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Title

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Journal

Alzheimer's & Dementia Diagnosis Assessment & Disease Monitoring, 16(3)

ISSN

2352-8729

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Publication Date

2024-07-01

DOI

10.1002/dad2.12602

Peer reviewed

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University of California

Received: 2 August 2023 | Revised: 7 December 2023 | Accepted: 19 January 2024

DOI: 10.1002/dad2.12602

Alzheimer's & Dementia
Diagnosis, Assessment & Disease Monitoring

RESEARCH ARTICLE

Comorbid neuropathology and atypical presentation of Alzheimer's disease

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Funding information
National Institute for Health, Grant/Award Numbers: P30-AG062422, P01-AG019724, K24AG053435, U01 AG057195, R01AG075802; National Institutes of Health Pharmaceutical Sciences and Pharmacogenomics Training, Grant/Award Numbers: GM007175, R35-AG072362, R01 AG045611; Alzheimer's Association, Grant/Award Number: AARG-22-926899

Abstract

INTRODUCTION: Alzheimer's disease (AD) neuropathological changes present with amnestic and nonamnestic (atypical) syndromes. The contribution of comorbid neuropathology as a substratum of atypical expression of AD remains under investigated.

METHODS: We examined whether atypical AD exhibited increased comorbid neuropathology compared to typical AD and if such neuropathologies contributed to the accelerated clinical decline in atypical AD.

RESULTS: We examined 60 atypical and 101 typical AD clinicopathological cases. The number of comorbid pathologies was similar between the groups ($p = 0.09$). Argyrophilic grain disease was associated with atypical presentation ($p = 0.008$) after accounting for sex, age of onset, and disease duration. Vascular brain injury was more common in typical AD ($p = 0.022$). Atypical cases had a steeper Mini-Mental Status Examination (MMSE) decline over time ($p = 0.033$).

DISCUSSION: Comorbid neuropathological changes are unlikely to contribute to atypical AD presentation and the steeper cognitive decline seen in this cohort.

KEYWORDS
atypical Alzheimer's disease, clinicopathological correlation, comorbidities, neuropathology, *post mortem*, selective vulnerability

Highlights

- Autopsy cohort of 60 atypical and 101 typical AD; does comorbid pathology explain atypical presentation?
- Atypical versus Typical AD: No significant differences in comorbid neuropathologies were found ($p = 0.09$).

Stefanie D. Pina-Escudero and Renaud La Joie, contributed equally to this work.

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- Argyrophilic Grain Disease Association: significantly correlates with atypical AD presentations, suggesting a unique neuropathological pattern ($p = 0.008$).
- Vascular Brain Injury Prevalence: Vascular brain injury is more common in typical AD than in atypical AD ($p = 0.022$).
- Cognitive Decline in Atypical AD: Atypical AD patients experience a steeper cognitive decline measured by MMSE than those with typical AD despite lacking more comorbid neuropathology, highlighting the severity of atypical AD pathogenesis ($p = 0.033$).

1 | INTRODUCTION

The goal of this study is to investigate whether age-related comorbid neuropathologies serve as a substrate for atypical presentations of Alzheimer's disease (AD) pathology and whether they contribute to the more rapid clinical decline observed in atypical AD compared to typical cases. AD neuropathological changes, that is, a stereotypical accumulation of beta-amyloid plaques and phospho-tau neurofibrillary tangles, usually manifest clinically as a progressive amnestic predominant syndrome, with or without dysexecutive features.[1] In the past few decades, clinicopathological studies demonstrated that AD pathology can also manifest as nonamnestic clinical syndromes, collectively known as atypical AD. These syndromes include a behavioral variant (bvAD)[2] in which many cases also meet criteria for behavioral variant frontotemporal dementia, corticobasal syndrome (CBS), logopenic variant primary progressive aphasia (lvPPA), posterior cortical atrophy syndrome (PCA), and a primary dysexecutive syndrome.[3] Atypical AD presentations are enriched in early-onset (EOAD) (< 65 years of age) cases, are mostly nonfamilial and have a weaker risk association than typical cases with apolipoprotein E (APOE) ε4 allele genotype.[4]

Three primary factors may contribute to the atypical AD presentation: quantitative regional disparities in the abundance of plaques and/or tangles, intrinsic factors that affect resilience and vulnerability (e.g., inherent anatomical variation, genetic background), and neuropathological comorbidity. *Post mortem* brain neuropathology studies and tau PET imaging studies, including those conducted by our research group, have consistently identified a robust correlation between regional tau burden and atypical AD manifestations.[5–10] In contrast, the influence of variations in plaque distribution appears to be modest at best.[5,10,11] Relatively little is known about the contribution of genetic or anatomical variations, although there have been reports of an association between dyslexia diagnosis and lvPPA,[12] and specific genetic risks associated with atypical AD syndromes[13–17] Neuropathological comorbidity frequently leads to unexpected symptoms, atrophy patterns, and accelerated clinical decline in neurodegenerative conditions.[3,18–21] The frequency of comorbid neuropathology in AD is significant, extending to sporadic EOAD cases.[22,23] However, the potential role of comorbid neuropathological alterations in explaining atypical AD presentations remains largely uncharted, primarily due to the absence of biomarkers capable of in vivo detection of non-AD neurodegenerative changes and the scarcity of atypical AD cases in most brain repositories. The present study aims to address this gap by investigating the association between common comorbidities, longitudinal clinical/cognitive trajectories, and the clinical phenotype of AD in a well-characterized clinicopathological cohort of primary AD cases.

2 | MATERIALS AND METHODS

2.1 | Cohort

The study was approved by the University of California, San Francisco (UCSF) Internal Review Board under the number 10-00619. We selected all 178 individuals with a primary pathological diagnosis of AD[24] from a total of 516 cases from the Neurodegenerative Diseases Brain Bank (NDBB) of the Memory and Aging Center/Alzheimer's Disease Research Center UCSF between 2008 and 2020. The *post mortem* brains were processed and analyzed according to the NDBB research protocol.[23] All individuals underwent at least once in-depth clinical assessment, including neurological history and examination, functional evaluation, neuropsychological testing, and genotyping for common genes related to dementia. Cases with a primary diagnosis of a non-AD pathology were not included, as the significant burden of non-AD pathology could affect the clinical presentation.

2.2 | Clinical, sociodemographic, and genetic variables

The clinical presentation was determined based on accepted guidelines following a thorough consensus review of extensive patient records. This approach ensured that cases from the past were classified using current criteria, maintaining consistency.[25–29] Cases with amnestic syndrome and/or dysexecutive features constituted the typical AD group. The atypical AD group included participants meeting criteria for PCA,[29] lvPPA,[27] CBS,[28] and bvAD.[24] Individuals who were clinically categorized as being cognitively intact ($n = 2$), with a nonspecific mild cognitive impairment ($n = 8$), with an unclear clinical phenotype ($n = 3$),

or with a clinical phenotype of Dementia with Lewy body disease ($n = 4$) were excluded from the analysis. (Figure 1)

The baseline and follow-up cognitive and functional scores were considered continuous variables, with lower scores indicating worse performance. The Mini-Mental State Examination (MMSE)[30] the California Verbal Learning Test (CVLT),[31] Trial Making test (TMT),[24] Digit Backwards, Verbal Fluency,[32] Stroop test, Digit Forwards, Modified Rey Test, Design Fluency, Visual Object and Space Perception Battery (VOSP), Boston Naming Tests, Comprehensive Affect Testing System test (CATS), Clinical Dementia Rating Scale sum of boxes (CDR-Sb),[33] and the Geriatric Depression Scale (GDS) were the selected measures of global cognition, memory and learning, executive functions, complex attention, visuospatial and constructional abilities, language, social cognition, functional impairment, and mood respectively. Out of the 161 participants, 153 had at least one MMSE datapoint totalizing 400 datapoints (median number of time points = 3, max = 10; median follow-up duration (time between baseline and last test) = 2.2 years, maximal follow-up duration = 12.8 years). 156 participants had at least one CDR-Sb datapoint totalizing 488 datapoints (median number of time points = 3, max = 10; median follow-up duration = 3.5 years, maximal follow-up duration = 12.7 years).

Sociodemographic continuous variables included the age at onset, age at death, disease duration, and years of education. Sex was dichotomized as male and female.

Genetic screening for pathogenic mutations in the *APP*, *PSEN1*, *PSEN2*, *C9ORF72*, *GRN*, *MAPT*, *FUS*, and *TARDBP* was conducted on 151 participants. No case was positive for any of these mutations. Individuals with one or two *APOEε4* alleles were classified as carriers vs. noncarriers (no *APOE ε4* allele).

2.3 | Neuropathological assessment

Brain weight was collected upon procurement. AD neuropathological changes were scored according to the ABC score.[24] Lewy body disease (LBD) staging (Braak PD stages 0–6) was assessed through immunohistochemistry.[34] Cases with LBD pathology nonconforming to the Braak criteria and primarily confined to the amygdala were classified as 'amygdala-predominant[35] Frontotemporal lobar degeneration (FTLD) was classified according to accepted norms.[36] LATE-NC was classified as stage 0–3.[37] Argyrophilic grain disease (AGD) was dichotomized as positive or negative. In all AGD-positive cases, AGD pathology was restricted to limbic and paralimbic regions (equivalent to stage II of Saito et al.[38]). A diagnosis of hippocampal sclerosis was given to cases with above 90% neuronal loss in the CA1/subiculum.[39] Vascular brain injury (VBI) was considered present when infarct (territorial or lacunar) or microinfarct pathology were observed. Cerebral amyloid angiopathy (CAA) pathology was assessed as mild, moderate, or severe.[40] White-matter thorny-shaped astrocyte pathology, a form of ARTAG[41] associated with regional functional decline,[21] was also included in the analysis. A final neuropathological diagnosis for all cases was achieved through consensus meetings involving four experts (E.H., L.T.G., S.S., W.W.S.).

RESEARCH IN CONTEXT

1. **Systematic review**: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. While the frequency of neuropathological comorbidities in atypical Alzheimer's disease not yet as widely studied, there have been a few publications investigating neuropathological aspects of atypical Alzheimer's disease. These relevant citations are appropriately cited.
2. **Interpretation**: Our findings led to clarification that neuropathological comorbidities are unlikely responsible to atypical presentation of Alzheimer's disease pathology. Nevertheless, Alzheimer's disease expressing as an atypical syndrome correlates with worse clinical progression and brain atrophy.
3. **Future directions**: The manuscript proposes that clinical expression of Alzheimer's disease pathology is likely dictated by factors underlying selective neuronal vulnerability. Thus, contrasting atypical and typical Alzheimer's disease cases is an attractive framework to understand these factors underlying selective vulnerability in Alzheimer's disease pathology.

2.4 | Statistical analysis

Descriptive statistics were used to compare the sample characteristics. For the neuropathology analysis, categorical variables (except for AD neuropathologic changes) were dichotomized as present or absent, and a continuous composite was built to represent the number of comorbid neuropathologies.

To compare the frequencies of the main categorical variables between the typical and atypical groups, chi-squared tests were run with continuity correction, and the magnitude of the differences was assessed using Cramer's V tests. A result between > 0.2 and 6 suggests a moderate difference, while values > 6 suggest a strong difference. To compare means for continuous variables, T-test and analysis of variance (ANOVA) were used, and Cohen's d was calculated to measure effect size. Cutoff points of 0.2, 0.5, and 0.8 were considered small, medium, and large effect sizes, respectively. A $p < 0.05$ value was considered statistically significant in all tests. Analyses were run in the whole group, and sensitivity analyses were conducted in the subgroup of patients with an age of onset ≤ 65 years (i.e., early onset AD, EOAD), to confirm that differences between typical and atypical syndromes were not due to differences in the proportion of cases with EOAD.

Simple logistic regression analyses were performed to investigate the predictors of the clinical presentation of AD (atypical versus atypical phenotype) and the comorbid neuropathologies and to test the association between the clinical phenotype and each copathology. Variables with $p < 0.05$ were retained in the final regression models.

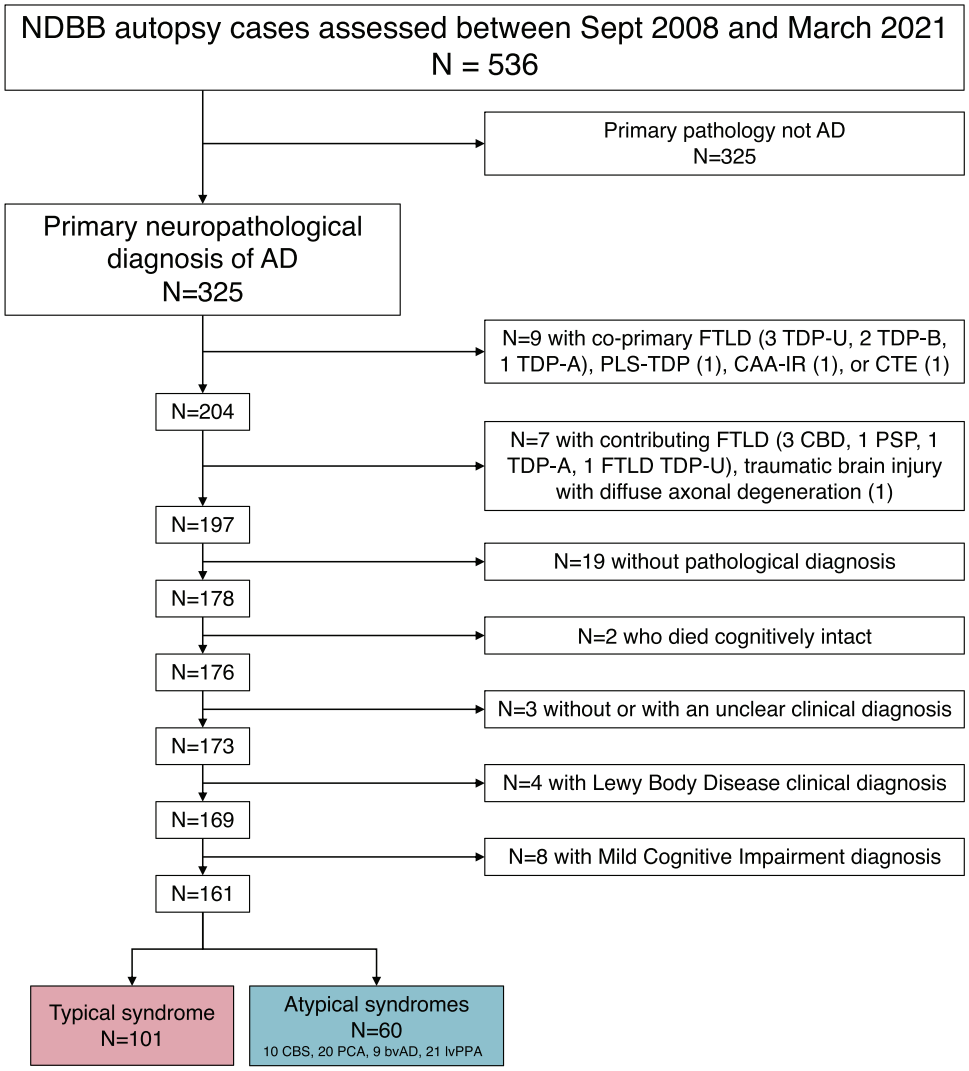

FIGURE 1 Consort diagram illustrating participant selection.

To compare the clinical/functional trajectories of participants with typical AD versus atypical AD, we used neuropsychological evaluations, CDR-Sb, and MMSE captured during the participants' follow-up as continuous variables. Linear mixed models were used to examine changes in these scores in typical versus atypical syndromes; models included random intercepts and slopes for patients. Age, sex, and their interaction with time were included as predictors in all models. Additional models were run including the number of copathologies and their interaction with time.

The analyses were conducted using RStudio Version 1.4.1106 (2009–2021 RStudio, PBC), and Jamovi Version 2.0.0.

3 | RESULTS

A total of 161 participants were included in the study (Figure 1). Table 1 presents a descriptive analysis of typical and atypical cases. Most subjects were male (55%) with high educational attainment (16.5+3 years). The cohort was predominantly composed of non-Hispanic White individuals (94%). The typical group comprised 101 (63%) individuals. As shown in Table 2, Sixty participants formed the atypical group: 20 with PCA (12% of total cases), 9 with bvAD (6% of total cases), 21 with lvPPA (13% of total cases), and 10 with CBS (6% of total cases).

In concordance with previous studies, participants in the atypical group had a younger age at onset ($p = 0.009$), died at a younger age ($p = 0.005$), had a lower brain weight ($p = 0.003$), and were less likely to be an *APOEε4* carrier ($p = 0.039$). In contrast to some previous observations, the atypical group included more females than the typical group (58% vs. 38%, $p = 0.017$). No significant differences were observed in years of education, disease duration, Braak stage, or the beta-amyloid Thal phase.

A total of 114 participants (71% of the total cohort) had clinical onset before age 65. Table S1 shows that these EOAD cases formed 63% ($n = 64/101$) and 83% ($n = 50/60$) of the typical and atypical groups, respectively ($p = 0.012$), including 18 with PCA (11% of total cases), 7 with bvAD (4% of total cases), 17 with lvPPA (11% of total cases), and 8 with CBS (5% of total cases). Most of the participants in the typical EOAD group were males (62.5%), and most of the

TABLE 1 Characteristics of the population according to the typicality of the clinical phenotype.

Parameter	All	Typical AD	Atypical AD	Effect size	*p*-Value
n	161	101	60		
Females, *n* (%)	73 (45%)	38 (38%)	35 (58%)	V = 0.20	**0.017**
Years of education, mean ± SD	16 ± 3	16 ± 4	16 ± 2	d = 8.21	0.64
Race					
Non-Hispanic White, *n* (%)	144 (94%)	94 (95%)	50 (93%)		
Black, *n* (%)	1 (1%)	1 (1%)	0 (0%)	V = 0.20	0.16
Asian, *n* (%)	2 (1%)	2 (2%)	0 (0%)		
Hispanic, *n* (%)	5 (3%)	1 (1%)	4 (7%)		
Other, *n* (%)	1 (1%)	1 (1%)	0 (0%)		
Age of onset Years, mean ± SD	60 ± 10	62 ± 11	58 ± 8	d = 0.43	**0.009**
Age at death Years, mean ± SD	71 ± 10	72 ± 11	68 ± 8	d = 0.46	**0.005**
Disease duration Years, mean ± SD	11 ± 4	11 ± 4	10 ± 4	d = 0.11	0.49
Brain weight Grams, mean ± SD	1094 ± 156	1122 ± 156	1045 ± 144	d = 0.50	**0.003**
APOEε4 carriers, *n* (% available) *	78 (52%)	54 (59%)	24 (41%)	V = 0.18	**0.039**
APOEε2 carriers, *n* (% available) *	11 (7%)	5 (5%)	6 (10%)	V = 0.09	0.28
ADNC level, *n* low/inter/high (% high) #	1/6/154 (96%)	1/4/96 (95%)	0/2/58 (97%)	V = 0.13	0.93
Thal phase, *n* 1/2/3/4/5 (% 5) #	1/1/4/8/147 (91%)	1/0/3/5/92 (91%)	0/1/1/3/55 (92%)	V = 0.01	1
Braak stage, *n* III/IV/V/VI (% VI) #	1/4/9/147 (91%)	1/3/7/90 (89%)	0/1/2/57 (95%)	V = 0.10	0.32
No. of copathologies, mean ± SD	2.6 ± 1.4	2.8 ± 1.4	2.4 ± 1.3	d = 0.28	**0.09**
Lewy body present, *n* (%)	76 (47%)	51 (50%)	25 (42%)	V = 0.09	0.36
Lewy body amygdala only present, *n* (%)	24 (15%)	17 (17%)	7 (12%)	V = 0.07	0.51
TDP-43 present, *n* (%)	26 (16%)	18 (18%)	8 (13%)	V = 0.06	0.60
Argyrophilic grain disease present, *n* (%)	78 (48%)	44 (44%)	34 (57%)	V = 0.13	0.15
Vascular brain injury present, *n* (%)	68 (42%)	50 (50%)	18 (30%)	V = 0.19	**0.024**
Hippocampal sclerosis present, *n* (%)	10 (6%)	8 (8%)	2 (3%)	V = 0.09	0.41
Cerebral amyloid angiopathy present, *n* (%)	140 (87%)	90 (89%)	50 (83%)	V = 0.08	0.42
WM-TSA present, *n* (%)	23 (14%)	17 (17%)	6 (10%)	V = 0.09	0.335

Note: p-Values correspond to Student's *t*-test (continuous variables) or chi-squared with continuity correction (categorical variables). Number of copathologies: CAA (0/1) + LBD (0/1) + TDP43 (0/1) + Hip. Scler. (0/1) + AGD (0/1) + VBI (0/1) + WM-TSA (0/1) + CTE (0/1) + FTLD-tau (0/1) → 0 to 9.

**APOEε4* data: 11 missing (10 typical, 1 atypical).

#For Alzheimer's disease Neuropathologic changes (ADNC), Thal, and Braak variables, the group comparison was performed by analyzing the proportion of cases with maximal values (high ADNC, Thal 5, Braak VI) between the two samples.

participants who formed the atypical EOAD group were female (64%) ($p = 0.009$). The significant differences between the typical and atypical groups in brain weight ($p = 0.041$) and *APOEε4* carriers ($p = 0.035$) remained in a subanalysis with EOAD only (Table S1).

We observed a trend toward significance for a higher number of comorbid neuropathologies ($p = 0.092$) in the typical (2.8 ± 1.4) group compared to the atypical group (2.4 ± 1.3, Table 1). Thus, we ran logistic regression models to test further the association between the number of comorbid neuropathologies (as a predictor) and the clinical phenotype (as an outcome, Table 3). Neither the simple regression model (*OR* 0.81, $p = 0.09$, 95% CI: 0.63 to 1.03) nor models adjusted for sex, disease duration, *APOEε4* status, and age at onset (*OR* 0.93, $p = 0.63$, 95% CI: 0.70 to 1.24) showed an association between the number of co-pathologies and an atypical phenotype. However, the regressions showed an impact of sex and *APOEε4* on the clinical phenotype, with males and APOE4 carriers being more likely to have a typical phenotype. Sensitivity analyses were run independently for females and males and *APOEε4* status to investigate whether the clinical AD phenotype, the presence of comorbid neuropathologies, or the number of comorbid neuropathologies varied by sex and *APOEε4* status *APOEε4* noncarriers. In the female group, the simple regression analysis showed a significant association between the number of

TABLE 2 Characteristics of the population according to the clinical phenotype.

Parameter	Typical AD	bvAD	CBS	lvPPA	PCA	*p*-Value
n	101	9	10	21	20	
Females, *n* (%)	38 (38%)	3 (33%)	7 (70%)	14 (67%)	11(55%)	**0.04**
Age of onset Years, mean ± SD	62 ± 11	58 ± 12	60 ± 9	58 ± 8	57 ± 6	0.11
Age at death Years, mean ± SD	72 ± 11	70 ± 12	69 ± 10	68 ± 8	67 ± 7	0.07
Disease duration Years, mean ± SD	11 ± 4	12 ± 5	10 ± 4	10 ± 3	10 ± 3	0.67
Brain weight Grams, mean ± SD	1122 ± 156	1084 ± 203	1050 ± 112	1015 ± 154	1056 ± 119	**0.034**
APOEε4 carriers, *n* (% available) *	54 (59%)	7 (78%)	2 (20%)	8 (38%)	7 (37%)	**0.019**
ADNC level, *n* low/inter/high (% high) #	1/4/96 (95%)	0/1/8 (89%)	0/1/9 (90%)	0/0/21 (100%)	0/0/20 (100%)	0.45
Thal phase, *n* 1/2/3/4/5 (% 5) #	1/0/3/5/92 (91%)	0/1/0/0/8 (89%)	0/0/1/1/8 (80%)	0/0/0/2/19 (90%)	0/0/0/0/20 (100%)	0.46
Braak stage, *n* III/IV/V/VI (% VI) #	1/3/7/90 (89%)	0/1/0/8 (89%)	0/0/0/10 (100%)	0/0/1/20 (95%)	0/0/1/19 (95%)	0.67
No. of copathologies, mean ± SD	2.8 ± 1.4	2.8 ± 1.9	2.3 ± 1.7	2.3 ± 0.9	2.4 ± 1.10	0.44
Lewy body present, *n* (%)	51 (50%)	5 (56%)	4 (40%)	9 (43%)	7 (35%)	0.69
Lewy body amygdala only present, *n* (%)	17 (17%)	1 (11%)	2 (20%)	0 (0%)	4 (20%)	0.32
TDP-43 present, *n* (%)	18 (18%)	4 (44%)	2 (20%)	0 (0%)	2 (10%)	**0.037**
Argyrophilic grain disease present, *n* (%)	44 (44%)	5 (56%)	6 (60%)	11 (52%)	12 (60%)	0.58
Vascular brain injury present, *n* (%)	50 (50%)	1 (11%)	4 (40%)	8 (38%)	5 (25%)	0.08
Hippocampal sclerosis present, *n* (%)	8 (8%)	1 (11%)	0 (0%)	0 (0%)	1 (5%)	0.56
Cerebral amyloid angiopathy present, *n* (%)	90 (89%)	8 (89%)	7 (70%)	17 (81%)	18 (90%)	0.43
WM-TSA present, *n* (%)	17 (17%)	1 (11%)	0 (0%)	2 (10%)	3 (15%)	0.61

Note: p-Values correspond to one-way ANOVAs (continuous variables) or chi-squared with continuity correction (categorical variables). Number of copathologies: CAA (0/1) + LBD (0/1) + TDP43 (0/1) + Hip. Scler. (0/1) + AGD (0/1) + VBI (0/1) + ATAC (0/1) + CTE (0/1) + FTLD-tau (0/1) → 0 to 9.
Abbreviations: bvAD, behavioral variant Alzheimer's disease, CBS, corticobasal syndrome, lvPPA, logopenic variant of primary progressive aphasia, PCA, posterior cortical atrophy.
**APOEε4* data: 11 missing (10 typical, 1 atypical).
#For Alzheimer's disease Neuropathologic changes (ADNC), Thal, and Braak variables, group comparisons were performed by analyzing the proportion of cases with maximal values (high ADNC, Thal 5, Braak VI) between the samples.

comorbid neuropathologies and atypical AD clinical phenotype (*OR* 0.65, $p = 0.027$, 95% CI: 0.45 to 0.95). However, the association lost significance when controlling for age at onset, disease duration, and *APOEε4* status (*OR*: 0.73, $p = 0.16$, 95% CI: 0.47 to 1.14). In the male group, the simple model results were not significant (*OR*: 1.00, $p = 0.98$, 95% CI: 0.70 to 1.43). The *APOEε4* carrier (*OR*: 0.86, $p = 0.38$, 95% CI: 0.61 to 1.21) and noncarrier (*OR*: 0.84, $p = 0.41$, 95% CI: 0.57 to 1.26) groups did not show significant associations between the number of comorbid neuropathologies and atypical AD clinical phenotype.

Next, we created eight simple logistic regression models to test the association between clinical phenotype and each comorbid pathology (except for chronic traumatic encephalopathy and FTLD-tau because of low numbers of cases; $n = 2$ each). Table 2 and Figure 2 show the distribution of comorbid neuropathologies across the amnestic (- dysexecutive) predominant syndrome, CBS, lvPPA, PCA, and bvAD

TABLE 3 Logistic regression models analyzing the associations between copathologies and typicality of the clinical phenotype (N = 161).

	Model 1 (*n* = 161)					Model 2 (*n* = 161)					Model 3 (*n* = 150)				
Parameter	Estimate	SE	*p*-Value	OR	95% CI	estimate	SE	*p*-Value	OR	95% CI	estimate	SE	*p*-Value	OR	95% CI
No. of copathologies	−0.21	0.13	0.09	0.81	[0.63, 1.04]	−0.11	0.14	0.42	0.89	[0.67, 1.18]	−0.07	0.15	0.63	0.93	[0.70, 1.24]
Age of Onset (years)	–	–	–	–	–	−0.04	0.02	0.054	0.96	[0.93, 1.00]	−0.04	0.02	0.07	0.96	[0.93, 1.00]
Sex (male vs. female)	–	–	–	–	–	−0.78	0.34	0.023	0.46	[0.23, 0.90]	−0.77	0.36	0.03	0.47	[0.23, 0.93]
Disease duration (years)	–	–	–	–	–	−0.04	0.05	0.38	0.96	[0.87, 1.06]	−0.03	0.05	0.50	0.97	[0.87, 1.09]
APOEε4 (carrier vs. non-carrier)	–	–	–	–	–	–	–	–	–	–	−0.70	0.36	0.053	0.50	[0.25, 1.01]

Note: All models are logistic regression predicting clinical phenotype (atypical vs. typical). Negative estimated and odd ratios (OR) below 1 indicate that higher values on the predictor are associated with a lower likelihood of atypical syndrome.

variants. VBI was found in 50% (50/101) of patients with the amnestic (-dysexecutive) predominant syndrome while it was only found in 30% (18/60) of the atypical group ($p = 0.016$). This difference remained significant after accounting for sex, age at onset, disease duration, and *APOEε4* ($p = 0.022$). Conversely, AGD was less prevalent in typical AD (44% vs. 57%, $p = 0.11$) and the association between AGD and atypical disease was significant after accounting for sex, age, and *APOEε4* ($p = 0.008$) (Table S2). Finally, Table 2 and Figure 2 show the frequency of each neuropathology in each phenotypic subgroup after splitting the atypical group into specific syndromes. The presence of TDP-43 proteinopathy was different across syndromes ($\chi^2 = 10.2$, with 4 degrees of freedom, $p = 0.035$), with a maximal frequency in the bvAD subgroup (4/9, 44%).

Next, we interrogated whether typical and atypical cases showed differences in clinical and cognitive scores; we used linear mixed models that allowed to assess both baseline differences and differences in slopes over time. MMSE score was available for 153 patients, with 400 measurements overall (Figure 3, Table S3) Baseline MMSE scores were higher in participants whose age at onset was older (0.15 points/year of age, $p = 0.007$) but were not significantly influenced by patient sex ($p = 0.23$) or atypical phenotype ($p = 0.20$). However, a faster MMSE score decline over time was associated with atypical presentation ($p = 0.033$), female sex ($p = 0.052$), and younger age at onset ($p < 0.001$). (Table S3). Adding the number of copathologies and its interaction with time to the model did not change the results (see Table S4 and Figure S1). The CDR sum of boxes (CDR-Sb) scores, a measure of functional cognition, were available in 156 patients (488 measurements). Baseline scores were independent from atypical syndrome ($p = 0.82$) and sex ($p = 0.24$), were slightly lower in patients with an older age of onset ($p = 0.065$); see Figure 3 and Table S5. Moreover, the rate of functional decline over time, measured by the CDR-Sb, was independent of age of onset ($p = 0.11$) and atypical phenotype ($p = 0.88$); however, sex differences were significant ($p = 0.05$), with CDR-SB scores increasing more rapidly in females than in males (Table S5 and Figure 3). Adding the number of copathologies to the model did not impact the results (Table S4).

Regarding specific cognitive tests, differences in baseline and longitudinal trajectories in clinical/cognitive scores were analyzed using linear mixed effect models that included age of onset, sex, clinical phenotype (atypical vs. typical), number of copathologies, and their interaction with time. Results are presented in detail in Table S4 and Figure S1. At the baseline visit, patients with atypical phenotypes had lower (i.e., worse) scores on digits forward, digit backward, Stroop color naming, modified Rey figure copy, phonemic fluency, and Boston naming test than patients with typical phenotypes (all *p's* < 0.05). In contrast, atypical AD patients had better memory performance as evidenced by higher CVLT scores (CVLT 10 min recall and cued recall) and higher modified Rey figure recall (*p's* < 0.05). Longitudinal differences were also observed across groups. Patients with atypical presentations progressed more rapidly on several CVLT subscores (sum of 4 learning trials, $p = 0.073$, 30-sec recall, $p = 0.078$, 10 min recall, $p = 0.03$ and cued recall, $p = 0.018$), design fluency ($p = 0.012$), and affect naming ($p = 0.045$). Not a single score showed a more rapid decline in typical

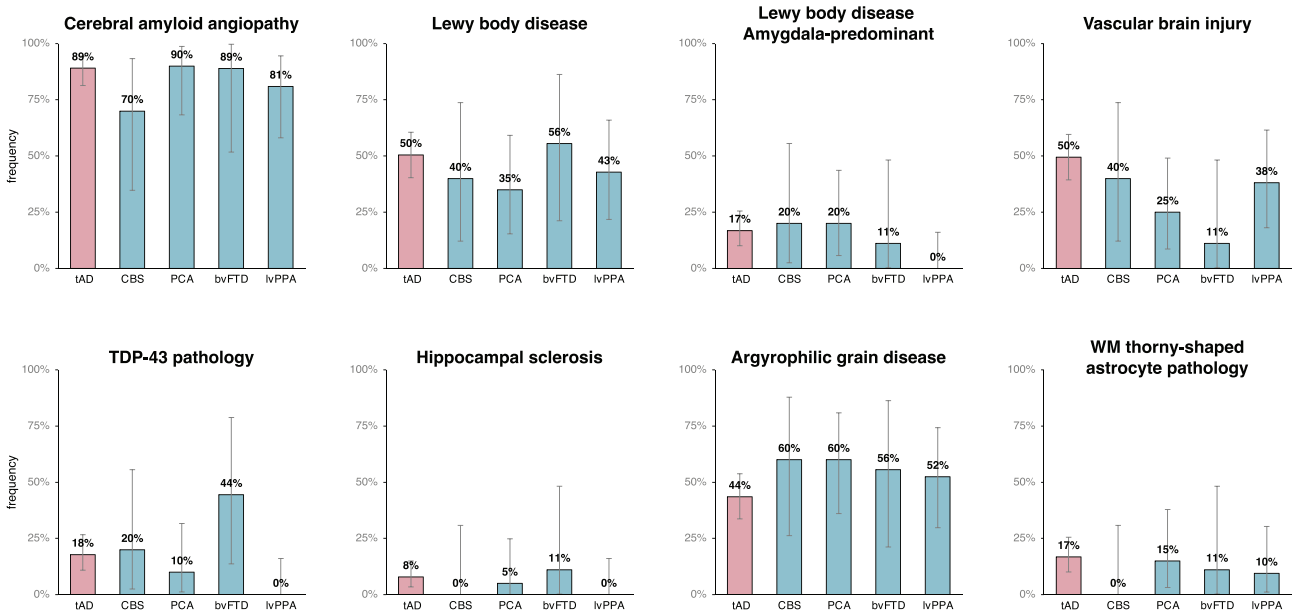

FIGURE 2 Distribution of comorbid pathologies per clinical syndrome, that is, $N = 101$ with a typical syndrome (tAD, red) and $N = 60$ with atypical syndromes (blue): $N = 10$ corticobasal syndrome (CBS), $N = 20$ posterior cortical atrophy (PCA), $N = 9$ behavioral variant of frontotemporal dementia (bvFTD), and 21 with logogenic variant of primary progressive aphasia (lvPPA). Error bars indicate 95% Confidence Intervals calculated using the binomial exact method.

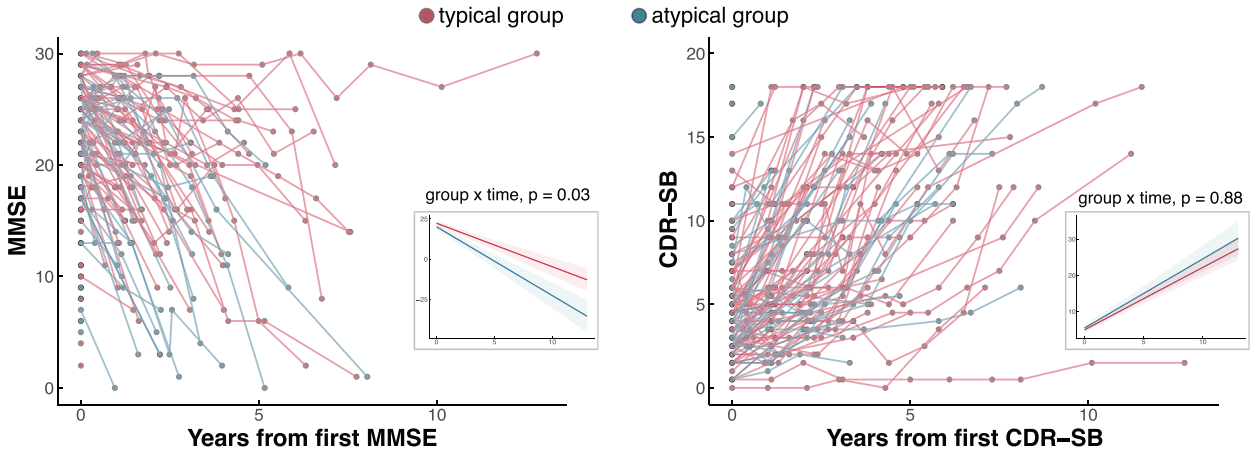

FIGURE 3 Clinical and Cognitive trajectories over time, measured by MMSE and CDR sum of boxes, respectively. Spaghetti plots show the raw trajectories for all available participants. Inserts show the output of linear mixed effect models that include MMSE/CDR-SB as the outcome, a group x time interaction as a fixed effect, and random intercepts and slopes for each patient (age of onset, sex, and their interaction with time were also included in the model).

compared to atypical presentations. A higher number of copathologies at death was associated with worse baseline scores for CVLT 10 min recall, Modified Rey recall, TMT, and design fluency (p's < 0.05). and greater decline in design fluency over time($p = 0.004$).

4 | DISCUSSION

In this study, we examined a well-characterized clinicopathological cohort consisting of 161 cases with a primary AD pathology to investigate the possibility that comorbid neuropathology may be a driving factor behind atypical clinical syndromes. Our findings indicate that the impact of comorbid neuropathology in underlying an atypical AD presentation is minimal, at most. Also, we compared the functional cognitive decline trajectory between typical and atypical AD cases and their relationship to copathology. Despite atypical cases having less VBI than typical cases, and similar frequencies of other comorbid neuropathologies that can affect cognition, atypical AD cases exhibited a steeper decline in MMSE scores.

Among the cases we examined, there was a trend toward more comorbid neuropathologies in the typical AD group. Additionally, the typical AD group showed a greater frequency of VBI compared to

atypical cases. Interestingly, out of the eight comorbid neuropathological conditions tested, AGD emerged as the only one more frequent in atypical cases. AGD is an age-associated four-repeat tauopathy associated with mild and extremely protracted amnestic decline.[42,43] Noticeably, AGD is usually limited to limbic structures, and none of our atypical AD cases had widespread neocortical AGD. Thus, even considering that AGD is more frequent in atypical AD, it is unlikely that AGD is a substrate for more severe regional neocortical atrophy in atypical AD because AGD pathology did not reach the neocortex in these cases. A speculative hypothesis warranting further investigation is if AGD has a protective nature, as suggested by some studies[44] that may lead to sparing the hippocampus of more severe effects of tau pathology, resulting in a more cortical phenotype. Remarkably, TDP-43 pathology was more frequent in bvAD than in other AD types. However, as in AGD, the TDP-43 proteinopathy found in bvAD cases are unlikely to provide a substrate for the atypical presentation. Three out of four bvAD cases positive for TDP-43 proteinopathy, only showed TDP-43 inclusions in limbic areas, and only a single bvAD case (out of nine) had neocortical TDP-43 inclusions. As the current literature on bvAD with neuropathological confirmation is limited to a few small studies and did not address comorbid pathologies,[45] it is difficult to draw comparisons with our results, underscoring the need for more research in this area.

There is a shortage of literature available that enables a comprehensive comparison of our findings. Neuroimaging and biofluid biomarker studies are not particularly useful since biomarkers are not sensitive enough to detect the entire spectrum of age-related comorbid neuropathologies in the brain. In a study with neuropathological data, Buciuc et al.[44] reported an association between Lewy body disease and lvPPA phenotype. However, this study focused on understanding the neuropathological substrate of lvPPA syndrome rather than investigating the substrate of lvPPA manifestation in cases with primary AD neuropathology. In a subanalysis with participants showing advanced AD pathology, Buciuc et al.[46] also failed to find an association between LBD and lvPPA. Research that employs the neuropathological AD subtyping model introduced by Murray et al.[47] indicates that the subtype characterized by hippocampal sparing, which is more commonly found in atypical AD cases, has lower levels of VBI compared to both the typical and limbic-predominant subtypes, which are more frequent in typical AD cases.

Clinicopathological studies suggest a direct correlation between the presence of comorbid neuropathologies and severity of brain atrophy and a faster pace of cognitive decline, in EOAD and late-onset AD.[23,48,49] These findings served as motivation for our current study. Nonetheless, our atypical cases displayed a steeper decline in MMSE scores, irrespective of the presence or quantity of comorbid neuropathologies. Interestingly, the CDR-Sb slopes were similar in both groups. It may reflect that CDR has been optimized to measure the decline in amnestic syndromes, whereas the MMSE may have a higher utility in measuring language and behavior decline.[50] A faster clinical decline was also observed in individuals with a (analogous) hippocampal-sparing AD neuropathological subtype (based on neuropathological exam or MRI).[51,52]

We found an overrepresentation of females in the atypical AD group, which diverges from other clinical cohorts,[53,54] although some studies, including LEADS, also point to a predominance of females.[11,55–57] Regardless, sample bias cannot be excluded from any of these studies, including ours. All *post mortem* brains of atypical AD come from specialized clinics. Broader recognition and referral of atypical AD cases in the community will help to clarify whether there is a sex predominance in atypical AD cases.

This study's strengths include the availability of well-characterized longitudinal clinicopathological cohort and the relatively young age at death in the typical AD group (62 ± 11 years). This is particularly advantageous because the number of comorbid neuropathologies increases with age, thus comparing the frequency of comorbidities in atypical cases versus amnestic late-onset AD will likely show that comorbidities are even less frequent in atypical cases. The predominance of end-stage cases, an inherent limitation of most *post mortem* studies could be a potential limitation as it is challenging to determine when comorbid pathology emerged compared to AD pathology and progression. It is possible that atypical cases developed comorbid neuropathologies at an earlier disease stage than typical cases, explaining the atypical presentation, greater neocortical atrophy, and steeper decline. Still, the number of comorbid pathologies turned out to be small in the atypical cases, often limited to limbic areas, and we have demonstrated before that differences in regional tau burden in this cohort is a strong predictor of atypical presentation and syndrome-specific worse neuropsychological scores.[7] Also, our cohort lacks racial and ethnic diversity and was studied at a tertiary center with expertise in atypical and early-onset dementia. This might introduce referral and selection biases and more diverse or community-dwelling cohorts may show different results. While the atypical AD group is relatively large for a *post mortem* study, subgrouping reduced the sample sizes and analysis power. For instance, more cases of bvAD are necessary to power the analysis exploring the correlation between TDP-43-proteinopathy as a possible contributing neuropathological substrate of bvAD.

In conclusion, this study has presented compelling evidence suggesting that comorbid neuropathologies are unlikely to be a contributing factor for atypical presentation of AD pathology.

Thus far, it is regional variability in phospho-tau burden that has emerged as the most robust predictor of an atypical AD presentation[5–10] or the absence of clinical symptoms.[17] This underscores the need for further investigations into the intricate relationship between tau pathology and cellular intrinsic factors that may either amplify or mitigate the expected regional tau burden, thereby shedding light on the pathogenesis. Employing advanced single-cell techniques in rigorously characterized atypical AD cases holds promise for unraveling the mechanisms underpinning this hypothesis, including potential disparities in neuroinflammatory patterns. The exploration of the neurobiological underpinnings of AD clinical phenotypes may pave the way for identifying pivotal pathogenic pathways and vulnerability factors, ultimately fostering the development of superior biomarkers and innovative therapeutic interventions for AD, which until today have remained solely focused on amyloid.

ACKNOWLEDGMENTS

The authors are indebted to the research participants and their families for their generous contribution to science. Funding was provided by the National Institute for Health: P30-AG062422 (ADRC), P01-AG019724 (PPG), K24AG053435 (LTG), U01 AG057195 (LTG), R01AG075802 (LTG). National Institutes of Health Pharmaceutical Sciences and Pharmacogenomics Training Grant (GM007175), R35-AG072362 (GDR), R01 AG045611 (GDR). Alzheimer's Association grant (AARG-22-926899).

CONFLICT OF INTEREST STATEMENT

L.T.G. receives research support from NIH, Tau Consortium, Genentech Inc. S.P.E., R.L.J., S.S., E.J.H., A.B., M.L.G.T., H.R., J.H.K., B.L.M., W.W.S. receive research support from Tau Consortium. GDR receives research support from NIH, Alzheimer's Association, American College of Radiology, Rainwater Charitable Foundation, Avid Radiopharmaceuticals, GE Healthcare, Life Molecular Imaging, and Genentech. He has served as a paid consultant to Eli Lilly, Genentech, Roche, Merck, and Johnson & Johnson. He is an Associate Editor for JAMA Neurology. R.L.J., S.S., E.J.H., M.L.G.T., H.R., J.H.K., B.L.M., W.W.S. receive support from the NIH. R.L.J. receives support from the Alzheimer's Association. A.B. has served as a consultant to AGTC, Alector, Alzprotect, Amylyx, Arrowhead, Arvinas, Aviado, Boehringer Ingelheim, Denali, Eli Lilly, GSK, Humana, Life Edit, Arkuda, Merck, Modalis, Oligomerix, Oscotec, Roche, Transposon and Wave. He has received research support from Biogen and Eisai for serving as a site investigator for clinical trials, as well as from Regeneron. He has received research support from the NIH Tau Consortium, Bluefield Project to Cure FTD, GHR Foundation, Alzheimer Association, Association for FTD, Gates Ventures, and ADDF. H.G., N.S.M., Z.M., and J.H.H. report no competing interests. Author disclosures are available in the supporting information.

CONSENT STATEMENT

All human subjects provided informed consent to participate in this study. The study was approved by the University of California, San Francisco (UCSF) Internal Review Board under the number 10-00619.

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SUPPORTING INFORMATION

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How to cite this article: Pina-Escudero SD, La Joie R, Spina S, et al. Comorbid neuropathology and atypical presentation of Alzheimer's disease. *Alzheimer's Dement*. 2024;16:e12602. https://doi.org/10.1002/dad2.12602