Posterior Cortical Atrophy
A Case Report of a 6-Year Natural Progression

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Key Words: dementia, posterior cortical atrophy, Alzheimer disease

(*Alzheimer Dis Assoc Disord* 2015;00:000–000)

BACKGROUND

We describe a 6-year natural history of a patient with posterior cortical atrophy (PCA), demonstrating the difficulties of diagnosis in the early stages of the disease. First clinical signs were predominantly visual with normal neuroimaging and neurodegeneration markers. The mild clinical signs were followed by a progressive decline of various cognitive functions, including perception, attention, memory, and executive function. Repeated neuroimaging and cerebrospinal fluid (CSF) measurements finally revealed a PCA with underlying atypical Alzheimer disease (AD) pathology.

PCA is a neurodegenerative syndrome characterized by progressive deterioration of visuospatial, visuoperceptual, praxic, and literacy abilities due to degeneration of posterior cortical regions.[1] Pathologic studies show that this often underrecognized syndrome is associated with a range of different disease pathologies. Most commonly it is attributed to AD, but it may also be caused by Lewy body dementia, corticobasal degeneration, and prion diseases, such as Creutzfeld-Jakob disease or familial fatal insomnia.[2] PCA often presents a considerable challenge in differential diagnostics because of its initial disease characteristics being quite distinct from other dementias. Here we present a case of PCA which was followed up for almost 6 years with extensive clinical, neuropsychological, neuroimaging, and CSF biomarker testing.

CASE REPORT

The patient (L.V.) is a 54-year-old right-handed woman with 12 years of formal education, normal intelligence level, and no prior history of neurological, psychiatric, or other major medical disease. In August 2006, at the age of 46, she had a bicycle accident resulting in multiple facial fractures and hematoma, as well as a concussion. Cranial computed tomography (CCT) on the day of the accident as well as 8 days after did not show any signs of cortical or subcortical injury or bleeding. L.V. was hospitalized for 15 days. She returned to work in September 2006. Two months later, she consulted a neurology practitioner for symptoms of agitation, impatience, occasional tinnitus, and muffled hearing. Moreover, she reported problems in visual perception, which caused a referral to a neuropsychology consultant. Her first neuropsychological assessment (2006) showed moderate to severe deficits in the domains of visual attention, perception, and (visual) memory (Table 1). At this time, symptoms of neglect were described. A few months after the accident, L.V. reported improved subjective functioning; except for decreased sustained attention. Given the close temporal relation to the accident, L.V.'s cognitive symptoms were attributed to traumatic brain injury (TBI), and she was treated in several rehabilitation settings (inpatient, outpatient, and consultancy).

Whereas in 2007 mainly deficits in visuospatial attention, verbal memory recall, and spatial visualization were reported, the neuropsychological deficits progressed and additional problems in visuoconstructive abilities and working memory emerged in 2008. Longitudinal evaluations by neurologists and neuropsychologists revealed an increase of predominantly perceptual symptoms. In 2008, L.V. received extensive neuropsychological training over the course of several months. Although she did show some improvement in general attention and visual scanning, her visuospatial abilities remained poor. The training was additionally confounded by emotional instability and pronounced fluctuations in motivation. Subsequently, L.V. was referred to a psychotherapist for depression and adjustment disorder. In 2008, data from functional imaging using 2-fluoro-2-deoxy-D-glucose positron emission tomography (^{18}FDG-PET) showed mild to moderate hypometabolism in the right superior parietal cortex as well as in mesiofrontal areas, including the anterior cingulate gyrus. Until 2011, L.V. was treated for TBI and depression (psychotherapy and antidepressants) due to failed vocational reintegration.

In May 2011, L.V. sought consultation at our memory clinic for reevaluation of her visuospatial deficits as well as progressive apraxia, but neither she nor her family reported subjective memory deficits. The neuropsychological testing verified the symptoms and revealed additional severe deficits in the domains of attention, executive function, and memory. Neurological examinations were normal except for symmetrical limb apraxia. In 2011/2012, the second CCT and magnetic resonance imaging (MRI) data (Fig. 1, upper panel) showed advanced temporal-parietal atrophy, when compared with the initial neuroimaging data of 2006/2007. In 2012, the second ^{18}FDG-PET showed considerably reduced FDG metabolism bilaterally in parietotemporal areas and the precuneus, but also mildly reduced metabolism in the lateral frontal cortices and a normal glucose metabolism in the occipital cortices (Fig. 1, lower panel).

CSF profile analysis in 2011 showed normal AD biomarkers (Table 1). However, a subsequent CSF analysis (carried out by identical procedure within the same laboratory) 1 year later

Received for publication June 29, 2015; accepted November 17, 2015.

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K.R. was partly funded by the German Federal Ministry of Education and Research (BMBF 01GQ1402) and by the Alzheimer Forschung Initiative e.V. (AFI 13812). A.S.C. was supported by a Doctoral Fellowship from Fundação para a Ciência e Tecnologia (FCT), Portugal.

The authors declare no conflicts of interest.

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TABLE 1. Overview of Longitudinal Clinical Measures From 2006 to 2012

Measures	2006	2007	2008		2011	2012
Subjective complaints	October: Perceptual insecurities, eg, "bumping into doors with her left side." Concentration disturbances Less resilient at work. Tinnitus.	January: Improvements in perception. Low sustained attention. Low stress resilience. September: Difficulties at work. Increased distractibility. Changes in visual perception (brightness, skewedness, macropsia).	April: Pronounced visual problems, including contrast, size and movement fluidity of objects. Problems in keeping track of objects. Slowing in ADL. Concentration disturbances.	No known medical interventions, except for psychotherapy in 2009-2010.	May: Increasing problems in spatial orienting. Apraxia. Memory problems.	January: Severe difficulties in spatial orientation at home and outside. Apraxia. Severe ADL problems.
Clinic/VOG	October: Hypesthesia of right cheek.	January: Intact visual field, except for a peripheral scotoma in the right visual field.	May: Prosaccades preceding the antisaccades (VOG).		May: Symmetrical limb apraxia. Visual agnosia, alexia, acalculia.	January: Symmetrical limb apraxia. Visual agnosia, alexia, akalkulia.
Neuropsychological	October: Deficits in spatial reasoning and orientation, visual memory, sustained attention, and concentration. Dissociation between verbal and practical intelligence. Neglect of the left visual field.	January: Deficits in visual scanning (visuospatial attention), but no visuospatial neglect. September: Deficits in verbal memory recall, spatial visualization ability, attention, and psychomotor speed.	April: Decreased visuoconstructive abilities, visuospatial reasoning, visuospatial short-term working memory, visual selective attention, and visual scanning. Decreased saccadic reaction times in the left visual field.		May: MMSE: 17.	January: Severely limited visuoconctructive abilities as well as spatial and object perception. Alexia, simultaneous and finger agnosia. Decreased verbal fluency and verbal memory. MMSE: 18. MOCA: not feasible. GDS: 10 (moderate depression).
CCT	August: No signs of intracranial injuries or subdural hematomas.				May: Global cerebral volume loss. Parietal atrophy. Discrete WMH.	
MRI		June: No focal signal disturbances or residual blood				October: Pronounced parietal, mesiotemporal,

TABLE 1. (*continued*)

Measures	2006	2007	2008	2011	2012
		traces. Increased signal in the nervus opticus, suspectible of opticus neuritis.			and mesencephalic atrophy. Reduction of global cortical volume, corpus callosum, and fornix, bilateral small WMH.
^{18}FDG-PET			September: Moderate hypometabolism in the right superior parietal cortex. Mild to moderate mesiofrontal hypometabolism (ACC).		November: Considerably reduced FDG retention, parietotemporal and in the precuneus bilaterally. Mildly reduced retention in the lateral frontal cortices.
CSF				December*: $A\beta_{42}$: 1414 pg/mL; $A\beta_{40}$: 14212 pg/mL; $A\beta_{42}/A\beta_{40}$ ratio: 0.099. t-tau: 230 pg/mL; p-tau: 45 pg/mL.	November: $A\beta_{42}$: 369 pg/mL; $A\beta_{40}$: 5632 pg/mL; $A\beta_{42}/A\beta_{40}$ ratio: 0.066; t-tau: 244 pg/mL; p-tau: 45 pg/mL. NSE: 24 μg/L, S100: 0.09 μg/L.

*Cut-off values for AD are according to the neurochemistry laboratory of the University in Göttingen, Germany as follows: t-tau >450 pg/mL, p-tau$_{181}$ >61 pg/mL, $A\beta_{42}$ < 450 pg/mL, β-amyloid ratio [$(A\beta_{42}/A\beta_{40}) \times 10$] < 0.5.

ACC indicates anterior cingulated cortex; ADL, activities of daily life; CCT, cranial computed tomography; CSF, cerebrospinal fluid; FDG, 2-fluoro-2-deoxy-D-glucose; GDS, Geriatric Depression Scale; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; MRI, magnetic resonance imaging; NSE, neuron-specific enolase; VOG, video-oculography; WMH, white matter hypodensities.

detected a decrease in amyloid β peptide $(A\beta)_{42}$ from 1414 to 369 pg/mL (normal >450), but neither an AD-typical elevation of t-tau or p-tau, nor a decreased $A\beta_{42/40}$ ratio, although, the ratio decreased from 0.99 to a low-normal range with 0.66 (cut-off: <0.5).

DISCUSSION

PCA, clinically characterized by progressive deficits in visuospatial, visuoperceptual, literacy, and praxic skills, is a debilitating and underrecognized focal neurodegenerative syndrome, associated with a range of different disease pathologies. It is attributed to AD in most patients. However, diagnosis is often hampered by several years—as further illustrated by our case, L.V.

Retrospectively, L.V.'s neuropsychological core features involving visuospatial and visuoperceptual impairments as well as alexia and visual agnosia, but also working memory and limb apraxia, and their progression were typical for PCA.[3] Her deficits remained almost exclusively visual until 2012. Verbal functions, although being considerably substandard, remained distinctly superior to visual functions. This was illustrated by a gradual deterioration toward a pattern of global cognitive dysfunction, in which verbal cognition still remained qualitatively less impaired. By 2012, L.V. was almost completely dependent in activities of daily life because of severe cognitive problems in all domains.

The anatomic neuroimaging of the advanced temporal-parietal atrophy additionally reflect the structural hallmarks of PCA.[1] The gradual structural changes correspond well to the progression of the cognitive deficit profile of PCA. In addition, the structural changes show a considerable regional overlap in atrophy, which is characteristic for AD. Such findings have been reported for PCA phenotypes when associated with AD.[4] The hypometabolisms detected by ^{18}FDG-PET in parietotemporal areas bilaterally, the precuneus, the lateral frontal cortices reflect a rather characteristic pattern known for AD.[4] Additional hypometabolism in occipital areas, which can be found in some PCA patients, was not observed.

Previous PCA studies in which CSF biomarkers ($A\beta_{42}$, t-tau, and p-tau$_{181}$) were assessed have recorded similar findings in PCA compared with AD, and subsequently classified PCA into typical AD, atypical AD, and non-AD

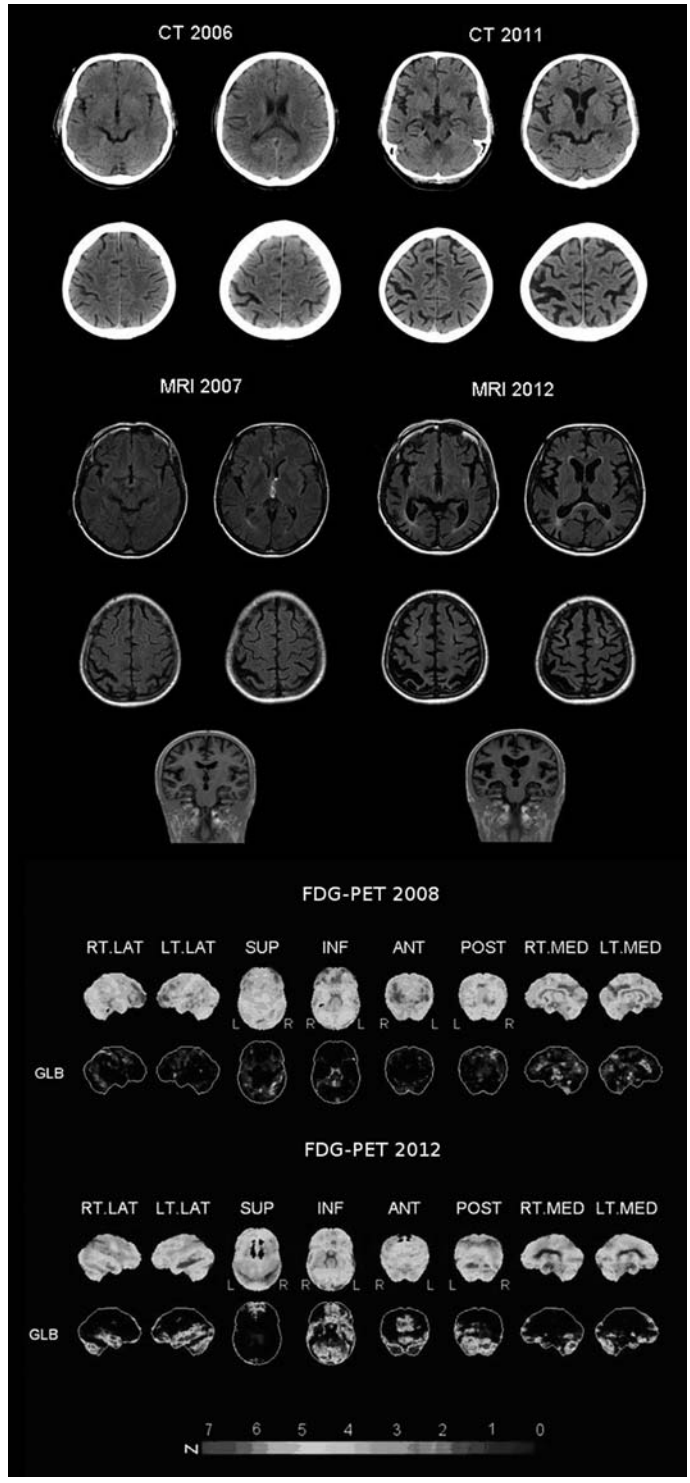

FIGURE 1. Clinical anatomic and functional neuroimaging: 2006 to 2012. Axial cranial computed tomography (CCT) and T1-weighted magnetic resonance imaging (MRI) were obtained after the accident to rule out structural damage in 2006 and 2007. Retrospectively, discrete right parietal atrophy can already be detected. In 2011 and 2012, the CCT and MRI images show marked parietal atrophy. The 2008 2-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) examination shows moderate hypometabolism in the right superior parietal cortex and mild to moderate mesiofrontal hypometabolism. In 2012, FDG metabolism was considerably reduced in bilateral parietotemporal areas and in the precuneus bilaterally, as well as mildly reduced in the lateral frontal cortices, thus showing a clear progression compared with the 2008 FDG.

pathologies.[6] Hereby the atypical AD group was classified by either t-tau >350 pg/mL and p-tau$_{181}$ >60 pg/mL, or Aβ_{42} <500 pg/mL. Prior data indicate that alterations in tau and Aβ_{42} occur early in the disease course and do not (Aβ_{42},) or only slightly (t-tau) change over time in AD.[6] Although our case does not fulfill typical AD-CSF criteria, a decline of the amyloid CSF parameters within 1 year can be observed. The emerging CSF profile can be classified in the atypical AD group for PCA patients.[5]

It still remains somewhat elusive whether the TBI in 2006 contributed to L.V.'s symptoms or accelerated PCA progression. Although TBI has been suggested to increase Aβ levels,[7] the relative long temporal distance to the emergence of increased Aβ_{42} in the 2011 CSF analysis seems not directly to support this cause, as amyloid precursor protein and Aβ increase in tissue and CSF happen rather acutely after TBI. Furthermore, neuroimaging already showed beginning parietal atrophy in 2006. Nevertheless, it is possible that the sustained concussion unmasked some prior subclinical cognitive decline by reducing compensation abilities.

Unfortunately, there is no amyloid PET available from L.V., which would help to further confirm the underlying pathology as indicated by the biomarkers. Some studies have assessed patterns of amyloid deposition with Pittsburgh compound B-PET in patients with PCA, showing an increased accumulation of Aβ, predominantly in the occipital and parietal lobes, relative to individuals with typical AD.[8]

Overall, this case is a comprehensive example of the vast diagnostic challenges regarding the relatively rare syndrome PCA. The comparably young age of onset, often (initially) unremarkable AD-CSF biomarkers and neuroimaging, and the very distinct, nonamnestic symptoms can mask the pathology in the early stages. As first symptoms of PCA are almost exclusively of visual,[9,10] but not amnestic nature, patients often seek ophthalmologic treatment first and the actual diagnosis is greatly delayed. The nature of complaints may also lead to suspicion of depression and/or malingering, or symptoms can be dismissed as psychosomatic.[3] Thus, dementia and PCA even less so is often not considered as differential diagnosis.

Also, while public AD awareness has been steadily rising, PCA is still widely unknown. However, as the deficit profile is vastly different from classic AD, experts need to be further sensitized for the disease. Our case stresses how regular follow-ups of neuropsychological and neuroimaging parameters are essential for differential diagnosis. In addition, early CSF testing offers the chance of early pharmacological intervention, for example, acetylcholinesterase inhibitors which might have some benefit for those PCA patients with underlying AD pathology. Most importantly, patients will benefit from timely specific disease management, including compensation training, instead of mostly futile restoration training and adaption of the patient's environment, as well as treatment of potential accompanying depression.

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