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# Posterior Cortical Atrophy

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**ABSTRACT**

**PURPOSE OF REVIEW:** This article presents an overview of the clinical syndrome of posterior cortical atrophy (PCA), including its pathologic underpinnings, clinical presentation, investigation findings, diagnostic criteria, and management.

**RECENT FINDINGS:** PCA is usually an atypical form of Alzheimer disease with relatively young age at onset. New diagnostic criteria allow patients to be diagnosed on a syndromic basis as having a primary visual (pure) form or more complex (plus) form of PCA and, when possible, on a disease-specific basis using biomarkers or underlying pathology. Imaging techniques have demonstrated that some pathologic processes are concordant (atrophy, hypometabolism, tau deposition) with clinical symptoms and some are discordant (widespread amyloid deposition). International efforts are under way to establish the genetic underpinnings of this typically sporadic form of Alzheimer disease. In the absence of specific disease-modifying therapies, a number of practical suggestions can be offered to patients and their families to facilitate reading and activities of daily living, promote independence, and improve quality of life

**SUMMARY:** While rare, PCA is an important diagnostic entity for neurologists, ophthalmologists, and optometrists to recognize to allow for early accurate diagnosis and appropriate patient management. PCA provides an important opportunity to investigate the causes of selective vulnerability in Alzheimer disease.

**INTRODUCTION**

Posterior cortical atrophy (PCA) is a neurodegenerative syndrome that primarily affects the parietal and occipital lobes.<sup>1</sup> While patients with progressive visual impairment with normal acuity had previously been described, the term *posterior cortical atrophy* was introduced by Benson and colleagues,<sup>2</sup> who described a series of patients with deficits in higher-order visual processing and features consistent with aspects of Gerstmann and Balint syndromes but with relatively preserved episodic memory until later in the disease. Subsequent case series determined that the most common underlying pathology was Alzheimer disease (AD),<sup>3–5</sup> leading to alternative nomenclature including the visual variant of AD and biparietal AD.<sup>4,6</sup> However, as PCA can be due to alternative pathologies, including corticobasal

degeneration,<sup>7</sup> Lewy body disease, and (very rarely) prion disease, the overarching term *posterior cortical atrophy* is now preferred to describe the syndrome, with contemporary criteria allowing for subdivisions into PCA-pure, PCA-plus, and pathologic subtypes depending on the clinical presentation and availability of biomarker evidence of underlying pathology.<sup>8</sup>

## EPIDEMIOLOGY

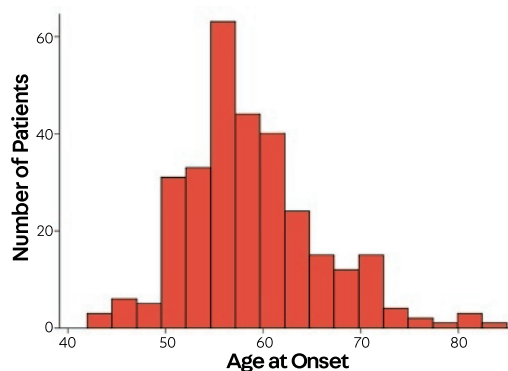
The changing definitions of PCA over recent years and its relative rarity make estimation of incidence and prevalence difficult. However, a striking feature of this syndrome is that the majority of affected individuals have an unusually early age at disease onset, typically presenting between 50 and 65 years of age, although patients with onset in the ninth decade are described.<sup>5,9</sup> In the largest series to date studying PCA, of 302 patients, the mean age of onset was 58.9 years (standard deviation 6.9), with 82.5% fulfilling criteria for early-onset dementia (onset before 65 years of age) (FIGURE 3-1).<sup>9</sup> The proportion of patients with AD presenting with PCA varies and is likely to depend on clinical context but has been estimated to be about 5% in a specialist cognitive clinic<sup>10</sup> and up to 13% in cases of early-onset AD.<sup>11</sup> In addition to patients with a clear PCA presentation, a population-based study showed that 14% of patients diagnosed with AD had cognitive profiles consistent with prominent visuospatial problems,<sup>12</sup> suggesting that visual problems are underrecognized in individuals diagnosed with “typical” AD and raising questions as to whether PCA is a distinct entity<sup>13</sup> or on a phenotypic continuum.<sup>14</sup> While some PCA studies have reported a slight overrepresentation of women<sup>9</sup> (which may simply reflect that AD is more prevalent in women), others have reported no sex differences.<sup>15–17</sup> Few prospective studies have examined disease duration in PCA; while patients with early-onset AD may have faster disease progression than those with later-onset disease, many patients with PCA have a more protracted course extending well over a decade.

## PATHOLOGIC UNDERPINNINGS

Most patients with PCA have underlying AD,<sup>4,5,17,18</sup> although cases of PCA can be associated with Lewy body pathology<sup>5,17</sup> (either in isolation or, commonly, in combination with AD) and, very rarely, with subcortical gliosis or prion disease.<sup>17,19</sup> On postmortem examination, most cases will naturally have end-stage disease, but even at late stages, differences in the distribution of neurofibrillary tangles compared to patients with typical AD have been noted, with particular involvement of primary visual cortices and visual association areas.<sup>3,18</sup> Conversely, most studies have not found major differences in amyloid burden across the cortex compared to other forms of AD.<sup>5,17</sup>

## KEY POINTS

- A striking feature of posterior cortical atrophy is that the majority of affected individuals have an unusually early age at disease onset, typically presenting between 50 and 65 years of age.
- Most patients with posterior cortical atrophy have underlying Alzheimer disease.



**FIGURE 3-1** Age of disease onset in posterior cortical atrophy. Data from an international study<sup>9</sup> of 302 patients shows a peak between 50 and 60 years of age, with diminishing incidence with increasing age.

## CASE 3-1

A 57-year-old woman presented because of progressive visual difficulties. She had initially presented to an optometrist at age 50, having noted difficulties when driving and problems while filling syringes and taking stitches out in her work as a hospital nurse. The optometrist noted a “difficulty with peripheral vision” and referred her to an ophthalmologist, who determined no ophthalmic basis for her difficulties. She subsequently returned to the optometrist, who prescribed multifocal lenses followed by two additional pairs of eyeglasses. The patient moved to a general practice nursing role but noticed further difficulties with visually demanding tasks, such as writing patient notes, reading prescriptions, and transcribing information to a computer. Her husband was also increasingly aware that the patient did not always see everything around her, particularly on the left side; she became lost during barn dances, and on one occasion they became separated when he turned left into the subway station they were walking to, while she continued straight ahead. Over the course of the next 6 years, the patient had five physician visits, including one visit to a memory clinic, which noted “there does not appear to be any evidence of a dementia.” It was only when her husband and son went through the radiologist report from a brain scan and noted the terms *posterior*, *cortex*, *atrophy*, and *parietal* that diagnostic progress was made. Her husband reported, “I just searched for those words online and what came up was posterior cortical atrophy.”

**Neuropsychological assessment revealed significant early visual, visuoperceptual, and visuospatial dysfunction; despite good visual acuity (Snellen equivalent: 6/9), she failed tests of shape discrimination, dot counting, and fragmented letter perception. She had additional deficits in numeracy, praxis, and auditory-verbal short-term memory. These deficits were observed in the context of relatively well-preserved episodic memory on verbal recognition tasks and only occasional errors in the phonologic components of word retrieval. This cognitive profile was consistent with the posterior cortical atrophy (PCA) syndrome, as per the PCA consensus criteria (classification level 1).**

Neurologic examination and review of neuropsychiatric symptoms revealed no evidence of symptoms consistent with any additional neurodegenerative syndromes (therefore, consistent with PCA-pure at classification level 2). Standard visual rating of [<sup>18</sup>F]amyloid imaging yielded results consistent with Alzheimer disease pathology (supportive of PCA-Alzheimer disease at classification level 3).

## COMMENT

This case is a typical example of the delayed diagnosis of PCA. The visual symptoms that typify this condition are commonly inaccurately presumed to result from ocular rather than cortical pathology, and, in the absence of “typical” memory problems, a neurodegenerative dementia is often not considered.

## CLINICAL PRESENTATION

The core features of PCA include visuospatial and perceptual deficits as well as features of **Gerstmann syndrome (acalculia, left-right disorientation, finger agnosia, and agraphia)**, **Balint syndrome (ocular motor apraxia, optic ataxia, and simultanagnosia)**, alexia, and apraxia.<sup>1,16</sup> In contrast to typical AD, episodic memory is relatively preserved at onset; compared with frontotemporal dementia, aside from the common feature of anxiety,<sup>20</sup> personality and behavior are not usually affected in PCA and insight is preserved.

### History

Because of its relative rarity, PCA is often diagnosed late, and by the time patients present to neurologists, symptoms will often have been present for many months or years (**CASE 3-1**). Very early symptoms can be rather nebulous: patients often describe nonspecific anxiety and a sense that something is wrong, before more concrete problems (usually centered on vision) become apparent. Patients may have a history of repeated visits to optometrists or ophthalmologists and multiple unsuccessful changes in eyeglasses or surgical procedures in an attempt to correct acuity. Patients can often express themselves very clearly and so are not considered as having a “dementia”<sup>21</sup> or are diagnosed as having had a stroke before progressive problems emerge.<sup>22</sup> **Patients often describe causing minor damage to their cars because of problems judging distances while parking. Problems reading analog clocks and digitized pixelated signs are common early features.**

Over time, **difficulties with reading** emerge in the vast majority of patients.<sup>15,16</sup> Patients typically get lost **while reading text, particularly when moving from line to line or when there is too much competing textual information (so-called crowding)**<sup>23</sup> or may describe a sense that words are moving or slipping off the page.<sup>24</sup> Most patients with PCA will be unable to read within a few years of symptom onset. Occasionally, patients may describe abnormalities with color vision, describing washes of color or prolonged afterimages.<sup>25</sup> Patients may describe difficulties in finding items in front of them, particularly in more cluttered environments (**simultanagnosia**, discussed later in this article) or a sensation that items are moving.<sup>26</sup> Patients often become anxious about riding on escalators, particularly when going down; can be cautious when crossing the road because of difficulties in **judging the speed of traffic**; and can have difficulty with revolving doors or identifying **steps or slopes** when walking on **patterned carpets**. Featureless environments, such as white-tiled bathrooms and shiny surfaces, can be particularly disorienting. Patients will often develop **impaired facial recognition (prosopagnosia)**,<sup>5,15,16</sup> often while still being able to identify people by voice. Some individuals describe unusual symptoms that can be misconstrued as nonorganic, including finding it easier to read small rather than large text, and difficulties in identifying static objects while being able to track items in motion. An extreme example of this phenomenon is rare patients who can play sports such as tennis or badminton but are unable to locate the ball or shuttlecock when it is on the floor.

Outside of the visual domain, common symptoms are those attributable to **impairments of dominant parietal lobe function**,<sup>5,16</sup> including difficulty with **calculation** and handling **money** or **spelling**. **Dyspraxia** (acquired deficits in performing complex motor programs) is very common.<sup>16,27</sup> Combinations of visual problems and dyspraxia have significant functional consequences,

## KEY POINTS

- The core features of posterior cortical atrophy include visuospatial and perceptual deficits as well as features of Gerstmann syndrome (acalculia, left-right disorientation, finger agnosia, and agraphia), Balint syndrome (ocular motor apraxia, optic ataxia, and simultanagnosia), alexia, and apraxia.
- Patients with posterior cortical atrophy may have a history of repeated visits to optometrists and ophthalmologists and multiple unsuccessful changes in eyeglasses or surgical procedures in an attempt to correct acuity.
- Over time, difficulties with reading emerge in the vast majority of patients with posterior cortical atrophy.
- Patients with posterior cortical atrophy often become anxious about riding on escalators, particularly when going down; can be cautious when crossing the road because of difficulties in judging the speed of traffic; and can have difficulty with revolving doors.
- Combinations of visual problems and dyspraxia in patients with posterior cortical atrophy have significant functional consequences, including difficulty in getting dressed; cooking; and using cell phones, remote controls, and computers.



including difficulty in **getting dressed** (eg, problems buttoning or zipping, tying neckties, or finding the sleeves of coats or putting on clothes backward); **cooking**; and using **cell phones, remote controls, and computers**.

**Episodic memory and executive impairments are typically not observed in the early stages, although patients may fail certain memory and executive tasks owing to visual, imagery, and other deficits, but emerge as the disease progresses.** **Language** impairment is typically considered a **late feature** of this disorder, although evidence exists that early anomia is relatively common when specifically looked for.<sup>5,28–30</sup> This may reflect that while in their purest forms, the different established symptoms of AD dementia can easily be distinguished, in practice and as expected for a neurodegenerative process that spreads over time, a degree of overlap exists between different syndromic variants; this becomes increasingly apparent as the disease advances.

Aside from **dyspraxia**, a number of **other motor features** can be seen in PCA, including limb rigidity, myoclonus, and tremor.<sup>31</sup> While these can reflect underlying pathologies other than AD (eg, **corticobasal degeneration**<sup>16</sup> or, when parkinsonism is present, **dementia with Lewy bodies**), these can also be seen in PCA underpinned by Alzheimer pathology.<sup>31</sup>

As PCA progresses, symptoms inevitably worsen. The majority of patients will become **functionally blind**, which has major implications for the level of care that is required and can be the cause of considerable distress to the individual, who will often have good insight into his/her problems. Being **unable to read** or **use other communication devices** and becoming **increasingly dependent** on others often leads individuals to feel disempowered and depressed.<sup>32</sup> Patients who already have severe visual problems will become at **high risk of falls** as other cognitive and motor problems emerge. In its later stages, PCA is often indistinguishable from advanced typical AD.

### Atypical Presentations

Considerable debate has existed as to whether the presence of early visual symptoms is essential for a diagnosis of PCA<sup>20</sup> or whether presentations with other parietal features (eg, early prominent dyspraxia) with subsequent emergence of more typical visual features should still be classified under the PCA umbrella. This has implications for diagnostic criteria, as **patients with early motor features can overlap with other conditions, such as corticobasal syndrome, an issue that is now addressed in the most recent consensus criteria.**<sup>8</sup> **Some patients with a pure PCA phenotype may have corticobasal degeneration or Lewy body pathology rather than AD.** However, the presence of features typical for these conditions (eg, **alien limb phenomena for corticobasal degeneration** or early **hallucinations**, rapid eye movement [REM] **sleep behavior disorder**, or **parkinsonism** for dementia with Lewy bodies) may provide evidence for these alternative pathologies. While the Heidenhain variant of **Creutzfeldt-Jakob disease (which presents with early visual impairment)** can, in theory, be mistaken for PCA, other clinical features, including the (usual) **rapidity** of the presentation and the nature of the visual disturbance (which, in **prion disease, is often associated with frightening visual distortions**), usually mean this is not a major diagnostic challenge. In rare overlap cases, the MRI features and evidence of diffusion changes, in particular in Creutzfeldt-Jakob disease, are particularly valuable.<sup>19</sup>

## BEDSIDE COGNITIVE ASSESSMENT

The bedside cognitive examination can be particularly revealing in PCA. Screening cognitive tests such as the Mini-Mental State Examination (MMSE)<sup>33</sup> or Addenbrooke's Cognitive Examination III (ACE-III)<sup>34</sup> will often clearly demonstrate preservation of orientation, repetition, and recall, with severe difficulties in dominant parietal tasks (eg, calculation and spelling) and right parietal function (eg, copying complex figures or clock drawing).

On additional testing, a marked discrepancy is often seen between patients' ability to read single letters and short words compared to blocks of texts as they will often get lost moving from word to word or line to line (FIGURE 3-2<sup>35</sup>); this may improve if they are allowed to use a finger to track. Simultanagnosia (the inability to interpret the entirety of a visual scene) can often be demonstrated by asking an individual to describe a complex picture; rather than describing it in its entirety, individuals with PCA will often hone in on specific features and fail to see the picture as a whole. This can be demonstrated on a research basis using eye tracking (FIGURE 3-3). A particularly striking and very common feature of PCA is the presence of an apperceptive agnosia. This can be easily demonstrated by showing patients degraded letters (FIGURE 3-4<sup>36</sup>), numbers, or objects, which they typically cannot make sense of, and then showing them the same letters in completed form, which they can recognize. Right parietal dysfunction can also be demonstrated through difficulties in dot counting, line bisection, or clock drawing.

Dominant parietal dysfunction can be demonstrated through bedside tests of calculation and spelling, although these should be administered verbally. Similarly, when testing for apraxia, to exclude problems solely related to visual difficulties, patients should be asked, for example, to put their thumb on their ring finger or to salute, rather than asking them to copy the examiner's hand movements.

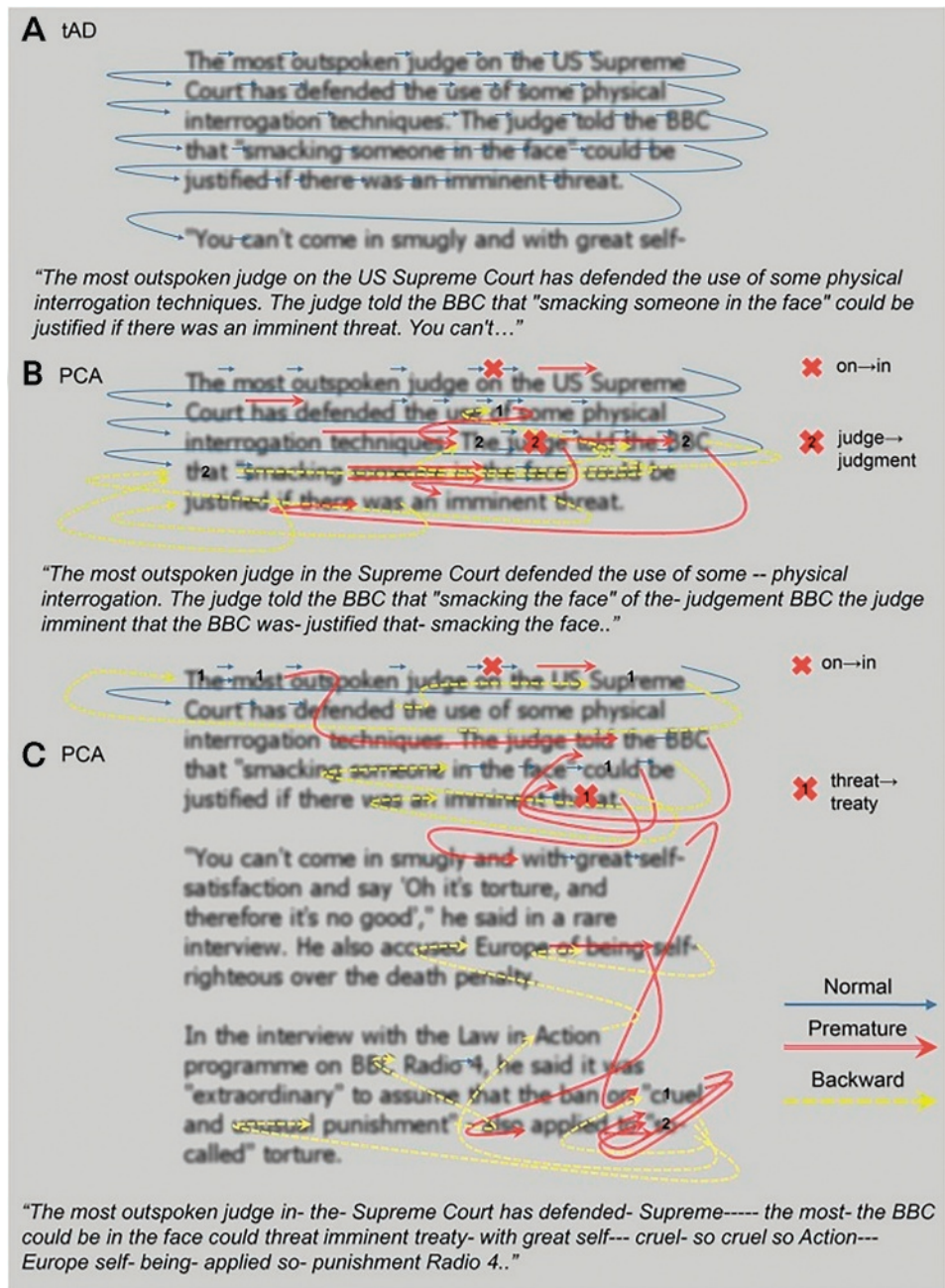
Visual disorientation (likely reflecting a combination of simultanagnosia and optic ataxia), when present, is a striking sign. The patient is seated in front of the examiner and asked to concentrate on the examiner's nose, as would be done with visual field testing. The patient is instructed to reach out and take the examiner's moving hand in the patient's peripheral vision. Typically, a patient with PCA will be able to see the hand and will often copy the hand movements but will have difficulties locating the examiner's hand in space (VIDEO 3-1, [links. lww.com/CONT/A266](https://www.ww.com/CONT/A266)). This phenomenon may be much more apparent in one hemifield than the other or may be present in both and is often present in central vision, distinguishing the misreaching in PCA from classic optic ataxia. In more advanced cases, the patient will reach instead toward the examiner's tie (the tie sign) or face instead of reaching for the target hand.

## NEUROLOGIC EXAMINATION

In patients with typical PCA due to AD, aside from demonstrating the higher-order visual signs and dyspraxia described above, the neurologic examination is typically unremarkable, although, as mentioned, a proportion of individuals will have mild motor signs or myoclonus.<sup>31</sup> Specific features that should be assessed include the presence of significant parkinsonism, which may reflect underlying Lewy body pathology, and very asymmetric motor features (dystonia, dyspraxia, myoclonus, and alien limb), which might reflect a corticobasal syndrome. Patients will not typically have upper motor neuron signs or features of amyotrophy. Watching the patient walk may be very informative, as mild balance problems are not infrequently encountered by patients with PCA, and the functional consequences

## KEY POINTS

- Simultanagnosia (the inability to interpret the entirety of a visual scene) can often be demonstrated by asking an individual to describe a complex picture; rather than describing it in its entirety, individuals with posterior cortical atrophy will often hone in on specific features and fail to see the picture as a whole.
- A particularly striking and very common feature of posterior cortical atrophy is the presence of an apperceptive agnosia.
- Visual disorientation (likely reflecting combinations of simultanagnosia and optic ataxia), when present, is a striking sign in patients with posterior cortical atrophy.



**FIGURE 3-2**

Eye tracking demonstrates preserved reading in typical Alzheimer disease (tAD) (A) and impaired reading in posterior cortical atrophy (PCA) (B, C). Blue arrows outline reading order, red arrows indicate omission of subsequent words through reading later sections of text, and yellow arrows indicate reading of earlier sections of text. Transcripts of the participants' corresponding spoken output are beneath each example (*italicized text*). Each hyphen in the transcript beneath each example indicates a pause of 3 seconds. Numbers refer to where words were repeated.

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**FIGURE 3-3**

Visual dysfunction in posterior cortical atrophy (PCA). Eye tracking studies in healthy individuals (A) and patients with PCA (B) demonstrate simultanagnosia in PCA. Circles represent fixation locations and circle size (and corresponding figure in milliseconds) indicates fixation durations. Individuals with PCA fixate on prominent features initially (eg, the dome on the pier) but subsequently fixate on relatively uninformative aspects of the scene (eg, the sea or sky), missing important contextual details (eg, the beachfront or near the end of the pier).

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of higher-order visual problems may be demonstrated if patients bump into walls or doorframes while walking.

### INVESTIGATIONS

While a syndromic diagnosis of PCA is usually apparent on the basis of the history and bedside examination, investigations can provide additional evidence for both the extent and nature of the cognitive and visual deficits and for the underlying causal pathology.





**FIGURE 3-4**  
 Fragmented letters. Individuals with posterior cortical atrophy will often be able to read individual letters, but not when they are presented in degraded form (apperceptive agnosia).  
 Reprinted with permission from Warrington EK.<sup>36</sup>  
 © 2010 National Hospital, Institute of Neurology.

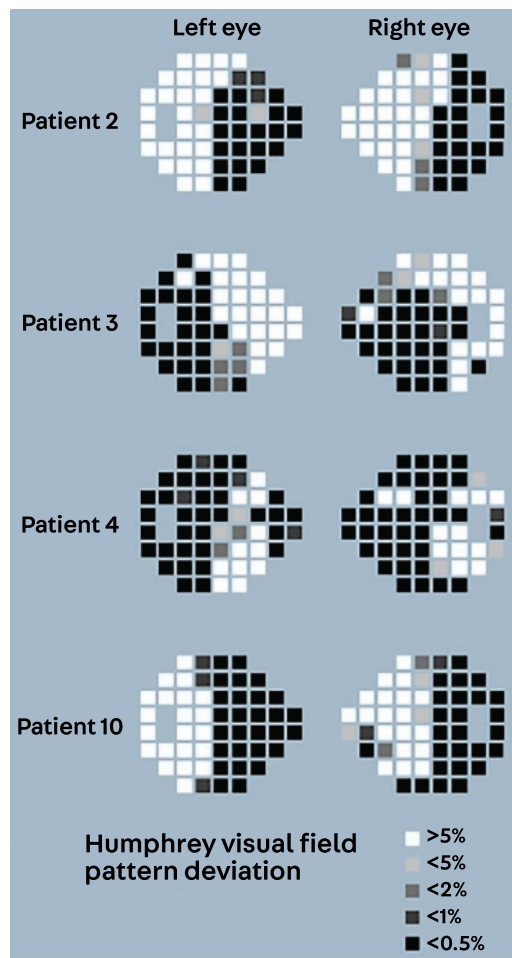
**Visual Fields**

While formal ocular assessment performed carefully can demonstrate normal acuity and fundi, visual field testing in PCA often reveals hemifield impairments or constriction,<sup>37</sup> including unusual and variable field deficits not confirming to classic cortical lesions,<sup>38</sup> which can be mistaken as being nonorganic (FIGURE 3-5).

**Neuropsychology**

Detailed neuropsychological assessment provides objective evidence for the cognitive domains that are both affected and preserved in PCA, with implications for diagnosis and potentially for management. A standard neuropsychometric battery can be employed in patients with PCA but with a few caveats. It is important that the testing psychologist is aware of the individual’s difficulties with vision, ensuring that test material is, whenever possible, presented in verbal rather than visual form (eg, nominal skills may be better determined by naming to description than to a picture). Similarly, assessment of premorbid IQ based on reading words from the National Adult Reading Test<sup>39</sup> may or may not be reliable depending on the extent of visual impairment.

Patients with PCA typically show a marked discrepancy between performance IQ (low) and verbal IQ and deficits in parietal tasks with preservation of memory and executive tests, provided that imagery and other deficits are taken into account (eg, recognition memory performance may remain preserved when recall appears



**FIGURE 3-5**  
 Visual fields in posterior cortical atrophy. In patient 2 and patient 10, visual field deficits are principally limited to a hemifield; in patient 3 and patient 4, both hemifields are affected to some extent.  
 Reprinted from Millington RS, et al, Neuroimage Clin.<sup>38</sup>  
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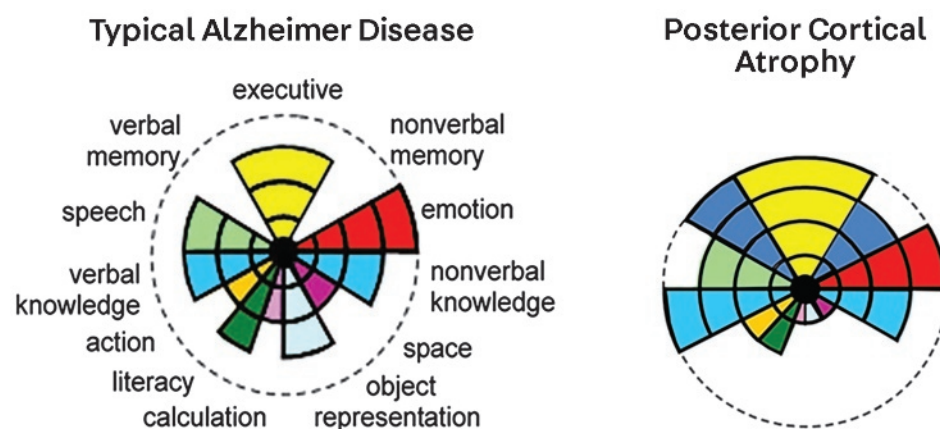
impaired) (FIGURE 3-6<sup>40</sup>). On this basis, neuropsychological research criteria for PCA have been described that require, for example, evidence for impairments (performance at less than the 5th percentile) on at least two out of four parietal tests (object perception, space perception, calculation, spelling) with evidence of preservation (greater than the 5th percentile) on a recognition memory test, in addition to fulfilling clinical criteria.<sup>41</sup>

### Structural Imaging

As the name of the condition implies, most individuals with PCA will have prominent volume loss reflecting neuronal tissue loss in posterior brain regions (FIGURE 3-7). On a group level, numerous studies have confirmed reductions in parietal and occipital volume and thinning in these regions in patients with PCA compared with both controls and patients with typical AD.<sup>41,42</sup> In practice, posterior volume loss is very clear in some cases, but others with very clear symptoms can have little volume loss, made more difficult to discern by natural variability of parietal lobe anatomy. Volumetric T1-weighted acquisitions in the coronal plane supplemented by sagittal views are often best for appreciating the distribution and extent of atrophy, and visual rating scales such as those introduced by Koedam and colleagues<sup>43</sup> may be helpful in providing an objective measure of parietal volume loss (FIGURE 3-8). However, in the presence of a typical history for PCA, the absence of marked parietal volume loss should not exclude the diagnosis. Hippocampal volumes are typically relatively preserved in PCA compared to typical AD dementia, in keeping with the relative preservation of episodic memory. It is also important to exclude vascular disease, inflammation, and mass lesions within the posterior cortices, which can mimic neurodegeneration; when Creutzfeldt-Jakob disease is possible, diffusion-weighted imaging (DWI) may be very helpful, typically showing cortical ribboning in occipital lobes in the Heidenhain variant (FIGURE 3-9).<sup>49</sup>

### KEY POINTS

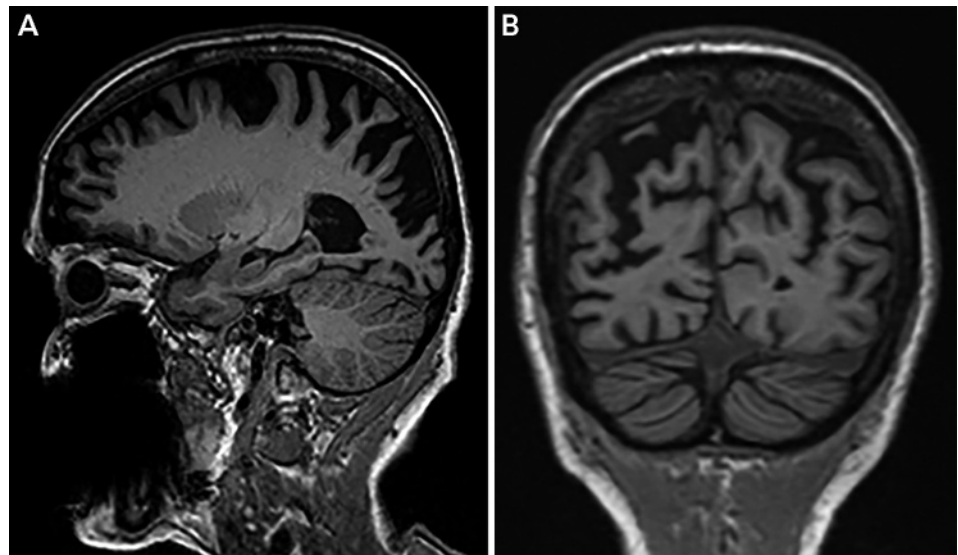
- When performing neuropsychological testing in posterior cortical atrophy, it is important that the testing psychologist is aware of the patient's difficulties with vision, ensuring that test material is, whenever possible, presented in verbal rather than visual form.
- In the presence of a typical history for posterior cortical atrophy, the absence of marked parietooccipital volume loss should not exclude the diagnosis.



**FIGURE 3-6**

Pattern of cognitive impairment in typical Alzheimer disease (A) and posterior cortical atrophy (B). Increasing impairment in a cognitive domain is represented by retreat of the color in its segment toward the center of the circle. Thus, verbal and nonverbal memory are profoundly affected in panel A but relatively preserved in panel B, while profound posterior cortical impairment is seen in panel B.

Modified with permission from Warren JD, et al, Nat Rev Neurol.<sup>40</sup> © 2012.



**FIGURE 3-7**

Typical MRI in posterior cortical atrophy. Sagittal (A) and coronal (B) MRIs show marked parietal lobe volume loss.

### Functional Imaging

In cases in which the clinical phenotype of PCA is clear and posterior atrophy is seen on MRI, further imaging is not typically required. However, in equivocal cases, fludeoxyglucose positron emission tomography (FDG-PET) may be extremely valuable in demonstrating hypometabolism within the parietooccipital cortices,<sup>44,45</sup> which is typically more extensive than the pattern of atrophy and may be seen earlier than structural changes are apparent (FIGURE 3-10). While not in routine clinical use, arterial spin labeling MRI (which provides a measure of cortical blood flow) may provide similar information, albeit reflecting blood flow rather than metabolism.<sup>46</sup>

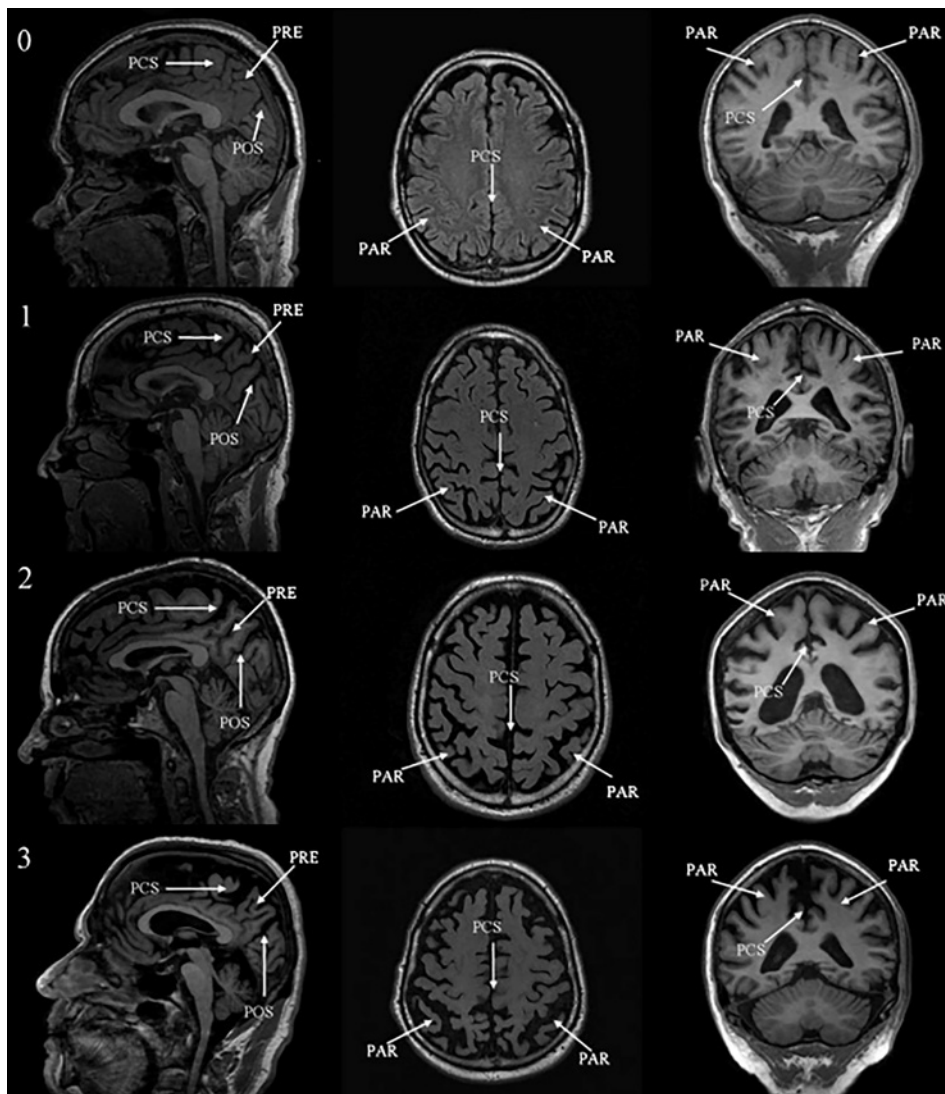
### Molecular Imaging

As patients with PCA, by definition, have atypical disease and almost all present with early-onset dementia, most will fall within appropriate use criteria for amyloid PET imaging.<sup>47</sup> Where available, amyloid PET can provide invaluable evidence for underlying AD. However, in contrast to the striking focality both of the symptom and structural imaging changes, amyloid deposition is usually seen across the cortex, with amyloid PET scans from patients with PCA often being indistinguishable from patients with more typical forms of AD.<sup>45,48</sup> Thus, while amyloid PET has a role in defining pathology, it is not useful in defining AD syndromes. By contrast, tau PET scanning, which is currently only available in a research setting, often shows very striking posterior cortical deposition of tau pathology in PCA (FIGURE 3-11).<sup>49</sup>

### Cerebrospinal Fluid

In keeping with PCA usually being underpinned by AD, CSF amyloid- $\beta$  ( $A\beta$ )<sub>1-42</sub> is depressed and concentrations of total tau and phosphorylated tau are increased. However, while levels of  $A\beta$ <sub>1-42</sub> depression are similar to other forms of AD, some evidence indicates that levels of total tau and phosphorylated tau are not





**FIGURE 3-8** Visual rating scale for the posterior brain regions. In sagittal, axial, and coronal orientation, this rating scale rates atrophy as follows: 0 = no atrophy, 1 = minimal atrophy, 2 = moderate atrophy, and 3 = severe atrophy.

PAR = parietal lobe; PCS = posterior cingulate sulcus; POS = parietooccipital sulcus; PRE = precuneus. Reprinted with permission from Koedam EL, et al, *Eur Radiol*.<sup>43</sup> © 2011 The Authors.

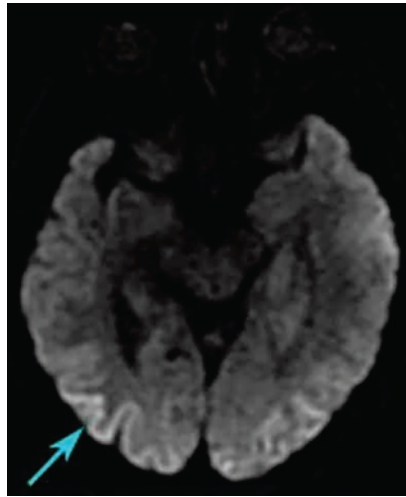
## KEY POINTS

- Fludeoxyglucose positron emission tomography may be extremely valuable in demonstrating hypometabolism within the parietooccipital cortices.
- While amyloid positron emission tomography has a role in confirming the presence or absence of amyloid pathology, it is not useful in distinguishing between Alzheimer disease syndromes.
- Tau positron emission tomography, which is currently only available in a research setting, often shows very striking posterior cortical deposition of tau pathology.
- Posterior cortical atrophy due to Alzheimer disease is a sporadic condition, and routine testing for the autosomal dominant forms of the disease is not usually indicated.

as elevated as in typical AD, perhaps relating to either different intensities or extent of neurodegeneration.<sup>50</sup> In practice, therefore, clinicians should be aware that tau to A $\beta_{1-42}$  ratios may be less elevated in PCA than in typical AD. As with other forms of AD, the total cell count and protein are not elevated; if these are seen, other diagnoses should be considered.

## Genetic Testing

PCA due to AD is a sporadic condition, and routine testing for the autosomal dominant forms of the disease is not usually indicated. Testing for *APOE* genotyping is not recommended as part of the diagnostic workup for any form of AD, and this is particularly the case for PCA, in which evidence indicates



**FIGURE 3-9**  
Cortical ribboning in Heidenhain variant of Creutzfeldt-Jakob disease. Axial diffusion-weighted 1.5T MRI shows right occipital lobe cortical ribboning (arrow) in a patient presenting with the Heidenhain phenotype, which can clinically resemble posterior cortical atrophy.

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that possession of an *APOE*  $\epsilon$ 4 allele may be less frequent than in typical cases.<sup>9</sup>

### DIAGNOSTIC CRITERIA

Original diagnostic criteria from Mendez and colleagues<sup>15</sup> and Tang-Wai and colleagues<sup>7</sup> have been recently updated with the 2017 international consortium criteria (TABLE 3-1).<sup>8</sup> These updated criteria describe a three-level classification. Level 1 describes the core clinical, cognitive, and neuroimaging features and exclusions, ie, the clinicoradiologic syndrome. Level 2 distinguishes between a PCA-pure syndrome and, allowing for individuals who also fulfill criteria for another neurodegenerative syndrome, a PCA-plus categorization. Level 3 classifies patients with PCA attributable to a specific underlying disease (eg, PCA due to AD, PCA due to Lewy bodies, PCA due to corticobasal degeneration, or PCA due to prion disease) based on the availability of biomarkers (or histopathologic assessment at autopsy) that can define the

underlying pathology. This classification aims also to be complementary to the diagnostic classifications for AD, which increasingly recognize PCA as an atypical form of AD,<sup>51,52</sup> providing a framework that can be adapted for different purposes. Thus, for providing appropriate support to individuals, the underlying pathology may be less relevant than the clinical picture, while for research studies aiming to determine the causes of phenotypic heterogeneity, it may be important to classify patients on the basis of both syndrome and pathology.

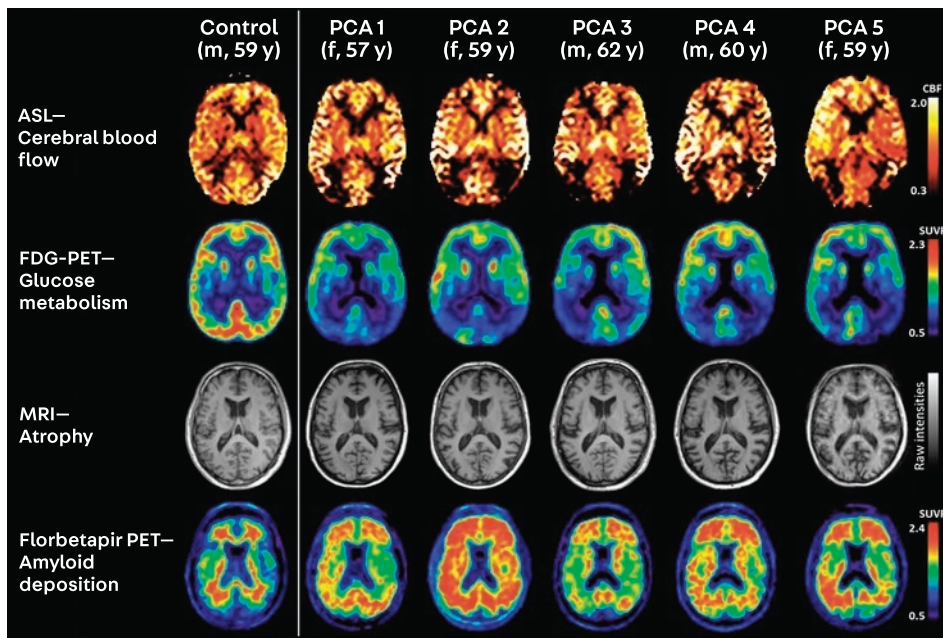
### MANAGEMENT

While much of the management of PCA is similar to that for typical AD, the dominant visual problems encountered by most patients mean that some specific issues require consideration.

#### Medical Treatment

Pharmacologic treatments for PCA should be directed to the underlying pathologic substrate. For most patients with PCA due to AD, treatment with acetylcholinesterase inhibitors or memantine, as would be standard treatment for AD, is appropriate. While pivotal clinical trials for the licensing of these drugs focused on typical amnesic AD, individual reports have shown that patients with PCA also benefit.<sup>53</sup>

Progressive visual impairment and increasing dependence emerging in the face of intact insight often results in significant anxiety, depression, and feelings of guilt.<sup>32</sup> While no controlled trials have been conducted, anecdotal evidence suggests that patients may benefit from counseling and other psychological



### KEY POINT

- For most patients with posterior cortical atrophy due to Alzheimer disease, treatment with acetylcholinesterase inhibitors or memantine, as would be standard treatment for Alzheimer disease, is appropriate.

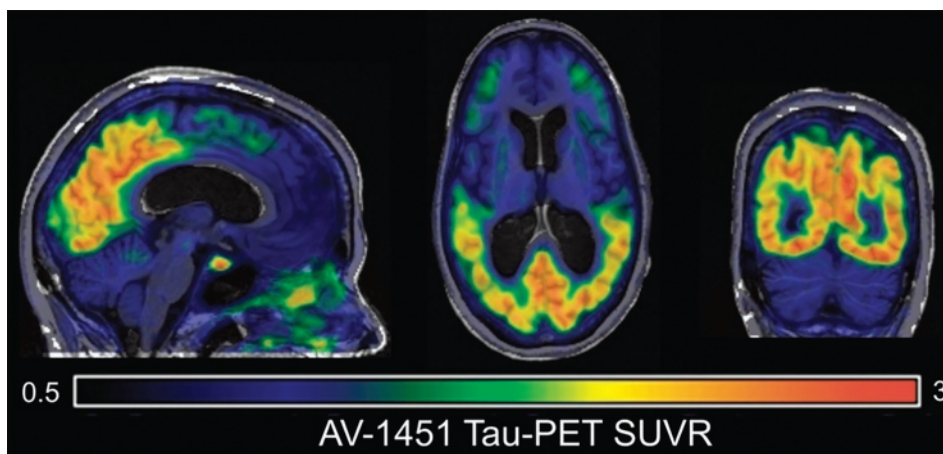
**FIGURE 3-10**

Multimodal imaging in posterior cortical atrophy (PCA). Single-participant axial images for one control participant and five patients with posterior cortical atrophy showing cerebral blood flow (CBF) (arterial spin labeling [ASL]), glucose metabolism (fludeoxyglucose positron emission tomography [FDG-PET]), atrophy (structural MRI), and amyloid deposition (florbetapir PET). Amyloid deposition varies between individuals but is distributed throughout the cortex in all. Cerebral blood flow, hypometabolism, and atrophy are, by contrast, all restricted to posterior cortical areas.

f = female; m = male; SUVR = standardized uptake value ratio.

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**FIGURE 3-11**

Tau imaging in posterior cortical atrophy. [<sup>18</sup>F]Flortaucipir positron emission tomography (PET) imaging reveals focal parietooccipital tau pathology.

SUVR = standardized uptake value ratio.



TABLE 3-1

**Core Features of the Posterior Cortical Atrophy Clinicoradiologic Syndrome<sup>a,b</sup>****Clinical Features**

- ◆ **Insidious onset**
- ◆ **Gradual progression**
- ◆ **Prominent early disturbance of visual with or without other posterior cognitive functions**

**Cognitive Features**

- ◆ **At least three of the following must be present as early or presenting features with or without evidence of their impact on activities of daily living**

- ◇ Space perception deficit
- ◇ Simultanagnosia
- ◇ Object perception deficit
- ◇ Constructional dyspraxia
- ◇ Environmental agnosia
- ◇ Oculomotor apraxia
- ◇ Dressing apraxia
- ◇ Optic ataxia
- ◇ Alexia
- ◇ Left/right disorientation
- ◇ Acalculia
- ◇ Limb apraxia (not limb-kinetic)
- ◇ Apperceptive prosopagnosia
- ◇ Agraphia
- ◇ Homonymous visual field defect
- ◇ Finger agnosia

- ◆ **All of the following must be evident**

- ◇ Relatively spared anterograde memory function
- ◇ Relatively spared speech and nonvisual language functions
- ◇ Relatively spared executive functions
- ◇ Relatively spared behavior and personality

**Neuroimaging**

- ◆ **Predominant occipitoparietal or occipitotemporal atrophy/hypometabolism/hypoperfusion on MRI/FDG-PET/SPECT**

**Exclusion Criteria**

- ◆ **Evidence of a brain tumor or other mass lesion sufficient to explain the symptom**
- ◆ **Evidence of significant vascular disease including focal stroke sufficient to explain the symptoms**
- ◆ **Evidence of afferent visual cause (eg, optic nerve, chiasm, or tract)**
- ◆ **Evidence of other identifiable causes for cognitive impairment (.g, renal failure)**

FDG-PET = fludeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography.

<sup>a</sup> Reprinted from Crutch, et al, *Alzheimers Dement*.<sup>8</sup> © 2017 The Authors.

<sup>b</sup> Clinical, cognitive, and neuroimaging features are rank ordered in terms of (decreasing) frequency at first assessment as rated by online survey participants.<sup>8</sup>

approaches and from standard pharmacologic treatments for mood and anxiety (eg, with selective serotonin reuptake inhibitors [SSRIs]). When **myoclonus emerges and becomes problematic, small doses of levetiracetam may be helpful.**

### Nonpharmacologic Treatments

In the absence of disease-modifying therapies, the mainstay of management of patients with PCA (as with typical AD) is the provision of practical and psychological support to affected patients and their caregivers. Even in the absence of specific therapies, an accurate diagnosis is a vital staging point in an individual patient's journey, not least as diagnosis is often delayed and symptoms overlooked, misinterpreted, or ignored for many years. Most patients will have stopped, or been stopped from, driving by the time a diagnosis is made, but determining whether patients with PCA are fit to drive is clearly of paramount importance.

The major functional problems in PCA involve everyday skills and self-care.<sup>54</sup> Loss of ability to read may be helped with the provision of audio books. Technologic advances such as voice recognition on smartphones, computers, and mobile devices can be invaluable in maintaining an individual's independence. Specific apps have been developed to help the reading problems in PCA, moving text into the individual's central vision at an appropriate speed and thus avoiding the need to make saccadic movements from word to word (refer to the Useful Websites section).<sup>35</sup> When out of the home, the provision of a white cane is a simple measure that ensures that others are aware of the patient's potential impairments. Within the house, measures to help with identification of objects and navigation (eg, by putting colored tape on doorframes) or labeling specific items may be helpful. As the disease progresses, home adaptations to minimize stair use and help with bathing and washing may be required. Involving a multidisciplinary team with occupational and physical therapy is often invaluable. Practical tips for patients with PCA and their families are summarized in **TABLE 3-2.**<sup>55</sup> The relative rarity of PCA can lead to isolation. The development of specific support groups for these individuals locally and, increasingly, nationally and internationally can provide a valuable source of support to individuals and their families (for more information, refer to the Useful Websites section).

### FUTURE DIRECTIONS

PCA has the potential to provide invaluable insights into the factors underpinning the development of AD generally and the factors influencing phenotypic diversity.<sup>56</sup> It is unknown, for example, why patients develop these symptoms on a sporadic basis and at a considerably younger age than patients with typical AD. The single biggest genetic study in AD confirmed that possession of an *APOE*  $\epsilon_4$  allele was a risk factor for PCA but conferred less risk than for typical AD. This study highlighted a number of genes that may potentially influence risk, some of which are implicated in neurodevelopment.<sup>9</sup> A 2018 study has also provided evidence that patients with PCA are more likely to report nonlanguage mathematical and visuospatial learning disabilities compared to patients with typical AD and controls.<sup>57</sup> From a pathologic perspective, emerging evidence shows different strains of A $\beta$  in PCA compared to typical AD, raising the suggestion that different forms of A $\beta$  may propagate through different brain networks and associate with different forms of the disease.<sup>58</sup> These findings, while in their infancy, may in time provide a more detailed understanding

### KEY POINTS

- The mainstay of management of patients with posterior cortical atrophy (as with typical Alzheimer disease) is the provision of practical and psychological support to affected patients and their caregivers.
- Most patients with posterior cortical atrophy will not be fit to drive. Establishing driving safety is of paramount importance.

TABLE 3-2

## Home Safety Tips and Recommendations for Patients With Posterior Cortical Atrophy and Other Dementias With Visual Dysfunction<sup>a</sup>

### General Environment

#### ◆ Simplify the environment

- ◇ Remove clutter and objects no longer in use; keep pathways clear
- ◇ Remove unsafe furniture and accents (eg, low-height stools, chairs, or tables)
- ◇ Options to decrease the potential falls risk from scatter rugs and doormats:
  - Remove unsafe scatter rugs/mats
  - Install nonslip underpadding
  - Replace with rugs/mats with a rubber backing
  - Secure all edges with double-sided carpet tape (not for outdoor use)
- ◇ Relocate and secure trailing cords that are in high-traffic areas
- ◇ Ensure adequate lighting: use night-lights, install extra light fixtures
- ◇ Leave lights on before nightfall
- ◇ Diffuse bright light areas; reduce glare by covering windows with blinds, shades, or sheer curtains to block direct bright sunlight; avoid using bare light bulbs without shades
- ◇ Obtain a door alarm and/or safety lock
- ◇ Place stickers on large glass windows or large glass doors to prevent people from bumping or walking into to them

#### ◆ Increase contrast

- ◇ Label room doors; use yellow paper with black writing
- ◇ Paint doorframes and light switch plates in a contrasting color to the wall
- ◇ Use a contrasting color dot to mark the number/button to release automatic door
- ◇ Use contrasting color strips (paint or tape) or tactile cue at top and bottom of stairs as well as on the edge of each individual step (both inside and outside)
- ◇ Use contrasting color adhesive strips to mark pathways to important areas: bathroom, kitchen, living room, laundry

### Kitchen

- ◆ **Mark burners and stove dials with contrasting color to make them easier to identify and to know when elements are hot**
- ◆ **Dials at the front of the stove are more desirable than dials at the back of the stove to avoid reaching over the elements**
- ◆ **Mark frequently used settings on the oven or other dials (eg, 350° or normal cycle for the dishwasher) with a bumper dot or contrasting tactile marker**
- ◆ **Supervise patients while they are using the stove, and, if necessary, disconnect the stove and other appliances when they are home alone**
- ◆ **Mark the 1-minute button on the microwave with a contrasting color bumper dot, tactile marker, bright tape, or nail polish**
- ◆ **Place cleaning supplies away from food supplies (very important)**
- ◆ **Dispose of hazardous substances that are no longer needed and store other potentially hazardous substances in secured storage (locked cupboard, childproof door locks)**

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- ◆ **Keep cupboard doors and drawers closed at all times and ensure everything is put away in its proper place**
- ◆ **Problem-solve an appropriate organizational structure to the kitchen; consider having one designated area of counter space for preferred and usual foods; trial placing frequently used items on a contrasting mat or tray located in the same place every day to increase independence in finding items and participating in meal preparation**
- ◆ **Store/relocate frequently used items at accessible and visible level**
- ◆ **Keep counters clear and minimize clutter**
- ◆ **Consider using appliances with automatic shutoff (eg, kettle)**
- ◆ **Use other items to optimize safety, independence, and participation in the kitchen:**
  - ◇ Elbow-length oven mitts to ensure maximum protection
  - ◇ Knife guard aid to enable safe use and pressure when cutting
  - ◇ Cutting board with a black side and a white side to enhance contrast while cutting
  - ◇ Gooseneck lamp above the cutting area may also assist with vision
  - ◇ Large-print timer
  - ◇ Liquid measure tool to assist in pouring liquids and avoiding spills
  - ◇ Relabel jars and canned goods using a thick black marker, white recipe card, single words, and elastic bands
  - ◇ Audio labeler

### Eating

- ◆ **Use brightly colored contrasting dishes and ensure they are all one solid color (no patterns and no ridged edges)**
- ◆ **Use a dark solid-color placemat if using light-colored plates and use a light solid-color placemat if using dark plates**
- ◆ **Light-colored food will be easier to see on a solid dark-colored dish and dark food on a light dish**
- ◆ **Avoid patterned tablecloths**
- ◆ **Maintain a strict pattern for mealtime setup (eg, always place the same utensils, drinking glass, and condiments in the same place for every meal)**
- ◆ **Avoid cluttering the eating area and only have necessary items within reach**
- ◆ **Use verbal directions as reminders of where items are located (eg, “your glass is on your right” and “salt and pepper are on your left”)**
- ◆ **Use plate guards during mealtimes**

### Bedroom

- ◆ **Use bright, contrasting-color fitted sheet, top sheet, pillowcases. Each should be a different color to optimize identification and orientation to and within the bed**
- ◆ **Place a brightly colored mat on nightstand to contrast with items placed on it**

CONTINUED FROM PAGE 69

### Dressing

- ◆ Label drawers and shelves with high-contrast wording or pictures
- ◆ Remove clothes that are no longer being used, including permanent removal of clothes no longer worn and temporary storage of out-of-season clothing
- ◆ Simplify and organize arrangement of clothing (eg, group similar items together, one drawer for shirts and another drawer for pants)
- ◆ Lay out clothing for the day
- ◆ Minimize clothing requiring buttons and zippers and replace with elastic waists, pull-over/on, and loose clothing
- ◆ Pin socks together when placing them in the laundry so they will stay matched

### Bathroom

- ◆ Reduce clutter on bathroom floor, countertop, in drawers and cabinets.
- ◆ Use high-contrast nonslip bath mat and install high-contrast grab bars in the shower or bathtub; use contrasting tactile strip on existing grab bars to differentiate from tub or towel bar
- ◆ Pick up bath mat after each use and store appropriately to prevent falls
- ◆ If difficulty in accurately locating the toilet is noted, consider obtaining a toilet seat in a contrasting bright color; also consider obtaining a raised toilet seat with arms and then taping arms with a bright color that contrasts with the toilet seat
- ◆ Tape toilet-flushing handle in a contrasting bright color
- ◆ Label important areas in the bathroom: toilet, sink, bathroom door (yellow paper with black writing).
- ◆ Tape sink faucet handles with brightly colored tape (use color such as red, green, blue) to distinguish handle from the rest of the sink
- ◆ Keep soap in a bright container (eg, red) with contrasting color soap (eg, white)
- ◆ Use sign as reminder to wash hands, flush toilet, brush teeth
- ◆ Keep frequently used items (toothbrush, toothpaste) in small shallow basket or on a mat to contrast items against the counter
- ◆ Use toothpaste that contrasts in color to the toothbrush and bristles (eg, red toothpaste on white brush and bristles)
- ◆ Cover mirrors if necessary; often people with vision problems may not be able to recognize the item as a mirror

### Personal Care

- ◆ Ensure nail care is done by a professional; can be provided in-home
- ◆ Ensure appropriate footwear is used: flat, nonslip sole, enclosed toe and heel, Velcro fasteners

CONTINUED ON PAGE 71

### Medication Routine

- ◆ Supervision of medication routine is usually recommended
- ◆ Store medications in a secure place
- ◆ Remove and properly dispose of medications that are no longer needed or have expired
- ◆ Inquire whether the medication routine can be simplified (eg, to once a day instead of 3 times a day)
- ◆ Other ways to simplify a medication routine: prefilled blister packs, dosette; list of current medications, medication schedule, medication alarms/reminders

### Stairs

- ◆ Ensure adequate lighting on the stairs, with switches at both the top and bottom
- ◆ Install secure railings on one or both sides
- ◆ Install railing extensions beyond the top and bottom of the stairs
- ◆ Remove or replace unsafe flooring with a nonslip surface
- ◆ Contrasting-color tape or paint on the edge of each step
- ◆ Contrasting-color tape or paint and/or tactile strip at the top and bottom of the stairs
- ◆ With progression:
  - ◇ Safety gate to prevent use of stairs
  - ◇ Arrange living area on one level

### Communication and Scheduling

- ◆ Use a phone with large print and high-contrast numbers as well as one-touch programmable numbers
- ◆ Program emergency and frequently used numbers to the one-touch programmable numbers and add tactile markers to increase ease of identification
- ◆ Set up a “memory center,” with the phone, keys, note pad, whiteboard with large writing area, and black marker
- ◆ Include a paper, pen/pencil, and task lamp beside the phone for messages
- ◆ Place telephone on a bright contrasting-color mat
- ◆ Use contrasting-color tape to outline the phone cradle
- ◆ If possible, utilize a service that requires voice activation for phone dialing
- ◆ Use talking watches or clocks to indicate the time and appointments

<sup>a</sup> Reprinted with permission from Lake A, et al, UHN Multidisciplinary Memory Clinic, University of Toronto.<sup>55</sup>



of the mechanisms underlying the development of both PCA and typical AD and lead to the development of new and more specific treatments of these conditions.

## CONCLUSION

PCA is a rare but important neurodegeneration syndrome typically underpinned by AD. Patients with this condition are often diagnosed late or are misdiagnosed as having a primary ocular or psychologically mediated illness. Recognition of PCA as a distinct syndrome and determination of its underlying cause allow for appropriate nonpharmacologic and pharmacologic treatments to be instigated and for appropriate support to be provided for patients and families. PCA provides a valuable paradigm for exploring the causes of phenotypic heterogeneity in AD.

## ACKNOWLEDGMENT

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## VIDEO LEGEND

### VIDEO 3-1

**Visual disorientation in posterior cortical atrophy.** A 77-year-old man with posterior cortical atrophy. The patient is asked to fixate on the examiner's face and to reach out and take the examiner's moving hand. The patient is able to see the moving hand (which he imitates) but has major difficulties in locating it in space. [links.lww.com/CONT/A266](https://www.links.lww.com/CONT/A266)

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## USEFUL WEBSITES

### POSTERIOR CORTICAL ATROPHY SUPPORT USA

Posterior Cortical Atrophy Support USA is a website run by caregivers for and supporters of patients with posterior cortical atrophy. [pinterest.co.uk/pcasupportusa/](https://pinterest.co.uk/pcasupportusa/)

### RARE DEMENTIA SUPPORT

Rare Dementia Support is a UK website that provides a rich support of information for patients with posterior cortical atrophy and their caregivers. [raredementiasupport.org/pca](https://raredementiasupport.org/pca)

### READ-CLEAR

Read-Clear is an app designed to help reading in patients with posterior cortical atrophy and related disorders. [readclear.co.uk](https://readclear.co.uk)

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## DISCLOSURE

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