J Neuropathol Exp Neurol
Vol. 75, No. 3, March 2016, pp. 284–290
doi: 10.1093/jnen/nlv028

ORIGINAL ARTICLE

Neuropathology of Autosomal Dominant Alzheimer Disease in the National Alzheimer Coordinating Center Database

John M. Ringman, MD, MS, Sarah Monsell, MS, Denise W. Ng, MD, Yan Zhou, PhD, Andy Nguyen, BS, Giovanni Coppola, MD, Victoria Van Berlo, BS, Mario F. Mendez, MD, PhD, Spencer Tung, BS, Sandra Weintraub, PhD, Marek-Marsel Mesulam, MD, Eileen H. Bigio, MD, Darren R. Gitelman, MD, Amanda O. Fisher-Hubbard, MD, Roger L. Albin, MD, and Harry V. Vinters, MD

Abstract

Alzheimer disease (AD) represents a genetically heterogeneous entity. To elucidate neuropathologic features of autosomal dominant AD ([ADAD] due to *PSEN1*, *APP*, or *PSEN2* mutations), we compared hallmark AD pathologic findings in 60 cases of ADAD and 120 cases of sporadic AD matched for sex, race, ethnicity, and disease duration. Greater degrees of neuritic plaque and neurofibrillary tangle formation and cerebral amyloid angiopathy (CAA) were found in ADAD (p values < 0.01). Moderate to severe CAA was more prevalent in ADAD (63.3% vs. 39.2%, $p = 0.003$), and persons with *PSEN1* mutations beyond codon 200 had higher average Braak scores and severity and prevalence of CAA than those with mutations before codon 200. Lewy body pathology was less extensive in ADAD but was present in 27.1% of cases. We also describe a novel pathogenic *PSEN1* mutation (P267A). The finding of more severe neurofibrillary pathology and CAA in ADAD, particularly in carriers of *PSEN1* mutations beyond codon 200, warrants consideration when designing trials to treat or prevent ADAD. The finding of Lewy body pathology in a substantial minority of ADAD cases supports the assertion that development of Lewy bodies may be in part driven by abnormal β-amyloid protein precursor processing.

Key Words: Alzheimer disease, Amyloid plaques, Autosomal dominant, Cerebral amyloid angiopathy, Neurofibrillary tangles, Neuropathology, P267A.

From the Mary S. Easton Center for Alzheimer's Disease Research, University of California, Los Angeles, Department of Neurology, Los Angeles, California (JMR, DWN, YZ, AN, GC, MFM, ST, HVV); Memory and Aging Center, Keck School of Medicine of University of Southern California, Los Angeles, California (JMR); Department of Biostatistics, University of Washington, Seattle, Washington (SM); Department of Pathology, David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, California (DWN, ST, HVV); Semel Institute for Neuroscience and Human Behavior, Los Angeles, California (GC,VVB); Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, Illinois (SW, M-MM, EHB, DRG); Advocate Lutheran General Hospital, Park Ridge, Illinois (DRG); Department of Medicine, Rosalind Franklin University of Medicine and Science, North Chicago, Illinois (DRG); Department of Pathology, University of Michigan, Ann Arbor, Michigan (AOF-H); VA Ann Arbor Healthcare System, Geriatrics Research, Education, and Clinical Center, Ann Arbor, Michigan (RLA); and Department of Neurology, University of Michigan, Ann Arbor, Michigan (RLA).

Send correspondence to: John M. Ringman, MD, MS, Keck School of Medicine of University of Southern California, Center for the Health Professionals, 1540 Alcazar Street, Suite 209F, Los Angeles, CA 90089-0080; E-mail: john.ringman@med.usc.edu

Dr Ringman reports grants from National Institute on Aging (NIA) during the conduct of the study and grants from Biogen-Idec, grants from Eli-Lilly, and personal fees from InnoSense, LLC, outside the submitted work. Dr Zhou, Dr Albin, Dr Fisher-Hubbard, Dr Mendez, Dr Bigio, Ms Monsell, Dr Ng, Mr Nguyen, Dr Weintraub, and Mr Tung report grants from NIA during the conduct of the study. Dr Gitelman reports grants from Merck & Co. and Forum Pharmaceuticals and personal fees from Gerson Lehrman Group, O'Neill, McFadden & Willett, Neurometrika, Community Hospital of South Bend, Traveler's Insurance Co, J Reckner, Bluespark Communication, Elsevier, and Silverado Senior Living outside the submitted work. Dr Coppola reports grants from NIA during the conduct of the study and grants from Tau Consortium, Takeda Pharmaceuticals, French Foundation, and National Institute of Health (NIH) outside the submitted work. Dr Vinters reports grants from NIA during the conduct of this study; his trust owns shares in biotechnology and pharma companies, from which he receives dividends; these holdings have no conflict with the work described. Dr Van Berlo and Dr Mesulam have no duality or conflicts of interest to declare.

This study was supported by funding received by the lead author, John M. Ringman, from NIH (U19AG032438, P50 AG-16570, P50 AG-005142, and 1UL1-RR033176). The National Alzheimer's Coordinating Center (NACC) database is funded by NIA/NIH Grant U01 AG016976. NACC data are contributed by the NIA-funded Alzheimer's Disease Centers (ADCs): P30 AG019610 (PI Eric Reiman, MD), P30 AG013846 (PI Neil Kowall, MD), P50 AG008702 (PI Scott Small, MD), P50 AG025688 (PI Allan Levey, MD, PhD), P30 AG010133 (PI Andrew Saykin, PsyD), P50 AG005146 (PI Marilyn Albert, PhD), P50 AG005134 (PI Bradley Hyman, MD, PhD), P50 AG016574 (PI Ronald Petersen, MD, PhD), P50 AG005138 (PI Mary Sano, PhD), P30 AG008051 (PI Steven Ferris, PhD), P30 AG013854 (PI M. Marsel Mesulam, MD), P30 AG008017 (PI Jeffrey Kaye, MD), P30 AG010161 (PI David Bennett, MD), P30 AG010129 (PI Charles DeCarli, MD), P50 AG016573 (PI Frank LaFerla, PhD), P50 AG016570 (PI David Teplow, PhD), P50 AG005131 (PI Douglas Galasko, MD), P50 AG023501 (PI Bruce Miller, MD), P30 AG035982 (PI Russell Swerdlow, MD), P30 AG028383 (PI Linda Van Eldik, PhD), P30 AG010124 (PI John Trojanowski, MD, PhD), P50 AG005133 (PI Oscar Lopez, MD), P50 AG005142 (PI Helena Chui, MD), P30 AG012300 (PI Roger Rosenberg, MD), P50 AG005136 (PI Thomas Montine, MD, PhD), P50 AG033514 (PI Sanjay Asthana, MD, FRCP), and P50 AG005681 (PI John Morris, MD).

INTRODUCTION

The amyloid hypothesis of Alzheimer disease (AD) posits that alteration in amyloid precursor protein (APP) processing is central to the pathogenesis of all forms of AD (1). This is supported by the recognition that rare autosomal dominantly inherited forms of AD (autosomal dominant AD or ADAD) caused by mutations in the *APP*, *PSEN1*, and *PSEN2* genes lead to aberrant levels of APP cleavage products (2, 3), including β-amyloid (Aβ). Evidence for altered APP cleavage in sporadic AD (sAD) is weaker, although there is support for altered trafficking (4–6), transport (7), and degradation (8) of Aβ playing roles. Documentation of neuropathologic distinctions between these forms of AD is critical to understanding variability in pathways leading to their development (9).

AD is defined by the presence of extracellular deposition of protein aggregates containing APP derivatives, intracellular accumulation of cytoskeletal elements containing hyperphosphorylated tau (neurofibrillary tangles), and synapse and neuronal loss. Deposition of Aβ in the walls of small arterioles (ie, cerebral amyloid angiopathy [CAA]) is frequently present. Similarly, intraneuronal aggregates containing hyperphosphorylated α-synuclein (Lewy bodies) often coexist with AD changes. These features are also seen in ADAD, though their nature and distribution are variable. Extensive descriptions of the neuropathologic features of ADAD cases are prevalent in the literature (10, 11), but there are few large systematic comparisons with sAD.

Prior studies comparing neuropathology between persons with ADAD and sAD found increased levels of Aβ42 and neurofibrillary tangles in ADAD, with differences existing both between and within specific ADAD mutations (12, 13). A large study assessing the neuropathologic changes in 54 *PSEN1* mutation cases found higher levels of Aβ42 in frontal cortex. Greater degrees of amyloid pathology in the cerebellum and more severe CAA were seen in persons with *PSEN1* mutations after codon 200 (14). In a more recent study in which detailed immunohistochemical analyses were performed in 10 ADAD cases compared to 19 sAD cases, more extensive deposits of tau and Aβ42 were found in subcortical structures in ADAD and of Aβ42 in cortical regions in sAD (15). The finding of greater correlation of Aβ with proteins associated with its metabolism in ADAD but with markers of synaptic loss in sAD was interpreted as revealing potentially distinct pathogenic pathways.

The clinical relevance of CAA is becoming increasingly appreciated. In addition to increasing the risk of spontaneous (16) and anticoagulant-related (17) lobar hemorrhages, CAA appears to predispose to vasogenic edema and hemorrhagic complications of antiamyloid therapies (amyloid-related imaging abnormalities or ARIA), which are being evaluated for the treatment of AD (18). Because such therapies are in trials to prevent clinical disease in carriers of ADAD mutations, and it is important to understand CAA prevalence in this population.

In the current study, we used the National Alzheimer Coordinating Center (NACC) database to compare neuropathologic autopsy findings between persons dying with AD due to ADAD mutations to those found in sAD.

MATERIALS AND METHODS

The NACC collects clinical and neuropathologic data from National Institute on Aging (NIA)-funded Alzheimer's Disease Centers (ADCs). Participants and study partners provide informed consent and undergo comprehensive evaluations on an approximately annual basis. ADCs began collecting clinical (19) and neuropathological (20) data that were forwarded to the NACC starting in 1999. In 2005, the evaluations were expanded and standardized as the Uniform Data Set, such that, at each visit, a summary of findings is elaborated and a diagnosis is rendered (21). *APOE* genotyping is available on a subset of participants. The present study is a secondary analysis of anonymized data acquired under institutional review board approval at each center.

We queried the NACC database for cases for which key neuropathologic data (Braak staging, neuritic plaque, and CAA grading) were available and were coded as having either *PSEN1*, *APP*, or *PSEN2* mutations. We then contacted sites to verify the specific mutation present in each patient. Eight additional ADAD patients from University of California, Los Angeles (UCLA) who underwent identical neuropathologic assessments but had not been forwarded to the NACC were also included.

Controls were chosen from sAD subjects for whom data on the same key neuropathologic variables were available. The sAD cases were selected as follows: (1) they had a primary clinical diagnosis during life of dementia due to probable or possible AD (22); (2) to confirm the presence of amyloid pathology, they met the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropathologic criteria (20) for possible, probable, or definite AD; (3) they did not have frontotemporal lobar degeneration or other non-AD primary pathologic diagnoses; and (4) both parents were known to have lived beyond age 65 without dementia. Subjects were chosen by matching for sex, race, ethnicity, and disease duration (time from onset of symptoms until death, in years) with the ADAD group. Matching for ethnicity was performed based on a previous observation in the NACC dataset of a suggestion of increased risk of severe CAA among persons of Hispanic origin (23).

Sex, race, and Hispanic ethnicity were compared between ADAD and sAD groups. *APOE* genotypes were collapsed into one of 3 groups consisting of ε3 homozygotes (3/3), ε4 carriers (3/4 and 4/4), or ε2 carriers (2/3 and 2/2), and their frequencies were compared between groups. The neuropathologic variables that were compared between groups included ratings for diffuse and neuritic amyloid plaques. Diffuse and neuritic plaques were semiquantitated on a scale from 0 to 3 (none, sparse, moderate, or frequent) in 3 neocortical regions (middle frontal, superior temporal, and inferior parietal regions). Braak staging (0–VI) was also determined and compared between groups. Braak stages I and II reflect involvement mainly of entorhinal cortex and hippocampus; stages III and IV reflect more severe involvement of entorhinal cortex and hippocampus with early neocortical involvement in stage IV; stages V and VI reflect increasingly severe involvement of neocortex (24). CAA was also scored

on a scale from 0 to 3 (none, mild, moderate, and severe). Lewy body pathology was also rated and compared (0–3: none, brainstem predominant, intermediate or transitional, diffuse neocortical, respectively, or 4: "unspecified or not further assessed"). Because Lewy body pathology was coded as "unspecified or not further assessed" in 10 of 60 ADAD cases, cases coded as such were excluded and the analysis repeated for determining severity. Cerebrovascular variables were also compared between ADAD and sAD cases; these included the presence or absence of (1) any cerebrovascular pathology, (2) one or more large artery infarcts, (3) one or more cortical microinfarcts, (4) one or more lacunes, (5) single or multiple hemorrhages, (6) subcortical arteriosclerotic leukoencephalopathy/rarefaction, and (7) cortical laminar necrosis. Severity of (8) atherosclerotic vascular pathology of the Circle of Willis and (9) small parenchymal arteriolar disease were also assessed and scored as 0–3 (none, mild, moderate, and severe). We repeated the same analyses in the subset of persons with *PSEN1* mutations, comparing those with mutations before and after codon 200.

Comparisons were made using 2-tailed *t* tests for quantitative variables and chi-square and Fisher exact tests for categorical variables. All analyses were performed on IBM Statistical Package for the Social Sciences (SPSS), version 22.

RESULTS

Study Population

Fifty-two cases in the NACC from 15 ADCs and 8 additional cases from UCLA for whom an ADAD mutation could be verified were included (total = 60). There were 46 cases with *PSEN1* mutations (23 distinct mutations), 10 with *APP* mutations (4 mutations), and 4 with *PSEN2* mutations (all N141I [25]) (Table 1). Information on disease duration was available for 48 ADAD mutation carriers and had a mean value of 9.6 years (SD = 3.8 years). Mean age at death was 53.5 years (range 34–85), 50% were male, and *APOE* genotype was available for 50 cases (Table 2).

All but one of the 28 mutations had been previously reported and are thought to be pathogenic for ADAD (http://www.molgen.vib-ua.be/ADMutations/). One patient had a novel *PSEN1* mutation (P267A), which is included because the patient had AD neuropathology and the case for the pathogenicity of the mutation is strong. The patient with a P267A substitution was an African American male who presented with memory problems beginning at age 62, causing him to leave work at age 63. At age 67, he was hospitalized for severe behavioral changes; he died at age 69. The patient's identical twin was also diagnosed with AD at age 59, and their mother had died at age 79 with the onset of dementia symptoms in her mid 60s. The index patient had a nucleotide change at position 1047, which is predicted to cause an amino acid substitution of alanine for proline at codon 267. Two other pathogenic substitutions at this codon, which is located just outside the sixth transmembrane portion of presenilin-1, have been previously reported: P267S (26) and P267L (27). The P267A variant was not found in the Alzheimer's Disease and Frontotemporal Dementia Mutation Database (AD-FTD), Exome Aggregation Consortium (ExAC), Exome Variant Server (EVS), or 1000 genomes databases of human genetic variation. Further support for the pathogenicity of this mutation is the independent observation (at another ADC) of another African American man with an autosomal dominant family history of dementia, onset of symptoms at age 45, and meeting criteria for dementia at age 51, who was also found to have the P267A *PSEN1* variant. This variant is predicted to be deleterious by SIFT (http://sift.jcvi.org) and probably damaging by PolyPhen (http://genetics.bwh.harvard.edu/pph2/). This amino acid residue is conserved in mouse *PSEN1* and human *PSEN2* and would be classified as probably pathogenic according to the criteria of Guerreiro et al (28). The neuropathology associated with the P267A *PSEN1* mutation in the index patient was characterized by frequent neuritic plaques, Braak stage VI, severe CAA, and absence of Lewy body pathology. A single remote microscopic hemorrhage (vs. hemorrhagic microinfarct) was identified in the left putamen.

TABLE 1. Autosomal Dominant Alzheimer Disease Mutations

***PSEN1* (n = 46)**		
A79V (5 cases)	I143T (2 cases)	M233L (2 cases)
Y115C (2 cases)	M146L (2 cases)	L235V
Y115H	Y156insFI	T245P (2 cases)
E120D	H163R (4 cases)	V261F
N135D	S170F	P267A[a]
N135S (2 cases)	G206A (6 cases)	A431E (6 cases)
M139I	G209V	L435F
M139V	L226R	
***APP* (n = 10)**		
E693G	V717I (3 cases)	
V717F (4 cases)	V717L (2 cases)	
***PSEN2* (n = 4)**		
N141I (4 cases)		

[a]Novel *PSEN1* mutation.

One hundred twenty sAD cases were identified from 21 ADCs, of which 106 had diagnoses of probable AD and 14 possible AD during life. Mean age at death was 79 years of age (range 45–101), mean disease duration was 9.5 years, 53% were male, and *APOE* genotype was available for 104 (Table 2).

Twenty percent of the ADAD patients were of Hispanic origin, due largely to the inclusion of 6 persons with the A431E and 6 with the G206A *PSEN1* mutation, which represent founder effects arising from Jalisco, Mexico (29, 30), and Puerto Rico (31), respectively. Persons of Hispanic origin are underrepresented in the NACC; thus, we were unable to match the groups perfectly with respect to ethnicity; however, no statistically significant difference between groups with respect to ethnicity was present. Distribution of *APOE* genotype differed between the ADAD and sAD groups, with an overrepresentation of the ϵ4 allele in 51.7% of the sAD group versus 23.2% of the ADAD group ($p < 0.001$).

Patients with ADAD had significantly higher neuritic plaque scores than those with sAD (2.9 vs. 2.7, $p = 0.006$), despite having comparable diffuse plaque and CERAD scores (Table 3). Braak stage was also higher in ADAD (5.8 vs. 5.3,

TABLE 2. Demographic Data and *APOE* Genotypes in Study Population[a]

	Autosomal Dominant AD (n = 60)	Sporadic AD (n = 120)	p Values
Gender, number of males	30 (50%)	63 (52.5%)	0.76
Age at death, in years (SD)	53.5 (10.9)	79.3 (9.6)	< 0.001
Disease duration, years (SD)	9.6 (n = 48, 3.8)	9.5 (3.9)	0.97
Ethnicity, number of Hispanic	12 (20%)	16 (13.3%)	0.28
Race			0.62
White	55 (91.7%)	107 (89.2%)	
Black	1 (1.7%)	4 (3.3%)	
American Indian	0 (0%)	2 (1.7%)	
Pacific Islander	1 (1.7%)	0 (0%)	
Asian	2 (3.3%)	5 (4.2%)	
Other	1 (1.7%)	2 (1.7%)	
APOE genotypes			0.001
3/3	33 (58.9%)	40 (33.3%)	
3/4	13 (23.2%)	44 (36.7%)	
2/3	4 (7.1%)	2 (1.7%)	
4/4	0 (0%)	16 (13.3%)	
2/4	0 (0%)	2 (1.7%)	
Unknown	10 (10.7%)	16 (13.3%)	

AD, Alzheimer disease; SD, standard deviation.

[a]Results are based on 2-sided chi-square tests except for age, death, and disease duration, which were 2-tailed *t* tests.

$p < 0.001$) cases, as was CAA score (1.8 vs. 1.2, $p = 0.002$). When the prevalence of CAA grades (absent/mild vs. moderate/severe) was compared, moderate or severe CAA was more common in ADAD than sAD (63.3% vs. 39.2%, $p = 0.003$). Lewy body pathology was present in 27.1% of ADAD and 30.8% of sAD cases. When the degree of Lewy body pathology was compared by *t* test between ADAD and sAD for those in whom it was staged (n = 49 and 111, respectively), a greater extent of Lewy body pathology was noted in sAD (0.59 vs. 0.24, $p = 0.021$). The prevalence of lacunes, severity of atherosclerosis of the Circle of Willis, and parenchymal arteriosclerosis was greater in sAD (all p values < 0.008, Table 3).

The 22 cases with *PSEN1* mutations after codon 200 did not differ in sex or *APOE* genotype distribution, or disease duration from 24 *PSEN1* cases with mutations before codon 200 (Table 4). Those with mutations after codon 200 had higher Braak (6 vs. 5.5, $p = 0.024$) and CAA (2.4 vs. 1.2, $p = 0.001$) scores than those with mutations before codon 200. Persons with *PSEN1* mutations after codon 200 were more likely to be described as having "ischemic, hemorrhagic, or vascular pathology present" (86.4% vs. 50%, $p = 0.02$).

DISCUSSION

In the current study, we verified the increased severity of AD neuropathologic changes in persons dying with ADAD mutations relative to those with sAD of later onset but of similar duration. Neurofibrillary pathology in the form of neurofibrillary tangles and neuritic plaques was increased, although diffuse plaques were not. Despite having a lower frequency of the *APOE* ϵ4 allele, a known risk factor for CAA, ADAD patients more commonly had more severe degrees of CAA pathology. Finally, we report a novel *PSEN1* mutation (P267A) and strong evidence for its pathogenicity.

Consistent with prior reports, we found more aggressive AD pathology in ADAD. It is likely that the misprocessing of APP with resulting aberrant levels of its cleavage products (eg, increased levels of Aβ42 or other Aβ derivatives) is a strong driver of the neuritic plaque formation and tau pathology observed. These indices are more tightly linked to synaptic and neuronal loss, as well as clinical manifestations (32). Despite the higher degree of neuritic plaque and tangle pathology in ADAD, we did not find a difference in the degree of diffuse plaque pathology, suggesting that such plaques are not in the causal pathway to neurodegeneration. The mechanisms through which APP mismetabolism drives neuritic plaque and neurofibrillary tangle formation, however, are incompletely understood as the topographic distribution of neuritic plaques and neurofibrillary tangles differs (33), and there appear to be diverse events leading to neurofibrillary tangle pathology (34, 35), including normal aging (36). The specific differences in APP processing that account for the more aggressive AD pathology seen in ADAD are unclear because qualitative differences have been shown in APP processing between ADAD and sAD (37–39) and even between *APP* mutations at the same codon (40). Furthermore, additional effects of *PSEN1* mutations on γ-secretase activity beyond those on APP processing cannot be excluded (3).

We found greater severity of CAA and increased prevalence of moderate and severe CAA in persons with ADAD mutations. This effect was present despite the facts that sAD subjects were older and had a higher prevalence of the *APOE* ϵ4 allele, both of which are known risk factors for CAA (23, 41). Although this effect was most dramatic in persons with *PSEN1* mutations beyond codon 200, severe CAA was also seen in 5 *PSEN1* cases with mutations before codon 200 and in 2 of 4 cases with the N141I *PSEN2* mutation (Table 5). It was also seen in 2 of 9 cases with mutations near the γ-secretase site of *APP* and has been reported in patients with duplication of the *APP* locus (42) and in Down syndrome (43). This indicates that the effect is not driven solely by *APP* mutations within the coding region of APP that have been well documented to cause severe CAA, perhaps by virtue of unique effects on Aβ aggregation (10, 44). In our study, a single patient with the E693G *APP* mutation, which has been shown to be associated with severe CAA (10), had only mild CAA. Although the causes of CAA are not completely understood, defective clearance of Aβ species, particularly of Aβ40, across the endothelium has been proposed as one mechanism (7, 45). Why this would occur in association with ADAD mutations awaits further exploration.

Because CAA increases the risk of spontaneous (16) and anticoagulant-related (17) lobar hemorrhage and appears to predispose to ARIA (18), it is important to identify its presence during life to help understand the response and adverse-effect profile of putative antiamyloid therapies. These cases represent late-stage disease, and we do not know at what point CAA develops. Therefore, the relevance of this observation in

TABLE 3. Comparisons of National Alzheimer's Coordinating Center Neuropathology Variables Between Autosomal Dominant Alzheimer Disease and Sporadic Alzheimer Disease

	Autosomal dominant AD (n = 60)	Sporadic AD (n = 120)	p Values
Neuritic plaque score[a] (SD)	2.93 (0.41)	2. 73 (0.53)	0.006*
Braak score[b] (SD)	5.8 (0.63)	5.3 (1.1)	< 0.001*
Cerebral amyloid angiopathy score[c] (SD)	1.8 (1.2)	1.2 (1.0)	0.002*
CERAD score[d] (SD)	2.87 (n = 47, 0.54)	2.78 (0.54)	0.34*
Diffuse plaque score[e] (SD)	2.6 (n = 52, 0.78)	2.7 (0.66)	0.39*
Lewy body pathology score[f] (SD)	0.24 (n = 49, 0.72)	0.59 (n = 111, 1.1)	0.021*
Ischemic, hemorrhagic, or vascular pathology present, n (%)	41 (n = 58, 70.7%)	89 (74.2%)	0.72**
One or more large artery infarcts present, n (%)	2 (n = 58, 3.4%)	11 (9.2%)	0.23**
One or more cortical microinfarcts present, n (%)	3 (n = 58, 5.2%)	16 (13.3%)	0.12**
One or more lacunes present, n (%)	2 (n = 58, 3.4%)	21 (17.5%)	0.008**
Single or multiple hemorrhages present, n (%)	3 (n = 58, 5.2%)	4 (3.3%)	0.68**
Subcortical arteriosclerotic leukoencephalopathy present, n (%)	5 (n = 57, 8.8%)	14 (n = 119, 11.8%)	0.62***
Cortical laminar necrosis present, n (%)	0 (n = 59, 0%)	1 (0.8%)	1.0**
Medial temporal sclerosis present, n (%)	7 (n = 57, 12.3%)	14 (11.7%)	1.0**
Atherosclerotic vascular pathology (of the circle of Willis) grading[g] (SD)	1.6 (n = 57, 0.78)	2.3 (0.92)	< 0.001*
Arteriosclerosis (small parenchymal arteriolar disease) grading[h] (SD)	1.64 (0.90)	2.29 (n = 108, 0.90)	< 0.001*

AD, Alzheimer disease; SD, standard deviation.
[a]Neuritic plaque score: 0 = no neuritic plaques, 1 = sparse neuritic plaques, 2 = moderate neuritic plaques, 3 = frequent neuritic plaques.
[b]Braak stage: 0 = no neurofibrillary degeneration present, 1 – 6 = Braak stages I–VI.
[c]Cerebral amyloid angiopathy (CAA): 0 = no CAA present, 1 = mild, 2 = moderate, 3 = severe CAA.
[d]CERAD (Consortium to Establish a Registry for Alzheimer's Disease) score: 0 = did not meet CERAD criteria, 1 = possible AD, 2 = probable AD, 3 = definite AD.
[e]Diffuse plaques: 0 = no diffuse plaques, 1 = sparse, 2 = moderate, 3 = frequent diffuse plaques.
[f]Lewy Body pathology: 0 = no Lewy bodies, 1 = brainstem predominant, 2 = intermediate or transitional (limbic) type, 3 = diffuse (neocortical) type.
[g]Atherosclerotic pathology of the Circle of Willis: 0 = none, 1 = mild, 2 = moderate, 3 = severe.
[h]Arteriosclerosis: 0 = none, 1 = mild, 2 = moderate, 3 = severe.
*2-tailed *t* test. **2-sided chi-square test. ***Fisher exact test.

early stage or secondary prevention trials is unclear. Nonetheless, individual case reports and Table 5 (which documents those ADAD cases in which severe CAA was observed in this study) are helpful in predicting the ultimate presence of CAA.

Not surprisingly, we found a higher prevalence of lacunes, severity of atherosclerosis of the Circle of Willis, and parenchymal arteriosclerosis in sAD versus ADAD. This is likely due to the older age and associated vascular risk factors in sAD and supports these processes as being independent of AD and CAA (46).

Though cases with ADAD had less frequent and severe Lewy body pathology than sAD cases, such pathology was found in 16/59 (27.1%) of ADAD cases; therefore, it was more common than would be expected to occur by chance in the relatively young ADAD population. The presence of Lewy body pathology in ADAD has been characterized in previous case reports and series (47, 48), suggesting it arises from processes downstream of APP mismetabolism. The nature of this interaction is unclear, however, because introduction of a mutant human α-synuclein transgene into an ADAD mouse was found to exacerbate amyloid, tau, and α-synuclein pathologies (49), but a recent study found that intracerebral injection of α-synuclein preparations into *APP/PSEN1* transgenic mice inhibited amyloid plaque formation (50). The variable presence of Lewy bodies across persons with the same ADAD mutation suggests that their development is subject to additional factors (47).

In-depth descriptions of ADAD cases have elaborated distinctive neuropathologic features, including atypical amyloid plaque morphology (39) and plaque and tangle distribution (11, 51). Unfortunately, the dataset from which the current observations are derived provided only summary data of typical AD neuropathologic characteristics, and therefore, we were unable to assess these specific features. Furthermore, the NACC neuropathology dataset consists of semiquantitative ratings, and more rigorous quantitative methods (eg, area of Aβ42 positivity) would have enhanced the sensitivity and interpretability of our results.

Another limitation of this study is the comparability of the sAD cases. By design, the sAD cases were, on average, older and therefore had higher degrees of medical comorbidity. Though disease durations were comparable, we cannot exclude the possibility that some sAD patients died at an earlier stage of disease because of these comorbidities, whereas the younger ADAD patients were likely to have died more directly from AD-related complications. Furthermore, while we reduced the genetic contribution to disease in the sAD cases by choosing only subjects whose parents were known to have died after age 65 without dementia, the higher prevalence of the *APOE* ϵ4 allele in this population nevertheless indicates that a contribution by a genetic risk factor was present in many cases; in other words, they were not truly entirely "sporadic" in nature.

Another weakness of this study was missing data. Although all subjects had the primary neuropathologic variables

TABLE 4. Neuropathologic Variables That Differed Between *PSEN1* Mutation Carriers With Mutations Before or After Codon 200

	***PSEN1* mutation < 200 (n = 24)**	***PSEN1* mutation > 200 (n = 22)**	**p Values**
Gender, number of males	13 (54.2%)	8 (36.4%)	0.25**
Disease duration, years (SD)	8.3 (n = 17, 3.6)	9.9 (n = 21, 4.4)	0.23*
APOE genotypes			
3/3	11 (45.8%)	12 (54.5%)	
3/4	6 (25.0%)	5 (22.7%)	0.59**
2/3	2 (8.3%)	1 (4.5%)	
Unknown	5 (20.8%)	4 (18.1%)	
Braak score[a] (SD)	5.5 (0.93)	6.0 (0.0)	0.024*
Cerebral amyloid angiopathy score[b] (SD)	1.2 (1.3)	2.4 (0.85)	0.001*
Ischemic, hemorrhagic, or vascular pathology present	11 (n = 22, 50.0%)	19 (86.4%)	0.02**

SD, standard deviation.
[a]Braak stage: 0 = no neurofibrillary degeneration present, 1–6 = Braak stages I–VI.
[b]Cerebral amyloid angiopathy (CAA): 0 = no CAA present, 1 = mild, 2 = moderate, 3 = severe CAA.
*2-tailed *t* test. **2-sided chi-square test.

TABLE 5. Proportion of Cases Showing Severe Cerebral Amyloid Angiopathy (CAA) Among All Mutations in Which at Least 1 Patient Had Severe CAA

PSEN1		
Y115C (1/2 cases)	G206A (2/6 cases)	V261F (1/1 case)
M139V (1/1 case)	G209V (1/1 case)	P267A (1/1 case)
M146L (1/2 cases)	L235V (1/1 case)	A431E (4/6 cases)
Y156insFI (1/1 case)	T245P (1/2 cases)	L435F (1/1 case)
S170F (1/1 case)		
APP		
V717F (2/4 cases)		
PSEN2		
N141I (2/4 cases)		

of interest (neuritic plaque score, Braak staging, and CAA grading), many subjects lacked other variables and *APOE* genotype. This was particularly true for 12 earlier-enrolled ADAD subjects for whom the age of onset (and therefore disease duration) was missing. Though this was suboptimal, disease duration and *APOE* genotype were not principal outcomes in this study, and it was necessary to include such cases to achieve the relatively large numbers for the main analyses.

Finally, variability in neuropathologic protocols across ADCs and across the 15-year duration of data collection is a major limitation. For example, the protocols for identifying the presence of microinfarcts and the immunostains and procedures used to identify Lewy bodies have varied over time and between centers. This may account for the lower frequency of microinfarcts in sAD (52) cases and Lewy bodies in ADAD (47, 48) found in our population relative to other studies. Also, relatively recently identified pathological changes of relevance in AD (eg, TDP-43 positivity) were not systematically added to the Uniform Data Set protocol until after the majority of data for this study were collected, thereby precluding our ability to assess such features in ADAD.

In summary, we used the NACC database to identify neuropathologic differences between cases of ADAD and sAD of later onset. We found higher degrees of neuritic plaque and neurofibrillary tangle pathology as well as more extensive and prevalent CAA in ADAD. We replicated the previous finding that persons with *PSEN1* mutations beyond codon 200 had a greater severity of neurofibrillary pathology and CAA than those before codon 200. Although Lewy body pathology was less frequent than in sAD, we observed a high frequency of such pathology in ADAD, supporting the view that it is a process at least partly driven by abnormal APP metabolism. Finally, we report a novel pathogenic *PSEN1* mutation (P267A). These observations shed light on common and distinct pathways in these etiologically distinct forms of AD and may help us design and interpret future and ongoing therapeutic trials.

REFERENCES

1. Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: Progress and problems on the road to therapeutics. Science 2002;297:353–6
2. Scheuner D, Eckman C, Jensen M, et al. Secreted amyloid β-protein similar to that in the senile plaques of Alzheimer's disease is increased in vivo by the presenilin 1 and 2 and APP mutations linked to familial Alzheimer's disease. Nat Med 1996;2:864–70
3. Xia D, Watanabe H, Wu B, et al. Presenilin-1 knockin mice reveal loss-of-function mechanism for familial Alzheimer's disease. Neuron 2015; 85:967–81
4. Reitz C, Tokuhiro S, Clark LN, et al. SORCS1 alters amyloid precursor protein processing and variants may increase Alzheimer's disease risk. Ann Neurol 2011;69:47–64
5. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 2009;41:1088–93
6. Naj AC, Jun G, Beecham GW, et al. Common variants at MS4A4/MS4A6E, CD2AP, CD33 and EPHA1 are associated with late-onset Alzheimer's disease. Nat Genet 2011;43:436–41
7. Bell RD, Sagare AP, Friedman AE, et al. Transport pathways for clearance of human Alzheimer's amyloid β-peptide and apolipoproteins E and J in the mouse central nervous system. J Cereb Blood Flow Metab 2007;27:909–18
8. Tanzi RE, Moir RD, Wagner SL. Clearance of Alzheimer's Aβ peptide: The many roads to perdition. Neuron 2004;43:605–8
9. Ringman JM, Goate A, Masters CL, et al. Genetic heterogeneity in Alzheimer disease and implications for treatment strategies. Curr Neurol Neurosci Rep 2014;14:499

10. Basun H, Bogdanovic N, Ingelsson M, et al. Clinical and neuropathological features of the arctic APP gene mutation causing early-onset Alzheimer disease. Arch Neurol 2008;65:499–505
11. Ringman JM, Gylys KH, Medina LD, et al. Biochemical, neuropathological, and neuroimaging characteristics of early-onset Alzheimer's disease due to a novel PSEN1 mutation. Neurosci Lett 2011;487:287–92
12. Ishii K, Lippa C, Tomiyama T, et al. Distinguishable effects of presenilin-1 and APP717 mutations on amyloid plaque deposition. Neurobiol Aging 2001;22:367–76
13. Gómez-Isla T, Growdon WB, McNamara MJ, et al. The impact of different presenilin 1 and presenilin 2 mutations on amyloid deposition, neurofibrillary changes and neuronal loss in the familial Alzheimer's disease brain: Evidence for other phenotype-modifying factors. Brain 1999;122: 1709–19
14. Mann DM, Pickering-Brown SM, Takeuchi A, et al. Amyloid angiopathy and variability in amyloid β deposition is determined by mutation position in presenilin-1-linked Alzheimer's disease. Am J Pathol 2001;158: 2165–75
15. Shinohara M, Fujioka S, Murray ME, et al. Regional distribution of synaptic markers and APP correlate with distinct clinicopathological features in sporadic and familial Alzheimer's disease. Brain 2014;137: 1533–49
16. Viswanathan A, Greenberg SM. Cerebral amyloid angiopathy in the elderly. Ann Neurol 2011;70:871–80
17. Rosand J, Hylek EM, O'Donnell HC, et al. Warfarin-associated hemorrhage and cerebral amyloid angiopathy: A genetic and pathologic study. Neurology 2000;55:947–51
18. Weller RO, Boche D, Nicoll JA. Microvasculature changes and cerebral amyloid angiopathy in Alzheimer's disease and their potential impact on therapy. Acta Neuropathol 2009;118:87–102
19. Morris JC, Heyman A, Mohs RC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part I. Clinical and neuropsychological assessment of Alzheimer's disease. Neurology 1989;39: 1159–65
20. Mirra SS, Heyman A, McKeel D, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part II. Standardization of the neuropathologic assessment of Alzheimer's disease. Neurology 1991; 41:479–86
21. Beekly DL, Ramos EM, Lee WW, et al. The National Alzheimer's Coordinating Center (NACC) database: The Uniform Data Set. Alzheimer Dis Assoc Disord 2007;21:249–58
22. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 1984;34:939–44
23. Ringman JM, Sachs MC, Zhou Y, et al. Clinical predictors of severe cerebral amyloid angiopathy and influence of *APOE* genotype in persons with pathologically verified Alzheimer disease. JAMA Neurol 2014;71: 878–83
24. Braak H, Braak E. Neuropathological stageing of Alzheimer-related changes. Acta Neuropathol 1991;82:239–59
25. Bird TD, Lampe TH, Nemens EJ, et al. Familial Alzheimer's disease in American descendants of the Volga Germans: Probable genetic founder effect. Ann Neurol 1988;23:25–31
26. Hutton M, Busfield F, Wragg M, et al. Complete analysis of the presenilin 1 gene in early onset Alzheimer's disease. Neuroreport 1996;7:801–5
27. Kowalska A, Wender M, Florczak J, et al. Molecular genetics of Alzheimer's disease: Presenilin 1 gene analysis in a cohort of patients from the Poznan region. J Appl Genet 2003;44:231–4
28. Guerreiro RJ, Baquero M, Blesa R, et al. Genetic screening of Alzheimer's disease genes in Iberian and African samples yields novel mutations in presenilins and APP. Neurobiol Aging 2010;31:725–31
29. Yescas P, Huertas-Vazquez A, Villarreal-Molina MT, et al. Founder effect for the Ala431Glu mutation of the presenilin 1 gene causing early-onset Alzheimer's disease in Mexican families. Neurogenetics 2006;7: 195–200
30. Murrell J, Ghetti B, Cochran E, et al. The A431E mutation in PSEN1 causing familial Alzheimer's disease originating in Jalisco State, Mexico: An additional fifteen families. Neurogenetics 2006;7:277–9
31. Athan ES, Williamson J, Ciappa A, et al. A founder mutation in presenilin 1 causing early-onset Alzheimer disease in unrelated Caribbean Hispanic families. JAMA 2001;286:2257–63
32. Serrano-Pozo A, Frosch MP, Masliah E, et al. Neuropathological alterations in Alzheimer disease. Cold Spring Harb Perspect Med 2011;1: a006189
33. Arnold SE, Hyman BT, Flory J, et al. The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cereb Cortex 1991; 1:103–16
34. Uchihara T. Pretangles and neurofibrillary changes: Similarities and differences between AD and CBD based on molecular and morphological evolution. Neuropathology 2014;34:571–7
35. Lucke-Wold BP, Turner RC, Logsdon AF, et al. Linking traumatic brain injury to chronic traumatic encephalopathy: Identification of potential mechanisms leading to neurofibrillary tangle development. J Neurotrauma 2014;31:1129–38
36. Delacourte A, David JP, Sergeant N, et al. The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158–65
37. Portelius E, Andreasson U, Ringman JM, et al. Distinct cerebrospinal fluid amyloid β peptide signatures in sporadic and PSEN1 A431E-associated familial Alzheimer's disease. Mol Neurodegener 2010;5:2
38. Pera M, Alcolea D, Sanchez-Valle R, et al. Distinct patterns of APP processing in the CNS in autosomal-dominant and sporadic Alzheimer disease. Acta Neuropathol 2013;125:201–13
39. Miravalle L, Calero M, Takao M, et al. Amino-terminally truncated Abeta peptide species are the main component of cotton wool plaques. Biochemistry 2005;44:10810–21
40. Suarez-Calvet M, Belbin O, Pera M, et al. Autosomal-dominant Alzheimer's disease mutations at the same codon of amyloid precursor protein differentially alter Aβ production. J Neurochem 2014;128:330–9
41. Vinters HV, Gilbert JJ. Cerebral amyloid angiopathy: Incidence and complications in the aging brain. II. The distribution of amyloid vascular changes. Stroke 1983;14:924–8
42. Rovelet-Lecrux A, Hannequin D, Raux G, et al. APP locus duplication causes autosomal dominant early-onset Alzheimer disease with cerebral amyloid angiopathy. Nat Genet 2006;38:24–6
43. Belza MG, Urich H. Cerebral amyloid angiopathy in Down's syndrome. Clin Neuropathol 1986;5:257–60
44. Nilsberth C, Westlind-Danielsson A, Eckman CB, et al. The 'Arctic' APP mutation (E693G) causes Alzheimer's disease by enhanced Aβ protofibril formation. Nat Neurosci 2001;4:887–93
45. Hawkes CA, Jayakody N, Johnston DA, et al. Failure of perivascular drainage of β-amyloid in cerebral amyloid angiopathy. Brain Pathol 2014;24:396–403
46. Zheng L, Vinters HV, Mack WJ, et al. Cerebral atherosclerosis is associated with cystic infarcts and microinfarcts but not Alzheimer pathologic changes. Stroke 2013;44:2835–41
47. Leverenz JB, Fishel MA, Peskind ER, et al. Lewy body pathology in familial Alzheimer disease: Evidence for disease- and mutation-specific pathologic phenotype. Arch Neurol 2006;63:370–6
48. Lippa CF, Fujiwara H, Mann DM, et al. Lewy bodies contain altered alpha-synuclein in brains of many familial Alzheimer's disease patients with mutations in presenilin and amyloid precursor protein genes. Am J Pathol 1998;153:1365–70
49. Clinton LK, Blurton-Jones M, Myczek K, et al. Synergistic Interactions between Abeta, tau, and alpha-synuclein: Acceleration of neuropathology and cognitive decline. J Neurosci 2010;30:7281–9
50. Bachhuber T, Katzmarski N, McCarter JF, et al. Inhibition of amyloid-β plaque formation by α-synuclein. Nat Med 2015;21:802–7
51. Sepulveda-Falla D, Matschke J, Bernreuther C, et al. Deposition of hyperphosphorylated tau in cerebellum of PS1 E280A Alzheimer's disease. Brain Pathol 2011;21:452–63
52. Smith EE, Schneider JA, Wardlaw JM, et al. Cerebral microinfarcts: The invisible lesions. Lancet Neurol 2012;11:272–82