Staging cerebral amyloid angiopathy: from marker to model

Koemans, E.A.

8

CEREBELLAR SUPERFICIAL SIDEROSIS IN CEREBRAL AMYLOID ANGIOPATHY

Chapter 8 | Cerebellar superficial siderosis in Cerebral Amyloid Angiopathy

Emma A. Koemans[1], Sabine Voigt[1], Ingeborg Rasing[1], Thijs W. van Harten[2], Wilmar M.T. Jolink[3], Floris H.B.M. Schreuder[4], Erik W. van Zwet[5], Mark A. van Buchem[2], Matthias J.P. van Osch[2], Gisela M. Terwindt[1], Catharina J.M. Klijn[4], Marianne A.A. van Walderveen[2*], Marieke J.H. Wermer[1*]

[*]These authors contributed equally to this study

[1] Leiden University Medical Center, department of neurology

[2] Leiden University Medical Center, department of radiology

[3] Department of Neurology and Neurosurgery, University medical Center Utrecht Brain Center, Utrecht University, Utrecht, The Netherlands

[4] Department of Neurology, Donders Institute for Brain, Cognition and Behaviour, Radboud University Medical Center, Nijmegen, The Netherlands

[5] Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands

Stroke. 2022 Feb;53(2):552-557

Abstract

Background and purpose: Although evidence accumulates that the cerebellum is involved in Cerebral Amyloid Angiopathy (CAA), cerebellar superficial siderosis is not considered to be a disease marker. The objective of this study is to investigate cerebellar superficial siderosis frequency and its relation to hemorrhagic MRI markers in patients with sporadic and Dutch-type hereditary Cerebral Amyloid Angiopathy (D-CAA) and patients with deep perforating arteriopathy related intracerebral hemorrhage (DPA-ICH).

Methods: We recruited patients from three prospective 3-Tesla MRI studies and scored siderosis and hemorrhages. Cerebellar siderosis was identified as hypointense linear signal loss (black) on susceptibility weighted or T2* weighted MRI which follows at least one folia of the cerebellar cortex (including the vermis).

Results: We included 50 subjects with D-CAA, (mean age 50 years), 45 with sporadic Cerebral Amyloid Angiopathy (sCAA) (mean age 72 years) and 43 patients with DPA-ICH (mean age 54 years). Cerebellar superficial siderosis was present in 5/50 (10%, 95% CI 2-18) patients with D-CAA, 4/45 (9%, 95% CI 1-17) patients with sCAA and 0/43 (0%, 95% CI 0-8) patients with DPA-ICH. Patients with cerebellar superficial siderosis had more supratentorial lobar (median number 9 versus 2, relative risk 2.9, 95% CI 2.5-3.4) and superficial cerebellar macrobleeds (median number 2 versus 0, relative risk 20.3, 95% CI 8.6-47.6) compared to patients without the marker. The frequency of cortical superficial siderosis and superficial cerebellar microbleeds was comparable.

Conclusion: We conclude that cerebellar superficial siderosis might be a novel marker for CAA.

Introduction

Cerebral Amyloid Angiopathy (CAA) is one of the major causes of intracerebral hemorrhage (ICH) and vascular dementia in the world.[1] CAA is associated with characteristic MRI markers, including cortical superficial siderosis (cSS) of the cerebral hemispheres.[2] cSS is thought to be the result of repeated episodes of hemorrhage from fragile, amyloid-laden superficial vessels into the subarachnoid space.[3, 4] cSS is one of the most important predictors for future ICH in patients with CAA.[5, 6]

For many years, hemorrhagic MRI markers in the cerebellum were not considered to be a sign of CAA. Recently, evidence has emerged that microbleeds strictly located in the superficial cerebellum (the cerebellar cortex or vermis) are associated with CAA.[7, 8] This indicates that accumulation of amyloid-β is not restricted to supratentorial cortical vessels but also occurs in cerebellar arterioles supplying the superficial cerebellar structures. Following the same line of reasoning, amyloid-β deposition may also occur in leptomeningeal cerebellar vessels, and subsequent bleeding from these vessels may result in superficial siderosis (SS) of the cerebellum. A distinction is usually made between (supratentorial) cSS and infratentorial siderosis. Infratentorial siderosis is associated with progressive hearing loss and ataxia and has a wide range of causes, but is not associated with CAA.[9] Cerebellar SS has not yet been systematically investigated in CAA and has only been reported in one CAA case.[2]

We aimed to investigate the frequency of cerebellar SS in patients with sporadic CAA (sCAA) and Dutch-type hereditary CAA (D-CAA).[10] Secondly, we compared the frequency of cerebellar SS in patients with CAA compared to patients with deep perforating arteriopathy related ICH (DPA-ICH). Lastly, we assessed the association of cerebellar SS with supratentorial cSS and (micro and macro) hemorrhages on MRI.

Methods

Data availability statement

Further information about the dataset is available from the corresponding author upon reasonable request.

Study participants

We included participants from three prospective studies. Two of these studies are ongoing CAA natural history studies of the Leiden University Medical Center (LUMC): the AURORA study, which includes patients with D-CAA, and the FOCAS

study, which includes patients with sCAA. Both studies have the exact same study protocol. Patients with D-CAA and sCAA were included via the (outpatient) clinic of the LUMC. D-CAA (also known as Hereditary Cerebral Hemorrhage With Amyloidosis - Dutch type, HCHWA-D) is one of the hereditary forms of CAA. D-CAA is clinically, pathologically and biochemically similar to sporadic CAA but has an earlier onset and a more aggressive disease course.[10] Inclusion criteria for D-CAA were: age of 18 years and older and presence of the causal APP mutation or a history of symptomatic ICH on CT/MRI suspect for CAA and at least 1 first-degree relative with D-CAA. We included both D-CAA patients with and without a history of previous symptomatic ICH. Patients with sCAA were included if they fulfilled the criteria for probable CAA and had no family history of D-CAA.[2] The third study was the FETCH (Finding the Etiology in spontaneous Cerebral Hemorrhage) study, a collaborative study between the University Medical Centers of Utrecht, Nijmegen and Leiden. The FETCH study included patients who presented in one of the three centers with spontaneous ICH between 2013 and 2019.[11] From the FETCH study we included patients with probable CAA according to the modified Boston criteria as well as patients with non-lobar ICH who did not have any signs of CAA in the form of lobar located micro or macrobleeds, and who were, therefore, diagnosed with have deep perforating arteriopathy (DPA-ICH, also known as hypertensive arteriopathy).[2] We excluded participants who had signs of mixed type small-vessel disease, as well as patients in whom the cerebellum was not fully covered on MRI.[12] For all participants data on demographics, medical history and clinical symptoms including history of ICH were prospectively obtained via questionnaires and a neurological examination was performed on the same day of the MRI scan. The studies were approved by the local ethics review boards of the medical centers, and written informed consent was obtained from all participants.

MRI

Image acquisition

All participants underwent a MRI scan of the brain performed on a whole body human 3 Tesla (3T) MRI scanner. The participants of the AURORA and FOCAS study were scanned with the same 3T MRI scanner (Philips Healthcare, Best, The Netherlands), participants of the FETCH study were scanned using three different 3T systems (Siemens Healthineers, Erlangen, Germany; and two scanners from Philips Healthcare, Best, The Netherlands). The data were acquired using a standard 32-channel head coil. Participants were scanned using an extensive protocol. For the current study

only the susceptibility weighted images (SWI) of the FOCAS and AURORA study and either the T_2*-weighted images or SWI images of the FETCH study were analyzed. The SWI images of the FOCAS and AURORA study had a voxel size of 0.6x0.6x1 mm. The T_2*-weighted images of the FETCH had a voxel size of 0.98x0.98x3.00 mm, and the SWI of the FETCH had a voxel size of 0.96x0.96x3.00 mm.

Image analysis

Presence and location of cerebellar SS was scored in all participants by two independent observers (S.V. and E.A.K.). MRI scans that were scored positive for cerebellar SS were discussed with a third observer with >15 years of experience in the field (M.A.A.v.W.) for confirmation. Observers could not be blinded for CAA diagnosis, as this became apparent after assessment of the small vessel disease (SVD) markers on MRI. In all participants with CAA, hemorrhagic MRI markers associated with SVD were scored according to the Standards for Reporting Vascular Changes on neuroimaging (STRIVE) criteria.[13] All SVD markers were scored by one observer (E.A.K., 5 years of experience in the field). The following markers were assessed on SWI: cerebellar SS, supratentorial cSS, supratentorial and cerebellar hemorrhages (macrobleeds and microbleeds). Cerebellar SS was identified as hypointense linear signal loss (black) on SWI or T2* weighted MRI which follows at least one folia of the cerebellar cortex (including the vermis), and was scored according to location (vermis, anterior lobe, posterior lobe). Supratentorial cSS was scored as focal, defined as restricted to three or fewer sulci, or disseminated, defined as affecting four or more sulci, and cSS hemisphere score was calculated according to previously described methods.[3, 14] Macrobleeds were defined as hypointense lesions with either an irregular shape or a cystic cavity on SWI MRI, and were counted and scored according to the following locations: deep cerebellum (grey nuclei and white matter), superficial cerebellum (cortex and vermis), and supratentorial lobar.[7] Microbleeds were defined as a well-defined, round or oval hypointense lesions on SWI MRI (generally 2-5mm in diameter, but sometimes up to 10mm), and were scored in the following categories: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 microbleed(s), 11-20 microbleeds, 21-50 microbleeds, 51-100 microbleeds, more than 100 microbleeds, and according to the following locations: deep cerebellum, superficial cerebellum, and supratentorial lobar.

Statistics

Descriptive statistics were used to describe baseline characteristics. We used a Kruskal-Wallis test to determine differences in age and Chi-square testing to determine

differences in the other baseline characteristics between the groups. Interobserver variation and the grading of interobserver agreement was assessed for cerebellar SS by calculating the Kappa statistic.[15] The proportion of patients with cerebellar SS in D-CAA, sCAA and DPA-ICH was calculated including 95% confidence intervals (95% CI). We calculated odds ratios (OR) or relative risks (RR) with 95% CI for history of symptomatic ICH, the proportion of supratentorial cSS, superficial cerebellar macro- and microbleeds and the number of supratentorial lobar and superficial cerebellar macrobleeds on MRI in CAA patients with and without cerebellar SS using binary logistic regression or Poisson regression adjusted for age at the time of MRI.

Data availability statement

Further information about the dataset is available from the corresponding author upon reasonable request.

Results

We included 95 patients with CAA; 50 with D-CAA (mean age 50 years, 58% women) and 45 with sCAA (mean age 72, 49% women), and 43 patients with DPA-ICH (mean age 54, 35% women). Twenty-three (46%) of the patients with D-CAA, 35 (78%) of the patients with sCAA and all (100%) of the DPA-ICH patients had a history of symptomatic ICH (table 1). For all 43 DPA-ICH patients this was their first symptomatic ICH. Two (4%) of the patients with sCAA and 12 (24%) of the patients with D-CAA had a history of more than one symptomatic ICH. In all patients with CAA the symptomatic ICH were supratentorial lobar. Twenty-nine (67%) of the patients with DPA had a deep ICH, 11 (26%) had a cerebellar ICH and three (7%) an ICH in the brainstem. Of the 11 patients with DPA and a cerebellar ICH, three had an ICH in the superficial cerebellum, seven in the deep cerebellum and one had an ICH which was located in both the deep and superficial cerebellum.

In total nine (9%, 95% CI 4-15) of the patients with CAA and none (0%, 95% CI 0-8) of the patients with DPA-ICH had cerebellar SS (for examples of cerebellar SS see figure 1). Five (10%, 95%CI 2-18) of the 50 patients with D-CAA had cerebellar SS; 0/27 (0%) without and 5/23 (22%) with a history of symptomatic ICH. Four (9%, 95%CI 1-17) of the 45 patients with sCAA had cerebellar SS; 1/10 (10%) without and 3/35 (9%) with a history of symptomatic ICH. Six patients had cerebellar SS in

Table 1: Baseline characteristics.

	D-CAA (n=50)	sCAA (n=45)	DPA-ICH (n=43)	P-value
Mean age in years (range)	50 (28-75)	72 (57-86)	54 (19-83)	0.000
Women (%)	29 (58)	22 (49)	15 (35)	0.083
Hypertension* (%)	11 (22)	24 (53)‖	14 (33)	0.002
Diabetes type 2† (%)	1 (2)	3 (7)#	5 (12)	0.175
Hypercholesterolemia‡ (%)	12 (24)	17 (38)#	3 (7)	0.004
History of smoking, ever§ (%)	33 (66)	25 (56)**	20 (47)	0.225
History of symptomatic ICH (%)	23 (46)	35 (78)	43(100)	0.000

**Defined as reported in medical history or use of antihypertensive medication.*

†Defined as reported in medical history or use of oral antidiabetics or insulin.

‡Defined as reported in medical history or use of statins.

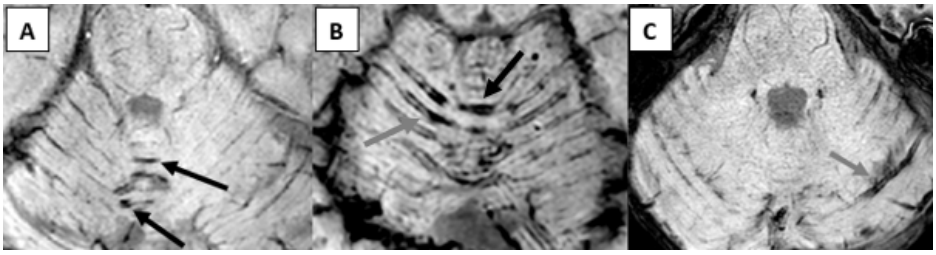
§Defined as having ever smoked for at least one year.

‖Hypertension status was unknown in 3 sCAA patients.

#Hypercholesterolemia and diabetes type 2 status was unknown in 2 sCAA patients.

***Smoking status was unknown in 5 sCAA patients.*

Figure 1: *Examples of cerebellar superficial siderosis in CAA.*



Examples of cerebellar superficial siderosis on susceptibility weighted 3 Tesla MRI in a 73 year old patient with sCAA and previous symptomatic ICH (A) and two patients (both 58 years old) with symptomatic D-CAA (B and C). Cerebellar superficial siderosis occurs most frequently around the vermis (shown in A and B, black arrows) and less often in cerebellar hemisphere (shown in B and C, grey arrows).

multiple locations; four (44%) of the nine patients had cerebellar SS in the anterior lobe, four (44%) in the posterior lobe and eight (89%) in the vermis. None of the nine participants had siderosis around the brainstem. The interobserver variation (Kappa statistic) for cerebellar SS was perfect (1.0).

Eight (89%) of the nine patients with cerebellar SS had a history of symptomatic ICH. None of these previous ICH was located in the cerebellum (table 2). Six (67%) patients with cerebellar SS had concomitant supratentorial cSS on MRI, most often disseminated (56%). All nine patients showed micro- and macrobleeds on MRI, of whom six (67%) had superficial cerebellar macrobleeds and six (67%) superficial cerebellar microbleeds (table 2). None of the cerebellar SS cases was contiguous with a macro- or microbleed.

Patients with cerebellar SS had more supratentorial lobar macrobleeds (median number 9 versus 2, RR 2.9, 95%CI 2.5-3.4) and superficial cerebellar macrobleeds (22.8, 95% CI 4.6-113.6, median number 2 versus 0, RR 20.3, 95%CI 8.6-47.6) on MRI compared with patients without cerebellar SS. The frequency of cSS and superficial cerebellar microbleeds was comparable between patients with and without cerebellar SS (table 2).

One of the nine patients with cerebellar SS had symptoms of vestibulopathy or ataxia syndrome, in the form of limb ataxia in one limb at neurological examination. None of the patients with cerebellar SS had a history of neurosurgery.

Discussion

We found cerebellar SS in 10% of the participants with (symptomatic) D-CAA and in 9% of patients with sCAA. CAA patients with cerebellar SS had more supratentorial lobar and superficial cerebellar macrobleeds on MRI compared to CAA patients without cerebellar SS. Cerebellar SS was not detected in the patients with DPA-ICH.

Table 2: Characteristics of CAA patients with and without cerebellar SS.

	No cerebellar SS (n=86)	Cerebellar SS (n=9)	OR/RR (95% CI)
History of symptomatic ICH (%)	50 (58)	8 (89)	4.6 (0.5-40.5)*
History of symptomatic cerebellar ICH (%)	0 (0)	0 (0)	
MRI markers			
Cortical superficial siderosis			
cSS (%)	36 (42)	6 (67)	2.5 (0.5-11.6)*
Focal (%)	15 (17)	1 (11)	
Disseminated (%)	21 (24)	5 (56)	
Median hemisphere score (SD)	0 (1.5)	2 (1.9)	
Macrobleeds			
Cerebral lobar macrobleeds (%)	61 (71)	9 (100)	
Median number of cerebral lobar macrobleeds (range)	2 (0-84)	9 (1-88)	2.9 (2.5-3.4) †
Superficial cerebellar macrobleeds (%)	7 (8)	6 (67)	22.8 (4.6-113.6)*
Median number of superficial cerebellar macrobleeds (range)	0 (0-2)	2 (0-4)	20.3 (8.6-47.5) †
Microbleeds			
Cerebral lobar microbleeds (%)	63 (73)	9 (100)	
Superficial cerebellar microbleeds (%)	29 (34)	6 (67)	3.7 (0.9-16.0)*
0 (%)	57 (66)	3 (33)	
1-10 (%)	19 (22)	4 (44)	
11-50 (%)	10 (12)	2 (22)	

**Odds Ratio (OR), corrected for age.*

†Relative Risk (RR), corrected for age.

One previous case of cerebellar SS in CAA has been reported.[2] This patient had extensive infratentorial SS (iSS), not only involving the cerebellum but also the brainstem. This more extensive form of iSS differs from the cerebellar SS in our study, which consisted of hemosiderin depositions following the cerebellar folia without involvement of the brainstem.[14] iSS is considered to be a progressive degenerative disorder associated with sensorineural hearing loss, peripheral vestibulopathy and ataxia, most likely caused by bleeding in the subarachnoid space from either a single or recurrent bleeding.[9, 14, 16] The cerebellar SS we detected in our study was related to a higher number of cerebellar macrobleeds but not directly located adjacent to micro- or macrobleeds.[4, 5] Interestingly, similar to iSS, cerebellar superficial siderosis was most often found in the vermis.[17] In

iSS it is hypothesized that this might be because the pattern of cerebrospinal fluid flow (CSF) irrigates the cerebellar convexities and flocculus first. These regions are, therefore, continuously exposed to (hemorrhagic) CSF.[9] In CAA, SS is probably caused by leakage of leptomeningeal vessels.[4] Future neuropathologic studies are necessary to investigate underlying mechanisms of CAA related SS in the cerebellum.

The finding of cerebellar SS as a new marker for CAA has several potential clinical implications. First, the novel marker could help identify CAA patients if the diagnosis is uncertain. Even though the marker seems to be related to severe CAA, it also occurred in patients without supratentorial cSS or ICH. Therefore it could strengthen the CAA diagnosis and might even improve the Boston criteria, as siderosis is one of the most distinctive hallmarks of CAA.[18] The prognostic value of cerebellar SS at this stage is unclear. However, if cerebellar SS can be seen as an extra focus of siderosis this could influence clinical decision making since disseminated cSS is related to a much higher ICH (recurrence) risk than focal cSS.[5] Last, the addition of cerebellar SS as a marker for CAA highlights the importance of the cerebellum as a location that is affected by this disease.

A limitation of this study is that although cerebellar SS was only found in patients with CAA, groups were small and age-matched healthy controls were lacking. Also, CAA is increasingly considered to be a spectrum of specific phenotypes. Because cerebellar SS was associated with a history of symptomatic ICH, it might be a marker for the hemorrhagic phenotype in particular, and not for CAA in general. Furthermore, selection bias might have occurred as in general patients who participate in scientific research are in relatively good clinical condition. Spatial resolution of the T_2*-weighted /SWI images of the FETCH protocol was lower and this might have influenced detection of cerebellar SS to some extent in this population. However in our experience, cerebellar SS is not a subtle finding and was also found in CAA patient of the FETCH cohort; the impact of the lower scan resolution on our results will therefore probably be limited. Lastly, we did not have any pathological material to investigate histological changes associated with cerebellar SS.

Strengths of our study are the prospective data collection and the possibility to study both hereditary and sporadic CAA. In contrast to sporadic CAA, D-CAA can be diagnosed with certainty in living patients by DNA analysis. D-CAA is considered to be a unique relatively pure form of CAA as mutation carriers are in general younger than sporadic patients and, therefore, less affected by age related SVD.

To conclude, the presence of cerebellar superficial siderosis in patients with D-CAA and sCAA supports the recent insight that the cerebellum is affected by CAA, and we propose it as a novel disease marker. Further research is necessary to investigate whether cerebellar SS is specific for CAA, whether it can improve the current diagnostic criteria and whether it has prognostic value.

References

1. Wermer MJH, Greenberg SM. The growing clinical spectrum of cerebral amyloid angiopathy. *Current opinion in neurology* 2018;31:28-35.
2. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, van Buchem MA, Bruckmann H, Greenberg SM. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology* 2010;74:1346-1350.
3. Charidimou A, Boulouis G, Roongpiboonsopit D, Auriel E, Pasi M, Haley K, van Etten ES, Martinez-Ramirez S, Ayres A, Vashkevich A et al. Cortical superficial siderosis multifocality in cerebral amyloid angiopathy: A prospective study. *Neurology* 2017;89:2128-2135.
4. Charidimou A, Perosa V, Frosch MP, Scherlek AA, Greenberg SM, van Veluw SJ. Neuropathological correlates of cortical superficial siderosis in cerebral amyloid angiopathy. *Brain : a journal of neurology* 2020.
5. Pongpitakmetha T, Fotiadis P, Pasi M, Boulouis G, Xiong L, Warren AD, Schwab KM, Rosand J, Gurol ME, Greenberg SM et al. Cortical superficial siderosis progression in cerebral amyloid angiopathy: Prospective MRI study. *Neurology* 2020;94:e1853-e1865.
6. Charidimou A, Boulouis G, Xiong L, Pasi M, Roongpiboonsopit D, Ayres A, Schwab KM, Rosand J, Gurol EM, Viswanathan A et al. Cortical Superficial Siderosis Evolution. *Stroke* 2019;50:954-962.
7. Pasi M, Pongpitakmetha T, Charidimou A, Singh SD, Tsai H-H, Xiong L, Boulouis G, Warren AD, Rosand J, Frosch MP, et al. Cerebellar Microbleed Distribution Patterns and Cerebral Amyloid Angiopathy. *Stroke* 2019;50:1727-1733.
8. Tsai H-H, Pasi M, Tsai L-K, Chen Y-F, Chen Y-W, Tang S-C, Gurol EM Yen R-F, Jeng J-S. Superficial Cerebellar Microbleeds and Cerebral Amyloid Angiopathy. *Stroke* 2020;51:202-208.
9. Wilson D, Chatterjee F, Farmer SF, Rudge P, McCarron MO, Cowley P, Werring DJ. Infratentorial superficial siderosis: Classification, diagnostic criteria, and rational investigation pathway. *Annals of neurology* 2017;81:333-343.
10. Bornebroek M, Haan J, Maat-Schieman ML, Van Duinen SG, Roos RA. Hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D): I--A review of clinical, radiologic and genetic aspects. *Brain pathology (Zurich, Switzerland)* 1996;6:111-114.
11. Jolink WM, Lindenholz A, van Etten ES, van Nieuwenhuizen KM, Schreuder FHBM, Kuijf HJ, van Osch MJP, Hendrikse J, Rinkel GJE, Wermer MJH et al. Contrast leakage distant from the hematoma in patients with spontaneous ICH: A 7 T MRI study. *J Cereb Blood Flow Metab* 2020;40:1002-1011.
12. Pasi M, Charidimou A, Boulouis G, Auriel E, Ayres A, Schwab KM, Goldstein JN, Rosand J, Viswanathan A, Pantoni L et al. Mixed-location cerebral hemorrhage/microbleeds: Underlying microangiopathy and recurrence risk. *Neurology* 2018;90:e119-e126.
13. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, Lindley RI, O'Brien JT, Barkhof F, Benavente OR et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology* 2013;12:822-838.
14. Charidimou A, Linn J, Vernooij MW, Opherk C, Akoudad S, Baron J-C, Greenberg SM, Jäger HR, Werring DJ. Cortical superficial siderosis: detection and clinical significance in cerebral amyloid angiopathy and related conditions. *Brain : a journal of neurology* 2015;138:2126-2139.
15. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33:159-174.

16. Yoo A, Jou J, Klopfenstein JD, Kattah JC. Focused Neuro-Otological Review of Superficial Siderosis of the Central Nervous System. *Frontiers in neurology* 2018;9.
17. Koeppen AH, Michael SC, Li D, Chen Z, Cusack MJ, Gibson WM, Petrocine SV, Qian J. The pathology of superficial siderosis of the central nervous system. *Acta neuropathologica* 2008;116:371-382.
18. Scheumann V, Schreiber F, Perosa V, Assmann A, Mawrin C, Garz C, Heinze H-J, Görtler M, Düzel E, Vielhaber S et al. MRI phenotyping of underlying cerebral small vessel disease in mixed hemorrhage patients. *J Neurol Sci* 2020;419:117173.