Association of Microglial Activation With Spontaneous ARIA-E and Cerebrospinal Fluid Levels of Anti-A Autoantibodies

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Abstract

**Background and Objectives:** Amyloid-related imaging abnormalities suggestive of vasogenic edema or sulcal effusion (ARIA-E) are the most common adverse events complicating Alzheimer’s disease (AD) immunotherapy with anti-amyloid-beta (A\(\beta\)) monoclonal antibodies (mAbs). ARIA-E can also occur spontaneously in cerebral amyloid angiopathy-related inflammation (CAA-ri), a rare autoimmune encephalopathy associated with increased cerebrospinal fluid (CSF) levels of anti-A\(\beta\) autoantibodies. Although the pathophysiological mechanisms of ARIA-E remain to be fully elucidated, experimental evidence from *ex-vivo* studies suggest that gantenerumab and aducanumab enable microglial activation. However, the *in vivo* evidence for a direct association between neuroinflammation and ARIA-E in patients with high CSF anti-A\(\beta\) (auto)antibody levels has never been demonstrated.

**Methods:** Spatial distribution and temporal variations of microglial activation associated with ARIA-E and CSF anti-A\(\beta\) autoantibody levels at (sub)acute presentation and after corticosteroid therapy, in a longitudinal case series of patients with CAA-ri, an increasingly recognized spontaneous model of the iatrogenic ARIA-E in AD immunotherapy. Multimodal and multiparametric magnetic resonance imaging (MRI) for CAA and ARIA-E quantification, as measured with validated MRI scoring systems; CSF testing for anti-A\(\beta\) autoantibodies and AD biomarkers; \(^{11}\)C-PK11195 positron emission tomography (PET) for activated microglia.

**Results:** At (sub)acute presentation, we found focal peaks of microglial activation having a greater spatial co-localization with ARIA-E compared to chronic age-related white matter change (ARWMC) imaging abnormalities. The severity of ARIA-E and the magnitude of the associated microglial activation was greater in patients having AD and severe CAA concomitant disease, compared to patients having CAA only. CSF anti-A\(\beta\) autoantibodies at presentation were high in all patients and markedly decreased at post-treatment follow-up, in parallel with clinical resolution of acute symptoms, reduced ARIA-E severity, and reduced microglial activation.
Discussion: Our findings extend the current notion of ARIA-E by providing the first in vivo $^{11}$C-PK11195-PET evidence for an association between microglial activation and the magnitude and severity of ARIA-E in patients with increased CSF concentration of anti-Aβ autoantibodies and comorbid AD and CAA disease.

Our results highlight CSF testing for anti-Aβ autoantibodies as a promising diagnostic, prognostic, and therapy response biomarker to help guide future treatment and management decisions in real clinical practice and clinical trials.

Introduction

Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a rare autoimmune encephalopathy associated with spontaneous symptomatic amyloid-related imaging abnormalities suggestive of vasogenic edema (ARIA-E) that are thought to be linked to an exaggerated autoantibody immune reaction against β-amyloid (Aβ) of CAA and Alzheimer’s disease (AD).\(^1,2\)

Evidence from a large cohort registry study of inpatients with CAA-ri showed that the natural history of spontaneous ARIA-E shares striking clinical, radiological, and biological similarities with the iatrogenic ARIA-E reported in up to 50% of AD patients exposed to several anti-Aβ monoclonal antibodies tested in clinical trials.\(^1,3-5\)

Clinically, CAA-ri presents with (sub)acute cognitive changes, seizures, focal neurological deficits, and altered mental state. Radiologically, CAA-ri patients present with magnetic resonance imaging (MRI) evidence of focal cortico-subcortical hyperintensities suggestive of parenchymal vasogenic edema (VE) and/or sulcal effusion on T2-weighted fluid attenuated inversion recovery (FLAIR) images, i.e. spontaneous ARIA-E.\(^1,6\)

Both spontaneous and iatrogenic ARIA-E have a transient and potentially relapsing nature, with a suggested positive effect of corticosteroid therapy on prognosis and for the prevention of subsequent recurrences.\(^1,7,8\)

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According to currently available criteria, at least one of the following imaging markers are also required to make a diagnosis of CAA-ri: lobar cerebral microbleeds (CMBs), intracerebral hemorrhage (ICH), and cortical superficial siderosis (cSS) on gradient echo-T2* weighted (GRE-T2*) images. Unlike ARIA-E, these MRI markers typically do not resolve at follow-up and the burden increases with disease progression.

Biologically, CAA-ri is characterized by high levels of anti-A\(\beta\) autoantibodies in the cerebrospinal fluid (CSF) during (sub)acute stage of the disease, returning within levels typically observed in AD and non-inflammatory CAA patients after clinicoradiological resolution of ARIA-E. Based on the above evidence, ARIA-E of AD immunotherapy is increasingly recognized as a iatrogenic manifestation of the spontaneous ARIA-E associated with increased CSF anti-A\(\beta\) autoantibodies occurring in both AD and CAA patients.

The pathophysiological mechanisms of ARIA-E remain to be fully elucidated. Experimental evidence from ex-vivo studies suggest that the monoclonal antibodies gantenerumab and aducanumab enable microglial activation. However, the in vivo evidence for a direct association between neuroinflammation and ARIA-E in patients with high CSF anti-A\(\beta\) (auto)antibody levels has never been demonstrated so far.

Given that microglia can either contribute to clearing A\(\beta\) by cell-mediated phagocytosis or increase the risk of ARIA-E by triggering an exaggerated neuroinflammatory response, elucidating the biology of the neuroinflammatory response associated with ARIA-E will be key for guiding future treatment decisions.

Here, through a multimodal and multiparametric MRI, CSF, and positron emission tomography (PET) study with \(^{11}\)C-PK11195, a tracer targeting the 18kDa translocator specific protein (TSPO) overexpressed in activated microglia cells, we describe the spatial distribution and temporal variations of in vivo microglial activation associated with ARIA-E at disease presentation and following corticosteroid therapy, in a longitudinal case series of well-defined CAA-ri patients.
Materials and Methods

Participants

We studied a case series of inpatients presenting with (sub)acute CAA-ri, diagnosed by clinical presentation, CSF testing, and neuroradiologic findings, according to current criteria. Participants were prospectively enrolled throughout the iCAβ International Network longitudinal cohort Registry of CAA-ri referred to the University of Milano Bicocca (UNIMIB) Coordinating Center. The description of the multicenter, hospital-based, prospective, longitudinal Cohort design has been previously reported. For this study, participants were selected based on the following eligibility criteria: 1) availability of MRI images and CSF samples collected at admission, before starting corticosteroids, 2) no contraindications to undergo a PET scan before starting treatment, 3) ability to travel to the Nuclear Medicine Unit at San Raffaele Hospital in Milan, 4) availability to undergo a second PET scan and lumbar puncture at post-treatment follow-up monitoring. The first four consecutive patients who matched eligibility criteria and agreed to participate were enrolled.

Participants underwent baseline MRI, CSF, and PET within 3 months from symptoms onset and before starting corticosteroid pulse therapy with five intravenous boluses of 1g/day methylprednisolone for five consecutive days, with or without subsequent oral tapering-off. All procedures were repeated at post-treatment monitoring, assessed from ≥3 to 12 months from symptoms onset. The therapeutic and follow-up monitoring schedule was defined according to the iCAβ International Network recommendations as described elsewhere. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

MRI images acquisition

T1-weighted, GRE-T2*, susceptibility-weighted imaging (SWI), FLAIR, and diffusion weighted imaging (DWI) images were acquired on 1.5 T imaging systems, as previously described. MRI acquisitions followed imaging standards requirements proposed by STandards for ReportIng
Vascular changes on nEuroimaging (STRIVE) working group. The reading of MRI images was centrally assessed by trained neuroradiologists (GB, RP), blind to clinical and therapeutic data, as previously described.

**ARIA-E assessment**

Semi-automated intensity-based drawing and editing tools (MRicr v.1.0.19) were used to segment the region of interest (ROI) comprising the specific parenchymal and sulcal hyperintensities which define ARIA-E (ARIA-E ROI) on baseline FLAIR images, according to current definitions. The extent and radiological severity of ARIA-E was quantified according to the validated 60-point Barkhof Grand Total Score (BGTS) as well as with the simplified ARIA-E severity score reported by Salloway et al.

**CAA load assessment**

Baseline T2*-GRE and FLAIR images were used to evaluate lobar CMBs number, distribution and severity of cSS, number of centrum semiovale perivascular spaces (CSO-PVS), and deep and periventricular white matter hyperintensities of chronic cerebral small vessel disease (cSVD) and aging (globally defined as Age-Related Withe Matter Changes – ARWMC). All markers were rated with previously standardized and validated rating scores, according to current consensus criteria and definitions.

MRicr v.1.0.19 editing tools were used to segment the ROI indicative of ARWMC (ARWMC ROI).

**Routine CSF and serum testing**

According to current CAA-ri criteria, all patients were tested for absence of neoplastic, infectious, and other causes. CSF/serum albumin quotient (QAlb) and age-related maximum normal CSF/serum albumin (QNorm) were also calculated. According to Puthenparampil et al., patients with QAlb > QNorm were considered as having increased blood-brain barrier (BBB) permeability.

**CSF anti-Aβ autoantibodies, AT(N) biomarker profile, and APOE genotype**
All tests were centrally assessed at the CAA and AD Translational Research and Biomarkers Laboratory of the University of Milano – Bicocca. The CSF level of anti-Aβ autoantibodies was quantified with an in-house immunoenzymatic beads-based ultrasensitive assay as previously described.\(^2\) CSF testing for Aβ42/Aβ40 ratio (A), p181-tau (T), and t-tau (N) was assessed with commercial enzyme-linked immunosorbent assays to determine the biomarker profile in the AD continuum, according to AT(N) research framework criteria.\(^{37, 38}\) Cutoff values were: A(+) <0.1, T(+) ≥30 pg/mL, N(+) ≥400 pg/mL, anti-Aβ autoantibodies(+) ≥32 ng/mL (borderline if ±10%). Values were settled according to previously published data\(^2\) and current internal research programs.\(^{27}\) A detailed description of the methods used for CSF testing and APOE genotyping can be found elsewhere.\(^2, 39, 40\)

\(^{11}\text{C-PK11195-PET}\)

\(^{11}\text{C-PK11195-PET}\) scans were performed on a multi-ring PET Discovery 690 General Electric Medical System (GEMS), injecting a dose of 380 ± 37 MBq of \(^{11}\text{C-PK11195}\) with a radiochemical and chemical purity > 95%. Acquisition protocol included a dynamic PET scan of 15 frames lasting 58 minutes (6 x 30 sec/2 x 1 min/1 X 3 min/3 x 5 min/2 x 10 min/1 x 15 min). PET data were corrected for attenuation, radioactive decay, and scatter. For each scan, movement correction was executed by realigning individual frames over time using SPM5 (http://www.fil.ion.ucl.ac.uk/spm/software/spm5/). Nuclear medicine experts, blind to clinical and therapeutic data, centrally assessed the reading of PET images.

The change in \(^{11}\text{C-PK11195-PET}\) binding potentials (BPs) was estimated using a Receptor Parametric Mapping (RPM) procedure, requiring a pre-set reference region. Imaging data were analyzed using the curve distance clustering algorithm (CDCA) adaption of the validated SuperVised Clustering Algorithm to estimate the similarity of the time-activity curve (TAC) of each voxel with four predefined TACs (tracer delivery in blood, white matter, gray matter with non-specific binding, and high specific binding).\(^{41, 42}\)
Each $^{11}$C-PK11195-PET BP was co-registered to the subject-specific FLAIR acquired at baseline. In order to remove non-specific binding, each image was subtracted voxel-by-voxel for an average BP map obtained from an in-house dataset of ten healthy volunteers. Before comparison, the average BP map in the MNI space was propagated to each patient’s native space by the inverse warping parameters identified through spatial normalization of the patient's FLAIR scan. All voxels with a BP $\geq 0.1$, namely above the across-subjects BP cerebral global mean plus one standard deviation, were considered BP-peaks.

The percentage of spatial interaction between $^{11}$C-PK11195-PET BP-peaks and each ROI, i.e. ARIA-E_roi and ARWMC_roi, was extracted considering the number of overlapping voxels normalized to the number of voxels of the ROI. Mean BP values extracted at baseline and at follow-up, within each ROI, were used to estimate post-treatment variations. For illustration purposes, single-patient delta reduction maps ($\Delta$BP map) resulting from the voxel-wise subtraction of the baseline BP-peaks from those at follow-up were also computed.

**Standards Protocol Approvals, Registration, and Patient Consent**

The University of Milano-Bicocca (UNIMIB) Institutional Ethical Committee on human experimentations approved the study (*biomarkARIA* protocol #268/02112016 and *modelCAA* Protocol #372/16042018). The San Raffaele Hospital Institutional Ethical Committee approved the $^{11}$C-PK11195-PET study (Protocol #DSAN854-A/2). All patients provided written informed consent for the use of clinical, laboratory, and imaging data.

**Data availability**

The data that support the findings of this study are available from the corresponding authors upon reasonable request.
Results

Case 1. A 76-year-old woman was admitted with focal epileptic seizure characterized by loss of contact with fixed gaze. The patient had a history of two lobar ICHs in the preceding three years, which led to the diagnosis of probable CAA.

The same day, an MRI scan (Figure 1) showed severe ARIA-E in the occipital lobe, bilaterally, with a BGTS value of 7. T2*-GRE images showed >100 CMBs in the right and the left occipital lobe, disseminated cSS, and late subacute ICH in the right occipital pole, corresponding to a CAA severity score of 5. The day after, CSF testing for anti-Aβ autoantibodies was positive. The AT(N) biomarker profile was A+T+(N)+, suggesting AD pathologic changes. APOE genotyping showed ε3/ε3 allele carriage. All results are shown in Table 1.

According to clinical presentation, MRI, and CSF findings a diagnosis of probable CAA-ri was made.

Five days later, $^{11}$C-PK11195 PET revealed diffused BP-peaks of microglial activation that were more evident within the ARIA-E anatomical region in the right occipital lobe (Figure 1). The spatial interaction of BP-peaks with ARIA-E_roi and ARWMC_roi was 30.1% and 4.6%, respectively (Figure 2).

Four days after PET, treatment with intravenous high dose corticosteroid pulse therapy was started, followed by 1mg/Kg of oral prednisolone and gradual tapering-off during the subsequent 5 months, with no recurrence of seizures.

Five and a half months after admission, a second MRI scan (5 months after the starting of corticosteroids) showed a marked improvement of ARIA-E, with a 3 points reduction of the BGTS. T2*-GRE images revealed two new CMBs that were not localized within the anatomical regions affected by ARIA-E.

Ten weeks later, $^{11}$C-PK11195 PET revealed a globally reduced, although persistent, microglial activation (Figure 1), with more evident BP-peaks reduction in the ARIA-E anatomical region.
(Figure 3). BPs mean value in ARIA-E_roi decreased from 0.49±0.17 at baseline to 0.30±0.14 at follow-up (-38%). BPs mean value in ARMWC_roi decreased from 0.29±0.13 to 0.19±0.11 (-34%).

CSF testing at follow-up was not performed, as a second lumbar puncture was not possible.

**Case 2.** A 74-year-old woman was admitted with pharmacoresistant headache, behavioral changes, and rapid cognitive decline. The patient had a medical history of arterial hypertension, dyslipidemia, breast cancer with negative oncological follow-up, and a history of possible CAA. Two months after the onset of symptom (delay due to an arm fracture), FLAIR-MRI images (Figure 4) revealed moderate ARIA-E in the left rolandic sulcus and parietal lobe with decreased sulcal spaces in the same area, with a BGTS value of 4. T2-GRE* images showed multiple CMBs in the left and right parietal and temporal lobes, corresponding to a CAA severity score of 2. The CSF testing for anti-Aβ autoantibodies was positive. The AT(N) biomarker profile resulted A+T+(N)-, suggesting AD pathologic changes. APOE genotyping showed ε2/ε4 allele carriage. All results are shown in Table 1.

According to clinical presentation, MRI images, and CSF findings a diagnosis of possible CAA-ri was made. One week after the MRI, 11C-PK11195 PET revealed BP-peaks of microglial activation mainly localized within the ARIA-E anatomical region (Figure 4). The spatial interaction of BP-peaks with ARIA-E_roi and ARWMC ROI was 3.7% and 1.9%, respectively (Figure 2).

Two weeks after PET, treatment with five intravenous boluses of 1g/day methylprednisolone for five consecutive days was started.

One week later, the patient presented with subacute left hemiparesis, compatible with a new inflammatory flare of CAA-ri and immunosuppressive therapy with oral azathioprine was started, with a progressive improvement of neurological symptoms.

Three and a half months after admission (2.5 months after starting azathioprine), a second MRI showed a partial resolution of ARIA-E, with a 1-point reduction of the BGTS and mild radiological...
severity. T2*-GRE images showed one new CMBs that was not localized within the ARIA-E anatomical region.

One month and a half after the second MRI, CSF testing for anti-Aβ autoantibodies proved to be borderline, suggesting a non-complete biological resolution. The AT(N) biomarker profile resulted A-T+(N)+, with markedly reduced levels of Aβ40 compared to baseline.

Four months and a half after the second MRI (seven months after starting azathioprine), 11C-PK11195 PET showed an overall decreased, although persistent, microglial activation (Figure 4), with a more evident BP peaks reduction in the ARIA-E anatomical region (Figure 3).

Mean BP values in ARIA-E_roi decreased from 0.30±0.10 at baseline to 0.22±0.12 at follow-up (-26%). Mean BP values in ARMWC_roi decreased from 0.22±0.10 to 0.18±0.12 (-17%).

**Case 3.** An 85-year-old man was admitted with a headache and altered mental state. The patient had a medical history of transient ischemic attack in antiplatelet treatment and left parietal subarachnoid hemorrhage followed by left parietal cortical-subcortical ICH, respectively, 8 and 9 years before admission.

A first computer tomography (CT) scan at admission excluded an acute hemorrhage and the patient was discharged. One month and a half later, the patient was re-admitted due to persistence of symptoms and the MRI scan (Figure 5) revealed mild ARIA-E in the left fronto-temporo-parietal area, with a BGTS value of 4. The T2*-GRE images showed disseminated cSS, bilaterally, consistent with a CAA severity score of 3.

The CSF testing for anti-Aβ autoantibodies was positive. The CSF sample was not sufficient to measure AT(N) biomarkers. APOE genotyping showed ε3/ε4 allele carriage. All results are shown in Table 1.

According to clinical presentation, MRI images, and CSF findings a diagnosis of possible CAA-ri was made.

One month after MRI, 11C-PK11195 PET revealed significant but scattered BP-peaks of diffuse microglial activation that was, however, only partially localized within the ARIA-E anatomical
region (Figure 5). The spatial interaction of BP-peaks with ARIA-E_roi and ARWMC_roi was 0.9% and 0.8%, respectively (Figure 2).

Three weeks later, treatment with intravenous high dose corticosteroid pulse therapy, without oral tapering, was started with a progressive resolution of the clinical symptoms.

Six months after admission (2.5 months after starting corticosteroids) a second MRI showed almost unchanged findings compared to baseline (Figure 5) and no change of both BGTS and ARIA-E severity scores. T2*-GRE images showed no new CMBs.

One month after the MRI, CSF testing for anti-Aβ autoantibodies was negative. The AT(N) biomarkers profile resulted A-T+(N)+, suggesting non-AD pathologic changes.

Two months and a half after the second MRI (5 months after starting corticosteroids), 11C-PK11195 PET showed a slight decrease of microglial activation (Figure 4) both globally and in the ARIA-E anatomical region (Figure 3).

Mean BP values in ARIA-E_roi decreased from 0.23±0.08 at baseline to 0.15±0.10 at follow-up (-33%). Mean BP values in ARMWC_roi decreased from 0.19±0.08 to 0.16±0.10 (-13%).

Case 4. A 76-year-old woman was admitted with gait unsteadiness, headache, agitation, and confusion. The patient had a medical history of systemic arterial hypertension, mild depression, amnestic mild cognitive impairment.

Two weeks after symptom onset, the MRI (Figure 6) showed severe ARIA-E in the left and right occipital lobes, with a BGTS value of 7. T2*-GRE showed cortical-subcortical CMBs in the left temporal lobe along with a convexity subacute subarachnoid hemorrhage in the left parietal lobe.

The patient received a CAA severity score of 4.

Two weeks later, CSF testing for anti-Aβ autoantibodies was positive. The AT(N) biomarker profile resulted A+T+(N)-, suggesting AD pathologic changes in the AD continuum. APOE genotyping showed ε3/ε4 allele carriage. All results are shown in Table 1.

According to clinical presentation, MRI images, and CSF findings a diagnosis of probable CAA-ri was made.
One week after MRI, $^{11}$C-PK11195 PET revealed diffuse BP-peaks of microglial activation that were more evident within the ARIA-E anatomical regions (Figure 6). The spatial interaction of BP-peaks with ARIA-E_roi and ARWMC_roi was 27.0% and 9.0%, respectively (Figure 2). Mean BPs value in ARIA-E_roi and in ARMWC_roi was 0.32±0.11 and 0.20±0.08, respectively. The day after, treatment with intravenous high dose corticosteroid pulse therapy was started, followed by 1 mg/Kg of oral prednisolone and gradual tapering-off, with marked clinical improvement.

Four months after admission (3.5 months after starting corticosteroids), a second MRI showed nearly complete resolution of ARIA-E, with a 6-point reduction of the BGTS value. Further assessments were not possible as the patients refused to continue the study.

**Discussion**

The exact mechanisms of ARIA-E remain to be fully elucidated. The review of lessons learned from the last decade of research confirmed the ARIA Paradox as the most accredited pathophysiological model to explain the biological complexity of ARIA-E. According to this model, ARIA-E is a complex and multifactorial phenomenon resulting from the imbalance between the removal of Aβ deposited in plaques, which is attributed to the dose, time, and type of anti-Aβ (auto)antibodies, and the downstream effects that an excessive mobilization of Aβ can cause on intramural periarterial drainage pathways, which may account for increased transient CAA, cerebrovascular impairment, greater vascular permeability, and an easier extravasation of proteinaceous fluid and VE, particularly in ApoE ε4 carriers.

In this proof of principle study, we extend the understanding of ARIA-E biology by providing the first in vivo evidence for an association between ARIA-E and microglial activation through multimodal and multiparametric MRI, CSF testing for anti-Aβ autoantibodies and AT(N) biomarkers, and $^{11}$C-PK11195-PET longitudinal assessments in patients with CAA-ri, a spontaneous human model of the iatrogenic ARIA-E of AD immunotherapy.
At (sub)acute presentation of ARIA-E, we observed scattered and diffused clusters of $^{11}$C-PK11195-PET BPs that, although heterogeneously distributed across subjects, were mainly localized in the posterior brain regions. At single-subject level, the patterns of increased microglial activation peaks showed a greater spatial interaction with ARIA-E than with chronic ARWMC of cSVD and aging, which was consistent in all participants (mean % overlap for ARIA-E 16% vs 4% for ARWMC). Together, these data suggest a specific association between the (sub)acute presentation of ARIA-E and the focal increase of microglial activation.

Our results also showed a clearly more marked spatial co-localization of ARIA-E with the focal clusters of increased microglial activation peaks in probable CAA-ri compared to possible CAA-ri, the latter showing a 10 times lesser overlap (on average 29% vs 2.3%, respectively). Probable CAA-ri also had the highest ARIA-E radiographic severity and BGTS values. Considering that CAA-ri criteria have a sensitivity of 82% and a specificity 97% in diagnosing probable CAA-ri, while the specificity reduces to 68% for possible CAA-ri, one could speculate that some of our participants have been misdiagnosed. However, we believe this hypothesis is unlikely. In fact, our participants underwent CSF testing for anti-Aβ autoantibody positivity and all showed good response to corticosteroids, which is in keeping with the 82% of clinical-radiological resolution of spontaneous ARIA-E following immunosuppressive therapy as recently reported by Antolini et al.

An alternative explanation, as suggested by our data is that the magnitude of microglial activation associated with ARIA-E could be mainly influenced by the co-existence of CAA and AD instead of the presence of one disease as a single entity. In fact, our results showed that the patients with co-presence of both CAA and AD pathology, as measured with MRI and CSF biomarkers, also had: (1) the highest $^{11}$C-PK11195-PET BP mean values; (2) the most severe ARIA-E radiological manifestations; and (3) the highest BGTS values. Notably, the diagnosis of CAA-ri is not affected by the CAA burden, as current criteria simply require the presence of $\geq$1 imaging marker of CAA to make both probable and possible diagnosis, irrespective of number and type of bleeding manifestations. Notwithstanding, case#2 and case#3, which both had only CAA but no evidence of
co-existing AD according to AT(N) biomarkers profiles framework, showed the lowest microglial activation. The finding is even more interesting if we consider that, despite case#3 having a more severe CAA pathology compared to case#2, both had similar ARIA-E radiological scores, i.e. mild/moderate ARIA-E severity and low BGTS values.

Together, our data provide a strong support to the hypothesis that ARIA-E is the expression of an increased overload of Aβ caused by an exaggerated therapeutic effect of (auto)antibodies in disassembling Aβ plaques and the related side effects that this overload can generate on the pre-existing CAA.\textsuperscript{1, 2, 10, 12}

In this framework, our findings highlight that MRI rating scales alone may not fully interpret the focal nature of the complex underlying biology underlying ARIA-E, and points out the need for additional CSF or plasma biomarkers to help reduce current heterogeneity in the interpretation of ARIAs.

At post-treatment monitoring, our results showed a marked 2.3-fold reduction of microglial activation associated with ARIA-E compared to ARWMC. This finding supports the potential therapeutic effectiveness of corticosteroids in the management of the neuroinflammatory processes associated with ARIA-E, which is in keeping with evidence from a large cohort of 110 patients with CAA-ri.\textsuperscript{1}

Notably, we would highlight that although all patients showed a full clinical resolution of acute symptoms, none of them reached a full radiological resolution of ARIA-E, as measured with current MRI rating systems, i.e. a BGTS=0. This could be interpreted in various ways. First, it could be that more than 5-months are necessary for the complete resolution of the neuroinflammation associated with ARIA-E, which is in keeping with the drastic but non-completely reduced microglial activation we observed in all but one patient, who was, however, the only one treated with azathioprine. Moreover, given the slight differences in the timing of PET acquisitions in respect to the first presentation of symptoms, further study are needed to exclude any temporal association of microglial activation with the symptomatic manifestation of ARIA-E. Second, given that current
ARIA-E rating scales have not been validated for their use outside the setting of a clinical trial, real-world data from large cohorts of CAA-ri are needed to prove their applicability in clinical practice, i.e. patients with no pre-event MRI images for making proper comparisons and patients with moderate/severe underlying cSVD comorbidity. Nevertheless, we believe this is a strength of our study, as it first provides a preliminary overview of the scenario we should expect to manage given the recent approval of aducanumab for its clinical use in the heterogeneous community of AD patients. Considering that at least some degree of CAA is present in most AD patients as well as older people, the burden of ARIA-E complications in the real clinical practice would be anticipated to potentially increase compared to the reported 43% incidence in the EMERGE and ENGAGE clinical trials with aducanumab.\textsuperscript{1, 10, 12, 21, 30, 43} Then, elucidating the nature and the response to treatment course of the neuroinflammation associated with ARIA-E will be of paramount importance for both diagnostic and treatment decisions.\textsuperscript{1}

In this framework, our findings give a strong support in the use of corticosteroids to manage the neuroinflammatory response mediated by increased CSF anti-A\(\beta\) (auto)antibodies\textsuperscript{1, 3} and highlights the urgency to define specific treatment and monitoring recommendations for ARIA-E.\textsuperscript{1, 10, 12} Indeed, CSF anti-A\(\beta\) autoantibodies were elevated at disease presentation and decreased at follow-up when cerebral microglial activation was reduced. This is in keeping with the hypothesis that immunotherapy-induced ARIA-E are iatrogenic manifestations of the spontaneously occurring ARIA-E of CAA-ri and points to CSF testing for anti-A\(\beta\) (auto)antibodies as a promising diagnostic, prognostic, and response to treatment biomarker of ARIA-E.\textsuperscript{2, 10, 12, 48, 49}

Further research to validate the utility of the biomarker is needed to reduce current heterogeneity in the interpretation of trials’ results and improve the detection, therapeutic management, and monitoring of ARIA-E side events.\textsuperscript{8}

In this context, our results are of paramount importance for expediting the design of future confirmatory studies, e.g. (1) the need of testing patients within the first month from ARIA-E diagnosis, as the rate of microglial activation may change very quickly; (2) the importance of
carefully considering pre-existing CAA in addition to the Aβ-plaques burden; (3) the potential of CSF testing for anti-Aβ (auto)antibodies; (4) the urgent need of randomized clinical trials to confirm the effectiveness of corticosteroids in the prevention of ARIA-E.1

Filling these knowledge gaps is of paramount importance if we consider that current guidelines suggest an empirical cutoff value of 5 microhemorrhages for patient enrollment in clinical trials and that no data exist on primary prevention with monoclonal antibodies in patients with CAA. If the ARIA Paradox is true, it is possible that patients with CAA, but no AD co-pathology, have a reduced risk of ARIA-E. This is of paramount importance as it may open to new therapeutic horizons also for this orphan disease, including reconsideration of current inclusion and exclusion recommendations in AD immunotherapy.

STRENGTHS AND LIMITATIONS

The main strength of our study is the first in vivo evidence for a temporal and regional association of microglial activation with ARIA-E and high CSF levels of anti-Aβ autoantibodies in the context of co-existing CAA and AD pathology.

Our study also has several limitations. Firstly, although the accurate characterization of our patients, including the use of gold-standard and state-of-the-art assessments for ARIA-E, anti-Aβ autoantibody dosage, and CAA, we would like to stress that the low number and the heterogeneous nature of ARIA-E manifestations of our cases prevented any statistical analyses. As such, our findings should not be interpreted outside the intention of a proof of concept study aimed to first verify the presumed association of ARIA-E and microglial activation, as suggested by few ex vivo studies18-20 and as hypothesized in the ARIA Paradox model.1, 2, 10, 12 Secondly, as only patients who were clinically stable and able to travel were included in this study, we cannot exclude our findings restrict to less severe presentations and thus do not represent the whole picture of such a heterogeneous and complex condition. Third, amyloid-PET imaging and neuropathology data were not available, and the longitudinal CSF testing for AT(N) biomarkers was available only for one case. This precluded any further analysis on the dynamic change variations of Aβ associated to an
ARIA-E event, such as the specific contribution of microglial activation in the focal removal of parenchymal Aβ vs an increased vascular deposition of Aβ in the form of CAA.
Table 1. Patient characteristics at (sub)acute presentation of spontaneous ARIA-E and at post-treatment monitoring following corticosteroid Therapy.

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<th>CASE 1</th>
<th>FUP</th>
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<th>CASE 3</th>
<th>FUP</th>
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<td>Possible</td>
<td>CAA-ri</td>
<td>Probable</td>
<td>CAA-ri</td>
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<td>73</td>
<td></td>
<td>85</td>
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<td>76</td>
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<td>ε2/ε4</td>
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<td>ε3/ε4</td>
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<td>Vascular Dementia</td>
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<td>Amnestic MCI</td>
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<td>History of CAA (Y/N)</td>
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<td></td>
<td>Yes</td>
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<td>No</td>
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<td>MRI markers of CAA</td>
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<td>3</td>
<td>+1 new</td>
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<td>CAA Severity Score</td>
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<td>5</td>
<td></td>
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<tr>
<td>ARIA-E Radiological Severity Score</td>
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<td>mild</td>
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<td>severe</td>
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<td>ARIA-E magnitude (BGTS value)</td>
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### Routine CSF testing

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<th>normal</th>
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<td>Glucose content</td>
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<td>Leucocyte (ref. values &lt;5 cells)</td>
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<td>na</td>
<td>No</td>
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<td>No</td>
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<td>A+T+(N)-</td>
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<td>A-T+(N)+</td>
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### Week(s) from Development of first Symptoms to:

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<th>10</th>
<th>25</th>
<th>6</th>
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<td>11C-PK11195 PET scan</td>
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<td>11</td>
<td>43</td>
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<td>13</td>
<td>--</td>
<td>13</td>
<td>--</td>
<td>3</td>
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<tr>
<td>End of oral tapering</td>
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<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>26</td>
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<tr>
<td>Initiation/end of second-line therapy with AZA</td>
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<td>--</td>
<td>15/90</td>
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</table>

### Table Legend

CAA-ri, cerebral amyloid angiopathy-related inflammation; FUP, follow-up; APOE, Apolipoprotein E; MRI, magnetic resonance imaging; CMBs, cerebral microbleeds; cSS: cortical superficial siderosis; CSO-PVS, centrum semiovale perivascular spaces ARIA-E, Amyloid-Related imaging Abnormalities; BGTS, Barkhof Grand Total Score; CSF, cerebrospinal fluid; BBB, blood brain barrier; A\(\beta\), amyloid-beta protein; AT(N), Amyloid Tau Neurodegeneration biomarkers profile framework criteria; AZA, azathioprine.
Longitudinal in vivo imaging of microglial activation during the course of spontaneous ARIA-E in a patient with probable CAA-ri (Case 1)

(A) Baseline MRI and $^{11}$C-PK11195 PET images acquired within 1 week from presentation of (sub)acute symptoms. (a) T2-weighted (FLAIR) images showed spontaneous ARIA-E in the occipital lobe, bilaterally (red lines indicate the anatomical regions affected by ARIA-E). (b) Gradient echo-T2* weighted imaging (GRE-T2*) sequence, co-registered to baseline FLAIR images, showed multiple cerebral microbleeds (CMBs) in the right and the left occipital lobe, disseminated cortical superficial siderosis (cSS), and late subacute intracerebral hemorrhage (ICH) in the right occipital pole. CSF testing confirmed high concentrations of anti-Aβ autoantibodies.$^2$ The diagnosis of probable CAA-ri was made.$^5$ (c) $^{11}$C-PK11195 PET images, co-registered and superimposed onto baseline FLAIR images, revealed diffused binding potential peaks (BP-peaks) of microglial activation, more evident within the ARIA-E anatomical region in the right occipital lobe. Treatment with high-dose corticosteroid pulse therapy was started, followed by slow tapering-off for the subsequent 5 months.

(B) Follow-up MRI and $^{11}$C-PK11195 PET acquired 5 months after the starting of corticosteroids. MRI and PET images are co-registered to baseline FLAIR. (a) FLAIR images showed a marked reduction of vasogenic edema within the ARIA-E anatomical regions defined at baseline (red lines). (b) GRE-T2* images showed a reduction of the extent of signal drop near the subacute ICH in the right occipital pole and the appearing of 2 new CMBs localized outside the ARIA-E anatomical regions. (c) $^{11}$C-PK11195 PET revealed a globally reduced microglial activation that was more evident in the ARIA-E anatomical region.
Figure 2. Title.

Microglial activation overlapping with ARIA-E and ARWMC at baseline

Figure 2 Legend.

(A) The figure shows baseline $^{11}$C-PK11195 binding potential peaks (BP-peaks) overlapping ARIA-E (ARIA-E_roi) and ARWMC (ARWMC_roi) regions of interest. For each patient, BP-peaks were extracted from the same baseline BP-peak maps displayed on the left lower rows of Figures 1–4 and superimposed on FLAIR images acquired at baseline. Intensity of microglial activation is represented using a yellow to red scale for BP peaks overlapping with ARIA-E_roi and a dark to light blue scale for BP-peaks overlapping with ARWMC_roi.

(B) Graphical representation of percentage of spatial interaction between microglial activation and ARIA-E_roi and ARWMC_roi computed, respectively, as the total number of BP-peaks and ROI overlapping voxels normalized to the number of voxels of the ROI.
Figure 3. Title.

Longitudinal *in vivo* imaging of microglial activation during the course of spontaneous ARIA in a patient with possible CAA-ri (Case 6)

Figure 3. Legend.

Baseline MRI images and $^{11}\text{C}-\text{PK11195}$ PET acquired 3 weeks after symptoms onset. (a) T2-weighted (FLAIR) images showed spontaneous ARIA-E in the left and right occipital lobes (red lines indicate the anatomical regions affected by ARIA-E). (b) Gradient echo-T2* weighted imaging (GRE-T2*) sequence, co-registered to baseline FLAIR, showed disseminated cortical and subcortical microbleeds in the left temporal lobe and subarachnoid hemorrhage in the left parietal lobe. CSF testing confirmed high concentrations of anti-A$\beta$ autoantibodies. A diagnosis of
probable CAA-ri was made.\textsuperscript{6} \textsuperscript{(c)} \textsuperscript{11}C-PK1195 PET binding potentials peaks (BP-peaks), co-registered and superimposed onto baseline FLAIR, reveals diffuse BP-peaks clusters of microglial activation that were mainly co-localized within the ARIA-E anatomical regions. The patient was treated with high-dose corticosteroid pulse therapy, with marked improvement of clinical symptoms.

Figure 4.

Longitudinal in vivo imaging of microglial activation during the course of spontaneous ARIA-E in a patient with possible CAA-ri (Case 2)

Figure 4. Legend.

(A) Baseline MRI and \textsuperscript{11}C-PK1195 PET images acquired 2 months after symptoms onset. (a) T2-weighted (FLAIR) images showed spontaneous ARIA-E, i.e. reduced amplitude of sulci in the left superior parietal and precentral areas consistent with vasogenic edema (red lines indicate the anatomical regions affected by ARIA-E). (b) Gradient echo-T2* weighted imaging (GRE-T2*)
sequence, co-registered to baseline FLAIR images, showed multiple cerebral microbleeds (CMBs) in the right and the left parietal lobes. CSF testing for anti-Aβ autoantibody was positive. The diagnosis of possible CAA-ri was made. (c) 11C-PK11195 PET images, co-registered and superimposed onto baseline FLAIR images, revealed clusters of microglial activation mainly localized within the ARIA-E region. Treatment with high-dose corticosteroid pulse therapy was started, followed by oral azathioprine 1 week later due acute clinical worsening attributed to a new inflammatory flare.

(B) Follow-up MRI and 11C-PK11195 PET images acquired 2 and a half months from starting immunosuppressive therapy. MRI and PET images are co-registered to baseline FLAIR. (a) FLAIR images showed only a partial reduction of vasogenic edema within the ARIA-E region identified at baseline (red lines). (b) GRE-T2* images showed 1 new CMB, not localized within the ARIA-E region. CSF testing for anti-Aβ autoantibodies confirmed reduced levels compared to baseline. (c) 11C-PK11195 PET revealed a global reduced microglial activation that was more evident in the ARIA-E region.
**Figure 5. Title**

Longitudinal in vivo imaging of microglial activation during the course of spontaneous ARIA in a patient with possible CAA-ri (Case 3)

**Figure 5. Legend.**

(A) Baseline MRI and $^{11}$C-PK11195 PET images acquired 2 and a half months after presentation of (sub)acute symptoms. (a) T2-weighted (FLAIR) images showed spontaneous ARIA-E in the left lateral fronto-temporo-parietal area (red lines indicate the anatomical regions affected by ARIA-E). (b) Gradient echo-T2$^*$ weighted imaging (GRE-T2$^*$) sequence, co-registered to baseline FLAIR images, showed disseminated cortical superficial siderosis in the left and right parietal lobes. CSF testing confirmed high concentrations of anti-Aβ autoantibodies. A diagnosis of possible CAA-ri was made. (c) $^{11}$C-PK11195 PET binding potentials (BP-peaks) co-registered and superimposed onto baseline FLAIR, revealed scattered clusters of microglial activation only partially localized within the ARIA-E anatomical region. Treatment with high-dose corticosteroid pulse therapy was started, with progressive resolution of clinical symptoms.

(B) Follow-up MRI and $^{11}$C-PK11195 PET acquired 3 and a half months after starting corticosteroids therapy. All images are co-registered to baseline FLAIR. (a) FLAIR images showed only slight decrease of microglial activation, compared to baseline. (b) GRE-T2$^*$ images did not reveal any new microbleeds. CSF testing for anti-Aβ autoantibodies confirmed reduced levels compared to baseline. (c) $^{11}$C-PK11195 PET revealed a slight decrease of microglial activation within and outside the ARIA-E anatomical region.
Figure 6. Title.

Longitudinal in vivo imaging of microglial activation during the course of spontaneous ARIA in a patient with possible CAA-ri (Case 4)

Figure 6. Legend.

Baseline MRI images and $^{11}$C-PK11195 PET acquired 3 weeks after symptoms onset. (A) T2-weighted (FLAIR) images showed spontaneous ARIA-E in the left and right occipital lobes (red lines indicate the anatomical regions affected by ARIA-E).

(B) Gradient echo-T2* weighted imaging (GRE-T2*) sequence, co-registered to baseline FLAIR, showed disseminated cortical and subcortical microbleeds in the left temporal lobe and subarachnoid hemorrhage in the left parietal lobe. CSF testing confirmed high concentrations of anti-Aβ autoantibodies. A diagnosis of probable CAA-ri was made.

(C) $^{11}$C-PK11195 PET binding potentials peaks (BP-peaks), co-registered and superimposed onto baseline FLAIR, reveals diffuse BP-peaks clusters of microglial activation that were mainly co-
localized within the ARIA-E anatomical regions. The patient was treated with high-dose corticosteroid pulse therapy, with marked improvement of clinical symptoms.

Bibliography

8. Fabrizio P, Lutz F, Alessandro P. The need for large collaborative registries from clinical trials and real-world data to define treatment and imaging recommendation for ARIA. 2022: Accepted manuscript.
Association of Microglial Activation With Spontaneous ARIA-E and Cerebrospinal Fluid Levels of Anti-A Autoantibodies
Fabrizio Piazza, Silvia Paola Caminiti, Marialuisa Zedde, et al.
*Neurology* published online August 8, 2022
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