



Shining a light on posterior cortical atrophy

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Abstract

Posterior cortical atrophy (PCA) is a clinicoradiologic syndrome characterized by progressive decline in visual processing skills, relatively intact memory and language in the early stages, and atrophy of posterior brain regions. Misdiagnosis of PCA is common, owing not only to its relative rarity and unusual and variable presentation, but also because patients frequently first seek the opinion of an ophthalmologist, who may note normal eye examinations by their usual tests but may not appreciate cortical brain dysfunction. Seeking to raise awareness of the disease, stimulate research, and promote collaboration, a multidisciplinary group of PCA research clinicians formed an international working party, which had its first face-to-face meeting on July 13, 2012 in Vancouver, Canada, prior to the Alzheimer's Association International Conference.

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1. Introduction

Posterior cortical atrophy (PCA) is a clinicoradiologic syndrome characterized by progressive decline in visual processing skills, relatively intact memory and language in the early stages, and atrophy of posterior brain regions [1]. Often considered an atypical or variant form of Alzheimer's disease (AD) [2,3], PCA typically presents in the mid-50s or

early 60s with a variety of unusual symptoms, such as difficulty interpreting, locating, or reaching for objects under visual guidance or difficulty navigating. Understanding numbers and reading and writing or spelling may also be affected and, as the disease progresses, patients often develop a more diffuse pattern of cognitive dysfunction, ultimately leading to dementia.

Misdiagnosis of PCA is common, owing not only to its relative rarity, unusual and variable presentation, but also because patients frequently first seek the opinion of an ophthalmologist who may note normal eye examinations

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by their usual tests but may not appreciate cortical brain dysfunction. Furthermore, many neurologists who evaluate these patients do not test for simultanagnosia (the inability to perceive more than one object at the same time) or other visuospatial or visuo-perceptual disturbances. Lack of validated diagnostic criteria and lack of awareness among clinicians and researchers also contribute to misdiagnosis.

Seeking to raise awareness of the disease, stimulate research, and promote collaboration, a multidisciplinary group of PCA research clinicians formed an international working party and had its first face-to-face meeting on July 13, 2012 in Vancouver, Canada, prior to the Alzheimer's Association International Conference (AAIC). Eighteen researchers attended the meeting and another 20 researchers representing a total of 23 institutions in 9 countries agreed to participate in the working party.

2. Developing consensus on diagnostic criteria

In 1988, D. Frank Benson and colleagues first coined the term PCA in reporting a series of patients with early visual dysfunction in the setting of neurodegeneration of posterior cortical regions [4]. Since the initial case series was published, multiple groups have proposed diagnostic criteria for the syndrome [5–8]. Although the core features are reasonably consistent across proposals (Table 1), subtle but significant differences in the definition of PCA have limited the ability to directly compare or harmonize findings across studies, thus hampering progress in the field. Centers have differed in how they define the boundaries between PCA and other, clinically overlapping variants of AD. Some investigators favor splitting PCA into distinct clinical variants (e.g., those primarily affecting dominant versus nondominant hemispheres; patients showing principal deficits in dorsal visual stream, ventral visual stream, or primary visual processing), whereas others have considered PCA a phenotypic continuum [9,10]. Studies have also differed as to how neuroimaging may be used to support the diagnosis. Standardizing diagnostic criteria would advance research by allowing for direct comparisons, pooling of common data, and providing a platform through which multiple investigators could share their expertise in order to optimize the diagnosis (e.g., by incorporating specific cognitive tests, neuroimaging techniques, and other biomarkers), study disease mechanisms, and ultimately test emerging therapies. The standardization of diagnostic criteria for PCA is one of this group's first goals.

3. Similarities and differences from typical AD

Many patients with PCA share biologic features with typical AD, which affects memory to a much greater degree than visual abilities. Most critically, the vast majority (>80%) of PCA patients are found to have AD pathology

Table 1
Characteristics of posterior cortical atrophy

Core features of PCA:
<ul style="list-style-type: none"> • Insidious onset and gradual progression • Prominent visuo-perceptual and visuospatial impairments but no significant impairment of vision itself • Relative preservation of memory and insight • Evidence of complex visual disorders (e.g., elements of Balint's syndrome or Gerstmann's syndrome, visual field defects, visual agnosia, environmental disorientation) • Absence of stroke or tumor
Other supportive features:
<ul style="list-style-type: none"> • Presenile onset • Alexia • Ideomotor or dressing apraxia • Prosopagnosia • Prolonged color after-images

as the cause of dementia at autopsy [8,11,12]. PCA and AD patients both show a similar pattern of high cortical binding on amyloid positron emission tomography (PET) imaging, and analogous changes in cerebrospinal fluid (CSF) level of A β 42, total tau, and phosphorylated tau [13–15]. PCA and AD show overlapping atrophy [on magnetic resonance imaging (MRI)] and hypometabolism/hypoperfusion [on fluorodeoxyglucose PET single-photon emission computed tomography (FDG-PET/SPECT)] in temporoparietal regions, suggesting a common anatomic focus of neurodegeneration [14,16].

There are also critical differences between the two conditions. Neuropsychologic tasks that test the dorsal visual stream (e.g., complex pictures and compound stimuli) are particularly sensitive to PCA, whereas episodic memory dysfunction, the hallmark of "typical" AD, is often absent early in PCA. Structural neuroimaging with either MRI or CT initially shows greater atrophy of visual processing areas in parietotemporo-occipital cortex and relative sparing of critical memory regions in the medial temporal lobe [5,17–20]. Over time, the neuroimaging profile of PCA may also merge with that of typical AD [21]. However, even at the time of autopsy, PCA patients show a greater burden of neurofibrillary pathology in visual cortical areas than is seen in typical AD [8,11,22].

The similarities and differences between PCA and AD may offer important clues about how AD evolves, and about mechanisms that drive heterogeneity in the disease. The clinical and anatomic differences highlight the need for PCA-specific cognitive and imaging outcome measures for drug trials. For example, neuropsychologic tests that rely on intact vision (e.g., visual memory) are not valid when administered to visually impaired PCA patients, whereas tests of memory tend to underestimate the degree or progression of cognitive impairment. The best imaging measures for longitudinal change (e.g., to estimate a drug effect) may also differ between PCA and typical AD.

Formalizing the integration of imaging, biofluid biomarkers and neuropsychologic testing into the diagnostic

evaluation of patients with PCA will benefit patients by providing more relevant diagnostic and prognostic information, and by streaming them into appropriate disease-specific therapy routes. Because the condition is relatively rare, however, acquiring sufficient numbers of subjects to yield statistically significant results requires drawing subjects from multiple research studies, which requires standardization of imaging, biomarkers, and neuropsychologic testing. Standardization of these measures is another goal of this group.

4. Providing a platform for collaboration

In their initial meeting, the working party discussed definitions of PCA at the syndrome and disease level, and further deliberated on whether there are distinct subtypes of PCA. Members debated the boundaries that divide PCA from other AD phenotypes. More importantly, however, there was great enthusiasm for sharing clinical experience and expertise to further research and improve the care of patients with PCA. Attendees at the Vancouver meeting agreed, as a first step, to craft a consensus statement defining PCA on the basis of the broad consensus that already exists.

Moreover, attendees agreed to pursue a more formal mechanism to enable collaborative efforts in education, clinical management, and patient support by forming a PCA Professional Interest Area (PIA) group. PIAs are supported by the Alzheimer's Association's International Society to Advance Alzheimer's Research and Treatment (ISTAART) to bring together professionals with shared interests, as a means of advancing research and treatment through sharing of resources and information. ISTAART provides a platform for this through discussion, administrative support, teleconferences, and feature research sessions at AAIC.

Additional collaborative projects were also suggested, such as a genome-wide association study (GWAS) to identify genetic risk factors; pooling and sharing demographic, biomarker, clinical, and cognitive data to identify other risk factors and better understand the natural history of the disease; and working together to evaluate the role of new biomarkers in the evaluation of PCA. In addition, the group shared ideas about treatment approaches and educational material for patients and families about ways to try to adapt to the symptoms of PCA. The feasibility of these projects would be greatly advanced through the efforts of a stronger, more visible, and internationally representative working party.

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