Kovacs Gabor G (Orcid ID: 0000-0003-3841-5511)

Klivenyi Peter (Orcid ID: 0000-0002-5389-3266)

Original Article

Identifying diagnostic and prognostic factors in cerebral amyloid angiopathy-related inflammation: a systematic analysis of published and seven new cases

Levente Szalardy[1,2], Bernadett Fakan[1], Rita Maszlag-Torok[1], Emil Ferencz[1], Zita Reisz[3,4], Bence L. Radics[3], Sandor Csizmadia[5], Laszlo Szpisjak[1], Adam Annus[1], Denes Zadori[1], Gabor G. Kovacs[2,6*], Peter Klivenyi[1*]

[1]Department of Neurology, Albert Szent-Györgyi Medical School, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary

[2]Department of Laboratory Medicine and Pathobiology and Tanz Centre for Research in Neurodegenerative Disease, University of Toronto, Toronto, Ontario, Canada

[3]Institute of Pathology, Faculty of Medicine, Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary

[4]Department of Clinical Neuropathology, King's College Hospital, London, United Kingdom

[5]Affidea Hungary Ltd., Budapest, Hungary

[6]Laboratory Medicine Program and Krembil Brain Institute, University Health Network, Toronto, Ontario, Canada

*Contributed equally

Corresponding author:

Peter Klivenyi MD, PhD, DSc

Department of Neurology, Albert Szent-Györgyi Medical School, Albert Szent-Györgyi Clinical Center, University of Szeged, Hungary

H-6725 Szeged, Semmelweis u. 6.

E-mail: klivenyi.peter@med.u-szeged.hu

Phone: +36-62-545-348

Short title: A systematic approach to CAA-RI

Key points

- A systematic analysis of 205 definite and 100 probable, including 7 unpublished, CAA-RI cases was conducted.
- Vasculitic pathology was more likely to be associated with the co-localisation of microbleeds with confluent white matter hyperintensities on MRI.
- Incorporating leptomeningeal enhancement and/or sulcal non-nulling (i.e., hyperintensity) on FLAIR may improve the diagnostic sensitivity of the criteria.
- Cerebrospinal fluid pleocytosis was associated with a decreased probability of clinical improvement and positive outcome, whereas future lobar intracerebral haemorrhage was associated with adverse outcomes, including mortality.
- Immunosuppression was associated with increased short-term improvement but the superiority of high-dose over low-dose corticosteroids is not well established.

Acknowledgements

Funding

Dr Szalardy was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences and the ÚNKP-20-5 New National Excellence Program of the Ministry for Innovation and Technology from the source of the National Research, Development and Innovation Fund. Dr Annus was supported by the National Talent Program NTP-NFTÖ-21-B-0206. The study was supported by grants TKP-2021-EGA-32, 2017-1-1.1.2.1-NKP-2017-0002, and 5S 725 (A202). The publication was supported by the University of Szeged Open Access Fund grant number 5962.

Declaration of interests

Dr Kovacs has served as an advisor for Biogen; received a royalty for 5G4 synuclein antibody and publishing royalties from Wiley, Cambridge University Press and Elsevier, received grants from Edmond J Safra Philanthropic Foundation, Rossy Family Foundation, Michael J. Fox Foundation, Parkinson Canada, Canada, and Canada Foundation for Innovation. The Editors of Neuropathology and Applied Neurobiology are committed to peer-review integrity and upholding the highest standards of review. As such, this article was peer-reviewed by independent, anonymous expert referees and the authors (GGK) had no role in either the editorial decision or the handling of the paper. Dr Szalardy received speaker's honoraria from Biogen and conference registration fees from Biogen, Sanofi-Genzyme, Bayer, and Sandoz. Dr Szpisjak received speaker's honoraria from Abbvie, a conference registration fee from Sandoz, and a teaching course registration fee from Boehringer-Ingelheim. Dr Annus received speaker's honoraria from Boehringer-Ingelheim and Nutricia, and a conference registration fee from Richter Gedeon Plc. Dr Zadori received speaker's honoraria, travel expenses, conference registration fees, and educational grants from Abbvie, Abbott, Goodwill Pharma, Ipsen, Medis, Medtronic, Sandoz, UCB, and Richter Gedeon Plc. All other authors declare no conflicts of interest.

Ethical approval statement

Five out of the seven presented patients or their next-of-kin gave informed consent to reporting. In two cases, informed consent could not be obtained as neither the patient nor the next-of-kin was available. The study adhered to the Declaration of Helsinki and was approved by the local Ethical Committee (46/2014, 44/2016, 22/2021).

Authors contribution

Dr Szalardy, Dr Kovacs, and Dr Klivenyi contributed to the study's conception and design. Dr Szalardy and Dr Fakan performed the literature search and data extraction. Dr Szalardy and Dr Zadori performed the analyses. Dr Szalardy, Dr Annus, Dr Csizmadia, Dr Szpisjak, and Dr Zadori contributed to the clinical-radiological diagnosis, management, and follow-up of the presented cases. Dr Reisz, Dr Radics, Dr Szalardy, and Dr Kovacs performed the neuropathological work-up. Dr Szalardy and Dr Zadori performed the cerebrospinal fluid analyses. Dr Maszlag-Torok and Dr Ferencz performed the genetic analyses. Dr Szalardy wrote the first draft of the manuscript and prepared the figures and tables. All authors read and made comments on the draft and approved the final manuscript.

ABSTRACT

Aims: Cerebral amyloid angiopathy-related inflammation (CAA-RI) is a potentially reversible manifestation of CAA, histopathologically characterised by transmural and/or perivascular inflammatory infiltrates. We aimed to identify clinical, radiological, and laboratory variables capable of improving or supporting the diagnosis of or predicting/influencing the prognosis of CAA-RI and to retrospectively evaluate different therapeutic approaches.

Methods: We present clinical and neuroradiological observations in seven unpublished CAA-RI cases, including neuropathological findings in two definite cases. These cases were included in a systematic analysis of probable/definite CAA-RI cases published in the literature up to December 31, 2021. Descriptive and associative analyses were performed, including a set of clinical, radiological, and laboratory variables to predict short-term, 6-month, and 1-year outcomes and mortality, first on definite, secondly on an expanded probable/definite CAA-RI cohort.

Results: Data on 205 definite and 100 probable cases were analysed. CAA-RI had a younger symptomatic onset than non-inflammatory CAA, without sex preference. Transmural histology was more likely to be associated with the co-localisation of microbleeds with confluent white matter hyperintensities on MRI. Incorporating leptomeningeal enhancement and/or sulcal non-nulling on fluid-attenuated inversion recovery (FLAIR) enhanced the sensitivity of the criteria. Cerebrospinal fluid pleocytosis was associated with a decreased probability of clinical improvement and longer-term positive outcomes. Future lobar haemorrhage was associated with adverse outcomes, including mortality. Immunosuppression was associated with short-term improvement, with less clear effects on long-term outcomes. The superiority of high-dose over low-dose corticosteroids was not established.

Conclusions: This is the largest retrospective associative analysis of published CAA-RI cases, and the first to include an expanded probable/definite cohort to identify diagnostic/prognostic markers. We propose points for further crystallisation of the criteria and directions for future prospective studies.

Keywords: amyloid beta-related angiitis; cerebral amyloid angiopathy; cerebral amyloid angiopathy-related inflammation; criteria; diagnosis; inflammatory cerebral amyloid angiopathy; outcome; predictor

INTRODUCTION

Despite being recognised as the leading cause of lobar intracerebral haemorrhages (ICHs), cerebral amyloid angiopathy (CAA) is an underdiagnosed condition [1]. In contrast to hypertension-related arteriolosclerosis, which predominantly affects arterioles of the basal ganglia, thalamus, and pons, CAA predominantly affects cortical leptomeningeal and parenchymal small vessels, with progressive deposition of amyloid-β (Aβ) in their wall [2]. The neuropathological prevalence of CAA increases with age, being comparable to Alzheimer's disease (AD). Indeed, Aβ is deposited in plaques in AD and vessel walls in sporadic CAA. The two diseases show 80% overlap; however, they both exist independently [3]. Similar to sporadic AD, polymorphisms in the *APOE* gene have been associated with increased risk (ε4) or more severe phenotype (ε2) of sporadic CAA [4].

The hallmark features of CAA are spontaneous haemorrhages, characteristically lobar in location, including cerebral microbleed (CMB), ICH, convexity subarachnoid haemorrhage (cSAH), and cortical superficial siderosis (CSS) as chronic cSAH [5]. These haemorrhagic alterations enable the *in vivo* diagnosis of CAA, using magnetic resonance imaging (MRI) with susceptibility-weighted imaging (SWI), sensitive to haemosiderin. The exclusive presence of such lobar haemorrhages allows the probable diagnosis of CAA as per the modified Boston [5] and most recently the Boston v2.0 criteria [6], whereas a definite diagnosis is provided by autopsy. The diagnostic MRI features in the Boston v2.0 criteria now include non-haemorrhagic alterations as well, comprising multispot white matter hyperintensity (WMH) pattern on FLAIR and dilated perivascular spaces in the centrum semiovale on T2. The presence of either non-haemorrhagic alteration in addition to one lobar haemorrhagic alteration now suffices for the diagnosis of probable CAA.

Conventional clinical manifestations of CAA include lobar ICH-related symptoms, slowly progressive dementia, and transient focal neurological episodes (TFNEs) possibly triggered by cSAH/CSS [3]. A subgroup of CAA patients, however, present with subacute cognitive/behavioural decline, focal neurological symptom(s), headache, and/or seizure(s), in association with the MRI appearance of asymmetric and confluent WMH(s) on T2/fluid-attenuated inversion recovery (FLAIR), representing vasogenic oedema (often overlooked on initial computed tomography), as in a proportion of patients with primary angiitis of the central nervous system (PACNS). This presentation is underpinned neuropathologically by infiltration of CAA-affected vessels by mononuclear inflammatory cells with or without granulomatous features (such as multinucleated giant cells (MNGCs)), and are classified as those presenting with transmural and perivascular (i.e., Aβ-related angiitis (ABRA) [7]) and those merely with

perivascular involvement (i.e., perivascular CAA-related inflammation (CAA-RI)) [8]. The vasculitic form (ABRA) was found in 1/3 of cases with an initial diagnosis of PACNS [9], with some authors considering ABRA as a subtype of PACNS [7, 9].

The first definition of this syndrome was given by Eng *et al.* and was termed *'CAA-related inflammation'* [10]; however, cases with similar phenotypes and inflammatory vasculopathy with CAA have been reported for >50 years. The clinical-radiological criteria were defined in 2011 by Chung *et al.* [8] and have recently been improved and validated by the Boston group (Auriel criteria [11]). Most patients respond to immunosuppression, with corticosteroids being the first line [12]. It is proposed that as opposed to PACNS (without CAA) where biopsy is the gold standard, the diagnosis of CAA-RI can be established solely on clinical-radiological grounds [8, 11, 13].

The striking 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 oedema and/or sulcal effusion) and associated haemorrhages (ARIA-H, including CMB and/or CSS) [14], implicated the pathogenic and biomarker roles of anti-Aβ autoantibodies in CAA-RI [15]. A further link between ARIA and CAA-RI is the high prevalence of ApoEε4 carriers in both [13, 14].

In addition to presenting an unpublished case series with probable/definite CAA-RI, the present study aimed to profile published probable/definite CAA-RI cases and conduct 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. Our findings identified leptomeningeal enhancement (LE) and sulcal non-nulling (SNN) on FLAIR as features enhancing the diagnostic sensitivity of probable CAA-RI, propose cerebrospinal fluid (CSF) pleocytosis as a negative prognostic factor, define future lobar ICH as a potentially preventable significant contributor to mortality, and implicate no superiority of high-dose over low-dose corticosteroids.

MATERIALS AND METHODS

Seven CAA-RI (including 2 definite) cases are reported and included in the analysis. Five patients or their next-of-kin gave informed consent to reporting. In two cases, informed consent could not be obtained as neither the patient nor the next-of-kin was available. The study adhered to the Declaration of Helsinki and was approved by the local Ethical Committee (46/2014, 44/2016, 22/2021).

The comprehensive description of the literature search, case collection, data extraction, the collected variables, and the methods of dichotomisation are presented in **Supplementary File 1**.

The following definitions were used for the classification of cases. Definite CAA-RI was considered in the presence of either perivascular or transmural/intramural inflammatory infiltrates associated with CAA as defined previously [8]. A modification was applied that meeting the clinical-radiological criteria was not a prerequisite for definite diagnosis; this allowed the measurement of the sensitivity of the clinical-radiological criteria. Probable CAA-RI was considered by adopting the recently validated criteria [11] with slight modifications in the wording (the rationale is described in **Supplementary File 1**); this is referred to as 'the present criteria' (**Table 1**). The category of possible CAA-RI was omitted since no patients meeting this category were confirmed to have definite CAA-RI in the validated criteria [11].

The first step of analysis focused on definite CAA-RI to reveal potential associations in an established cohort and to identify biomarkers with diagnostic/prognostic value. An expanded analysis included probable CAA-RI cases as well to reassess the significance of the initial findings. The sensitivity analyses were performed and reported in line with the STARD 2015 guideline [16]. The sensitivity of 'the present criteria' for probable CAA-RI was assessed and compared to that of 3 sets of 'extended criteria': 1) incorporating '*and/or* LE', 2) incorporating '*and/or* SNN', and 3) incorporating '*and/or* LE *and/or* SNN' into the non-haemorrhagic profile. The differences were addressed by the McNemar test, with exact 1-sided p-values. The statistics were performed by SPSS 22.0 software. The precision of estimates is presented using a 95% confidence interval (95% CI) by using the Wilson score interval calculated online [17]. A detailed description is found in **Supplementary File 1.** In the predictor analyses, a comparison of age was performed by Student's t-test (using Levene's test plus Welch's correction where appropriate) after refuting non-normal distribution by the Shapiro-Wilk test. Associations of categorical variables were assessed by Chi^2 tests, using Fischer's exact value where appropriate. The interdependence of associations and the influence of potential confounders were assessed by multivariable binary logistic regression (MBLR) models. A detailed description is found in **Supplementary File 1.** Data are presented as the mean ± the standard error of the mean or percentage.

RESULTS

Case presentations

Table 2 summarises the present case series, ranging from minimally symptomatic to fatal cases. The radiological and neuropathological findings of cases 1-2 are presented in **Figures 1-4**. Descriptions of cases 1-7 are presented in **Supplementary file 2**.

Systematic analysis of the literature

Nomenclature

The nomenclature of definite CAA-RI varied substantially. The Chung [8] and the Auriel [11] criteria used the term CAA-RI to cover cases with perivascular-only and transmural inflammation, similar to the largest case series [13]. Some authors differentiate two types of CAA-RI using the terms vasculitic (transmural) as opposed to perivasculitic, non-vasculitic, or non-destructive [18-21]. Many, however, use different nomenclatures, either using 'inflammatory CAA' or similar terms to cover the subtypes distinguished as ABRA (for transmural) and CAA-RI (for perivascular) [9, 22-24] or using CAA-RI to cover ABRA (for transmural) and inflammatory CAA (for perivascular) [25-29]. Others use 'tumefactive CAA' to refer to cases with extensive asymmetric confluent WMH(s) mimicking neoplasm(s) [30, 31]. Though each has its rationale (e.g., the clinical definition paper included only perivascular cases using the term *'syndrome of CAA-related perivascular inflammation'* [10]), here we use the term CAA-RI to cover the clinical-pathological entity and refer to the pathological subtypes with terms directly reflecting their nature.

Epidemiology of definite CAA-RI

The analysis detected 205 definite CAA-RI cases for descriptive analysis, 200 including a report of the conditions of obtaining the histopathological specimen for the diagnosis (i.e., by biopsy or autopsy). 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). This contrasts with CAA-related ICH, where the mean age of presentation is some 10 years higher and female predominance is well-documented [1, 10]. 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 were associated with age.

Neuropathology of definite CAA-RI

Some 71.7% of definite cases with sufficient data (132/184) had transmural inflammation (ABRA), the remaining 28.3% being consistent with perivascular CAA-RI, as reported also in a case series [9]. Transmural and perivascular-only involvement were frequently reported to co-occur in patients [8, 32-37], 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 [38], implicating the potential role of sample sizes in the classification. Our case with perivascular CAA-RI (Case 1, Supplementary File 2, Figures 1-2) is one of the 7 similar cases published with autopsy confirmation [39-42]. The predictor analysis revealed only a single variable to be associated with histology; specifically, the co-localisation of CMBs with confluent WMH(s) (i.e., when these alterations predominate in the same anatomical area) were more common in ABRA (87.0%) than in perivascular CAA-RI (52.6%; p=0.020; **Table S1** (Tables S1-15 are available in **Supplementary File 3**)). These implicate the pathogenic role of angiodestructive inflammation in haemorrhagic 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 (with a total of 88.4% for myeloid cells), 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 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 [7, 10, 43, 44], whereas others describe (seemingly) non-CAA vessels to be involved as well [32, 34, 41], in a case with exclusive association in biopsy and near-absolute dissociation at autopsy [45]. Some authors propose efficient immunological clearance of Aβ to underlie these observations [45]. The observation in an ABRA case that vascular Aβ deposition decreased by the increasing severity of inflammation supports this concept [46], similar to our observation (Case 2, Supplementary File 2, Figure 4).

Regarding concomitant AD pathology, Aβ plaques and neurofibrillary tangles (NFTs) were described in 81.3% (65/80) and 48.3% (28/58) 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 any, 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 [44].

Changes corresponding to WMHs comprise tissue rarefaction, myelin pallor, spongy vacuolation, and astrogliosis [7, 39, 47]. Considering the location of the biopsy evaluated for diagnostic pathology, many authors emphasise that biopsy should be targeted at the leptomeninges and cortex to rule in CAA/CAA-RI, whereas sampling from the white matter (WM) can only rule out an infiltrative neoplasm [48]. Reports with isolated WM samples resulting in non-diagnostic histology are common [15, 20, 31].

Clinical and radiological presentation in 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 [40, 49], whereas 1 case was a definite Creutzfeldt-Jakob disease (CJD) with ABRA [50], where CJD could be interpreted *per se* as a 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 definite cases with sufficient data had asymmetric confluent WMH(s) and 83.2% (94/113) had lobar CMB(s). Some 7.4% (14/188) had lobar ICH at onset (exactly as in a large single-centre report [48]); 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 [9, 48]. Of cases with sufficient data, 67.3% (68/101) met the radiological part of the present 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 haemorrhagic lesions (7.9%), and with deep CMB(s)/ICH(s) (not meeting probable CAA [5], 3.0%), often in combination. In patients with sufficient clinical and radiological data for decision-making, this yielded a 65.7% (67/102, 95% CI 56.1%-74.2%) 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 WMH(s) tended to co-localise with CMBs in 66.7% (38/57). The appearance of haemorrhagic alterations (e.g., CMB/CSS) was, in some cases, preceded by the symptomatic/radiological onset of CAA-RI [51, 52].

Regarding additional radiological features not part of the present criteria, 61.7% (79/128) of cases with contrasted MRI were reported to demonstrate enhancement (48.4%

leptomeningeal, 5.5% parenchymal, 5.5% both, 1 with deep perivenular enhancement (0.8%), 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 data on WMH, haemorrhagic, and enhancement profiles, adding *LE* to the criteria as an alternative (AND/OR) to *asymmetric confluent WMH(s)* increased the sensitivity (p=0.008) from 71.4% (45/63; 95% CI 59.3%-81.1%) to 82.5% (52/63; 95% CI 71.4%-90.0%). Importantly, the change in the sensitivity of the 'present criteria' is due to the subgroup analysis of subjects with all required data available (see the flowchart in **Figure S7** in **Supplementary File 3** and the description in **Supplementary File 1**). Notably, a similar criterion was used by Piazza *et al.* to establish probable CAA-RI [53]. A previous single-centre study reported 92.6% specificity for LE to distinguish between CAA-RI and non-inflammatory CAA [48]. Our present approach did not allow the estimation of specificity; however, our observation supports this finding.

Based on a prior observation that SNN (a.k.a. sulcal non-attenuation, hypoattenuation, hyperintensity, or effusion) on FLAIR can co-localise with LE [48] and that it is an established component of ARIA-E [14], we analysed 70 definite CAA-RI with non-contrast FLAIR image(s) of sufficient quality published and additional 2 where SNN was recognisably described, and found that SNN not only co-occurred with isolated LE (with no or patchy WMHs only) in 100.0% (7/7; with 77.8% (7/9) of isolated SNN cases (with no or with patchy WMHs only) presenting with LE), but it was present in 80.8% (21/26) of definite cases with LE regardless of WMH presence/pattern. Moreover, SNN was detectable in 50.0% (12/24) of definite 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 (prominent examples listed in **Table S2**). 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 [18] or minimal patchy WMHs [54, 55]) 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 haemorrhagic profile) increased the sensitivity from 72.2% to 81.5% (39/54 (95% CI 59.1%-82.4%) vs. 44/54 (95% CI 69.2%-89.6%); p=0.031). Furthermore, adding *LE and/or SNN* as alternatives to *asymmetric confluent WMH(s)* increased the sensitivity from 70.0% to 82.5% (28/40 (95% CI 54.6%-81.9%) vs. 33/40 (95% CI 68.1%-

91.3%), p=0.031, **Figure S7**, **Table 1**). Given that SNN was mostly assessed on a single FLAIR image, the true sensitivity of the SNN-supplemented sets of criteria might be even higher.

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

Laboratory biomarkers in definite CAA-RI

Lumbar puncture was reported in 63.4% (130/205). The prevalence of CSF pleocytosis and increased concentration of total protein were 44.2% (53/120) and 79.8% (95/119), respectively, with 82.8% (101/122) being pathological in at least one. Mononuclear cells (particularly lymphocytes) predominated, except in 1 report with polynuclear predominance [18]. Eosinophils were exceptionally reported, all in ABRA, with eosinophils consistently present also in their histology [32, 56, 57], being a significant component in 1 [32]. Notably, CSF pleocytosis and either CSF pleocytosis/elevated protein concentration were significantly associated with headache (CSF pleocytosis in 56.8% (25/44) and 34.6% (18/52) of those with and without headache, respectively, p=0.029; either alteration in 93.2% (41/44) and 73.1% (28/52), 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 concentration was decreased following immunosuppression in 80.0% (8/10) [18, 32, 41, 52, 54, 57-59], whereas it increased upon disease progression [8, 60-63] or relapse [54, 64, 65]. The CSF white blood cell count changed in parallel with protein concentration in most reports [8, 32, 52, 57-60, 65] with few exceptions [54, 62-64]. The CSF white blood cell count was decreased following immunosuppression in 87.5% (7/8). Therapy-associated improvement in pleocytosis and protein concentration was accompanied by clinical improvement only in 50% (3/6) [54, 57, 59] and 71.4% (5/7) [18, 41, 54, 57, 59], respectively. Overall, CSF pleocytosis and elevated protein concentration followed the clinical course (improvement/deterioration) in 45.5% and 85.7%. This suggests that elevated protein concentration is 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, the AD-core CSF biomarker profile [66] was addressed only in 10 definite cases [18, 53, 59, 67-71], including our 2 cases. The findings show decreased $A\beta_{1-42}$ in 80.0% (8/10), increased total Tau in 33.3% (3/9), and increased phosphorylated Tau (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 [59, 69]. Notably, CSF $A\beta_{1-42}$ was reported to change during the course in one case, being normal in the 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 [53]. However, therapy-associated changes in CSF $A\beta_{1-42}$ or $A\beta_{1-40}$ were not consistently found [15, 18].

Increased CSF levels of anti-Aβ autoantibodies were found in definite CAA-RI cases during an acute phase compared to spontaneous [53] or corticosteroid-induced remission [18, 53, 59] or compared to non-CAA-RI [53, 59]. 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 [72]. Notably, however, a recent study analysing probable/definite CAA-RI patients together found no difference in anti-Aβ antibody titres before and after immunosuppression [73].

The *APOE* ε genotype, an established risk factor for AD and a possible risk factor for CAA/CAA-related ICH [4] was reported in 28 definite cases. At least 1 *APOE* ε4 allele was carried by 60.7%, which is remarkably high compared to unselected and control populations, but comparable to that in AD and CAA in general [10, 74-77]. However, a striking 53.6% of cases were *APOE* ε4/ε4 homozygotes, suggesting that ε4/ε4 homozygosity represents a strong predisposition to CAA-RI. Notably, the carrier rate for *APOE* ε2 was also surprisingly high (32.1%), higher than in most CAA studies [4, 76-79], yielding a total prevalence of 85.7% of non-*APOE* ε3/ε3 (non-'normal') genotypes, an extremely high rate compared to controls or CAA *per se* [4, 55, 77]. These suggest that both non-'normal' alleles may predispose to CAA-RI. Though not significant at this subject number (10 vs. 10), this predominance of *APOE* ε4 allele carriership and *APOE* ε4/ε4 homozygosity in definite CAA-RI is due to perivascular CAA-RI rather than ABRA (70% vs. 40%, 60% vs. 30%, respectively). In ABRA, *APOE* ε2 tends to predominate (20% vs. 50%, **Table S1**). The genotype distribution in the probable CAA-RI cohort is more reminiscent of that seen among perivascular cases in the definite CAA-RI cohort (73.5% *APOE* ε4 carriers, 52.9% *APOE* ε4/ε4, 8.8% *APOE* ε2 carriers, and 82.4% non-*APOE* ε3/ε3; n=35).

Therapy, course, and dosing in definite CAA-RI

A total of 152 definite cases were eligible for treatment analysis, 149 with unequivocal data on the form 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 surgery (resection/lobectomy or shunting)). Among the immunosuppressed with sufficient data (130), 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 rarely used (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.

A disproportion of surgery between immunosuppressed (3.0%) and not immunosuppressed (31.6%) definite cases was observed. Therefore, we excluded the surgical cases from further analyses.

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 (**Table S3**).

Among immunosuppressed definite 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% of cases. 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 (**Tables S3 and S4**)). 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 (p=0.003), both within treated (p=0.027) and untreated (p=0.029) patients. Cerebrospinal fluid pleocytosis at presentation was associated with a decreased likelihood of clinical improvement in the total cohort (p=0.042), with a trend within the treated (p=0.066). No other baseline variables showed association with improvement (**Table S4**).

The prevalence of a symptomatic relapse (not related to ICH) in patients who improved to initial immunosuppression and had sufficient follow-up periods was 25.9% (15/58) within 6 m and 41.7% (20/48) within 1 y. Relapse generally resulted in repeated therapy, dose escalation, switch, or combination, leading to improvement in 83.3%.

The predictor analysis of positive outcomes at 6 m and 1 y among definite cases with appropriate data are presented in **Table S5** and **Table S6**, respectively. 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, **Tables S3 and S5**). This missed significance at 1 y (p=0.058, **Tables S3 and S6**). LE was associated with positive outcomes at 6 m (p=0.005) and 1 y (p=0.003) in the total cohort and among the immunosuppressed patients (p=0.044 and p=0.029). CSF pleocytosis at presentation was significantly associated with adverse outcomes at 6 m in the total cohort (p=0.015) and in the treated (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 (p=0.027) and among the treated (p=0.031), with a similar association for lobar ICH within 1 y with adverse outcome at 1 y in the total cohort (p=0.042) and a trend in the treated (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 (p=0.005 and p=0.007, respectively) and within the treated (p=0.006, p=0.010). No other independent variables showed associations with positive outcomes (**Tables S5 and S6**).

Regarding all-cause mortality, 16.7% and 25.4% of immunosuppressed definite cases died within 6 m and 1 y, respectively. These tended to be fewer compared to those not receiving immunosuppression (38.5% (p=0.065) within 6 m and 60% (p=0.057) within 1 y (**Table S3)**). 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 treated/untreated subgroups or analyses censored for fatalities due to causes unrelated to CAA-RI (**Tables S7 and S8**). 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 (p=0.039; as reported [80]). No other baseline variables predicted censored mortality. However, lobar ICH(s) presenting in the corresponding periods was

associated with an increased likelihood of mortality within 6 m (total cohort: p=0.0006; treated: p=0.0003, **Table S7**) and 1 y (total cohort: p=0.0005; treated: p=0.003, **Table S8**).

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 the ICH 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 (**Table S9**) 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, 6-m or 1-y outcome, all-cause mortality, and relapse (**Table S9**). 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 a combination at first intention regarding clinical improvement, and 6-m or 1-y outcome. 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 steroids (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).

Expansion of the observations by including probable CAA-RI cases in the analysis

Previous 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 level and headache (present in 85.5% and 65.5% with and without headache, respectively, p=0.009) as well as the association between CSF pleocytosis and LE (pleocytosis present in 40.7% and 21.7% of cases with and without LE, p=0.042) became significant.

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 (p=0.010; **Table S10**). Limited by the subject number, carriers of a non-*APOE* ε3 allele were more likely to be treated (p=0.048; **Table S10**), possibly reflecting a positive diagnostic/publication bias. These findings resemble those of a recent single-centre analysis [12]. Expectedly, clinical improvement occurred more frequently in the treated (85.4%, p=0.005, **Tables S10 and S11**). Spontaneous improvement was strikingly frequent (62.5%), still with a limited subject number though. Treatment itself, however, only tended to influence longer-term outcomes (**Table 3, Tables S10 and S12**), with no significant influence on mortality (**Tables S10, S13 and S14**). 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 (p=0.046) and did not remain significant for other outcomes. However, CSF pleocytosis at presentation remained a significant predictor of no clinical improvement (p=0.004 in total, p=0.011 in the treated, **Table S11**) and unfavourable outcomes at 6 m (p=0.0004 in total, p=0.001 in the treated, **Table 3**). Additionally, previous trends with CSF pleocytosis became significant for unfavourable outcomes at 1 y (p=0.002 in total, p=0.006 in the treated, **Table S12**) and 6-m mortality (p=0.047 in total, trend in the treated, **Table S13**), still with trends but closer to significance for 1-y mortality (**Table S14**). The presence of either CSF alteration showed significant associations at 6 m (p=0.034 for unfavourable outcome, **Table 3**; p=0.032 for mortality, **Table S13**). Lobar ICH within the respective period was still significantly associated with unfavourable outcomes at 6 m (p=0.0007 in total, p=0.0008 in the treated, **Table 3**) and 1 year (p=0.006 in total, p=0.009 in the treated**, Table S12**), with strong associations with 6-m (p<0.0001 in total, p<0.0001 in the treated, **Table S13**) and 1-y mortality (p=0.0002 in total, p=0.0005 in the treated, **Table S14**). Similarly, relapse within the respective periods was strongly associated with unfavourable outcomes at 6 m (p=0.0003 in total, p=0.0005 in the treated, **Table 3**) and 1 y (p=0.0008 in total, p=0.001 in the treated, **Table S12**), but not with mortality (**Tables S13 and S14**). Relapse among improvers to immunosuppression occurred in 21.6% and 37.5% within 6 m and 1 y, respectively.

The expanded analysis tends to support an association between inflammation and lobar ICH. Indeed, clinical improvement remained significantly associated with a lower probability of future lobar ICH within 1 y in the total cohort (11.9% in improvers vs. 33.3% in non-improvers, p=0.040). Relapse (per 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). These observations were limited by the low number of events during the follow-up periods.

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 (**Table S15**). Combinations only tended to include low-dose corticosteroids and were still introduced in younger patients (63.4±1.4 vs. 69.8±0.8 y, p=0.0003). Interestingly, co-localisation of CMBs with confluent WMH(s) prompted high-dose regimens (p=0.024, **Table S15**); whereas asymmetric confluent WMH(s) were associated with a lower probability of combined treatment (p=0.001, **Table S15**). This might be because most probable CAA-RI cases (by definition with asymmetric confluent WMH(s)) originate from recent publications, and only 3 received initially combined therapy, as per current recommendations. Though still underpowered, no future lobar ICHs occurred within 6 m or 1 y in the combined therapy group vs. 10.3% (p=0.193) and 17.4% (p=0.099) in the steroid-only group (**Table S15**).

DISCUSSION

We present a systematic analysis of published probable/definite CAA-RI cases including our 7 unpublished cases. This analysis confirmed CAA-RI to be a CAA manifestation associated with a younger age at presentation, no sex preference, and various symptomatic constellations. Vasculitic presentation (ABRA) was more prevalent than perivascular CAA-RI. The co-localisation of ARIA-E and ARIA-H was the sole differentiating feature in our analysis, favouring ABRA. Current elements of probable CAA-RI criteria were observed to have modest sensitivity to recognize definite CAA-RI, excluding several cases with isolated leptomeningeal process. Importantly, incorporating LE and/or SNN on FLAIR to the criteria significantly increased the sensitivity of our analyses. The predictor analysis implicated a possible positive prognostic role of LE but mostly within the definite CAA-RI cohort, which included cases with isolated LE. Initial CSF pleocytosis was associated with a decreased probability of clinical improvement and longer-term positive outcomes in our analyses, whereas future lobar ICH was associated with adverse outcomes and mortality. Though revealing a surprising frequency of spontaneous remission, our analysis confirmed the overwhelming benefit of immunosuppressive therapy regarding short-term improvement. The associations were less clear for longer-term outcomes, and the superiority of high-dose corticosteroids was not established in our analysis.

Our study has several clinical implications. First, it highlights the potential clinical utility of radiological and laboratory features that may be more closely related to the pathogenesis of CAA-RI than current elements of probable CAA-RI criteria. Indeed, the proposed pathogenesis is an anti-Aβ autoantibody-mediated autoimmune inflammation that involves microglia/macrophages, CD4+ lymphocytes, and (in a proportion of cases) MNGCs, forming vascular/perivascular infiltration of CAA-affected meningeal/cortical vessels [81]. From the diagnostic perspective, asymmetric confluent WMH is proposed to represent vasogenic oedema developing secondary to increased vascular permeability and impaired perivascular/intravascular drainage mechanisms [82-84]. This is thought to be a remote and likely secondary [82] consequence of overlying cortical/meningeal vascular inflammation without specific/diagnostic histopathological features. Likewise, though cortical/meningeal haemorrhages might also develop secondary to vascular inflammation [67, 83], they are equally essential features in non-inflammatory CAA. However, LE and SNN are proposed to be attributable to increased meningovascular permeability through blood-meningeal barrier disruption, representing focal extravasation of contrast agent [85] and proteinaceous material [82], respectively, into the leptomeningeal/subarachnoid space. Altogether these provide local reflections of meningovascular inflammation (**Table 4**).

Keeping in mind the limitations due to our study setting, we propose our extended diagnostic criteria with LE/SNN (**Table 1**) as a research framework that merits prospective clinicopathological validation. Altogether the aim is i) to facilitate the recognition of CAA-RI cases with isolated leptomeningeal process; ii) to emphasize the potential of LE and SNN as supportive features in cases meeting the present criteria for CAA-RI, and iii) to suggest these as possible surrogate markers of treatment response. Though our study setting did not provide specificity, a prior study found excellent specificity of LE in differentiating CAA-RI from non-inflammatory CAA at histology [48], with no data on SNN to date. Though incidental associations of other causes of LE/SNN (e.g., carcinomatous/lymphomatous/infectious meningitis) with an SWI picture consistent with CAA may influence specificity, CSF is likely to show alterations in these that would be interpreted as not typical for CAA-RI. These considerations, together with other findings of our analyses, suggest that routine CSF work-up is not only inevitable in the differential diagnostics of CAA-RI, but may serve i) as a low-cost and accessible source of a direct marker of meningeal inflammation (i.e., slight lymphocytic pleocytosis); ii) a possible surrogate marker of biological change (i.e., elevated levels of protein in CSF [18]); and iii) a possible negative prognostic marker (i.e., pleocytosis). Although our finding on the association between CSF pleocytosis and an unfavourable course is in agreement

with a recent prospective study [86], it warrants further validation. The observation that i) lobar ICHs occurring early after the first clinical presentation might be significant determinants of outcome; ii) their remarkable incidence during such short periods; and iii) the findings implicating the potential role of effective immunosuppression in preventing their development altogether highlight the relevance of ICH in CAA-RI, a feature that was previously considered to be less prominent in CAA-RI than in non-inflammatory CAA [9, 48]. From a therapeutic perspective, the observed gradual 'fading out' of the efficacy of corticosteroids is reminiscent of the findings reported by a prospective study [21]. Though a 3-5-day regimen of 0.5-1.0 g daily methylprednisolone with tapering is widely accepted as first-line treatment (restricting other immunosuppressants to refractory cases) [12, 87], the evidence supporting this practice is sparse. Our observation of no significant difference in outcomes between arbitrarily defined doses of corticosteroids, together with the notable short-term mortality (with putative contributory roles of corticosteroids in a fragile population) urge for prospective multi-centre trials to elaborate an optimal regimen, including early combinations with steroid-sparing agents.

Our study has some limitations: 1) the retrospective and literature-analytic nature is inherent to both publication and observer biases; 2) the targeted identification of published true positive cases did not allow specificity assessment for the proposed criteria, urging for prospective re-evaluation; 3) the varying subject numbers and the relatively low rate of negative events/outcomes limited the applicability of multivariable analyses; and 4) the lower subject numbers with longer follow-ups and 5) the surprisingly low proportion of reports with precise data on dosing limited the power of the corresponding analyses. The strengths include the unprecedented subject number, the case-wise collection, and the rigorously dichotomised data, enabling the horizontal/vertical evaluation of several potential predictors not having been previously addressed systematically.

REFERENCES

1. Fakan B, Reisz Z, Zadori D, Vecsei L, Klivenyi P, Szalardy L. Predictors of localization, outcome, and etiology of spontaneous intracerebral hemorrhages: focus on cerebral amyloid angiopathy. *J Neural Transm (Vienna).* 2020;127:963-972
2. Thal DR, Ghebremedhin E, Orantes M, Wiestler OD. Vascular pathology in Alzheimer disease: correlation of cerebral amyloid angiopathy and arteriosclerosis/lipohyalinosis with cognitive decline. *J Neuropathol Exp Neurol.* 2003;62:1287-1301
3. Yamada M. Cerebral amyloid angiopathy: emerging concepts. *J Stroke.* 2015;17:17-30
4. Greenberg SM, Vonsattel JP, Segal AZ, Chiu RI, Clatworthy AE, Liao A, Hyman BT, Rebeck GW. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. *Neurology.* 1998;50:961-965
5. Linn J, Halpin A, Demaerel P, Ruhland J, Giese AD, Dichgans M, van Buchem MA, Bruckmann H, Greenberg SM. Prevalence of superficial siderosis in patients with cerebral amyloid angiopathy. *Neurology.* 2010;74:1346-1350
6. Charidimou A, Boulouis G, Frosch MP, Baron JC, Pasi M, Albucher JF, Banerjee G, Barbato C, Bonneville F, Brandner S, Calviere L, Caparros F, Casolla B, Cordonnier C, Delisle MB, Deramecourt V, Dichgans M, Gokcal E, Herms J, Hernandez-Guillamon M, Jager HR, Jaunmuktane Z, Linn J, Martinez-Ramirez S, Martinez-Saez E, Mawrin C, Montaner J, Moulin S, Olivot JM, Piazza F, Puy L, Raposo N, Rodrigues MA, Roeber S, Romero JR, Samarasekera N, Schneider JA, Schreiber S, Schreiber F, Schwall C, Smith C, Szalardy L, Varlet P, Viguier A, Wardlaw JM, Warren A, Wollenweber FA, Zedde M, van Buchem MA, Gurol ME, Viswanathan A, Al-Shahi Salman R, Smith EE, Werring DJ, Greenberg SM. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. *Lancet Neurol.* 2022;21:714-725
7. Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, Ellison D, Hilton DA, Williams TL, MacKenzie JM, Xuereb JH, Love S. Abeta-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain.* 2005;128:500-515
8. Chung KK, Anderson NE, Hutchinson D, Synek B, Barber PA. Cerebral amyloid angiopathy related inflammation: three case reports and a review. *J Neurol Neurosurg Psychiatry.* 2011;82:20-26
9. Salvarani C, Hunder GG, Morris JM, Brown RD, Jr., Christianson T, Giannini C. Abeta-related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. *Neurology.* 2013;81:1596-1603
10. Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. *Ann Neurol.* 2004;55:250-256
11. Auriel E, Charidimou A, Gurol ME, Ni J, Van Etten ES, Martinez-Ramirez S, Boulouis G, Piazza F, DiFrancesco JC, Frosch MP, Pontes-Neto OV, Shoamanesh A, Reijmer Y, Vashkevich A, Ayres AM, Schwab KM, Viswanathan A, Greenberg SM. Validation of Clinicoradiological Criteria for the Diagnosis of Cerebral Amyloid Angiopathy-Related Inflammation. *JAMA Neurol.* 2016;73:197-202
12. Regenhardt RW, Thon JM, Das AS, Thon OR, Charidimou A, Viswanathan A, Gurol ME, Chwalisz BK, Frosch MP, Cho TA, Greenberg SM. Association Between Immunosuppressive Treatment and Outcomes of Cerebral Amyloid Angiopathy-Related Inflammation. *JAMA Neurol.* 2020;77:1261-1269
13. Kinnecom C, Lev MH, Wendell L, Smith EE, Rosand J, Frosch MP, Greenberg SM. Course of cerebral amyloid angiopathy-related inflammation. *Neurology.* 2007;68:1411-1416
14. Sperling RA, Jack CR, Jr., Black SE, Frosch MP, Greenberg SM, Hyman BT, Scheltens P, Carrillo MC, Thies W, Bednar MM, Black RS, Brashear HR, Grundman M, Siemers ER, Feldman HH, Schindler RJ. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. *Alzheimers Dement.* 2011;7:367-385
15. DiFrancesco JC, Brioschi M, Brighina L, Ruffmann C, Saracchi E, Costantino G, Galimberti G, Conti E, Curto NA, Marzorati L, Remida P, Tagliavini F, Savoiardo M, Ferrarese C. Anti-Abeta

autoantibodies in the CSF of a patient with CAA-related inflammation: a case report. *Neurology.* 2011;76:842-844
16. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig L, Lijmer JG, Moher D, Rennie D, de Vet HC, Kressel HY, Rifai N, Golub RM, Altman DG, Hooft L, Korevaar DA, Cohen JF. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ.* 2015;351:h5527
17. Sergeant, ESG. Epitools Epidemiological Calculators 2018. https://epitools.ausvet.com.au/ciproportion. Accessed 18 March, 2023.
18. Kimura A, Sakurai T, Yoshikura N, Hayashi Y, Takemura M, Takahashi H, Inuzuka T. Corticosteroid therapy in a patient with cerebral amyloid angiopathy-related inflammation. *J Neuroinflammation.* 2013;10:39
19. Rastogi V, Donnangelo LL, Asaithambi G, Bidari S, Khanna AY, Hedna VS. Recurrence of Lobar Hemorrhage: A Red Flag for Cerebral Amyloid Angiopathy-related Inflammation? *Innov Clin Neurosci.* 2015;12:20-26
20. Hagiwara Y, Yanagisawa T, Atsumi C, Maki F, Shimizu T, Hasegawa Y. [A case report of cerebral amyloid angiopathy-related inflammation treated with cyclophosphamide]. *Rinsho Shinkeigaku.* 2014;54:46-51
21. Rempe T, Sollero CEV, Rodriguez E, Viswanathan VT, Carlson A, Rees J, Tuna IS, Kresak J, Gyang TV. Corticosteroids lead to short-term improvement in cerebral amyloid angiopathy-related inflammation. *J Neuroimmunol.* 2020;348:577377
22. Castro Caldas A, Silva C, Albuquerque L, Pimentel J, Silva V, Ferro JM. Cerebral Amyloid Angiopathy Associated with Inflammation: Report of 3 Cases and Systematic Review. *J Stroke Cerebrovasc Dis.* 2015;24:2039-2048
23. Chen D, Roytman M, Kirou KA, Navi BB, Schweitzer AD. A case of inflammatory cerebral amyloid angiopathy after ischemic stroke - a potential risk factor related to blood-brain barrier disruption. *Clin Imaging.* 2022;82:161-165
24. Maddox D, Ward K, Robertson T, Boggild M. Cerebral amyloid angiopathy with related inflammation masquerading as crescendo transient ischaemic attacks. *Pract Neurol.* 2022;22:216-219
25. Poli L, De Giuli V, Piazza F, Volonghi I, Bigliardi G, Vallone S, Nichelli PF, Gasparotti R, Zini A, Padovani A, Pezzini A. A challenging diagnosis of reversible "vascular" dementia: Cerebral amyloid angiopathy-related inflammation. *J Neuroimmunol.* 2020;338:577109
26. Martin-Jimenez P, Sanchez-Tornero M, Llamas-Velasco S, Guerrero-Molina MP, Gonzalez-Sanchez M, Herrero-San Martin A, Blanco-Palmero V, Calleja-Castano P, Francisco-Gonzalo J, Hilario A, Ramos A, Salvador E, Toldos O, Hernandez-Lain A, Perez-Martinez DA, Villarejo-Galende A. Cerebral amyloid angiopathy-related inflammation: clinical features and treatment response in a case series. *Neurologia (Engl Ed).* 2021
27. Dumitrascu OM, Okazaki EM, Cobb SH, Zarka MA, De Souza SA, Kumar G, O'Carroll CB. Amyloid-Beta-Related Angiitis with Distinctive Neuro-Ophthalmologic Features. *Neuroophthalmology.* 2018;42:237-241
28. Chu S, Xu F, Su Y, Chen H, Cheng X. Cerebral Amyloid Angiopathy (CAA)-Related Inflammation: Comparison of Inflammatory CAA and Amyloid-beta-Related Angiitis. *J Alzheimers Dis.* 2016;51:525-532
29. Du Y, Liu C, Ma C, Xu X, Zhou X, Zhou H, Huang C. Cerebral amyloid angiopathy-related inflammation: a case report presenting with a rare variant in SORL1 gene. *BMC Neurol.* 2019;19:97
30. Safriel Y, Sze G, Westmark K, Baehring J. MR spectroscopy in the diagnosis of cerebral amyloid angiopathy presenting as a brain tumor. *AJNR Am J Neuroradiol.* 2004;25:1705-1708
31. Kotsenas AL, Morris JM, Wald JT, Parisi JE, Campeau NG. Tumefactive cerebral amyloid angiopathy mimicking CNS neoplasm. *AJR Am J Roentgenol.* 2013;200:50-56
32. Fountain NB, Eberhard DA. Primary angiitis of the central nervous system associated with cerebral amyloid angiopathy: report of two cases and review of the literature. *Neurology.* 1996;46:190-197

33. Tamargo RJ, Connolly ES, Jr., McKhann GM, Khandji A, Chang Y, Libien J, Adams D. Clinicopathological review: primary angiitis of the central nervous system in association with cerebral amyloid angiopathy. *Neurosurgery.* 2003;53:136-143; discussion 143
34. Marotti JD, Savitz SI, Kim WK, Williams K, Caplan LR, Joseph JT. Cerebral amyloid angiitis processing to generalized angiitis and leucoencephalitis. *Neuropathol Appl Neurobiol.* 2007;33:475-479
35. Hosoi Y, Uchiyama T, Yoshida M, Takechi D, Shimizu T, Ohashi T, Otsuki Y. [A case of cerebral amyloid angiopathy with reversible white matter lesions and multiple cerebral microbleeds]. *Rinsho Shinkeigaku.* 2012;52:90-95
36. Ryan NS, Lashley T, Revesz T, Dantu K, Fox NC, Morris HR. Spontaneous ARIA (amyloid-related imaging abnormalities) and cerebral amyloid angiopathy related inflammation in presenilin 1-associated familial Alzheimer's disease. *J Alzheimers Dis.* 2015;44:1069-1074
37. Szpak GM, Lewandowska E, Sliwinska A, Stepien T, Tarka S, Mendel T, Rafalowska J. Inflammatory cerebral amyloid angiopathy: the overlap of perivascular (PAN-like) with vasculitic (Abeta-related angiitis) form: an autopsy case. *Folia Neuropathol.* 2011;49:335-347
38. Takeda A, Tatsumi S, Yamashita M, Yamamoto T. [Granulomatous angiitis of the CNS associated with cerebral amyloid angiopathy--an autopsied case with widespread involvement]. *Brain Nerve.* 2007;59:537-543
39. DeWitt LD, Louis DN. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 27-1991. A 75-year-old man with dementia, myoclonic jerks, and tonic-clonic seizures. *New England Journal of Medicine.* 1991;325:42-54
40. Anders KH, Wang ZZ, Kornfeld M, Gray F, Soontornniyomkij V, Reed LA, Hart MN, Menchine M, Secor DL, Vinters HV. Giant cell arteritis in association with cerebral amyloid angiopathy: immunohistochemical and molecular studies. *Hum Pathol.* 1997;28:1237-1246
41. Annweiler C, Paccalin M, Berrut G, Hommet C, Lavigne C, Saint-Andre JP, Beauchet O. Association of angiitis of central nervous system, cerebral amyloid angiopathy, and Alzheimer's disease: report of an autopsy case. *Vasc Health Risk Manag.* 2008;4:1471-1474
42. Greenberg SM, Rapalino O, Frosch MP. Case records of the Massachusetts General Hospital. Case 22-2010. An 87-year-old woman with dementia and a seizure. *N Engl J Med.* 2010;363:373-381
43. Morishige M, Abe T, Kamida T, Hikawa T, Fujiki M, Kobayashi H, Okazaki T, Kimura N, Kumamoto T, Yamada A, Kawano Y. Cerebral vasculitis associated with amyloid angiopathy: case report. *Neurol Med Chir (Tokyo).* 2010;50:336-338
44. Bogner S, Bernreuther C, Matschke J, Barrera-Ocampo A, Sepulveda-Falla D, Leypoldt F, Magnus T, Haag F, Bergmann M, Bruck W, Vogelgesang S, Glatzel M. Immune activation in amyloid-beta-related angiitis correlates with decreased parenchymal amyloid-beta plaque load. *Neurodegener Dis.* 2014;13:38-44
45. Sakai K, Hayashi S, Sanpei K, Yamada M, Takahashi H. Multiple cerebral infarcts with a few vasculitic lesions in the chronic stage of cerebral amyloid angiopathy-related inflammation. *Neuropathology.* 2012;32:551-556
46. Ichimata S, Hata Y, Yoshida K, Nishida N. Autopsy of a multiple lobar hemorrhage case with amyloid-beta-related angiitis. *Neuropathology.* 2020;40:280-286
47. Munoz JE, Saiz A, Ribalta T, Graus F, Tolosa E. Cerebral amyloid angiopathy, leukoencephalopathy and dementia of acute onset. Clinicopathological study of a new case. *Eur J Neurol.* 1995;1:229-232
48. Salvarani C, Morris JM, Giannini C, Brown RD, Jr., Christianson T, Hunder GG. Imaging Findings of Cerebral Amyloid Angiopathy, Abeta-Related Angiitis (ABRA), and Cerebral Amyloid Angiopathy-Related Inflammation: A Single-Institution 25-Year Experience. *Medicine (Baltimore).* 2016;95:e3613
49. Hainline C, Rucker JC, Zagzag D, Golfinos JG, Lui YW, Liechty B, Warren FA, Balcer LJ, Galetta SL. Tumoral Presentation of Homonymous Hemianopia and Prosopagnosia in Cerebral Amyloid Angiopathy-Related Inflammation. *J Neuroophthalmol.* 2017;37:48-52

50. Matta G, Velakoulis D, Gaillard F, McLean CA, Yerra R. Creutzfeldt-Jakob disease, cerebral amyloid angiopathy and Abeta-related angiitis with neuropsychiatric manifestations. *Aust N Z J Psychiatry.* 2017;51:740-741
51. Raghavan P, Looby S, Bourne TD, Wintermark M. Cerebral amyloid angiopathy-related inflammation: A potentially reversible cause of dementia with characteristic imaging findings. *J Neuroradiol.* 2016;43:11-17
52. Aghetti A, Sene D, Polivka M, Shor N, Lechtman S, Chabriat H, Jouvent E, Guey S. Cerebral Amyloid Angiopathy Related Inflammation With Prominent Meningeal Involvement. A Report of 2 Cases. *Front Neurol.* 2019;10:984
53. Piazza F, Greenberg SM, Savoiardo M, Gardinetti M, Chiapparini L, Raicher I, Nitrini R, Sakaguchi H, Brioschi M, Billo G, Colombo A, Lanzani F, Piscosquito G, Carriero MR, Giaccone G, Tagliavini F, Ferrarese C, DiFrancesco JC. Anti-amyloid beta autoantibodies in cerebral amyloid angiopathy-related inflammation: implications for amyloid-modifying therapies. *Ann Neurol.* 2013;73:449-458
54. Machida K, Tojo K, Naito KS, Gono T, Nakata Y, Ikeda S. Cortical petechial hemorrhage, subarachnoid hemorrhage and corticosteroid-responsive leukoencephalopathy in a patient with cerebral amyloid angiopathy. *Amyloid.* 2008;15:60-64
55. Nelson T, Leung B, Bannykh S, Shah KS, Patel J, Dumitrascu OM. Cerebral Amyloid Angiopathy-Related Inflammation in the Immunosuppressed: A Case Report. *Front Neurol.* 2019;10:1283
56. Schwab P, Lidov HG, Schwartz RB, Anderson RJ. Cerebral amyloid angiopathy associated with primary angiitis of the central nervous system: report of 2 cases and review of the literature. *Arthritis Rheum.* 2003;49:421-427
57. Greenberg SM, Parisi JE, Keegan BM. A 63-year-old man with headaches and behavioral deterioration. *Neurology.* 2007;68:782-787
58. Melzer N, Harder A, Gross CC, Wolfer J, Stummer W, Niederstadt T, Meuth SG, Marziniak M, Grauer OM, Wiendl H. CD4(+) T cells predominate in cerebrospinal fluid and leptomeningeal and parenchymal infiltrates in cerebral amyloid beta-related angiitis. *Arch Neurol.* 2012;69:773-777
59. Boncoraglio GB, Piazza F, Savoiardo M, Farina L, DiFrancesco JC, Prioni S, Tagliavini F, Parati EA, Giaccone G. Prodromal Alzheimer's disease presenting as cerebral amyloid angiopathy-related inflammation with spontaneous amyloid-related imaging abnormalities and high cerebrospinal fluid anti-Abeta autoantibodies. *J Alzheimers Dis.* 2015;45:363-367
60. Caplan LR, Louis DN, Greenberg SM. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 10-2000. A 63-year-old man with changes in behavior and ataxia. *New England Journal of Medicine.* 2000;342:957-965
61. McHugh JC, Ryan AM, Lynch T, Dempsey E, Stack J, Farrell MA, Kelly PJ. Steroid-responsive recurrent encephalopathy in a patient with cerebral amyloid angiopathy. *Cerebrovasc Dis.* 2007;23:66-69
62. Weiss SA, Pisapia D, Mayer SA, Willey JZ, Lee K. Amyloid beta-Related Angiitis Causing Coma Responsive to Immunosuppression. *Case Rep Pathol.* 2012;2012:678746
63. Kolodny EH, Rebeiz JJ, Caviness VS, Jr., Richardson EP, Jr. Granulomatous angiitis of the central nervous system. *Arch Neurol.* 1968;19:510-524
64. Makol A, Parisi JE, Petty GW, Watson RE, Warrington KJ. A 60-year-old woman with headache, confusion, and hallucinations. *Arthritis Care Res (Hoboken).* 2011;63:1486-1494
65. Moussaddy A, Levy A, Strbian D, Sundararajan S, Berthelet F, Lanthier S. Inflammatory Cerebral Amyloid Angiopathy, Amyloid-beta-Related Angiitis, and Primary Angiitis of the Central Nervous System: Similarities and Differences. *Stroke.* 2015;46:e210-213
66. Szalardy L, Zadori D, Klivenyi P, Vecsei L. The Role of Cerebrospinal Fluid Biomarkers in the Evolution of Diagnostic Criteria in Alzheimer's Disease: Shortcomings in Prodromal Diagnosis. *J Alzheimers Dis.* 2016;53:373-392

67. Traschutz A, Tzaridis T, Penner AH, Kuchelmeister K, Urbach H, Hattingen E, Heneka MT. Reduction of microbleeds by immunosuppression in a patient with Abeta-related vascular inflammation. *Neurol Neuroimmunol Neuroinflamm.* 2015;2:e165
68. Schaumberg J, Trauscheid M, Eckert B, Petersen D, Schulz-Schaeffer W, Rother J, Heide W. [Cerebral amyloid angiopathy associated with inflammation]. *Nervenarzt.* 2018;89:682-691
69. Ringman JM, Joe E, Sheikh-Bahaei N, Miller C, Vinters HV, Guzman S, Chui HC. Cerebral Amyloid Angiopathy-related Inflammation Presenting With a Cystic Lesion in Young-onset Alzheimer Disease. *Alzheimer Dis Assoc Disord.* 2021;35:265-268
70. Kurian M, Burkhardt K, Assal F, Kovari E, Horvath J. Amyloid plaques and intraneuronal tau inclusions in A-beta-related angiitis (ABRA). *Neuropathol Appl Neurobiol.* 2012;38:391-394
71. Konig LS, Wiesmann M, Pjontek R, Sellhaus B, Schulz JB, Tauber SC. [Amyloid beta-related angiitis as rare cause of a generalized convulsive seizure]. *Nervenarzt.* 2015;86:1270-1272
72. Hermann DM, Keyvani K, van de Nes J, Weimar C, Wiltfang J, Nitsch RM, Szodorai A. Brain-reactive beta-amyloid antibodies in primary CNS angiitis with cerebral amyloid angiopathy. *Neurology.* 2011;77:503-505
73. Sakai K, Noguchi-Shinohara M, Ikeda T, Hamaguchi T, Ono K, Yamada M. Cerebrospinal fluid cytokines and metalloproteinases in cerebral amyloid angiopathy-related inflammation. *Acta Neurol Scand.* 2021;143:450-457
74. Mayeux R, Stern Y, Ottman R, Tatemichi TK, Tang MX, Maestre G, Ngai C, Tycko B, Ginsberg H. The apolipoprotein epsilon 4 allele in patients with Alzheimer's disease. *Ann Neurol.* 1993;34:752-754
75. Vemuri P, Wiste HJ, Weigand SD, Knopman DS, Shaw LM, Trojanowski JQ, Aisen PS, Weiner M, Petersen RC, Jack CR, Jr. Effect of apolipoprotein E on biomarkers of amyloid load and neuronal pathology in Alzheimer disease. *Ann Neurol.* 2010;67:308-316
76. Premkumar DR, Cohen DL, Hedera P, Friedland RP, Kalaria RN. Apolipoprotein E-epsilon4 alleles in cerebral amyloid angiopathy and cerebrovascular pathology associated with Alzheimer's disease. *Am J Pathol.* 1996;148:2083-2095
77. Ringman JM, Sachs MC, Zhou Y, Monsell SE, Saver JL, Vinters HV. Clinical predictors of severe cerebral amyloid angiopathy and influence of APOE genotype in persons with pathologically verified Alzheimer disease. *JAMA Neurol.* 2014;71:878-883
78. Rannikmae K, Kalaria RN, Greenberg SM, Chui HC, Schmitt FA, Samarasekera N, Al-Shahi Salman R, Sudlow CL. APOE associations with severe CAA-associated vasculopathic changes: collaborative meta-analysis. *J Neurol Neurosurg Psychiatry.* 2014;85:300-305
79. Charidimou A, Boulouis G, Haley K, Auriel E, van Etten ES, Fotiadis P, Reijmer Y, Ayres A, Vashkevich A, Dipucchio ZY, Schwab KM, Martinez-Ramirez S, Rosand J, Viswanathan A, Greenberg SM, Gurol ME. White matter hyperintensity patterns in cerebral amyloid angiopathy and hypertensive arteriopathy. *Neurology.* 2016;86:505-511
80. Sakaguchi H, Ueda A, Kosaka T, Yamashita S, Kimura E, Yamashita T, Maeda Y, Hirano T, Uchino M. Cerebral amyloid angiopathy-related inflammation presenting with steroid-responsive higher brain dysfunction: case report and review of the literature. *J Neuroinflammation.* 2011;8:116
81. Greenberg SM, Bacskai BJ, Hernandez-Guillamon M, Pruzin J, Sperling R, van Veluw SJ. Cerebral amyloid angiopathy and Alzheimer disease - one peptide, two pathways. *Nat Rev Neurol.* 2020;16:30-42
82. Barakos J, Sperling R, Salloway S, Jack C, Gass A, Fiebach JB, Tampieri D, Melancon D, Miaux Y, Rippon G, Black R, Lu Y, Brashear HR, Arrighi HM, Morris KA, Grundman M. MR imaging features of amyloid-related imaging abnormalities. *AJNR Am J Neuroradiol.* 2013;34:1958-1965
83. Sperling R, Salloway S, Brooks DJ, Tampieri D, Barakos J, Fox NC, Raskind M, Sabbagh M, Honig LS, Porsteinsson AP, Lieberburg I, Arrighi HM, Morris KA, Lu Y, Liu E, Gregg KM, Brashear HR, Kinney GG, Black R, Grundman M. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. *Lancet Neurol.* 2012;11:241-249

84. Carare RO, Aldea R, Agarwal N, Bacskai BJ, Bechman I, Boche D, Bu G, Bulters D, Clemens A, Counts SE, de Leon M, Eide PK, Fossati S, Greenberg SM, Hamel E, Hawkes CA, Koronyo-Hamaoui M, Hainsworth AH, Holtzman D, Ihara M, Jefferson A, Kalaria RN, Kipps CM, Kanninen KM, Leinonen V, McLaurin J, Miners S, Malm T, Nicoll JAR, Piazza F, Paul G, Rich SM, Saito S, Shih A, Scholtzova H, Snyder H, Snyder P, Thormodsson FR, van Veluw SJ, Weller RO, Werring DJ, Wilcock D, Wilson MR, Zlokovic BV, Verma A. Clearance of interstitial fluid (ISF) and CSF (CLIC) group-part of Vascular Professional Interest Area (PIA): Cerebrovascular disease and the failure of elimination of Amyloid-beta from the brain and retina with age and Alzheimer's disease-Opportunities for Therapy. *Alzheimers Dement (Amst).* 2020;12:e12053
85. Absinta M, Cortese IC, Vuolo L, Nair G, de Alwis MP, Ohayon J, Meani A, Martinelli V, Scotti R, Falini A, Smith BR, Nath A, Jacobson S, Filippi M, Reich DS. Leptomeningeal gadolinium enhancement across the spectrum of chronic neuroinflammatory diseases. *Neurology.* 2017;88:1439-1444
86. Plotzker AS, Henson RL, Fagan AM, Morris JC, Day GS. Clinical and Paraclinical Measures Associated with Outcome in Cerebral Amyloid Angiopathy with Related Inflammation. *J Alzheimers Dis.* 2021;80:133-142
87. Viswanathan A, Greenberg SM, MGH Stroke Service. Inflammatory CAA protocol 2022. https://www.massgeneral.org/assets/mgh/pdf/neurology/stop-stroke/inflammatory_caa_protocol.pdf. Accessed 15 November, 2022.

TABLE 1 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 haemorrhagic alteration(s).	2. Clinical features: headache, 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 haemorrhagic alteration(s).
3. MRI features (haemorrhagic)[#]: lobar ICH(s), lobar CMB(s), cSAH(s), *and/or* CSS(s) of any age; absence of deep (ganglionic/thalamic/brainstem) haemorrhagic alteration; cerebellar haemorrhagic alterations do not count either in favour or against the diagnosis.	3. MRI features (haemorrhagic)[#]: lobar ICH(s), lobar CMB(s), cSAH(s), *and/or* CSS(s) of any age; absence of deep (ganglionic/thalamic/brainstem) haemorrhagic alteration; cerebellar haemorrhagic alterations do not count either in favour or against the diagnosis.
4. MRI features (non-haemorrhagic): 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 oedema surrounding present ICH.	4. MRI features (non-haemorrhagic): 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 oedema 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. [11] with slight modifications and rephrasing;

[#], analogous with possible/probable CAA in terms of haemorrhagic alterations in the modified Boston criteria [5].

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

TABLE 2 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	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 confluent WMH(s)	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 haemorrhage; CSF, cerebrospinal fluid; DXM, dexamethasone; F, frontal; FLAIR, fluid-attenuated inversion recovery; I, insular; ICH, intracerebral haemorrhage; 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; pTau, phosphorylated Tau; 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.

TABLE 3 Predictors of positive outcome at 6 months in probable/definite CAA-RI cases

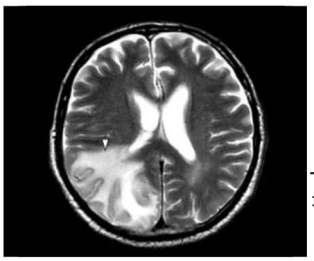
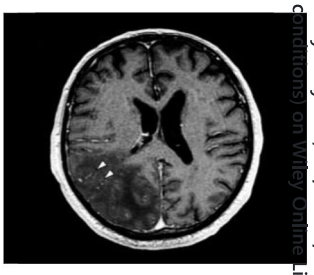
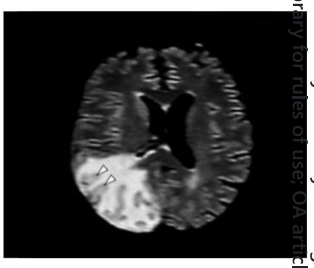
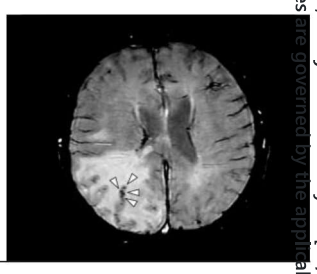
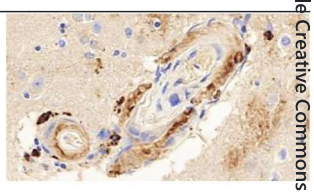
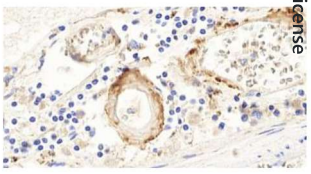
Predictors	*Treated and non-treated cases collectively*					*Treated cases*				
	Positive outcome	**Negative outcome**	**Subject # per group**	**p-value Chi²**	**p-value MBLR**	**Positive outcome**	**Negative outcome**	**Subject # per group**	**p-value Chi²**	**p-value MBLR**
Age (y)	67.4±1.0	69.0±1.4	94 vs 44	*0.390*	-	67.4 ±1.1	67.7±1.4	87 vs 35	*0.871*	-
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***	*n.a.*[0]	**100.0**	**22.2**	**87 vs 36**	***<0.0001***	*n.a.*[0]
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***	***0.009***[1]	**22.8**	**60.0**	**57 vs 25**	***0.001***	*n.a.*[10]
CSF elevated protein level	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***	*0.112*[2]	65.5	87.5	55 vs 24	*0.057*	-
ApoEε4 carrier	73.9	77.8	23 vs 9	*1.000*	-	77.3	87.5	22 vs 8	*1.000*	-
ApoEε4/ε4	60.9	55.6	23 vs 9	*1.000*	-	63.6	62.5	22 vs 8	*1.000*	-
ApoEε4 or ε2 carrier	82.6	88.9	23 vs 9	*1.000*	-	86.4	87.5	22 vs 8	*1.000*	-
ApoEε2 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***	***0.007***[1], ***0.015***[2]	**2.4**	**25.0**	**85 vs 28**	***0.0008***	*n.a.*[10]
Relapse within 6 m*	**13.0**	**75.0**	**92 vs 8**	***0.0003***	*n.a.*[10]	**14.1**	**75.0**	**85 vs 8**	***0.0005***	*n.a.*[10]

CAA-RI, cerebral amyloid angiopathy-related inflammation; CMB, cerebral microbleed; CSF, cerebrospinal fluid; FLAIR, fluid-attenuated inversion recovery; ICH, intracerebral haemorrhage; m, months; MBLR, multivariable binary logistic regression; *n.a.*[0], not applicable due to zero count in an outcome; *n.a.*[10], not applicable due to rule of 10; WMH, white matter hyperintensity on T2/FLAIR; y, year; #, number; *, sub-analysis of patients with initial clinical improvement.

[1], model 1 with CSF pleocytosis and Future lobar ICH within 6 m as covariates; [2], model 2 with CSF either alteration and Future lobar ICH within 6 m as covariates.

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

TABLE 4 Summary of hallmark radiological and histopathological features of CAA-RI

Radiological features (MRI)	
Non-haemorrhagic features	
Asymmetric confluent WMH sequence/phenomenon: T2 and FLAIR hyperintensity (T1 hypointensity) most common presentation reaches the immediately subcortical WM may represent vasogenic oedema (BBB disruption/impaired (peri)vascular drainage) may be associated with mass effect histology: rarefaction, gliosis, myelin pallor (non-diagnostic site for biopsy)	
Leptomeningeal enhancement (LE) sequence/phenomenon: Gad+ T1 (Gad+ FLAIR) hyperintensity a.k.a. pial-arachnoid contrast enhancement in association with asymmetric confluent WMH or isolated may represent increased vascular permeability (BMB disruption) and congestion prone to be associated/co-localise with SNN prone to be associated with CSF pleocytosis	
Sulcal non-nulling (SNN) sequence/phenomenon: FLAIR hyperintensity a.k.a. sulcal effusion, sulcal hyperintensity, or sulcal non-attenuation of CSF in association with asymmetric confluent WMH or isolated may represent altered CSF consistency (effusion of proteinaceous material) prone to be associated/co-localise with LE CAA-associated differential: cSAH (hypointense on SWI, hyperdense on CT scan)	
Haemorrhagic features	
Lobar ICH, lobar CMB, cSAH, and/or CSS sequence: SWI (T2*, GRE) may tend to co-localise with asymmetric confluent WMH ICH during the course is prone to be associated with poor outcome histology: perivascular erythrocytes, haemosiderin, siderophages, or haematoidin *(arrows point to CMBs)*	
Histopathological features	
Transmural inflammatory infiltrates associated with CAA a.k.a. vasculitic CAA-RI, destructive CAA-RI, or ABRA mural ± perivascular infiltration of CAA-associated vessels by: lymphocytes and/or microglia/macrophages, ±MNGCs	
Perivascular inflammatory infiltrates associated with CAA a.k.a. perivascular CAA-RI, non-vasculitic CAA-RI, or non-destructive CAA-RI perivascular-only infiltration of CAA-associated vessels by: lymphocytes and/or microglia/macrophages, ±MNGCs	

ABRA, amyloid beta-related angiitis; BBB, blood-brain barrier, BMB, blood-meningeal barrier; CAA, cerebral amyloid angiopathy; CAA-RI, CAA-related inflammation; CMB, cerebral microbleed; cSAH, convexity subarachnoid haemorrhage; CSF, cerebrospinal fluid; CSS, cortical superficial siderosis; CT, computed tomography; FLAIR, fluid-attenuated inversion recovery; Gad+, with Gadolinium; GRE, gradient-echo; ICH, intracerebral haemorrhage; MNGC, multinucleated giant cell; MRI, magnetic resonance imaging; SWI, susceptibility-weighted imaging; WM, white matter; WMH, WM hyperintensity.

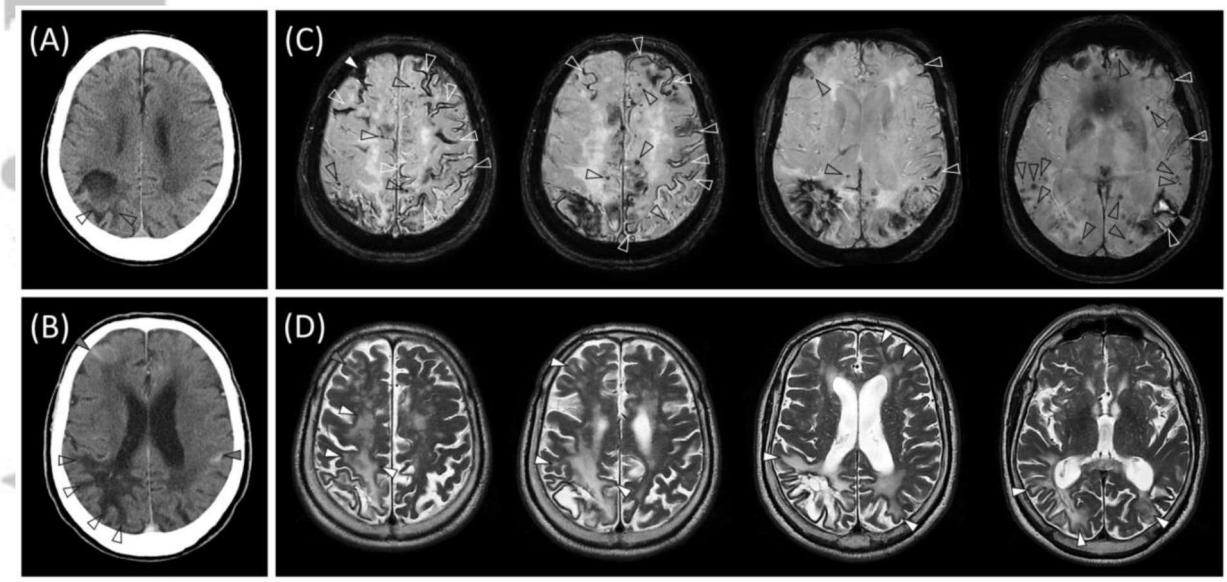


FIGURE 1 Imaging of Case 1. Minimal surrounding hypodensity on cranial computed tomography after regression of the first right parietal ICH (arrowheads), 6 years before presentation (A). Extensive hypodensity surrounding the site of prior ICH (hollow arrowheads) with a right frontal and a left parietal cSAH (grey-filled arrowheads, B). Multiple CMBs and diffuse CSS (a few examples marked with black and white hollow arrowheads respectively) with subacute cSAHs and ICHs (examples marked with a white-filled and a grey-filled arrowhead, respectively) on SWI (C). Asymmetric confluent WMHs reaching the immediate subcortex in each lobe of the right hemisphere and in the left frontal and parietal-occipital areas, consistent with probable CAA-RI (white-filled arrowheads, D). The right frontal 'SNN' (grey-filled arrowhead in D) is consistent with a cSAH (white-filled arrowhead in C).

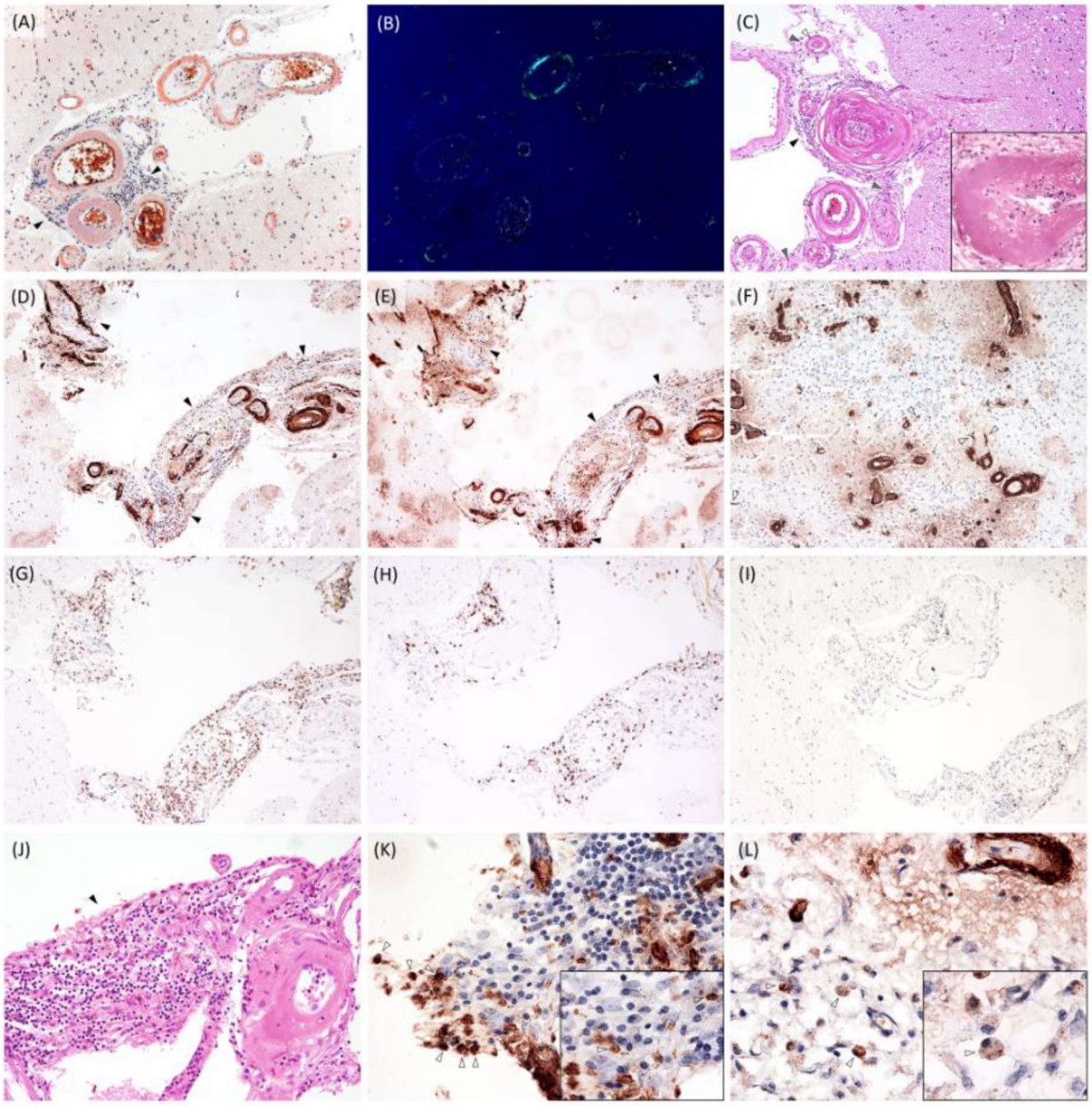


FIGURE 2 Neuropathological findings of Case 1. Prominent congophilic angiopathy (Congo red, A) with apple-green birefringence under the polarised microscope (B). Changes consistent with modified Vonsattel grade 4 with double-barrelling (black hollow arrowheads), wall fragmentation (grey hollow arrowhead), perivascular erythrocytes (grey-filled arrowheads, Haematoxylin-Eosin (HE), C), and fibrinoid necrosis (inlet of C). Prominent immunoreactivity against $A\beta_{1\text{-}40}$ (D) and less against $A\beta_{1\text{-}42}$ (E). Microinfarct around occluded CAA vessels and prominent capillary CAA (i.e., Type-1, a few capillaries marked with arrowheads, Aβ, F). The perivascular infiltrates apparent through A-K (black-filled arrowheads) 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 (arrowheads, Aβ, K), and in the microinfarcts (arrowheads, Aβ, L).

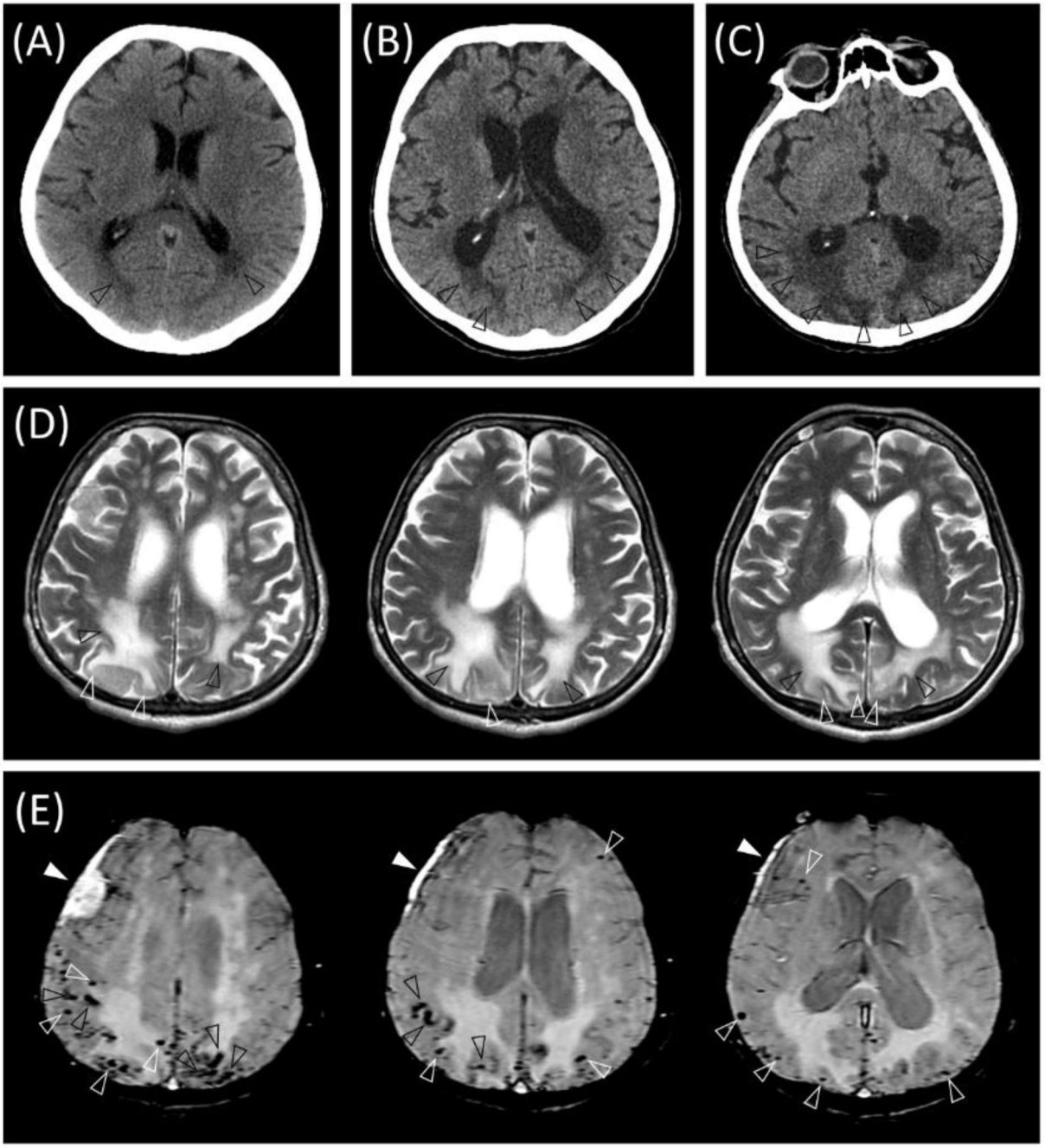


FIGURE 3 Imaging of Case 2. Minor bioccipital periventricular lucencies (arrowheads) 7 years before presentation (A). Increased atrophy and a moderate increase in bioccipital WMHs (arrowheads) at first seizure (B). The dramatic expansion of the occipital-parietal WMHs with right-sided predominance (arrowheads) 2.5 months later (C). MRI T2 demonstrates asymmetric confluent WMHs (black hollow arrowheads) with focal cortical involvement (white hollow arrowheads, D) and associated CMBs and CSSs (a few examples marked with white and black hollow arrowheads, respectively) on SWI (E). A right frontal meningioma with a dural tail is apparent (white-filled arrowheads in E).

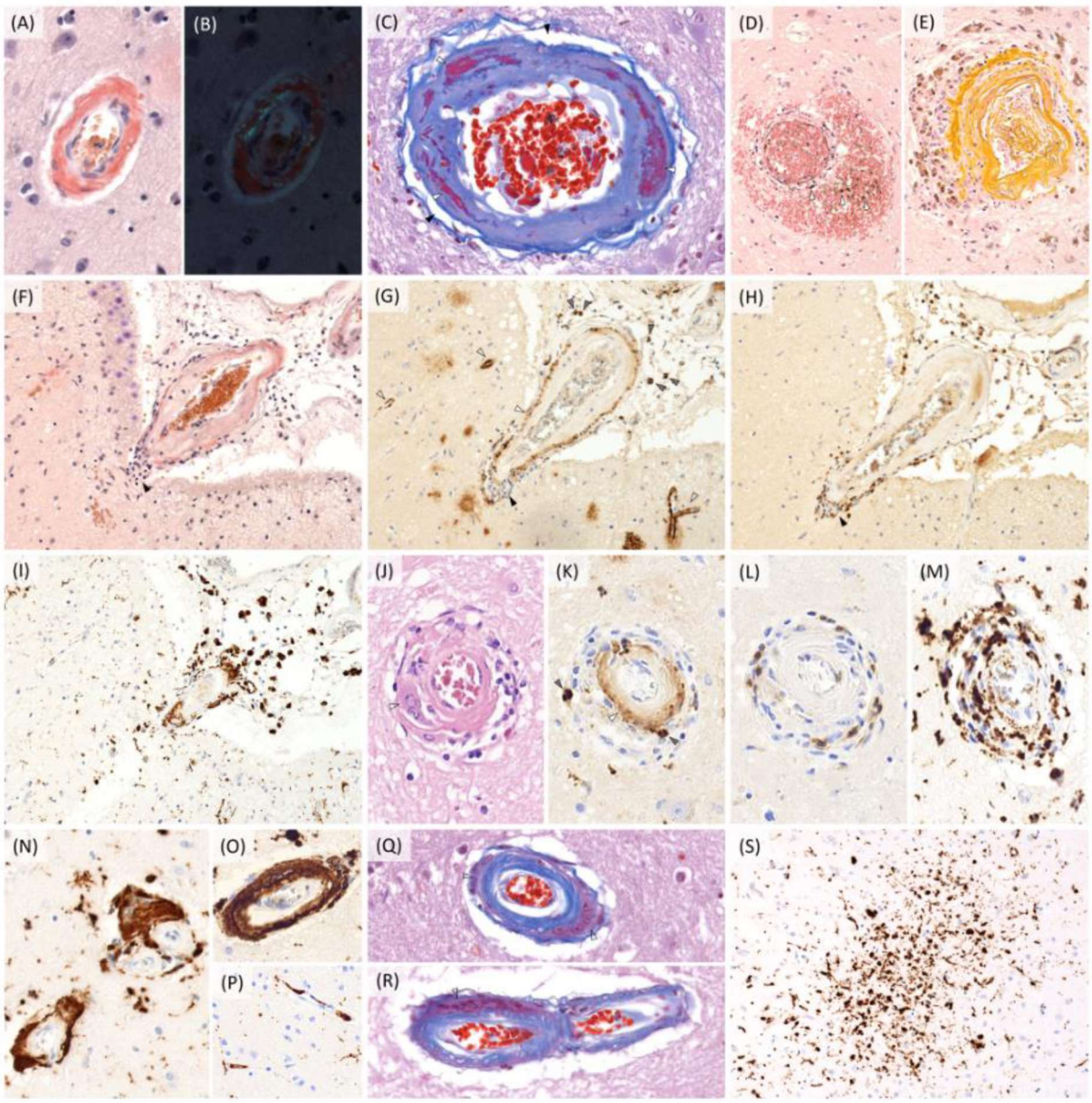


FIGURE 4 Neuropathological findings of Case 2. Congophilic angiopathy (Congo red, A) with apple-green birefringence under the polarised microscope (B). Severe vasculopathy (modified Vonsattel grade 4) with double-barrelling (black arrowheads in C), fibrinoid necrosis (white arrowheads, Crossmon's modified Mallory's trichrome (CMT), C), perivascular erythrocytes (forming a CMB) with haemosiderin (arrowheads, Haematoxylin-Eosin (HE), D) and a spectacular perivascular haematoidin deposition with haemosiderin-laden macrophages (HE, E). Type-1 CAA (capillaries marked with hollow arrowheads in G) and a perforating arteriole with disproportionately thin vascular Aβ positivity (white-filled arrowhead in G), Aβ-immunoreactive macrophages (grey-filled arrowheads in G), sparse perivascular mononuclear infiltration (black-filled arrowheads in F, G, and H; Congo red, F; Aβ, G) comprising 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, arrowhead, HE, J) involving an arteriole again with pale mural Aβ positivity (white-filled arrowhead in K) with Aβ-immunoreactive macrophages

(grey-filled arrowheads, Aβ, K), scattered lymphocytes (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 (arrowheads; Q, R). CD68 immunopositivity occasionally affects capillaries and small venules (P). Microglial nodules/clusters in the cortex (CD68, S).