Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 11436 - 11442
Received 25 April 2021; Accepted 08 May 2021.

Effect of Siderosis in General and Oral Health Systematic Review and Meta analysis

DrPandurangaiah R[1],Dr. Meghana H C[2], Dr. AmbikaHegde[3], Mr.Pantula Sumiran[4], Dr. KameswariKondreddy[5], Dr. Siva Kumar Pendyala[6], Dr. Rahul VC Tiwari[7]

[1]MBBS DNB (OBG), Assistant Professor, Department of Obstetrics and Gynaecology, Kannur Medical College, Anjarkandy, Kannur, Kerala.pandu.medico@gmail.com
[2]BDS, MDS, Assistant professor Department of oral medicine and radiology, A J Institute of dental sciences, Mangalore, Karnataka.meghanacharan2@gmail.com
[3]MBBS, MD, Assistant Professor, Department of Obstetrics and Gynaecology, Father Muller Medical College and Hospital, Kankanady, Mangalore.drambikahegde@gmail.com
[4]B.Sc Life Sciences and Chemistry Hons., MBA Hospital and Healthcare Management, Business Technology Analyst, Deloitte USI. sumiran265@gmail.com
[5]Senior Lecturer, Department of Periodontics, Faculty of Dentistry, AIMST UNIVERSITY, Semeling, Bedong, Kedah-08100, Malaysia.drkameswarikondreddy@gmail.com
[6]Associate Professor, Department of Oral & Maxillofacial Surgery, Faculty of Dentistry, AIMST UNIVERSITY, Semeling, Bedong, Kedah-08100, Malaysia.drsiva77@gmail.com
[7]OMFS, FOGS, PhD Scholar, Dept of OMFS, Narsinbhai Patel Dental College and Hospital, Sankalchand Patel University, Visnagar, Gujarat,384315. drrahulvctiwari@gmail.com

Corresponding author:
DrPandurangaiah R, MBBS DNB (OBG), Assistant Professor, Department of Obstetrics and Gynaecology, Kannur Medical College, Anjarkandy, Kannur, Kerala.pandu.medico@gmail.com

Abstract

Introduction: MRI biomarkers of small vessel damage in cerebral amyloidangiopathy (CAA) include small, and typically silent, strictly lobar cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS). To assess the association of cortical superficial siderosis (cSS) presence and extent with future bleeding risk including in CAA, other general and oral procedures.

Material and Methods: This was a meta-analysis of clinical cohorts of symptomatic patients with CAA who had T2*- MRI at baseline and clinical follow-up for future intracerebral hemorrhage (ICH). We pooled data in a 2-stage meta-analysis using random effects models. Covariate-adjusted hazard ratios (adjHR) from multivariable Cox proportional hazard models were used.

Results: We included data from 6 eligible studies (n = 1,239). cSS pooled prevalence was 34%. During a mean follow-up of 3.1 years, 162/ 1,239 patients experienced a symptomatic ICH-pooled incidence rate 6.9% per year. ICH incidence rates per year according to cSS status were 3.9% for patients without cSS, 11.1% for cSS presence, 9.1% for focal cSS, and 12.5% for disseminated cSS. In adjusted pooled analysis, any cSS presence was independently associated with increased future ICH risk. Focal cSS was linked with ICH risk, while disseminated cSS conferred the strongest bleeding risk.

Conclusion: In patients with CAA, cSS presence and extent are the most important MRI

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 11436 - 11442
Received 25 April 2021; Accepted 08 May 2021.

prognostic risk factors for future ICH, likely useful in treatment planning.
Key words: Cerebral amyloid angiopathy, Cortical superficial siderosis, bledding.

Introduction

Advanced cerebrovascular deposition of β-amyloid (Aβ), defined neuropathologically as cerebral amyloid angiopathy (CAA), is a prevalent small-vessel disease and a leading cause of spontaneous lobar intracerebral hemorrhage (ICH).[1] The clinical management of symptomatic patients with CAA (presenting with or without ICH, in stroke or memory clinics) is thus centered around preventing future ICH, either first-ever or recurrent, since these are associated with substantial morbidity and mortality. Identifying strong risk factors of future CAA-related ICH, including hemorrhagic s

MRI biomarkers, is thus a crucial focus in the field.[2] Putative hemorrhagic MRI biomarkers of small vessel damage in CAA include small, and typically silent, strictly lobar cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS). While more recently described in relationship to CMBs, cSS has been implicated as a specific MRI footprint of a more aggressive CAA phenotype. cSS quite characteristically follows the curvilinear shape of the surrounding cerebral gyri on T2*-weighted MRI, reflecting blood breakdown products deposition that line the outermost surface of the cortex or the subarachnoid space (figure 1).[3]cSS is thought to result from superficial cortical hemorrhages (designated as convexity subarachnoid hemorrhage, when acute), likely as a consequence of brittle superficial cortical penetrators or leptomeningeal vessels affected by advanced cerebrovascular Aβ deposition.[3,4]cSS is rapidly gaining particular relevance to clinical practice as a marker for increased future CAA-related ICH risk in various different CAA patient populations and clinical settings.[3,5,6]The aim of this work is to bring together the totality of evidence and obtain precise estimates on the effect sizes of cSS as an independent predictor of future ICH risk in patients with CAA, across the spectrum of different clinical presentations and settings. We investigate this clinical question in a systematic review and meta-analysis of published studies on the topic

Material and methods

Online data was collected from the search engines of EBSCO, Pubmed, Google Scholar, Scopus. The searched terms were Siderosis*, general health, oral manifestations, cortical superficial siderosis" or "convexity siderosis" or "convexalsiderosis" or "cortical hemosiderosis.* The study articles were collected that from Jan 2019 to Feb 2021. Two reviewers independently checked the data collected and disputes resolved by consensus. The study was conducted with reference to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),Meta-analysis of Observational Studies in Epidemiology guidelines, and the Cochrane Hand- book for Systematic Reviews of Interventions. We excluded case reports, cohorts selected by having isolated cSS at baseline, and cohorts on familial CAA or CAA-related inflammation.

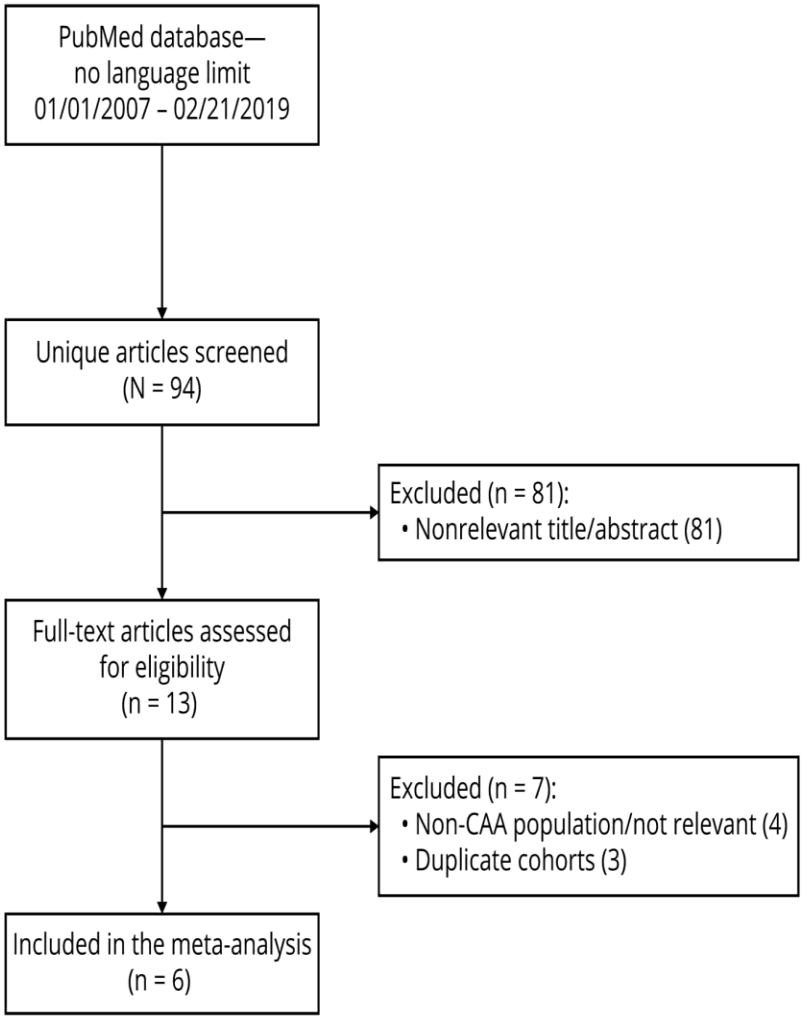
Results

We included data from 6 eligible studies (n = 1,239). Fig 1 cSS pooled prevalence was 34% (95% confidence interval [CI] 26%–41%; I2 87.94%; p < 0.001): focal cSS prevalence was 14% (95% CI 12%–16%; I2 6.75%; p = 0.37), and disseminated cSS prevalence was 20% (95% CI 13%–26%; I2 90.39%; p < 0.001). During a mean follow-up of 3.1 years (range 1–4 years), 162/ 1,239 patients experienced a symptomatic ICH-pooled incidence rate 6.9% per year (95% CI

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 11436 - 11442
Received 25 April 2021; Accepted 08 May 2021.

3.9%–9.8% per year; I2 83%; p < 0.001). ICH incidence rates per year according to cSS status were 3.9% (95% CI 1.7%–6.1%; I2 70%; p = 0.018) for patients without cSS, 11.1% (95% CI 7%–15.2%; I2 56.8%; p = 0.074) for cSS presence, 9.1% (95% CI 5.5%–12.8%; I2 0%; p = 0.994) for focal cSS, and 12.5% (95% CI 5.3%–19.7%; I2 73.2%; p = 0.011) for disseminated cSS. In adjusted pooled analysis, any cSS presence was independently associated with increased future ICH risk (adjHR 2.14; 95% CI 1.19–3.85; p < 0.0001). Focal cSS was linked with ICH risk (adjHR 2.11; 95% CI 1.31–2.41; p = 0.002), while disseminated cSS conferred the strongest bleeding risk (adjHR 4.28; 95% CI 2.91–6.30; p < 0.0001). Table 1, 2

FIGURE 1: FLOW CHART OF THE SELECTION OF THE STUDIES



Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 11436 - 11442
Received 25 April 2021; Accepted 08 May 2021.

TABLE 1 BASIC ELEMENT OF INCLUDED STUDIES.

Characteristics	Charidimou et al.[9]	Koo et al.[13]	Charidimou et al.[15]	Wollenweber et al.[16]	Charidimou et al.[7]	Moulin et al.[17]
Country/setting	European, retrospective, multicenter (4 hospitals)	Korea, retrospective, consecutive, singe-center (2005–2013)	United States, prospective, consecutive, single-center (2000–2015)	Prospective, multicenter cohort (4 hospitals): SuSPect-CAA (2013–2016)	United States, prospective, consecutive, singe-center	France, prospective, consecutive, single-center: PITCH (2004–2009)
Inception point	Hospital admission with lobar ICH at baseline	Hospital admission with lobar ICH at baseline	Patients with CAA without ICH admitted to stroke (TFNEs) or memory clinics (cognitive complains)	Patients presented at stroke services (n = 194) or memory clinics (n = 108)	Hospital admission with lobar ICH at baseline, survived 30 days after index event	Unselected survivors of spontaneous ICH with T2* MRI
T2* MRI measures (field strength/ET/ST)	T2*-GRE (1.5T/ 15–70 ms/5 mm)	T2*-GRE (3T/16 ms/5 mm)	T2*-GRE (SWI in 33%) (1.5T/50 ms/5 mm)	T2*-GRE/SWI (1.5 and 3T/?/?) (varied)	T2*-GRE (some cases: SWI) (1.5T/50 ms/5 mm)	T2*-GRE (1.5T/ 22.8 ms/5 mm)
Patient number (% men)	118 (51.7)	85 (57)	236 (60)	302 (40)	240 (53)	258 (58)
Diagnostic criteria used (possible/ probable CAA)	Original Boston criteria	Modified Boston criteria	Modified Boston criteria: all patients: probable CAA	Modified Boston criteria[a] (possible: 88; probable: 214)	Original Boston criteria (possible: 92; probable: 148)	Not applied or reported
Age, y, mean/ median (SD/IQR)	71.3 (95% CI 69.6–73)	70 (8)	81.8 (95% CI 66.6–97)	;73 (SD ;7)	75.2 (66.7–81.1)	;67
Hypertension (%)	66 (61.1)	46 (54)	154 (65)	229 (76)	152 (63.3)	165 (64)
Previous ICH (%)	30 (25.4)	—	0	109 (36)	29 (12.1)	13 (0.05) [69 (27) with MRI old ICH]
Advance WMH (grade 2–3) (%)	52 (44.8)	52 (61)	78 (33)	Not reported	140 (58.3)	157 (61)
CMBs prevalence (%)	80 (67.8)	57 (67)	227 (96)	252 (83)	116 (48.3)	108 (42)
Follow-up method	Clinical records review, recurrent lobar ICH outcome events confirmed on brain CT	Clinical records review, recurrent lobar ICH outcome events confirmed on brain CT	Phone calls at 3 months after enrollment and every 6 months, chart review	Clinical visits (at 6 and 12 months), telephone interview, medical record review	Telephone follow-up, supplemented by chart review, outcome events confirmed on brain CT	Clinical visits (at 6 and 12 months and annually thereafter), telephone
Follow-up time, y (IQR)	2 (0.4–1.8)	3 (range 0.08–10.1)	3.26 (1.42–5.50)	1	2.6 (0.9–5.1)	6.4 (2.9–8.4)
Variables included in survival analysis adjusted models and in our models	Age (per year increase)[b] Previous lobar ICH (other than index event) Total WMH volume, per milliliter increase >5 CMBs presence cSS presence, burden[b]	Post-ICH antithrombotics use[b] CMB burden CSO-PVS severity cSS presence, burden[b]	Age[b] >5 lobar CMBs presence; severe WMH cSS presence, burden[b]	Age Number of CMB mRS[c] cSS presence, disseminated cSS[b]	Age (per year increase)[b] Multiple (>2) CMBs cSS presence, burden[b]	Old ICH Lobar CMBs presence Disseminated cSS[b]

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 11436 - 11442
Received 25 April 2021; Accepted 08 May 2021.

TABLE 2: RISK OF BIAS BASED ON THE NEWCASTLE–OTTAWA SCALE

Key quality indicators	Charidimou et al.[6]	Koo et al.[13]	Charidimou et al.[16]	Wollenweber et al.[18]	Charidimou et al.[9]	Moulin et al.[17]
Prospective cohort	–	–	+	+	+	+
Clearly defined populations (and estimates separated per clinical setting/presentation)	+	+	+	+	–	–
Consecutive patients	+	+	+	–	+	+
Data on excluded patients presented among screened populations	–	–	+	–	+	+
Standardized and clearly defined MRI measures	+	+	+	–	+	+
Clear cSS definition, according to consensus guidelines	+	+	+	+	+	+
>1 year of mean/median follow-up	+	+	+	–	+	+
Completion of follow-up (>90%)	+	+	+	–	+	+
Fully adjusted survival models presented	+	–	+	? (OR vs HR)	+	–
No. of quality indicators fulfilled	7/9	6/9	9/9	3/9	8/9	7/9
Selection (Newcastle–Ottawa Scale)	****	***	****	***	****	***
Comparability (Newcastle–Ottawa Scale)	**	*	**	*	**	–
Outcome (Newcastle–Ottawa Scale)	***	***	***	**	***	***

Discussion

Patients with cSS on MRI appear to have approximately 2 times the HR for future hemorrhage, compared to those without cSS. While focal cSS was also associated with doubling the bleeding hazards, the major driver of the elevated bleeding risk seems to be disseminated cSS with pooled HRs 4 times greater than in patients without cSS. These estimates were independent of previously identified risk factors for CAA-related hemorrhage, including increasing age and lobar CMBs, and were stable irrespective of whether patients with CAA presented with lobar ICH or other non-ICH syndromes at baseline. These results add substantially to an in- creasing body of evidence supporting cSS as a central and specific hemorrhagic footprint of advanced CAA.[3] The major clinical relevance of current findings is that cSS should play a key part in the routine bleeding risk stratification in patients with symptomatic CAA, including decision-making around prognosis and treatment. This becomes particularly important for anticoagulation decisions in CAA—currently, one of the hotly debated topics in the field.[19,20] Clinicians are often hesitant to prescribe oral anticoagulation in patients with suspected underlying CAA, who would otherwise have a strong indication for the medication (e.g., nonvalvular atrial fibrillation).[20]

Our results demonstrate that hemorrhagic risk, and hence the balance between hemorrhagic and cardioembolic stroke, is not uniform in patients with CAA. Instead, different CAA phenotypes with varying propensities towards bleeding can be dissected out based on the MRI presence and extent of cSS. The exact tipping point for when oral anticoagulation treatment should be avoided in patients with CAA in light of ICH risk and anticoagulation-related complications is difficult to calculate. However, a future incident/recurrent ICH rate of 12.5% per year (and HR of ;4) in the presence of disseminated cSS in the current meta-analysis identifies a specific CAA patient group in which the benefits of oral anticoagulation for preventing ischemic strokes should be carefully balanced in order to outweigh the risks.[20] On the other hand, the presence of atrial fibrillation might confer enough risk for ischemic stroke to offset the presumed ICH risk in the subset of patients with CAA without cSS and a CHA_2DS_2 score >1–2. *APOE* e2 is known to be

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 11436 - 11442
Received 25 April 2021; Accepted 08 May 2021.

associated with CAA-related ICH, perhaps causally, and predisposes to larger volumes of CAA-related bleeding.In recent studies, the *APOE* e2 allele had a higher prevalence among patients with CAA with cSS, especially when disseminated. Often these patients have cSS occurring in multiple brain locations and hence a large hematoma is very likely to be close to a cSS region without a real statistical topographic correlation. There is also direct neuropathologic evidence that microbleeds and larger symptomatic hemorrhages (e.g., macrobleeds) might be pathophysiologically distinct, and not in a continuum. These findings highlight the fact that cSS is more than just a cerebral sulcus equivalent of a microbleed—cSS is a distinct hemorrhagic signature of CAA and is strongly associated with risk of bleeding.Few limitations were seen in our study: (1) inherent limitations of CAA cohorts looking at baseline MRI markers and risk of future hemorrhage; and (2) limitations related to this type of aggregate data group-level meta-analysis.We also hypothesized based on prior studies that the effect of cSS in elevating future bleeding risk is independent of whether patients had a history of ICH. However, we have hypothesized, and confirmed, that the effect of the marker—in this case cSS—has a consistent effect in increasing the relative risk for future ICH across the spectrum of CAA.

Conclusion

Altogether, data reported here solidify cSS as a biomarker of increased cortical and leptomeningeal small-vessel fragility and high CAA disease activity, heralding a high risk for future ICH. Our findings therefore provide a strong argument for using blood-sensitive T2*-weighted MRI sequences to identify specific subgroups of patients with CAA at high risk for ICH. This could be helpful to inform and tailor treatment planning. Large international efforts in the field are underway to validate and expand these findings.

References

1. Charidimou A, Boulouis G, Gurol ME, et al. Emerging concepts in sporadic cerebral amyloid angiopathy. Brain 2017;140:1829–1850.
2. Greenberg SM, Al-Shahi Salman R, Biessels GJ, et al. Outcome markers for clinical trials in cerebral amyloid angiopathy. Lancet Neurol 2014;13:419–428.
3. Charidimou A, Linn J, Vernooij MW, et al. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. Brain 2015;138:2126–2139.
4. Linn J, Herms J, Dichgans M, et al. Subarachnoid hemosiderosis and superficial cortical hemosiderosis in cerebral amyloid angiopathy. AJNR Am J Neuroradiol 2008; 29:184–186.
5. Linn J, Wollenweber FA, Lummel N, et al. Superficial siderosis is a warning sign for future intracranial hemorrhage. J Neurol 2013;260:176–181.
6. Charidimou A, Peeters AP, Jager R, et al. Cortical superficial siderosis and in- tracerebral hemorrhage risk in cerebral amyloid angiopathy. Neurology 2013;81: 1666–1673.
7. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ 2009;339:b2535.
8. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting: Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. JAMA 2000;283:2008–2012.
9. Charidimou A, Boulouis G, Roongpiboonsopit D, et al. Cortical superficial siderosis and recurrent intracerebral hemorrhage risk in cerebral amyloid angiopathy: large prospective cohort and preliminary meta-analysis. Int J Stroke Epub 2019 Feb 20

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 11436 - 11442
Received 25 April 2021; Accepted 08 May 2021.

10. Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: validation of the Boston criteria. Neurology 2001;56:537–539.
11. Linn J, Halpin A, Demaerel P, et al. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. Neurology 2010;74:1346–1350.
12. Kahneman. Thinking Fast, Thinking Slow. New York: Farrer Straus Giroux; 2011.
13. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol 2013;12:822–838.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clin trials 1986;7: 177–188.
15. Koo HW, Jo KI, Yeon JY, Kim JS, Hong SC. Clinical features of high-degree centrum semiovale-perivascular spaces in cerebral amyloid angiopathy. J NeurolSci 2016;367:89–94.
16. Charidimou A, Boulouis G, Xiong L, et al. Cortical superficial siderosis and first-ever cerebral hemorrhage in cerebral amyloid angiopathy. Neurology 2017;88:1607–1614.
17. Moulin S, Casolla B, Kuchcinski G, et al. Cortical superficial siderosis: a prospective observational cohort study. Neurology 2018;91:e132–e138.
18. Wollenweber FA, Opherk C, Zedde M, et al. Prognostic relevance of cortical superficial siderosis in cerebral amyloid angiopathy. Neurology 2019;92:e792–e801.
19. Steiner T. Resumption of oral anticoagulation after warfarin-associated intracerebral hemorrhage: yes. Stroke a J CerebCirc 2011;42:3661–3662.
20. Charidimou A, Shoamanesh A, Al-Shahi Salman R, et al. Cerebral amyloid angiopathy, cerebral microbleeds and implications for anticoagulation decisions: the need for a balanced approach. Int J Stroke 2018;13:117–120