Published in final edited form as:

Curr Opin Neurol. 2020 February ; 33(1): 68–73. doi:10.1097/WCO.0000000000000767.

Update on Posterior Cortical Atrophy

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Structured Abstract

Purpose of review: Non-amnesic (or atypical) presentations of neurodegenerative dementias are under-recognized and under-diagnosed, including posterior cortical atrophy (PCA) syndrome, which is characterized by prominent visuospatial and visuoperceptual dysfunction at presentation. It is most commonly due to Alzheimer's disease (AD) pathology, while Lewy body disease, corticobasal degeneration, and prion disease are pathologies less frequently associated with PCA. The diagnosis of PCA is often delayed, to the detriment of the patient, and awareness and understanding of PCA will improve detection, prognostication, and treatment.

Recent findings: The natural history of PCA appears to be distinct from typical AD and significant heterogeneity exists within the PCA syndrome, with the underlying causes of this heterogeneity beginning to be explored. Functional and molecular imaging can assist in better understanding PCA, particularly assessment of network disruptions that contribute to clinical phenotypes. CSF biomarkers are useful to detect underlying pathology, but measures of retinal thickness are less promising. There are currently no adequate treatment options for PCA.

Summary: Continued efforts to characterize PCA are needed, and greater awareness and understanding of atypical presentations of neurodegenerative dementias could serve to elucidate pathobiological mechanisms of underlying disease.

Keywords

posterior cortical atrophy; visuospatial function; Alzheimer's disease; neurodegeneration

Introduction

Posterior cortical atrophy (PCA) is a neurodegenerative syndrome characterized by early prominent visual dysfunction that cannot be explained by ocular causes. With terminology introduced by Benson and colleagues [1] in the late 1980s, the PCA syndrome includes impairments in visuospatial, visuoperceptual, reading, praxis, and mathematical functions. Features of Balint's (ocular apraxia, optic ataxia, simultanagnosia) and Gerstmann's

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Financial support and sponsorships: none

Conflicts: none

(acalculia, agraphia, left-right confusion, finger agnosia) syndromes can be present [2**], leading to significant impairments in day-to-day functioning for people with PCA. Episodic memory, executive functions, language, comportment, and insight are relatively preserved compared to typical AD, but progressive neurodegeneration leads to more global impairment over time. Oculomotor findings may also be present, including impaired saccades, smooth pursuits, and fixation stability. Typical structural neuroimaging findings include focal atrophy of the occipital and parietal lobes, with relative preservation of hippocampal volumes at onset.

Most commonly, PCA is associated with Alzheimer's disease (AD) pathology and less frequently with Lewy bodies, corticobasal degeneration (CBD), and prion disease [3]. In 2017, updated consensus criteria for the diagnosis and classification of PCA were published [2**], which now allows for consistency in definitions across research studies (Table 1). Classification includes the addition of disease entities, such as PCA-AD or PCA-Prion, that should supplant terms such as the 'visual variant of Alzheimer's disease' or the 'Heidenhain variant' of Creutzfeldt-Jakob Disease [2**]. PCA usually presents in the sixth or seventh decade, which is a younger age of onset than typical AD. While previously described as relatively rare, PCA accounts for at least 13% of early-onset AD cases [3] and is likely under-recognized and misdiagnosed due to limited awareness of non-amnesic presentations of AD combined with the younger age of onset. Recent PCA research has sought to 1) better characterize its clinical continuum, 2) improve methods for clinical detection, and 3) develop effective treatments, though this syndrome remains under-studied overall.

Longitudinal characterization of PCA

Though it is known that a progressive dementia develops over time in those with PCA, the natural history for an individual patient is challenging to predict due to the lack of longitudinal studies. In order to begin addressing this gap, PCA researchers, based in the UK, US, and Spain, compiled the largest longitudinal clinical and imaging database to date on a cohort of 117 PCA-AD cases for comparison to 116 typical AD and 138 healthy controls [4**]. Firth and colleagues found that PCA demonstrates distinct patterns of onset and spatial and temporal progression compared to typical AD, and shows expected early occipital and parietal atrophy, but also faster relative rates of atrophy in these regions compared to AD. Temporal atrophy also occurred in PCA, requiring about 10 years to reach a degree commensurate with the posterior regions. Medial temporal and frontal regions remained relatively spared. Cognitive performance on several measures associated with posterior cortical functions, including fragmented letters, dot counting, and 'A' cancellation, demonstrated both the greatest baseline impairment and subsequent decline in PCA and differed significantly between PCA and AD. Somewhat unexpectedly, digit span backwards was impaired earlier in PCA than AD, perhaps due to the use of visuospatial imagery for performing this task, in addition to working memory.

As many have suspected, Firth and colleagues also noted considerable heterogeneity within the PCA group, with variable rates of change on cognitive testing and atrophy patterns, highlighting that heterogeneity across the AD spectrum is common and remains to be elucidated. One possibility is that heterogeneity reflects a combination of the initial unique

location of neurodegeneration followed by variability in the direction and speed of spread along relevant functional networks that is due to undiscovered risk factors. Selective vulnerability of neuronal populations [5], as well as the role of both risk and protective factors, require further investigation in PCA.

Interest in impaired neuroanatomical reserve of developmentally altered networks and/or pre-existing learning disabilities as potential risk factors for expression and spread of AD has grown. Previous studies of logopenic primary progressive aphasia (lvPPA), another atypical AD presentation, have shown higher rates of language-based learning disabilities (LD), such as dyslexia [6]. Miller and colleagues evaluated 96 PCA patients, 84 lvPPA, and 100 amnesic AD by record review for histories of LD [7*], and discovered a higher than expected rate of LD in PCA (19%) and lvPPA (25%) groups than the general population (10%). In PCA, the majority (72%) were non-language LDs, while 100% of the lvPPA LDs were language-based or mixed. Interestingly, those PCA patients with a history of LD had greater preserved global cognition than those without, perhaps indicating a more focal visuospatial cognitive syndrome. On neuroimaging, the PCA patients with LD also had more asymmetric posterior atrophy than those without, with more right lateralization.

Posterior Cortical Deficits in PCA

As noted in Table 1, the main features of PCA involve symptoms consistent with impaired processing of visual stimuli along the occipitoparietal and/or the occipitotemporal pathways, as well as impaired visuomotor functions (i.e. optic ataxic, oculomotor apraxia), homonymous visual field loss, impaired literacy and numeracy, and apraxia. Two recent studies demonstrate that PCA-focused investigations can shed light on the importance of visual networks to behavior and general visual brain functions. First, a study by Pressman and colleagues [8] revealed relative preservation of facial expression versus facial identification in PCA compared to both typical AD and the behavioral variant of frontotemporal dementia. The authors postulated that these findings could account for the frequent observation of preserved social and emotional functions in PCA and support theories that the origins of ‘affective blindsight’ (i.e. ability to respond to emotionally relevant visual stimuli despite cortical visual loss) are due to intact retinotectal-pulvinar pathway in the setting of primary visual cortical dysfunction. A second study by de Best and colleagues [9] revealed that occipital receptive fields were larger than normal within the foveal occipital regions and smaller than normal outside of foveal regions in PCA patients compared to healthy controls. The authors conclude that visual crowding in PCA is due to inclusion of ‘non-salient’ visual stimuli within foveal receptive fields and that simultanagnosia is due to exclusion of ‘salient’ visual stimuli relevant to construction of global percepts in non-foveal occipital regions. These findings have important implications for visual crowding and simultanagnosia in other disorders (i.e., amblyopia, stroke), particularly with regards to rehabilitation approaches.

Non-visual cognitive deficits in PCA

Impaired reciprocal network connections in PCA, including the posterior connections to frontal and anterior temporal regions, also appear to contribute to clinical symptomatology.

For example, verbal episodic memory is, by definition, relatively preserved in PCA, but people with PCA often report and demonstrate impairments on testing [10,11]. Recent work on autobiographical memory (ABM) reveals that ABM requires not only remote episodic memory, but association with contextual details and emotional milieu, all within a spatiotemporal framework. While most previous work focused on the role of the medial temporal and prefrontal lobes, Ahmed and colleagues performed autobiographical interviews with 14 people with PCA, 18 with AD, and 28 healthy controls [12]. Unlike AD, patients with PCA produced more extraneous, off-target details. Frequently unable to constrain their search to one particular event, they jumped around and lacked perceptual and spatiotemporal details, repeating themselves and providing more semantic facts than personal experiences, suggesting an ABM ‘simultanagnosia’. The level of perceptual detail produced by PCA patients in this study was positively associated with gray matter density in the right precuneus, an area linked to mental and visuospatial imagery and episodic memory retrieval. Other authors have also found that episodic memory relies not only on medial temporal lobe functions, but on connectivity within the dorsal attention network (DAN), which includes the dorsal parietal regions, and that DAN disruption is responsible for episodic memory impairment in PCA [13].

It is worth noting that many tests of executive functions rely on vision, making it difficult to disentangle the relative contribution of ‘non-visual’ component to dysexecutive function. As with memory, there is reason to believe that dysexecutive function in PCA is due to network disruption, as the lateral and medial parietal regions are involved in executive functional networks. Putcha and colleagues administered a battery of neuropsychological tests to 19 PCA patients, finding mild executive and attention dysfunction in 89% and memory dysfunction in 79% [14]. These findings correlated with atrophy in the left inferior parietal lobule (IPL) and intraparietal sulcus (IPS), areas involved in mental manipulation and imagery of information. Selective vulnerability of the IPL/IPS may exist in neurodegenerative disease (NDD), owing to the high metabolic demands on this area as part of a vital ‘cortical hub’ in multiple large-scale networks, including the DAN, default mode network (DMN), and frontoparietal network (FPN). In contrast to pure storage deficits seen with temporolimbic atrophy of typical AD, posterior parietal and lateral temporal atrophy in PCA contributes to impaired encoding and retrieval of memories.

This work highlights the need to account for underlying neural networks in PCA, since the impairment of one network node, i.e. visual imagery, can have downstream effects on other brain functions within the same network. Thus, network disruption at different locations, can have very similar phenotypes [15].

Biomarkers for PCA

Currently, there are no biomarkers that are specific for the PCA syndrome. Sensitive disease biomarkers are available for AD and prion disease but not for dementia with Lewy bodies (DLB) or CBD. Investigations of network configurations as markers of clinical phenotypes do show some promise.

Functional Imaging Resting State Networks:

Agosta and colleagues found that patients with PCA (N = 21) had decreased white matter integrity of the corpus callosum, superior longitudinal fasciculus (linking frontal and parietal regions), and inferior longitudinal fasciculus (linking temporal and occipital regions) compared to 44 healthy controls [16]. Longer disease durations and more severe clinical disease in PCA was associated with more white matter damage in the cingulum, as well as more impaired functional connectivity in the frontostriatal, dorsal attention, and salience networks. The salience network, responsible for social-emotional functioning, is of particular interest, as its function is relatively spared, or even increased, early in the PCA disease course [17]. As visuospatial networks become increasingly impaired, a release phenomenon of increased salience network activity and connectivity may occur, which manifests clinically as anxiety and personal distress, especially when paired with preserved to increased connectivity of the DMN in some cases. This connectivity pattern could help distinguish PCA from typical AD, in which there is decreased activity of the DMN. Fredericks and colleagues have postulated that relative increases and decreases in functional connectivity may be modulated by particular thalamic nuclei, such as the medial pulvinar for the salience network [18].

Molecular Imaging:

Amyloid PET imaging can identify underlying AD pathology in PCA, and findings are remarkably similar between PCA and typical AD. Amyloid PET is not helpful for distinguishing AD from DLB, since Lewy body pathology is highly co-morbid with AD pathology. In contrast to amyloid imaging, a recent study by Nedelska and colleagues demonstrated high discriminant validity for tau imaging with [¹⁸F]AV-1451 in distinguishing PCA-AD from DLB [19*]. In comparing 18 PCA patients to 33 DLB, there was markedly higher AV-1451 uptake across the entire cortex in PCA, especially in lateral occipital association cortices. Even in PCA patients with clinical features of DLB, such as parkinsonism or REM behavior disorder, AV-1451 uptake was higher than in the DLB patients without clinical PCA features. This work lends itself to future investigations to determining if phenotypic trajectories and rates of functional change can be predicted by tau imaging features.

Cerebrospinal fluid (CSF):

Profiles of AD CSF biomarkers in PCA can be atypical, including reduced amyloid-beta-42 without corresponding elevated total or phosphorylated-tau levels [20*], while more typical AD CSF profiles are associated with left temporal changes and more widespread disease. Montembeault and colleagues demonstrated that five PCA patients without CSF biomarkers of AD all had abnormal dopamine transporter single-photon emission computed tomography (SPECT) scans, and within three years of follow-up, two patients developed clinical features of DLB [20]. This non-AD CSF biomarker group also displayed more specific atrophy in the left caudate nucleus, right dorsolateral prefrontal cortex, and anterior medial temporal lobes, which includes patterns more commonly seen in DLB and CBD. Importantly, there were no group level differences in clinical features or cognitive profiles between those with AD CSF

biomarker changes and those without, highlighting that PCA is a syndrome that manifests from varied underlying pathologies.

Retinal Imaging:

Although a number of studies reveal decreased inner retinal thickness measured by optical coherence tomography in AD [21], this has not been the case for PCA. Den Haan and colleagues found no differences in peripapillary retinal nerve fiber layer thickness or total macular thickness between PCA, typical AD, and healthy controls [22], and more work is necessary to understand these findings.

Treatment Updates for PCA

Disease-modifying therapies for PCA and other neurodegenerative dementias remain elusive. While symptomatic therapies with cholinesterase inhibitors are frequently used in PCA, there have been very few patients studied for evidence of clinical impact and no treatments are FDA approved for use specifically in PCA. A short duration, double-blind, placebo-controlled cross-over trial (at week 6 of 12) of donepezil in 18 patients with PCA revealed no significant cognitive benefit using the mini-mental status examination (MMSE) [23*]. Interestingly, there was a high rate of nightmares and vivid dreaming in the treatment group (44% versus 0% in placebo), which was higher than that reported in typical AD usage (8-18%) [24].

Mendez and colleagues reported decreased apathy and social withdrawal in three patients with PCA treated with low doses of methylphenidate, without significant side effects, though no objective cognitive improvements [25]. One case report described a combination of cognitive rehabilitation and transcranial direct current stimulation therapy for a patient with PCA [26], with noted improvement in visual memory and attention, although scores on the MMSE decreased. More work needs to be done to understand the best outcome measures and the best approach to treatment in PCA.

Conclusion

Evidence suggests that PCA may not be as uncommon as previously considered and is often under-recognized or misdiagnosed. The time from first symptom to diagnosis is protracted, making it more likely that a PCA patient will first be diagnosed at a stage of significant functional impairment. We propose that an appraisal of posterior visual and non-visual symptoms in aging adults, at a population level, will be necessary to delineate what constitutes the earliest stages of PCA, and by developing this knowledge, we will be able to increase awareness of non-amnesic presentations of neurodegenerative dementias and begin to unravel their underlying pathogenesis. Studying PCA through a lens of network dysfunction is promising and may allow for the appreciation of the earliest manifestations of the syndrome's far-reaching symptomatology. Reliable biomarkers are needed and may require novel measures to be developed specifically for PCA. Lastly, effective treatments are direly needed to improve day-to-day function and quality of life for those living with PCA.

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Key Points

1. Posterior cortical atrophy (PCA) is a syndrome characterized by dysfunction of posterior cortical regions and manifests as visuospatial, visuoperceptual, reading, praxis, and mathematical impairments, most commonly due to underlying Alzheimer's disease pathology.
2. Unexplained visual impairment, particularly homonymous visual field loss, without demonstrable ocular disease or MRI lesions, requires extensive neurological evaluation as this can be the earliest sign of PCA.
3. Non-visual cognitive functions, including autobiographical and episodic memory, attention, and executive function, may also be impaired in PCA, and are likely related to disruption of shared underlying neuronal networks.
4. Use of cholinesterase inhibitors for PCA has not been supported by one small randomized controlled trial, and there may be a higher risk of nightmares and vivid dreams with their use in PCA.
5. Future work should focus on early detection and risks factors for PCA, which could ultimately improve diagnosis and care, as well as our understanding of the pathogenesis of the underlying neurodegenerative disease.

Table 1.

Posterior Cortical Atrophy Syndrome consensus criteria adapted from Crutch and colleagues [2]

Clinical Features	<ul style="list-style-type: none"> • Insidious onset • Gradual progression • Prominent early disturbance of visual, other posterior cognitive functions, or both.
Cognitive Features	<p>At least three must be present as an early or presenting feature: Space perception deficit, Simultanagnosia, Object perception deficit, Constructional dyspraxia, Environmental agnosia, Oculomotor apraxia, Dressing apraxia, Optic ataxia, Alexia, Left/right disorientation, Acaculia, Limb apraxia (not limb-kinetic), Apperceptive prosopagnosia, Agraphia, Homonymous visual field defect, Finger agnosia</p>
Non-posterior cognitive features	<p>All must be evident:</p> <ul style="list-style-type: none"> • Relatively spared anterograde memory function • Relatively spared speech and nonvisual language functions • Relatively spared executive functions • Relatively spared behavior and personality
Neuroimaging	Predominant occipito-parietal or occipito-temporal atrophy/hypometabolism/hypoperfusion on MRI/FDG-PET/SPECT
Exclusion Criteria	<ul style="list-style-type: none"> • Evidence of a brain tumor or other mass lesion sufficient to explain the symptoms • Evidence of significant vascular disease including focal stroke sufficient to explain the symptoms • Evidence of afferent visual cause (e.g., optic nerve, chiasm, or tract) • Evidence of other identifiable causes for cognitive impairment (e.g., renal failure)

FDG-PET: fluorodeoxyglucose positron emission tomography; SPECT: single photon emission computed tomography