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Stroke

CLINICAL AND POPULATION SCIENCES

# Cerebellar Superficial Siderosis in Cerebral Amyloid Angiopathy

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**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 magnetic resonance imaging markers in patients with sporadic and Dutch-type hereditary CAA and patients with deep perforating arteriopathy–related intracerebral hemorrhage.

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

**RESULTS:** We included 50 subjects with Dutch-type hereditary CAA, (mean age 50 years), 45 with sporadic CAA (mean age 72 years), and 43 patients with deep perforating arteriopathy–related intracerebral hemorrhage (mean age 54 years). Cerebellar superficial siderosis was present in 5 out of 50 (10% [95% CI, 2–18]) patients with Dutch-type hereditary CAA, 4/45 (9% [95% CI, 1–17]) patients with sporadic CAA, and 0 out of 43 (0% [95% CI, 0–8]) patients with deep perforating arteriopathy–related intracerebral hemorrhage. 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 with patients without the marker. The frequency of cortical superficial siderosis and superficial cerebellar microbleeds was comparable.

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

**GRAPHIC ABSTRACT:** A graphic abstract is available for this article.

**Key Words:** cerebellum ■ cerebral amyloid angiopathy ■ intracerebral hemorrhage ■ magnetic resonance imaging ■ siderosis

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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 magnetic resonance imaging (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

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## Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **CAA** | cerebral amyloid angiopathy |
| **cSS** | cortical superficial siderosis |
| **D-CAA** | Dutch-type hereditary CAA |
| **DPA-ICH** | deep perforating arteriopathy–related intracerebral hemorrhage |
| **FETCH** | Finding the Etiology in Spontaneous Cerebral Hemorrhage |
| **ICH** | intracerebral hemorrhage |
| **iSS** | infratentorial SS |
| **sCAA** | sporadic cerebral amyloid angiopathy |
| **SS** | superficial siderosis |
| **SWI** | susceptibility-weighted images |

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 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] Second, 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. See the Data Supplement for the STROBE checklist required by the journal.

### *Study Participants*

We included participants from 3 prospective studies. Two of these studies are ongoing CAA natural history studies of the Leiden University Medical Center: the AURORA study, which includes patients with D-CAA, and the FOCAS study (Follow-Up in Sporadic Cerebral Amyloid Angiopathy 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 Leiden University Medical Center. D-CAA (also known as Hereditary Cerebral Hemorrhage With Amyloidosis–Dutch type) 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 (amyloid precursor protein) mutation or a history of symptomatic ICH on computed tomography/MRI suspect for CAA and at least 1 first-degree relative with D-CAA. We included both patients with D-CAA 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 study (Finding the Etiology in Spontaneous Cerebral Hemorrhage), a collaborative study between the University Medical Centers of Utrecht, Nijmegen, and Leiden. The FETCH study included patients who presented in 1 of the 3 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 nonlobar 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 DPA (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.

## Magnetic Resonance Imaging

### *Image Acquisition*

All participants underwent an MRI scan of the brain performed on a whole-body human 3 Tesla MRI scanner. The participants of the AURORA and FOCAS study were scanned with the same 3 Tesla MRI scanner (Philips Healthcare, Best, the Netherlands), participants of the FETCH study were scanned using 3 different 3 Tesla systems (Siemens Healthineers, Erlangen, Germany; and 2 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 0.6×0.6×1 mm. The $T_2$*-weighted images of the FETCH had a voxel size of 0.98×0.98×3.00 mm, and the SWI of the FETCH had a voxel size of 0.96×0.96×3.00 mm.

### *Image Analysis*

Presence and location of cerebellar SS was scored in all participants by 2 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 markers on MRI. In all participants with CAA, hemorrhagic MRI markers associated with small vessel disease were scored according to the Standards for Reporting Vascular Changes on Neuroimaging criteria.[13] All small vessel disease

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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 ≤3 sulci, or disseminated, defined as affecting ≥4 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 (gray 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 2-5 mm in diameter, but sometimes up to 10 mm) and were scored in the following categories: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 microbleed(s), 11 to 20 microbleeds, 21 to 50 microbleeds, 51 to 100 microbleeds, >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 $\chi^2$ testing to determine differences in the other baseline characteristics between the groups. Interobserver variation and the grading of interobserver agreement were 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% CI. We calculated odds ratios or relative risks with 95% CI for history of symptomatic ICH, the proportion of supratentorial cSS, superficial cerebellar macrobleeds and microbleeds, and the number of supratentorial lobar and superficial cerebellar macrobleeds on MRI in patients with CAA 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 [see the flow chart in the Data Supplement]). 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 patients with DPA-ICH, 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 >1 symptomatic ICH. In all patients with CAA, the symptomatic ICH was supratentorial lobar. Twenty-nine (67%) of the patients with DPA had a deep ICH, 11 (26%) had a cerebellar ICH, and 3 (7%) had an ICH in the brain stem. Of the 11 patients with DPA and a cerebellar ICH, 3 had an ICH in the superficial cerebellum, 7 in the deep cerebellum, and 1 had an ICH which was located in both the deep and superficial cerebellum.

In total, 9 (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 the Figure). Five (10% [95% CI, 2–18]) of the 50 patients with D-CAA had cerebellar SS; 0 out of 27 (0%) without and 5 out of 23 (22%) with a history of symptomatic ICH. Four (9% [95% CI, 1–17]) of the 45 patients with sCAA had cerebellar SS; 1 out of 10 (10%) without and 3 out of 35 (9%) with a history of symptomatic ICH. Six patients had cerebellar SS in multiple locations; 4 (44%) of the 9 patients had cerebellar SS in the anterior lobe, 4 (44%) in the posterior lobe, and

**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 |

CAA indicates cerebral amyloid angiopathy; D-CAA, Dutch-type hereditary CAA; DPA-ICH, deep perforating arteriopathy–related ICH; ICH, intracerebral hemorrhage; and sCAA, sporadic CAA.

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

†Hypertension status was unknown in 3 patients with sCAA.

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

§Hypercholesterolemia and diabetes type 2 status were unknown in 2 patients with sCAA.

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

¶Defined as having ever smoked for at least 1 y.

#Smoking status was unknown in 5 patients with sCAA.

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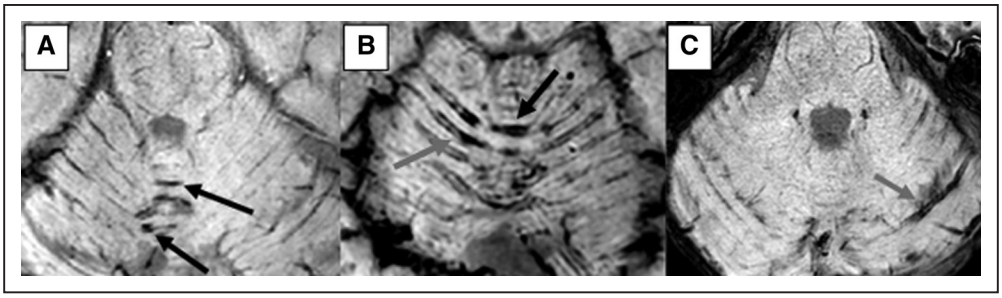


**Figure. Examples of cerebellar superficial siderosis in cerebral amyloid angiopathy (CAA).**
Examples of cerebellar superficial siderosis on susceptibility-weighted 3 Tesla magnetic resonance imaging in a 73-y-old patient with sporadic CAA and previous symptomatic intracerebral hemorrhage (**A**) and 2 patients (both 58-y-old) with symptomatic Dutch-type hereditary 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**, gray arrows).

8 (89%) in the vermis. None of the 9 participants had siderosis around the brain stem. The interobserver variation (Kappa statistic) for cerebellar SS was perfect (1.0).

Eight (89%) of the 9 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 9 patients showed microbleeds and macrobleeds on MRI, of whom 6 (67%) had superficial cerebellar macrobleeds and 6 (67%) superficial cerebellar microbleeds (Table 2). None of the cerebellar SS cases was contiguous with a macrobleeds or microbleed.

Patients with cerebellar SS had more supratentorial lobar macrobleeds (median number 9 versus 2, relative risks, 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, relative risks, 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).

**Table 2. Characteristics of Patients With CAA 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) | |

CAA indicates cerebral amyloid angiopathy; cSS, cortical SS; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; OR, odds ratio; RR, relative risk; and SS, superficial siderosis.
*OR, corrected for age.
†RR, corrected for age.

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One of the 9 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. Patients with CAA with cerebellar SS had more supratentorial lobar and superficial cerebellar macrobleeds on MRI compared with patients with CAA without cerebellar SS. Cerebellar SS was not detected in the patients with DPA-ICH.

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 brain stem. 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 brain stem.[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 microbleeds or macrobleeds.[4,5] Interestingly, similar to iSS, cerebellar SS was most often found in the vermis.[17] In iSS, it is hypothesized that this might be because the pattern of cerebrospinal fluid flow irrigates the cerebellar convexities and flocculus first. These regions are, therefore, continuously exposed to (hemorrhagic) cerebrospinal fluid flow.[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 patients with CAA if the diagnosis is uncertain. Although 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 small vessel disease.

To conclude, the presence of cerebellar SS 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.

## ARTICLE INFORMATION

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## Disclosures

None.

## Supplemental Material

Flow Chart
STROBE Checklist

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