Detection of cerebral microbleeds with venous connection at 7 Tesla MRI

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Abstract

Objective: Cerebral microbleeds (MBs) are a common finding in cerebral small vessel disease (CSVD) and Alzheimer's disease patients as well as in healthy elderly people, but their pathophysiology remains unclear. To investigate a possible role of veins in the development of MBs, we performed an exploratory study, to assess in vivo presence of MBs with a direct connection to a vein. We conducted this exploratory study to determine for the first time *in vivo* whether there is a spatial connection between small veins and MBs in different CSVD subgroups and controls. **Methods:** 7 Tesla (7 T) MRI was conducted and MBs were counted on Quantitative Susceptibility Mapping (QSM). A submillimeter resolution QSM-based venogram allowed identification of lobar, deep and infratentorial MBs with a direct spatial connection to a vein. **Results:** 51 subjects (mean age[SD] 70.5[8.6] years, 37% females) participated in the study: 20 were patients with CSVD (Cerebral Amyloid Angiopathy (CAA) with strictly lobar MBs (n=8), hypertensive Arteriopathy (HA) with strictly deep MBs (n=5), and mixed lobar and deep MBs (n=7), mean age [SD] 72.4 [6.1] years, 30 % females) and 31 were healthy controls (mean age [SD] 69.4 [9.9] years, 42 % females) were included in the study (whole sample: 51 subjects (mean age [SD] 70.5 [8.6], 37 % females). In our cohort, wWe counted a total of 96 MBs with a venous connection in our cohort, representing 14 % of all detected MBs on 7T QSM. Most venous MBs (86%, n = 83) were observed in lobar locations and all of these were cortical. CAA subjects showed the highest ratio of venous to total MBs (19%)…. **Conclusions:** Our findings establish a link between cerebral MBs and the venous vasculature, pointing towards a possible contribution of veins to CSVD in general and to CAA in particular. Pathological studies are needed to confirm our observations.

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Abbreviations

Aß	Amyloid-beta
AD	Alzheimer’s disease
BBB	Blood-brain barrier
BG	Basal ganglia
BW	receiver bandwidth
CAA	Cerebral Amyloid Angiopathy
CSO	Centrum semiovale
cSS	cortical superficial siderosis
CSVD	Cerebral Small Vessel Disease
FA	Flip angle
GRAPPA	Generalized autocalibrating partial parallel acquisition
HA	Hypertensive Arteriopathy
ICH	Intracerebral hemorrhage
MBs	Cerebral microbleeds
MSDI	Multi-Scale Dipole Inversion
MRI	Magnetic Resonance Imaging
PVS	Perivascular spaces
QSM	Quantitative Susceptibility Mapping
SWI	Susceptibility Weighted Imaging
TE	Echo time
TR	Repetition time
WMH	White matter hyperintensities

Introduction

Cerebral microbleeds (MBs) are small hypointense round lesions, visible on T2*-weighted magnetic resonance imaging (MRI) and susceptibility weighted imaging (SWI). They are a hallmark of cerebral small vessel disease (CSVD)~~, which affects cerebral vessels smaller than 1 mm and causes hemorrhagic and ischemic stroke, dementia, gait impairment[1] and represents an increasingly recognized contributing factor to Alzheimer's (AD) and further neurodegenerative diseases[2]~~.

The most common forms of sporadic CSVD are cerebral amyloid angiopathy (CAA), ~~which~~ mainly affecting~~s~~ the leptomeningeal and cortical small arteries, and hypertensive arteriopathy (HA) of the deep perforating arteries[3,4]. The distribution and number of MBs, which is lobar in CAA, deep ~~(thalamus, basal ganglia)~~ in HA[5,6] or mixed (lobar and deep)[7,8] aids in the stratification of the individual risk for intracerebral hemorrhage (ICH)[9].

Histopathological correlation studies claim that the majority of MBs seen on MRI are acute, subacute or chronic small focal lesions of accumulating intact erythrocytes or hemosiderin[10,11] resulting from leakage or rupture of a small vessel. The predominant pathological involvement of arterioles and small arteries in CSVD[12] thereby suggests that MBs mainly derive from the arterial tree[13]. However, cortical and leptomeningeal venous ~~β-~~amyloid-β (Aß)-accumulation has been observed in both animal models of

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CAA and AD[14] and in human CAA[15,16]. ~~Further, v~~Further, evidence of venous collagenosis~~, which is defined as the thickening of the venous vessel wall through accumulation of collagen, has~~ was ~~been~~ found ~~observed~~ in ageing[17], CSVD[14] and preclinical AD models[18]. Therefore, a role of small veins in the development of MBs~~, through leakage or rupture~~, caused by CSVD-related venous pathology is also conceivable.

So far, pathological and *in-vivo* studies have not aimed to ~~distinguish between~~assess venous ~~and arterial~~ contribution to the formation of MBs. We analyzed quantitative susceptibility mapping (QSM)-based venograms at submillimeter resolution in a cohort of CSVD patients and elderly controls to examine for the first time *in vivo* the relationship between small veins and MBs. ~~This is in part due to the technical difficulties in detecting small veins (and arteries) at widely available 1.5 Tesla (T) and 3T MRI[19]. A possible way of depicting small veins is the use of high-resolution Quantitative Susceptibility Mapping (QSM) at 7T MRI. QSM is a postprocessing method, able to quantify magnetic susceptibility[20] and allowing MBs detection with higher sensitivity than SWI[21]. Simultaneously, QSM enables a precise visualization of the brain's venous vasculature[22]. Additionally, high resolution MRI leads to better visibility of small structures, while given the same resolution, scanning at high field MRI increases signal-to-noise ratio.~~

~~We analyzed submillimeter resolution 7T QSM-based venograms in a cohort of CSVD patients (CAA, HA and mixed MBs) and elderly controls to examine for the first time *in vivo* the relationship between small veins and MBs. We aimed to determine (i) if there is a direct connection between small veins and MBs, to then (ii) identify the topographical localization of MBs with venous connection, and (iii) relate them to~~

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~~certain CSVD subgroups. The present approach will shed more light on the pathophysiology of MBs in small vessel disease.~~

Methods

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Participants

~~A total of 51 older adults (mean age [SD] 70.5 [8.6], 37 % females) were included in this 7T brain MRI study.~~ The scans of this 7T brain MRI study were acquired between December 2016 and July 2018. CSVD subjects ~~Twenty of the participants (mean age [SD] 72.4 [6.1], 30 % females) suffered from CSVD and~~ were recruited from a longitudinal 3T MRI study on the pathophysiology of CSVD conducted by the University Clinic of Magdeburg and German Center for Neurodegenerative Disease (DZNE), Magdeburg. Inclusion criteria for the 3T study was the presence of hemorrhagic CSVD markers, i.e. MBs, ICH and/or cortical superficial siderosis (cSS) on iron-sensitive MRI sequences (gradient recalled echo [GRE] T2*-weighted or susceptibility weighted imaging [SWI]) of a clinical 1.5T MRI conducted for diagnostic work-up. Clinical MRI prior inclusion was performed for several diagnostic reasons, including headache, epileptic seizures, gait disturbances, cognitive impairment and transient ischemic attack (for further details see Perosa *et al*[23].). CSVD participants were classified through the distribution of MBs on 3T SWI MRI as CAA, according to the modified Boston criteria, HA (strictly deep MBs) or mixed lobar and deep MBs[4,7,24]. ~~Thirty-one participants were considered as controls~~Controls were considered as such as they had no hemorrhagic markers (MBs, ICH, cSS) on 3T MRI ~~(mean age [SD] 69.4 [9.9], 42 % females); they~~ and were recruited from an already existing pool of cognitively normal community-dwelling elderly study participants of the

DZNE, Magdeburg. Regarding further CSVD MRI features, in controls only white matter hyperintensities (WMH) up to grade 1 (mild) on the Fazekas visual rating scale[25] and grade 1 perivascular spaces (PVS) in the basal ganglia (BG) or centrum semiovale (CSO) were allowed because they represent a common finding in aging[26].

Cardiovascular risk factors were additionally recorded for all participants (Table 1). Arterial hypertension was identified when blood pressure exceeded 130/80 mmHg. Diabetes mellitus was diagnosed as fasting plasma glucose level > 7.0 mmol/L or 11.1 mmol/L two hours after glucose tolerance test. Hyperlipidemia was defined as abnormal blood levels of low-density lipoprotein cholesterol (> 2.6 mmol/L) and/or triglycerides (> 1.7 mmol/L). Genetic neurological disease, history of psychiatric disease, alcohol or drug abuse, as well as cerebrovascular malformations were excluded in all participants. None of the subjects included in our study presented clinical (headache, altered conscious state, nausea) or neuroimaging signs (e.g. edema, hemorrhagic venous infarction, engorged cortical and transmedullary veins) of cerebral venous thrombosis. Likewise, an inspection of the 7T SWI images was negative with respect to the same markers, also in all the visible small veins. Contraindications for scanning at 7T, according to the recommendations of the German Ultrahigh Field Imaging network, were considered and represented a further exclusion criterion from our study.

Standard Protocol Approvals, Registrations, and Patient Consents

The study was approved by the local Ethics Committee (93/17; 28/16). All participants provided written informed consent according to the declaration of Helsinki and were compensated for travel costs.

MRI acquisition at 7T MRI

Kommentiert [JR9]: In a subsection within your Methods labeled "Standard Protocol Approvals, Registrations, and Patient Consents", please state that you:

a.Received approval from an ethical standards committee on human experimentation (institutional or regional) for any experiments using human subjects; If there was a waiver from your institution's ethical approval board, please note the waiver in this section and provide documentation to the editorial office that waiver was granted.

b.Received written informed consent was obtained from all patients (or guardians of patients) participating in the study (consent for research).

c.Provided the identity of the public trials registry and the clinical trial identifier number (if applicable).

d.Obtained authorization for disclosure (consent-to-disclose) of any recognizable persons in photographs, videos, or other information that may be published in the Journal, in derivative works by the AAN, or on the Journal's Web site (when applicable).

MRI acquisition was conducted on a high-field 7T MRI (Siemens Healthineers, Erlangen) equipped with a 32-channel head-coil (Nova Medical, Wilmington). SWI acquisition was conducted with a voxel size of 0.35 x 0.35 x 1.5 mm^3 in a 3D GRE sequence. The acquisition parameters were as follows: echo time (TE) 9 ms, repetition time (TR) 18 ms, flip angle (FA) 10°, receiver bandwidth (BW) 100 Hz/pixel, 3D matrix dimensions 200 x 169 x 132. GRAPPA (generalized autocalibrating partial parallel acquisition) was enabled with an acceleration factor of 2 and 32 reference lines. The T1-weighted sequence with 3D magnetization-prepared rapid gradient echo (3D-MPRAGE) was acquired with a voxel size of 1 x 1 x 1 mm^3 and the following parameters: TE 2.89ms, TR 2250 ms, FA 5°, inversion time 1050 ms, BW 130 Hz/pixel, echo spacing 8.3 ms, 3D matrix dimensions 256 x 256 x 176; GRAPPA was enabled with acceleration factor 3 and 32 reference lines. The protocol included more sequences that were not used in our study. Total scanning time was 50 minutes.

7T MRI QSM reconstruction

In order to calculate quantitative susceptibility maps, which allow the generation of the brain venogram and depiction of MBs, the acquired complex SWI data underwent the following reconstruction steps. First, multiple-channel complex image data were combined using an adaptive algorithm[27] followed by automatic reference channel selection. The combined phase data were then unwrapped using a continuous Laplacian approach[28]. Adopting FSL's BET routing (threshold 0.1), a brain mask was calculated from the magnitude image and applied to the phase image. Then, the background field was removed in two steps: Laplacian boundary value (LBV)[29] with two-layer region of interest (ROI)-peeling, followed by variable mean spherical value (vSMV)[30] with r0 = 40 mm and step size/final kernel radius of 1 mm. Finally, a Multi-

Scale Dipole Inversion (MSDI) [22] was carried out in order to reconstruct quantitative susceptibility maps from the local field maps obtained in the previous step. This reconstruction algorithm provides high specificity for venous blood susceptibilities.

Count of MBs with and without venous connection

MBs were defined as hyperintense, round lesions of up to 5 mm in the QSM reconstruction. For verification, their appearance was matched on the SWI sequence where MBs are hypointense and associated with a blooming effect[31] (Figure 1). According to the Microbleed Anatomical Rating Scale (MARS)[32], MBs were counted in lobar (frontal, parietal, temporal, occipital, insular), deep (deep and periventricular white matter, basal ganglia, thalamus, internal capsule, external capsule and corpus callosum) and infratentorial (brainstem, cerebellum) regions separately, and additionally summed up (i.e. whole-brain number of MBs, MB_{tot}). The localization of lobar MBs was additionally distinguished as cortical, if they were located within the cortex, or non-cortical.

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MBs with a direct link to a vein were assessed in the QSM sequence. They were defined as “MBs with venous connection” (MB_{ven}) if the connection was visible at least on one slice (Figure 2A). Number and localization (lobar [cortical, non-cortical], deep, infratentorial, total) were recorded using the same approach described in the previous paragraph. To double check the spatial relationship between small veins and MBs on 7T QSM images, MBs and the venogram were visualized in 3 dimensions applying MeVisLab Version 3.1.1 (MeVis, Bremen, Germany) (Figure 2B). In lobar, deep, infratentorial and total regions, we further determined the ratio between MBs with venous connection and all MBs (MB_{ven}/MB_{tot}) in the respective region, hereby calculating the ratio of venous MBs to all detected MBs.

In all 51 subjects, number of MBs was counted by two independent raters (J.R. 2 years of experience; V.P. 5 years of experience). Interrater reliability was very good to excellent (intraclass correlation coefficient for SWI 0.96, for QSM 0.86). Presence and localization of MB_{ven} was assessed in consensus by the same raters, disagreement rate was low (< 10%). All visual image analysis was performed on MRIcron (CNRL, University of South Carolina, USA).

Data Availability

De-identified data are available from the corresponding author upon reasonable request subject to a material transfer agreement.

Statistics

We applied Kruskal-Wallis test with Dunn-Bonferroni post-hoc test to evaluate group differences (controls, CAA, HA, mixed MBs) for the respective number of lobar, deep, infratentorial and total (i) MBs, (ii) MB_{ven} (iii) MB_{ven}/MB_{tot}. Statistical analyses were two-tailed and conducted using the Statistical Package for Social Science (IBM SPSS Statistics), version 23.

Results

A total of 51 older adults (mean age [SD] 70.5 [8.6], 37 % females) were included in this 7T brain MRI study. Twenty ~~of the participants~~were patients with CSVD (mean age [SD] 72.4 [6.1], 30 % females) ~~suffered from CSVD~~ while thirty-one participants were healthy elderly ~~considered as~~ controls (mean age [SD] 69.4 [9.9], 42 % females). There were n = 8 (40 %) CAA, n = 5 (25 %) HA patients and n = 7 (35%) subjects with mixed MBs. All groups were comparable with regard to age and sex. CSVD patients (all

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subgroups) had a higher prevalence of arterial hypertension compared to controls (Table 1).

The use of 7T QSM allowed to observe at least one MB in 80% (n = 25) of the healthy elderly controls. The finding is remarkable, given the fact that none of the control subjects presented MBs on the baseline 3T MRI (see inclusion criteria of healthy controls). Considering that the repercussion on the classification into the different groups, based on the additional MBs detected applying 7T QSM, was not the aim of our study, we maintained the classification based on the baseline 3T MRI. Both, CAA (Mdn=15.5) and mixed MBs subjects (Mdn=16) presented more MB_{tot} than controls (Mdn=1) (Dunn-Bonferroni post-hoc tests: $p < 0.001$, $r = 0.64$ and $p = 0.002$, $r = 0.59$ respectively). As expected, the number of lobar MBs was higher in CAA (Mdn= 11.5) than in HA (Mdn=0) and controls (Mdn=1) ($p = 0.006$, $r = 0.91$ and $p < 0.001$, $r = 0.65$); the number of lobar MBs was higher in mixed MBs subjects (Mdn=10) than in controls (Mdn=1) ($p = 0.024$, $r = 0.47$); the number of deep MBs was higher in mixed MBs subjects (Mdn=4) compared to controls (Mdn=0) ($p = 0.006$, $r = 0.53$); the number of infratentorial MBs was higher in mixed MBs subjects (Mdn=4) than in CAA (Mdn=0) and controls (Mdn=0) ($p = 0.022$, $r = 0.80$ and $p < 0.001$, $r = 0.82$).

In our cohort, we counted a total of n = 96 MB_{ven}, representing 14 % of all detected MBs on 7T QSM (n = 674). N = 19 (37%) of all subjects showed MB_{ven}, including n = 7 CAA (88% of all CAA cases), n = 2 HA (40%), n = 7 mixed MBs (100%) patients and n = 3 controls (10%). The prevalence of MBven in MB-presenting controls was consequently 12% (3/25). The vast majority of MB_{ven} (87%, n = 83) were observed in lobar locations, and all of them were cortical. CAA patients (Mdn= 3.5) showed significantly more lobar MB_{ven} than controls (Mdn=0) (r = 0.57, p = 0.002~~, r = 0.57~~) (Table 2). Also, subjects with mixed MBs (Mdn=2) presented significantly more lobar

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MB_{ven} than controls (Mdn=0) ($p < 0.001$, $r = 0.76$) and HA subjects ($r = 0.85$, $p = 0.020$, ~~$r = 0.85$~~). Only n = 5 (5%) and n = 8 (8%) of MB_{ven} were found in deep and infratentorial regions, respectively (Table 2 and) ~~(Table~~ 3). In each group, m~~M~~edian (range) of total MB_{ven} number and mean [SD] MB_{ven}/MB_{tot} was 3.5 (0-23) and 19% [15] in CAA, 0 (0-1) and 9% [14] in HA, 2 (1-13) and 18% [15] in mixed MBs, and 0 (0-1) and 5% [20] in controls, resulting in significant group differences (Mdn: $H(3) = 29.73$, $p < 0.001$; Mean: and $H(3) = 21.33$, $p < 0.001$, respectively). Post-hoc tests revealed that number of total MB_{ven} and MB_{ven}/MB_{tot} was higher in CAA and mixed MBs compared to controls (for MB_{ven}: $r = 0.63$, $p < 0.001$; $r = 0.72$, $p < 0.001$, and for MB_{ven}/MB_{tot}: $r = 0.54$, $p = 0.005$; $r = 0.62$, $p = 0.001$, respectively), with no differences between the remaining groups (Figure 3; Table 2). ~~We detected a total of 3 MB_{ven} in controls. Consequently, the~~

Discussion

This high-resolution 7T neuroimaging study investigated if a spatial relationship between small veins and MBs could be detected in a cohort of CSVD patients. QSM enabled depiction of cerebral MBs with a direct connection to a vein and their localization. These lesions accounted for 14% of all MBs.
Our data support the notion that MBs might not exclusively derive from arteries, but that venous contribution could play an important, yet not much explored, role in MBs and – presumably – CSVD pathogenesis. Venous collagenosis, for example, leads to thickening of the walls of small cerebral veins[33]. This could result in increased luminal pressure and leakage of the blood-brain barrier (BBB), a pivotal mechanism of CSVD and (maybe) MB initiation[34–36]. Venous collagenosis further relates to the development of WMH[37] and lacunes[18]. In line with this, in CSVD, a semiquantitative visual score

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created to assess pathological changes of the deep medullary veins was also independently associated with WMH volume[38] and presence of multiple MBs[39]. A direct relationship between a vein and a MB has also previously been observed in a 7 T MRI study[40]. However, to date, no dedicated studies have been carried out in order to distinguish between MBs of arterial and venous origin[10].

The distribution of MBs with venous connection in our study was predominantly lobar (87% of all venous MBs) and all of these MBs were located in the cortex. Conversely, only 5% of all venous MBs were found in deep, and 8% in infratentorial regions. Furthermore, CAA patients presented the highest ratio of venous MBs to total MBs (19%). These findings could suggest a relation to CAA pathology, in that the association between small veins and MBs could involve vascular Aß-pathology[41] or the related vessel wall remodelling[42]. However, other pathological mechanisms might play a role as well. Unfortunately, pathological studies that investigated MBs so far have not systematically distinguished whether the ruptured vessel was a vein or an artery[10].

Setting a focus on presence and kind of venous pathology in CSVD in general, and in CAA in particular, can have important repercussions on our understanding of clearance pathways in the human brain. ~~While the hypothesis of clearance through the glymphatic system implies that metabolic waste, such as Aß, exits the brain along perivascular spaces[43], the intramural periarterial drainage pathway postulates an exit route along the arterial walls and does not foresee an involvement of cerebral veins[2,44]. A coexistence of both pathways is of course also possible.~~

A major strength of our study is the use of high-resolution QSM at 7T MRI~~, which conveys high sensitivity for MB detection[45]~~. High-resolution MRI leads to better visibility of small structures, while given the same resolution, scanning at high field MRI increases signal-to-noise ratio. QSM is a postprocessing method[20], which allows MBs

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detection with higher sensitivity than SWI[21]. Simultaneously, QSM enables a precise visualization of the brain's venous vasculature[22]. In particular, t~~. As QSM – compared to SWI - removes the blooming effect[46], we can exclude the possibility that the connection we see between small veins and MBs is due to this artifact. Furthermore, not only QSM is an innovative reconstruction technique, but also the high-resolution used in this study enabled visualization of small veins. T~~he MSDI algorithm adopted for QSM reconstruction[22] provides ~~in fact~~ high specificity for venous blood susceptibilities, making it highly unlikely that we measured arterioles or small arteries with slow blood flow instead. As QSM – compared to SWI - removes the blooming effect[46], we can also exclude the possibility that the connection we see between small veins and MBs is due to this artifact. Moreover, higher sensitivity and reliability of SWI compared to T2*-weighted GRE MRI in the detection of MBs and veins, suggest that the observation of MBs with a venous connection would not benefit from the use of the latter.

Previous studies that matched ex-vivo ultra-high resolution MRI with the corresponding pathological changes[11] showed that increasing resolution and field-strength in MRI not only allowed to detect more MBs, but also non-hemorrhagic vasculopathic changes. One might therefore argue that what we observed are not MBs of venous origin but vasculopathic changes, such as microaneurysms. However, at a similar MRI resolution (voxel size: 0.2 mm^3 isotropic) as in our study, ~~(voxel size: 0.2 mm^3 isotropic)~~ 90% of all detected susceptibility artifacts were confirmed to be hemorrhagic lesions in pathology[11].

It is thought that the majority of cortical MBs originate from medullary arteries in CAA. The combined use of ultra-high resolution time of flight angiography[47] (down to a voxel size of 0.15 mm^3) and of a QSM derived venogram could allow to observe "leaky"

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cortical arteries as concurring vessel of origin of the MBs. At present, we cannot ~~completely~~ rule out the possibility that the spatial relationship that we observe is not a causal one. Only ~~patho~~histopathol~~l~~ogical correlation studies specifically targeting venous MBs can confirm the nature of these lesions and shed further light on the role of veins in CSVD.

The main limitation of our study is the small size of the cohort. However, this needs to be set into relation with the difficulties of acquiring 7T MRI, which has several contraindications, especially when taking into account ~~account of~~ an elderly hospital-based population suffering from vascular disease. In fact, previous studies adopting 7T MRI in similar cohorts were not larger[48–50]. For the same reasons, a selection bias towards healthier participants that do not mirror the full spectrum of CSVD, might have occurred. Despite the predictable higher sensitivity at submillimeter resolution 7T MRI, detection of MBs of venous origin is also possible using QSM at 3T (authors' observation), which can allow to broaden the number of study's participants in the future.

To our best knowledge, this is the first human neuroimaging study to systematically investigate the spatial relation between cerebral small veins and MBs in-vivo. Our findings establish a link between the venous microvasculature and, especially lobar, cerebral MBs, highlighting the role of small veins in CSVD, particularly suggesting a link to CAA pathology. Deepening the knowledge on these lesions could convey new insight into CSVD.

Acknowledgements

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Name	Location	Contribution
Johanna Rotta, MD	Otto-von-Guericke University, Magdeburg, Germany	Study design; analyzed the data; drafted manuscript for intellectual content
Valentina Perosa, MD	Massachusetts General Hospital, Boston, USA	Study design; analyzed the data; drafted manuscript for intellectual content
Renat Yakupov, MSc	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany	Processed part of the data; revised the manuscript for intellectual content
Hugo J Kuijf, PhD	University Medical Center Utrecht, the Netherlands	Revised the manuscript for intellectual content
Frank Schreiber, MSc	Otto-von-Guericke University, Magdeburg, Germany	Processed part of the data; revised the manuscript for intellectual content
Laura Dobisch, MSc	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany	Visualized the data; revised the manuscript for intellectual content
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Anne Assmann, MD	Otto-von-Guericke University, Magdeburg, Germany	Revised the manuscript for intellectual content
Oliver Speck, PhD	Otto-von-Guericke University, Magdeburg, Germany	Revised the manuscript for intellectual content
Hans-Jochen Heinze, MD	Otto-von-Guericke University, Magdeburg, Germany	Revised the manuscript for intellectual content
Julio Acosta-Cabronero, MSc	Tenoke Limited, Cambridge, United Kingdom	Revised the manuscript for intellectual content

Formatierte Tabelle

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Emrah Düzel, MD	German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany	Revised the manuscript for intellectual content
Stefanie Schreiber, MD	Otto-von-Guericke University, Magdeburg, Germany	Study design; analyzed the data; drafted manuscript for intellectual content

Appendix 1: Authors

Kommentiert [JR22]: Jetzt portrait statt landscape format

hat formatiert: Hervorheben

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Tables

	CAA (n = 8)	HA (n = 5)	Mixed MBs (n = 7)	Controls (n = 31)	Group differences
Age years	71.6 [+/- 7.5]	76.4 [+/- 2.1]	70.3 [+/- 5.4]	69.4 [+/- 9.9]	H(3) = 3.93, p = 0.27
Female %	50	0	29	42	H(3) = 3.96, p = 0.27
BMI kg/m^2	26.8 [+/- 2.4]	26.3 [+/- 4.8]	27.8 [+/- 3.9]	25.2 [+/- 2.4]	H(3) = 4.51, p = 0.21
Diabetes mellitus %	13	40	43	10	H(3) = 5.92, p = 0.12
Arterial hypertension %	100	80	100	52	H(3) = 10.42, p = 0.015 post-hoc tests not significant
Hyperlipidemia %	50	80	71	39	H(3) = 4.20, p = 0.24

Table 1. Characteristics of groups. The table reports the characteristics of the study participants, including demographics and vascular risk factors. If not stated otherwise, mean and SD are given. Kruskal-Wallis test is reported. Key: BMI: body mass index; CAA: cerebral amyloid angiopathy; HA: hypertensive angiopathy; MBs = microbleeds.

	CAA (n = 8)	HA (n = 5)	Mixed MBs (n = 7)	Controls (n = 31)	Group differences
Lobar MBs	11.5 (3-168)	0 (0-6)	10 (1-51)	1 (0-5)	H(3) = 23.34, **p < 0.001** CAA/HA*, CAA/CON*, Mixed MBs/CON*
Deep MBs	0.5 (0-6)	0 (0-5)	4 (0-22)	0 (0-18)	H(3) = 11.02, **p = 0.012** Mixed MBs/CON*
Infratentorial MBs	0 (0-10)	1 (0-2)	4 (1-14)	0 (0-2)	H(3) = 27.36, **p < 0.001** Mixed MBs/CON*, Mixed MBs/CAA*
Total MBs (MB_{tot})	15.5 (4-168)	2 (1-11)	16 (2-69)	1 (0-21)	H(3) = 24.6, **p < 0.001** CAA/CON*, Mixed MBs/CON*
Lobar MB_{ven}	3.5 (0-23)	0 (0-1)	2 (1-10)	0 (0-1)	H(3) = 29.67, **p < 0.001** CAA/CON*, Mixed MBs/CON*, Mixed MBs/HA*
Deep MB_{ven}	0	0	0 (0-2)	0 (0-1)	H(3) = 7.92, p = 0.048 post-hoc tests ns
Infratentorial MB_{ven}	0 (0-4)	0 (0-1)	0 (0-1)	0	H(3)= 8.65, p = 0.034 post-hoc tests ns
Total MB_{ven}	3.5 (0-23)	0 (0-1)	2 (1-13)	0 (0-1)	H(3) = 29.73, **p < 0.001** CAA/CON*, Mixed MBs/CON*
MB_{ven}/MB_{tot} % mean [+/-SD]	19 [15]	9 [14]	18 [15]	5 [20]	H(3) = 21.33, **p < 0.001** CAA/CON*, Mixed MBs/CON*

Table 2. Total and venous microbleeds. This table reports the number of total microbleeds (MB_{tot}) and MBs with a venous connection (MB_{ven}) according to brain localization for each of our study's subgroup. If not stated otherwise, median and range are given. Kruskal-Wallis and post-hoc Dunn-Bonferroni test statistics are reported and highlighted bold and with an asterisk in case of significant group/subgroup differences. Key: CAA: cerebral amyloid angiopathy; HA: hypertensive arteriopathy.

Subject no	Sex	Age at 7T MRI	CSVD subgroup (based on 3T SWI)	Cortical superficial siderosis (cSS)	Intracerebral Hemorrhage (ICH)	Lobar total MBs	Deep total MBs	Infratentorial total MBs	Total MBs (MB_{tot})	Lobar MBs with venous connection	Deep MBs with venous connection	Infratentorial MBs with venous connection	Total MBs with venous connection (MB_{ven})
1	F	74.8	Possible CAA			88	0	0	88	23	0	0	23
2	F	79.1	Probable CAA		Lobar ICH	6	3	0	9	3	0	0	3
3	M	76.2	Probable CAA	yes		168	0	0	168	14	0	0	14
4	M	60.3	Probable CAA			26	4	10	40	10	0	4	14
5	F	64.3	Probable CAA	yes	Lobar ICH	6	0	1	7	0	0	1	1
6	F	75.1	Probable CAA	yes		3	1	0	4	0	0	0	0
7	M	78.8	Probable CAA		Lobar ICH	10	6	2	18	0	0	0	0
8	M	64.2	Probable CAA			13	0	0	13	4	0	0	4
9	M	79.7	HA		Deep ICH	6	5	0	11	0	0	1	1
10	M	76.8	HA			0	1	0	1	0	0	0	0
11	M	74.1	HA			1	0	2	3	1	0	0	1
12	M	76.0	HA			0	0	1	1	0	0	0	0

13	M	75.3	HA		1	0	2	3	0	0	0	0
14	M	73.3	Mixed		41	22	4	67	5	2	0	7
15	M	76.6	Mixed		1	5	2	8	1	0	0	1
16	M	61.1	Mixed		45	10	14	69	10	2	1	13
17	M	72.5	Mixed		51	2	8	61	6	0	1	7
18	F	74.4	Mixed		5	4	4	13	1	0	0	1
19	F	66.5	Mixed		10	3	3	16	2	0	0	2
20	M	68	Mixed		1	0	0	1	1	0	0	1
21	M	66.5	CON		1	0	0	1	0	0	0	0
22	F	69.2	CON		2	0	0	2	0	0	0	0
23	F	81.1	CON		0	1	0	1	0	0	0	0
24	F	76.7	CON		1	0	0	1	0	0	0	0
25	M	89.4	CON		0	0	0	0	0	0	0	0
26	M	70.1	CON		2	1	0	3	0	0	0	0
27	M	78	CON		1	3	0	4	0	0	0	0
28	M	55.6	CON		0	0	0	0	0	0	0	0
29	M	78.6	CON		1	1	0	2	0	0	0	0
30	F	70.7	CON		0	2	0	2	0	0	0	0
31	F	74.8	CON		1	0	0	1	0	0	0	0
32	M	77.7	CON		1	0	0	1	1	0	0	1
33	M	75.3	CON		1	0	0	1	0	0	0	0

34	F	76.8	CON		2	0	0	2	1	0	0	1
35	F	77.2	CON		1	0	0	1	0	0	0	0
36	F	48.5	CON		1	0	0	1	0	0	0	0
37	M	71.6	CON		3	0	0	3	0	0	0	0
38	M	68.8	CON		3	3	0	6	0	1	0	1
39	F	68.3	CON		2	0	2	4	0	0	0	0
40	F	65.8	CON		0	0	0	0	0	0	0	0
41	M	62.2	CON		1	3	0	4	0	0	0	0
42	M	50.6	CON		1	0	0	1	0	0	0	0
43	M	70.3	CON		2	0	0	2	0	0	0	0
44	M	64.4	CON		0	0	0	0	0	0	0	0
45	M	69	CON		5	0	0	5	0	0	0	0
46	M	73.2	CON		0	0	0	0	0	0	0	0
47	F	45.1	CON		0	0	0	0	0	0	0	0
48	F	79.0	CON		0	1	1	2	0	0	0	0
49	M	71.2	CON		0	1	0	1	0	0	0	0
50	M	58.6	CON		2	18	1	21	0	0	0	0
51	F	65.9	CON		1	0	0	1	0	0	0	0
∑					517	100	57	674	83	5	8	96

Table 3: Detailed information on each study's participant, including location and number of total microbleeds and microbleeds with venous connection. Key: QSM = quantitative susceptibility mapping, CSVD = cerebral small vessel disease, CAA = cerebral amyloid angiopathy, CON = control, HA = hypertensive arteriopathy, M = male, F = female, No = number, ∑ = sum.

Figure Legend

Figure 1

Title: Example of the visualization of a microbleed.

Legend: Example of a microbleed on 7T SWI, depicted as a hypointense round structure (A) and on 7T QSM, where it appears hyperintense (B). The inlays respectively show an enlargement of the vision.

Figure 2

Title: Venous microbleed.

Legend: Example of a microbleed (arrow) with a direct connection to a small vein (luminal diameter of ca. 700 µm) on 7T QSM (A). 3-dimensional visualization of the venogram of a subject with CSVD (B). One microbleed (arrow) with connection to a vein is colored in blue, while those without connection are marked in red. One example of each is also shown in the enlargement in A.

Figure 3

Title: Differences in microbleeds with venous connection between groups.

Legend: (A) Violin plot showing the number of microbleeds with venous connection (MB_{ven}) in each subgroup. CAA and mixed MBs patients showed a higher number of MB_{ven} compared to controls. (B) Violin plot showing the ratio of venous to total microbleeds (MB_{ven}/MB_{tot}) in each subgroup. CAA and mixed MBs patients showed a higher ratio compared to controls. * $p < 0.05$; ** = $p < 0.01$; *** = $p < 0.001$.
CAA = cerebral amyloid angiopathy, CON = controls, HA = hypertensive arteriopathy.