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One Size Does Not Fit All: Micro-, Meso-, and Macrobleeds in Cerebral Amyloid Angiopathy

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Keywords
Cerebral amyloid angiopathy · Hemorrhage · MRI

Abstract

Introduction: MRI rating criteria for small vessel disease markers include definitions for microbleeds and macrobleeds but do not account for small (<10 mm) hemorrhages with a cystic cavity and/or irregular shape. Such hemorrhages, however, are often present in patients with cerebral amyloid angiopathy (CAA). In this study, we aimed to investigate the frequency, diameter, and volume distribution of these hemorrhages (which we called mesobleeds) in patients with CAA. ***Methods:*** We selected participants with Dutch-type hereditary CAA (D-CAA) and sporadic CAA (sCAA) and scored microbleeds, mesobleeds, and macrobleeds on 3T susceptibility-weighted images MRI. Hemorrhage diameter and volume were calculated in a subset of participants using a semi-automatic tool; their distribution was evaluated on a logarithmic scale. ***Results:*** We included 25 participants with D-CAA (mean age 56 years) and 25 with sCAA (mean age 73 years). In total, 11,007 microbleeds, 602 mesobleeds, and 195 macrobleeds were observed. Eighty-two percent of participants had ≥1 mesobleed. Hemorrhage diameter and volume were calculated in four participants with 272 microbleeds (median diameter 1.52 mm, volume 0.004 mL), 84 mesobleeds (median diameter 5.61 mm, volume 0.06 mL), and 37 macrobleeds (median diameter 19.58 mm, volume 1.33 mL). Mesobleed diameter and volume were larger than microbleeds (optimal cut-off 0.02 mL) but showed overlap with macrobleeds. ***Conclusion:*** Hemorrhages <10 mm with an irregular shape and/or cystic cavity are frequently found in participants with CAA and have a distinct diameter and volume distribution. We propose to name these hemorrhage mesobleeds and to rate them separately from micro- and macrobleeds. Future research is necessary to investigate their pathophysiology and prognostic value.

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Introduction

Well-known hemorrhagic manifestations of cerebral amyloid angiopathy (CAA) on MRI are lobar intracerebral hemorrhages (ICH), lobar cerebral microbleeds, convexity subarachnoid hemorrhage, and cortical superficial siderosis. The underlying pathophysiology of ICH and cerebral microbleeds is thought to differ [1, 2]. According to the Neuroimaging Standards for Reporting Vascular Changes on Neuroimaging Criteria (STRIVE criteria version 1.0 and 2.0), a chronic small ICH (commonly referred to as a macrobleed) on MRI can be differentiated from a microbleed because of diameter (large, usually considered >10 mm) and shape (irregular) and because it usually contains a cystic cavity [3, 4]. Cerebral microbleeds, on the other hand, are well-defined, homogenous, round or oval signal losses on susceptibility-weighted MRI, usually <5 mm but may sometimes be as large as 10 mm [1, 3, 5]. Diameters of cerebral microbleeds and macrobleeds have been shown to follow a naturally bimodal distribution, with a cut-off value of 5.7 mm at 1.5 T MRI for typical susceptibility-weighted sequences [1, 6].

The STRIVE criteria (both version 1.0 and 2.0) do not account for hemorrhages that share characteristics of both microbleeds and macrobleeds (<10 mm hemorrhages with an irregular shape and/or an atypical cavitary appearance); it is our experience that such hemorrhages, however, are frequently encountered in patients with CAA. At the moment, it is unclear whether these hemorrhages should be classified as either microbleeds or macrobleeds or if they represent a separate – third – hemorrhagic entity. We aimed to evaluate the frequency of hemorrhagic lesions that do not fulfill the criteria for a microbleed or macrobleed, in patients with hereditary Dutch-type CAA (D-CAA) and sporadic CAA (sCAA). Additionally, we investigated the diameter and volume distribution of these hemorrhages in comparison with the diameter and volume distribution of micro- and macrobleeds, to investigate whether these hemorrhages should be considered a separate entity.

Methods

Participants

We included patients diagnosed with D-CAA or sCAA who participated in the ongoing CAA natural history studies from the Leiden University Medical Center (LUMC). Patients were recruited via the (outpatient) clinic of the LUMC. For this study we included the first 25 participants of the AURORA (natural history study including patients with D-CAA) and FOCAS (natural history study including patients with sCAA) studies. We included only those participants with at least one hemorrhage (of any type) on 3T susceptibility-weighted imaging (SWI), thereby excluding presymptomatic D-CAA participants who did not yet have any hemorrhagic disease activity. Who had at least one hemorrhage (of any type) on 3T SWI MRI. The diagnosis of sCAA was made before study entry according to the modified Boston criteria by an experienced radiologist and neurologist based on clinical symptoms and CAA features on previous 1.5 or 3T MRI scans [7]. The diagnosis of D-CAA was established by genetic testing for the causal mutation at codon 693 of the APP gene, or when a patient suffered from an ICH with CAA characteristics on MRI and had at least one first-degree relative with D-CAA.

MRI

All participants underwent 3T MRI (Philips Achieva, Best, the Netherlands), and data were acquired using a standard 32-channel head coil. The MRI protocol included three-dimensional T1-weighted images (time (TR)/echo time (TE) = 9.7/4.6 ms, flip angle (FA) 7°, 130 slices with no interslice gap and a field of view (FOV) of 217 × 172 × 156 mm, voxel size of 1.2 × 1.2 × 1.2 mm), T2-weighted images (TR/TE = 4,744/80 ms, flip angle 90°, 48 slices with no interslice gap, a FOV of 220 × 176 × 144 mm with a voxel size of 0.5 × 0.6 × 3 mm), and SWI (TR/first TE/echospacing = 31/7.2/6.2 ms, flip angle 17°, 130 slices and a FOV of 230 × 190 × 130 mm with a voxel size of 0.6 × 0.6 × 1 mm).

MRI Analysis

We followed the definitions of the STRIVE criteria (2.0) to categorize microbleeds and macrobleeds [3, 4]. Cerebral microbleeds were defined as homogeneous round or ovoid hypointense lesions without a cystic cavity, visible on SWI MRI, not visible on T1- and T2-weighted images, which are <10 mm; macrobleeds were defined as hypointense lesions visible on SWI MRI as well as on T1- and T2-weighted images, which are larger than 10 mm, with a cystic cavity on T2-weighted MRI (a T2 hyperintensity within the lesion) and/or irregular shape (a shape that is not round or ovoid).

Additionally, a third hemorrhage category was defined including hypointense lesions visible on SWI MRI, which are smaller than 10 mm and have an irregular shape and/or cavitary appearance. These hemorrhages are referred to as mesobleeds. Cortical superficial siderosis (cSS) was scored on SWI by one observer (E.A.K.) according to the STRIVE criteria (2.0) and was scored as present or absent [4].

Periventricular and deep white matter hyperintensities were scored according to the FAZEKAS score, and enlarged perivascular spaces in the centrum semiovale (CSO-EPVS) were scored according to previously published methods [3, 8, 9].

All hemorrhages were scored on 3T SWI MRI by one observer with >5 years of experience in the field (E.A.K). A second observer with over 15 years of experience in the field of neuroradiology (M.A.A.v.W) supervised the first 5 scans and was consulted in case of doubt. In scoring cerebral microbleeds, we only counted those that could be considered separate entities from larger ICHs. If a microbleed was connected to a larger (macro) bleed, they were not rated as separate hemorrhages but seen as part of the larger bleed. For each of the 50 participants the hemorrhages were manually annotated, specifying each lesion as a micro-, meso-, or macrobleed using the SWI images. This resulted in a "map" of all hemorrhages for each participant. Second, we randomly selected $n = 4$ participants, the first two participants of the AURORA study and the first two participants of the FOCAS study, to calculate hemorrhage diameter and volume distribution using an in-house developed software tool in the MeVisLab framework (version 3.2). We chose to perform this in 4 participants only due to the time-consuming nature of the calculations (approximately 24 h per participant). For each of these four participants, the manually made "hemorrhage maps" were used in the following way: the SWI images were preprocessed using tools available in FSL v 6.0. (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). First, images were skull stripped using the Brain Extraction Tool to exclude non-brain tissue [10]. Second, N4 bias field correction was applied; and a local minimum for each specified lesion was determined to correct for possible local misclassification [11]. Third, a 3D-6-neighborhood growing seed region algorithm was used to segment the area of the susceptibility artefact of the specified hemorrhages from surrounding normal-appearing tissue. This segmentation was then used to calculate the volume and maximum diameter in the XY-plane. Segmentations were visually inspected for errors and manually corrected when needed.

Statistics

Descriptive statistics were used for baseline characteristics and the number and prevalence of cerebral micro-, meso-, and macrobleeds and reported separately for participants with D-CAA and sCAA. We investigated the presence of mesobleeds in participants with and without symptomatic ICH and the presence of cSS in participants with and without cSS using a Fisher's exact test. We investigated differences in micro-, meso-, and macrobleed counts in participants with and without cSS using χ^2 tests. We investigated differences in age, sex, D-CAA/sCAA status, and sICH history between participants with and without mesobleeds using a Mann-Whitney U test and Fisher's exact tests respectively. We used binary logistic regression corrected for age, sex, D-CAA/sCAA status, and sICH history to investigate odds ratios for differences in the presence of microbleeds, macrobleeds, and cSS between participants with and without mesobleeds. We used poison regression, again corrected for the factors mentioned above, to investigate relative risks for differences in microbleed and macrobleed amount, cSS focality, and white matter hyperintensities and CSO-EPVS scores in participants with and without mesobleeds. Lastly, we used adjusted ordinal logistic regression to calculate odds ratios for differences in microbleed counts according to cSS focality score. Diameter and volume of hemorrhages, calculated in the subset of four participants, were plotted on a natural log scale to evaluate their distribution and additionally displayed using a boxplot to explore volume differences between the three hemorrhage categories.

Results

We included 50 participants: 25 sCAA (mean age 73 years [range 59–86], 60% women) and 25 D-CAA (mean age 56 years [range 36–71], 40% women). Seventeen (68%) of the participants with sCAA and 18 (72%) of the participants with D-CAA had a history of symptomatic ICH. Descriptive data are described in Table 1.

Micro-, Meso-, and Macrobleeds

In total, 11,007 microbleeds (median 94.5 [range 0–1,906]), 602 mesobleeds (median 5.5 [range 0–54]), and 195 macrobleeds (median 1.5 [range 0–26]) were present in the 50 participants. Mesobleeds were present in 41 (82%) of participants (76% of the participants with sCAA, 88% of the participants with D-CAA). Baseline characteristics between participants with and without mesobleeds were comparable, although participants with mesobleeds had significantly more often and higher counts of macrobleeds on MRI compared to those without (Table 2). Other hemorrhagic and non-hemorrhagic MRI markers were comparable.

There was no difference in the presence of mesobleeds between participants with and without a history of sICH (31/35 [89%] vs. 10/15 [67%], $p = 0.07$). Forty/41 participants with ≥1 mesobleed had at least one microbleed on MRI. An illustrative example of an MRI scan of a patient with sCAA with the three types of hemorrhages is shown in Figure 1. There was no difference between patients with and without

Table 1. Baseline characteristics and hemorrhage prevalence and counts on MRI

	Participants with sCAA (n = 25)	Participants with D-CAA (n = 25)
Mean age, years (range)	73 (59–86)	56 (36–71)
Women, n (%)	15 (60)	10 (40)
History of symptomatic ICH, n (%)[1]	17 (68)	18 (72)
MRI characteristics		
Microbleeds, n (%)	24 (96)	25 (100)
Total number of microbleeds, median (IQR)	4,274 [51 (156)]	6,733 [113 (297)]
Mesobleeds, n (%)	18 (72)	22 (88)
Total number of mesobleeds, median (IQR)	171 [2 (10)]	431 [15 (27)]
Macrobleeds, n (%)	14 (56)	20 (80)
Total number of macrobleeds, median (IQR)	44 [1 (2)]	151 [4 (9)]
cSS, n (%)[2]	15 (60)	13 (52)

sCAA, sporadic cerebral amyloid angiopathy; D-CAA, Dutch-type CAA; ICH, intracerebral hemorrhage; IQR, interquartile range. [1]Participants with sCAA without sICH were diagnosed based on MRI performed due to TFNE or cognitive complaints (n = 8). Participants with D-CAA without sICH were diagnosed based on genetic testing. [2]cSS >3 gyri of an ICH only.

Table 2. Characteristics of participants with and without mesobleeds

	Participants with mesobleeds (n = 41)	Participants without mesobleeds (n = 9)	p value
Mean age, years (range)	63 (36–86)	68 (50–82)	0.220
Women, n (%)	19 (46)	6 (67)	0.463
History of symptomatic ICH, n (%)[1]	31 (76)	4 (44)	0.106
D-CAA, n (%)	22 (54)	3 (33)	0.463
MRI characteristics			OR or RR (95% CI) [p value]
Microbleeds, n (%)	40 (98)	9 (100)	0 (0) [1]
Median number of microbleeds (IQR)	101 (289)	29 (140.5)	1.00 (0.99–1.00) [0.669]
Macrobleeds, n (%)	32 (78)	2 (22)	9.82 (1.07–90.35) **[0.044]**
Median number of macrobleeds (IQR)	3 (5)	0 (0)	1.02 (1.00–1.03) **[0.014]**
cSS, n (%)[1]	24 (59)	4 (44)	1.53 (0.30–7.90) [0.612]
Focal cSS, n (%)	9 (22)	1 (11)	1.03 (0.88–1.21) [0.691]
Disseminated cSS, n (%)	15 (37)	3 (33)	
Median FAZEKAS score periventricular WMH (range)	3 (0–3)	3 (0–3)	0.89 (0.55–1.45) [0.636]
Median FAZEKAS score deep WMH (range)	2 (0–3)	1 (0–3)	0.73 (0.40–1.36) [0.325]
Median CSO-EPVS score (range)[2]	4 (2–4)	4 (3, 4)	1.07 (0.71–1.60) [0.757]

sCAA, sporadic cerebral amyloid angiopathy; D-CAA, Dutch-type CAA; ICH, intracerebral hemorrhage; IQR, interquartile range; WMH, white matter hyperintensities; CSO-EPVS, enlarged perivascular spaces in the centrum semiovale; OR, odds ratio; RR, relative risk; 95% CI, 95% confidence interval. [1]cSS >3 gyri of an ICH only. [2]Categories: 0 = no CSO-EPVS, 1 = 1–10 CSO-EPVS, 2 = 10–20 CSO-EPVS, 3 = 20–40 CSO-EPVS, 4 = >40 CSO-EPVS. Statistically significant values are highlighted in bold.

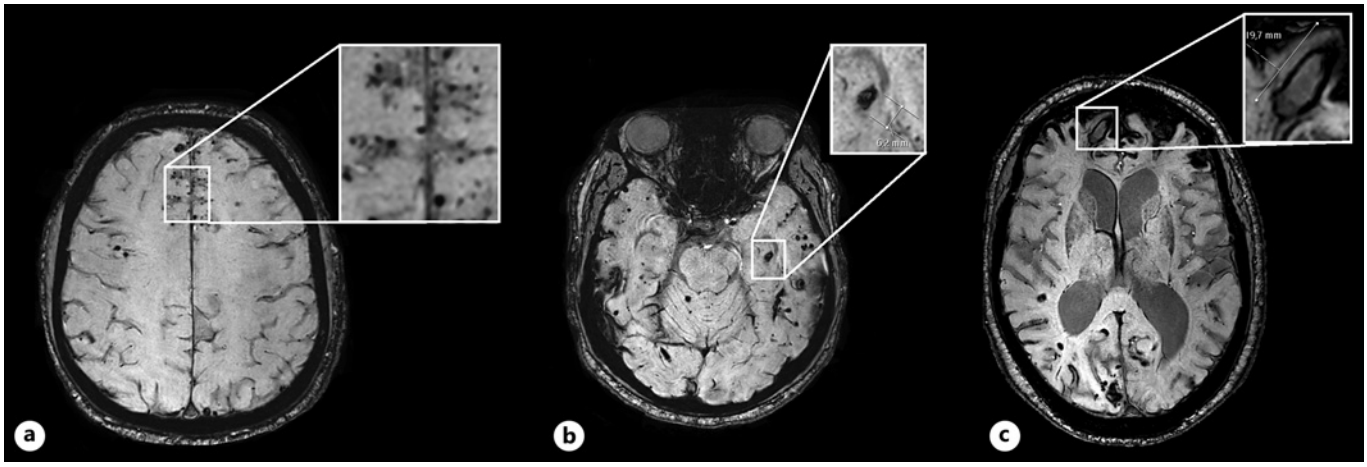

Fig. 1. Example of a micro-, meso-, and microbleed in CAA. 3T susceptibility-weighted images MRI at three levels in the brain of a participant with D-CAA showing examples of several microbleeds, typical round or ovoid small lesions with homogeneous aspect (**a**); a single mesobleed, with an irregular shape and a central cavity, the diameter is 6.2 mm (**b**); and a single macrobleed, with an irregular shape, diameter 19.7 mm (**c**).

macrobleeds regarding the presence of cSS on MRI (76% [26/34] compared to 50% [8/16], $p = 0.06$). As there was only one participant in the dataset without any microbleeds, the presence of cSS in participants with and without microbleeds could not reliably be performed. Median counts of microbleeds in participants with and without cSS were comparable (median 96 vs. 87 CMB, $p = 0.39$). There was no correlation between cSS focality and CMB count (adjusted odds ratio 0.99 [95% CI: 0.99–1.0], $p = 0.06$). Participants with cSS had similar counts of meso- and macrobleeds (mesobleeds: median 8.5 vs. 4 [$p = 0.20$], macrobleeds: median 3 vs. 0.5 [$p = 0.67$]) compared to those without cSS.

Hemorrhage Volume and Diameter Distribution

We assessed the diameter and volume distribution of the three different hemorrhage classes. In the four participants, we identified a total of 393 hemorrhages (272 microbleeds, 84 mesobleeds, 37 macrobleeds). Microbleeds had a median diameter of 1.52 mm (IQR: 0.73) and median volume of 0.004 mL (IQR: 0.004). Mesobleeds had a median diameter of 5.61 mm (IQR: 2.35) and median volume of 0.06 mL (IQR: 0.06). Macrobleeds had a median diameter of 19.58 mm (IQR: 15.61) and median volume of 1.33 mL (IQR: 6.01). Per our definition, the cut-off diameter between micro-/mesobleeds and macrobleeds was 10 mm. Diameters of micro- and mesobleeds showed some overlap (Fig. 2a), with the largest microbleed having a diameter of 3.26 mm and the smallest mesobleed 2.47 mm. Of all microbleeds, 94% had a diameter smaller than the smallest mesobleed. Of all mesobleeds, 92% had a diameter larger than the largest microbleed.

Volume of hemorrhages (Fig. 2b, displayed on a natural logarithmic scale) showed an almost perfect differentiation between micro- and mesobleed volumes with a volume of the largest microbleed of 0.022 mL and of the smallest mesobleed of 0.020 mL. A possible optimal cut-off value would therefore be a volume of 0.02 mL. Of all microbleeds, 99.6% had a volume smaller than the smallest mesobleed. Of all mesobleeds, 96% had a volume larger than the largest microbleed. There was an overlap between volumes of meso- and macrobleeds (Fig. 2c), despite the clear diameter cut-off of 10 mm, with the largest mesobleed having a volume of 1.57 mL and the smallest macrobleed having a volume of 0.13 mL. Of all mesobleeds, 88% had a volume smaller than the smallest macrobleed. Of all macrobleeds, 49% had a volume larger than the largest mesobleed.

Discussion

We found that hemorrhages <10 mm with an irregular shape and/or cystic cavity (mesobleeds), are present on 3T MRI in approximately 80% of participants with sCAA and D-CAA. Mesobleeds were larger than cerebral microbleeds and had a distinct volume distribution (optimal volume cut-off value of approximately 0.02 mL). Participants with mesobleeds had significantly more often and higher counts of macrobleeds on MRI. Our results therefore suggest that mesobleeds should be rated separately from microbleeds, and more cautiously, that they could either represent a third hemorrhagic entity (different from macrobleeds) or could be seen as "small macrobleeds."

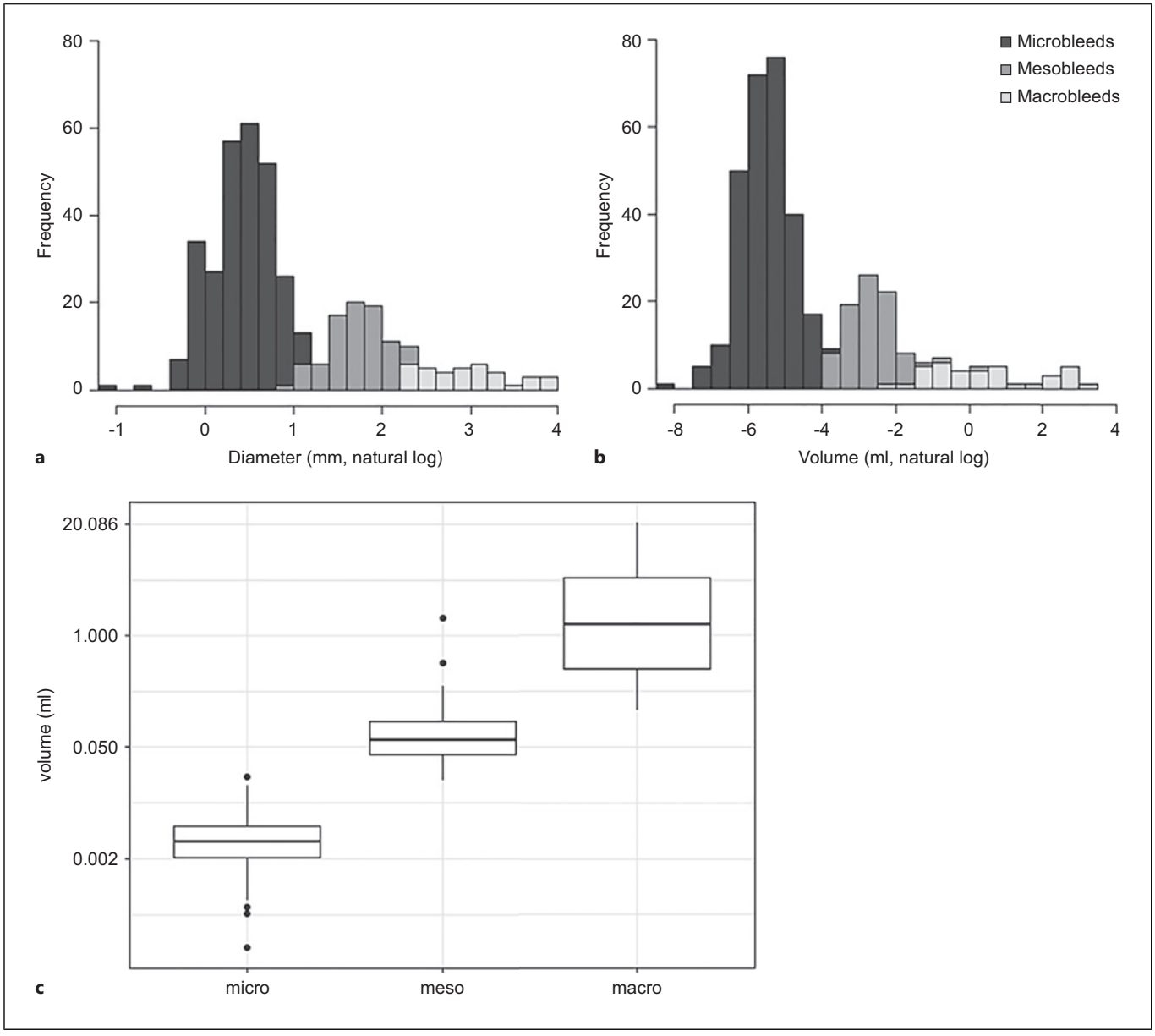

Fig. 2. Hemorrhage diameter and volume distribution. Volume and diameter distribution of n = 393 hemorrhages in n = 4 participants (two with D-CAA 2 with sCAA). Microbleeds are defined as homogeneous round or ovoid hypointense lesions without a cystic cavity with a diameter, <10 mm. Mesobleeds are defined as lesions with an irregular shape and/or cavitary appearance with a diameter <10 mm. Macrobleeds are lesions with a diameter ≥10 mm, often with an irregular shape and/or cystic cavity. Stacked histogram illustrating diameter (**a**) and volume distribution (**b**) of all 393 hemorrhages on a natural logarithmic scale. **c** Boxplot illustrating the volumes of the three hemorrhage categories on a logarithmic scale.

It is hypothesized that the pathophysiology of micro- and macrobleeds differ. In a previous study, CAA patients with many microbleeds had significantly thicker amyloid-positive vessels compared to CAA patients with few microbleeds, suggesting that thicker vessels are more likely to produce microbleeds [1]. In contrast, a hypothesis for the origin of macrobleeds is that they occur in tissue areas that have already weakened, for example, by the presence of previous hemorrhages or enlarged perivascular spaces, or in vessels with a higher general blood flow which, when ruptured, produce a larger leak [12]. The pathophysiology of mesobleeds is unknown. Due to

their volume overlap with macrobleeds, they may share a pathophysiology, or they might, for example, originate not from hemorrhage but from primary ischemic lesions with secondary hemorrhage [13]. It is intriguing that despite a pre-defined cut-off of 10 mm, there was such overlap in the volumes of meso- and macrobleeds. From this, we have to conclude that visual assessment of hemorrhage diameter might not always be reliable. We furthermore found that the macrobleeds with relatively low volumes were often linear in shape but with only minimal extension into the Z-plane, leading them to have a diameter >10 mm but a relatively small volume. We found that in patients with mesobleeds cSS, a marker for CAA disease severity and hemorrhagic phenotype, was more often present; however, this difference was not statistically significant possibly due to limited power. The results were similar to the analysis comparing patients with and without macrobleeds. It is possible that microbleeds may also have a cystic cavity or irregular shape, but that these lesions are simply too small to show these characteristics on MRI. In other words, the round and oval shape suggests that we are looking at mainly the blooming effect of a very small hemorrhagic lesion. Future studies should investigate pathophysiology, clinical implications and predictive value in terms of (recurrent) ICH of mesobleeds. In our study, we often encountered microbleeds surrounding a larger (macro) bleed. In literature, this finding has also been described, and it is hypothesized that these microbleeds together with the macrobleed could be considered a single entity [14]. Future studies are necessary to determine if this is indeed the case, or if for instance, macrobleeds occur in locations where previously many microbleeds were located. In contrast to previous studies, we did not find an inverse correlation between the presence of cSS and the presence of cerebral microbleeds. The reason for this discrepancy is unclear. One possible explanation is the relatively small number of participants and therefore limited power of our study.

Our study did not reproduce the bimodal hemorrhage volume distribution curve as was demonstrated in a previous publication [1]. Although we saw some evidence for multi-modality (Fig. 2b), the volume curves in our study contain on average smaller hemorrhage volumes compared to the previous study [1]. There could be several explanations for this. First, due to the time-consuming nature of the hemorrhage diameter and volume calculations, we included only four participants for our volume measurements and subsequently our study includes relatively few large macrobleeds. Second, severely affected persons who survived large ICH are less likely to participate in prospective research. Lastly, the use of 3T MRI with optimized imaging protocol probably favored the detection of smaller hemorrhages in our study as compared to others, possibly accounting for the high number of microbleeds in our study and the relatively low median diameter of these lesions [1]. It is also possible that we are experiencing a selection bias: participants were selected from the (outpatient) clinic of the LUMC, a national specialized CAA center. We cannot exclude that relatively severe cases of CAA (with high numbers of hemorrhages) are referred to our center and subsequently included in our study [15].

The strengths of this study are the use of prospectively collected data from sCAA and hereditary patients with CAA. A limitation of this study is the lack of pathological data to investigate differences in the pathophysiology of micro-, meso-, and macrobleeds. Furthermore, as mentioned above, we included only 50 participants and investigated a very limited number of participants in detail. This limited number allowed us to explore hemorrhage size distribution but not to draw definite conclusions [16]. Future studies are necessary to investigate histopathology and clinical implications of mesobleeds, any correlation with non-hemorrhagic markers such as white matter spots, and their presence in different populations of CAA patients.

Statement of Ethics

The Ethics Committee of the Leiden University Medical Center approved the studies (P17.235, P17.259) and written informed consent was obtained from all participants.

Conflict of Interest Statement

E.A. Koemans, T.W. van Harten, S. Voigt, I. Rasing, E.W. van Zwet, and M.A.A. van Walderveen report no disclosures. G.M. Terwindt reports independent support from the Netherlands Organization for Scientific Research, European Community, the Dutch Heart Foundation, the Dutch Brain Foundation, and the Dutch CAA Foundation. M.J.P. van Osch reports support from a NWO-VICI grant (016.160.351) and a NWO-Human Measurement Models 2.0 grant (18969) as well as support from the Netherlands Organization for Scientific Research, European Community, the Dutch Heart Foundation, and the Dutch Brain Foundation. M.J.H. Wermer reports independent support from the Netherlands Organization for Scientific Research ZonMw (VIDI grant 91717337), the Netherlands Heart Foundation, and the Dutch CAA Foundation.

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Author Contributions

E.A.K.: conceptualization, methodology, image analysis and data analysis, investigation, writing – original draft, and resources. T.W.v.H.: resources, methodology, investigation, and writing – review and editing. S.V. and I.R.: resources, conceptualization, and writing – review and editing E.W.v.Z.: formal analysis and writing – review and editing. G.M.T. and M.J.P.v.O.: conceptualization and writing – review and editing. M.A.A.v.W.: conceptualization, supervision, and writing – review and editing. M.J.H.W.: conceptualization, writing – review and editing, supervision, and funding acquisition.

Data Availability Statement

The data that support the findings of this study are not publicly available due to privacy regulations protecting our research participants. Further information about the dataset is available from the corresponding author (E.A.K.) upon reasonable request.

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