

The Neuropathology of Alzheimer Disease in African American and White Individuals

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Background: Data from neuropathologic studies of the frequency of Alzheimer disease (AD) among African American persons conflict as to whether the neuropathologic phenotype of AD is identical in African American and white persons.

Objectives: To examine clinical and neuropathologic phenotypes of AD in African American individuals and to compare AD and vascular burdens between African American and white persons.

Design, Setting, and Patients: Ten African American decedents who underwent brain autopsy at the Washington University Alzheimer's Disease Research Center were matched for age, sex, and Clinical Dementia Rating with 10 white decedents between January 1, 1990,

and January 1, 2000. The presence and degree of neurofibrillary tangles, senile plaques, Lewy bodies, cerebral infarcts, and cerebral amyloid angiopathy were determined.

Results: All 20 individuals had a neuropathologic diagnosis of AD. There were no group differences in the presence or number of infarcts, plaques, tangles, Lewy bodies, or amyloid angiopathy.

Conclusion: In this small sample, we found no substantive differences in the neuropathology of AD among African American and white individuals.

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WHETHER DEMENTIA in African American individuals is more likely to be caused by cerebrovascular factors than Alzheimer disease (AD) as compared with white persons is controversial. Clinically diagnosed vascular dementia is reported more frequently in African Americans,¹⁻⁴ although a recent study of older adults in northern Manhattan reported a 2-fold increase in AD among African American as compared with white individuals.⁵ The few clinicopathological studies of older African American subjects offer conflicting data. One study of demented individuals aged 65 years or older found no differences in the frequency of AD neuropathology between African American and white individuals,⁶ but another study found more AD pathology in white persons whereas African American individuals were more likely to have multiple cerebral infarcts.⁷ Perceived differences in causes of dementia between African American and white persons may affect diagnosis and management.

Studies of dementia in the African American population have been limited. In particular, few (if any) have correlated

clinical and neuropathologic diagnoses. The higher incidence of vascular disease risk factors such as diabetes mellitus⁸ and hypertension⁹ in African American persons has resulted in the perception that they may be more likely to have vascular dementia. Prior neuropathologic studies of vascular dementia have focused primarily on the presence and location of infarcts and not other vasculopathies, such as cerebral amyloid angiopathy.

We report the clinicopathological findings in well-characterized African American participants at the Alzheimer's Disease Research Center (ADRC) at Washington University in St Louis, Mo, in comparison with those in white subjects. The goal of the study was to compare the burden of AD and vascular disease neuropathology between African American and white individuals.

METHODS

PARTICIPANTS

We evaluated all 10 African American participants who came to autopsy in the Washington University ADRC between January 1, 1990, and January 1, 2000; 9 had been participants

in longitudinal studies in the ADRC and another presented to the ADRC at death. These participants were compared with 10 white ADRC participants matched on sex, age at death (± 5 years), and Clinical Dementia Rating (CDR) at death.

The ADRC enrolls cognitively healthy and demented participants aged 50 years or older from the greater metropolitan St Louis area. Except for dementia, participants generally are healthy. Inclusion and exclusion criteria for dementia of the Alzheimer type correspond to the probable AD categories of the NINCDS/ADRDA (National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association) Work Group.¹⁰

CLINICAL ASSESSMENT

The assessment protocol includes past medical, social, and family history, current medications, a depressive features battery, Mini-Mental State Examination, Short Blessed Test, and neurologic examination.¹¹⁻¹³ A clinician also obtains information on the cognitive function of the participant from a reliable informant, usually the spouse or an adult child, using semi-structured interviews. The clinician then assigns a CDR¹⁴ and diagnosis.

Each participant completes a psychometric battery that examines primary, working, episodic, and semantic memory, mental control, visuospatial function, psychomotor speed, and language.¹⁵ The clinical variables compared in this study were hypertension (including treatment), history of stroke, smoking (current or past), hyperlipidemia, diabetes, and depression. Information about these variables was obtained by health history and, where appropriate, medical record review at each assessment.

DEATH SUMMARY

At autopsy, a validated retrospective postmortem interview is conducted with the informant to assess cognitive status from time of last assessment until death.¹⁶ Before the results of the autopsy are known, a senior clinician reviews all clinical assessments and the postmortem interview and generates a death summary, which yields a final CDR score and dementia diagnosis for the participant.¹⁷

NEUROPATHOLOGY METHODS

All autopsies were performed at Washington University Medical Center. The overall autopsy rate in ADRC participants over the entire duration of the program was 55% (627 autopsies in 1138 deaths); during the period of this study, the 10 autopsies on African American participants were obtained from a total of 41 African American participant deaths. The neuropathologic diagnosis of AD was based on Washington University ADRC criteria,¹² a modification of the criteria reported by consensus recommendations.¹⁸ The following regions from the left cerebral hemisphere were sampled for microscopic morphometric analyses: middle frontal gyrus, superior temporal gyrus, inferior parietal lobule, CA1 portion of the hippocampus and subiculum, and entorhinal cortex between the levels of the mamillary and lateral geniculate bodies. Additional sections were examined of occipital cortex, basal ganglia, thalamus, brainstem, and cerebellum as part of the general neuropathologic examination. Sections (6 μ m) were cut from each paraffin-embedded block perpendicularly to the pial surface. The staining and counting procedures for neurofibrillary tangles (NFTs) and senile plaques (SPs) were detailed previously.¹⁹ Two modifications of the Bielschowsky ammoniacal silver method were used. One was optimized to demonstrate neurofibrillary neuritic plaques. The other, adapted from Hedreen and colleagues,²⁰ provided optimal detection of all SPs, including diffuse and neuritic plaques.

In the microscopic sections from each region, densities of NFTs and SPs (total and subtypes), expressed as an average number per square millimeter, were determined in a standardized method previously detailed²¹ based on variations of lesion densities or distributions in individual cases. Counts were taken in 10 consecutive 1-mm cortical fields per side, 5 along the pial surface and 5 along the white matter cortex junction. Both intracellular and extracellular tangles were included in the NFT counts. Total SPs included all varieties of argyrophilic diffuse and neuritic plaques. Diffuse plaques are amorphous or finely fibrillar deposits and lack abnormal argyrophilic neurites or central cores. Neuritic plaques contain abnormal swollen argyrophilic neurites. Cored SPs are a subset of neuritic plaques and contain central compact cores. Neuritic plaque densities were determined by means of one silver method on a section of frontal cortex within 50 μ m of the sections used for total SP densities with the other silver method.

Cortical Lewy bodies (LBs) were assessed with anti-ubiquitin-stained sections of entorhinal cortex, chosen to be representative of the limbic system where cortical LBs tend to be prevalent. The LBs were noted as present or absent after search through consecutive 1-mm fields from the medial edge of the entorhinal cortex to the depth of the collateral sulcus. The LBs were distinguished from NFTs by being circular or oval, nonfibrillar, and usually associated with an eccentric nucleus.

Presence and degree of infarcts were determined in the cortex, white matter, gray matter, brainstem, and cerebellum. The burden of cerebral amyloid angiopathy was determined by using Gallyas silver staining and immunoperoxidase staining (brown DAB chromogen) with antibody to A β protein (Athena/Elan10D5, 1:40 000 dilution) monoclonal antibody in leptomeningeal and parenchymal blood vessels. Pretreatments included pepsin (1:2500) for 10 minutes, 88% formic acid for 3 minutes, and microwave-citrate at a pH of 6 for 5 minutes. The numbers of positive blood vessels per section were reported using the following system: grade 0 (none), grade 1 (1-2 positive), grade 2 (3-5 positive), and grade 3 (≥ 5 positive).

The pathologic variables compared were diagnosis; burden of plaques, tangles, and cerebral amyloid angiopathy; and presence of LBs.

Statistical comparisons between the African American and white groups on relevant variables were based on the technique of statistical hypothesis testing. Owing to the limited sample size, Fisher exact test²² was used to compare the 2 groups on binomial variables (eg, presence or absence of hypertension). The *t* test was used to compare the 2 groups on continuous variables (eg, years of education). The Mantel-Haenszel χ^2 test was used to compare the severity of neuropathologic changes (plaques, tangles, infarcts, and amyloid angiopathy) between African American and white subjects. These tests were implemented using PROC FREQ and PROC TTEST in SAS/STAT software.²³ The accuracy of the clinical diagnosis of dementia in African American subjects as compared with the neuropathologic diagnosis was assessed using the κ coefficient.²⁴

RESULTS

Each group consisted of 5 men and 5 women. African American individuals had a higher level of education compared with white subjects (**Table 1**). There was no difference in history of stroke, tobacco use, apolipoprotein E (APOE) genotype, or performance on the cognitive tests between the groups. Hypertension was reported more often in African American than white subjects (Table 1). No participant had diabetes mellitus.

All African American participants had neuropathologic diagnoses of AD, 2 with coexisting cerebrovascular infarcts and 1 with a subdural hematoma. All white subjects also had AD, 1 with coexisting cerebrovascular infarcts and 1 with coexisting Parkinson disease (**Table 2**). The mean brain weight in the African American subjects was 1090 g (SD, 191 g) compared with 1100 g (SD, 157 g) for white subjects. Group comparisons showed no difference in the presence or number of infarcts, plaques, tangles, or LBs (Table 2). Amyloid angiopathy was present in 33% of parenchymal vessels in African American subjects compared with 0% in white subjects ($P=.08$) and in 62.5% of meningeal vessels in

African American vs 25% in white subjects ($P=.12$). There was no difference in the presence of amyloid angiopathy by *APOE* e4 carrier state.

COMMENT

In this study, the burden of amyloid plaques and NFTs in neuropathologically confirmed AD was no different among African American and white subjects of similar clinical dementia severity. Our results are consistent with those of Miller et al⁶ but differ from the findings of de la Monte et al,⁷ who found African American subjects to have more vascular dementia and white subjects to have more AD pathology. de la Monte and colleagues⁷ also reported more AD lesions in clinically normal white adults. Neither study provided much clinical data, including history of vascular disease or its risk factors.

Our findings cannot be generalized because of the small number of participants. By comparing participants who are similar clinically (have the same CDR and age), we diminish the chances of finding significant differences between the groups that would be more attributable to disease severity than to race or ethnicity. The high educational level of the African American subjects also makes them nonrepresentative of the general population. The major finding of this study, however, that there is no difference in AD neuropathology between African American and white individuals of similar dementia severity and socioeconomic status, suggests that race is not a major influence for the neuropathologic phenotype of AD.

Table 1. Sample Demographics and Clinical Status at Death

	African American Subjects (n = 10)	White Subjects (n = 10)	P Value
Age, mean (SD), y	84.8 (6.4)	85.9 (8.4)	.71
Education, mean (SD), y	16.7 (2.7)	12.0 (4.5)	.04
History of stroke, No. (%)	2 (20)	4 (40)	.67
Presence of hypertension, No. (%)	10 (100)	1 (10)	.001
Presence of an <i>APOE</i> 4 allele, No./total*	4/6	3/9	.22
Short Blessed Test score, mean (SD)†	18.14 (8.9)	19.20 (7.8)	.24

*Apolipoprotein E (*APOE*) genotyping was available for 6 African American and 9 white subjects.

†Test range, 0 to 28, with 0 indicating no errors.

Table 2. Neuropathologic Burden and Diagnoses

Clinical Diagnoses at Death	CDR Score	Plaques*			Tangles*			CAA		Lewy Bodies	Pathologic Diagnoses
		Total	Neuritic	Diffuse	Hippocampal	Entorhinal	Midfrontal	Parenchymal	Meningeal		
African American Subjects											
DAT	2	3	2	3	3	2	1	1	3	-	AD
DAT	2	3	0	0	3	2	0	2	3	-	AD
DAT	3	3	1	3	2	1	0	0	1	-	AD
DAT	3	3	0	2	2	2	0	3	3	-	AD, subdural hematoma
DAT	3	3	2	2	0	0	1	1	1	+	AD
DAT	1	2	1	1	3	1	0	3	3	-	AD
DAT	2	3	1	3	1	3	1	2	3	-	AD, infarcts
DAT + vascular dementia	0.5	2	0	2	1	0	0	0	1	-	AD, infarcts
DAT	3	3	1	3	3	3	1	1	2	+	AD
DAT	3	3	3	2	3	1	2	1	1	-	AD
White Subjects											
DAT + infarcts	1	2	2	1	1	2	0	0	0	+	AD
DAT	2	3	2	3	2	2	0	1	3	-	AD
DAT	3	3	1	1	3	1	1	0	2	-	AD
DAT + PD	3	3	2	3	1	1	0	0	0	-	AD, PD
DAT	3	3	2	2	2	1	0	1	2	-	AD
DAT	1	3	2	2	2	1	1	2	3	-	AD
DAT	2	3	1	3	2	1	0	0	0	-	AD
DAT	3	2	2	2	3	2	2	2	3	+	AD
DAT	0.5	3	2	1	0	1	0	0	3	-	AD, infarcts
DAT	3	3	2	3	3	3	1	1	3	-	AD

Abbreviations: AD, Alzheimer disease; CAA, cerebral amyloid angiopathy; CDR, Clinical Dementia Rating (range, 0-3); DAT, dementia of the Alzheimer type; PD, Parkinson disease.

*0 indicates none; 1, mild; 2, moderate; and 3, severe.

We found a nonsignificant increase in the frequency of cerebral amyloid angiopathy in African American compared with white individuals. Prior studies note the presence of cerebral amyloid angiopathy in up to 83% of participants aged 80 years or older with AD, suggesting that the white group in this study had an unusually low frequency of cerebral amyloid angiopathy, possibly reflecting a spurious finding owing to the small sample size.

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