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This information is current as of April 20, 2024.

AJNR Am J Neuroradiol 2016, 37 (2) 223-227

doi: <https://doi.org/10.3174/ajnr.A4496>

<http://www.ajnr.org/content/37/2/223>

Diagnostic Significance of Cortical Superficial Siderosis for Alzheimer Disease in Patients with Cognitive Impairment

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ABSTRACT

BACKGROUND AND PURPOSE: Because the diagnostic significance of cortical superficial siderosis for Alzheimer disease and the association between cortical superficial siderosis and the topographic distribution of cerebral microbleeds have been unclear, we investigated the association between cortical superficial siderosis and clinicoradiologic characteristics of patients with cognitive impairment.

MATERIALS AND METHODS: We studied 347 patients (217 women, 130 men; mean age, 74 ± 9 years) who visited our memory clinic and underwent MR imaging (3T SWI). We analyzed the association between cortical superficial siderosis and the topographic distribution of cerebral microbleeds plus clinical characteristics including types of dementia. We used multivariate logistic regression analysis to determine the diagnostic significance of cortical superficial siderosis for Alzheimer disease.

RESULTS: Twelve patients (3.5%) manifested cortical superficial siderosis. They were older ($P = .026$) and had strictly lobar cerebral microbleeds significantly more often than did patients without cortical superficial siderosis (50.0% versus 19.4%, $P = .02$); the occurrence of strictly deep and mixed cerebral microbleeds, however, did not differ in the 2 groups. Alzheimer disease was diagnosed in 162 (46.7%) patients. Of these, 8 patients (4.9%) had cortical superficial siderosis. In the multivariate logistic regression analysis for the diagnosis of Alzheimer disease, lacunar infarcts were negatively and independently associated with Alzheimer disease ($P = .007$).

CONCLUSIONS: Although cortical superficial siderosis was associated with a strictly lobar cerebral microbleed location, it was not independently associated with Alzheimer disease in a memory clinic setting. Additional studies are required to investigate the temporal changes of these cerebral amyloid angiopathy–related MR imaging findings.

ABBREVIATIONS: AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; cSS = cortical superficial siderosis; DLB = dementia with Lewy bodies; MBs = cerebral microbleeds; MCI = mild cognitive impairment

Cortical superficial siderosis (cSS) is characterized by linear hypointensities on the surface of cerebral cortex gyri on T2*-weighted gradient-echo MR imaging or SWI.^{1,2} cSS reflects subtle hemorrhages from amyloid-affected fragile cortical or leptomeningeal vessels and occurs often in patients with cerebral amyloid angiopathy (CAA); associations of cSS with repeat lobar hemorrhages have been reported.^{3–5} Several studies showed that patients with cognitive impairment manifested a higher prevalence of cSS compared with the general population.^{6,7} cSS, along with lobar cerebral microbleeds

(MBs), was described as a characteristic neuroimaging marker of CAA.^{8,9}

Alzheimer disease (AD) is the most common cause of dementia in the elderly, and CAA is assumed to have a pivotal function in the underlying pathogenesis of AD.¹⁰ In the aforementioned studies, cSS was associated with the presence of MBs, and the authors speculated that a relatively high prevalence of cSS in patients with AD indicates this pathogenesis.^{6,7} We therefore hypothesized that cSS itself may be a significant diagnostic marker of AD and that lobar MBs would be observed more frequently in patients with cSS than in patients without cSS.

The primary aim of the present study was thus to clarify the diagnostic significance of cSS for AD, with the secondary aim being to explore the radiologic markers of small-vessel disease in relation to cSS in patients with cognitive impairment.

MATERIALS AND METHODS


Study Population

This study consisted of a subanalysis of a prospective clinicoradiologic study described previously.¹¹ Consecutive patients who

Received January 12, 2015; accepted after revision June 18.

From the Departments of Neurology (Y.I., M.N., M.U., M.W., Y.A.), Diagnostic Radiology (H.U., T.H., M.K., D.U., Y.Y.), and Psychiatry and Neuropathobiology (M.H., M.I.), Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

Please address correspondence to Yasuteru Inoue, MD, Department of Neurology, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan; e-mail: yinoue@fc.kuh.kumamoto-u.ac.jp

 Indicates article with supplemental on-line table.

<http://dx.doi.org/10.3174/ajnr.A4496>

attended the Dementia Clinic of the Department of Neuropsychiatry, Kumamoto University Hospital, were recruited prospectively from January 2008 to February 2010. The Ethics Committee of Kumamoto University Hospital approved this study. The patients received information about the purpose and method of the study, and written informed consent for participation in the study was obtained from them or their caregivers.

Patients with cognitive impairment associated with posttraumatic brain injury, brain tumor, idiopathic normal pressure hydrocephalus, history of psychiatric diseases or substance abuse, and neurodegenerative diseases, including Pick disease, corticobasal degeneration, and spinocerebellar degeneration, were excluded from this study. Patients whose MR images had severe motion artifacts and patients who did not provide informed consent were also excluded.

All patients received independent neuropsychological evaluations conducted by 2 neuropsychiatrists (M.I., M.H.). Neuropsychological tests including the Mini-Mental State Examination, brain MR imaging, and SPECT were used for diagnosing dementia. Diagnostic criteria included the following: for AD, criteria from the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association¹²; for vascular dementia, criteria from the National Institute of Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences¹³; for mild cognitive impairment (MCI), general criteria from the International Working Group on Mild Cognitive Impairment¹⁴; for dementia with Lewy bodies (DLB), clinical criteria from the Consortium on Dementia with Lewy Bodies¹⁵; and for frontotemporal lobar dementia, the Lund-Manchester criteria for behavioral variant frontotemporal lobar dementia, semantic dementia, or progressive nonfluent aphasia.¹⁶ If results of all clinical investigations were normal, patients were classified in a subgroup labeled “subjective memory symptoms.”

MR Imaging Protocol

MR imaging was performed with a 3T whole-body system (Magnetom Trio; Siemens, Erlangen, Germany). Axial SWI, axial FLAIR, axial T2-weighted turbo spin-echo sequences, 3D T1-weighted magnetization-prepared rapid acquisition of gradient echo sequences, diffusion-weighted imaging, MR spectroscopy, and MRA were performed by using the same section thickness, matrix, and parameters as described previously.¹¹

Evaluation of cSS and Other Radiologic Data

We defined cSS as linear hypointensities on the surface of cerebral cortex gyri on SWI; cSS related to previous symptomatic subarachnoid hemorrhage, traumatic subdural hematoma, or intracranial surgery was not included. cSS was classified as focal (restricted to 3 sulci) or disseminated (≥ 4 sulci).

We defined MBs as small (< 10 mm in diameter), homogeneous, round foci of low signal intensity. We excluded symmetric hypointensities in the globi pallidi and dentate nuclei, which we identified as physiologic calcifications or iron deposits; we also excluded hypointense signals inside a lesion that were consistent with infarcts. Lacunar infarcts and white matter hyperintensities were defined according to criteria reported previously.^{11,17,18} The distribution of MBs

was categorized as lobar (frontal, temporal, parietal, and occipital) or deep (thalamoganglionic, brain stem, and cerebellum).

Patients with MBs were divided into 3 groups according to the microbleed distribution. The strictly lobar group had MBs localized exclusively in the lobar region. The strictly deep group had MBs located only in the thalamoganglionic and infratentorial regions. The mixed group had MBs throughout both lobar and deep regions. All radiologic findings were assessed by 2 experienced neuroradiologists (H.U., T.H.) who were blinded to the clinical information.

Clinical Data Collection

Baseline clinical information, including age, sex, history of hypertension, length of education, and Mini-Mental State Examination results, was recorded at registration. Hypertension was defined as a history of hypertension or prescription of antihypertensive medications.

Statistical Analyses

We compared baseline demographics and clinical characteristics for patients with any cSS and patients with no cSS. Categorical data were evaluated by using the χ^2 test and the Fisher 2-tailed exact test. Continuous variables were compared by using the Mann-Whitney *U* test. We next conducted multivariate logistic regression analysis to investigate the predictors for diagnosing AD. The independent variables included age, sex, hypertension, length of education, distribution of MBs (strictly lobar, strictly deep, or mixed), lacunar infarcts, white matter hyperintensities, and cSS. Backward stepwise logistic regression analysis was performed by adjusting for age,^{19–21} sex,²² length of education,²³ and variables that were automatically selected in a backward stepwise selection method. We performed a backward selection procedure for each outcome by using $P > .10$ of the likelihood ratio test for exclusion of variables. The OR and 95% CI were obtained. The statistical significance level was set at $P < .05$. In addition, we calculated the sensitivity, specificity, positive predictive value, and negative predictive value of cSS for the clinical diagnosis of AD. Statistical analyses were performed by using JMP 9.0 statistical software (SAS Institute, Cary, North Carolina).

RESULTS

Prevalence of cSS

A total of 347 patients (217 women, 130 men; mean age, 74 ± 9 years) with cognitive impairment visited our hospital from January 2008 to February 2010. Of these patients, 12 (3.5%) had cSS.

Clinical Characteristics Related to cSS

Table 1 provides demographic and clinical characteristics of the patients. Patients with cSS were older ($P = .026$) compared with patients without cSS. No significant differences were observed in the occurrence of cSS across different types of dementia ($P = .337$), and a bivariate analysis also demonstrated no differences between patients with and without AD ($P = .239$). Sensitivity, specificity, positive predictive value, and negative predictive value of cSS for the clinical diagnosis of AD were 4.9%, 97.8%, 66.7%, and 54.0%, respectively (4 patients had cSS but no AD, 8 patients had both cSS and AD, 181 patients had no cSS or AD, and 154 patients had AD but no cSS).

Table 1: Demographic and clinical characteristics of patients with or without cSS

Parameter	No. of Patients (%)			P Value
	Total	Any cSS	No cSS	
No. of patients	347	12	335	
Age (yr) (mean)	74 ± 9	79 ± 5	74 ± 9	.026
No. of women	217 (62.5%)	6 (50.0%)	211 (63.0%)	.361
No. of patients with hypertension	160 (46.1%)	9 (75.0%)	151 (45.1%)	.073
Length of education (yr) (mean) (range)	11 (9–12)	11 (9–13)	11 (9–12)	.506
MMSE (mean)	21 ± 5	19 ± 7	21 ± 5	.457
Types of dementia				.337
AD	162 (46.7%)	8 (66.7%)	154 (46.0%)	
DLB	41 (11.8%)	1 (8.3%)	40 (11.9%)	
FTLD	33 (9.5%)	0 (0%)	33 (9.9%)	
VaD	28 (8.1%)	1 (8.3%)	27 (8.1%)	
MCI	51 (14.7%)	2 (16.7%)	49 (14.6%)	
SC	32 (9.2%)	0 (0%)	32 (9.6%)	

Note:—MMSE indicates Mini-Mental State Examination; FTLD, frontotemporal lobar dementia; VaD, vascular dementia; SC, subjective symptoms.

Table 2: Radiologic characteristics of patients with or without cSS

Type of MBs	No. of Patients (%)			P Value
	Total	Any cSS	No cSS	
No. of patients	347	12	335	
Lobar MBs				
Frontal	69 (19.9%)	7 (58.3%)	62 (18.5%)	.003
Temporal	65 (18.7%)	8 (66.7%)	57 (17.0%)	<.001
Parietal	78 (22.5%)	7 (58.3%)	71 (21.2%)	.007
Occipital	63 (18.2%)	7 (58.3%)	56 (16.7%)	.002
Deep MBs				
Thalamoganglionic	62 (17.9%)	3 (25.0%)	59 (17.6%)	.456
Brain stem	32 (9.2%)	3 (25.0%)	29 (8.7%)	.088
Cerebellum	48 (13.8%)	3 (25.0%)	45 (13.4%)	.222
Topographic distribution of MBs				
Strictly lobar	71 (20.5%)	6 (50.0%)	65 (19.4%)	.020
Strictly deep	10 (2.9%)	0 (0%)	10 (3.0%)	1.00
Mixed	79 (22.8%)	5 (41.7%)	74 (22.1%)	.154
No MBs	187 (53.9%)	1 (8.3%)	186 (55.5%)	.002
Lacunar infarcts	71 (20.5%)	6 (50.0%)	65 (19.4%)	.020
WMH (mean) ^a	1.5 ± 0.8	1.9 ± 0.8	1.4 ± 0.8	.053
0	32 (9.2%)	0 (0%)	32 (9.6%)	
1	166 (47.8%)	4 (33.3%)	162 (48.4%)	
2	107 (30.8%)	5 (41.7%)	102 (30.4%)	
3	42 (12.1%)	3 (25.0%)	39 (11.6%)	

Note:—WMH indicates white matter hyperintensities.

^a WMH were graded according to the scale of Fazekas et al¹⁷: 0, absent; 1, punctate; 2, early confluent; and 3, confluent.

Location and Topographic Distribution of MBs

Strictly lobar MBs were observed more frequently in patients with cSS than in patients without cSS ($P = .020$), whereas the 2 groups did not differ with regard to the occurrence of strictly deep MBs ($P = 1.00$) and mixed MBs ($P = .154$). MBs in each cerebral lobe (frontal [$P = .003$], temporal [$P < .001$], parietal [$P = .007$], and occipital [$P = .002$]) had a significant association with the presence of cSS. However, patients with cSS and those without cSS showed no significant differences in the presence of thalamoganglionic MBs ($P = .456$), brain stem MBs ($P = .088$), and cerebellar MBs ($P = .222$) (Table 2). We also performed a separate analysis of demographic and clinicoradiologic characteristics in patients with AD and found similar tendencies in location and topographic distribution of MBs for that whole population (On-line Table). Among patients with AD, strictly lobar MBs were ob-

served more frequently in patients with cSS than in patients without cSS ($P = .004$). MBs in each cerebral lobe (frontal [$P = .040$], temporal [$P < .001$], parietal [$P = .040$], and occipital [$P = .006$]) also had a significant association with the presence of cSS.

Clinicoradiologic Characteristics of Patients with cSS

We further investigated the clinicoradiologic characteristics of 12 patients with cSS (6 women, 6 men; mean age, 79 ± 5 years) (Table 3). Of these, AD was diagnosed in 8 patients (66.7%); DLB, in 1 patient (8.3%); vascular dementia, in 1 patient (8.3%); and MCI, in 2 patients (16.7%). cSS was observed in 22 cerebral lobes, and its location corresponded to locations of MBs in 13 lobes (72.2%). We noted a tendency of cSS to occur in temporal and occipital lobes, and the distribution was focal in 7 patients (58.3%) and disseminated in 5 patients (41.7%). Six patients (50%) had strictly lobar MBs, 5 patients (41.7%) had mixed MBs, no patient with cSS had strictly deep MBs, and 1 patient (8.3%) had no MBs (case 2, Table 3). Four patients (33.3%) were classified as having grade 1 white matter hyperintensities; 5 patients (41.7%), grade 2 white matter hyperintensities; and 3 patients (25.0%), grade 3 white matter hyperintensities. No correlations between age-related white matter change rating scores and the location of cSS were found.

Relationship among cSS, MBs, and AD

Table 4 shows the results of multivariate logistic regression analysis for the diagnosis of AD. In the multivariate model, lacunar infarcts (OR, 0.46; 95% CI, 0.25–0.81; $P = .007$) were negatively and independently associated with AD, and the presence of cSS was not associated with AD (OR, 2.99; 95% CI, 0.88–12.0; $P = .08$).

DISCUSSION

This study is the first to investigate the diagnostic significance of cSS for AD and the relationships between cSS and the location of MBs in patients with cognitive impairment. The major new finding was that patients with cSS had strictly lobar MBs significantly more often than patients without cSS.

With respect to spatial distributions of MBs, past histopathologic studies of patients with intracerebral hemorrhage revealed that strictly lobar MBs strongly suggested CAA.²⁴ The population-based Rotterdam Scan Study showed a tendency for MBs to be located in the lobar region, especially in the temporal lobes.²⁵ A

Table 3: Clinicoradiologic characteristics of patients with cSS

Subject No.	Type of Dementia	Age (yr)	Sex	Location of cSS	Topographic Distribution				WMH ^a	ARWMC Rating Scale ^b (R/L)			
					Frontal	Temporal	Parietal	Occipital		Frontal	Temporal	Parieto-Occipital	
1	AD	79	M	Right frontal	–	–	+	+	Mixed	1	1/1	1/0	1/1
2	AD	81	F	Left occipital	–	–	–	–	No MBs	2	1/0	2/2	2/2
3	AD	84	M	Right occipital									
4	AD	83	F	Left temporal	–	+	–	–	Strictly lobar	3	2/2	3/3	2/1
5	AD	83	F	Left temporal	+	+	–	–	Strictly lobar	2	2/2	2/2	2/2
6	AD	78	F	Right temporal	–	+	+	+	Strictly lobar	1	0/0	1/1	0/0
7	AD	80	M	Right frontal	+	+	+	+	Strictly lobar	2	2/2	2/2	2/2
8	AD	78	F	Right temporal	+	+	+	+	Strictly lobar	1	0/1	1/0	1/1
9	AD	70	F	Right parietal	+	+	–	+	Strictly lobar	1	1/1	1/1	1/1
10	DLB	69	F	Right occipital	+	–	+	–	Mixed	2	2/2	2/2	2/2
11	VaD	87	M	Right frontal	+	+	–	+	Mixed	2	1/1	2/2	2/2
12	VaD	87	M	Right temporal									
				Right occipital									
				Left temporal									
				Left occipital									
11	MCI	82	M	Right occipital	–	–	+	–	Mixed	3	3/3	3/2	3/3
12	MCI	80	M	Left occipital									
				Left temporal	+	+	+	+	Mixed	3	3/3	3/3	3/3

Note:—ARWMC indicates age-related white matter changes; R/L, right/left; WMH, white matter hyperintensities; VaD, vascular dementia.

^a WMH were graded according to the scale of Fazekas et al¹⁷: 0, absent; 1, punctate; 2, early confluent; and 3, confluent.

^b ARWMC rating scale¹⁸: 0, no lesions (including symmetric, well-defined caps, or bands); 1, focal lesions; 2, beginning confluence of lesions; 3, diffuse involvement of the entire region, with or without involvement of U fibers.

Table 4: Multivariate logistic regression analysis for AD^a

Parameter	OR (95% CI)	P Value
Age (per 1-yr increase)	0.99 (0.96–1.02)	.400
Female sex	0.88 (0.55–1.41)	.593
Education (per 1-yr increase)	1.72 (0.43–7.02)	.448
Lacunar infarcts	0.46 (0.25–0.81)	.007
cSS	2.99 (0.88–12.0)	.080

^a The model was adjusted for age, sex, length of education, and variables that showed a relationship to AD in a backward stepwise selection method.

case-control and memory clinic-based cross-sectional study including patients with AD showed that the microbleed topography was significantly predominant in the occipital region.²⁶ Our study indicated that strictly lobar MBs are closely related to cSS, which was shown to be a marker of CAA. This tendency also persisted among patients with AD with or without cSS, 2 groups who were barely distinguishable from each other except for a higher prevalence of a lobar microbleed location in patients with AD and cSS.

With respect to the diagnostic significance of cSS for AD, though AD was diagnosed in most patients with cSS, multivariate logistic regression analysis showed that neither cSS nor MBs in any location were independent significant predictors for the diagnosis of AD. An explanation of this result is that CAA pathogenesis also occurs in patients with dementias other than AD. Other histopathologic studies reported CAA in patients with DLB and vascular dementia and a low prevalence of CAA in patients with frontotemporal lobar dementia.^{27–29} MCI was reportedly a transitional state of AD,³⁰ so our patients with cognitive impairment may have had CAA pathologic features. Thus, the similar occurrence of cSS and pathologic findings of CAA in patients with cognitive impairment again indicated the same underlying pathophysiologic mechanisms.

As an interesting finding, 1 female patient had AD and cSS without MBs in the present study, whereas all other patients manifested both cSS and MBs. As with convexity subarachnoid hemorrhage, cSS has causes other than CAA: posterior reversible leukoencephalopathy syndrome, reversible cerebral vasoconstriction syndrome, and lupus vasculitis.³¹ One study indicated that cSS or convexity subarachnoid hemorrhage does not always reflect CAA pathogenesis.³¹ Given the older age and impaired cognition of our patients, however, most cSS in our study presumably resulted from CAA, as in another study that found CAA in >80% of patients with AD.³² A cross-sectional study including patients with probable or definite CAA, diagnosed on the basis of the Boston criteria,³³ found inverse associations among the severity of cSS, number of MBs, and *apolipoprotein E ε4*.³⁴ These authors also speculated that cSS may arise from vasculopathic mechanisms different from those associated with CAA-related microbleeds.³⁴ Because this patient in our study had no history of possible underlying causes of cSS other than CAA, cSS may have manifested as an initial radiologic finding of CAA.

Limitations of the present study included using a relatively small population and a heterogeneous patient population without AD (DLB, frontotemporal lobar dementia, vascular dementia, MCI, and subjective symptoms) as a reference group in the multivariate logistic regression analysis.

Our study results indicated that cSS was associated with a lobar location of MBs and may be an initial radiologic finding of CAA in patients with cognitive impairment. Additional prospective studies to investigate temporal changes of these CAA-related MR imaging findings may help in understanding the mechanisms of cognitive decline.

CONCLUSIONS

The prevalence of cSS was 3.9% in our memory clinic. Most patients with cSS were diagnosed as having AD, and the specificity of cSS for the clinical diagnosis of AD was high. Strictly lobar MBs were observed more frequently in patients with cSS than in patients without cSS.

Disclosures: Mitsuharu Ueda—UNRELATED: Grants/Grants Pending: Grants-in-Aid for Science Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 25870541). *Manabu Ikeda—UNRELATED: Grants/Grants Pending: Daiichi Sankyo, *Eisai, *FUJIFILM RI, *Janssen Pharmaceuticals, *Nihon Medi-Physics, *Novartis, *Pfizer, *Takeda, *Tsumura, *Comments: as the chairman of the department; Payment for Lectures (including service on Speakers Bureaus): Daiichi Sankyo, Eisai, FUJIFILM RI, Janssen Pharmaceuticals, Nihon Medi-Physics, Novartis, Pfizer, Takeda, Tsumura, MSD, Ono Pharmaceutical. *Money paid to the institution.

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