MRI phenotyping of underlying cerebral small vessel disease in mixed hemorrhage patients

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ABSTRACT

OBJECTIVE: To investigate underlying cerebral small vessel disease (CSVD) in patients with mixed cerebral hemorrhages patterns and phenotype them according to the contribution of the two most common sporadic CSVD subtypes: cerebral amyloid angiopathy (CAA) vs. hypertensive arteriopathy (HA).

METHODS: Brain MRIs of patients with intracerebral hemorrhages (ICHs) and/or cerebral microbleeds (CMBs) were assessed for the full spectrum of CSVD markers using validated scales: ICHs, CMBs, cortical superficial siderosis (cSS), white matter hyperintensities, MRI-visible perivascular spaces (PVS). PVS predominance pattern was grouped as centrum-semiovale (CSO)-PVS predominance, basal-ganglia (BG)-PVS predominance, CSO-PVS and BG-PVS equality. Patients with mixed cerebral hemorrhages were classified into mixed CAA-pattern or mixed HA-pattern according to the existence of cSS and/or a CSO-PVS predominance pattern and comparisons were performed.

RESULTS: We included 110 patients with CAA (strictly lobar ICHs/CMBs), 33 with HA (strictly deep ICHs/CMBs) and 97 with mixed lobar/deep ICHs/CMBs. Mixed patients were more similar to HA with respect to their MRI-CSVD markers, vascular risk profile and cerebrospinal fluid (CSF) measures. In the mixed patients, 33 (34%) had cSS, a CSO-PVS predominance pattern, or both, and were defined as mixed CAA-pattern cases. The mixed CAA-pattern patients were more alike CAA patients regarding their MRI-CSVD markers, CSF and genetic profile.

CONCLUSION: Our findings suggest that the heterogeneous group of patients with mixed cerebral hemorrhages distribution can be further phenotyped according to the predominant underlying CSVD. cSS presence and a CSO-PVS predominance pattern could serve as strongly suggestive markers of a contribution from CAA among patients with mixed hemorrhages.

ABBREVIATIONS

Aβ	Amyloid-β
AD	Alzheimer's disease
BG	Basal ganglia
ApoE	Apolipoprotein E
CAA	Cerebral amyloid angiopathy
CHARTS	Cerebral Haemorrhage Anatomical RaTing instrument
CMB	Cerebral microbleed
CMB-R	Cerebral microbleed ratio
CSF	Cerebrospinal fluid
CSO	Centrum semiovale
cSS	Cortical superficial siderosis
CSVD	Cerebral small vessel disease
PVS	MRI-visible perivascular spaces
FLAIR	Fluid-attenuated inversion recovery
GRE	Gradient-recalled echo
HA	Hypertensive arteriopathy
HDL	High-density lipoprotein
ICH	Spontaneous intracerebral hemorrhage
MARS	Microbleed Anatomical Rating Scale
ttau	Total tau
ptau	Phosphorylated tau
STRIVE	STandards for ReportIng Vascular Changes on nEuroimaging
SWI	Susceptibility-weighted imaging
TE	Echo time
TR	Repetition time
WMH	White matter hyperintensities

1 INTRODUCTION

The two common subtypes of sporadic cerebral small vessel disease (CSVD) are cerebral amyloid angiopathy (CAA) and hypertensive arteriopathy (HA)[1]. The pattern of associated brain hemorrhages reflects a mirror distribution: CAA is associated with strictly lobar and HA with deep gray matter hemorrhages, though they can also occur in lobar regions at advanced disease[2–4].

The modified Boston Criteria provide high diagnostic certainty for CAA when blood-sensitive magnetic resonance imaging (MRI) sequences demonstrate multiple lobar hemorrhages[5], including cortical superficial siderosis (cSS) (a highly specific CAA signature)[6]. A predominance pattern of MRI-visible perivascular spaces (PVS) in the centrum semiovale (CSO) vs. basal ganglia (BG) is further strongly associated with CAA, but not HA[7].

In clinical practice, up to 40% of all CSVD patients show a pattern of mixed lobar and deep hemorrhages[8,9]. According to available clinical-radiologic criteria, these patients cannot be classified as having CAA or HA, leaving their stratification and therapeutic advice an open question. Two possibilities exist in these patients: (a) the co-occurrence of both CAA and HA; (b) the presence of advanced HA[8,10].

We hypothesize, that applying MRI markers that are specific for CAA (cSS, CSO-PVS predominance) might allow a more precise and clinically relevant classification of CSVD patients with mixed hemorrhages into (a) a mixed “CAA-pattern”; and (b) a mixed “HA-pattern”. We aimed to demonstrate the validity of this classification, by showing that the mixed CAA-pattern group should be more similar to CAA patients and the mixed HA-pattern group to HA patients with regard to their imaging and clinical characteristics.

2 MATERIALS AND METHODS

2.1 Study population

We designed a retrospective cross-sectional study and screened our neuroimaging database for cerebral MRI (cMRI) scans with blood-sensitive sequences conducted for diagnostic work-up at the University Clinic Magdeburg between 10/21/2003 and 07/31/2020. Patients were included in the study if they had spontaneous ICH(s) and/or CMBs on cMRI; n=262 subjects were identified. We excluded n=22 (13%) because of having just a single lobar CMB (n=16), i.e. possible CAA according to the modified Boston criteria which (according to MRI histopathological correlation studies) has low specificity for underlying CAA[11], or because of poor scan quality (n=6) **(Supplemental Figure I)**. There was a remainder of n=240 patients presenting the final study cohort with the following clinical diagnoses: n=117 (49%) had ICH, n=50 (21%) ischemic (i.e. lacunar) stroke or transient ischemic attack, n=43 (18%) dementia (i.e. Alzheimer's disease [AD] or vascular dementia), n=8 (3%) epileptic seizures, n=8 (3%) subarachnoid hemorrhage, n=4 (2%) CAA-related inflammation, n=5 (3%) Parkinson's disease, n=1 (1%) multiple sclerosis, n=2 (1%) renal encephalopathia, and n=2 (1%) in whom cerebral metastases were initially suspected, but excluded through MRI.

According to the locations of ICHs and CMBs, patients were divided into three groups: strictly lobar ICHs and/or CMBs (probable CAA according to the modified Boston criteria), strictly deep ICHs and/or CMBs (HA), lobar and deep ICHs and/or CMBs in any combination (mixed). Cerebellar ICHs and/or CMBs were allowed to occur in all three groups, but did not count in the classification. Mixed patients were further split into a mixed CAA-pattern group and a mixed HA-pattern group. Split was based on the existence of cSS or CSO-PVS predominance pattern, which defined the mixed CAA-pattern group, and was absent in the mixed HA-pattern group[6,7,12,13]. Subtyping/split of mixed patients was not based on the presence or number of hemorrhages (ICHs, CMBs).

In addition, the cohort was characterized with regard to its demographic (age and sex), clinical (existence of arterial hypertension, diabetes mellitus, hyperlipidemia, obesity), cerebrospinal fluid (CSF, see below) and apolipoprotein E (ApoE) data.

2.2 Standard Protocol Approvals, Registrations, and Patient Consents

This retrospective study was approved by the local ethics committee (No. 28/16).

2.3 MRI acquisition

MRI was performed using a 1.5T (Siemens Healthineers; n=126[53%] of the patients) and 3T Scanner (Philips Medical Systems; n=114[48%]), including T2*-gradient-recalled echo (GRE) (slice thickness: 3 to 4 mm, repetition time [TR]: 500 to 1.000 milliseconds, echo time [TE]: 11-13 milliseconds) or susceptibility-weighted imaging (SWI) (slice thickness: 1 to 2 mm, TR: 20 milliseconds, TE: 20-40 milliseconds), fluid-attenuated inversion recovery (FLAIR) (slice thickness: 4 to 5 mm, TR: 6.000 to 11.000 milliseconds, TE: 90 to 140 milliseconds), and T2 sequences (slice thickness: 3 to 4 mm, TR: 3.000 to 1.000 milliseconds, TE: 80 to 10 milliseconds).

2.4 MRI analysis

MRI analysis of all patients was performed in a semiquantitative manner according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE)[14] by a trained investigator (VS), blinded to all demographic, clinical, CSF and genetic information. The images were evaluated using specific software (Mango for 1.5T dicom images, Osirix for 3T nii images) and established methods and scales (see below). With the exception of PVS (see below), per patient all available MRI slices were analyzed, respectively. Intra-rater reliability based on a sample of 20 randomly chosen cases and inter-rater reliability based on a sample of 11 randomly chosen cases (by a second independent and blinded rater (VP)) was excellent for all investigated variables (intra-class correlation coefficient (ICC) >0.86 and >0.81, respectively).

CMBs were defined as small (diameter 2-5mm, maximum up to 10mm), round or oval in axial T2*-GRE (n=235)/SWI (n=5) hypointense lesions, not visible in FLAIR, T1-, or T2-weighted sequences. They were categorized into lobar (frontal, temporal, parietal, occipital, insula), deep (BG, thalamus, internal capsule, external capsule, corpus callosum, deep and periventricular white matter, brainstem), and infratentorial (cerebellum) CMBs applying the

Microbleed Anatomical Rating Scale (MARS)[14–16]. The total CMB count was calculated for the whole-brain and for each anatomical region separately (lobar, deep, infratentorial). Additionally, a CMB ratio (CMB-R) was created by dividing the number of lobar CMBs through the number of deep CMBs[17].

ICHs (diameter >10 mm) were classified using axial T2*-GRE sequences (n=235) or SWI (n=5) according to the Cerebral Haemorrhage Anatomical RaTing instrument (CHARTS) as lobar (frontal, parietal, temporal, occipital, insular), deep (BG, thalamus, brainstem) and infratentorial ICHs (cerebellum)[18]. ICHs were summed up for the whole brain and for each region, as described for CMBs (see above). Anatomical location was determined according to the largest size/diameter and epicenter of the ICH[14,18,19].

cSS was defined as a homogeneous T2*-GRE/SWI hypointensity found in the superficial cortex layers and subarachnoid space corresponding to hemosiderin deposition[13]. cSS was evaluated qualitatively on axial sequences using T2*-GRE (n=235) or SWI (n=5) and categorized as present/absent and classified as either focal (restricted to ≤3 sulci) or disseminated (≥4 sulci), in line with the modified Boston Criteria[6].

White matter hyperintensities of presumed vascular origin (WMHs) were divided into four recently defined patterns (present or absent): (1) multiple subcortical spots, (2) peri-BG ("around BG") WMHs, (3) anterior subcortical pattern, and (4) posterior subcortical pattern[20]. We thereby took account of axial FLAIR images (n=202), or, if absent, coronary FLAIR images (n=38).

MRI-visible PVS are fluid-filled spaces around small vessels with a maximum diameter of 3mm and a CSF-like signal behavior on FLAIR and T2-weighted images[21]. The severity of PVS was counted separately in the CSO (above the lateral ventricle/corpus callosum) and the BG. CSO and BG PVS were graded using axial T2- (n=174), and/or sagittal T2-weighted (n=66) scans[22]. CSO-PVS analysis took place in planes superior to the lateral ventricles/corpus callosum. For the BG the caudate nucleus, internal capsule, thalamus, lentiform nucleus, external/extreme capsules, and insular cortex were taken into account. At least 3 slices per subject were reviewed for the number of CSO- and BG-PVS, respectively,

taking account of both hemispheres, but counting the side (left or right) with the highest PVS number only. CSO- and BG-PVS were classified separately as either mild to moderate (<20 PVS) or frequent to severe (>20 PVS). In addition, each individual patient was assigned to one of the following three categories comparing the degree of CSO-PVS and BG-PVS: CSO-PVS predominance (higher degree of CSO-PVS: CSO-PVS > BG-PVS), BG-PVS predominance (higher degree of BG-PVS; BG-PVS > CSO-PVS), or equal degree of PVS in the CSO and BG (CSO-PVS = BG-PVS) [7].

2.4.1 CSF measures

Within 20 minutes of lumbar puncture, CSF samples were centrifuged at 4°C, aliquoted and stored at -80°C until analysis. CSF biomarkers were measured with commercially available ELISA (for Aβ 1-40: Innotest β-Amyloid(1-40); for Aβ 1-42: Innotest β-Amyloid(1-42); for total tau (ttau): Innotest hTauAg; for phosphorylated tau (ptau): Innotest p-Tau; Fujirebio, Ghent, Belgium), following the instructions provided by the manufacturer. Locally established thresholds were 485pg/ml for Aβ 1-42, 350pg/ml for ttau and 70pg/ml for ptau[23]. In addition, we also determined the Aβ 1-42/Aβ-1-40 ratio - which is commonly used for Aβ pathology detection - to normalize CSF Aβ 1-42 in terms of a better control for fluctuations in total CSF amyloid levels[24–27].

2.5 Statistical analysis

Shapiro-Wilk test was used to assess Gaussian distribution of the data. For group comparisons between CAA, HA and mixed, Kruskal-Wallis one-way analysis of variance (ANOVA) with post hoc pairwise Mann-Whitney U testing or ANOVA with Bonferroni post hoc testing was conducted. For group comparisons between mixed CAA-pattern and mixed HA-pattern, a Mann-Whitney U test or an independent-samples t-test was used. Bivariate variables were analyzed using logistic regression analysis. Age and sex were always considered as covariates. Significance levels for group comparisons were determined after Bonferroni adjustment for 17 studied imaging markers as $p \leq 0.05/17 = 2.9 \cdot 10^{-3}$. Analyses were performed using the IBM SPSS Statistics 24.0 software.

2.6 Data availability

Anonymized grouped data will be shared by request from a qualified investigator.

3 RESULTS

MRI markers and demographics, clinical, CSF and genetic data for the whole cohort, comprising CAA, HA and mixed patients, are given in **Table 1**. Our final cohort included 110(46%) CAA patients, 33(14%) HA and 97(40%) patients classified as mixed. A total of n=117 (49%) patients have suffered from ICH; 80 (33%) had lobar ICH, 33 (14%) deep and 4 (1%) cerebellar ICH. Total ICH prevalence did not differ between CAA, HA and mixed cases **(Supplemental Table I)**.

CAA compared to HA and mixed patients was associated with cSS, multiple subcortical WMH spots, severe CSO-PVS, a CSO-PVS predominance pattern, and less frequent peri-BG WMHs and severe BG-PVS. In addition, CAA compared to the mixed group had less cerebellar CMBs and a lower frequency of anterior subcortical WMHs (trend). HA compared to mixed patients had more deep ICHs, less deep and cerebellar CMBs and lower prevalence of severe CSO-PVS **(Table 1)**. Patients with CAA tended to be older than HA or mixed cases. In CAA compared to mixed patients, prevalence was lower for arterial hypertension (trend) and diabetes mellitus (trend); CAA patients were further less obese and had higher HDL levels (trend). CAA compared to HA or mixed was related to a lower Aβ 1-42/Aβ 1-40 ratio and a higher prevalence of Aβ 1-42-positivity (trend) **(Table 1)**.

3.1 Mixed CAA-pattern vs. mixed HA-pattern

MRI markers and demographics, clinical, CSF and genetic data for the patients with mixed cerebral hemorrhages, comparing the mixed CAA-pattern and mixed HA-pattern groups, are given in **Table 2.**

Of the 97 patients with mixed cerebral hemorrhages, n=33(34%) patients had cSS (n=5(5%)), a CSO-PVS predominance pattern (n=17(18%)) or both (i.e. cSS and a CSO-PVS predominance pattern (n=11(11%))) and were therefore classified as mixed CAA-pattern **(Figure 1A-D)**. The remainder of n=64(66%) was classified as mixed HA-pattern **(Figure 1E-H)**.

Mixed CAA-pattern compared to mixed HA-pattern showed trends towards more lobar CMBs, a higher CMB-R, more lobar and less deep ICHs, and significantly less frequently peri-BG WMHs. Mixed CAA-pattern patients tended to be more often Aβ 1-42 positive, along with trends towards a lower Aβ 1-42/Aβ-1-40 ratio and more ApoEε4-carriers than mixed HA-pattern cases **(Table 2)**.

3.2 Mixed CAA-pattern vs. CAA and mixed HA-pattern vs. HA

Comparison of MRI markers and demographics, clinical, CSF and genetic data between mixed CAA-pattern vs. CAA and mixed HA-pattern vs. HA is given in **Supplemental Table II** and **Supplemental Table III.** Patients with mixed CAA-pattern compared to CAA were younger, more often female (trend), had lower HDL and a higher Aβ 1-42/Aβ-1-40 ratio (trend). Mixed HA-pattern compared to HA had more commonly CMBs, less deep ICHs, trends towards higher frequencies of posterior subcortical WMH patches and arterial hypertension.

4 DISCUSSION

In this cross-sectional study we provide proof-of-concept evidence for MRI phenotyping of underlying CSVD subtypes in mixed hemorrhage patients. We tested the prespecified hypothesis that mixed hemorrhage patients could either have a (a) co-occurrence of CAA and HA, or (b) advanced HA affecting deep and lobar regions, and developed a simple MRI approach to potentially discriminate the two. Our results indicate that mixed hemorrhage patients with a mixed CAA-pattern (34% of mixed patients) could be identified through the presence of cSS and/or CSO-PVS predominance. Mixed hemorrhage patients without cSS and/or CSO-PVS predominance seem to better fit into a category of a mixed HA-pattern (66%).

We confirmed that, at a group-level, a mixed cerebral hemorrhage pattern is associated with a higher vascular risk profile when compared to CAA. As a whole, the mixed group showed more similarities with HA patients with regard to arterial hypertension, diabetes mellitus, obesity and dyslipidemia prevalence. These results replicate findings of a recent study that showed that patients with a mixed hemorrhage pattern presented a clinical phenotype sharing more similarities with patients with a deep hemorrhage than with those with a lobar hemorrhage pattern[8]. Also with regard to their MRI and CSF characteristics, there were far more similarities between mixed and HA patients than between mixed and CAA patients.

Interestingly, up to 34% of the mixed patients displayed a mixed CAA-pattern, in terms of prespecified neuroimaging features that are highly specific for CAA, i.e. cSS presence and CSO-PVS predominance. Hence, the mixed cerebral hemorrhage patient group is more heterogeneous than appreciated, and not all mixed patients have an advanced HA-driven CSVD process. Recent studies support this hypothesis in that the mixed hemorrhage group also shares some similarities with CAA, such as increased risk for ICH recurrence or higher amyloid load[8,28]. The two putative CAA MRI markers used in our approach seem thereby to provide a strong indication of at least concomitant advanced underlying CAA cases within this mixed group. Accordingly, mixed CAA-pattern patients had a higher prevalence of lobar

hemorrhages (ICHs, CMBs) and a higher CMB-R, confirming that our subtyping method results in a predominant lobar hemorrhage pattern quite characteristic for CAA. Likewise, mixed CAA-pattern patients had less frequently peri-BG WMHs, recently proposed to be an imaging marker for HA[20]. Furthermore, mixed CAA-pattern was related to CSF Aβ 1-42 positivity and ApoEε4 carrier status, mirroring the association between CAA and low CSF Aβ 1-42 levels and ApoEε4 positivity[24,26,29–34]. Both low CSF Aβ 1-42 concentration and low CSF Aβ 1-42/Aβ 1-40 ratio (which was found in the CAA-mixed pattern as well) indicate the deposition of the Aβ 1-42 isoform in the brain parenchyma and, to a lesser extent, in the cerebral vasculature. Positive CSF Aβ 1-42 biomarker status and a low CSF Aβ 1-42/Aβ 1-40 ratio both, together with CSF ptau elevation, are commonly used to determine AD pathology comprising parenchymal Aβ[31,32]. The fact, that just a minority of the mixed CAA-pattern group had AD (3%) and that CSF ptau was unaltered, points towards vascular Aβ 1-42 deposition to be the (dominant) driver of the CSF Aβ findings in the CAA-mixed pattern patient group.

Compared to mixed CAA-pattern, mixed HA-pattern had more often peri-BG WMHs and less often signature findings determining CAA (e.g. less lobar CMBs/ICHs, a lower CMB-R, a lower prevalence of CSF Aβ 1-42 positivity). Those findings deem mixed HA-pattern to reflect HA. Interestingly, when comparing mixed HA-pattern against HA, in mixed HA-pattern patients HA seemed to be even more severe as indicated by a higher load of deep CMBs, more extended WMHs and a higher prevalence of arterial hypertension. The latter results let us speculate that mixed HA-pattern fit the proposed category (b) of advanced HA affecting deep and lobar regions. Supporting our classification, a 56-year-old male patient classified as mixed MRI HA-pattern underwent brain biopsy to elucidate the underlying pathology of rapidly progressive cognitive decline together with WMH. MRI rating displayed mixed CMBs, equally severe PVS in BG and CSO, and WMH with multiple, subcortical spots (**Supplemental Figure II**). Neuropathology examination demonstrated no CAA (Vonsattel grade 0) [35] but severe arteriolosclerosis, i.e. HA. Further details about the patient's clinical and biomarker data are displayed in **Supplemental Table IV**.

The strength of our study is the comparatively high number of mixed hemorrhage patients, compared to previous studies which typically included significantly less mixed cases[8,9,17,33]. This high occurrence rate of such mixed cases in a hospital-based population points to the clinical relevance of our study, seeking for a better understanding of the presumed underlying CSVD pathology in this particular patient population. In addition, we assessed the full spectrum of MRI CSVD markers using standardized and validated scores to test our prespecified hypothesis. We provided compelling evidence that cohorts of mixed hemorrhages are heterogeneous with regards to the underlying CSVD and provided an actionable strategy to further subgroup them based on key MRI markers. The use of MRIs from everyday clinical practice makes our findings easily translated for clinical practice. Our results could be of significance for both, further research and clinical practice, and additional prospective studies with adequate sample sizes are needed to validate our findings. Potentially, our proposed classification, i.e. mixed cerebral hemorrhages together with CSS and/or PVS-CSO predominance, could become a useful addition to the modified Boston criteria to find CAA cases within the mixed group. This approach also highlights the growing significance of non-hemorrhagic markers for CSVD subtype classification[21,36]. Thus, hemorrhagic and non-hemorrhagic markers together will prospectively help to aid in a more subtle classification of CAA and non-CAA CSVD patients. One may consider that mixed CAA-pattern cases might behave, to a certain extent, more similar to CAA patients: they could have a higher risk of recurrent ICHs, especially under oral anticoagulation or intravenous thrombolysis, and of cognitive decline, particularly in contrast to HA patients[2,34,37]. These aspects make the identification of mixed CAA-pattern cases within the mixed group a clinically highly relevant goal; they thus need to be considered in the future focusing on longitudinal studies.

Our study has some limitations. First, patients were selected retrospectively according to the existence of ICHs and/or CMBs within MRIs that were performed as a part of routine diagnostic work-up. As a result, the scanning protocol was not completely harmonized and different imaging parameters and sequences might affect CSVD markers assessments.

Likewise, there were several missing data especially for CSF and genotyping. This is explained by the fact, that this diagnostic is not part of the routine work-up for ICH or ischemic stroke/transient ischemic attack presented by 2/3 of the patients of our cohort. The time of recruitment (from 2003 to 2020) is very long which lead to a changing MRI acquisition - using 1.5T as well as 3T MRI. Furthermore, the study population is heterogeneous and in a small part of the population the finding of CMB on MRI could be incidental. Selection bias could be another limitation in that diagnostic MRI in the clinic is usually performed in more stable patients. Lastly, in the mixed patients there was a relationship between cSS and ICH presence (data not shown), which has already been well established in former studies[38,39]. CSS presence could thus be considered a proxy for higher ICH prevalence in the mixed CAA group. In our cohort, ICH prevalence nevertheless did not significantly differ between mixed CAA and mixed HA (61% vs. 41%, p=0.06). We are thus convinced, that ICH presence has not introduced a bias towards assigning the mixed patients to the mixed CAA group.

5 CONCLUSIONS

In conclusion, our findings indicate that patients with mixed cerebral hemorrhages are highly prevalent amongst CSVD patients with and without ICHs. This group as a whole has a vascular risk profile, which is similar to that of HA patients. Our study provided novel evidence that that one third of patients with mixed cerebral hemorrhages present a more CAA-pattern phenotype, easily characterized on clinical MRI by the assessment of two key imaging markers – cSS and CSO-PVS predominance. Our approach requires external validation in larger patient cohorts. Further work will need to explore mixed cerebral hemorrhage subgroup and phenotypes with regards to risk profile in terms of ICH recurrence and cognitive decline. Neuropathological studies are finally warranted to confirm and refine the contribution of suspected CAA within the mixed CAA-pattern phenotype.

Name	Location	Role	Contribution
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7 Tables

Table 1. Comparison of MRI markers and demographics, clinical, CSF and genetic data between CAA, HA and mixed patients from the Magdeburg CSVD cohort.

	CAA n=110	HA n=33	Mixed n=97	p-value
Age, in years	75[8]	69[13]	71[11]	0.01
Female sex, n(%)	52(47)	13(39)	55(56)	0.1
Arterial hypertension[1], n(%)	79(88)	25(86)	78(98)	0.03
Diabetes mellitus[2], n(%)	15(18)	9(33)	28(39)	0.005
BMI kg/m²,[3]	25[4]	27[4]	28[4]	**0.001**
HDL < 1 mmol/l[4], n(%)	9(13)	7(28)	17(30)	0.02
ApoEε4 positivity[5], n(%)	10(36)	0	8(35)	0.9
CSF Aβ 1-40 pg/ml[6]	8196(1539-11932)	7823(2440-7907)	6808(3008-12994)	0.4
CSF Aβ 1-42 <485pg/ml, n(%)[6]	25(68)	1(33)	12(41)	0.03
CSF Aβ 1-42 pg/ml[6]	401(169-1342)	533(396-899)	688(207-1269)	0.04
CSF Aβ 1-42/Aβ 1-40 ratio[6]	0.6(0.3-1.4)	1.1(0.7-1.6)	0.9(0.3-2.8)	**<0.001**
CSF ttau > 350pg/ml, n(%)[6]	20(54)	1(33)	8(28)	0.03
CSF ttau pg/ml[6]	376(142-2369)	317(276-580)	279(92 -2000)	0.3
CSF ptau >70pg/ml, n(%)[6]	12(32)	0	6(21)	0.3
CSF ptau pg/ml[6]	58(22-158)	29(0-44)	47(18-122)	0.02
Lobar CMB count	7(0-360)	na	7(0-286)	0.01
Deep CMB count	na	0(1-7)	3(1-30)	**<0.001**
Cerebellar CMB count	0(0-5)	0(0-8)	0(0-16)	**<0.001**
CMB–Ratio (lobar/deep)	na	na	2(0-72)	na
Lobar ICH (≥1), n(%)	44(40)	na	36(37)	0.6
Deep ICH (≥1), n(%)	na	21(63)	12(12)	**<0.001**
Cerebellar ICH (≥1), n(%)	1(1)	0	3(3)	0.3
cSS presence, n(%)	56(51)	2(6)	16(17)	**<0.001**
Multiple subcortical spots, n(%)	76(70)	12(36)	47(49)	**0.002**
Peri-BG WMHs, n(%)	16(15)	11(33)	41(43)	**<0.001**
Anterior subcortical patches, n(%)	28(26)	13(39)	41(43)	0.01
Posterior subcortical patches, n(%)	77(70)	13(39)	65(68)	0.6
CSO-PVS severe >20, n(%)	91(86)	8(24)	59(62)	**<0.001**
BG-PVS severe >20, n(%)	21(20)	17(52)	53(55)	**<0.001**
CSO-PVS predominance, n(%)	72(68)	2(6)	28(29)	**<0.001**
BG-PVS predominance, n(%)	2(2)	10(30)	22(22)	**<0.001**
CSO-BG PVS equal, n(%)	32(30)	22(67)	48(50)	0.004

Unless otherwise reported mean [SD] or median (range) is given. Aβ, β-amyloid; ApoE, Apolipoprotein E; BG, basal ganglia; BMI, body mass index; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSF, cerebrospinal fluid; CSO, centrum semiovale;

PVS, MRI-visible perivascular spaces; HA, hypertensive arteriopathy; HDL, high-density lipoprotein; ICH, intracerebral hemorrhage; ptau, phosphorylated tau; ttau, total tau; WMHs, white matter hyperintensities; na, not applicable. P-values ≤0.05/17=$2.9 \cdot 10^{-3}$ were deemed statistically significant after Bonferroni correction and marked bold. Results are adjusted for age and sex. Missing data: [1]n=41(17%), [2]n=59(25%), [3]n=75(31%), [4]n=91(38%), [5]n=187(78%), [6]n=161(67%). Thresholds were set for high-density lipoprotein (HDL) at <1mmol/l [40], and for Aβ 1-42 at 485pg/ml, for ttau at 350pg/ml [23] and for ptau at 70pg/ml [23].

Table 2. Comparison of MRI markers and demographics, clinical, CSF and genetic data between mixed CAA-pattern and mixed HA-pattern patients from the Magdeburg CSVD cohort.

	Mixed CAA-pattern (n=33)	Mixed HA-pattern (n=64)	p-value
Age, in years	70[12]	73[9.6]	0.3
Female sex, n(%)	21(63)	30(47)	0.3
Arterial hypertension, n(%)[1]	21(91)	57(100)	0.02
Diabetes mellitus, n(%)[2]	7(33)	21(41)	0.5
BMI kg/m²,[3]	28 [5]	27 [4]	0.8
HDL < 1 mmol/l, n(%)[4]	7(38)	11(28)	0.4
ApoEε4 positivity, n(%)[5]	4(57)	4(25)	0.07
CSF Aβ 1-40 pg/ml[6]	7175(4118-12994)	7405(3008-12641)	0.9
CSF Aβ 1-42 < 485 pg/ml, n(%)[6]	7(78)	5(25)	0.008
CSF Aβ 1-42 pg/ml[6]	440(207-1057)	704(213-1269)	0.03
CSF Aβ 1-42/Aβ1-40 ratio[6]	0.75(0.3-2.8)	0.9(0.4-1.7)	0.04
CSF ttau > 350 pg/ml, n(%)[6]	2(22)	6(30)	0.7
CSF ttau pg/ml[6]	230(124-2000)	290(127-1334)	0.9
CSF ptau > 70 pg/ml, n(%)[6]	2(22)	4(21)	0.9
CSF ptau pg/ml[6]	51(25-122)	47(18-85)	0.9
Lobar CMB count	7(0-286)	4(1-150)	0.03
Deep CMB count	2(1-18)	3(1-30)	0.05
Cerebellar CMB count	0(0-14)	1(0-16)	0.9
CMB-Ratio (lobar/deep)	3(0-72)	1.2(0-50)	**<0.001**
Lobar ICH (≥ 1), n(%)	19(58)	17(27)	0.03
Deep ICH (≥ 1), n(%)	1(3)	11(17)	0.05
Cerebellar ICH (≥ 1), n(%)	0	3(5)	0.2
cSS presence, n(%)	16(49)	na	na
Multiple subcortical spots, n(%)	16(50)	31(49)	0.9
Peri-BG WMHs, n(%)	4(13)	37(59)	**<0.001**
Anterior subcortical patches, n(%)	11(34)	30(48)	0.2
Posterior subcortical patches, n(%)	21(66)	44(70)	0.7
CSO-PVS severe > 20, n(%)	30(91)	29(46)	**<0.001**
BG-PVS severe > 20, n(%)	5(15)	48(76)	**<0.001**
CSO-PVS predominance, n(%)	27(82)	na	na
BG-PVS predominance, n(%)	2(6)	19(30)	0.007
CSO- & BG-PVS equal, n(%)	4(12)	44(70)	**<0.001**

Unless otherwise reported mean [SD] or median (range) is given. Aβ, β-amyloid; ApoE, Apolipoprotein E; BG, basal ganglia; BMI, body mass index; CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; CSF, cerebrospinal fluid; CSO, centrum semiovale; PVS, MRI-visible perivascular spaces; HA, hypertensive arteriopathy; HDL, high-density lipoprotein; ICH, intracerebral hemorrhage; ptau, phosphorylated tau; ttau, total tau; WMHs, white matter hyperintensities; na, not applicable. P-values ≤0.05/17=2.9·10^{-3} were deemed statistically significant after Bonferroni correction and marked bold. Results are adjusted for age and sex. Missing data: [1]n=17(18%), [2]n=25(24%), [3]n=35(34%), [4]n=41(42%), [5]n=74(76%), [6]n=58(56%). Thresholds were set for high-density lipoprotein (HDL) at <1mmol/l [40], and for Aβ1-42 at 485pg/ml, for ttau at 350pg/ml [23] and for ptau at 70pg/ml [23].

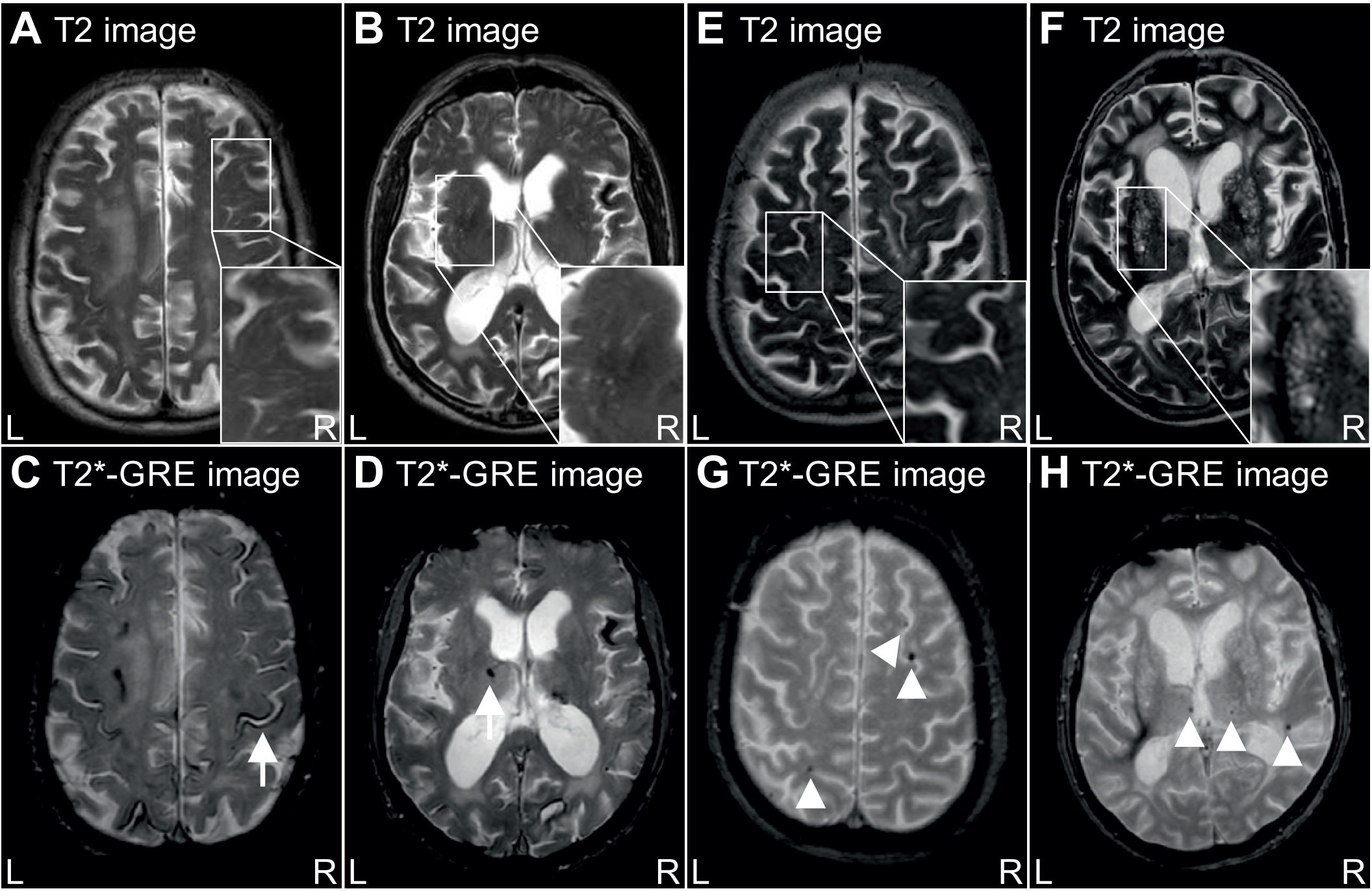
8 Figure legend

Figure 1: Mixed CAA- and mixed HA pattern.

Figure A-D demonstrates the 1.5 T MRI of a 77-year old man with mixed CAA-pattern. The T2-weighted images show in A frequent MRI-visible perivascular spaces (PVS) in the centrum semiovale (CSO) (inlay) and in B mild PVS in the basal ganglia (BG) (inlay), indicative of a CSO-PVS predominance pattern. The T2*-gradient-recalled echo (GRE) image in C exhibits a disseminated form of cortical superficial siderosis (arrow) and in D one deep cerebral microbleed (arrow) in the left thalamus.

Figure E-G demonstrates the 1.5 T MRI of a 69-year old man with mixed HA-pattern. The T2-weighted images show in E mild MRI-visible PVS in the CSO (inlay) and in F severe PVS in the BG (inlay), indicative of a BG-PVS predominance pattern. The T2*-GRE image in G exhibits three lobar CMBs in the right frontal and left parietal cortex (arrowheads) and in H two deep CMBs in the left and right thalamus (arrowheads). Note in H another lobar CMB in the right temporal cortex (arrowheads).

Figure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