Demographic, clinical, biomarker, and neuropathological correlates of posterior cortical atrophy: an international cohort study and individual participant data meta-analysis

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See **Comment** page 127

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Summary

Background Posterior cortical atrophy is a rare syndrome characterised by early, prominent, and progressive impairment in visuoperceptual and visuospatial processing. The disorder has been associated with underlying neuropathological features of Alzheimer's disease, but large-scale biomarker and neuropathological studies are scarce. We aimed to describe demographic, clinical, biomarker, and neuropathological correlates of posterior cortical atrophy in a large international cohort.

Methods We searched PubMed between database inception and Aug 1, 2021, for all published research studies on posterior cortical atrophy and related terms. We identified research centres from these studies and requested deidentified, individual participant data (published and unpublished) that had been obtained at the first diagnostic visit from the corresponding authors of the studies or heads of the research centres. Inclusion criteria were a clinical diagnosis of posterior cortical atrophy as defined by the local centre and availability of Alzheimer's disease biomarkers (PET or CSF), or a diagnosis made at autopsy. Not all individuals with posterior cortical atrophy fulfilled consensus criteria, being diagnosed using centre-specific procedures or before development of consensus criteria. We obtained demographic, clinical, biofluid, neuroimaging, and neuropathological data. Mean values for continuous variables were combined using the inverse variance meta-analysis method; only research centres with more than one participant for a variable were included. Pooled proportions were calculated for binary variables using a restricted maximum likelihood model. Heterogeneity was quantified using I^2.

Findings We identified 55 research centres from 1353 papers, with 29 centres responding to our request. An additional seven centres were recruited by advertising via the Alzheimer's Association. We obtained data for 1092 individuals who were evaluated at 36 research centres in 16 countries, the other sites having not responded to our initial invitation to participate to the study. Mean age at symptom onset was 59·4 years (95% CI 58·9–59·8; I^2=77%), 60% (56–64; I^2=35%) were women, and 80% (72–89; I^2=98%) presented with posterior cortical atrophy pure syndrome. Amyloid β in CSF (536 participants from 28 centres) was positive in 81% (95% CI 75–87; I^2=78%), whereas phosphorylated tau in CSF (503 participants from 29 centres) was positive in 65% (56–75; I^2=87%). Amyloid-PET (299 participants from 24 centres) was positive in 94% (95% CI 90–97; I^2=15%), whereas tau-PET (170 participants from 13 centres) was positive in 97% (93–100; I^2=12%). At autopsy (145 participants from 13 centres), the most frequent neuropathological diagnosis was Alzheimer's disease (94%, 95% CI 90–97; I^2=0%), with common co-pathologies of cerebral amyloid angiopathy (71%, 54–88; I^2=89%), Lewy body disease (44%, 25–62; I^2=77%), and cerebrovascular injury (42%, 24–60; I^2=88%).

Interpretation These data indicate that posterior cortical atrophy typically presents as a pure, young-onset dementia syndrome that is highly specific for underlying Alzheimer's disease pathology. Further work is needed to understand what drives cognitive vulnerability and progression rates by investigating the contribution of sex, genetics, premorbid cognitive strengths and weaknesses, and brain network integrity.

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Introduction

Posterior cortical atrophy is a clinically defined syndrome characterised by early, prominent, and progressive impairment of visuoperceptual or visuospatial processing due to cumulative atrophy of the parietal, posterior temporal, and occipital brain regions. The Crutch 2017 consensus criteria for posterior cortical atrophy[1] describe the core clinical, cognitive, and neuroimaging features of the syndrome and define two types: posterior cortical atrophy pure, which captures the core clinical and

Panel: Research in context

Evidence before this study

We searched PubMed from database inception to Aug 1, 2021, with the terms "posterior cortical atrophy", "posterior cortical atrophy pathology", "posterior cortical atrophy Alzheimer's disease", "visual variant of Alzheimer's disease", "atypical Alzheimer's disease", and "non-amnestic Alzheimer's disease", with no language restrictions, focusing on studies that reported neuropathological findings. A few studies have investigated the neuropathological profiles of people with posterior cortical atrophy and have shown a high prevalence of Alzheimer's disease pathology, with some case series reporting Lewy body pathology, corticobasal degeneration, and prion disease. However, these studies had small sample sizes (20–40 participants).

Added value of this study

This study is—to our knowledge—the first to systematically analyse and report clinical, biomarker, and neuropathological data from a large sample of people with posterior cortical atrophy from multiple research centres around the world. By analysing individual participant data, this study has refined our understanding of the relationship between pathology, biomarkers, and clinical features in posterior cortical atrophy. Our findings highlight the early age-of-onset and female predominance of this syndrome. We have shown that Alzheimer's disease pathological findings are highly prevalent, and that posterior cortical atrophy could be the most predictive syndrome for Alzheimer's disease neuropathological features. We have also shown that co-pathologies are frequent.

Implications of all the available evidence

Our international cohort study provides up-to-date demographic, clinical, biomarker, and neuropathological data for posterior cortical atrophy. Our findings show the value of in-vivo biomarkers of Alzheimer's disease and of imaging methods to capture atrophy and hypometabolism patterns, which closely mirror the symptoms of posterior cortical atrophy. Our results are consistent with the Crutch 2017 consensus criteria that state the importance of distinguishing posterior cortical atrophy pure (core posterior cortical atrophy syndrome only) versus posterior cortical atrophy plus (core posterior cortical atrophy syndrome and core features of another neurodegenerative syndrome) presentations, because these two groups might reflect distinct pathophysiological processes. Further work is needed to understand what drives cognitive vulnerability and progression rates by investigating the contribution of sex, genetics, premorbid cognitive strengths and weaknesses, and brain network integrity. This study will provide clinicians, individuals with posterior cortical atrophy, and caregivers with a better understanding of the specific clinical features of the syndrome and their associations with underlying disease.

neuroimaging features of the syndrome; and posterior cortical atrophy plus, which additionally includes features suggestive of other neurodegenerative diseases (eg, corticobasal degeneration or Lewy body disease). Although the clinical and radiological presentations of the pure and plus syndrome types are heterogeneous, most people present with visual difficulties (eg, space perception deficits, simultagnosia, object perception deficit, constructional dyspraxia, and environmental agnosia). The syndrome is often associated with an early age of onset (<65 years).

Most cases of posterior cortical atrophy reported in published literature have been attributed to Alzheimer's disease at autopsy, although individual cases due to primary diffuse Lewy body disease, corticobasal degeneration, and prion disease have been reported.[2–4] Posterior cortical atrophy is often sporadic and is rarely present in autosomal dominant cases of Alzheimer's disease. The *APOE* ε4 allele (*APOE4*) is associated with increased risk of posterior cortical atrophy, although the strength of the association is less than that observed in amnestic Alzheimer's disease.[5] In-vivo biomarkers (PET, CSF, and plasma) of amyloid β or tau can provide evidence for or against the presence of Alzheimer's disease neuropathology in individuals presenting with clinical posterior cortical atrophy,[6] whereas brain imaging with MRI or [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) PET can support the diagnosis by demonstrating a characteristic pattern of atrophy or hypometabolism in parieto-occipital and parieto-temporal regions.[7]

Because posterior cortical atrophy is a rare syndrome, most reports of case series have been from single centres, included modest sample sizes, and usually focused on specific clinical, genetic, neuroimaging, or fluid biomarker features. No comprehensive clinical overview has been reported of the features of posterior cortical atrophy in a large and representative sample. We aimed to describe demographic, clinical, biomarker, and neuropathological correlates of posterior cortical atrophy in a large-scale cohort by pooling individual participant data from multiple research centres around the world.

Methods

Study design and data collection

To obtain individual participant data for a meta-analysis, we first needed to identify centres that conduct research into posterior cortical atrophy. We did a literature review following PRISMA guidelines to find relevant published work. We searched PubMed using the search terms "posterior cortical atrophy", "PCA", "Benson syndrome", "visual variant of Alzheimer's disease", and "progressive posterior cortical dysfunction" combined with "biomarkers", "neuropathology", "autopsy", "cerebrospinal fluid", "CSF", "positron emission tomography", and

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"PET". Reports published in English from database inception to Aug 1, 2021 were considered. 1353 papers were identified from the literature search, which were from 55 research centres. An additional seven research centres were recruited by advertising via the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART) atypical Alzheimer's disease professional interest area.

We contacted the corresponding authors to request deidentified, single-subject data for people with posterior cortical atrophy (published and unpublished) at the first diagnostic visit (1988–2021). Inclusion criteria were a clinical diagnosis of posterior cortical atrophy (according to the local centre's criteria)[1] and availability of Alzheimer's disease biomarkers (PET or CSF), or diagnosis at autopsy. Not all individuals with posterior cortical atrophy fulfilled the Crutch 2017 consensus criteria, because they had been diagnosed either using centre-specific procedures or before development of the consensus criteria. After contacting all the research centres that we had identified from our literature search and by advertising, we surveyed potential collaborators to gather data. We used data obtained in this way to create the main database.

Variables included in the database are presented in the appendix (pp 2–3). Demographic variables gathered were age at diagnostic visit, age at death, age at symptom onset, sex, education, and handedness. Clinical variables were *APOE4* carrier status, mini-mental state examination (MMSE) total score, Clinical Dementia Rating (CDR) global score, any other severity or staging information, diagnosis (posterior cortical atrophy pure or posterior cortical atrophy plus, by Crutch 2017 criteria), diagnosis details (other features, if diagnosed as posterior cortical atrophy plus), Mendez criteria[8] or Tang-Wai criteria[2] (fulfilled or not), and other clinical and cognitive information based on the Crutch 2017 consensus criteria.[1] We also asked collaborators at the research centres which of the four non-visuospatial cognitive or neuropsychiatric domains were spared relative to visuospatial function at the time of diagnosis—ie, anterograde memory, speech and non-visual language, executive functions, and behaviour. For the analyses, these variables were reverse coded to estimate the frequency of the domains being impaired in people with posterior cortical atrophy.

Biomarker variables that were obtained for the database included amyloid β in CSF, phosphorylated tau (p-tau) in CSF, amyloid-PET, tau-PET, MRI showing predominant posterior atrophy, [^{18}F]FDG-PET showing predominant posterior hypometabolism, and dopamine transporter (DaT)-SPECT showing nigrostriatal loss. The full list of biomarker variables is provided in the appendix (pp 2–3). All research centres used their own thresholds and criteria for defining a biomarker as positive or negative.

Neuropathological data were collected to establish the main and contributing neuropathological diagnoses, according to the most recent diagnostic criteria (appendix pp 2–3). Variables for which data were obtained pertaining to Alzheimer's disease neuropathological changes were Braak stage (to assess neurofibrillary tangles), Thal phase (for amyloid plaques), and CERAD score (for neuritic plaques). Alternative or contributing neuropathological diagnoses were Lewy body disease (diagnosed according to Braak staging), amygdala-predominant Lewy body disease, limbic-predominant age-related TDP-43 encephalopathy (LATE; which was assessed by neuropathological change staging), argyrophilic grain disease, hippocampal sclerosis, vascular injury, cerebral amyloid angiopathy, ageing-related tau astrogliopathy, chronic traumatic encephalopathy, corticobasal degeneration, and prion disease. All neuropathological variables were considered as binary variables (present or absent) due to small sample sizes and differences in procedures across research centres.

The University of California in San Francisco (UCSF) was the lead institution for our study. The study was granted an exemption from review because it did not contain identified participant data. This waiver was acquired through the institutional review board of the UCSF Research Protection Program, which reviews and monitors research involving human subjects at UCSF and affiliated institutions to ensure the ethical treatment of the research participants.

	Pooled estimate (mean or frequency)	95% CI	$N_{participants}$	N_{sites}	I^2
Sex					
Women	60%	56–64	1092	36	35·0
Men	40%	36–44	1092	36	35·0
Handedness (% right)	93%	90–95	872	32	42·8
Years of education	14·1	13·9–14·2	949	35	93·1
APOE (% ε4 allele carriers)	43%	35–50	451	22	55·5
Age at symptom onset, years	59·4	58·9–59·8	1031	34	77·4
Age at diagnosis, years	63·2	62·8–63·6	1067	36	76·8
Age at death, years	70·5	69·5–71·4	227	20	72·7
Diagnosis					
Posterior cortical atrophy pure	80%	72–89	968	34	97·9
Posterior cortical atrophy plus	20%	11–28	968	34	97·9
MMSE at diagnosis, points (range 0–30)	20·7	20·4–21·1	904	31	69·9
CDR at diagnosis (% CDR ≥1)	62%	53–71	558	27	81·1
Mendez criteria[8] (% fulfilled)	75%	60–90	535	21	99·4
Tang-Wai criteria[2] (% fulfilled)	80%	68–92	535	21	98·6
Early disturbance of posterior function (%)	91%	85–97	992	36	98·1
Insidious onset and gradual progression (%)	99%	98–99	809	34	0

Mean values or frequency and corresponding 95% CIs are derived from the meta-analysis of all available data. Research centres with only one available datapoint (MMSE score, two sites; age at death, one site) were not included in the meta-analysis. Raw data, including breakdowns for each research centre, are presented in the appendix (pp 9–18). MMSE=mini-mental state examination. CDR=Clinical Dementia Rating scale.

Table 1: **Demographic and clinical characteristics of participants**

Data analysis

The primary goal of the study was to describe key demographic, clinical, biomarker, and neuropathological data for all participants by aggregating data across research centres using a meta-analysis framework. No duplicate data across centres was found in this study. One site accidentally sent longitudinal data from the same participants, so we kept the first timepoint for these patients. This was the only duplicate data in the study. Mean values for continuous variables (eg, age and MMSE score) were combined using the inverse variance meta-analysis method. Only research centres with at least two participants for a variable were included in the meta-analysis (site-specific variance cannot be computed if n=1), but the Appendix includes data for all centres, including these with available data for just one patient. Pooled proportions were calculated for binary variables (eg, sex and APOE4 status), using a restricted maximum likelihood model. In all meta-analyses, heterogeneity was quantified using I^2.

In secondary analyses, we compared two groups of participants (eg, amyloid β positive *vs* amyloid β negative, men *vs* women, posterior cortical atrophy pure *vs* posterior cortical atrophy plus), using linear mixed effect models for continuous outcomes or mixed-effect logistic regression for categorical outcomes. A random intercept was included for each research centre, and 95% CIs were estimated using a likelihood profile method.

Because our study is exploratory and descriptive, correction for multiple comparisons was not applied. All statistical tests were done using Jamovi 1.2.27.0 and Stata 18 version 18.0. This study was not registered.

Role of the funding source

There was no specific funding for this study. While individual research centres involved in this project had their own funding sources, these funding sources did not contribute to the study design, data collection, analysis, interpretation, writing of the report, or the decision to submit the paper for publication.

Results

We collected individual participant data from 1092 people who were under assessment at 36 research centres in 16 countries (appendix p 8). Inclusion was without date restriction, until Oct 8, 2021. 495 (45%) participants (104 [72%] with data from autopsy) were evaluated in the USA (appendix p 5).

Group-level pooled estimates for main demographic and clinical variables are presented in table 1; granular (ie, site-level) data are presented in the appendix (pp 9–18). 60% (95% CI 56–64) of participants were women and 40% (36–44) were men. Mean age at symptom onset was 59·4 years (95% CI 58·9–59·8) and mean age at first diagnostic visit was 63·3 years (62·8–63·6). The presentation for 80% (72–89) of participants was posterior cortical atrophy pure, and for 20% (11–28) it was posterior cortical atrophy plus. At the first diagnostic visit, participants had a mean MMSE score of 20·7 (95% CI 20·4–21·1), and 62% (53–71) had a global CDR score of at least 1. 93% of participants were right-handed (90–95) and 43% carried at least one copy of the *APOE-ε4* allele (35–50). In the subsample of 228 participants (from 21 research centres with at least two available data points) who were reported to be deceased, mean age at death was 70·5 years (69·5–71·4).

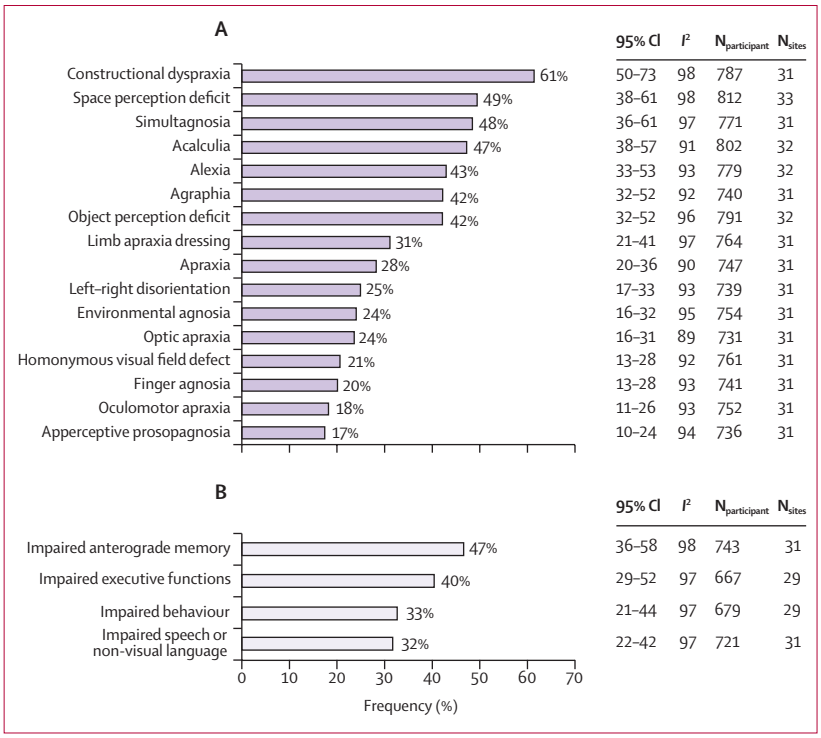


Figure 1: **Frequencies of core features and involvement of additional cognitive or neuropsychiatric domains at the first diagnostic visit**
(A) Frequency of core features. (B) Involvement of additional cognitive or neuropsychiatric domains. Frequency estimates are derived from the meta-analysis.

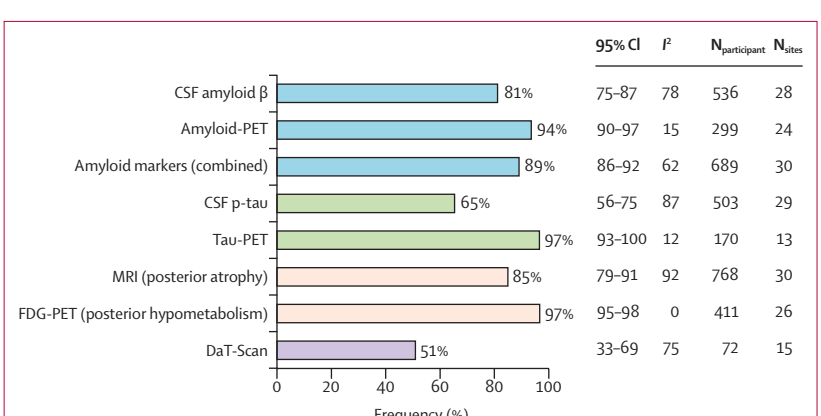


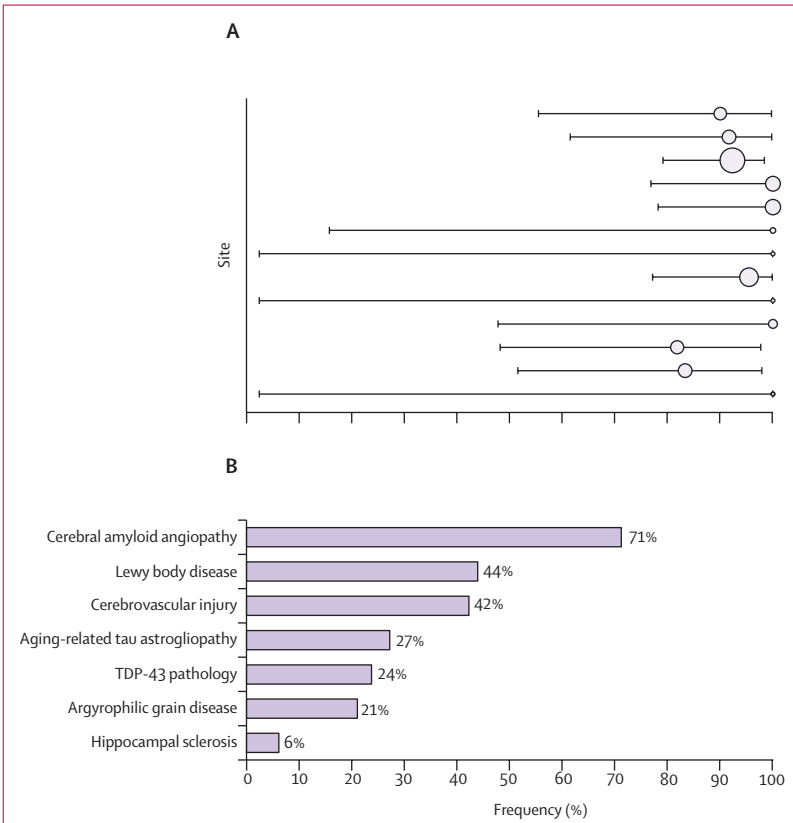
Figure 2: **Frequency of biomarker abnormality**
FDG=fluorodeoxyglucose. p-tau=phosphorylated tau. DaT-SPECT=dopamine transporter SPECT. Frequency estimates are derived from the meta-analysis; site specific raw frequencies are available in the appendix (pp 20–27).

The frequencies of core features and involvement of additional cognitive or neuropsychiatric domains at the first diagnostic visit are shown in figure 1. Data for the frequency of clinical features were highly heterogeneous across studies (I^2 >89%). Constructional dyspraxia was the most frequently reported core posterior cortical atrophy clinical feature (61%, 95% CI 50–73), followed by space perception deficit (49%, 38–61), simultagnosia

	$N_{participants}$	N_{sites}	Estimate (95% CI)	p value	Marginal means (95% CI)	
					Amyloid-negative	Amyloid-positive
Age at symptom onset	644	28	–1·32 (–3·13 to 0·48)	0·15	60·4 (58·4 to 62·4)	59·1 (57·8 to 60·4)
Age at diagnosis	671	30	–1·41 (–3·18 to 0·35)	0·12	63·9 (62·0 to 65·8)	62·5 (61·4 to 63·6)
MMSE score at diagnosis	596	28	–0·06 (–1·35 to 1·29)	0·93	20·8 (19·5 to 22·2)	20·7 (19·9 to 21·6)
CDR at diagnosis (CDR ≥1)	413	21	0·12 (–0·57 to 0·82)	0·74	61% (42 to 77)	58% (46 to 70)
Sex (% women)	689	30	0·41 (–0·06 to 0·87)	0·085	53% (42 to 63)	63% (59 to 67)
APOE (% ε4 allele carriers)	342	22	0·09 (–0·64 to 0·82)	0·81	45% (29 to 62)	47·5% (40 to 55)
PCA diagnosis (% PCA pure)	625	29	1·51 (0·77 to 2·26)	<0·0001	81% (56 to 94)	95% (86 to 98)
MRI (% posterior atrophy)	543	27	0·23 (–0·61 to 1·06)	0·59	92% (78 to 97)	94% (85 to 97)
FDG-PET (% posterior hypometabolism)	324	22	0·58 (–0·90 to 2·05)	0·44	97% (84 to 99)	98% (94 to 99)

For each variable, a separate linear mixed model (continuous outcomes) or generalised mixed effect model (binary outcomes) was run, using amyloid status as a fixed effect and research centre as a random effect. Estimate 95% CIs were obtained using the likelihood profile method. Numbers of participants and research centres with available data vary from one variable to the other. Amyloid-positive participants include those who received a positive result on CSF analysis or amyloid-PET, and amyloid-negative participants received negative results on CSF analysis or PET. This sample included 390 with CSF samples only, 153 with PET only, and 146 with both; in this subgroup 27 participants had discrepant results (three CSF-positive and PET-negative, 24 CSF-negative and PET-positive) and were included in the amyloid-positive group.

Table 2: **Demographic and clinical characteristics according to amyloid positivity**



N_{total}	N_{AD}	Alzheimer's disease (%)	Site
10	9	90%	S01
12	11	92%	S03
39	36	92%	S05
14	14	100%	S06
15	15	100%	S07
2	2	100%	S08
1	1	100%	S09
22	21	95%	S20
1	1	100%	S21
5	5	100%	S23
11	9	82%	S24
12	10	83%	S26
1	1	100%	S33

95% CI	I^2	$N_{participants}$	N_{sites}
54–88	89	141	13
25–62	77	92	11
24–60	88	137	13
9–46	87	85	11
7–40	68	72	9
3–39	75	68	7
2–10	0	104	10

Figure 3: **Frequency of neuropathological findings in the sample**
(A) Frequency of Alzheimer's disease as the primary neuropathology. Error bars correspond to 95% CIs calculated using the binomial exact method. (B) Frequency of non-Alzheimer's disease neuropathological findings. AD=Alzheimer's disease. Frequency estimates are derived from the meta-analysis; site specific raw frequencies are available in the appendix (p 28).

(48%, 36–61), and acalculia (47%, 38–57). The least frequently reported core clinical features were finger agnosia (20%, 13–28), oculomotor apraxia (18%, 11–26), and apperceptive prosopagnosia (17%, 10–24). Associations between core features are shown in the appendix (p 19). Besides visuoperceptual functions, at the time of diagnosis, 47% (95% CI 36–58) of participants had impaired anterograde memory, 40% (29–52) had impaired executive functions, 33% (21–44) had impaired behaviour, and 32% (22–42) had impaired non-visual language and speech.

Biomarker findings are reported in figure 2 (site-level data are in the appendix pp 20–27). When reported, CSF amyloid β was positive (ie, in the range consistent with underlying brain amyloid or tau deposition) in 81% (95% CI 75–87) of participants and CSF p-tau was positive in 65% (56–75), but findings were heterogeneous across research centres (I^2 >75%). Amyloid-PET and tau-PET were positive for most participants (amyloid-PET, 94% [95% CI 90–97]; tau-PET 97% [93–100]), and heterogeneity statistics were low (I^2 ≤15%). Predominant posterior cortical atrophy on MRI was found in 85% (79–91) of participants, and predominant posterior [^{18}F]FDG-PET hypometabolism was reported for 97% (95–98). DaT-SPECT scan results were reported in a small subsample (72 participants from 15 research centres) and showed evidence of nigrostriatal loss in 51% (95% CI 33–69) of participants.

To assess associations between Alzheimer's disease biomarker results and clinical variables, 689 participants from 30 research centres who had either amyloid-PET or CSF amyloid biomarker data (or both) were classified as amyloid-positive when at least one of the biomarkers was positive, and as amyloid-negative when both markers (or the only available marker) were negative. Group comparisons are shown in table 2. Patients who were amyloid-positive were more likely to have posterior cortical atrophy pure than were amyloid-negative patients (95% *vs* 81%, p<0·0001). Age at symptom onset and age at diagnosis, sex, and other clinical features did not differ by amyloid status.

13 research centres had autopsy data for 145 participants (appendix p 4). This subsample included 50% (95% CI 38–61) women, with a mean age at symptom onset of 58·6 years (57·4–59·8), and a mean age at death of 69·4 years (68·2–70·6). The primary neuropathological diagnosis was Alzheimer's disease (figure 3A), with a pooled estimate of 94% (95% CI 90–97) and minimal heterogeneity (I^2=0). Most participants with primary Alzheimer's disease were found to have one or more co-pathologies, the most common being cerebral amyloid angiopathy (71% [95% CI 54–88]), Lewy body disease (44% [25–62]), and cerebrovascular injury (42% [24–60]; figure 3B; appendix p 28).

Only ten participants from six research centres had a primary neuropathological diagnosis that was not Alzheimer's disease (table 3). Four had a primary neuropathological diagnosis of Lewy body disease, all of whom also had significant levels of Alzheimer's disease neuropathological changes. Other primary diagnoses

	Primary diagnosis	Age at symptom onset, years	Age at death, years	Diagnosis	Sex	APOE ε4 status	Thal phase	NFT Braak stage	CERAD score	ADNC level	Site
1	Lewy body disease	67	71	PCA plus	Male	ε4 carrier	5	IV	Moderate	Intermediate	S01
2	Lewy body disease	61	70	PCA pure	Female	..	..	IV	Frequent	Intermediate	S03
3	Lewy body disease	58	68	..	Male	ε4 carrier	5	VI	Frequent	High	S05
4	Lewy body disease	79	87	..	Male	Non-carrier	4	V	Frequent	High	S05
5	FTLD-tau (corticobasal degeneration)	58	64	PCA plus	Male	ε4 carrier	2	II	Sparse	Low	S20
6	FTLD-tau (corticobasal degeneration)	51	57	PCA pure	Male	Non-carrier	0	0	None	None	S24
7	Brain infarct	90	91	..	Female	..	1	0	Sparse	Low	S26
8	Brain infarct	88	94	..	Female	..	0	0	None	None	S26
9	FTLD-TDP-43 type A	59	68	PCA pure	Male	..	0	0	None	None	S24
10	FTLD-tau (Pick's disease)	58	68	PCA pure	Female	ε4 carrier	2	I	Moderate	Low	S05

Corresponding site descriptions can be found in the appendix (p 4). FTLD=frontotemporal lobar degeneration. TDP-43=TAR DNA-binding protein 43. NFT=neurofibrillary tangles. CERAD=Consortium to Establish a Registry for Alzheimer's Disease. ADNC=Alzheimer's disease neuropathological changes. MMSE=mini-mental state examination. CDR=Clinical Dementia Rating scale.

Table 3: **Clinical characteristics of ten participants with non-Alzheimer's disease neuropathological findings, by primary diagnosis**

were frontotemporal lobar degeneration with non-Alzheimer's disease tauopathy (n=3, two with corticobasal degeneration and one with Pick's disease) or TDP-43 type A (n=1, due to a pathogenic granulin [*GRN*] mutation), and brain infarct with minimal comorbid Alzheimer's disease neuropathology (n=2; both cases had late age at onset [ages 88 years and 90 years] and were from the same research centre).

Demographic and clinical characteristics mostly did not differ much by sex, except for MMSE score and posterior cortical atrophy type (appendix p 6). On average, women had lower MMSE scores at their first diagnostic visit than did men (difference 1·08, 95% CI 0·34–1·83; p=0·0046), and women were more likely to have posterior cortical atrophy pure syndrome than posterior cortical atrophy plus (95% [95% CI 87–98] *vs* 91% [78–97]; p=0·0048). No other sex differences were observed (appendix p 6).

Differences between participants with a diagnosis of posterior cortical atrophy pure versus posterior cortical atrophy plus were noted for age at symptom onset and age at diagnosis, and for amyloid positivity (appendix p 7). Participants with a diagnosis of posterior cortical atrophy pure had a younger age of symptom onset than did those with posterior cortical atrophy plus (difference 2·4 years, 95% CI 0·9–3·9; p=0·0018), and a younger age at diagnosis (difference 3·6 years, 2·1–5·0; p<0·0001). The proportion of participants with positive amyloid biomarkers was higher in the posterior cortical atrophy pure group than in the posterior cortical atrophy plus group (92% [95% CI 88–95] *vs* 74% [60–84]; p<0·0001; appendix p 7).

Discussion

In this international study, which was done at multiple sites around the world, individual participant data for 1092 people diagnosed with posterior cortical atrophy who had available data for Alzheimer's disease biomarkers, or data from autopsy, were analysed using a meta-analysis framework. We found that posterior cortical atrophy generally had an early age of onset (around age 60 years), affected women more than men (60% *vs* 40%), and often presented in its pure form (ie, without clinical features of other neurodegenerative diseases), as per Crutch 2017 diagnostic criteria.[1] By the time of diagnosis, participants usually met diagnostic criteria for dementia (according to CDR scores of 1 or above), and additional cognitive domains were often impaired by the time of diagnosis (most often episodic memory and executive functions). Although the *APOE4* genotype prevalence was higher than in cognitively normal individuals, it was lower than in people with amnestic Alzheimer's disease,[9] suggesting a weaker link between *APOE4* genotype and posterior cortical atrophy. Importantly, amyloid biomarkers were positive in more than 89% of individuals, and Alzheimer's disease was the primary diagnosis in 94% of individuals with data from autopsy (145 participants from 13 centres), indicating that the posterior cortical atrophy clinical syndrome is usually caused by underlying Alzheimer's disease neuropathology.

Our cohort consisted of 60% women and 40% men. This ratio is consistent with previous findings from smaller studies, which showed that posterior cortical atrophy affects women to a larger extent than men.[5] Reports on sex predilection have varied across Alzheimer's disease variants, with more women than men having amnestic Alzheimer's disease (just over 50% women in most studies)[10] and dysexecutive Alzheimer's disease (62% women),[11] and a higher proportion of men than women having logopenic-variant primary progressive aphasia (52% men)[12] and behavioural-variant Alzheimer's disease (62% men).[13] A previous study reported that the prevalence of mathematical and visuospatial learning disabilities is greater in people with posterior cortical atrophy than in other clinical presentations of Alzheimer's disease.[14] Since the prevalence of mathematical learning disabilities is greater in girls than in boys during schooling,[15] women could have a greater cognitive vulnerability to posterior cortical atrophy syndrome. In our study, we found that the frequency of acalculia was significantly greater in women than in men, which is consistent with this hypothesis.

Posterior cortical atrophy is often associated with an early age of onset.[16,17] In our study, average age of onset was 59·4 years and 75% of participants had an age at onset younger than 65 years (the 3rd quartile of the distribution; appendix p 13), which is the common threshold for early-onset dementia.[18] At the time of diagnosis, mean MMSE was 21 and mean global CDR was 1 (mild dementia), suggesting that symptoms are advanced at the time of first diagnosis.[19] Consistent with this observation, some clinicians reported involvement of additional cognitive or behavioural domains at first diagnostic visit, such as episodic memory, and executive functions, probably reflecting progression from an initial pure visuoperceptual or visuospatial syndrome to multi-domain dementia. People with posterior cortical atrophy often face a delay in diagnosis because of their young age and visual-predominant symptoms.[20] Better awareness of the syndrome of posterior cortical atrophy among neurologists, primary care providers, optometrists, and ophthalmologists is needed for early detection and treatment.

In previous clinicopathological studies,[2–4] Alzheimer's disease was the most common neuropathological cause of posterior cortical atrophy, although some cases were due to Lewy body disease, corticobasal degeneration, and prion disease. These studies were done at various research centres and the samples were generally small because of the rareness of the syndrome and challenges associated with post-mortem data collection. In our large international sample from multiple research centres, we found a strong association between posterior cortical atrophy syndrome and Alzheimer's disease neuropathology, which was more pronounced than reported relationships between other

clinical variants and underlying Alzheimer's disease.[12,21] In these previous studies,[12,21] Alzheimer's disease pathological features were noted in about 70% of individuals with an amnestic presentation and 76% of those presenting with logopenic-variant primary progressive aphasia. In our study, Alzheimer's disease pathological findings was recorded in 94% of participants with posterior cortical atrophy (145 participants from 13 centres). Only ten individuals in our study received a primary neuropathological diagnosis that was not Alzheimer's disease, and four of these people were found to have an intermediate or high level of Alzheimer's disease neuropathological changes. Therefore, posterior cortical atrophy might be the most predictive clinical syndrome for underlying Alzheimer's disease. As has been shown in previous small case series,[2,4] other neuropathological findings that should be considered in the differential diagnosis of posterior cortical atrophy include Lewy body disease, corticobasal degeneration, frontotemporal lobar degeneration-TDP-43 type A, and Pick's disease. No cases of prion disease were reported in our sample, but these have been reported previously.[4] Two cases of posterior cortical atrophy due to brain infarcts were reported in our cohort, which occurred at an older age (88–90 years). It is unclear if these two cases would have met current clinical criteria for posterior cortical atrophy, which exclude acute or non-progressive presentations. These cases raise the possibility of alternative causes for posterior cortical atrophy in the very old.

Biomarkers are useful for supporting or excluding Alzheimer's disease as the cause of the dementia syndrome during life, particularly in individuals presenting with non-amnestic syndromes or at an early age of symptom onset.[22] Similar to other clinical variants of Alzheimer's disease, concentrations in CSF of the amyloid β peptide Aβ1–42, or the ratio of Aβ1–42 to Aβ1–40, are reduced and total tau and p-tau181 concentrations are increased in the early stages of posterior cortical atrophy.[23–25] Previous studies[26–28] have reported high proportions of amyloid-PET and tau-PET positivity in posterior cortical atrophy cohorts. In our study, amyloid β in CSF, amyloid-PET, and tau PET results in people with posterior cortical atrophy were very frequently in the range associated with Alzheimer's disease, including in individuals with Alzheimer's disease confirmed at autopsy. By contrast, amounts of p-tau in CSF showed limited sensitivity in our cohort (ie, positive in 65% of participants). Previous studies have indicated limited sensitivity of p-tau in CSF as a stand-alone biomarker for Alzheimer's disease neuropathological changes, and diagnostic accuracy is improved by calculating the ratio in CSF of p-tau to Aβ1–42.[25] We found atrophy and hypometabolism in posterior cortical regions in 89% and 97% of participants respectively, indicating that both MRI and [^{18}F]FDG-PET are robust techniques to help with posterior cortical atrophy diagnosis, by establishing a neurodegenerative basis and posterior cortical localisation. The frequency of features of the posterior cortical atrophy plus syndrome was significantly higher in people who were amyloid biomarker-negative than in those who were amyloid-positive, which suggests that non-Alzheimer's disease pathologies might account mostly for the posterior cortical atrophy plus clinical findings (eg, limb apraxia and parkinsonism).

Our results corroborate syndrome and disease level descriptions outlined in the posterior cortical atrophy consensus classification. The frequency of each of the core clinical features in our study was very similar to those described in the consensus classification paper,[1] predominantly including mixed ventral and dorsal visual stream features. Constructional dyspraxia, space perception deficit, simultanagnosia, and acalculia were commonly reported in our study (in >50% of participants). In the consensus classification paper,[1] the most frequent clinical features were also constructional dyspraxia, space perception deficit, and simultagnosia, although acalculia was slightly less common. Less frequent features in both cohorts were finger agnosia, oculomotor apraxia, and apperceptive prosopagnosia.

One of the major strengths of our study is the size and the geographical diversity of our sample. We collected data from 1092 individuals in 16 different countries and from 36 research centres, which represents the largest and most representative study on posterior cortical atrophy to date. Another strength of our study is the number of cases with autopsy data. We obtained the main neuropathological diagnosis for 145 participants and quantified the frequency of other common neuropathological features in subsamples of 50–145 participants.

Our study has some limitations. It is a retrospective study that aggregated data from multiple centres without a standard clinical protocol. All data, including most notably the diagnosis of posterior cortical atrophy, were based on the standards applied at the local site. This variability enhances the generalisability of the findings, but it also can lead to high heterogeneity (as evidenced by high I^2 values for some variables) and non-randomness of missing data. It is probable that some biases affected whether certain clinical features were assessed or whether biomarkers were ordered (eg, DaT-SPECT imaging was only available for 74 participants, and it might have been ordered only for people with suspected Lewy body disease). We took a conservative approach, by assuming clinical features were absent if missing, which could lead to underestimation of their true prevalence. Data were aggregated at research centres over many years, during which time clinical definitions of posterior cortical atrophy evolved. The site survey, while extensive, was still potentially missing some variables or details. Future prospective studies of posterior cortical atrophy should promote cross-centre comparability through standardised protocols and include age-matched and severity-matched disease control groups (especially with other variants of Alzheimer's disease) for comparison.[29]

Future work should also include data for race or ethnicity in posterior cortical atrophy, and provide more detailed information on biomarkers (eg, the specific CSF assays used). Lastly, since our study is an exploratory descriptive study, correction for multiple comparisons in the statistical models was not applied, and no adjustment for confounders was included in the analyses.

In conclusion, our international cohort study at multiple sites refines our understanding of the relationship between pathology, biomarkers, and clinical features in posterior cortical atrophy, and provides up-to-date descriptive statistics related to this syndrome. Our results highlight the strong link between posterior cortical atrophy and underlying Alzheimer's disease, and they emphasise the importance of Alzheimer's disease biomarker testing as part of the diagnostic assessment of individuals with posterior cortical atrophy.

Contributors

MC contributed to the literature search, figures, study design, data collection, data curation, data analysis, data interpretation, project administration, and writing the original draft. GDR contributed to data interpretation, supervision, writing, review, and editing. RLJ contributed to data curation, data analysis, data interpretation, supervision, writing, review, and editing. KY, FA, IEA, LA, JB, BDCB, SC, MF, GGF, DG, JGR, LTG, DJI, KAJ, MFM, PCM, RM, ZAM, MM, MEM, SN, VP, DP, JP, YP, ER, JMS, WS, ACS, SS, JT, JW, JLW, DAW, and RO contributed to data collection, writing, review, and editing. MC and RLJ accessed and verified the data and both MC and GDR were responsible for the decision to submit the manuscript. All authors have seen and approved of the final text.

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Data sharing

Applications for data sharing by qualified investigators can be made to the UCSF Alzheimer's Disease Research Center (https://memory.ucsf.edu/research-trials/professional/open-science). Data sharing requests will be subject to the limitations specified in data transfer agreements between UCSF and the individual research centres providing data for this single-subject meta-analysis.

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