Title: Can patients without early, prominent visual deficits still be diagnosed of Posterior Cortical Atrophy?

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Background: Early and progressive disabling visual impairment is a core feature for the diagnosis of posterior cortical atrophy (PCA). However, some individuals that fulfil criteria over time might initially present with an onset of prominent posterior dysfunction other than visuoperceptual. **Methods:** The clinical profile of five patients with a predominantly 'non-visual' posterior presentation (PCA2) was investigated and compared with sixteen individuals with visually predominant PCA (PCA1) and eighteen with typical amnestic Alzheimer disease (tAD). **Results:** PCA2 patients showed significantly better performance than PCA1 in one visuospatial task and were free of Balint's syndrome and visual agnosia. Compared to tAD, PCA2 showed trends towards significantly lower performance in visuoperceptual tasks, more severe apraxia and more symptoms of Gerstmann's syndrome. **Conclusions:** Our sample of PCA2 patients did not present with clinically prominent visual symptoms but did show visual dysfunction on formal neuropsychological assessment (less pronounced than in PCA1 but more than in tAD) in addition to other posterior deficits. Broadening the definition of PCA to encompass individuals presenting with prominent 'non-visual' posterior dysfunction should be potentially considered in clinical and research contexts.

1. Introduction

Posterior cortical atrophy (PCA) [1] is characterised by early, prominent and progressive impairment of visual function and other posterior cortical functions in the context of relatively preserved memory and insight and a pattern of atrophy involving the parietal, occipital and posterior temporal lobes [2, 3, 4, 1, 5]. The most common pathology in PCA is Alzheimer's disease, and it is now recognized in Alzheimer's disease diagnostic and research criteria as the most common atypical Alzheimer's disease phenotype [6, 7]. In a small number of cases the syndrome can also be caused by Lewy body disease and corticobasal degeneration [1, 8, 9].

PCA is a relatively heterogeneous syndrome, [10]. The most commonly described PCA presentation is parieto-occipital [1, 11, 12] and roughly comparable to what it has been called 'biparietal AD' [13, 14, 15, 16]. The new IWG criteria [7] contrast this biparietal subtype of PCA, characterised primarily by visuospatial deficits (e.g simultagnosia) with an occipito-temporal subtype, characterised by visuoperceptual deficits (e.g. failing to recognise objects). Both variants share in common the presence of early visual impairment as a core feature for the diagnosis.

Some patients with posterior presentations of AD may develop posterior features others than vision like apraxia, agraphia, acalculia and difficulties in navigation. Although visual symptoms may develop over time, the initial presentation in these individuals is dominated by other posterior features [17, 16]. Strictly speaking, some of these patients do not meet criteria for PCA due to the lack of prominent visual complaints (Mendez et al., 2012 [17] criteria require 'presentation with visual complaints with intact primary visual functions'; while Tang-Wai et al., 2004 [1] criteria require 'presentation of visual complaints in the absence of significant primary ocular disease explaining the symptoms'). However, comprehensive neuropsychological testing of patients presenting with posterior non-visual complaints may uncovers evidence of impairments in visual cognition. These individuals are the focus of the current study.

Here we compare the clinical features of a sample of patients with a 'non-visual' posterior presentation AD (PCA2) with a group of patients with visually-predominant PCA (PCA1) and a group of individuals with typical amnestic AD (tAD). We hypothesized that detailed investigation of the PCA2 patients would yield evidence of cortical visual impairment sufficient to justify their potential classification as PCA, whilst also exhibiting groupwise differences in cognitive profile compared with patients with PCA1 and tAD.

2. Methods

2.1. Participants

Participants were recruited at the Memory Disorders Unit of the Hospital Virgen del Rocio and consisted of 16 patients diagnosed with PCA (classical visually-predominant PCA, labelled PCA1), 18 typical amnestic AD (tAD) and 5 with a predominantly 'non-visual' posterior presentation AD (labelled PCA2). Inclusion criteria required that AD patients met diagnosis criteria for probable AD [6], and PCA patients met Tang-Wai et al. criteria for PCA [1]. The 5 patients with PCA2 presented with a history of insidious onset and progression of bilateral apraxia/constructive apraxia/dysgraphia, dyscalculia, anomia and navigation difficulties to variable degrees (see Figure 1 for a case example and Supplementary Material for a brief description of the five participants), which were confirmed during the clinical interview and neurological examination. Most of them reported environmental disorientation, which might be interpreted as a visuospatial function, but none of the cases had this as the most prominent symptom or main cause of restriction of independence in daily activities. According to the current diagnostic criteria for AD [6], these PCA2 patients might be classified as a non-amnestic presentation AD. Within the non-amnestic forms, given their navigation difficulties and constructive apraxia, they might be classified as the visuospatial presentation of AD. However, they do not meet the current criteria for PCA, as they do not present with visual complaints, which is a core feature for the diagnosis. For example, a typical case study reported by Crutch [5] shows a 62-year-old woman "Her first symptom was difficulty seeing when driving at night. In the following years she frequently dented her car when parking, tended to bump into doors … and had trouble locating items even when they were directly in front of her". Our case example in Figure 1 shows the clinical picture of one of our patients in the PCA2 group and represents an example of how our five PCA2 participants differ from the visually predominant (PCA1) presentation.

Participants were diagnosed and reviewed once or twice per year enabling the authors to gather further supportive evidence regarding the diagnosis over time. The study was approved by the Virgen del Rocío Hospital Ethics Committee and conducted according to the Principles of Helsinki Declaration.

2.2. Cognitive testing

A comprehensive cognitive assessment was performed with all participants by the same neuropsychologist (ASG) including evaluation of memory, executive function, reading, writing, praxis, object and space perception and elements of Balint's and Gerstmann's syndromes. The formal testing consisted of nineteen tasks including: Mini Mental State Examination (MMSE) [18], attention, executive functions and working memory [19], episodic memory [20] and object naming [21], for which a verbal description of each item was provided to avoid bias due to visual impairment. The posterior function assessment included tests of spoken and written word comprehension, copy and dictation, upper limb ideomotor and ideational praxis [19], and early visual, visuoperceptual and visuospatial processing (Visual Object and Space Perception [VOSP] battery) [22]. The assessment of Balint´s and Gerstmann´s syndromes and other posterior features involved tests of simultanagnosia (description of the Cookie Theft picture) [21], ocular apraxia (following a moving target with the eyes) [23], optic ataxia (reach a moving target with the right hand in the four visual quadrants) [24], acalculia (subtraction, addition, writing and reading numbers), agraphia (as above), left-right disorientation (pointing to 10 body parts on own/examiner´s body) [19], finger agnosia (finger identification to visual and verbal command), alexia (reading single words and short sentences), constructional praxis (MMSE pentagons and cube copying), and patient and carer ratings of spatial disorientation and dressing apraxia.

2.3. Neuroimaging data

All patients underwent neuroimaging assessments (CT or MRI) but only 30 MRIs were available for visual assessment. MRI were evaluated using the Scheltens scale for medial temporal lobe atrophy (MTA; range 0-4) [25] and Koedam scale for posterior atrophy (PA; range 0-3) [26]. The rater was blinded to the clinical diagnosis and clinical data and the MTA and PA were rated once.

2.4. Genetic analysis

DNA was extracted from blood samples collected from patients and APOE genotype was determined using the polymerase chain reaction (PCR) amplification method modified by Wenham [27].

2.5. Statistical analysis

Pairwise comparisons were performed using unmatched t-tests or Mann-Whitney U tests for quantitative variables and Fisher´s exact or Chi square tests for qualitative variables.

3. Results

3.1. Demographics and cognitive data

Demographic and clinical characteristics of the sample are summarized in Table 1. There were no significant differences between subgroups in age, disease duration or MMSE. Performance on formal neuropsychological tests and pairwise comparisons between the PCA1, PCA2 and tAD groups are shown in Table 2 and Table 3. No differences were found between PCA2 and the other two groups in attention, executive function, working memory, verbal memory and language. Compared with patients with visually-predominant PCA (PCA1), PCA2 patients were significantly less impaired on VOSP Number location (visuospatial processing) (p = .03). However there was no evidence of PCA2 patients performing significantly worse than PCA1 patients on any of the cognitive tasks administered. Compared with tAD patients, PCA2 patients demonstrated a significantly greater impairment in praxis, as measured by symbolic, object use ideomotor praxis and ideational praxis subtests (p = .03, p = 0.005 and p = .006, respectively). These significant differences in praxis performance were not observed between PCA1 and PCA2. Table 3 also displays the number of patients performing under percentile 5 in the visuospatial/perceptual tests. All the patients in PCA1 and PCA2 groups failed at least one test of visual function, while this proportion was half in the tAD group.

The frequency and pairwise comparisons of posterior symptoms in each group are shown in Table 4. With regard to the features of Gerstmann´s syndrome (typically associated with left parietal lesions), PCA2 patients showed the highest frequency of finger agnosia (20%) and the second highest behind the PCA1 group of acalculia, agraphia, left-right disorientation and

alexia. By contrast, PCA1 patients frequently showed features of Balint´s syndrome (typically associated with bilateral occipitoparietal lesions), namely simultanagnosia (50%), ocular apraxia (31%) and optic ataxia (6%) whilst these features were not detected in any of the patients with PCA2. None of the PCA2 participants showed visual agnosia whilst it was present in 33% of the PCA1 group.

3.2. Neuroimaging

MRI scans were available for 30 of the 39 individuals that constituted the sample. No significant differences were found in MTA or PA across groups (see Table 1).

3.3. Genetics

APOE genotype was available for 34 individuals. Within tAD group, 21% of the patients were ε4 homozygotes, whereas none of the PCA1 or PCA2 patients had more than one ε4 allele (see Table 1).

4. Discussion

In this study, 5 individuals with a predominantly 'non-visual' posterior cortical impairment (PCA2) were compared with 16 individuals with visually-predominant PCA (PCA1) and 18 typical amnestic AD (tAD). Patients with PCA2 showed significantly worse performances in praxis and a higher proportion of Gerstmann's syndrome symptoms than the tAD group. Consistent with their predominantly 'non-visual' presentation, none of the PCA2 patients assessed showed any of the symptoms of Balint's syndrome or visual agnosia, and they were significantly better than PCA1 patients on one of the tests of visuospatial processing (VOSP Number location). However, despite the absence of significant visual impairment at presentation, 100% of the patients in the PCA2 group failed at least 1 test of visual processing. We also found a high degree of overlap between PCA2 and the two other syndromes, as demonstrated by the absence of inter-group differences in attention, working memory, verbal memory and language.

In the present study patients with PCA2 showed considerable variability in the praxis scores. This variability is mainly driven by participant P23. Interestingly, this is the highest educated individual in the PCA2 sample (see Supplementary Material) and although there are no differences between P23 and the rest of PCA2 in terms of reported disease duration, P23

performs better in most of the cognitive tasks. His high education level might have a protective effect that explains these differences. It is also possible that because his occupation was highly demanding in terms of visuospatial and calculation skills he had noticed the symptoms earlier than the rest of the participants (who were exposed to less demanding environments) and therefore having been seen in clinic at an earlier stage. Regarding the pairwise comparison of cognitive scores between PCA2 and PCA1, significant differences were found only in one test of visuospatial processing. One possibility to explain why no more significant differences were found between groups is that the tests used might lack sensitivity to capture degrees of impairment (i.e. not graded in difficulty). Additionally, the size of the PCA2 sample was small, and the PCA samples consisted of individuals at different stages of the disease (range of MMSE between 9 and 23) with the consequent variability.

Similar clinical presentations to those reported for the PCA2 have been described previously in the literature. For instance, Green et al. [13] reports a patient with slowly progressive apraxia, alien hand syndrome and AD pathology. Ross et al. [28] described four patients with a history of early visuospatial problems, agraphia of a predominantly peripheral type and difficulty with bimanual tasks. Neuroimaging in this patient disclosed bilateral parietal lobe atrophy and authors discussed the existence of two main clinical syndromes with features reflecting involvement of the occipitotemporal and biparietal cortical areas respectively. Aharon et al. [3] described 2 patients presenting with symptoms suggestive of PCA and 2 more presenting with apraxia as the initial manifestation and also impairment of functions related to the dominant parietal lobe. In this study the authors suggested that PCA represents two clinically related behavioural phenotypes, one characterised by visuospatial disturbances and the other one by apraxia. Four years later Galton et al. [15] presented two patients with progressive biparietal syndrome and pathologically proven AD. Both individuals presented with moderate memory impairment but the dominant symptoms were apraxia, dysgraphia and visual disorientation in one case and simultanagnosia in the other. Mendez et al. [17] also described, in a retrospective series, a group of patients with prominent limb apraxia who met diagnostic criteria for AD. Characteristically these patients presented with dysgraphia and limb apraxia, and acalculia was a common feature. Marques et al. [16] also reported a case of a young patient with progressive limb apraxia and choreiform movements, severe impairment in visuoconstructive abilities, dyscalculia, β-amyloid reduction and tau increase in CSF. The studies above show historical evidence of patients with probable or definite AD presenting

with early and prominent involvement of parietal functions and a lesser degree of visuoperceptual impairment. In this context, a possible explanation to the milder visual impairment showed by our PCA2 group might be that the involvement of the occipital lobe occurs later in the course of the disease compared to PCA1. Although damage to the parietal lobe is sufficient to produce visuospatial impairment (e.g. poor performance on judgment of line orientation tasks), other visual symptoms usually result from lesions extending to the occipital regions (e.g. simultanagnosia). It is therefore possible that late involvement of these regions might explain the later decline of these functions in the PCA2 group.

For all groups in our sample, the mean MTA ratings were indicative of mild atrophy and the mean PA ratings indicated moderate atrophy. This pattern has been reported in patients with young onset AD [29] and therefore expected to be found in our amnestic AD sample, for which the mean age was 60 years. However no differences were found across groups. PCA1 and PCA2 tend to be ε4 negative [30, 31, 32]. In our sample, ε4/ε4 homozygocity was present only in individuals with tAD, similar to previous studies [31, 32]. However, it is notable that the percentage of individuals with at least one ε4 allele was as high in the PCA1 and PCA2 as in the tAD. This may be due to the small size of the PCA groups, not accurately representing the actual distribution of ε4 in this population. It might also be that our individuals with PCA2 may represent a point in the early-onset AD phenotypic spectrum on the boundaries between amnestic (ε4+) and atypical non-amnestic presentations (ε4-), as it has been reported that different clinical presentations of AD reflect variability along a neuroanatomical continuum [33, 29].

This study is not without limitations. First, the small size of the PCA2 group reduces the power of the analysis. Second, differences in both cognitive and anatomical profiles are easier to capture in early stages of the disease but some patients were at moderate stages at the time of assessment, which might have hindered the detection of significant discrepancies both in the cognitive and radiological profile. Lastly, the lack of pathological studies in the present sample makes impossible to exclude the presence of non-AD pathologies contributing to the clinical picture.

In summary, our ‘non-visual’ PCA sample represents a minority of patients with predominantly posterior AD that do not fulfil the current clinical diagnostic criteria for PCA given the absence of prominent visual deficits at the onset of the disease. Impairments of

visuoperceptual and visuospatial processing were less pronounced in 'non-visual' PCA than in visual PCA; however a certain degree of visual dysfunction was confirmed on formal neuropsychological examination along with other markedly impaired posterior functions. The umbrella of the term PCA should allow flexibility to potentially consider patients with predominant posterior dysfunction without prominent visual symptoms in clinical and research contexts.

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Table 1. Demographics, clinical characteristics, visual ratings of medial temporal lobe and posterior atrophy and APOE genotypes of all patients

				Pairwise comparison[†]	
Patient group	tAD	PCA1	PCA2	PCA2 vs PCA1	PCA2 vs tAD
N	18	16	5		
Symptom onset	Memory	Vision	Posterior non-vision		
Gender (%female)	11 (61%)	9 (56%)	3 (60%)	0.64[*]	1.00[*]
Disease duration	4.4 ±2.5	4.2±2.9	3.6±1.3	0.86	0.70
Age at assessment	60.1±4.8	63.1±5.3	62±5.9	0.70[‡]	0.54[‡]
MMSE	18±4.8 (11-28)	15±3.5 (10-21)	18±5.8 (9-23)	0.25[‡]	0.78[‡]
MTA[§]	0.8±0.9 1 (0-3)	1.1±0.9 1 (0-4)	1.5±1.0 1 (0-3)	0.74	0.20
PA[§]	2.0±1.0 2 (0.3)	2.3±0.7 2 (1-3)	2.3±0.8 2.5 (1-3)	0.95	0.52
APOE ε2/ε3 (%)[¶]	2 (14%)				
APOE ε3/ε3 (%)	4 (28%)	9 (60%)	2 (40%)	0.63[*]	0.58[*]
APOE ε4/ε3 (%)	5 (35%)	6 (40%)	3 (60%)	0.59[*]	0.31[*]
APOE ε4/ε4 (%)	3 (21%)				

Data presented as N (%), median (range) or mean (SD). Abbreviations: MTA, medial temporal atrophy visual rating scale; PA, posterior atrophy visual rating scale.

[†] Mann-Whitney U test (except indicated)
[*] Fisher exact test.
[‡] Unpaired t-test.
[§] MR available for 30 individuals: 9 tAD, 16 PCA1, 5 PCA2.
[¶] APOE available for 34 individuals: 14 tAD, 15 PCA1, 5 PCA2.

Table 2. Background neuropsychological data: mean±SD and significance of pairwise comparison between groups

				Pairwise comparison	
Patient groups	tAD	PCA1	PCA2	PCA2 vs PCA1	PCA2 vs tAD
N	18	16	5	$p^{\dagger}$	$p^{\dagger}$
Verbal Fluency					
Phonemic	10.6±12.1	8.8±7.6	16.8±11.0	*0.08*‡	0.29
Semantic	8.4±4.9	5.1±3.9	3.4±3.3	0.39‡	**0.04**‡
Digit forward	4.0±1.2	3.3±1.1	4.2±1.0	0.16	0.76
Digit backward	2.2±1.2	1.0±1.1	1.8±1.7	0.32	0.66
WL immediate	9.3±7.5	6.5±6.3	10.6±7.4	0.20	0.60
WL delayed	0.5±1.2	0.1±0.7	0.8±1.7	0.33	0.82
Brief BNT	11.6±3.0	9.0±3.7	9.6±4.1	0.67	0.24
Praxis					
Imitation	6.7±2.2	3.3±3.1	4±3.7	0.71‡	*0.08*
Symbolic	9.8±0.4	9.3±1.7	6±5.4	0.11	**0.03**
Object use	8.5±2.9§	4.8±4.2	2±4.4	0.15	**0.005**
Ideational	2§	1.6±0.8	1.3±1.0	0.34	**0.006**

Bold means statistically significant. Italics means trends towards significance. WL: Word List (Wechsler et al., 1987); BNT: Boston Naming Test (Goodglass et al., 2000).

†Mann-Whitney U test (except indicated).

‡ unpaired t-test.

§ n=14

Table 3. Performances in VOSP subtests, number of patients scoring under 5%ile pairwise and comparison between groups

							Pairwise comparison	
Patient groups	tAD		PCA1		PCA2		PCA2 vs PCA1	PCA2 vs tAD
N	18	n (%) under 5%ile	16	n (%) under 5%ile	5	n (%) under 5%ile	$p^{\dagger}$	$p^{\dagger}$
Screening (Figure-ground discrimination)	18.5±2.4	10 (45%)	13.4±6.4	10 (62%)	14.8±5.4	4 (80%)	0.70	*0.06*
Incomplete letters	12.2±6.7	11 (61%)	3.8±5.8	14 (88%)	7.0±6.9	4 (80%)	0.18	0.13‡
Silhouettes	12.0±6.4	6 (27%)	7.5±5.8	15 (93%)	7.6±7.9	4 (80%)	0.97‡	0.20‡
Dot counting	7.2±3.6	2 (11%)	5.0±3.7	10 (62%)	6.8±4.3	2 (40%)	0.31	0.90
Position discrimination	14.3±5.9	8 (44%)	10.1±5.3	13 (81%)	9.8±5.1	4 (80%)	0.77‡	*0.06*
Number location	5.1±4.1	8 (44%)	1.0±1.3	16 (100%)	3.6±4.1	3 (60%)	**0.03**‡	0.44
Cube analysis	5.8±3.8	10 (45%)	1.0±1.3	16 (100%)	3.6±4.5	3 (60%)	0.32	0.27‡
% of patients failing at least 1 visual test		10 (55%)		16 (100%)		5 (100%)		

Performances expressed in mean ± SD. Bold means statistically significant. Italics means trends towards significance.

†Mann-Whitney U test (except indicated).

‡ unpaired t-test.

Table 4. Frequency of posterior symptoms and pairwise comparison in each group

				Pairwise comparison	
Patient group	tAD	PCA1	PCA2	PCA2 vs PCA1	PCA2 vs tAD
N	18	16	5	p^*	p^*
Ocular apraxia	1 (5%)	5 (31%)	0	0.21	0.78
Optic ataxia	0	1 (6%)	0	0.76	-
Simultagnosia	1 (5%)	8 (50%)	0	*0.06*	0.78
Acalculia	5 (27%)	11 (68%)	3 (60%)	0.55	0.26
Agraphia	2 (11%)	12 (75%)	1 (20%)	**0.04**	0.57
Left-Right disorientation	3 (16%)	8 (50%)	2 (40%)	0.55	0.49
Finger agnosia	0	3 (18%)	1 (20%)	0.71	0.21
Alexia	3 (16%)	9 (56%)	2 (40%)	0.45	0.33
Spatial disorientation	7 (38%)	13 (81%)	1 (20%)	**0.02**	0.41
Dressing apraxia	5 (27%)	9 (56%)	2 (40%)	0.45	0.49
Constructive apraxia	12 (66%)	14 (87%)	3 (60%)	0.22	0.58
Visual agnosia	1 (5%)	6 (33%)	0	0.14	0.78

* Fisher exact test.

Patients with PCA2 show the second highest percentage (after PCA1) of individuals showing acalculia, alexia, dressing apraxia and visuospatial difficulties at the assessment time. However, they do not show any of the components of Balint syndrome or visual agnosia.

Figure captions

Figure 1. Illustrative case of a PCA2 patient. Magnetic resonance T1-weighted images showing pronounced atrophy of the posterior cortices (L>R) with moderate hippocampal involvement. R = right.