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Citation

Rasing, I., Voigt, S., Koemans, E. A., Zwet, E. van, Kruijff, P. C. de, Harten, T. W. van, ... Wermer, M. J. H. (2021). Occipital cortical calcifications in cerebral amyloid angiopathy. *Stroke*, 52(5), 1851-1855. doi:10.1161/STROKEAHA.120.033286

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Note: To cite this publication please use the final published version (if applicable).

BRIEF REPORT

Occipital Cortical Calcifications in Cerebral Amyloid Angiopathy

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BACKGROUND AND PURPOSE: Cortical calcifications have been reported in patients with cerebral amyloid angiopathy (CAA), although their prevalence and pathophysiology are unknown. We investigated the frequency of calcifications on computed tomography, their association with intracerebral hemorrhage (ICH) and their coexistence with a striped pattern of the occipital cortex reflecting microcalcifications on ultra-high-field 7T-magnetic resonance imaging in Dutch-type hereditary CAA (D-CAA) and sporadic CAA.

METHODS: We included D-CAA mutation carriers with a proven APP (amyloid precursor protein) mutation or ≥ 1 lobar ICH and ≥ 1 first-degree relative with D-CAA and sporadic CAA patients with probable CAA according to the modified Boston criteria. D-CAA carriers were regarded symptomatic when they had a history of symptomatic ICH. We assessed the presence, location, and progression of calcifications and their association with ICH and the striped occipital cortex.

RESULTS: We found cortical calcifications in 15/81 (19% [95% CI, 11–29]) D-CAA mutation carriers (15/69 symptomatic and 0/12 presymptomatic) and in 1/59 (2% [95% CI, 0–9]) sporadic CAA patients. Calcifications were all bilateral located in the occipital lobes. In 3/15 (20%) of the symptomatic D-CAA patients the calcifications progressed over a period up to 10 years. There was evidence of an association between cortical calcifications and new ICH development (hazard ratio, 7.1 [95% CI, 0.9–54.9], log-rank $P=0.03$). In 7/25 D-CAA symptomatic carriers in whom a 7T-magnetic resonance imaging was performed, a striped pattern of the occipital cortex was present; in 3/3 (100%) of those with calcifications on computed tomography and 4/22 (18%) of those without calcifications.

CONCLUSIONS: Occipital cortical calcifications are frequent in D-CAA but seem to be rare in sporadic CAA. Their absence in presymptomatic carriers and their association with ICH might suggest that they are a marker for advanced CAA. Cortical calcifications on computed tomography seem to be associated with the striped occipital cortex on 7T-magnetic resonance imaging which may possibly represent an early stage of calcification.

GRAPHIC ABSTRACT: An online [graphic abstract](#) is available for this article.

Key Words: cerebral amyloid angiopathy ■ cerebral hemorrhage ■ magnetic resonance imaging ■ mutation ■ prevalence

Cerebral amyloid angiopathy (CAA) is characterized by lobar intracerebral hemorrhages (ICHs) and cognitive decline.¹ Several CAA-related imaging markers facilitate the diagnosis of CAA and increase insight into underlying disease development.² Recently,

we identified a new CAA-related marker in Dutch-type hereditary CAA (D-CAA): a subtle striped pattern in the occipital cortex visible on ultra-high-field 7T-magnetic resonance imaging (MRI) that was shown to result from macrocalcification along with iron accumulation in the

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The Data Supplement is available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.120.033286>.

For Sources of Funding and Disclosures, see page 1854.

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Stroke is available at www.ahajournals.org/journal/str

Nonstandard Abbreviations and Acronyms

| | |
|--------------|--------------------------------------|
| CAA | cerebral amyloid angiopathy |
| CT | computed tomography |
| D-CAA | Dutch-type hereditary CAA |
| ICH | intracerebral hemorrhage |
| MRI | magnetic resonance imaging |
| OPN | osteopontin |
| sCAA | sporadic cerebral amyloid angiopathy |

wall of penetrating arteries in a subsequent postmortem pathology study.^{3,4}

Occipital cortical calcifications have previously been reported on computed tomography (CT) in a few hereditary forms of CAA caused by APP (amyloid precursor protein) mutations.^{5–7} Until now, they have not been studied in D-CAA and have only been described in case-reports in sporadic (sCAA).⁸ We aimed to assess the frequency and location of cortical calcifications on CT in both D-CAA and sCAA. In addition, we investigated whether the calcifications on CT are associated with ICH and the striped pattern of the occipital cortex on 7T-MRI.

METHODS

We included D-CAA and sCAA patients who visited our CAA-(out)patient clinic or participated in our CAA-natural history studies between 2012 and 2020. Inclusion criteria for D-CAA participants were a DNA-proven Glu693Gln-mutation in the APP gene or a history of ≥ 1 lobar ICH(s) and ≥ 1 first-degree relative(s) with D-CAA. Symptomatic D-CAA was defined as ≥ 1 prior symptomatic ICH. sCAA patients were eligible when they fulfilled the modified Boston criteria for probable CAA.⁹ Subjects were excluded when no CT scan was available. A 7T-MRI was performed in the subpopulation that participated in our CAA studies. This study population was followed every year with 3T-MRI and 7T-MRI. Demographics, clinical data, and imaging that were performed in a clinical setting was also included in a prospective D-CAA database for all participants. The Medical Ethical Committee waived the need for patient consent.

Two independent raters assessed the presence and location of calcifications and the number and location of new ICHs on noncontrast CT. We defined cortical calcifications as linear hyperdensities following the cortex.⁶ In participants with calcifications, subsequent CT scans were assessed to evaluate first appearance and progression. 7T-MRI T2*-weighted-gradient-echo images were screened for a striped pattern of the occipital cortex defined as hypointense lines perpendicular to the pial surface.³

We performed descriptive statistics and calculated the proportion of D-CAA and sCAA participants with calcifications including 95% CI. To investigate the association with calcifications, we added the occurrence of a new ICH and cumulative number of new ICH as time-dependent predictors in a Cox-regression-model and calculated hazard ratios including 95% CI with sex as covariate.

The data that support the findings of this study are available from the corresponding author upon reasonable request.

RESULTS

Dutch-Type Hereditary CAA

We included 81 D-CAA mutation carriers (mean age 58 years, 47% women, 12 presymptomatic; Figure 1, Table 1 in the [Data Supplement](#)). Cortical calcifications on CT were identified in 15 carriers (19% [95% CI, 11–29]), all in symptomatic patients, all bilateral, and all in the occipital cortex (Figure 2). In 56 carriers including the 15 with calcifications, multiple CT scans were performed. No calcifications were found in absence of prior ICH. In 4 patients, calcifications were not visible on their first CT scan (in 3 patients, this CT was performed for the initial ICH, one had a normal CT before a CT with ICH). Calcifications were detected after intervals of 4, 4, 11, and 11 years after the first scan, in which all patients had ≥ 1 ICH. Progression of calcifications over time (7, 7, and 11 years) was observed in another 3 (20%) of the 15 patients, all had multiple ICHs during this period.

7T-MRI was performed in 25 D-CAA mutation carriers (3 presymptomatic), including 3 of the 15 patients with calcifications (intervals between CT and MRI: 0, 2, and 5 months). The MRI showed a striped pattern of the occipital cortex in all 3 patients (Figure 3). The location

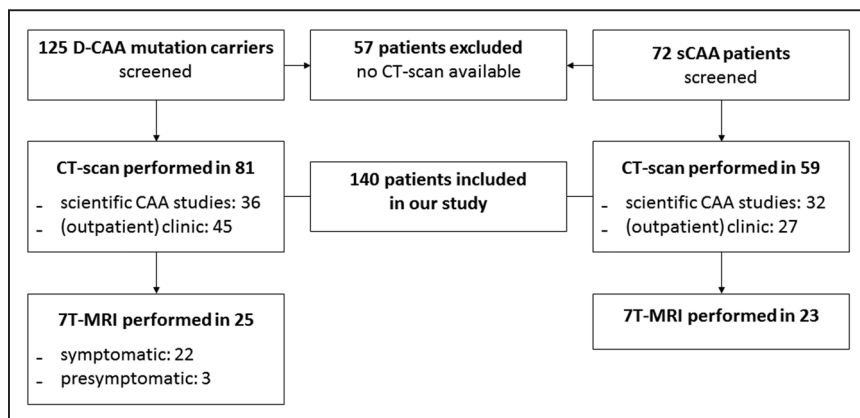


Figure 1. Flowchart.

CAA indicates cerebral amyloid angiopathy; CT, computed tomography; D-CAA, Dutch-type hereditary CAA; MRI, magnetic resonance imaging; and sCAA, sporadic CAA.

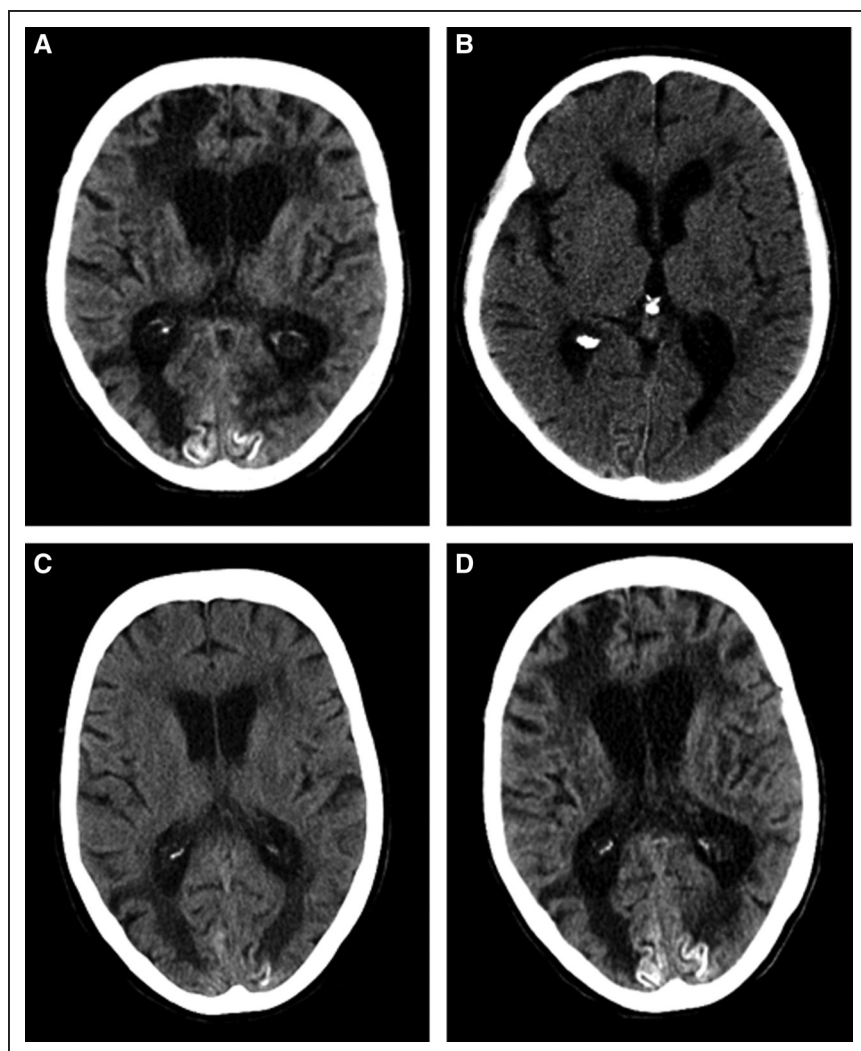


Figure 2. Examples of occipital cortical calcifications.

Occipital calcifications on computed tomography (CT) in Dutch-type hereditary cerebral amyloid angiopathy (D-CAA; **A**) and sporadic CAA (sCAA; **B**) patients, expressing the typical gyriform pattern of linear hyperdensities. Progression of calcification in density and extent in a D-CAA patient (**C**) between the first (2012; 55 years old) and most recent (**D**; 2019; 61 years old) CT scan. Six intracerebral hemorrhages (ICHs) occurred, none occipital.

and pattern of the calcifications on CT and 7T-MRI overlapped. In the 22 D-CAA mutation carriers without calcifications on CT and available 7T-MRI, 4 symptomatic patients (18%) demonstrated a striped pattern of the occipital cortex.

Cox-regression-analyses with the occurrence of a new ICH as time-dependent covariate showed an association with occipital calcifications (hazard ratio, 7.1 [95% CI, 0.9–54.9], log-rank $P=0.03$). For the cumulative number of new ICH, this association was not statistically significant (hazard ratio, 1.3 [95% CI, 0.8–1.9], log-rank $P=0.2$).

Sporadic CAA

Fifty-nine sCAA patients, mean age 71, 46% women, 64% with prior ICH, were included. In only one (2% [95% CI, 0–9] overall, 3% of patients with ICH) bilateral cortical calcifications were detected in the occipital cortex on CT (Figure 2A). This 74-year-old woman presented with acute frontal ICH and signs of 2 previous occipital ICHs. A CT scan after 6 months showed no progression. She had no 7T-MRI. In 23 sCAA patients without

calcifications a 7T-MRI was performed, in none a striped cortex was present.

DISCUSSION

We found that cortical calcifications on CT are frequent in D-CAA. In contrast, calcifications are rare in sCAA. Calcifications are located exclusively occipitally and are associated with new ICH. Microcalcifications on 7T-MRI, seen as a striped occipital cortex, are associated with calcifications on CT and may represent an early stage of calcification.

Given the resemblances in clinical manifestations and underlying biochemical processes in D-CAA and sCAA, the contrast in the frequency of occipital calcifications is notable. The more aggressive disease course and earlier onset in D-CAA is a possible explanation for this difference. Other contributing factors could be more severe amyloid pathology of the occipital vessels. In our study, calcifications were not present in the presymptomatic stage and correlated with new ICH suggesting that the calcifications are a marker for an advanced CAA.

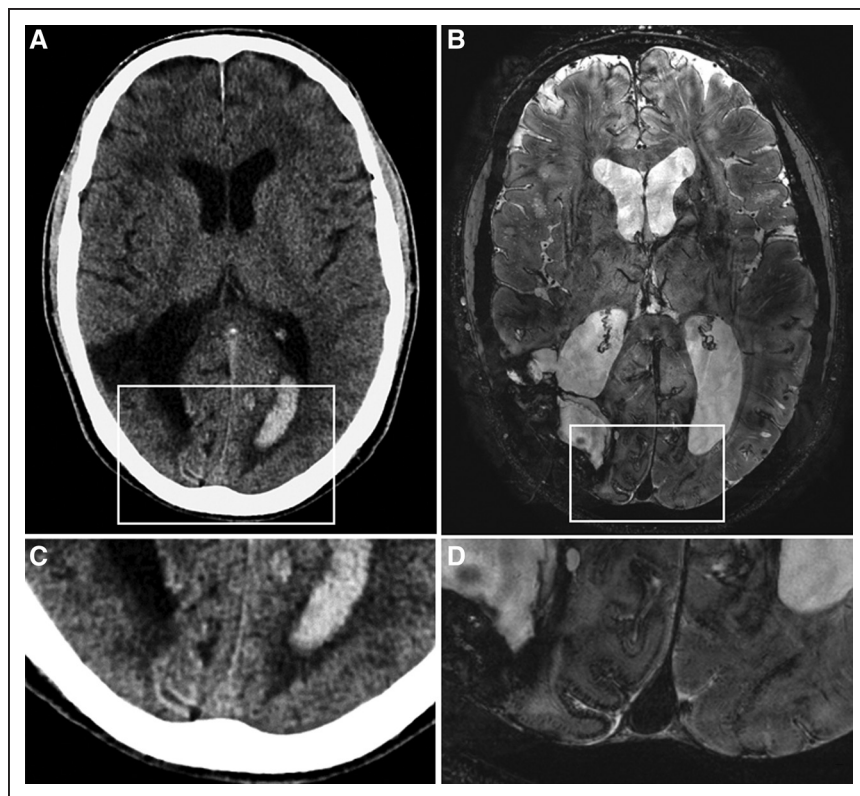


Figure 3. Coexistence of computed tomography (CT)-calcifications and 7T striped cortex pattern.

Fifty-eight-year-old Dutch-type hereditary cerebral amyloid angiopathy (D-CAA) patient with occipital calcifications on CT (A) and a striped cortical pattern in the same region on 7T-magnetic resonance imaging (MRI; B). C and D, Magnification.

Although we had limited 7T-MRI scans in D-CAA patients with calcifications, the coexistence of the striped cortex pattern is striking and fits previous findings suggesting the striped cortex to be due to microcalcifications along with iron accumulation.⁴ A recent immunohistochemistry study investigated the role of potential modulators of vascular calcification in D-CAA and found that both phospho-SMAD2/3 and OPN (osteopontin) gradually accumulate in cortical arterioles before calcification.¹⁰ OPN, a constituent of the normal extracellular matrix was proposed to induce calcification in vessels. Interestingly, the effect of OPN on calcification appeared to be independent of vascular amyloid. Calcifications have been detected in non-CAA vessels in an sCAA patient and heterogeneous patterns of calcifications were observed in areas with comparable CAA-load.^{4,10} This suggests that vascular calcifications could also be a consequence of CAA-related events such as ICH, microbleeds, microinfarcts, chronic ischemia, and impaired vascular reactivity and could be an expression of tissue stress particular in the occipital region. This hypothesis seems consistent with the posterior predominance of CAA and the impaired occipital autoregulation in both D-CAA and sCAA.^{1,11} However, occipital microcalcifications are also found in non-CAA-related conditions such as primary familial brain calcification.⁸ It is also remarkable that the pattern resembles that of laminar necrosis that can be seen after cortical ischemia.

Unfortunately, 7T-MRI was not available in all participants and not all CT and 7T-MRIs were performed on

the same day. Also, no genetic testing for D-CAA was performed in the sCAA patient with calcifications, but she had no family ties with Katwijk, no family history of ICH or dementia and had her ICH at age 74 whereas in D-CAA the mean age of the first ICH is 50. Further prospective studies are needed to assess the association between occipital calcifications and clinical symptoms, future hemorrhage risk and MRI markers such as vasoreactivity to further unravel the pathophysiology underlying the calcifications.

ARTICLE INFORMATION

Received October 26, 2020; final revision received December 16, 2020; accepted February 23, 2021.

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Sources of Funding

This work was supported by an Clinical Established Investigator grant of the Netherlands Heart Foundation 2016T086 to Dr Wermer. The funding agency had no role in the design or conduct of the study. Dr Wermer reports independent support from Netherlands Organization for Scientific Research (NWO) ZonMw (VIDI grant 91717337) and the Netherlands Brain Foundation and the Dutch Cerebral Amyloid Angiopathy foundation (Dutch CAA foundation). Dr van der Weerd reports independent support from NWO; Innovational Research Incentives Scheme (VIDI grant 864.13.014). Dr van Osch reports independent support from NWO (VICI grant 016.160.351), European Community (CDS-QUAMRI, Grant/Award Number 634541), the Netherlands Heart Foundation and NWO (Brain@Risk) and research support from Philips. Dr Terwindt reports independent support from NWO, European Community, the Netherlands Brain Foundation, the Dutch Brain Foundation, and the Dutch CAA foundation.

Disclosures

Dr Terwindt reports consultancy support from Novartis, Lilly, Teva, and Allergan. The other authors report no conflicts.

Supplemental Materials

Expanded Methods
Online Table 1

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