SYSTEMATIC ANALYSIS OF CEREBRAL AMYLOID ANGIOPATHY-RELATED INTRACEREBRAL HEMORRHAGE AND INFLAMMATION – IDENTIFYING DIAGNOSTIC AND PROGNOSTIC BIOMARKERS

Bernadett Nagy-Fakan MD

PhD Thesis

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TABLE OF CONTENT

I. INTRODUCTION

Stroke is one of the leading causes of death and disability globally. After ischemic stroke, intracerebral hemorrhage (ICH) is the second most prevalent type, accounting for some 10% of all cases [1]. The most common known risk factors of spontaneous ICHs include advanced age, chronic hypertension, cerebral amyloid angiopathy (CAA), alcohol and drug abuse, and antithrombotic medications [2]. Based on etiological considerations, ICHs are commonly classified into deep ICHs (i.e., originating from blood vessels in the basal ganglia, thalamus, or brainstem), predominantly associated with chronic hypertensive arteriopathy, and lobar ICHs, which are most frequently related to CAA and, relatively less frequently, to other etiologies such as vascular malformations or tumors [3]. The distribution of cerebral microbleeds (CMBs) follows a similar anatomical pattern, with chronic hypertensive (a.k.a. hyaline) arteriopathy associating primarily with CMBs in deep localizations and CAA typically associating with lobar CMBs, sparing the deep structures [4]. Of note, cerebellar ICHs and CMBs can be attributable to either chronic hypertensive arteriopathy or CAA [5]; therefore, their classification in the literature is not unequivocal, some authors classifying them as deep [6] or non-lobar [7, 8] while others omitting them from analyses [9], analyzing them separately [10] or using alternative classifications [11].

The neuropathological prevalence of CAA increases with age, being comparable to that of Alzheimer's disease (AD), with which CAA is biochemically and pathogenetically interrelated, as similar pathological Aβ proteins build up in parenchymal plaques in AD. The two diseases show some 80% overlap; however, they both exist independently [12]. Similarly to sporadic AD, polymorphisms in the *APOE* gene have been associated with increased risk (ε4) or more severe phenotype (ε2) of sporadic CAA [13].

In CAA, cortical and leptomeningeal small arteries/arterioles and capillaries are degenerated due to the progressive deposition of Aβ peptides. Histopathologically, Type I and II CAA are differentiated, according to the presence of capillary involvement (i.e., Type I) [14-16]. The deposition of amyloid peptides causes both CAA-related ischemic alterations (including microinfarctions and leukoaraiosis) and different types of hemorrhages. These include lobar cerebral microbleeds (CMBs), lobar ICHs of various size (ranging from a few centimeters to lethal giant ICHs), convexity subarachnoid hemorrhages (cSAHs) due to rupture of leptomeningeal arteries, and cortical superficial sideroses (CSSs) as chronic manifestations of cSAHs [12, 17]. Clinical manifestations of CAA can be various, ranging from asymptomatic stage to fatal ICHs. Typically, CAA-related ICHs are recurrent and cause various neurological

deficits (depending on localization), headache, and epileptic seizures with or without loss of consciousness [12]. Patients usually develop slowly or step-wise progressive cognitive impairment due to multiple vascular lesions (i.e., vascular neurocognitive disorder or a mixed-type neurocognitive disorder in the presence of concomitant AD pathology). In addition, CAA patients frequently experience transient ischemic attack (TIA)-like events, a.k.a. transient focal neurological episodes (TFNEs) or 'amlyoid spells'. These events are, however, presumed to be due to focal epileptic activity or cortical spreading depression secondary to cSAH/CSS and are not thrombotic in origin [12].

Magnetic resonance imaging (MRI) sequences sensitive to susceptibility artifacts generated by hemosiderin deposits of previous micro- and macrobleeds, such as gradient echo (GRE), susceptibility-weighted imaging (SWI), or T2*sequences, in addition to a set of clinical characteristics, enable a probabilistic diagnosis of CAA *in vivo* with high diagnostic accuracy [5]. The original Boston criteria was modified in 2010, recognizing CSS as part of CAA-related alterations [17]. This Modified Boston criteria (with increased sensitivity and retained specificity) enables establishing the diagnosis of possible CAA and probable CAA without histological confirmation (i.e., biopsy specimen or *post mortem* tissue) in patients above 55 years (y), with the presence of a single lobar hemorrhagic alteration (ICH, CMB, or cSAH/CSS) or isolated multifocal cSAHs/CSSs without other cause allowing the diagnosis of possible CAA, and >1 lobar ICHs and/or CMBs in any combination or ≥1 ICH/ CMB plus ≥1 cSAH/CSS (again without other cause) meeting the diagnosis of probable CAA [17]. While deep (i.e., basal ganglionic, thalamic, and brainstem) hemorrhagic alterations preclude the diagnosis of both possible and probable CAA, cerebellar bleeds are allowed, albeit not counted for the diagnosis [5]. Definite CAA diagnosis can be established only via full *post mortem* histological investigation. Most recently, the Boston v2.0 criteria has been published, updating the definition of probable CAA [18]. The updated criteria allows probable CAA to be diagnosed based on (1) ≥1 ICH/CMB/cSAH/CSS (thus allowing multifocal cSAHs/CSSs without parenchymal lobar ICH(s)/CMB(s) as well to meet the criteria) or (2) the presence of a CAA-related white matter lesion (i.e., severe MRI-visible perivascular spaces in the centrum semiovale and/or white matter hyperintensities (WMHs) in a multispot pattern) together with a single CAA-typical hemorrhagic marker [18].

Body fluid biomarkers in the cerebrospinal fluid (CSF) and, less frequently, plasma, have recently been studied in CAA patients, focusing predominantly on the core biomarkers of amyloid metabolism (i.e., $A\beta_{1-42}$ and $A\beta_{1-40}$), neurodegeneration (total Tau), and neurofibrillary tangle (NFT) pathology (phosphorlyated Tau (pTau)), with the aim of offering complimentary

approaches [19]. In CAA, both $A\beta_{1-40}$ and $A\beta_{1-42}$ can be found in the vessel walls by immunohistochemical approaches, with $A\beta_{1-40}$ being the major isoform, while in AD, the amyloid plaques mainly consist of $A\beta_{1-42}$ [16, 20, 21]. In CAA patients, decreased levels of $A\beta_{1-40}$ and $A\beta_{1-42}$ have been reported in the CSF, secondary to an excessive intracerebral deposition [22]. These are at present not incorporated to the diagnostic criteria, in part due to a substantial overlap with presymptomatic/prodromal AD [23].

CAA as a pathology is by no means infrequent. Aβ deposition can be detected in the cerebral (particularly cortical leptomeningeal and perforating) vessels in some 10-40% of the elderly. It is estimated that CAA pathology is present in 2.3% of people between the age of 65 and 74, in 8.0% of those who are between 75 and 84, and in 12.1% of the patients over 85 y [24]; however, autopsy series with prevalence values of up to 20%, 40%, and 60% in the corresponding age groups have also been reported [25, 26]. Its clinical significance is indisputable, as CAA-related hemorrhages were reported to account for some 5-20% of all cases with spontaneous ICH [24]. The prevalence of CAA is comparable to that of AD [27] (with which it shows some 70–80% overlap [28, 29]) and atrial fibrillation (AF), for comparison [30].

Most patients have sporadic CAA; however, hereditary forms are also known, which are generally more severe and characterized by earlier onset and death compared to sporadic AβCAA. These conditions are extremely rare and present in selected families [24]. Hereditary CAAs can be further divided into Aβ and non-Aβ groups, based on the accumulating peptide in the vessels [24]. Hereditary forms of CAA include hereditary cerebral hemorrhage with amyloidosis Icelandic type (HCHWA-I, with vascular deposition of cystatin C) [31, 32], hereditary cerebral hemorrhage with amyloidosis Dutch type (HCHWA-D, with vascular deposition of Aβ) [33], familial amyloidosis-Finnish type (FAF, with vascular deposition of gelsolin), familial British dementia (FBD, with vascular deposition of ABri), familial Danish dementia (FDD, with vascular deposition of ADan), and Hungarian familial meningo-cerebrovascular amyloidosis a.k.a. cerebral transthyretin CAA [34]. CAA is also a common feature of familial AD caused by mutations of the *amyloid precursor protein (APP)*, *presenilin-1*, or *presenilin-2* genes [35], and is an established pathology in Down's syndrome (harboring an extra copy of *APP*, located on chromosome 21) [36]. Based on the overhelming predominance of sporadic AβCAA in terms of prevalence, the term CAA will be used hereinafter to refer to this entity.

In addition to the common phenotype of sporadic CAA described above (i.e., ICHs, TFNEs, and cognitive decline), a subgroup of CAA patients present with subacute

cognitive/behavioral decline, focal neurological symptom(s), headache, and/or seizure(s) [37]. These symptoms are associated with the typical CAA imaging alterations as well as the MRI appearance of asymmetric and confluent WMHs on T2/fluid-attenuated inversion recovery (FLAIR), representing vasogenic edema (often overlooked on initial computed tomography (CT)), similar to the clinical-radiological presentation of a subtpye of primary angiitis of the central nervous system (PACNS) [38, 39]. In this inflammatory form of CAA, the CAA-affected vessels are infiltrated by inflammatory cells (i.e., lymphocytes and macrophages) with or without granulomatous features (including multinucleated giant cells (MNGCs)) [40]. This entity can be classified as Aβ-related angiitis (ABRA), referring to transmural/intramural and perivascular inflammatory involvement [41] and perivascular CAA-related inflammation (CAA-RI) with perivascular infiltrates only [42]. The vasculitic form (i.e., ABRA) was found in 1/3 of cases with initial PACNS diagnosis [43], with some authors considering ABRA as a PACNS subtype [41, 43]. The first systematic clinical definition of this syndrome was given by Eng *et al.* and was termed *'CAA-related inflammation'* [44]; however, cases with similar phenotype and inflammatory vasculopathy associated with CAA have been reported for more than 50 y. The clinical-radiological criteria were defined in 2011 by Chung et al. [42] and have been improved and validated by the Boston group (a.k.a., the Auriel criteria) [45]. Most patients with this phenotype respond to immunosuppression, with corticosteroids in the first line [46]. It is proposed that, as opposed to PACNS (without CAA) where biopsy is gold standard, the diagnosis of CAA-RI can be established solely on clinical-radiological grounds [37, 42, 45]. The pathogenic role of anti-Aβ autoantibodies was first implicated by the similarity to the phenotype of a rare adverse event in AD trials with monoclonal antibodies (termed amyloid-related imaging abnormalities (ARIA)), presenting with vasogenic oedema (ARIA-E, including parenchymal edema and/or sulcal effusion) and associated hemorrhages (ARIA-H, including CMBs and/or CSSs) [47, 48]. A further link between ARIA and CAA-RI is the high prevalence of *APOE* ε4 allele carriers in both conditions [37, 47].

Though curative therapy in CAA is lacking, the clinical relevance of the diagnosis is high. Indeed, the use of anticoagulants is contraindicated in CAA according to current guidelines due to a seven to tenfold increase in the risk of ICH [49, 50]. The use of antiplatelet therapy should also be carefully considered in CAA, due to an up to fourfold increase in the risk of recurrent ICH in general population after lobar ICH [51] and a twofold prevalence of lobar CMBs in patients suffering ICH while on antiplatelet therapy [11]. Though a prior ICH has always been an absolute contraindication for systemic thrombolysis in acute ischemic stroke, a >10 CMB number *per se* has recently been introduced as a contraindication due to

uncertain benefit [52]. The potential reversibility of inflammation-related symptoms in patients presenting with CAA-RI also necessitates an increased survaillence not only to CAA itself but to its less frequent complications.

Despite the high prevalence and relevance among the elderly, the clinical diagnosis of CAA was anecdotal and sporadic in our center before the initation of our studies.

II. OBJECTIVES

Based on the discrepancy between the expected frequency of CAA among the elderly and the experienced occurrence of CAA diagnosis in routine clinical practice, our aim was to asses the frequency of the different types of spontaneous ICHs in our stroke center, with special focus on estimating the underlying prevalence of CAA, by a retrospective re-evaluation of written and imaging documentation. Emphasis was given on the analysis of the predictive value of putative risk factors for ICH location, probable/definite CAA diagnosis, and fatal outcome.

Our second study aimed to identify and profile published probable/definite CAA-RI cases (including and presenting 7 new cases) and to perform an in-depth systematic analysis of subject-wise collected neuropathological, radiological, clinical, and laboratory variables to provide insights into previously unrevealed associations and identify diagnostic/prognostic biomarkers.

III. PATIENTS, MATERIALS, AND METHODS

In the CAA-related ICH study, via screening the electronic database of our center, patients who received acute in-patient care between 01/07/2014 and 01/07/2018 with any of the intracranial hemorrhage-related International Classification of Diseases (ICD) diagnosis codes were identified. Reviewing the imaging scans and medical records, spontaneous ICHs were separated from intracranial hemorrhages with traumatic etiology, cases with basal SAH, primary intraventricular hemorrhage, and hemorrhagic transformation of ischemic stroke, and from cases with inadequate coding. Spontaneous ICHs were further classified according to hematoma localization as deep ICHs (basal ganglia, thalamus, or brainstem) and lobar/cerebellar ICHs (regions compatible with the diagnosis of probable CAA, enabling the estimation of the prevalence of underlying CAA).

The prevalence of different etiologies behind lobar/cerebellar ICHs was assessed in a subpopulation who underwent ‘complete’ clinical work-up, defined as being subjected to computed tomography angiography (CTA) or MR angiography (MRA) as well as SWI (if

structural etiology was not identified by the above modalities) and/or *post mortem* neuropathological work-up. Definite CAA, probable CAA, and possible CAA diagnoses were retrospectively established or revised as per the Modified Boston criteria (**Table 1**, note that the Boston criteria v2.0 was published 2 y after our related publication) [17, 18]. An ICH was considered CAA-related if met the criteria for probable and/or definite CAA.

Table 1. Modified Boston criteria – based on the work of Linn et al. 2010 [17]

Definite CAA	full *post mortem* examination revealing lobar, cortical, or cortical-subcortical hemorrhage and pathological evidence of severe cerebral amyloid vasculopathy; in the absence of other cause
Probable CAA with supporting pathological evidence	clinical data and pathological tissue (evacuated hematoma or cortical biopsy specimen) revealing lobar, cortical, or cortical-subcortical hemorrhage and some degree of cerebral vascular amyloid deposition; in the absence of other cause
Probable CAA	patient age ≥55 years CT/MRI findings demonstrate I. multiple hemorrhages restricted to lobar, cortical, or cortical-subcortical regions (cerebellar hemorrhages allowed) of varying sizes/ages without another cause, or II. a single lobar, cortical, or cortical-subcortical hemorrhage and focal (three or less sulci) or disseminated (more than three sulci) cortical superficial siderosis without another cause
Possible CAA	patient age ≥55 years CT/MRI findings demonstrate I. a single lobar, cortical, or cortical-subcortical hemorrhage without another cause, or II. focal or disseminated cortical superficial siderosis without another cause

Clinical data collected about the patients included their age at the time of ICH, sex, history of intracranial vascular events (including TIA, clinical episode of ischemic or hemorrhagic stroke), family history of any stroke, prior episodes of loss of consciousness, chronic hypertension, hypertensive excess at presentation (defined as ≥180 mmHg systolic blood pressure), current use of antiplatelet and/or anticoagulant drugs, as well as the international normalized ratio (INR) values on admission for ICH. Case fatality (lethality) was defined as fatal outcome within 1 month (m) secondary to the ICH event, in the absence of evidence for unrelated cause of death (e.g., cardiac arrest). This retrospective study was conducted in accordance the Declaration of Helsinki and was approved by the Ethics Committee of the University of Szeged (44/2016).

In our CAA-RI study, we systematically collected and reviewed previously published cases in PubMed, using the terms 'ABRA', 'amyloid beta-related angiitis', 'CAA-RI', 'cerebral amyloid angiopathy-related inflammation', or 'inflammatory cerebral amyloid angiopathy'. Original papers with full text available were accepted if published until December 31, 2021. Non-English papers were considered and data used if deemed unambiguous by using an online translator software. Additional papers were looked for in reviews and reference lists of papers identified. Papers reporting only collective data from mixed groups of definite + probable or probable + possible CAA-RI patients were excluded. Papers reporting only descriptive data from well-defined groups were included only in the descriptive analysis. The in-depth analysis of associations was performed on cases with subject-wise data available. Duplicate/multiplicate reports were carefully looked for and for and were used as single merged cases. In addition to cases collected from the literature, 7 cases diagnosed with CAA-RI (including 2 definite CAA-RI) in our center until the completion of the study, were included in the analysis. The reports were prepared in line with the CARE guidelines [53]. The patients or their next-of-kin gave informed consent to reporting unless both were unavailable, and the studies on our own patients were approved by the local Ethical Committee (46/2014, 44/2016, 22/2021). The process of patient collection is presented in **Figure 1**.

Definite CAA-RI was considered in the presence of either perivascular or transmural/intramural inflammatory infiltrates associated with CAA vessels as defined previously [42], with a modification that meeting the clinical-radiological criteria was not a prerequisite of definite diagnosis (hence allowing the measurement of their sensitivity). Probable CAA-RI was considered by adopting the Auriel criteria [45], with slight modifications in wording, presented in **Table 2**, and referred to as 'the present criteria'.

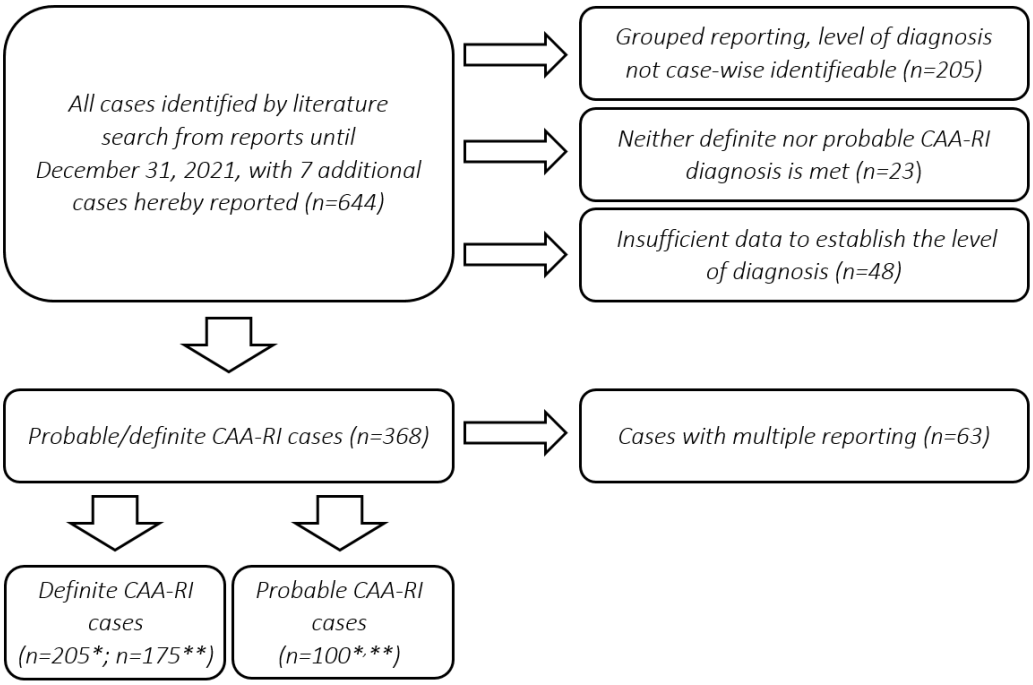

Figure 1. Flow-chart of the process of identifying definite CAA-RI and probable CAA-RI cases as per the present criteria. *, eligible for descriptive analysis (including group-wise data); **, eligible for associative analyses (case-wise data available). Original publication in: [54].

The collected variables included age at presentation, sex, and binary (yes/no) data on clinical signs (headache, focal sign (including sustained and TFNE), altered mental state (including behavior, cognition, consciousness, and hallucination), and seizure (of any type), prior lobar ICH, radiological signs (patchy WMH(s), confluent WMH(s), asymmetry, leptomeningeal enhancement (LE), parenchymal enhancement, sulcal non-nulling (SNN) on FLAIR, lobar CMB(s), lobar ICH(s), deep CMB(s)/ICH(s), co-localization of confluent WMH(s) with CMBs, and concentric beading on angiography), neuropathological features (autopsy, biopsy, definite CAA-RI, perivascular, transmural, lymphocytes, histiocytes/macrophages, MNGCs, eosinophils, Aβ-immunopositive macrophages, Aβ plaques, and neurofibrillary tangles (NFTs)), CSF data (lumbar puncture, pleocytosis (≥5 white blood cells/μL or reported as elevated), elevated protein level (≥45 mg/dl total protein or reported as elevated), oligoclonal bands (OCB), low $A\beta_{1-42}$ (<500 pg/ml or reported as low), high Tau (≥450 or 600 pg/ml for cases below and above 70 y of age, respectively, or reported as high), high phosphorylated Tau (pTau; ≥60 pg/ml or reported as high), anti-Aβ antibodies present), *APOE* genotype (ε4 carrier, ε2 carrier, ε4 or ε2 carrier, ε4/ε4), therapy-related data (any treatment, surgery (including resection, lobectomy, and CSF drainage), immunosuppression, corticosteroid (low-dose and high-dose), cyclophosphamide, other immunosuppressant, combined therapy), and outcome measures (clinical improvement,

radiological improvement, positive clinical outcome at and clinical relapse/mortality/future lobar ICH within 6 m and 1 y after putative *therapeutic decision point* (i.e., initiation of therapy for the treated, clinical (hospital) presentation for the non-treated), and relapse responding to treatment). Binary parameters were marked as yes/present (1) or no/absent (0) if the information presented was deemed unambiguous, with ambiguous or unreported data regarded as missing values. For radiological and pathological features, visual representations and in-text descriptions were both evaluated, depending on their availability. For LE, apparent linear or nodular hyperintensity of the pial-arachnoid surface in Gadolinium-enhanced T1-weighted scans (as compared with the non-enhanced T1-weighted scans) in ≥1 sulcus and/or a direct in-text description were considered as present. For SNN, apparent linear hyperintensity filling the (otherwise normally hypointense) sulcal CSF space on the presented non-contrast FLAIR images of sufficient quality in ≥1 sulcus and/or a direct in-text description (without reported/presented concomitant cSAH in the territory) were considered as present. Data from CSF obtained shortly after therapy initiation were used only if they were pathological. Clinical outcomes at each time point were considered not positive (unfavorable) if no clinical improvement was declared or death related to CAA-RI (i.e., in association with no clinical improvement, relapse, or lobar ICH) and/or non-improving relapse/lobar ICH occurred within the examined period irrespective of the true length of follow-up, whereas the declaration of positive outcomes at 6 m or 1 y required sufficient follow-up periods, censoring improved cases with follow-ups shorter than 6 m or 1 y, respectively. Positive outcome and mortality were censored for deaths of causes unrelated to CAA-RI, except for the analysis of treatment (since treatment-related adverse events can contribute to death). Event variables, i.e., relapse or future lobar ICH, were censored for respective event-negative cases who died within the examined period when used as outcomes and were uncensored when used as predictors. Low- and high-dose corticosteroid therapies were defined arbitrarily as < or ≥1.5 g of methylprednisolone or dose-equivalent within the first 3 days, respectively; oral therapy with unspecified dose was considered low-dose, whereas intravenous/unspecified administration of unspecified doses were censored from dose analyses.

The statistical analysis was performed by the SPSS 20.0 and 22.0 software for the first (CAA-related ICHs) and second (CAA-RI) study, respectively. For comparative assessment of continuous variables, parametric (Student's t) or non-parametric (Mann-Whitney U) tests were used after normality analysis with the Shapiro-Wilk test. For comparative analysis of discrete variables, cross-tabulation analysis was used by the Chi^2 test, applying Fisher's exact values

when appropriate. Differences between sensitivities of the ‘present’ and the ‘extended’ sets of probable CAA-RI criteria were addressed by the McNemar with exact 1-sided p values.

Multivariable binary logistic regression analyses were used to assess the effect of predictors found to be significant in the univariable comparative analyses. The binary outcomes in the first study were deep ICHs vs. lobar/cerebellar ICHs, case fatality at 1 m vs. alive at 1 m, and probable/definite CAA vs. non-probable CAA (including all deep ICHs and the subgroup of lobar/cerebellar ICH with ‘complete’ clinical work-up not meeting the criteria for probable/definite CAA). The binary outcomes in the second study were perivascular vs transmural CAA-RI, treated vs. non-treated with immunosuppression, improved vs. not improved clinically, positive vs. negative outcome at 6 m, positive vs. negative outcome at 1 y, survived vs. deceased at 6 m, survived vs. deceased at 1 y, high-dose vs. low-dose corticosteroids, pure steroid vs. combined steroid therapy.

The level of significance was $p<0.05$. Data within the text are presented as mean±standard error of the mean (SEM) or median [23] for normal or non-normal distribution, respectively.

IV. RESULTS

A. Results of the CAA-related ICH study

1. Revision of diagnoses, estimation of CAA-related ICH prevalence

A total of 324 patients having received any intracranial hemorrhage-related ICD codes as leading diagnosis in the given period were identified. After exclusions, 213 spontaneous ICHs were identified (**Figure 2**). Among spontaneous ICHs, 121 deep ICHs (110 (51.6%) localized to the basal ganglia/thalamus and 11 (5.2%) to the brainstem) and 92 lobar/cerebellar ICHs (85 (39.9%) localized to any cerebral lobe and 7 (3.3%) to the cerebellum) were detected (**Figure 3A**).

Table 2. Present and proposed extended clinical-radiological criteria for probable CAA-RI

Present criteria for probable CAA-RI*	**Proposed extended criteria for probable CAA-RI**
1. Age ≥40 years.	1. Age ≥40 years.
2. Clinical features: headache(s), altered mental state (related to behaviour, cognition, consciousness, and/or hallucination), focal central neurological deficit(s) (either sustained or transient), *and/or* epileptic seizure(s) of any type; symptoms cannot be explained merely by novel hemorrhagic alteration(s).	2. Clinical features: headache(s), altered mental state (related to behaviour, cognition, consciousness, and/or hallucination), focal central neurological deficit(s) (either sustained or transient), *and/or* epileptic seizure(s) of any type; symptoms cannot be explained merely by novel hemorrhagic alteration(s).
3. MRI features (hemorrhagic)[#]: lobar ICH(s), lobar CMB(s), cSAH(s), *and/or* CSS(s) of any age; absence of deep (ganglionic/thalamic/brainstem) hemorrhagic alteration; cerebellar hemorrhagic alterations do not count either in favor or against the diagnosis.	3. MRI features (hemorrhagic)[#]: lobar ICH(s), lobar CMB(s), cSAH(s), and/or CSS(s) of any age; absence of deep (ganglionic/thalamic/brainstem) hemorrhagic alteration; cerebellar hemorrhagic alterations do not count either in favor or against the diagnosis.
4. MRI features (non-hemorrhagic): asymmetric confluent WMH(s) on T2 or FLAIR extending to the immediately subcortical white matter, not merely attributable to gliosis surrounding past ICH.	4. MRI features (non-hemorrhagic): asymmetric confluent WMH(s) on T2 or FLAIR extending to the immediately subcortical white matter, not merely attributable to gliosis surrounding past ICH or to perilesional edema surrounding present ICH, *and/or* leptomeningeal contrast enhancement, *and/or* sulcal non-nulling on FLAIR not attributable to cSAH.
5. Clinical and MRI features are not attributable to non-CAA-related cause(s).	5. Clinical and MRI features are not attributable to non-CAA-related cause(s).

*, adapted from the validated criteria by Auriel et al. [45] with slight modifications and rephrasing;

[#], analogous with possible/probable CAA in terms of hemorrhagic alterations in the modified Boston criteria [17].

CAA, cerebral amyloid angiopathy; CAA-RI, CAA-related inflammation; CMB, cerebral microbleed; cSAH, convexity subarachnoid hemorrhage; CSS, cortical superficial siderosis; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; WMH, white matter hyperintensity.

Original publication in: [54].

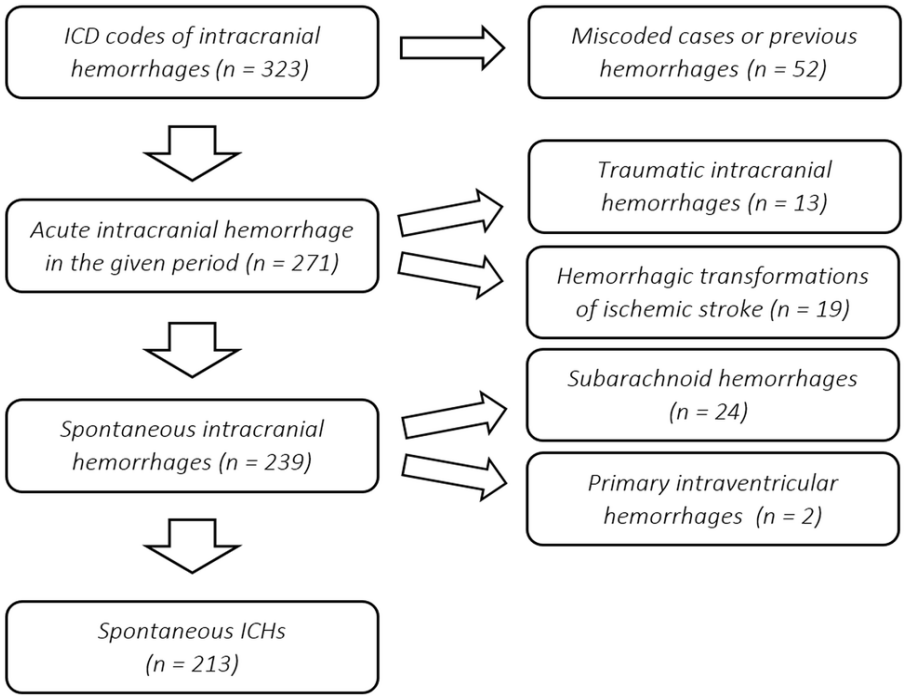

Figure 2. Flow diagram of the process of identifying spontaneous intracerebral hemorrhages (ICHs). Original publication in [55].

Out of lobar/cerebellar ICHs, 47 had ‘complete’ clinical work-up, of whom 2 proved to be definite CAA *post mortem* and 14 were consistent with the diagnosis of probable CAA clinically (one of them also became definite *post mortem*), rendering (16/47) 34.0% of all ‘completely’ worked-up lobar/cerebellar ICHs and (considering this rate as representative for all lobar/cerebellar ICHs) an estimated 14.7% of all spontaneous ICHs to be CAA-related. CMBs were present in 92.9% of probable CAA cases, with 42.9% having >10 CMBs, whereas CSS was present in 78.6%, with 57.1% of probable CAA cases having diffuse CSS. In addition, 10 patients met the criteria for possible CAA, and another 5 patients would have also met criteria for probable (1) and possible CAA (4) except for their age being under 55. In 12 cases (25.5%), structural (i.e., secondary) etiologies such as arteriovenous malformation, ruptured aneurysm, sinus thrombosis, dural arteriovenous fistula or metastatic tumor were detected, whereas 4 cases (8.5%) were consistent with hypertensive arteriopathy (i.e., presenting with deep hemorrhagic alteration(s) as well; **Figure 3B**). Out of the 14 probable CAA cases identified, originally only 4 had received CAA as suspected diagnosis (28.6%).

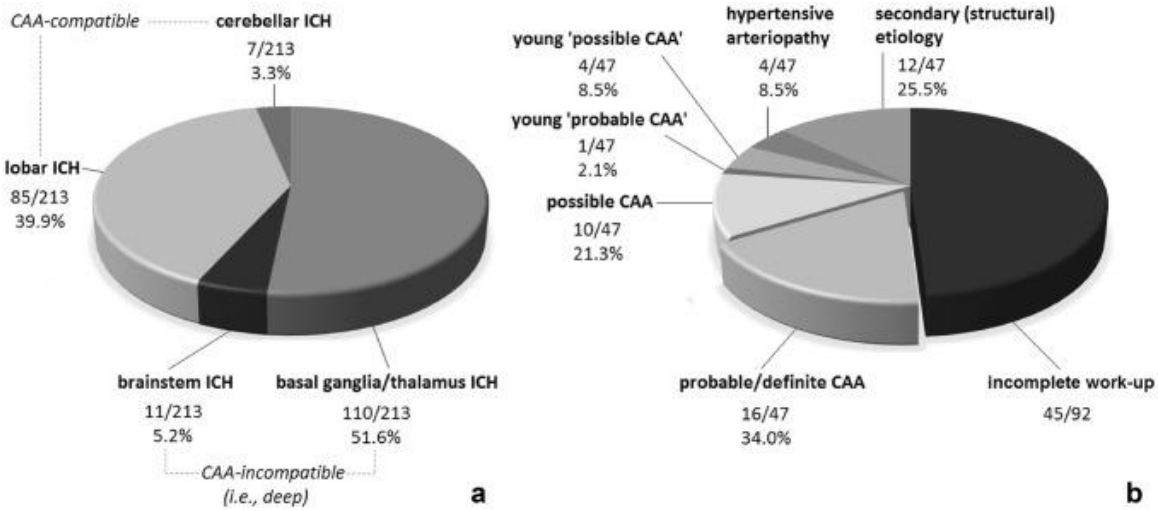

Figure 3. Localization of spontaneous ICHs (A). The distribution of underlying etiologies within lobar/cerebellar ICHs (B). Original publication in: [55].

2. Analysis of possible discriminators of ICH subgroups

The median age of the 213 patients with spontaneous ICH was 69.1 [60.3–79.0] y, with the lobar/cerebellar ICH group being significantly older compared to deep ICHs (74.5 [65.9–82.0] vs. 64.7 [57.9–76.6] years; p<0.001; **Table 3**).

The distribution of sex was significantly different between deep and lobar/cerebellar ICH groups (p=0.029), with a remarkable male preponderance in deep ICHs (66.9%) and a close to even ratio in lobar/cerebellar ICHs.

The frequency of prior episode(s) of TIA (TFNE), ischemic stroke, intracranial hemorrhage, and loss of consciousness in all ICHs were 10.5%, 12.4%, 8.1%, and 8.1%, respectively, being comparable between deep and lobar/cerebellar ICH groups.

The family history for either ischemic or hemorrhagic stroke (specification was not possible) was positive in 32.5%, with no between-group difference.

Table 3. Discriminators of spontaneous ICHs with regard to localization

	Lobar/cerebellar ICH	Deep ICH	MW/Chi^2	Multivariable logistic regression	
			p value	p value	OR (95% CI)
Patient number	92	121	–	–	
Age at event[a] (y)	**74.5 [65.9–82.0]**	**64.7 [57.9–76.6]**	**< 0.001**	**0.014**	**1.03 (1.01–1.06)**
Sex (male/all)	**52.2**	**66.9**	**0.029**	> 0.05	–
Prior ischemic stroke	12.0	12.7	> 0.05	–	–
Prior intracranial hemorrhage	7.7	8.5	> 0.05	–	–
Prior TIA (TFNE)	14.1	7.6	> 0.05	–	–
Prior loss of consciousness	9.8	6.8	> 0.05	–	–
Family history for any stroke	37.5	28.8	> 0.05	–	–
Anticoagulant use	20.9	13.4	> 0.05	–	–
INR > 1.4	18.4	11.4	> 0.05	–	–
Antiplatelet use[a]	**43.3**	**23.7**	**0.003**	**0.043**	**1.96 (1.02–3.75)**
Combined antithrombotic use	**13.3**	**3.4**	**0.016**	> 0.05	**–**
Hypertensive excess[a]	**48.9**	**71.2**	**0.001**	**0.002**	**0.39 (0.21–0.71)**
Chronic hypertension	88.0	90.9	> 0.05	**–**	**–**
Case fatality (1-m)	34.8	33.1	> 0.05	**–**	**–**

CI, confidence interval; ICH, intracerebral hemorrhage; INR, international normalized ratio; m,month; MW/Chi^2, Mann–Whitney test (for Age at event) or Chi^2 test (for other variables); OR, odds ratio; TIA, transient ischemic attack; TFNE, transient focal neurological episode; y, year.
[a] Indicates significant predictors in the multivariable analyses.
Bold font indicates variables with significant difference in univariable analyses.
Age is presented as median [interquartile range]). Other variables are presented as % prevalence within the columns.
Original publication in: [55].

A total of 16.7% of ICH cases were on anticoagulant therapy at presentation, 74.3% because of AF. Three-quarter (77.1%) of anticoagulated patients were on a vitamin K antagonist (VKA; warfarin (4/27) or acenocoumarol (23/27)), 88.9% of whom had an INR>1.4 at presentation. Two patients were on rivaroxaban, one on apixaban, together making up 8.6% of anticoagulated patients, while other direct oral anticoagulants (DOACs) were not represented. In 5 patients (14.3%), different doses of low-molecular-weight heparin (LMWH) were used. The frequency of anticoagulant use at presentation was comparable between ICHs in deep and lobar/cerebellar localizations. Notably, out of the 7 lobar/cerebellar ICH patients with a positive history of intracranial hemorrhage, 3 were on therapeutic anticoagulation, and 2 of them were on antiplatelet treatment as well. Antiplatelet use was present in 32.2%, with a significant preponderance in lobar/cerebellar (43.3%) compared to deep ICHs (23.7%; p=0.003). Altogether 7.7% of ICH patients were on combined antithrombotic regimen (on both anticoagulant and antiplatelet therapy), the significant majority (75.0%) suffering a lobar/cerebellar ICH (p=0.016).

A total of 191 ICH patients were known for chronic hypertension (89.7%), which was the most prevalent risk factor for both deep and lobar/cerebellar ICHs, with no significant between-group difference. On the other hand, 61.5% of ICH patients experienced hypertensive excess (systolic blood pressure >180 mmHg) at presentation, in a significantly higher rate in the deep compared to the lobar/cerebellar ICH group (71.2% vs. 48.9%, respectively, p=0.001).

Analyzing the risk factors with significant between-group difference (age, sex, antiplatelet use, combined antithrombotic treatment, and hypertensive excess at presentation) in a multivariable binary logistic regression model revealed advanced age (p=0.014; odds ratio (OR)=1.03) and antiplatelet use (p=0.043; OR=1.96) to be statistically significant independent predictors of a lobar/cerebellar ICH, and hypertensive excess to be a strong significant independent predictor of deep ICH (p=0.002; OR=0.39).

3. Case fatality of ICH patients

The 1-m case fatality of ICH patients was 33.8%, with no significant difference between deep and lobar/cerebellar ICH groups (**Table 3**). Significant determinants of 1-m case fatality in ICHs as a whole were age (75.3 y vs 65.4 y, p<0.001), current anticoagulant use (25.7 % vs 11.7%, p=0.010), and INR>1.4 (23.6 % vs 8.7 %, p=0.004) in univariable comparisons, with only advanced age (p=0.003; OR=1.04) and INR>1.4 (p=0.035; OR=2.51) proven to be independent predictors of case fatality in multivariable analysis.

4. Analysis of factors to predict CAA

The probable/definite CAA subgroup had the highest mean age at ICH presentation (75.9±2.3 y), significantly higher compared to non-probable CAA patients (65.6±1.1 y; p=0.002). This was associated with a significant female predominance in probable/definite CAA (62.5%) as opposed to the male predominance (64.5%) in the comparator (p=0.035).

Some 31.3% of probable/definite CAA cases had prior clinical event(s) of intracranial hemorrhage and exactly the same rate had prior TIA/TFNE, significantly higher than in the non-probable CAA group (6.8% (p=0.008) and 7.4% (p=0.010), respectively).

The ratio of patients on antiplatelet (56.3%) within the definite/probable CAA subgroup was remarkably higher compared to non-probable CAA patients (25.2% (p=0.009)).

Other factors and case fatality were not significantly different in the comparative analyses; of note, chronic hypertension was invariably prominent (**Table 4**).

Multivariable analysis of factors significant in the univariable comparative analyses revealed older age (p=0.012; OR=1.08), prior intracranial hemorrhage (p=0.005; OR=8.53), and antiplatelet use (p=0.042; OR=3.45) as independent significant predictors of definite/probable CAA diagnosis.

Table 4. Discriminators of spontaneous ICHs with regards to probable/definite CAA diagnosis

	Probable/definite CAA	Non-probable CAA	St/Chi^2	Multivariable logistic regression	
			p value	p value	OR (95%CI)
Patient number	16	152	–	–	
Age at event[a] (y)	**75.9±2.3**	**65.6±1.1**	**0.002**	**0.012**	**1.08 (1.02–1.15)**
Sex (male/all)	**37.5**	**64.5**	**0.035**	>0.05	–
Prior ischemic stroke	18.8	10.7	>0.05	–	–
Prior intracranial hemorrhage	**31.3**	**6.8**	**0.008**	**0.005**	**8.53 (1.94–37.58)**
Prior TIA (TFNE)	**31.3**	**7.4**	**0.010**	>0.05	–
Prior loss of consciousness	18.8	6.0	>0.05	–	–
Family history for any stroke	42.9	29.1	>0.05	–	–
Anticoagulant use	18.8	12.8	>0.05	–	–
INR>1.4	20.0	10.4	>0.05	–	–
Antiplatelet use[a]	**56.3**	**25.2**	**0.009**	**0.042**	**3.45 (1.05–11.38)**
Combined antithrombotic use	6.4	4.1	>0.05	–	–
Hypertensive excess	46.7	64.2	>0.05	–	–
Chronic hypertension	93.8	88.8	>0.05	–	–
Case fatality (1-m)	31.3	28.9	>0.05	–	–

CI, confidence interval; ICH, intracerebral hemorrhage; INR, international normalized ratio; m, month; OR, odds ratio; St/Chi^2, Student's t test (for Age at event) or Chi^2 test (for other variables); TIA, transient ischemic attack; TFNE, transient focal neurological episode; y, year.

[a] Indicates significant predictors in multivariable analyses. Bold font indicates variables with significant difference in univariable analyses.

Age is presented as mean±standard error of the mean. Other variables are presented as % prevalence within the columns.

Original publication in: [55].

5. Representative cases identified as probable CAA

Figures 4 presents 3 of the 14 cases identified as consistent with the diagnosis of probable CAA as per the Modified Boston criteria.

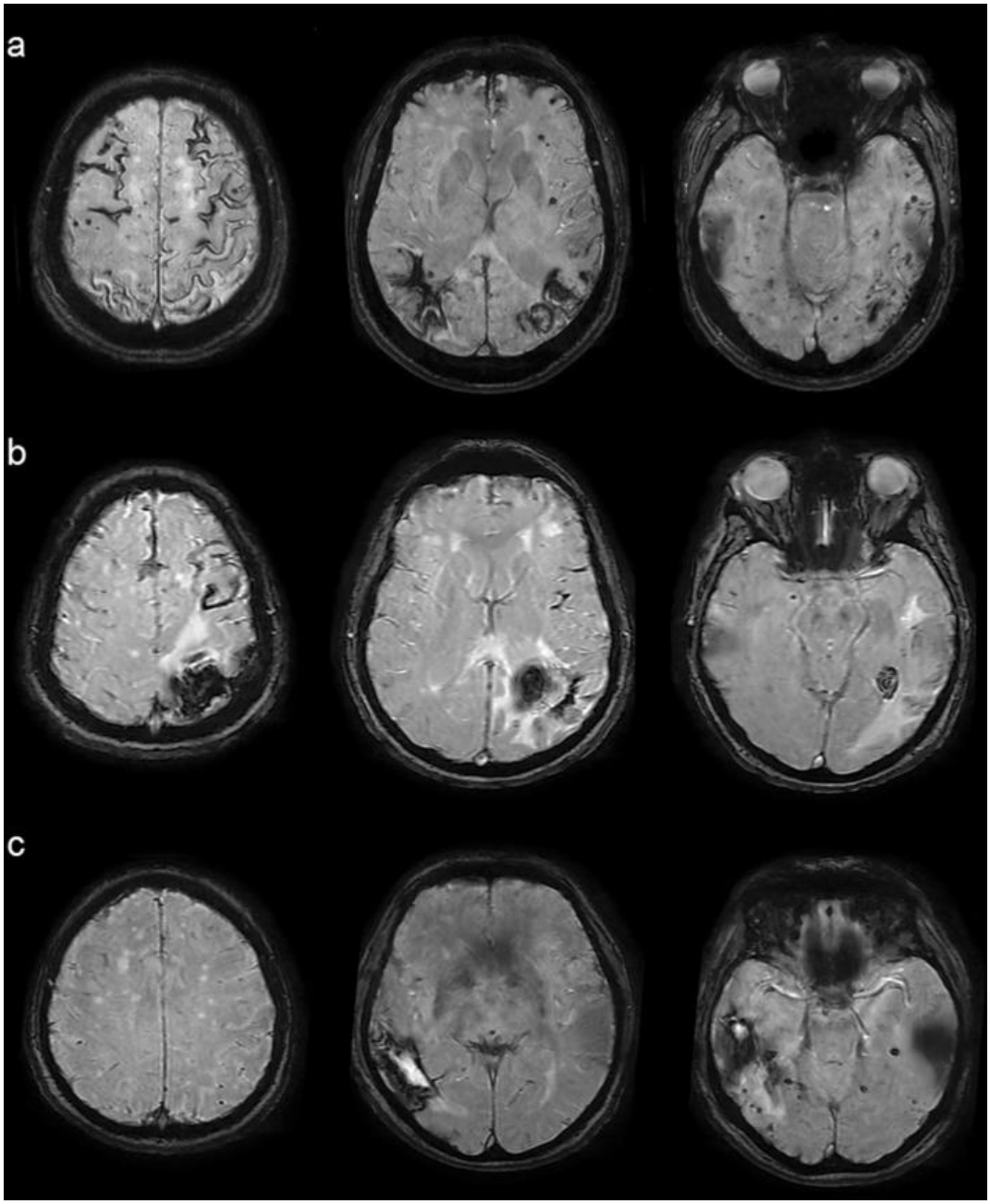

Figure 4. Representative axial MRI-SWI images of probable CAA patients at different parts of the spectrum. Diffuse CSS with multiple lobar CMBs and ICHs of different ages (A). Diffuse (but less extensive) CSS with a recurrent lobar ICH and a single CMB (B). No CSS but multiple lobar CMBs accompanying a recent lobar ICH (C). The deep structures (i.e., basal ganglia, thalamus, and brainstem) are consistently devoid of hemorrhagic pathology.
CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed, CSS, cortical superficial siderosis; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging.
Original publication in: [55].

B. Results of the CAA-RI study

1. The CAA-RI cases diagnosed in our center

Seven patients diagnosed with probable CAA-RI (2 with definite histopathological confirmation) in our center until the completion of our second study were included in the analysis. Their courses ranged from minimally symptomatic through keenly steroid-responsive to non-responsive, fatal cases. The clinical, radiological, and laboratory characteristics of the case series are summarized in **Table 5**. Four of them had already been identified as probable CAA in our first study, where they were enrolled due to their prior/concomitant lobar ICH; one of them already had clinical/pathological probable/definite CAA-RI diagnosis at the time of the first study (Case 1), 2 was retrospectively diagnosed with probable CAA-RI (in addition to probable CAA) by the first study (Cases 3 and 7), and 1 developed CAA-RI between the two studies (Case 4). The 2 cases with definite diagnosis are presented hereby as representative cases.

Case 1 – fulminant course with adverse response to steroids and multiple intracranial bleeds

A 65-year-old male patient presented in the Department of Neurology with a 3-m history of progressive behavior alterations, impairments in memory, speech, and certain movements, and depression. His history was relevant for TNFEs (considered as TIAs) some 24 and 0.5 y before. In addition, he had 2 episodes of loss of consciousness 12 and 7 y before presentation, with electroencephalograms (EEGs) showing no evidence of epileptic activity. Six years before presentation, he suffered a right parietal-occipital ICH (**Figure 5A**), with no residual symptoms after rehabilitation. He had mild controlled hypertension throughout. The family history was notable for fatal ICH in the mother.

On present admission, he presented with disorientation in time, right-sided hemianopsia and hemineglect, brisk and pathological reflexes bilaterally, bilateral lower limb-predominant cerebellar ataxia, acalculia, agraphia, alexia, paratonia, magnet sign, executive dysfunction, frontal gait, and anomic aphasia with fluctuating sensory involvement. In addition, the previously normally functioning patient showed severe dementia with a Mini-Mental State Examination (MMSE) score of 10/30.

Table 5. Summary of clinical, radiological, and laboratory characteristics of the presented case series of CAA-RI

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Level of diagnosis	Definite	Definite	Probable	Probable	Probable	Probable	Probable
Histopathological subtype	Perivascular	Transmural	-	-	-	-	-
Age at presentation	65	75	67	72	71	74	72
Sex	male	female	female	female	female	male	female
Headache	none	none	none	present	present	present	present
Focal sign	hemianopsia, ataxia, neglect, anomia, F and dominant P signs	hemiparesis, gait impairment, aphasia	1st: faciobrachial sensory TFNEs 2nd (2 y later): none	hemiparesis, aphasia	none	aphasia, agraphia, right arm paraesthesia/paresis	gait ataxia
Seizure	TC(s)	TC(s), NCSE	none	none	none	myoclonus	none
Altered mental state	RPD, behavioural change	RPD	2nd: cognitive, affective issues	RPD, hallucinations	memory issues	memory issues	memory issues
Asymmetric confluent WMH(s)	multiple, right>left	bilateral P-O, right>left	1st: left F 2nd: left I-T-P	left F, right P	bilateral O (migrating)	left P	right F, left O
Leptomeningeal enhancement	-	none	none	none	none	present	none
Sulcal non-nulling on FLAIR	none (only cSAH)	present	1st: none; 2nd: present	on follow-up	present	present	none
Lobar CMB(s)	multiple	multiple	multiple	few	multiple	few	multiple
Co-localising CMBs and WMHs	no	yes	no	no	yes	yes	yes
Lobar ICH(s)	6 y before; during CAA-RI	none	at 1st presentation*	11 and 3 y before; during CAA-RI	11 m before	12 m before	at onset*; 3.5 m later
CSF pleocytosis (/µl)	none (0)	none (3)	none (0)§	none (0)§	none (4)	none (3)	-
CSF elevated protein level (mg/dl)	present (58)	present (60)	none (35)§	none (32)§	present (51)	none (31)	-
Albumin quotient ($*10^{-3}$)	high (9.0)	high (13.4)	normal (2.8)§	high (11.5)§	high (7.3)	normal (5.0)	-
Link (IgG) index	normal (0.62)	normal (0.47)	high (0.85)§	normal (0.42)§	normal (0.49)	normal (0.42)	-
CSF OCB	none	none	Type-4§	Type-4§	Type-4	none	-
CSF amyloid-$\beta_{1\text{-}42}$ (pg/ml)	low (200)	low (227)	low (380)§	low (306)§	low (421)	low (356)	-
CSF total Tau (pg/ml)	high (512)	normal (502)	normal (213)§	high (2045)§	normal (267)	normal (218)	-
CSF pTau (pg/ml)	normal (22)	normal (54)	normal (51)§	normal (59)§	normal (57)	normal (37)	-
APOE genotype	-	ε4/ε4	ε3/ε4	ε2/ε3	ε3/ε3	ε3/ε4	-
Immunosuppressive therapy	500 mg mPSL i.v. for 8 days, oral taper	250 mg mPSL i.v. for 5 days	1st and 2nd: oral mPSL taper (weeks)	4x4 mg DXM i.v. for 13 days, oral mPSL taper	125 mg mPSL i.v. for 5 days, oral taper	500 mg mPSL i.v for 4 days, oral taper	none
Clinical improvement	none	none	1st: yes; 2nd: yes	yes (partial)	yes	yes	-
Radiological improvement	-	-	1st: yes; 2nd: yes	none	yes (partial)	yes (partial)	-
Mortality	died	died	alive	died	alive	alive	alive
Follow-up	1.5 m	0.5 m	72 m	2 m	5 m	3 m	4 y

CAA-RI, cerebral amyloid angiopathy-related inflammation; CMB, cerebral microbleed; cSAH, convexity subarachnoid hemorrhage; CSF, cerebrospinal fluid; DXM, dexamethasone; F, frontal; FLAIR, fluid-attenuated inversion recovery; I, insular; ICH, intracerebral hemorrhage; IgG, immunoglobulin G; i.v., intravenous; L, left; m, month(s); mPSL, methylprednisolone; NCSE, non-convulsive status epilepticus; O, occipital; OCB, oligoclonal bands; P, parietal; R, right; RPD, rapidly progressive dementia; T, temporal; TC, tonic-clonic seizure; TFNE, transient focal neurological episode; WMH, white matter hyperintensity; y, year(s); -, not available; *, not explaining all clinical symptoms; §, in remission.
Original publication in: [54].

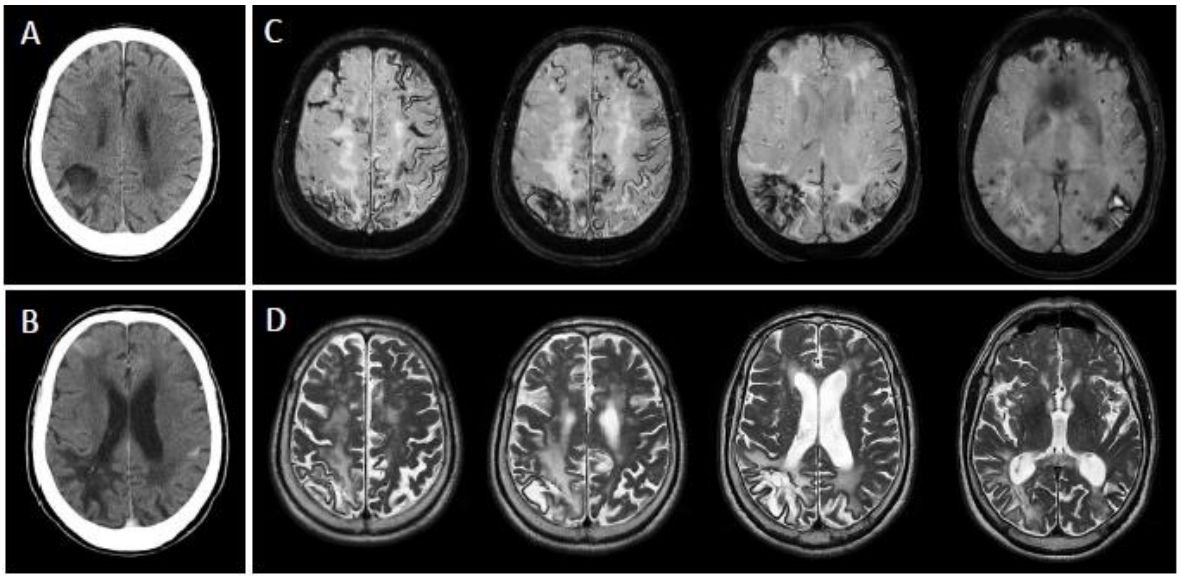

Figure 5. Imaging of Case1. Minimal surrounding hypodensity on cranial CT after regression of the first parietal ICH, 6 years before presentation (A). Extensive hypodensity surrounding the site of prior ICH with a right frontal and a left parietal cSAH (B). Multiple CMBs, with diffuse CSS, subacute cSAHs and ICHs on SWI (C). Asymmetric confluent WMHs reaching the immediate subcortex in each lobe of the right hemisphere and in the left frontal and occipital areas, with a subacute ICH, consistent with probable CAA-RI (D). Original publication in: [54].

A cranial CT 3 days before admission requested by an outpatient neurologists revealed a right frontal and a left parietal cSAH (**Figure 5B**), with normal angiogram. His antiplatelet was immediately stopped. The inpatient MRI SWI revealed abundant strictly-lobar CMBs accompanied by diffuse and extensive CSS, the cSAHs seen on CT, the old lobar ICH, and a small subacute left occipital ICH not present on the CT (**Figure 5C**); consistent with probable CAA. The T2/FLAIR sequences revealed asymmetric confluent WMHs predominating in the right hemisphere, reaching the immediate subcortex at multiple lobes (**Figure 5D**). A few foci of hyperintensity was observable on diffusion-weighted imaging (DWI) bilaterally. The analysis of CSF revealed normal cell count with elevated protein level (58 mg/dl) and elevated albumin ratio. Probable CAA-RI was diagnosed as per the Chung criteria (at that time) and intravenous methylprednisolone was initiated (500 mg daily for 8 days). No improvement was observed at the end of infusions (MMSE 9/30), but episodes of nighttime agitation developed, responding to antipsychotics and benzodiazepine. Two weeks after admission, the patient was discharged home in a stable (unimproved) condition on tapering doses of oral corticosteroids with a close follow-up scheduled. Seven days later, he was transported to the emergency room (ER) in a delirious state, with novel bifrontal cSAHs on CT. The patient was referred and admitted to the Department of Psychiatry, where corticosteroid therapy was rapidly de-escalated, assuming steroid psychosis. Within the next 2 weeks, the patient suffered 2 episodes of loss of consciousness (the second with convulsion), and levetiracetam was initiated. This

period associated with further rapid dementia, resulting in a bedridden state. Meanwhile, he developed septicemia due to urinary infection followed by pneumonia, a left-sided common femoral artery thrombosis, and eventually a massive melena due to a Forest I/B ulcer, successfully treated by gastroscopy. The patient was admitted to the Gastroenterology in a soporous state, received blood transfusion for moderate anemia, but passed away 3 days later, 2 m after presenting in our Department.

Neuropathology revealed severe CAA (modified Vonsattel grade 4 [56]), with prominent immunoreactivity to Aβ (more to $A\beta_{1-40}$ than $A\beta_{1-42}$). Only small amount of diffuse Aβ plaques were detected, without any Tau pathology (AT8), excluding concomitant AD. Completely occluded CAA vessels were surrounded by microinfarcts. In addition, numerous CAA vessels demonstrated marked perivascular lymphomonocytic infiltration, without evidence of transmural involvement, in keeping with *perivascular CAA-RI* (**Figure 6**).

Retrospective analysis of CSF core AD biomarkers revealed dramatically depleted $A\beta_{1-42}$ levels (200 pg/ml), with elevated total Tau (519 pg/ml) and normal pTau levels (33 pg/ml), reflecting Aβ deposition and neuronal loss without evident NFT pathology, corresponding to the neuropathological findings. *Post mortem* genotyping for *APOE* was unsuccessful.

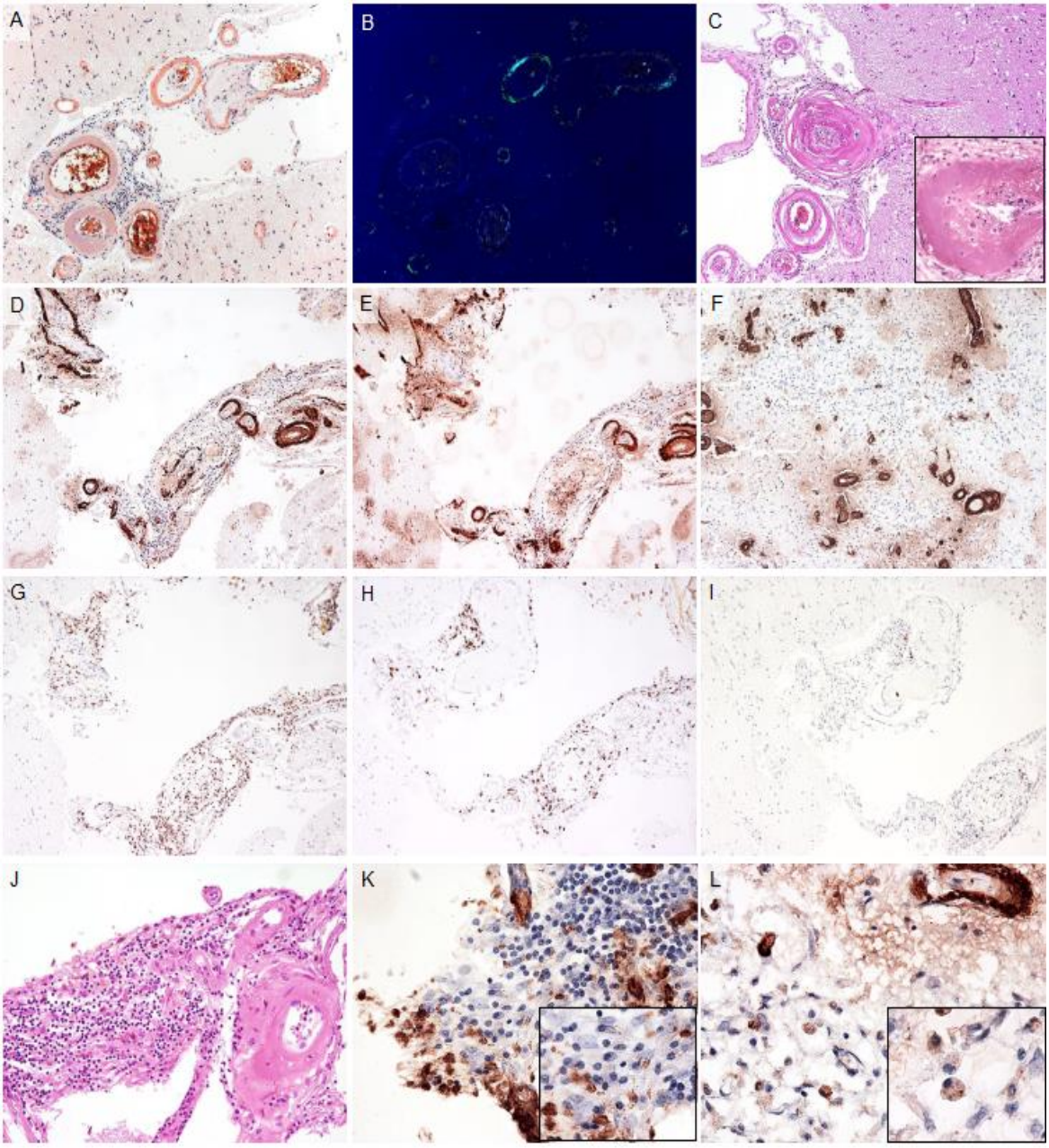

Figure 6. Neuropathological findings of Case 1. Prominent congophilic angiopathy (Congo Red, A) with apple-green birefringence under the polarized microscope (B). Changes consistent with modified Vonsattel grade 4 with double-barreling, wall fragmentation (Hematoxylin-Eosin (HE), C), perivascular eryrthrocytes, and fibrinoid necrosis (inlet of C). Prominent immunoreactivity against $A\beta_{1\text{-}40}$ (F) and less against $A\beta_{1\text{-}42}$ (E). Microinfarct around occluded CAA vessels and prominent capillary CAA (i.e., Type 1; Aβ, F). The perivascular infiltrates apparent through A-K contain several T lymphocytes (CD3, G), including cytotoxic T cells (CD8, H), and a few B cells (CD20, I). Macrophages are abundant in the infiltrate (HE, J), frequently with Aβ-immunopositive cytoplasm (Aβ, K), and in the microinfarcts (Aβ, J). Original publication in: [54].

Case 2 – rapid cognitive decline with intractable epilepsy

A 75-year-old female patient presented to the ER after a loss of consciousness while sitting, preceded by a few seconds of right-sided hemiparesis without convulsive signs. Her history was remarkable for mild cognitive impairment started some 8 y before. Cranial CT 7 y before noted mild biparietal periventricular WMHs (**Figure 7A**). MMSE was 26/30 that time and nootropics were prescribed by psychiatrists. Some 2 y later, she had a 3-day episode of global amnesia and a slight progression to MMSE 24/30; donepezil was initiated. The family described a stable cognitive state afterwards until the loss of consciousness, though the course became complicated by night-time awake state in the last year, with occasional episodes of aggressive and impulsive behavior.

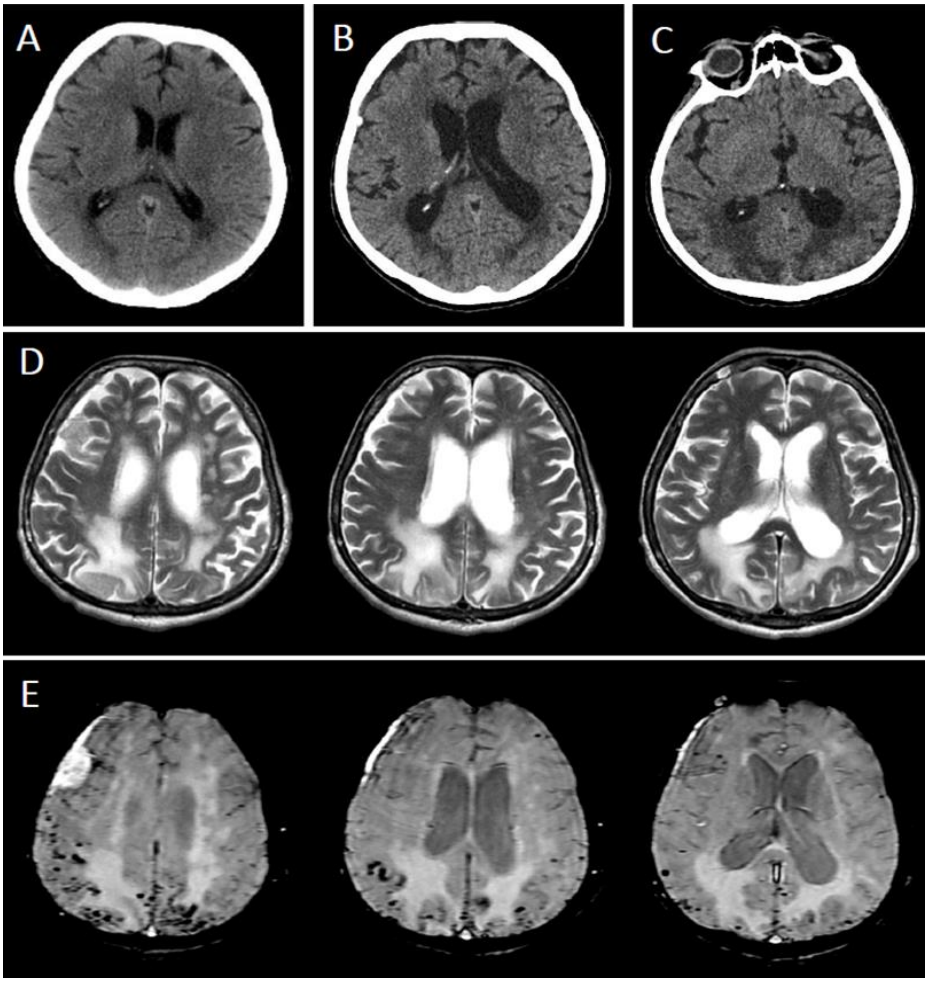

Figure 7. Imaging of Case 2. Minor bioccipital periventricular lucencies 7 years before presentation (A). Increased atrophy and moderate increase in bioccipital WMHs at first seizure (B). Dramatic expansion of the occipital-parietal WMHs with right-sided predominance 2.5 months later (C). MRI T2 demonstrates asymmetric confluent WMHs with focal cortical involvement (D) and associated CMBs and CSSs on SWI (E). Right frontal meningeoma with dural tail is apparent. Original publication in: [54].

In the ER, she was disoriented, she complained of subjective right lower limb weakness, with no other focalities observed. Cranial CT noted a moderate increase in the biparietal lesions, a notable progression in medial temporal lobe atrophy bilaterally, and a right frontal meningioma previously unnoticed, with increased size (**Figure 7B**). The EEG demonstrated bifrontal-temporal slowing and a few singular spike-and-slow waves predominantly in the right temporal-occipital area. Antiepileptic was initiated, with no further inpatient work-up upon the family's request due to increased in-hospital agitation requiring antipsychotics.

After discharge, her speech and cognition rapidly deteriorated to no meaningful speech and later to no comprehension within a few weeks, followed by progressively impaired gait, frequent falls, and eventually a tonic-clonic seizure 2.5 m after the first episode. Repeat cranial CT demonstrated a remarkable increase in the WMHs with right occipital-parietal predominance, focal cortical involvement, and sulcal effacement, indicative of edema (**Figure 7C**). The patient was somnolent, bedridden, incooperative, with sensorimotor aphasia and bilateral Babinski reflex. Parenteral valproic acid resulted in transient improvement in consciousness/cognition. On the 3rd in-hospital day, her consciousness deteriorated and the EEG was compatible with non-convulsive status epilepticus. Antiepileptics were expanded to full-dose tetra-therapy, again with only temporary improvements. The routine CSF was notable only for slightly elevated protein level (60 mg/dL) and elevated albumin quotient. Re-evaluating the CT, 3 CMB-like hyperdensities were noted, and based on these, the course, and the novel edema, a contrasted cranial MRI was performed specifically addressing and supporting probable CAA-RI, with asymmetric confluent WMHs and correlating CMBs (**Figure 7D-E**). Few foci of SNN not attributable to sulcal effacement could also be appreciated, without LE. An extensive screening for autoimmune/infective etiologies was initiated, and intravenous methylprednisolone was given (250 mg/day for 5 days). Repeat EEG demonstrated semiperiodic generalized sharp wave complexes throughout the recording, reminiscent of Creutzfeldt-Jakob disease (CJD; the MRI and the clinical picture was not supportive). Her consciousness never returned and a decision of comfort measures only was made together with the family. She died at the 15th hospital day. The genotype is *APOE* ε4/ε4. Biomarkers yielded dramatically decreased CSF $A\beta_{1-42}$ (227 pg/ml) levels, with Tau (502 pg/ml) and pTau (54 pg/ml) levels within normal range, in favor of Aβ deposition and against CJD [57].

Neuropathology demonstrated massive CAA, affecting arterioles (modified Vonsattel grade 4), venules, and capillaries, with numerous Aβ plaques (**Figure 8**).

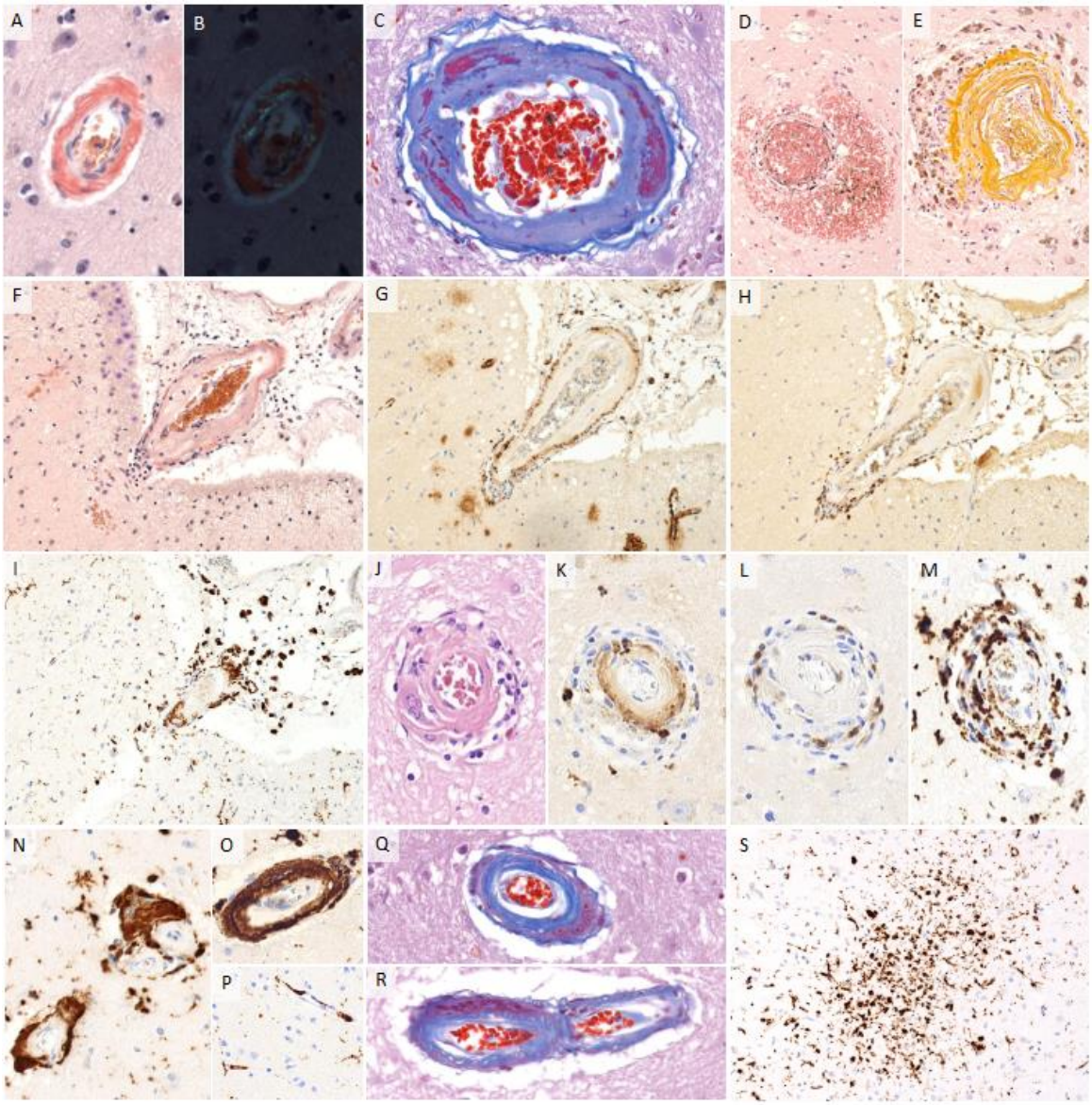

Figure 8. Neuropathological findings of Case 2. Congophilic angiopathy (Congo red, A) with apple-green birefringence under the polarized microscope (B). Severe vasculopathy (modified Vonsattel grade 4) with double-barreling, fibrinoid necrosis (Crossmon's modified Mallory's trichrome (CMT), C), paravascular erythrocytes (forming a CMB) with hemisoderin (Hematoxylin-Eozin (HE), D) and a spectacular perivascular hematoidin-deposition with hemosiderin-laden macrophages (HE, E). Type 1 CAA and a perforating arteriole with disproportionately thin vascular Aβ positivity, Aβ-immunoreactive macrophages, sparse perivascular mononuclear infiltration (Congo red, F; Aβ, G) comprizing a few T lymphocytes (CD3, H), and abundant macrophages/microglia within and around the vessel wall (CD68, I). Perivascular and transmural granulomatous infiltration with mononuclear cells and multinucleated giant cells (MNGCs, HE, J) involving an arteriole again with pale mural Aβ positivity with amyloid-containing macrophages (Aβ, K), scattered lympocytes (CD3, L), and abundant intramural and perivascular microglia/macrophages (CD68, M). MNGCs often seemingly replace the complete vessel wall (CD68, N, O) and are also apparent in CMT staining (Q, R). CD68 immunopositivity occasionally affects capillaries and small venules (P). Microglial nodules/clusters in the cortex (CD68, O). Original publication in: [54].

At the lesion sites, in addition to some CAA vessels with predominantly perivascular infiltrates, immunostaining for CD68 revealed abundant transmural macrophage/microglial infiltration of several meningeal and parenchymal CAA vessels, frequently with intramural MNGCs, consistent with *ABRA (i.e., transmural CAA-RI,* **Figure 8***)*. Immunopositivity of Aβ was disproportionately mild in severely inflamed vessels, suggesting effective phagocytosis. Indeed, macrophages/microglia with intracytoplasmic Aβ were common in the infiltrates and the parenchyma. Occasional CD68-positive large microglial nodules/clusters were observed in the cortex, similar to those reported in a pivotal study [41]. The NFT pathology corresponded to Braak stage IV. There was a lack of spongiform change in the cortex, basal ganglia, or cerebellum to suggest associated prion disease.

2. Nomenclature analysis of the literature in definite CAA-RI

The nomenclature of definite CAA-RI varied substantially. The Chung [42] and the Auriel [45] criteria used the umbrella term CAA-RI to cover cases with perivascular-only and transmural inflammation, similarly to the largest case series [37]. Some authors differentiate two types of CAA-RI using the terms vasculitic (transmural) as opposed to perivasculitic, non-vasculitic, or non-destructive [53, 58-60]. Many others use different nomenclatures, either using 'inflammatory CAA' or similar terms to cover the two subtypes distinguished as ABRA (for transmural) and CAA-RI (for perivascular) [43, 57, 61, 62], or using CAA-RI to cover the ABRA (for transmural) and inflammatory CAA (for perivascular) [40, 63-66]. Others use 'tumefactive CAA' referring to cases with extensive asymmetric confluent WMH(s) mimicking neoplasm(s) [67, 68]. Though each approach has its rationale (e.g., the clinical definition paper included only perivascular cases using the term *'syndrome of CAA-related perivascular inflammation'* [44]), we use the term CAA-RI to cover the clinical-pathological entity and refer to the pathological subtypes with terms directly reflecting their nature.

3. Epidemiologic analysis of the literature in definite CAA-RI

Including our 2 cases, our analysis detected 205 definite CAA-RI cases for descriptive analysis, 200 including a report of the conditions of obtaining the histopathological specimen. Of these, 87.0% were diagnosed with biopsy and 13.0% at autopsy, 4.0% had both. (2 autopsy-confirmed cases with biopsy disclosing only CAA, and 6 biopsy-confirmed cases with autopsy detecting various amounts of CAA-RI, from none to severe). The mean age at diagnosis was 67.2±0.6 y (ranging from 43-92 y), without sex preference (51.7% males). These contrast with

CAA-related ICH, where the mean age of presentation is some 10 y higher and female predominance is well-documented, as demonstrated by our first study as well [44, 55]. Male definite CAA-RI patients were younger than females (65.1±1.0 y vs. 68.5±1.0 y; p=0.017). No other baseline variables associated with age.

4. Neuropathology of definite CAA-RI cases in the literature analysis

Some 71.7% of definite CAA-RI cases with sufficient data (132/184) had transmural inflammation (ABRA), the remaining 28.3% being consistent with perivascular CAA-RI, resembling the finding of a case series [43]. Transmural and perivascular-only involvement of vessels are frequently reported to co-occur in patients [42, 69-74] (as seen also in our Case 2), suggesting that these might represent a spectrum. In addition, CAA-RI in one report was found to be perivascular by biopsy and transmural at autopsy [75], implicating the potential role of sample size in the classification. Our presented perivascular CAA-RI case (Case 1) is one of the 7 similar cases published with autopsy confirmation [76-79]. The predictor analysis revealed a single variable to associate with histology; specifically, the co-localization of CMBs with confluent WMHs were more common in ABRA (87.0%) than in perivascular CAA-RI (52.6%; p=0.020) implicating the pathogenic role of angiodestructive inflammation in the development of hemorrhagic alterations.

Among the 138 cases where cellular components were described or well presented, lymphocytes were almost unequivocally demonstrated (97.1%), macrophages/histiocytes (72.5%) and MNGCs (69.6%) were frequent, whereas eosinophil granulocytes were seldom reported (8.0%; almost exclusively in ABRA (9/11) with MNGCs (10/11)). Aβ phagocytosis was described in 36.2%, including our 2 definite CAA-RI cases, involving MNGCs in 74.0%, macrophages/histiocytes in 48.0%, and microglia in 20.0% of them. The reports are somewhat discordant regarding the association of infiltrates with CAA, with most authors reporting only CAA-affected vessels to be associated with inflammation [41, 44, 80, 81], whereas others describe (seemingly) non-CAA vessels to be involved as well [69, 71, 78], in a case with exclusive association in biopsy and near-absolute dissociation at autopsy [82]. Some authors propose efficient immunological clearance of Aβ to underlie these observations [82]. The observation in an ABRA case that vascular Aβ deposition decreased by the increasing severity of inflammation supports this concept [83], our related observation in Case 2.

Regarding concomitant AD pathology, Aβ plaques and NFTs were described in 81.3% and 48.3% of cases where addressed, frequently described as mild, especially regarding NFTs.

This may be attributable to the relatively younger age of patients being early in their AD continuum if at all, and/or to excessive immune-mediated Aβ clearance mechanisms, based on the lower Aβ plaque burden observed in ABRA compared to age-matched non-inflammatory CAA [81].

Changes corresponding to WMHs comprise tissue rarefaction, myelin pallor, spongy vacuolation, and astrogliosis [41, 79, 84]. Considering the localization of diagnostic pathology, many authors emphasise that biopsy should be targeted at the leptomeninx with cortex to rule in CAA/CAA-RI, whereas sampling from the WM can only rule out infiltrative neoplasm [85]. Reports with isolated WM samples resulting in non-diagnostic histology are common [48, 60, 68].

5. Clinical and radiological presentation of definite CAA-RI

Regarding core clinical signs, the prevalence of headache, focal neurological sign(s), seizure(s), and altered higher mental state were 39.3%, 58.1%, 42.9%, and 77.6%, respectively. Of the 170 definite cases with sufficient data, 98.2% met the clinical part of the present criteria. Two cases had symptoms compatible with their concomitant ICH [39, 77], whereas 1 case was a definite CJD with ABRA [86], where CJD can be interpreted *per se* as morphological substrate of the symptoms and the clinicopathological relevance of CAA-RI could not be clarified.

Regarding core radiological features, 76.6% (111/145) of analyzable cases had asymmetric confluent WMHs and 82.3% (94/113) had lobar CMBs. Some 7.4% (14/188) had lobar ICH at onset (exactly as in a single-center report [85]; however, this rate was 33.7% (28/83) when extended to ‘at or within 1 y after onset’, suggesting that the previously proposed difference between CAA-RI and non-inflammatory CAA regarding their association with ICH might be a matter of shorter disease duration and younger age in CAA-RI [43, 85]. Of cases with sufficient data, 67.3% (68/101) met the present radiological criteria of probable CAA-RI. Patients not meeting the radiological part included patients with no WMHs (13.9%), patchy WMHs (12.9%), symmetric confluent lesions (2.0%), no lobar hemorrhagic lesions (7.9%) and with deep CMB(s)/ICH(s) (not meeting probable CAA [87], 3.0%), often in combination. In patients with sufficient clinical and radiological data for decision-making, this yielded a 65.7% (67/102) sensitivity of the present criteria for probable CAA-RI to diagnose definite CAA-RI. Among cases with unequivocal written implications or sufficient visual presentation, confluent

WMHs co-localized with CMBs in 66.7%. The appearance of CMBs/CSSs was in some cases preceded by the symptomatic/radiological onset of CAA-RI [88, 89].

Regarding additional radiological features not part of the present criteria, 61.7% (79/128) of cases with contrasted MRI demonstrated enhancement (48.4% leptomeningeal, 5.5% parenchymal, 5.5% both, 0.8% with deep perivenular enhancement, and 1.6% with equivocal pattern. Notably, LE was present in 20 cases with isolated leptomeningeal involvement (i.e., with no or patchy WMHs only; 18.7% of those addressed). In a subgroup with subject-wise available data on WMH, hemorrhagic, and enhancement profiles, adding *LE* to the criteria as an alternative (AND/OR) to *asymmetric confluent WMH(s)* (still in the presence of appropriate hemorrhagic profile) increased the sensitivity from 71.4% to 82.5% (45/63 vs. 52/63, p=0.008). Notably, a similar set of criteria was used by Piazza *et al.* to establish probable CAA-RI in their study [90]. Though the present approach did not allow the estimation of specificity, the previous finding of a 92.6% specificity for LE to distinguish between CAA-RI and non-inflammatory CAA in a single-center study is supportive [85].

Based on a prior observation that SNN (a.k.a. sulcal non-attenuation, hypoattenuation, hyperintensity, or effusion) on FLAIR can co-localize with LE [85] and that it is an established component of ARIA-E [47], we analyzed 70 definite CAA-RI cases with FLAIR image(s) of sufficient quality published and additional 2 where SNN was recognizably described. We found that SNN not only co-occurred with an isolated LE (with no or patchy WMHs only) in 100.0% (7/7), but it was in fact present in 80.8% of definite CAA-RI cases with LE regardless of the presence/pattern of WMH (21/26). Moreover, SNN was detectable in 50.0% (12/24) of definite CAA-RI cases without LE (rendering the association between LE and SNN significant; p=0.022) and in 45.5% (10/22) of cases without enhancement-related information. These yield a 59.7% overall prevalence of SNN within definite CAA-RI cases with sufficient data. Notably, in 13.9%, SNN was the predominant ('isolated') FLAIR alteration at presentation (i.e., with no (5.6%) or patchy WMHs only (8.3%)). In certain cases, the evolution of isolated SNN (with no [53] or minimal patchy WMHs [91, 92] into confluent WMHs was observed on disease progression/recurrence, suggesting that SNN might be an early manifestation of CAA-RI. The subgroup analyses revealed that adding *SNN on FLAIR* to the criteria as an alternative (AND/OR) to *asymmetric confluent WMH(s)* (still with appropriate hemorrhagic profile) increased the sensitivity of from 72.2% to 81.5% (39/54 vs. 44/54; p=0.031). Furthermore, adding *LE and/or SNN* as an alternative to *asymmetric confluent WMH(s)* increased the sensitivity of the present criteria from 70.0% to 82.5% (28/40 vs. 33/40, p=0.031).

Vasculitic angiographic profile of large vessels (beading, concentric narrowing) were found in 6.6% (4/61) of cases where addressed, refuting its diagnostic value.

6. Laboratory biomarkers in definite CAA-RI

Lumbar puncture was reported in 63.4% (130/205). The prevalence of CSF pleocytosis and elevated total protein concentration were 44.2% and 79.8%, respectively, with 82.8% being pathological in at least one. Lymphocytes predominated, except in 1 report with granulocytic predominance [53]. Eosinophils were exceptionally reported, all in ABRA, with eosinophils consistently present also in their histology [69, 93, 94] (being a significant component in 1 [69]). Of clinical interest, CSF pleocytosis and either CSF pleocytosis/elevated protein concentration were significantly associated with headache (CSF pleocytosis in 56.8% and 34.6% of those with and without headache, respectively, p=0.029; either alteration in 93.2% and 73.1%, respectively, p=0.014), implicating the role of focal meningitis underlying the headache. In addition, CSF pleocytosis tended to be associated with LE (53.8% in those with LE vs. 32.0% in those without; p=0.087). Notably, elevated CSF protein contentration was decreased to immunosuppression in 80.0% (8/10) [53, 69, 78, 89, 91, 94-96], whereas it increased upon disease progression [42, 97-100] or relapse [91, 101, 102]. The CSF white blood cell count changed in parallel with protein levels in most reports [42, 69, 89, 94-97, 102], with few exceptions [91, 99-101], decreasing to immunosuppression in 87.5% of cases (7/8). However, therapy-associated improvement in pleocytosis and elevted protein content was accompanied by clinical improvement only in 50% (3/6) [91, 94, 96] and 71.4% (5/7) [53, 78, 91, 94, 96] of the cases, respectively. On larger grounds, CSF pleocytosis and elevated protein levels followed the clinical course (improvement/deterioration) in 45.5% and 85.7%, suggesting a role for elevated protein concentration as a surrogate biomarker of clinical change.

Oligoclonal bands of immunoglobulin in the CSF were reported in 16.0% of cases where addressed (4/25).

Surprisingly, AD core CSF biomarker profile [23] was addressed in 10 definite cases (only 7 reporting on all 3 proteins [90, 96, 103-105], including our 2 cases, being the first autopsy-confirmed definite CAA-RI cases reporting on any CSF AD biomarker). The findings showed decreased $A\beta_{1-42}$ in 80.0% (8/10), increased total Tau in 33.3% (3/9), and increased pTau in 28.6% (2/7). This is comparable to that seen in probable CAA-RI (91.7% (22/24); 23.5% (4/17); and 23.1% (3/13), respectively). This pattern aligns with reports on concomitant AD pathology on histology; indeed, pTau was elevated only in the 2 cases where significant

NFT pathology was noted [96, 105]. Notably, CSF $A\beta_{1-42}$ was reported to change during the course in a case, being normal in acute phase and pathologically low on spontaneous remission, with similar trends for Tau, pTau, and $A\beta_{1-40}$ and similar therapy-related/spontaneous patterns in probable cases [90]. However, therapy-associated changes in CSF $A\beta_{1-42}$ or $A\beta_{1-40}$ were not consistently found [48, 53].

Of pathogenic relevance, CSF levels of anti-Aβ autoantibodies were found increased in definite CAA-RI cases during an acute phase compared to spontaneous [90] or corticosteroid-induced remission [53, 90, 96] or compared to non-CAA-RI [90, 96]. Consistent with an antibody-mediated process, a study found an increased number of memory B cells directed against anti-$A\beta_{1-42}$ in the blood of an ABRA patient [106]. Notably, however, a recent study analysing definite/probable CAA-RI patients together found no difference in anti-Aβ antibody titres before and after immunosuppression [107].

The *APOE* ε genotype, an established risk factor for AD and a possible risk factor for CAA or CAA-related ICH [13], was reported in 28 definite CAA-RI cases. At least 1 *APOE* ε4 allele was carried by 60.7%, which is remarkably high compared to control populations, but comparable to that in AD and CAA as a whole [44, 108-111]. However, a striking 53.6% of cases were *APOE* ε4/ε4 homozygotes (including our Case 2), suggesting that ε4/ε4 homozygosity represents a strong predisposition to CAA-RI. Notably, the carrier rate for *APOE* ε2 was also high (32.1%), higher than in most studies with CAA [13, 110-113] yielding a total prevalence of 85.7% of non-ApoEε3/ε3 genotypes, an extreme high rate compared to that in control population or in CAA *per se* [13, 92, 110]. These suggest that both non-'normal' ApoEε alleles may predispose to inflammatory changes in CAA.

7. Analysis of therapy, responsiveness, dosing, and course of definite CAA-RI cases

A total of 152 definite CAA-RI cases were eligible for the analysis of treatment, 149 with unequivocal data on the type of immunosuppression. Some 91.4% received some form of therapy, 3.9% were treated only with surgical resection/lobectomy and 87.5% with immunosuppression (including 2.6% with additional surgical intervention (resection/lobectomy or shunting)). Among the immunosuppressed with sufficient data, 99.2% received corticosteroids, 56.2% as monotherapy and 43.1% where it was combined/replaced with other immunosuppressant(s), whereas only 1 patient (0.8%) received cyclophosphamide monotherapy (no other drugs were used as monotherapy). The combinations predominantly included cyclophosphamide (78.6% of all combinations), whereas other immunosuppressants

were rare (mycophenolate mofetil and azathioprine in 16.1% and 16.1%, methotrexate in 3.6%, and rituximab, intravenous immunoglobulin, and plasma exchange in 1.8%, 1.8%, and 1.8% of combinations). Among combinations (i.e., corticosteroid plus or replaced with another), 75.0% received the additional immunosuppressant at first intention and not after progression/relapse. For comparison, all treated probable CAA-RI cases received corticosteroids, almost exclusively as monotherapy (91.7%), with 7 combined-treatment cases altogether (57.1% with cyclophosphamide, 28.6% with mycophenolate, 14.3% with azathioprine, and 14.3% with intravenous immunoglobulin), with only 3 at first intention.

Due to the influential disproportion of surgery between immunosuppressed (3.0%) and not immunosuppressed (31.6%) definite cases, further analyses were performed excluding surgical cases.

Definite CAA-RI patients not receiving immunosuppression were older than the treated (72.3±2.8 y vs. 66.2±0.8 y; p=0.031), suggesting a decision bias based on age and possibly concomitant diseases. Note that untreated patients were exclusively ABRA (vs. 67.3% in the treated; p=0.018), which should be kept in mind when extrapolating findings on spontaneous outcomes to CAA-RI altogether. No other baseline difference was found between the treated and untreated (not shown).

Among immunosuppressed definite CAA-RI cases, 78.8% showed clinically meaningful improvement and radiological improvement was observable in 89.7%. The clinical and radiological responses were concordant in 92.5%. Though being significantly lower than the treatment effect, the spontaneous clinical remission rate was considerably high at this relatively low untreated subject number (30.8% (4/13); p=0.0007 vs. treated (**Table 6**). The spontaneous radiological remission rate was even more marked (57.1% (4/7); p=0.042 vs. treated). The predictor analysis identified LE as a predictor of clinical improvement in the total cohort (present in 66.2% of the improved vs. 16.7% of the not improved; p=0.003), both wihin treated (p=0.027) and untreated (p=0.029) patients. CSF pleocytosis at presentation was associated with a decreased likelihood of clinical improvement in the total cohort (present in 65.0% of the not improved vs. 39.1% of the improved; p=0.042), with a trend within the treated (p=0.066). No other baseline variables showed association with improvement (not shown).

Table 6. Predicted outcomes of immunosuppressive treatment in definite CAA-RI cases

Predicted outcomes	Treated with immunosuppression	Non-treated with immunosuppression	Subject # per group	p value Chi^2
Clinical improvement	**78.8**	**30.8**	**118 vs 13**	***0.0007***
Radiological improvement	**89.7**	**57.1**	**87 vs 7**	***0.042***
Positive outcome at 6 m	**61.0**	**25.0**	**82 vs 12**	***0.028***
Positive outcome at 1 y	50.0	18.2	68 vs 11	*0.058*
Mortality at 6 m	16.7	38.5	84 vs 13	*0.065*
Mortality at 1 y	25.4	60.0	67 vs 10	*0.057*
Future lobar ICH within 6 m	8.3	22.2	72 vs 9	*0.216*
Future lobar ICH within 1 y	11.8	42.9	51 vs 7	*0.067*

ICH, intracerebral hemorrhage; m, months; y, year; #, number.
Variables are presented as % prevalence within column. Bold font indicates significant difference.
Original publication in: [54].

The prevalence of symptomatic relapse (not related to ICH) of patients who improved to initial immunosuppression and had sufficient follow-up periods was 41.7% within 1 y and 25.9% within 6 m. This generally resulted in repeated therapy, dose escalation, switch, or combination, leading to improvement in 83.3%.

The rate of positive outcome at 6 m after initiating immunosuppression was 61.0%, significantly higher than in spontaneous improvers at 6 m after admission (25.0%; p=0.028, **Table 6**). This missed significance at 1 y (p=0.058), though with less subjects. LE was associated with positive outcomes at 6 m (present in 64.9% vs. 20.0% in those with positive and negative outcome, respectively, p=0.005) and 1 y (76.2% vs 25.0%; p=0.003) in the total cohort and among the immunosuppressed patients (61.8% vs. 25.0%, p=0.044 at 6 m; 73.7% vs. 30.8, p=0.029 at 1 y). CSF pleocytosis at presentation was significantly associated with adverse outcome at 6 m in the total cohort (present in 28.6 vs. 60.9% of those with positive and negative outcome, respectively; p=0.015) and in the treated (29.4% vs. 60.0%; p=0.027), with trends at 1 y. Lobar ICH(s) presenting within 6 m was associated with adverse outcomes at 6 m in the total cohort (occurring in 2.0% vs. 16.1% in those with positive and negative outcomes, respectively, p=0.027) and among the treated (2.1% vs. 18.2%, p=0.031), with a similar association for lobar ICH within 1 y with adverse outcome at 1 y in the total cohort (2.9% vs. 20.7%; p=0.042) and a trend in the treated (3.1% vs. 19.0%; p=0.074). Among those who improved, relapse within 6 m and 1 y were associated with adverse outcomes at corresponding time points in the total cohort (occurring in 15.1% vs. 80.0% on those with positive and negative outcome at 6 m, respectively; p=0.005; and in 22.2% vs. 83.3% at 1 y; p=0.007) and within the treated (16.0% vs. 80.0% at 6 m, p=0.006; 23.5% vs. 83.3% at 1 y; p=0.010). No other variables showed associations with positive outcomes (not shown).

Regarding all-cause mortality, 16.7% and 25.4% of immunosuppressed definite cases died within 6 m and 1 y, respectively, trending to be less than those not receiving

immunosuppression (38.5% (p=0.065) within 6 m and 60% (p=0.057) within 1 y, **Table 6**). Advanced age at presentation was associated with higher all-cause 6-m (p=0.043) and 1-y mortality (p=0.024) in the total cohort, but not in the subgroups, but lost significance in analyses censored for unrelated causes of death. Neither age nor immunosuppression significantly influenced all-cause mortality at any point in logistic regression models controlling for both (not shown). LE was associated with lower rates of censored mortality at 1 y (70% in survivors vs. 25% in the deceased; p=0.039) in the total cohort. No other baseline variables predicted censored mortality. However, lobar ICH(s) presenting in the corresponding periods was associated with an increased likelihood of censored mortality within 6 m (total cohort: 2.7% vs. 38.5% incidence in survivors vs. the deceased, respectively, p=0.0006; treated: 1.5% vs. 50.0%, p=0.0003) and 1 y (total cohort: 2.0% vs. 37.5%, p=0.0005; treated: 2.2% vs. 40.0%, p=0.003).

Regarding predictors of future lobar ICH(s), while immunosuppression itself tended to influence the occurrence of ICH(s) within 1 y (occurring in 11.8% of the treated vs. 42.9% of the untreated, p=0.067), clinical improvement (spontaneous and/or treatment-related) significantly decreased their incidence within 1 y in the total cohort (7.3% vs. 33.3%, p=0.026), with a trend in the treated (5.3% vs. 27.3%, p=0.068). This association at 6 m was a trend in the total cohort (5.1% vs. 21.1%, p=0.056) and in the treated (3.6% vs. 21.4%, p=0.053).

Analysis of treatment regimens in definite cases with sufficient information revealed that among patients treated exclusively by corticosteroids until evaluation, low-dose therapy (applied in 50.0% as first therapy, defined arbitrarily as <1.5 g methylprednisolone or dose-equivalent within the first 3 days) was non-inferior to high-dose therapy regarding clinical improvement (81.8% vs. 82.7%), positive outcome (66.7% vs. 64.3% at 6 m; 58.3% vs. 33.3% 1 y), all-cause mortality (26.7% vs. 16.7% at 6 m; 33.3% vs. 37.5% at 1 y), and relapse (43.8% vs. 18.2% at 6 m; 53.8% vs. 42.9%; all without signficance). Future lobar ICH occurred exclusively in the low-dose group, but the low subject numbers with follow-up precluded statistical significance. Similarly, no significant difference was observed between patients treated with corticosteroids only and those with combination at first intention regarding clinical improvement, and 6-m or 1-y outcome (not shown). All-cause mortality, future lobar ICH, and relapse showed trends to less frequently occur in the combination group, similarly underpowered. No baseline clinical/radiological variables were associated with different doses; however, combination therapy was more likely to include low-dose steroid (82.4% vs. 50.0% for combination vs. steroid-only, p=0.040) and was introduced in younger patients (63.2±1.5 y vs. 67.8±1.1 y, p=0.020). Controlling for these variables in logistic regression models, however, did not influence the results (not shown).

8. Expansion with probable CAA-RI cases

Previous horizontal associations between explanatory variables remained significant, such as between SNN and LE (SNN observable in 72.5% and 49.0% of cases with and without LE, respectively, p=0.024) and between CSF pleocytosis or CSF either alteration and headache (pleocytosis present in 46.6% and 27.3% of those with and without headache, p=0.017; either alteration in 89.5% and 66.3%, p=0.002). Additionally, the association between CSF elevated protein levels and headache (present in 85.5% and 65.5% with and without headache, respectively, p=0.009) as well as between CSF pleocytosis and LE (pleocytosis present in 40.7% and 21.7% of cases with and without LE, respectively, p=0.042) became significant.

A total of 88.8% of the cases received immunosuppressive therapy in the probable/definite CAA-RI cohort (214/241). Age was not a significant predictor of treatment in the expansion; however, altered mental state was a decisive trigger for immunosuppression (present in 83.5% vs. 63.0% in the treated and non-treated, respectively, p=0.010). Limited by the subject number of genotyped patients, carriers of a non-*APOE* ε3 allele were more likely to be treated (present in 87.5% vs. 50.0% of treated and untreated genotyped patients, respectively, p=0.048), possibly reflecting a positive diagnostic/publication bias. These findings resemble those of a recent single-center analysis [46]. Expectedly, clinical improvement occurred more frequently in the treated (85.4%, p=0.005); however, spontaneous improvement was strikingly frequent (62.5%). Treatment itself, however, only tended to influence longer-term outcomes (**Tables 6 and 7**), with no significant influence on mortality (**Table 8**). Keeping in mind that the add-on probable CAA-RI cases by definition lacked patients with strictly leptomeningeal process, LE remained only a marginally significant predictor of clinical improvement (in the total cohort: present in 52.3% vs. 21.4% of the improved vs. not improved, p=0.046; trending in the treated) and did not remain significant for other outcomes. However, CSF pleocytosis at presentation remained a significant predictor of no clinical improvement (in total: present in 29.4% vs. 60.9% of the improved vs. not improved, respectively, p=0.004; in the treated: 30.5% vs. 60.0%, p=0.011) and unfavorable outcome at 6 m (in total: p=0.0004, in the treated: p=0.001, **Table 7**). Additionally, previous trends with CSF pleocytosis became significant for unfavorable outcomes at 1 y (in total: present in 21.6% vs. 58.6% in favorable and unfavorable outcomes, respectively, p=0.002; in the treated: 22.9% vs. 57.7%, p=0.006) and 6-m mortality (p=0.047 in total, trend in the treated, **Table 8**), still with trends but closer to significance for 1-y mortality (not shown). CSF either alteration showed significant associations at 6 m (p=0.034 for unfavorable outcome, **Table 7**; p=0.032 for mortality, **Table 8**). Lobar ICH within

the respective period still significantly associated with unfavorable outcome at 6 m (p=0.0007 in total, p=0.0008 in the treated, **Table 7**) and 1 y (p=0.006 in total, p=0.009 in the treated; table not shown), with strong associations with 6-m (p<0.0001 in total, p<0.0001 in the treated, **Table 8**) and 1-y mortality (p=0.0002 in total, p=0.0005 in the treated; table not shown). Similarly, relapse within the respective periods strongly associated with unfavorable outcomes at 6 m (p=0.0003 in total, p=0.0005 in the treated, **Table 7**) and 1 y (p=0.0008 in total, p=0.001 in the treated; table not shown), but not with mortality (**Table 8**). In the expansion, relapse among improvers to immunosuppression occurred in 21.6% and 37.5% within 6 m and 1 y, respectively.

Of pathophysiological relevance, the expanded analysis tends to support an association between inflammation and lobar ICH. Indeed, clinical improvement remained significantly associated with a lower probability of lobar ICH within 1 y in the total cohort (11.9% in improvers vs. 33.3% in non-improvers, p=0.040), with trends at 6 m and in the treated (not shown). Relapse (by definition not related to ICH) within 6 m after treatment was associated with the occurrence of lobar ICH within 6 m (in 16.7% and 1.4% of cases with and without relapse, respectively, p=0.023), trending within 1 y (p=0.060).

As before, no significant differences regarding clinical improvement and 6-m or 1-y outcomes could be observed between high- vs. low-dose corticosteroids, and between steroids only vs. combination at first intention (not shown). Combinations tended to include low-dose corticosteroids (in 73.7% in the combination vs. in 51.0% in the steroid-only group; p=0.070) and were introduced in younger patients (63.4±1.4 vs. 69.8±0.8 y, p=0.0003). Interestingly, co-localization of CMBs with confluent WMH(s) prompted high-dose regimens (co-localizing in 91.3% in high vs. in 63.0% in low-dose regimens; p=0.006); whereas asymmetric confluent WMHs associated with a lower probability of combined treatment (present in 70.0% in the combination vs. 92.1% in the steroid-only group; p=0.0006), probably reflecting that most probable CAA-RI cases (by definition with asymmetric confluent WMHs) came from recent publications, and only 3 received initially combined therapy, as per current recommendations. Though still underpowered, no lobar ICHs occurred within 6 m or 1 y in the combined group vs. 10.3% (p=0.193) and 17.4% (p=0.099) in the steroid-only group.

Table 7. Predictors of positive outcome at 6 months in definite/probable CAA-RI cases

Predictors	*Treated and non-treated cases collectively*				*Treated cases*			
	Positive outcome	**Negative outcome**	**Subject # per group**	**p value St/Chi²**	**Positive outcome**	**Negative outcome**	**Subject # per group**	**p value St/Chi²**
Age (y)	67.4±1.0	69.0 ±1.4	94 vs 44	*0.390*	67.4 ±1.1	67.7±1.5	87 vs 34	*0.304*
Sex (male/all)	49.5	57.8	93 vs 45	*0.359*	48.8	63.9	86 vs 36	*0.129*
Immunosuppressive treatment	92.6	82.4	94 vs 51	*0.061*	-	-	-	-
Clinical improvement	**100.0**	**17.8**	**94 vs 45**	***<0.0001***	**100.0**	**22.2**	**87 vs 36**	***<0.0001***
Headache	36.2	38.6	94 vs 44	*0.780*	36.8	38.9	87 vs 36	*0.826*
Focal sign	70.2	68.2	94 vs 44	*0.809*	70.1	69.4	87 vs 36	*0.941*
Seizure	29.0	38.6	93 vs 44	*0.261*	31.4	36.1	86 vs 36	*0.613*
Altered mental state	77.4	84.4	93 vs 45	*0.336*	79.1	86.1	86 vs 36	*0.364*
Asymmetric confluent WMH	90.5	78.8	84 vs 33	*0.089*	90.9	79.3	77 vs 29	*0.105*
Leptomeningeal enhancement	48.5	23.5	66 vs 17	*0.099*	48.3	28.6	60 vs 14	*0.238*
Sulcal non-nulling on FLAIR	56.0	52.6	50 vs 19	*0.802*	55.6	52.9	45 vs 17	*0.854*
Lobar CMB(s)	96.6	86.4	58 vs 22	*0.125*	98.1	85.7	54 vs 21	*0.064*
Co-localising CMBs and confluent WMH(s)	66.7	75.0	48 vs 12	*0.735*	67.4	72.7	46 vs 11	*1.000*
CSF pleocytosis	**22.0**	**60.7**	**59 vs 28**	***0.0004***	**22.8**	**60.0**	**57 vs 25**	***0.001***
CSF elevated protein concentration	64.8	85.2	54 vs 27	*0.070*	64.2	83.3	53 vs 24	*0.111*
CSF either alteration	**66.1**	**88.9**	**56 vs 27**	***0.034***	*65.5*	*87.5*	*55 vs 24*	*0.057*
APOE ε4 carrier	73.9	77.8	23 vs 9	*1.000*	77.3	87.5	22 vs 8	*1.000*
APOE ε4/ε4	60.9	55.6	23 vs 9	*1.000*	63.6	62.5	22 vs 8	*1.000*
APOE ε4 or ε2 carrier	82.6	88.9	23 vs 9	*1.000*	86.4	87.5	22 vs 8	*1.000*
APOE ε2 carrier	13.0	22.2	23 vs 9	*0.604*	13.6	12.5	22 vs 8	*1.000*
Future lobar ICH within 6 m	**2.2**	**21.6**	**92 vs 37**	***0.0007***	**2.4**	**25.0**	**85 vs 28**	***0.0008***
Relapse within 6 m*	**13.0**	**75.0**	**92 vs 8**	***0.0003***	**14.1**	**75.0**	**85 vs 8**	***0.0005***

CAA-RI, cerebral amyloid angiopathy-related inflammation; CMB, cerebral microbleed; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; ICH, intracerebral hemorrhage; m, months; St/Chi², Student's t test (for Age) or Chi2 test (for other variables); WMH, white matter hyperintensity on T2/FLAIR; y, year; #, number; *, sub-analysis of patients with initial clinical improvement.

Age is presented as mean±standard error of the mean. Other variables are presented as % prevalence within the column. Bold font indicates significant difference.

Original publication in: [54].

Table 8. Predictors of 6-month mortality in definite/probable CAA-RI cases

Predictors	*Treated and non-treated cases collectively*				*Treated cases*			
	Survived	**Deceased**	**Subject # per group**	**p value St/Chi²**	**Survived**	**Deceased**	**Subject # per group**	**p value St/Chi²**
Age (y)	67.3±0.9	70.4±2.3	124 vs 21	*0.169*	67.2±0.9	68.4±2.7	108 vs 16	*0.651*
Sex (male/all)	53.2	50.0	124 vs 22	*0.780*	54.6	58.8	108 vs 17	*0.747*
Immunosuppressive treatment	87.2	82.1	125 vs 28	*0.482*	-	-	-	-
Clinical improvement	**87.3**	**22.7**	**118 vs 22**	***<0.0001***	**89.6**	**29.4**	**106 vs 17**	***<0.0001***
Headache	36.8	47.6	125 vs 21	*0.345*	37.6	47.1	109 vs 17	*0.458*
Focal sign	70.4	71.4	125 vs 21	*0.924*	71.6	70.6	109 vs 17	*0.934*
Seizure	29.8	42.9	124 vs 21	*0.236*	31.5	35.3	108 vs 17	*0.754*
Altered mental state	77.4	86.4	124 vs 22	*0.412*	80.6	88.2	108 vs 17	*0.736*
Asymmetric confluent WMH	85.6	86.7	111 vs 15	*1.000*	85.6	92.3	97 vs 13	*1.000*
Leptomeningeal enhancement	46.3	33.3	82 vs 9	*0.506*	47.1	42.9	70 vs 7	*1.000*
Sulcal non-nulling on FLAIR	56.5	36.4	62 vs 11	*0.327*	57.1	33.3	56 vs 9	*0.282*
Lobar CMB(s)	94 6	91.7	74 vs 12	*0.537*	95.5	90.9	67 vs 11	*0.463*
Co-localising CMBs and confluent WMH(s)	67.9	83.3	56 vs 6	*0.657*	67.3	80.0	52 vs 5	*1.000*
CSF pleocytosis	**29.7**	**57.1**	**74 vs 14**	***0.047***	30.6	54.5	72 vs 11	*0.117*
CSF elevated protein concentration	69.6	92.3	69 vs 13	*0.169*	69.1	90.0	68 vs 10	*0.267*
CSF either alteration	**70.4**	**100.0**	**71 vs 13**	***0.032***	70.0	100.0	70 vs 10	*0.056*
APOE ε4 carrier	68.8	80.0	32 vs 5	*1.000*	75.9	80.0	29 vs 5	*1.000*
APOE ε4/ε4	53.1	60.0	32 vs 5	*1.000*	58.6	60.0	29 vs 5	*1.000*
APOE ε4 or ε2 carrier	81.3	80.0	32 vs 5	*1.000*	86.2	80.0	29 vs 5	*1.000*
APOE ε2 carrier	18.8	0.0	32 vs 5	*0.567*	17.2	0.0	29 vs 5	*1.000*
Future lobar ICH within 6 m	**4.1**	**36.8**	**122 vs 19**	***<0.0001***	**2.8**	**42.9**	**106 vs 14**	***<0.0001***
Relapse within 6 m*	16.8	50.0	101 vs 4	*0.149*	18.3	50.0	93 vs 4	*0.171*

CAA-RI, cerebral amyloid angiopathy-related inflammation; CMB, cerebral microbleed; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; ICH, intracerebral hemorrhage; m, months; St/Chi², Student's t test (for Age) or Chi2 test (for other variables); WMH, white matter hyperintensity on T2/FLAIR; y, year; #, number; *, sub-analysis of cases with initial clinical improvement.

Age is presented as mean±standard error of the mean. Other variables are presented as % prevalence within the columns. Bold font indicates significant difference.

Original publication in: [54].

Though the use of multivariable regressions in the predictor analyses of this study was limited due to rule violations, all identified associations remained significant in valid models controlling for other significant variables in univariable analyses, except for CSF either alteration not remaining an independent predictor of adverse outcome at 6 m in the expanded cohort when the analyses included Future lobar ICH as covariate (not shown).

V. DISCUSSION

CAA is a largely underrecognized clinical entity in the elderly, associating with debilitating complications, including ICHs, TFNEs, progressive neurocognitive dysfunction, and, in a subgroup of patients, with subacute encephalopathy in various symptomatic presentations (i.e. CAA-RI).

Aiming to assess the predictors and outcome of spontaneous ICHs of different localization with particular focus on the prevalence of underlying CAA, our first study identified hypertensive excess and younger age as independent predictors of deep whereas antiplatelet use of lobar/cerebellar localization, age and INR>1.4 as independent predictors of 1-m case fatality, and age, prior intracranial hemorrhage, and antiplatelet use as independent predictors of probable/definite CAA diagnosis, in addition to an estimated prevalence of CAA-related ICHs comparable to prior publications.

The timely identification of patients with probable CAA is imperative, as it is associated with serious therapeutic consequences, especially regarding the avoidance of antithrombotic/thrombolytic medications, with increasing literature demonstrating a higher risk of harm compared to benefit [12]. Despite these, CAA is considered to be underdiagnosed worldwide, its epidemiology is largely based on neuropathological case series, and the prevalence of CAA among ICH patients (i.e., CAA-related ICH) with/without associated potential risk factors have only been addressed by a few studies on clinical grounds [114-118]. Consequently, our aim was to revise all spontaneous ICH cases in our center in a 4-y period, with special focus on identifying patients with probable/definite CAA, and analyzing associated risk factors and fatal outcome.

The 213 ICH cases detected represent an incidence of approximately 13.3/100,000 persons/year, resembling the 12-15/100,000 persons/year reported in the U.S. [2]. In our study, 51.6% of spontaneous ICHs originated in the basal ganglia/thalamus, 3.3% in the cerebellum, 5.2% in the brainstem, and 39.9% were of lobar localization. According to international data reporting 35-70%, 5-10%, 5-10%, and 15-30%, respectively [2], this suggests a relative

overrepresentation of lobar ICHs compared to expectations, highlighting the relevance and necessity of an increased awareness of CAA in this population. This ratio is similar to Swedish and U.S. findings with 43.2% and 40.5% rates of lobar ICHs, respectively [7, 119]. The analysis of risk factors confirmed ICH as the disease of the elderly (the median 69.1 y being consistent with previous reports [120]. In particular, older age proved to be an independent predictor of lobar/cerebellar (i.e., CAA-compatible) ICH localization, resembling findings for lobar ICHs [6, 121, 122]. Hypertension was by far the most common coexistent factor (~90%) irrespective of ICH localization. Identifying hypertension as primary risk factor for ICHs is consistent with international meta-analyses [3, 120, 123]; however, its prevalence was higher than in many individual studies [7, 114, 119], albeit similar to some reports from Europe [124, 125]. Despite the concept that chronic hypertension would associate more with deep ICHs, our results emphasize that it is essentially present in any subtypes of ICHs (in line with some prior observations [119]) and only an extreme hypertension around the event demonstrated to be a significant (in fact the strongest) predictor of deep ICHs. Male sex, a factor frequently reported as a risk for ICH [6, 123, 126], was also slightly overrepresented in the pooled cohort (60.6%), driven, however, entirely by deep ICHs (66.9%), with the sex rate of lobar/cerebellar ICHs being ~50%, recapitulating prior observations [6, 7, 114]. The use of antithrombotics were frequent (41.1%), with antiplatelet use proven to be an independent predictor of lobar/cerebellar ICH localization. The results were practically identical when using the traditional lobar vs. non-lobar comparison (not shown).

The 1-m case fatality of all ICHs was 33.8%, with no significant effect of localization. This rate is consistent with a previous report from this region [127] and similar to reports from U.S. [6], being somewhat favorable compared to international median of 40.4% in a recent meta-analysis [126]. The identification of age as an independent decisive factor recapitulates this meta-study [126]. Though resembling findings of SMASH-U studies for medication-related ICHs [114, 117], the independent prognostic value of admission INR>1.4 (but not of anticoagulant use *per se* in the multivariable analysis) is a novelty (to our knowledge reported previously only in primary lobar ICHs [9]), giving an additional context to the risk posed by anticoagulants, particularly VKAs.

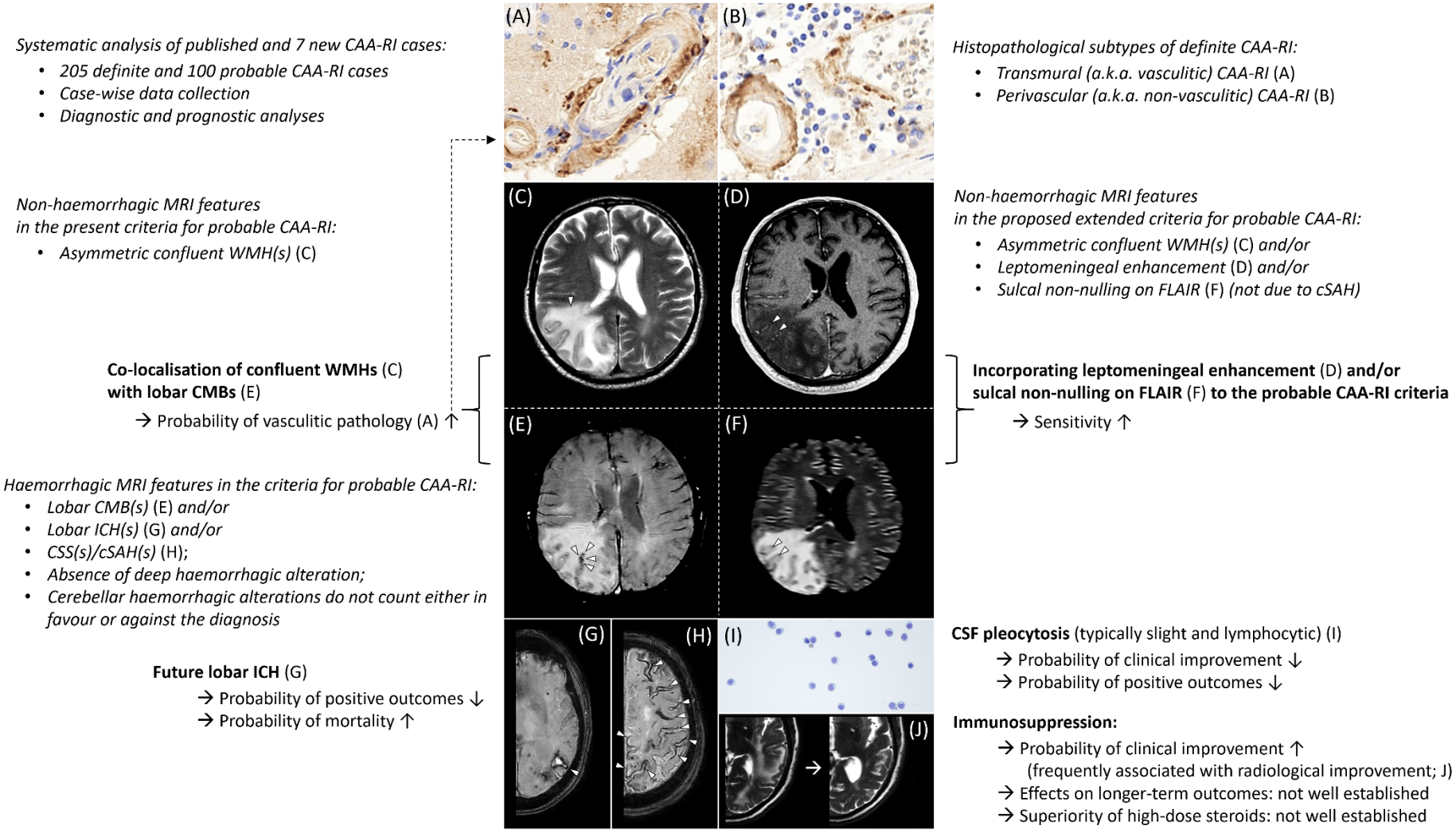

Figure 9. Summary of the findings of the systematic analysis of published and our new CAA-RI cases (second study). Original publication in: [54].

The analysis of potential clinical predictors of CAA-related ICHs revealed older age (~8% increase in risk per year) and prior intracranial hemorrhage (~8.5-fold risk) as independent significant predictors of probable/definite CAA diagnosis, which is consistent with the notion that CAA is the disease of the elderly [12] and CAA-related ICHs are often recurrent [24]. These, together with the female predominance in probable/definite CAA (though proven to be not independent of age) recapitulate key observations of a recent study from the U.S. comparing their probable/definite CAA-related ICH group with hypertension-related ICHs (as per SMASH-U) [115] and concord with autopsy studies demonstrating female predominance in CAA-related ICHs [26, 128]. Highlighting its primary role in ICH development irrespective of etiology, our data indicates that pre-existing hypertension is invariably associated with definite/probable CAA diagnosis (93.8%), with the prevalence of hypertensive excess at presentation (46.7%) not being significantly different from the comparator group either.

Though significant only at the univariable level, a remarkably high rate of definite/probable CAA patients (31.3%) had experienced prior 'TIA' compared to non-probable CAA (7.4%), presumably representing 'amyloid spells', suggested to be of epileptic or cortical spreading depression-linked origin. Interpreting these events as 'ischemic' necessarily adds to the inherited risk of ICH in CAA, due to the consequent initiation of antiplatelet therapy. Indeed, antiplatelet and anticoagulant drugs are considered a risk for ICH in CAA. Our study concords with this, revealing 68.8% of ICH patients with definite/probable CAA to be under at least one type of antithrombotic medication, with the multivariable analysis identifying antiplatelet (but not anticoagulant) use as an independent predictor of probable/definite CAA diagnosis. The 3.3-times higher prevalence of probable/definite CAA diagnosis in antiplatelet users vs. non-users resembles the 2-fold prevalence of lobar CMBs in antiplatelet user ICH patients in a previous study [11].

As a potentially reversible manifestation of CAA, in our second study we conducted an ever detailed systematic retrospective analysis of previous case reports on CAA-RI, in addition to our case series (findings summarized in **Figure 9**). This study confirmed that CAA-RI associates with earlier symptomatic presentation than CAA-related ICH, no sex preference, and a variety of symptomatic constellations. Vasculitic presentation (ABRA) was more prevalent than perivascular CAA-RI; however, they might be overlapping manifestations. Co-localization of ARIA-E (confluent WMHs) and ARIA-H (CMBs) was the sole differentiating feature in our analysis, favoring ABRA. *APOE* ε4/ε4 homozygosity was extremely prevalent, suggesting the need for an increased surveillance for CAA-RI development in

possible/probable CAA patients harboring this genotype, implicating the relevance of genotyping.

Current elements of the diagnostic criteria for probable CAA-RI had modest sensitivity, excluding several published cases with isolated leptomeningeal process. Incorporating LE and/or SNN on FLAIR (an underrecognized phenomenon, thought to represent focal changes in CSF consistency) to the criteria increased the sensitivity in our analysis. Keeping in mind the limitations due to our study setting, we propose our extended diagnostic criteria (**Table 2**) as a research framework that merits prospective clinicopathological validation. Altogether the aim is a) to facilitate the recognition of CAA-RI cases with isolated leptomeningeal process; b) to emphasize the potential of LE and SNN as supportive features in cases meeting the present criteria for CAA-RI, and c) to suggest these as possible surrogate markers of treatment response. The retrospective identification of published true positive cases did not allow the assessment of specificity, which urges for a prospective re-evaluation. However, a prior study found excellent specificity of LE to differentiate CAA-RI from non-inflammatory CAA at histology [85], with no existing data on SNN. Though incidental associations of other causes of LE (e.g., carcinomatous/lymphomatous/infectious meningitis) with an SWI picture consistent with CAA may influence specificity, CSF is expected to show more robust (if not diagnostic) alterations in these scenarios, which would be atypical to CAA-RI. Besides the diagnostic relevance, the analysis implicated a positive prognostic role of LE, but mostly within definite CAA-RI (notably including cases with isolated leptomeningeal involvement). A positive prognostic role of LE has previously been suspected regarding mortality [129]; however, our analysis did not confirm this observation.

Among fluid biomarkers, CSF appears to be essential in the work-up of CAA-RI, not only as an irreplaceable source of exclusionary diagnoses. Though CSF pleocytosis and elevated protein levels are non-specific to CAA-RI, the data suggest that elevated protein level might be a valuable surrogate biomarker of biological changes, including therapy responsiveness and relapse. Indeed, a group used re-emerging levels of CSF protein as a marker of breakthrough disease on deciding to add cyclophosphamide [53]. On the other hand, CSF pleocytosis, with its typically slight and lymphocytic presentation, might be a strong support for meningeal inflammation in challenging CAA cases. In addition, our analysis identified an association between CSF pleocytosis and an unfavorable course, which accords well with the findings of a recent prospective study [130]. These findings expand the relevance of CSF by representing a cheap and accessible potential tool for differential diagnosis and possibly for patient selection for more potent/escalated therapies. The role of CSF AD biomarkers in CAA-

RI is yet unclear, with implications on the possibility for an acute exacerbation to masquerade otherwise pathologically low levels of CSF $A\beta_{1-42}$ [48, 53, 90]. Nevertheless, the finding of low CSF $A\beta_{1-42}$, especially in younger patients, can be interpreted as a strong support for associated Aβ pathology in cases with less overwhelming hemorrhagic profile. Although the potential diagnostic relevance of CSF anti-Aβ autoantibodies is inevitable, the low number of definite cases analyzed (8) and the correlation of its levels with CSF protein levels [53] (with analogous changes reported to therapy or spontaneous remission) necessitate further studies on their utility.

Among event variables, lobar ICH occurring after presenting with CAA-RI proved to be a significant determinant of morbidity/mortality during the follow-up, which together with the findings implicating the potential role of effective immunosuppression in preventing future ICHs and their remarkable incidence during such short periods highlights a feature previously noted as less typical for CAA-RI vs. non-inflammatory CAA [43, 85]. Accordingly, most patients in our series had antecedent/concomitant ICH(s).

Though revealing a surprizing frequency of spontaneous remission, our analysis confirmed the overwhelming benefit of immunosuppressive therapy in CAA-RI (with improvements rates even higher than the ~70% reported previously [42]), at least on the short term. The data on long-term outcomes, especially on mortality, however, are less clear; though the lower subject numbers with longer follow-ups should be considered as limitation. This fading out of efficacy is reminiscent of the finding of only short-term benefits of steroids by a prospective study [59].

Consensus guidelines for the optimal treatment approach of CAA-RI are lacking. The online available protocol of a flagship institute in CAA suggests a regimen of 0.5-1.0 g daily corticosteroids for 5 days with rapid taper as first-line, restricting other immunosuppressants to refractory cases [131]. A similar protocol was considered reasonable in a recent retrospective analysis of consecutive patients, not powered to assess difference between regimens [46]. Our analysis of arbitrarily dichotomized doses revealed no difference in outcomes between high-dose and low-dose corticosteroids, which together with the notable intermediate-term mortality of CAA-RI (with putative contributory roles of corticosteroids in a fragile population) urge for prospective multi-center randomized trials to elaborate an optimized regimen, including early combinations with steroid-sparing agents. We emphasise the surprisingly low proportion of reports with precize data on dosing, limiting the strength of analysis.

Our studies have limitations, including a) their retrospective and (for the second study) literature analytic nature inherent to observer and publication biases, b) the lack of specificity

provided by targeted identification of true positive CAA-RI cases, c) the varying subject numbers, d) .the lower subject numbers with longer follow-ups, and e) the surprisingly low proportion of reports with precise data on therapy dosing in the second study. Strengths include the large subject number in both studies. To our knowledge, our first study to the date of publication was among the largest studies reporting multivariable binary analysis of clinical discriminators of ICH localization. Additional strength is the unprecedented rigor that probable and possible CAA diagnoses were established in (and thus CAA-related ICH prevalence estimated based on) a subgroup with 'complete' work-up including MRI-SWI and angiography (not allowing CT-only), increasing diagnostic sensitivity and specificity. Furthermore, we provided an unprecedented subject number with case-wise data collection of published CAA-RI cases to allow for the evaluation of associations between several potential predictors not having been previously addressed systematically.

VI. CONCLUSION

Our studies highlight the need for an increased awareness of CAA and CAA-RI by both neurologists and radiologists, providing an in-depth retrospective analysis of spontaneous ICHs, with particular focus on the prevalence and clinical predictors of CAA-related ICH, and drawing attention to a less widely recognized entity, CAA-RI. We conclude that CAA-related ICHs are at least as frequent (14.7%) in our population as reported internationally (5-20%). Notably, the world-wide low rate of clinically and radiologically established probable CAA diagnosis puts a significant percentage of the population, especially the elderly under antiplatelet therapy (as demonstrated), at a high risk of possibly lethal ICHs. Our first study set the stage for the establishment of a microcerebrovascular outpatient office in our center, specifically designated to the comprehensive diagnosis, management, and follow-up of patients with cerebral hemorrhagic alterations.

The unprecedented number of definite CAA-RI cases analyzed enabled the evaluation of the current diagnostic criteria in terms of its sensitivity, and proposals have been made to include currently unused radiological features (i.e., LE and SNN) in the diagnosis. Being the first to analyze an expanded probable/definite CAA-RI cohort, our study propose CSF pleocytosis as a negative prognostic factor, define future lobar ICH as a potentially preventable significant contributor to mortality, and implicate no evident superiority of high-dose over low-dose corticosteroids. Though confirming the short-term superiority of immunosuppression over observing a natural course, by revealing an unexpectedly high rate of spontaneous remission

and less clear benefits of immunosuppression on the long term, our study raises important concerns on the paucity of evidence delineating which cases would benefit the most from what strategy of immunosuppression. The identified predictors of short and long-term outcomes (i.e. initial CSF alterations and recurrent lobar ICH) may aid the clinical decision-making regarding the choice on the intensity and duration of immunosuppressive therapy.

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IX. CO-AUTHOR CERTIFICATION

I, myself as the first author of the following publication declare that the authors have no conflict of interest, and **Bernadett Nagy-Fakan MD** PhD candidate had significant contribution to the jointly published research. The results discussed in her thesis were not used and not intended to be used in any other qualification process for obtaining a PhD degree.

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