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Cortical superficial siderosis in memory clinic patients: further evidence for underlying cerebral amyloid angiopathy

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Abstract

Background—Cerebral amyloid angiopathy (CAA) is associated with many cases of spontaneous symptomatic lobar intracerebral hemorrhage in older individuals and is emerging as an important contributor to cognitive impairment. Cortical superficial siderosis (cSS) is an increasingly recognized hemorrhagic neuroimaging manifestation of CAA. We sought to investigate its prevalence and its association with underlying CAA among memory clinic patients.

Methods—We included consecutive eligible patients who presented to the out-patient memory clinic at the Massachusetts General Hospital (MGH) from 2007 to 2010 and had appropriate MR

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imaging, including blood-sensitive sequences. We analyzed the prevalence and topography of cSS according to demographic, clinical, APOE and MRI data.

Results—Our cohort consisted of 339 memory clinic patients: Alzheimer’s disease (n=86); mild cognitive impairment (n=162); vascular dementia/mixed dementia (n=18); other dementia/undetermined (n=42); and subjective cognitive complaints (n=31). cSS was detected in 10 patients (3%; 95%CI: 1.4%–5.4%); in 7 cases cSS was focal and in 3 cases disseminated. In multivariable logistic regression analysis the presence of cSS was associated with lobar microbleeds (OR: 1.08; 95%CI: 1.03–1.13; p=0.001, per each additional microbleed) and severe white matter hyperintensities (Fazekas score 5–6, OR: 4.43; 95%CI: 1.21–26.28; p=0.028) after adjusting for age. These associations were not influenced by the clinical diagnosis. In patients with APOE data, the APOE $\epsilon 4/\epsilon 4$ genotype was overrepresented among subjects with vs. without cSS. In the subgroup of patient with probable CAA (n=68; 9 with cSS) based on the presence of strictly lobar microbleeds, cSS was also associated with a higher prevalence of severe white matter hyperintensities (66.7% vs. 10.2%; p=0.001), high centrum semiovale perivascular spaces burden (88.9% vs. 52.4%; p=0.041) and higher counts of lobar microbleeds (median: 13; IQR: 10–36 vs. median: 1; IQR: 1–2; p<0.00001), compared to patients without cSS.

Conclusions—Our data provide further evidence supporting the hypothesis that cSS is a manifestation of advanced CAA in memory clinic populations. Future longitudinal studies should explore any direct effect of cSS on cognition or hemorrhage risk and disease progression.

Search terms

Alzheimer’s disease; MCI (mild cognitive impairment); MRI; cerebral amyloid angiopathy; cortical superficial siderosis

Introduction

Cortical superficial siderosis (cSS) has been suggested as a third cardinal haemorrhagic neuroimaging signature of cerebral amyloid angiopathy (CAA), alongside symptomatic intracerebral hemorrhage and microbleeds. cSS reflects curvilinear residues of blood breakdown products, including haemosiderin, over the cortical surface of the supratentorial cerebral convexities. Although the exact mechanisms remain elusive, it is currently thought that cSS is due to recurrent blood leaking episodes in the subarachnoid space from brittle CAA-affected vessels. Previous research has shown that cSS can improve the diagnosis of CAA-related intracerebral haemorrhage,[1] while it also carries a high risk of future symptomatic lobar haemorrhage,[2] often at the location of pre-existing cSS, with potentially important clinical implications.

CAA might present without major lobar intracerebral haemorrhage but instead contribute to cognitive impairment; it is also almost invariably found in Alzheimer’s disease. Despite the recent interest in the field, systematic studies of cSS including memory clinic patients are relatively scarce.[3,4] We sought to investigate the prevalence and determine whether cSS among memory clinic patients could represent underlying CAA. In addition, in the subgroup of patients with possible or probable CAA based on the presence of strictly lobar cerebral

microbleeds (CMBs),[5] the most characteristic marker of the disease, we investigated whether cSS presence is associated with more severe small vessel disease burden overall.

Methods

Case selection and clinical data collection

We included consecutive eligible patients who presented to the out-patient memory clinic at the Massachusetts General Hospital (MGH) from 2007 to 2010. Patients seen in the memory clinics from 2011–2014 did not have completed dataset at the time of writing. MRI scanning with a standardised protocol is a routine investigation for cases of suspected cognitive impairment, unless there are contraindications. Demographic and clinical information were obtained from prospective databases and medical records using standardised data collection forms. The following clinical variables were recorded: age at the time of MRI, gender, history of hypertension, diabetes, hypercholesterolemia, antithrombotic drug use and global CDR score. Hypertension was defined as previous diagnosis of hypertension (140/90 mm Hg) or use of antihypertensive treatment for control of blood pressure. Diabetes was defined as previous diagnosis of diabetes or current use of antidiabetic drugs. Hypercholesterolemia was defined as previous diagnosis of hypercholesterolemia or current use of antihyperlipidemic medications.

APOE genotype was determined in a subset of patients who provided blood samples and specifically consented to genetic testing as previously described and without knowledge of clinical or neuroimaging data.

Standard Protocol Approvals, Registrations, and Patient Consents

The study received ethical approval by the Institutional Review Board of MGH.

Neuroimaging data and analysis

Imaging for all patients throughout the study period was at 3.0T and included T2-weighted, FLAIR and T2*-weighted GRE (slice thickness: 5mm, echo time: 20–25.7, repetition time: 500–791) or susceptibility-weighted imaging (SWI). MR images were reviewed blinded to all clinical data by trained observers.

Cerebral microbleeds (CMBs) were evaluated according to current consensus criteria.[6] Periventricular and deep white matter hyperintensities were visually assessed on axial FLAIR images on the four-point Fazekas rating scale for each adding up to a total score on 7-point scale.[7]

Perivascular spaces were assessed in line with STRIVE recommendations;[8] they were rated on axial T2-weighted MR images, in the basal ganglia and centrum semiovale (i.e. cerebral hemisphere white matter), using a validated 4-point visual rating scale (0=no perivascular spaces, 1=<10, 2=11–20, 3=21–40 and 4=>40 no perivascular spaces).[9–11] The numbers refer to no perivascular spaces on one side of the brain: after reviewing all relevant slices for the anatomical area being assessed, the slice and side with the highest number of no perivascular spaces was recorded. The assessment of perivascular spaces was performed only in patients with possible or probable CAA based on the presence of strictly

lobar CMBs. The rater was blinded to CMB number, cSS ratings and leukoaraiosis status. We pre-specified a dichotomised classification of no perivascular spaces degree as high (score >2) or low (score ≤ 2). This definition is in line with the no perivascular spaces burden used in previous studies (and found to relate with different vascular risk factors and imaging markers of small vessel disease).[11–13]

cSS was defined by a single trained rater as linear residues of chronic blood products in the superficial layers of the cerebral cortex showing a characteristic “gyriform” pattern of low signal on blood-sensitive images; FLAIR images were used for anatomical confirmation of the gyral location of these signal hypointensities.[14] The distribution and severity of cSS was classified as focal (restricted to ≤ 3 sulci) or disseminated (> 4 sulci).[1] There was an excellent inter-rater reliability for cSS detection ($\kappa=0.91$, in 20 preselected scans to represent the range of cSS in the cohort).

Statistical analysis

Categorical variables were analysed using Pearson’s χ^2 or Fisher exact test, and continuous variables by the 2-sample t test (for normal distributions), and Wilcoxon rank sum (for non-normal distributions). We compared demographic and imaging characteristics as well as APOE data of patients with and without cSS. A logistic regression model was used to assess the relationship between cSS (presence or burden) and other markers of small vessel disease. In a sensitivity analysis the logistic regression model was repeated with CMB counts log-transformed for normality. The same analyses were also performed in the patient subgroup with possible or probable CAA based on the presence of strictly lobar CMBs, in line with the Boston criteria (i.e. not including cSS presence in the criteria).[1,5,15] Significance level was set at 0.05. Stata software (Version 11.2, StataCorp.) was used.

Results

Our cohort consisted of 339 memory clinic patients, diagnosed based on clinical criteria: Alzheimer’s disease (n=86); mild cognitive impairment (n=162); vascular dementia/mixed dementia (n=18); other dementia/undetermined (n=42); and subjective cognitive complaints (n=31). cSS was detected in 10 patients (3%; 95%CI: 1.4%–5.4%): 5/86 (5.8%) with Alzheimer’s disease, 3/162 (1.1%) with mild cognitive impairment and 2/42 (3.3%) with other dementia/undetermined. In 7 cases cSS was focal and in 3 cases disseminated: overall, cSS affected a single sulcus in 4 patients, 2 sulci in 2 patients, 3 sulci in one patient, 4 sulci in 2 patients and 6 sulci in one patient. The most commonly affected areas were the frontal lobe (60%), followed by the occipital and parietal lobes (50% and 40%); no case of cSS in the temporal lobe was detected.

Comparisons of clinical and imaging characteristics between patients with vs. without cSS are summarised in Table 1. All cSS cases had multiple lobar CMBs (in 9 qualifying for the diagnosis of probable CAA based on Boston criteria), compared with 7.3% in non-cSS patients ($p<0.001$), higher lobar CMBs counts and white matter hyperintensities burden (Table 1).

In multivariable logistic regression analysis the presence of cSS was associated with lobar CMBs (OR: 1.08; 95%CI: 1.03–1.13; $p=0.001$, per each additional microbleed) and severe white matter hyperintensities (Fazekas score 5–6, OR: 4.43; 95%CI: 1.21–26.28; $p=0.028$) after adjusting for age. The results were consistent and of similar effect size in a sensitivity analysis with CMBs log-transformed for normality and in ordinal regression with cSS burden as the dependent variable. These associations were not influenced by the clinical diagnosis of the cognitive syndrome.

In patients with APOE data, the APOE $\epsilon 4/\epsilon 4$ genotype was overrepresented among subjects with vs. without cSS (Table 2). The presence of APOE $\epsilon 2$ allele was more common in cases with cSS, although this did not reach statistical significance.

Comparison of patients with possible or probable CAA with vs. without cSS

The patient subgroup with possible or probable CAA based on the presence of strictly lobar CMBs presence included 68 cases in total. The distribution of CAA cases according to Boston criteria across diagnostic categories was as follows: 25/86 (29%) in Alzheimer's disease; 29/162 (18%) in mild cognitive impairment; 3/18 (17%) in vascular dementia/mixed dementia; 8/42 (19%) in other dementia/undetermined; and 1/31 (3%) in subjective cognitive complaints. In this subgroup of CAA patients, 9 (13.3%; 95%CI: 6.2–23.7%) had cSS. The two groups were not different in baseline demographic and clinical characteristic. However, patient with cSS had a higher prevalence of severe WMH (66.7% vs. 10.2%; $p=0.001$), high centrum semiovale perivascular spaces burden (88.9% vs. 52.4%; $p=0.041$) and higher number of lobar CMBs (median: 13; IQR: 10–36 vs. median: 1; IQR: 1–2; $p<0.00001$), compared to patients without cSS. These associations remained consistent in a multivariable model.

Imaging and clinical follow-up in patients with cSS

Clinical follow-up data were available in all patients with cSS at baseline. During a median follow-up time of 2.9 years (IQR: 0.5–6 years), 2 of the 10 patients with cSS and 0 of 60 patients without cSS (follow-up time 2.8 years; IQR: 0.4–5.5 years), but with lobar CMBs, experienced a symptomatic lobar ICH. In 4/10 patients with cSS who had follow-up blood-sensitive MRI scans cSS did not disappear with time. Instead, in 2 of these patients with cSS exhibited new areas of affected sulci (Figure 1).

Discussion

In our single centre, unselected cohort of a consecutive memory clinic-based population with MRI we detected cSS in 10 out of 339 patients (3%). This prevalence is in line with other similar recent studies in patients with cognitive impairment, including Alzheimer's disease [3,4,16], but much higher compared to the frequency of cSS in healthy elderly [17]. Secondly, we found that cSS was strongly associated with lobar CMBs (a putative CAA biomarker) in addition to white matter hyperintensities severity (a marker of small vessel disease in general), further supporting the hypothesis that cSS is a manifestation of advanced CAA in memory clinic populations without symptomatic lobar intracerebral haemorrhage. [3,4,16] These associations were also present within the subgroup of possible/probable CAA

cases, in which cSS was further associated with high burden of MRI-visible perivascular spaces in the centrum semiovale, another recent marker of the disease.[18] While white matter hyperintensity burden is not specific for CAA, in patients with possible/probable CAA, more severe white matter hyperintensities have been shown to be associated with higher cerebrovascular amyloid burden, and hence may be a marker of disease severity.[19] Finally, despite the small sample size and similar to a previous study [3], we found an association between APOE $\epsilon 4$ homozygosity and cSS presence, reinforcing the notion of an amyloid-related pathophysiologic mechanism.

Despite the recent interest in cerebral small vessel disease markers in patients with cognitive impairment or dementia, there are still limited data on cSS in this population. Three previous studies have focused on cSS in the context of patients with cognitive impairment or dementia.[3,4,16] The first study on the topic had a relatively small sample size and an emphasis on cSS prevalence in this clinical setting.[4] Recently, a cohort from Korea reported interesting associations between cSS presence and higher global amyloid burden, APOE $\epsilon 2$, and a strictly lobar distribution of microbleeds.[16] However, these results might not be generalisable given that this cohort was defined based on the PiB-PET availability and included patients with Alzheimer disease-related cognitive impairment (n=90) and subcortical vascular cognitive impairment (n=142).[16] The largest and most comprehensive study to date included 809 patients from the Amsterdam Dementia Cohort.[3] The prevalence of cSS was different according to diagnostic groups (higher in Alzheimer's disease patients, lower mild cognitive impairment and absent in patients with subjective cognitive complaints). Interestingly, similar to our findings, cSS presence was associated with APOE $\epsilon 4$, presence of microbleeds, and white matter hyperintensities independent of diagnosis.[3] However, none of these studies presented data on the specific subgroup of patients with high suspicion for CAA. In addition, only the Korean PiB-PET study provided available follow-up data on the clinical and imaging evolution in cSS cases.[16] Our study included a comprehensive assessment of these aspects related to cSS pathophysiology and hence extends the findings of previous studies in another, fairly large cohort.

Centrum semiovale perivascular spaces on MRI are attracting increasing attention as a promising indicator of cerebrovascular amyloid deposition.[20] Emerging evidence suggests that cerebrovascular amyloid deposition is a "protein elimination failure angiopathy" [21]: as perivascular drainage pathways fail with age (or are overloaded by reduced capacity of other elimination mechanisms), amyloid- β is increasingly trapped in the perivascular compartment and deposited in the walls of small arteries.[22] Hence, centrum semiovale perivascular spaces are an important marker to consider in the context of CAA in memory clinic populations,[13] as they might reflect the impaired interstitial fluid drainage.[22]. This notion was recently supported by an MRI/PiB-PET study showing an association between higher overall cortical amyloid burden and overall centrum semiovale perivascular spaces severity in patients with CAA.[23]

It is quite intriguing that, overall, cSS seems to occur less often compared to the much higher prevalence of lobar CMBs in memory clinic populations[3,4,16] and in healthy elderly subjects.[17] The prevalence of cSS in the possible/probable CAA subgroup (13%) in our study was also lower compared to CAA cases presenting with spontaneous lobar

intracerebral hemorrhage or pathologically-proven symptomatic CAA (around 40%).[1,14] Although the exact mechanisms are not well established, these neuroimaging markers probably reflect related but distinct aspects of CAA pathophysiology.[24,25] A plausible explanation is that there are different phenotypes of amyloid deposition, e.g. more leptomeningeal vs. parenchymal, which might be potentially responsible for cSS vs. lobar CMBs respectively. In this context, patients with cognitive impairment and cSS might thus have a distinct clinical phenotype, e.g. with worse cognitive outcome, high APOE $\epsilon 2$ [24] or $\epsilon 4/\epsilon 4$ frequency,[16] and increased lobar intracerebral haemorrhage risk.

The main limitations of our study include the cross-sectional design, the relatively small number of patients with cSS and the availability of APOE data and follow-up information and MRIs only in a subset of this cohort. For example our multivariable models were based on 10 outcome events, limiting the number of covariates one can include as well as the statistical power. This limitation is essentially inherent in any single centre memory clinical cohort, given the low prevalence of cSS in this population. This prevents additional analyses on the clinical relevance of cSS in the setting of a memory clinic, including any direct effect on cognition or haemorrhage risk and disease progression. However, these are important questions, especially in light of the recently published results of the MISTAL study, reporting that Alzheimer's disease patients with lobar microbleeds have an increased risk for stroke and stroke-related mortality [26]. Given the general lack of longitudinal data on the topic, further prospective studies should investigate the relation between cSS, cognitive impairment and CAA. These studies should shed light on whether cSS identifies distinct phenotypes of CAA or Alzheimer's disease (e.g. worse cognitive outcome, high APOE $\epsilon 4$ genotype frequency, increased stroke or amyloid-related imaging abnormalities-ARIA risk).

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Figure 1. Axial T2*-GRE MRI of a patient with disseminated cSS affecting multiple sulci at baseline (A). (B–C) Follow-up MRI scans showing new areas of cSS (yellow and green arrowheads).

Table 1

Comparison of clinical and imaging characteristics patients with vs. without cSS.

	Whole cohort (N=339)	Cases with cSS (N=10)	Cases without cSS (N=329)	p-value
Age, mean (95% CI), years	73.3 (72.4–74.3)	78.4 (73.3–83.6)	73.1 (72.2–74.1)	0.0579
Sex, male n (%)	148 (43.7)	4 (40)	144 (43.8)	1.000
Hypertension, n (%)	184 (54.4)	4 (40)	180 (54.9)	0.522
Diabetes mellitus, n (%)	38 (11.6)	0	38 (11.6)	0.611
Hypercholesterolemia, n (%)	175 (51.8)	5 (50)	170 (51.7)	1.000
Antiplatelet use, n (%)	57 (16.8)	3(30)	54 (16.4)	0.381
Anticoagulant, n (%)	28 (8.3)	0	28 (8.5)	1.000
Statin use, n (%)	160 (47.2)	3 (30)	157 (47.7)	0.344
Clinical Dementia Rating (CDR) score, median (IQR)	0.5 (0.5–1)	1 (0.75–1)	0.5 (0.5–1)	0.158
Mean total Fazekas WMH, (95%CI)	3.12 (2.99–3.24)	5 (4.33-5-69)	3.01 (2.94–3.19)	<0.0001
Severe (Fazekas 5–6) WMH, n (%)	42 (12.4)	6 (60)	36 (10.9)	<0.0001
Lobar CMBs presence, n (%)	74 (22.1)	10 (100)	64 (19.5)	<0.0001
Lobar CMBs count, median (IQR)	0	19 (10–60)	0	<0.0001

Table 2

APOE genotype in patient with vs. without cSS and genetic data available.

APOE genotype, n (%)	Whole cohort (n=68)	Cases with cSS (n=6)	Cases without cSS (n=62)	p-value
$\epsilon 2/\epsilon 2$	0	0	0	-
$\epsilon 2/\epsilon 3$	6 (8.8)	1 (16.7)	5 (8.1)	0.438
$\epsilon 2/\epsilon 4$	3 (4.4)	1 (16.7)	2 (3.2)	0.245
$\epsilon 3/\epsilon 3$	22 (32.4)	1 (16.7)	21 (33.9)	0.656
$\epsilon 3/\epsilon 4$	29 (42.7)	0	29 (46.8)	0.034
$\epsilon 4/\epsilon 4$	8 (11.8)	3 (50)	5 (8.1)	0.019
APOE $\epsilon 2$, n (%)	9 (13.2)	2 (33.3)	7 (11.3)	0.177
APOE $\epsilon 4$, n (%)	39 (57.4)	3 (50)	36 (58.1)	1.000