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Effect of Vascular Lesions on Cognition in Alzheimer's Disease: A Community-Based Study

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Abstract

OBJECTIVES—To investigate whether clinical and neuropathological differences exist between Alzheimer's disease (AD) cases with and without vascular lesions neuropathologically diagnosed using Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria.

DESIGN—Descriptive observational study.

SETTING—A community-based registry that identified incident dementia cases.

PARTICIPANTS—Of the 124 subjects with available clinical and neuropathological assessments, 30 had AD lesions alone, and 18 had AD with vascular lesions. Patients with other neuropathological findings were excluded.

MEASUREMENTS—Dependent measures included demographic, clinical, and neuropathological characteristics. Neuropathological diagnoses were made using the CERAD criteria and Braak and Braak staging.

RESULTS—Of the 124 autopsied cases, 85 cases were diagnosed with neuropathological AD. Of these, 30 had pathology consistent with “pure” AD, whereas 18 had AD pathology with significant vascular lesions (AD/V). There were no differences in age, sex, or education between groups. AD/V cases had higher baseline and final Mini-Mental State Examination (MMSE) scores than pure AD cases, but after adjusting for education, differences in MMSE scores were not statistically significant.

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The AD/V group had significantly lower Braak staging than the pure AD group, after adjusting for education and final MMSE scores.

CONCLUSION—In this comparison study of AD cases with and without vascular lesions, AD/V cases had less severe AD pathology than those with AD alone, indicating that cerebrovascular disease likely contributes to the severity of cognitive impairment in those with AD. Controlling for vascular risk factors in patients with AD may have a significant effect on severity of dementia.

Keywords

Alzheimer's disease; vascular lesions; clinical-neuropathological; autopsy; dementia

Alzheimer's disease (AD) is the most common cause of dementia in the elderly. In the United States alone, there are almost 4 million persons with AD, with roughly 360,000 new cases of AD identified each year.[1] The number of prevalent cases is expected to more than triple in the next 50 years, resulting in more than 14 million persons likely to have AD by 2050.[1,2] Approximately 5% of those aged 65 to 74 and more than 30% of those aged 85 and older have AD.[2,3] AD is thought to constitute approximately 55% of all cases of dementia, although mixed dementia is also common, with a prevalence between 20% and 40% in neuropathological studies, and is estimated to be the second most common form of dementia.[4]

Recently, the relationship between vascular and AD pathology has received increased scrutiny. Several risk factors are implicated in the development of vascular disease, including diabetes mellitus, hypertension, hyper-cholesterolemia, smoking, and atrial fibrillation. These factors may also play an integral role in the development of AD.[5,6] Furthermore, vascular dementia and AD share some pathological characteristics.[7,8] These findings suggest that the atherosclerotic vascular disease process may be associated with the development of AD pathology.

Some studies suggest that vascular lesions, when occurring in the setting of incipient AD, may lower the threshold for developing clinical signs of dementia.[9-12] A recent study reported that subjects who exhibited silent infarcts on brain magnetic resonance imagings had a greater risk of developing dementia than those without these lesions.[13] According to another study, clinical AD is three times more likely to occur after a cerebrovascular episode.[8,14,15] In the Nun Study, neuropathological AD cases with concomitant vascular pathology were more likely to be demented than those without infarcts (88% vs 57%).[12]

The severity of concomitant AD pathology may be an important variable in predicting whether the presence of vascular lesions will be associated with cognitive impairment. A group of researchers reported that cerebrovascular disease exerted a greater effect on cognition in autopsied cases with mild AD pathology (Braak Stages I and II) than in those with more advanced disease (Braak Stages V and VI).[9] These findings suggest that comorbid cerebral infarctions may hasten the onset of dementia.

Alternatively, individuals with AD may have an increased risk for developing cerebral infarctions. Two recent studies showed that elderly individuals without a previous history of stroke were more likely to have a cerebrovascular episode after they were cognitively impaired. This association existed even after controlling for other known risk factors for cerebrovascular events.[16,17] Other studies have suggested that the infiltration of amyloid into the adventitia and media of cerebral blood vessels may lead to the development of cerebral infarctions.[8,18,19]

Clinical-neuropathological studies are necessary to investigate whether concurrent vascular infarctions and AD lesions contribute to the development of clinical dementia. However,

current clinical-neuropathological correlative studies are limited by study samples obtained from highly selective or specialized research settings (e.g., Alzheimer's disease research centers, the Nun Study). Therefore, these findings may not be as applicable to patients evaluated in the community at large. Clinical and neuropathological findings of a community-based incident dementia case series have been previously reported.[20-22] Demographic characteristics in the AD cases were comparable with those of other individuals aged 65 and older in the Puget Sound region.[23] It was also demonstrated that there were no substantial differences in demographic characteristics between the autopsied and nonautopsied sample in this community-based case series.[22] The current study compares the demographic, clinical, and neuropathological characteristics of cases with AD pathology alone (pure AD) with those of cases with both AD pathology and significant vascular lesions (AD/V).

METHODS

Subjects were obtained from the University of Washington/Group Health Cooperative Alzheimer's Disease Patient Registry (ADPR). The ADPR was designed to identify and enroll newly recognized cases of dementia from Seattle area clinics of the largest health maintenance organization in the Puget Sound region between 1987 and 1996. The eligibility of persons arriving at clinics with symptoms potentially consistent with previously undiagnosed dementia was determined through the review of specialty and primary care clinic logs, hospital records, head computed tomography (CT) scans, and referrals from primary care practitioners and neurologists. Almost half of the referred cases (48.8%) were from the subject's primary care physician,[24] 19.8% were based on a subject's head CT scan, and 10% were referred from hospital admission records. Other sources for subjects included emergency room logs and mental health specialists. Persons with symptoms of memory loss suggestive of dementia were enrolled into the ADPR, where they were given a full evaluation for possible dementia, followed by a differential diagnosis. Those persons who previously had been diagnosed with dementia more than 1 year earlier (prevalent cases) were excluded from the study. In addition, approximately 20% of persons initially identified as having cognitive impairment declined to participate in the ADPR, and an additional 14% declined to give informed consent.[25] Demographic and clinical assessments were obtained at enrollment. After undergoing standard medical, neurological, and neuropsychological assessments used for the diagnosis of dementia, the ADPR clinical investigators assigned a consensus diagnosis to each subject. Diagnosis of AD was determined using National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association[26] and *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R) criteria.[27] Enrolled subjects had demographic characteristics similar to those of the Puget Sound's regional population aged 65 and older (approximately 90% Caucasian).[23]

The ADPR assessment has been described previously in detail.[20,21,24,28] All cases were followed annually until the time of death. Clinical diagnoses were revised if symptoms and signs indicated that the original diagnosis might be in doubt. For 137 of 1,028 enrolled subjects, the initial clinical diagnosis was revised during follow-up. Subjects with no evidence of cognitive impairment and subjects with any terminal or unstable severe medical conditions at baseline were excluded.

The Mini-Mental State Examination (MMSE) was used to assess the severity of cognitive impairment. For dementia screening, the MMSE has been demonstrated to have high validity, with good test-retest reliability.[29,30] Therefore, it was administered at subject enrollment into the ADPR and annually thereafter throughout the study. The difference between initial MMSE score and last MMSE score before death was calculated as the change in MMSE score. This difference in MMSE scores between baseline and final assessment was divided by the number

of years between the initial and last assessment before death and was determined to be the rate of change in MMSE score.

Neuropathologists from the Department of Pathology and the Alzheimer's Disease Research Center conducted all autopsies at the University of Washington Medical Center. The pathologists were provided with a brief clinical synopsis of the patient before neuropathological assessment. Examinations focused on the following neocortical areas: cingulate gyrus; superior and middle frontal gyri; medial orbital cortex; superior, middle, and inferior temporal gyri; inferior parietal lobule; and medial occipital cortex. The hippocampus, amygdala, parahippocampal gyrus, basal ganglia (caudate, putamen, globus pallidus, and claustrum), posterior hypothalamus, thalamus, midbrain, pons, medulla, and cerebellum were also assessed.[31]

Tissues were stained with hematoxylin-eosin, thioflavin-S, and the modified Bielschowsky silver method. Neuropathological assessments for AD pathology were initially conducted semiquantitatively according to Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria, primarily assessing the density and distribution of neocortical senile plaques.[32] This was the standard at the inception of the study. All cases that met the research criteria of CERAD “definite” and “probable” AD were included in this study.

All cases previously staged according to CERAD neuropathological criteria were then staged according to Braak and Braak criteria.[31,33] These neuropathological assessments were blinded to clinical and pathological diagnoses. According to these researchers, AD neuropathology, specifically neurofibrillary tangles, evolves in a relatively predictable pattern.[33,34] Braak staging for neurofibrillary tangles encompasses seven different stages, with Stage 0 indicative of no AD pathology. Stages I and II are the transentorhinal stages. In these stages, AD pathology is primarily located in the transentorhinal region of the temporal lobe but also extends into the entorhinal cortex with mild involvement of the hippocampus. Stages III and IV, the limbic stages, are characterized by greater involvement of the hippocampus and additional involvement of the amygdala, thalamus, hypothalamus, and basal forebrain. Clinical symptoms usually become evident at these stages of brain involvement.[35] The most severe stages are the neocortical stages, Stages V and VI, in which AD pathology is detected throughout the neocortex.[33,34]

Vascular lesions were identified and characterized for age and location using clinical records and neuropathological assessments.[36] Recent infarcts (acute/subacute—occurring less than 1 year before) were presumed to be terminal events that occurred after clinical assessments and therefore unlikely to contribute substantially to any clinical dementia during the study. These lesions were excluded from analyses. Vascular lesions, including lacunar infarcts, occurring more than 1 year before death, and located above the tentorium, were considered to be significant regardless of volume. Such lesions were considered to be potentially contributory to the development of dementia and were included in this study. Lacunar infarcts included cystic lesions in noncortical regions (e.g., basal ganglia and thalamus) and deep white matter that were less than 20 mm in diameter. Lesions greater than 20 mm in diameter in noncortical regions were considered large. In addition, cortical infarcts were further classified as large (>10 mm in diameter), small (<10 mm in diameter), or microscopic (only visible upon microscopic review).[36-39] Cerebral blood vessels were evaluated for the presence of atherosclerosis, significant obstruction, aneurysms, hemorrhage, and other abnormalities. Cases that exhibited any additional neuropathological diagnoses likely to contribute to dementia were excluded from the current analysis (e.g., Lewy bodies).

Sample Selection

For this study, 970 subjects were enrolled and assessed. A detailed outline of cases has been presented previously.[24] Of the subjects who were enrolled into the study, 224 did not meet DSM-III-R criteria for dementia. Of the 746 who were diagnosed with dementia according to DSM-III-R, 471 had clinical probable AD, 91 had clinical possible AD, and 184 were clinically diagnosed with dementia other than AD. Of the 970 enrolled subjects, 425 died before March 1996. Of these, 124 had an autopsy. Thirty-nine subjects (31.5%) did not meet CERAD neuropathological criteria for AD. The remaining 85 subjects (68.5%) had findings consistent with neuropathological AD (CERAD "definite" and "probable" AD). Of these 85 AD cases, 38 (44.7%) had additional significant vascular lesions (i.e., a vascular lesion of any size that was more than 1 year old and located above the tentorium); 47 (55.3%) did not. Of the 38 AD cases with additional significant vascular lesions, 20 were excluded because they had other pathology (e.g., Lewy bodies, Pick bodies, hippocampal sclerosis, cerebral hemorrhage including subdural hematoma, and significant tumors, including one subject with a glioblastoma multiforme). Inclusion of these cases would have limited the ability to assess the effect AD and vascular lesions have on cognition. Therefore, 18 cases fulfilled the research criteria for AD/V. Of the 47 cases without significant vascular lesions, 30 had pathology consistent with AD alone. These cases were classified as pure AD. The analyses were focused on those cases with pathology consistent with AD/V (n = 18) and those with pure AD (n = 30).

Of the 39 subjects who did not meet CERAD criteria for AD, eight had significant vascular lesions alone that likely contributed to dementia without other identifiable pathology. These subjects were not included in the analyses.

Data Analysis

Demographic, clinical, and neuropathological characteristics were compared between cases with AD pathology alone (pure AD; n = 30) and cases with only AD pathology and significant vascular lesions (AD/V; n = 18). Two-sample Student *t* test was used for comparison of continuous variables, and Pearson chi-square (χ^2) analysis was used for comparison of categorical variables. Characteristics found to be related to group status (pure AD vs AD/V) were further explored for associations with other demographic, clinical, and neuropathological characteristics to determine whether they should be included as covariates in logistic models. For each clinical and neuropathological characteristic that was significantly related to group status, multivariate logistic regression was used to examine the odds of being AD/V versus pure AD for that characteristic, adjusted for any relevant covariates. By convention, the logistic model regressing change in MMSE score against group status was also adjusted for baseline MMSE score. To explore whether the odds of being AD/V differed for two subjects with the same degree of cognitive impairment before death but different Braak staging, a second logistic model regressing Braak stage against group status was examined that controlled for final MMSE score along with other relevant covariates. Analyses were conducted using SPSS software version 10.1 (SPSS, Inc., Chicago, IL) and Stata software version 7.0 (Stata Corporation, College Station, TX).

RESULTS

Demographic and Clinical Characteristics

Demographic characteristics (ethnicity, education, and sex) of the AD/V and pure AD groups were compared (Pearson χ^2 analyses; Table 1). Fewer neuropathological pure AD subjects pursued education beyond high school than AD/V subjects, but the difference did not reach significance (33.3% vs 55.6%; $P = .131$).

In the comparison of final DSM-III-R diagnoses, neuropathological pure AD cases were more likely to be clinically diagnosed with probable AD than neuropathological AD/V cases. The neuropathological AD/V cases contained more other dementia cases than the neuropathological pure AD cases. In addition, two neuropathological AD/V cases were not clinically diagnosed with dementia (Pearson $\chi^2 = 6.95$, degrees of freedom (*df*) = 2, *P* =.031; Table 2).

There were no significant differences in age at onset, age at intake, age at death, or duration of illness between the AD/V and pure AD groups (Student *t* test; Table 2), but the severity of cognitive impairment differed according to baseline and final MMSE scores. Baseline mean MMSE score was lower in the pure AD group than in the AD/V group ($t = -2.48$, $df = 46$, $P = .017$; Table 2). Even after controlling for education, this trend persisted (OR = 1.14, $df = 1$, $P = .053$).

The mean final MMSE score standard deviation (SD) was also lower in the pure AD group than in the AD/V group ($t = -2.31$, $df = 46$, $P = .026$). After controlling for education, differences were not statistically significant (OR = 1.09, $df = 1$, $P = .077$).

Of the 48 cases, 40 had two or more clinical assessments. The overall change and change in MMSE scores per year was similar in both groups after controlling for education and baseline MMSE score.

Neuropathological Characteristics

Of the 18 cases with significant vascular lesions, seven had large cortical ischemic lesions. One of these cases also exhibited a small cortical lesion. Six cases had lacunae. Lacunae were detected in the basal ganglia, thalamus, or subcortical white matter. Detailed neuropathological descriptions of vascular lesions are listed in Table 3.

Cases in the pure AD group had significantly higher Braak staging than in the AD/V group (mean ± SD = 4.83 ± 0.65 vs 3.94 ± 0.94; $t = 3.88$, $df = 46$, $P < .001$). Adjusting for final MMSE score, this difference remained significant (OR = 0.277, $df = 1$, $P = .011$). After adjustment for education and final MMSE score, these differences persisted (OR = 0.194, $df = 1$, $P = .006$).

DISCUSSION

In this community-based dementia case series, there were no significant differences in demographic characteristics (including ethnicity, education, and sex) between selected cases with AD alone and cases with AD/V. Even though AD/V subjects tended to pursue higher education than pure AD subjects, the difference between the groups was not significant. However, there were differences in MMSE scores and Braak staging between the two groups. Most significantly, after controlling for final MMSE score and education, pure AD cases had significantly higher Braak staging than AD/V cases. These findings suggest that the presence of vascular lesions contributed to the severity of cognitive impairment in the community-based cases with AD/V.

Several previous studies, using selective research samples, have reported that AD subjects with significant vascular lesions exhibited fewer neuritic plaques and neurofibrillary tangles than those without vascular lesions,[11,12,40] but not all studies support these findings.[10,41] A recent study showed no difference in a semiquantitative assessment of neuritic plaques and neurofibrillary tangles between the two groups from the CERAD sample,[10] although this sample included only AD cases from highly specialized AD research centers. Therefore, patients with clinical evidence of cerebrovascular disease were excluded from enrollment and subsequent neuropathological examinations. Furthermore, it has previously been demonstrated

that cases from AD research centers are much younger than cases from community-based registries.[42] Therefore, research center cases are likely to be healthier and have less severe vascular pathology.

The effect of specific characteristics of vascular lesions, such as their volume or location, is not well delineated. Some studies have suggested a correlation between the volume of vascular lesions and the severity of dementia.[43,44] According to one study, there may be a critical volume that must be exceeded before vascular lesions become associated with dementia.[45] Beyond that threshold, there is no direct relationship between the volume of each vascular lesion and the severity of dementia.[40] Vascular infarctions in strategic brain regions, specifically the hippocampus, corpus callosum, basal ganglia, deep white matter, and thalamus, may be more likely to result in dementia.[12,45] Some studies have shown that even lacunar infarcts, especially those located in these strategic sites, are likely to lead to more severe dementia in persons with AD pathology,[10,12,46] although one research group did not find a correlation between cognitive decline and small cerebral infarcts involving a total volume of less than 10 cm^3.[47] The sample size of the current study did not allow us to assess the effect of various sized ischemic lesions. Consequently, lesions of any size were included in this study.

In this sample, pure AD cases had statistically significantly lower MMSE scores at enrollment and shortly before death than AD/V cases. This could have biased the results of the study, but after controlling for education, there were no significant differences in MMSE scores between groups at enrollment or last evaluation. In addition, MMSE scores were controlled for in the primary analyses.

One obstacle in this area of research is the lack of clinical consensus concerning the relationship between vascular lesions and dementia in AD. For example, no accepted standard for diagnosing mixed dementia exists.[4] This results in difficulty diagnosing persons with both AD and significant vascular lesions in the clinical setting. In the current study, only one neuropathological AD/V case carried the clinical diagnosis of mixed dementia. In addition, the presence of significant vascular lesions in those with AD limited the clinicians' ability to diagnose AD. Of the neuropathological AD/V cases, fewer than 56% were diagnosed as having AD, whereas upon autopsy, 87% of the pure AD cases were diagnosed clinically with AD. Therefore, coexistent vascular disease may impair the ability to clinically diagnose AD, especially with currently used cognitive instruments, including the MMSE.[48,49] Antemortem clinical diagnosis of mixed dementia needs additional refinement. Furthermore, better neuropathological criteria are needed to competently define vascular dementia.[50] Not all vascular lesions result in dementia, and the effects of lesion characteristics, such as age, size, and location, have not been fully explored.

There are several limitations to this study. First, it was found that AD subjects with concomitant vascular lesions had less severe cognitive impairment at the time of enrollment than pure AD subjects. There may be a bias in enrolling AD/V subjects earlier into the study, but even after adjusting for differences in final MMSE, cases with AD/V still had less AD pathology than cases with pure AD. Second, certain weaknesses inherent to all neuropathological studies (including selection bias and temporal relationship to dementia) limited this study. Cases that undergo neuropathological examination may not be representative of the entire study sample.[51,52] Therefore, these findings may not be generalizable to the entire study population. In addition, because the outcome (presence or absence of comorbid vascular lesions) can only be assessed at the time of neuropathological examination, the temporal relationship between vascular infarcts and the development of cognitive impairment cannot be definitively determined. Third, the MMSE is not the optimal neuropsychological test for early detection of cognitive impairment.[53] Therefore, the ADPR protocol likely underdiagnosed cases with mild cognitive impairment or predominantly frontal lobe dysfunction. However, the initial goal of

this study was to identify those with AD, for which the MMSE has relatively high detection rates.[29] Finally, cases with additional neuropathological diagnoses likely to contribute to dementia were excluded from the current analysis. Thus, the findings have limited applicability beyond AD alone or AD with vascular lesions (e.g., excluding cases with three or more pathological findings). In addition, sample sizes in this study were limited. Therefore, the findings will need to be replicated in a larger sample.

In conclusion, these findings suggest that cerebrovascular disease may contribute to the severity of dementia in patients with AD. It has also been suggested that the presence of vascular lesions may also shorten the preclinical phase of AD.[54] Therefore, given the evidence that adequate control of vascular risk factors can delay the development of cerebrovascular disease,[55] appropriate management of vascular risk factors in AD may delay the onset and severity of dementia in AD patients. These findings continue to stress the importance of the assessment and treatment of vascular risk factors in cognitively intact and cognitively impaired elderly individuals.

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Table 1

Demographic Characteristics of Subjects with Pure Alzheimer's Disease (AD) (n = 30) and AD with Significant Vascular Lesions (AD/V) (n = 18)

Characteristic	Pure AD	AD/V	*P*-value
	n (%)		
Ethnicity			
Native American	1 (3.3)	0 (0)	.322
Asian American	2 (6.7)	0 (0)	
African American	0 (0)	1 (5.6)	
Caucasian	27 (90.0)	17 (94.4)	
Education			
≤ High school	20 (66.7)	8 (44.4)	.131
>High school	10 (33.3)	10 (55.6)	
Sex			
Male	11 (36.7)	8 (44.4)	.594
Female	19 (63.3)	10 (55.6)	

Table 2

Clinical Characteristics of Subjects with Pure Alzheimer's Disease (AD) (n = 30) and AD with Significant Vascular Lesions (AD/V) (n = 18)

Characteristic	Pure AD	AD/V	*P*-value
Age at first noted symptom, mean ± SD	75.03 ± 7.3	76.89 ± 6.5	.378
Age at intake, mean ± SD	77.35 ± 7.0	78.98 ± 6.4	.424
Age at last assessment, mean ± SD	79.56 ± 6.5	81.38 ± 6.4	.351
Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised diagnosis at last assessment, n (%)*			.031
AD	26 (86.7)	10 (55.6)	
Dementia, other	4 (13.3)	6 (33.3)	
No clinical dementia	0 (0)	2 (11.1)	
Age at death, mean ± SD	80.55 ± 6.6	82.56 ± 6.3	.306
Years between last assessment and death, mean ± SD	0.98 ± 0.8	1.17 ± 0.9	.455
Years between symptom onset and death, mean ± SD	5.51 ± 2.6	5.67 ± 2.2	.835
MMSE score at baseline, mean ± SD†	18.63 ± 5.9	22.72 ± 4.9	.017
Final MMSE score, mean ± SD‡	11.13 ± 7.3	16.11 ± 7.1	.026
Change in MMSE score, mean ± SD§	9.78 ± 5.3	7.00 ± 5.4	.114
Change in MMSE score/years from enrollment to last intake, mean ± SD§	4.07 ± 2.9	3.28 ± 3.3	.424

MMSE = Mini-Mental State Examination.

*Because of small cell sizes, “dementia, mixed” was combined with “dementia, other.” One AD/V case was clinically identified as mixed dementia. Pearson chisquare = 6.95, $df = 2$, $P = .031$.

†Student t test, $t = -2.48$, $df = 46$, $P = .017$.

‡Student *t* test, $t = -2.31$, $df = 46$, $P = .026$.

§Data available in only 23 pure AD and 17 AD/V cases that had two or more annual assessments.

Table 3

Neuropathological Description of Infarcts in Cases of Alzheimer's Disease with Significant Vascular Lesions (n = 18)

Case Number	Location of Vascular Lesion	Size
1	Left frontal, parietal, and temporal lobe	Large
2	Right head of caudate nucleus	Lacune
3	(1) Right basal ganglia; (2) left basal ganglia; (3) bilateral hippocampi	(1) Lacune; (2) lacune; (3) microinfarcts
4	(1) Left parietal white matter; (2) left occipital white matter	(1) Lacune; (2) lacune
5	(1) Left superior parietal lobe; (2) left anterior hippocampus	(1) Small; (2) small
6	Right middle and inferior frontal lobe	Large
7	Left temporal lobe	Microscopic
8	(1) Right globus pallidus; (2) left motor cortex; (3) right occipital lobe; (4) right inferior parietal lobe	(1) Lacune; (2) small; (3) small; (4) small
9	Left frontal lobe	Large
10	Left frontal lobe	Microscopic
11	(1) Right inferior parietal lobe; (2) frontal lobe	(1) Small; (2) microscopic
12	(1) Right frontal lobe; (2) right corona radiata and basal ganglia; (3) right optic radiations	(1) Small; (2) lacune; (3) lacune
13	(1) Right parietal lobe; (2) right insular cortex	(1) Large; (2) small
14	Right frontal-temporal lobe, claustrum and insula, parietal lobule, and right putamen	Large
15	Right parietal and occipital lobe	Large
16	Left frontal lobe and basal ganglia	Large
17	(1) Right middle frontal lobe; (2) thalamus; (3) left inferior temporal gyrus	(1) Small; (2) lacune; (3) small
18	Left hippocampus	Microscopic