011, Seguin et al. 2011). However, these biomarkers are not yet widely available to practicing clinicians. MRI and FDG-PET (classified as “neurodegenerative” (NIA-AA) or “topographic” (IWG) biomarkers in the new criteria) are far more accessible, but the early degenerative changes in our PCA patient were distinct from those seen in typical AD, and initially spared regions considered to be sensitive to early AD changes such as the hippocampus/medial temporal lobes and posterior cingulate cortex (Figures 2, 3). A similar anatomic pattern was described in the patient reported by Kennedy et al., though statistical comparisons between that patient and normal controls were not presented. In implementing the new diagnostic criteria it will be important for clinicians to be familiar with the distinct neurodegenerative pattern of PCA, and to recognize that biomarkers found to be sensitive in studies of “typical” amnestic AD (such as the Alzheimer’s Disease Neuroimaging Initiative) may not generalize to non-amnestic presentations of AD. The use of molecular biomarkers such as amyloid PET may be particularly important in PCA, since an identical topographic pattern can be seen in PCA patients with non-AD pathology (Lee et al. 2011).

It has been proposed that PCA can be divided into three distinct clinicoanatomic variants: (1) a biparietal syndrome reflecting primary dorsal visual stream dysfunction; (2) an occipitotemporal syndrome primarily involving ventral visual stream failure; and (3) a primary visual variant reflecting impairment in basic visuo-perceptual abilities (Alladi et al. 2007). While individual cases that conform to these specific categories are reported in the literature (Galton et al. 2000, Alladi et al. 2007), larger cohort studies suggest that most patient with PCA show mixed dysfunction of the dorsal and ventral visual streams as well as primary visuo-perceptual deficits when assessed with sensitive tests, and demonstrate atrophy in all the corresponding cortical regions (Tang-Wai et al. 2004, McMonagle et al. 2006, Lehmann et al. 2011). However, most patients included in such studies have already experienced symptoms for years, and it is difficult to gauge where in the visual system the disease most often originates. The presenting symptoms in our patient (difficulty driving and alexia) are common early features of PCA (Tang-Wai et al. 2004, McMonagle et al. 2006), but can result from a variety of different disturbances in visual processing (Mendez and Chierri 1998). The atrophy pattern at Year 1 suggests primary involvement of left extra-striate cortex and occipito-temporal cortex, though subtle atrophy was also detected in parieto-occipital regions (Figure 3). One of her more striking early symptoms (perceived motion of static stimuli, i.e. written words) may be related to unsteady eye fixation and impaired visuo-vestibular integration (Crutch et al. 2011). Over time her symptoms and

neuropsychological test performance suggest involvement of primary visuoperceptual, ventral and dorsal visual streams, with atrophy apparent in all associated regions in the left hemisphere and analogous regions in the right hemisphere. Keeping in mind the limited conclusions that can be drawn from a single case, this evolution is consistent with the hypothesis of “network-based” degeneration (Seeley et al. 2009), with spread of the disease from an initial “epicenter” in the visual system to inter-connected primary and higher-order visual processing regions (Lehmann et al. 2013, Lehmann et al. 2013).

The patient showed excellent correlation between clinical symptoms and regional gray matter loss (as detected by VBM), though atrophy appeared to precede clinical signs. Atrophy in left-sided ventral visual regions was evident at least one year before the onset of associated symptoms (e.g. alexia), and involvement of left calcarine cortex was apparent on VBM in Year 2 while a hemianopia evolved only in Year 4. This suggests that significant gray matter atrophy on neuroimaging may precede clinically apparent symptoms and signs in PCA, or alternatively that VBM is more sensitive than the clinical tools used to assess this patient. Arguably, the neuropsychometric tests we employed were least sensitive to the evolution of PCA in this patient, with a two year lag between clinical complaints and clear-cut psychometric deficits. Interestingly, impaired testing on visuospatial tasks coincided with the appearance of significant right parietal atrophy in Year 4. Neuropsychological probing of visuospatial function often relies on tests of constructional praxis (e.g. intersecting pentagons or Rey-Osterrieth figure copy in our battery) and judgment of spatial relationships (e.g. VOSP number location), and thus may bias towards detection of right hemisphere dorsal visual stream dysfunction. Our tests of ventral stream integrity (e.g. face recognition) are also biased towards right hemisphere functions. While most PCA series report a clinical and anatomic predilection for right over left hemisphere and dorsal over ventral visual streams (Nestor et al. 2003, McMonagle et al. 2006, Whitwell et al. 2007), our patient presented with asymmetric left sided dysfunction and atrophy in ventral greater than dorsal visual areas, rendering our neuropsychometric tests even less sensitive to her deficits. Furthermore, this case highlights the limitations of traditional measures of global and functional disease stage in AD, such as MMSE and CDR, in gauging the severity of PCA, as our patient met criteria for dementia despite an MMSE of 29 and CDR of 0.

The focal and asymmetric neurodegenerative pattern in this patient contrasts with the diffuse pattern of PIB binding (Figure 4), which provides evidence for bilateral fibrillar amyloid deposits throughout cortex, without any clear predilection for the left hemisphere or for visual regions. This finding agrees with previous histopathologic and PIB studies that found no difference in the distribution of amyloid plaques between PCA and “typical” AD (Renner et al. 2004, Tang-Wai et al. 2004, de Souza et al. 2011, Rosenbloom et al. 2011), though other studies have reported higher plaque load in visual areas in PCA (Hof et al. 1997, Formaglio et al. 2011). The neurodegenerative pattern may correlate better with the distribution of neurofibrillary pathology (not imaged by PIB), which is consistently found to be more severe in primary and association visual areas in PCA compared to amnesic AD (Hof et al. 1997, Renner et al. 2004, Tang-Wai et al. 2004). The biological mechanisms that underlie the spatial differences in pathology and neurodegeneration between PCA and typical AD are not known.

Our longitudinal data support the notion that PCA is clinically and anatomically distinct from typical AD. While case series report various degrees of memory, language and executive impairment in PCA (Renner et al. 2004, Tang-Wai et al. 2004, McMonagle et al. 2006, Migliaccio et al. 2009), our patient's symptoms were restricted to the visuospatial domain for at least three years, and atrophy was initially limited to visual association regions, with notable sparing of the hippocampi (Figures 2 and 3). Notably, our patient was homozygous for the apolipoprotein E ϵ 4 allele (ApoE4), the strongest genetic risk factor for sporadic AD. The relationship between PCA and ApoE4 is inconsistent in the literature, with some studies reporting a similar proportion of ApoE4 carriers in PCA and amnesic AD, and others reporting a lower prevalence of ApoE4 in PCA (summarized in (Crutch et al. 2012)). It has been proposed that ApoE4 may predispose patients to an amnesic phenotype and medial temporal lobe degeneration, while cortical presentations of AD may be more common in the absence of the ϵ 4 allele (van der Flier et al. 2010, Murray et al. 2011). Though this hypothesis may hold true at the group level, our case illustrates that focal PCA can occur in E4 homozygotes. Identifying both common and distinct genetic risk factors for PCA and AD represents an important area for future work. We elected to treat our patient with a cholinesterase inhibitor given the very high likelihood of underlying AD pathology. However, it is important to keep in mind that evidence for efficacy of cholinesterase inhibitors in PCA is limited to case reports (Kim et al. 2005). Unfortunately, the patient has not been evaluated since initiating treatment and we cannot report on her response.

In summary, our case highlights the clinical and anatomic changes associated with the prodromal and early symptomatic stage of PCA. The inclusion of PCA in new diagnostic criteria for AD represents a major advance, though our report demonstrates some of the challenges of translating these criteria into clinical practice. Our patient illustrates the importance of promptly investigating early visual complaints with sensitive neurological and ophthalmological investigations. Greater awareness and education about PCA in the neurologic and ophthalmologic communities are clearly needed, and a multi-disciplinary approach is essential to providing optimal patient care. Recently, an international working party on PCA has formed with the goal of standardizing clinical criteria and encouraging prospective multi-center collaborative studies (Crutch et al. 2013). Major goals of such multi-site studies will include developing better clinical, cognitive and imaging tools for early diagnosis, tracking longitudinal change and predicting the underlying histopathology. Furthermore, investigating the specific developmental, genetic and environmental factors associated with PCA may provide insight into the mechanisms that underlie clinicoanatomic heterogeneity in AD, and thus provide important clues about disease pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Humphrey visual field testing

Central 24-2 threshold visual fields using a SITA-FAST protocol on a Humphrey perimeter in year 5 showed an incomplete, partially congruous, right hemianopia. Reliability indices and foveal thresholds were normal.

Figure 2. Serial T1-weighted MRI scans
Representative axial and coronal slices are presented in neurological orientation.

Figure 3. Voxel-based morphometry assessing gray matter volumes in serial MRIs versus matched controls

T score maps are displayed on the ch2 template brain. Statistical maps are thresholded at $p < 0.001$, uncorrected for multiple comparisons, and displayed in neurologic orientation. Scale bar represents t-values.

Figure 4. PET scans

FDG images (top row) represent standardized uptake value ratios (SUVR) normalized to mean activity in the pons. PIB images (bottom row) represent distribution volume ratios (DVR) applying the cerebellum time-activity curve as the input function. All images are displayed in neurologic orientation.

Table 1

Performance on neuropsychological tests.

	Year 1	Year 2	Year 4	Year 5
Age	63	64	66	67
MMSE (30) [29.2±1.2]*	30	29	27	29
CDR Box Score (18)	0	0	0	0.5
CDR Total (3)	0	0	0	0
<u>Visuospatial function:</u>				
MMSE - Pentagons (1)	1	1	1	0
Modified Rey-O Copy (17) [15.9±1.4]	17	17	14	14
VOSP Number Location (10) [9.4±1.0]	9	10	4	4
Face Matching (12) [11.7±0.6]	--	--	10	--
<u>Visual memory:</u>				
Modified Rey-O Delay (17) [11.4±3.1]	8	15	9	8
Modified Rey-O Recognition	Yes	Yes	Yes	Yes
<u>Verbal memory:</u>				
CVLT-SF				
4-Trial Total Correct (36) [27.17±3.75]	28	--	--	24
30 sec Free Recall (9) [8.2±1.4]	9 + 1 In	--	--	7
10 min Free Recall (9) [7.8±1.4]	8 + 1 In	--	--	7
10 min Recognition (9) [8.7±0.5]	9	--	--	8 + 2 FPs
CVLT-II				
List A 5 Trials Total Correct (80) [48] [†]	62	56	59	--
List A Short-Del Free Recall (16) [9–10] [†]	13 (Z= 1.0)	14 (Z= 1.5)	9 (Z= 0)	--
List A Long-Del Free Recall (16) [10–11] [†]	15 (Z= 1.5)	15 (Z= 1.5)	15 (Z= 1.5)	--
List A Long-Del Recognition (16) [15] [†]	16 (Z= 0.5)	15 (Z= 0)	16 (Z=0.5) + 2 FPs	--
<u>Attention & Working memory:</u>				
Digit span forward [6.3±1.4]	6	--	5	6
Digit span backward [4.5±1.4]	4	4	4	3
WORLD backward (5)	5	5	5	5
<u>Executive functions:</u>				
Design Fluency [11.2±2.9]	10	--	6	5 + 1 error
Modified Trails speed (120) [34.4±26.4]	84	117	101	58
Modified Trails correct lines (14)	14 + 2 errors	14 + 1 error	14 + 1 error	14
Abstract Reasoning (6)	5	5	5	5
Stroop Color Naming (100) [89.9±5.5]	--	--	69	69
Stroop Interference (100) [56.6±14.1]	42 + 1 error	41	32, lost track	26 + 6 errors
<u>Calculations</u> (5)	5	5	4	5

	Year 1	Year 2	Year 4	Year 5
<u>Language & Semantics:</u>				
Phonemic fluency: "D" words [16.3±6.0]	10	11	10	10 + 3 errors
Category fluency: Animals [23.6±5.5]	25	17	20 + 1 error	19
Boston Naming Test (15) [14.3±1.3]	15	15	15	15
PPVT-R comprehension (16)	14	--	15	16
PALPA Reading: Regular Words (15)	15	--	--	--
PALPA Reading: Irregular Words (15)	15	--	--	--
PALPA Reading: Regular Words (30)	--	30	--	--
PALPA Reading: Irregular Words (30)	--	30	--	--
WRAT-4 Reading (70) [48–66]	--	--	--	46
<u>Psychiatric / Behavioral:</u>				
Geriatric Depression Scale (30)	8	7	15	11

FP = False Positive. In = Intrusion. Short-Del = Short-Delay. Long-Del = Long-Delay. Z = Age- and gender-specific standard score.

Normative Data: [age group-specific mean±SD] - University of California San Francisco Memory & Aging Center norms; [mean±SD] - National Alzheimer's Coordinating Center Uniform Data Set norms; [mean range][†] - CVLT-II normative data (Delis et al. 2000).

Table 2

Summary of patient's longitudinal clinical, cognitive and structural neuroimaging data.

	Year 1	Year 2	Year 4	Year 5	Year 6
Clinical symptoms	- Subtle change in driving	- Difficulty reading - Decreased peripheral vision	- Slowly progressive decline in visuospatial abilities; trouble reading & walking - Decreased peripheral vision but no visual field defect - Mild impairment in memory, executive & language - Depression	- Increased spatial dysfunction; also affected depth, light & motion perception - Semi-congruous right homonymous hemianopia - Memory loss - Depression	- Further decline in visuospatial function & memory
Neuropsychology	- Visuospatial tasks within normal limits - Visual memory low average - Phonemic fluency low average - Modified Trails and Stroop interference below average	- Visuospatial tasks within normal limits - Improved visual memory - Decline in Modified Trails	- Impaired performance on visuospatial tasks - Visual memory fell back to low average range - Performance on executive tests impacted by visual dysfunction	- Visuospatial scores & visual memory were unchanged - Mild decline in executive function, working memory & verbal episodic memory	
Brain atrophy (VBM)	- Left lateral occipital cortex and lingual gyrus - Small region of right superior parietal lobule	- Extension into the left primary visual cortex & bilateral inferior occipital gyri	- Left hemisphere gray matter loss more extensive - Left inferior temporal gyrus - Right lateral occipital cortex - Right superior parietal lobule		