

CASE REPORT OPEN ACCESS

Fatal Outcome of Intravenous Thrombolysis With an Unexpected Finding of Amyloid- β -Related Angiitis—A Case Report Highlighting a Relevant Scenario With Acute Focal Neurological Deficits and Minimal Radiological Presentation

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ABSTRACT

Cerebral amyloid angiopathy (CAA) has been implicated as a risk for developing lobar intracerebral hemorrhage (ICH) after intravenous thrombolysis (IVT) applied for acute ischemic stroke (AIS). However, there is a paucity of cases reported with histopathological CAA diagnosis in this setting, with a single report to imply the role of CAA-related inflammation (CAA-RI). We report clinical, radiological, and neuropathological observations of a 65-year-old woman who presented with acute left-hemispheric symptoms with an initially unrevealing cranial computed tomography (CT) and received IVT for presumed AIS. The course was rapidly complicated by a huge lobar ICH and a fatal outcome. The autopsy revealed severe CAA, unexpectedly with transmural CAA-RI, a.k.a. amyloid- β -related angiitis (ABRA), and histopathological evidence for vascular amyloid- β phagocytosis. Re-evaluation of initial imaging did not reveal signs of asymmetric confluent white matter edema characteristic of CAA-RI, but raised the suspicion of a tiny left central convexity subarachnoid hemorrhage, a substrate of amyloid spells. The genotype of the apolipoprotein E (ApoE) gene (*ApoE*) was $\epsilon 3/\epsilon 3$. Being the second published thrombolysis-associated fatality with ABRA and among the few with definite CAA, the present case confirms CAA/CAA-RI to be a potential hidden risk for IVT-associated ICHs, urging for awareness of CAA-associated pathologies and clinical-radiological hints in an AIS setting. The findings implicate the relevance of vascular A β phagocytosis in the pathogenesis, confirm that CAA-RI may present without prominent edema, highlight that CAA/CAA-RI-related focal neurological deficits (including amyloid spells) can be potential AIS mimics within the IVT time window, and urge for rigorous analysis of pre-IVT CT scans for even subtle sulcal hyperdensities suggesting cSAH/amyloid spell in elderly patients, prompting consideration of magnetic resonance imaging.

Abbreviations: ABRA, A β -related angiitis; AD, Alzheimer's disease; AIS, acute ischemic stroke; *ApoE*, apolipoprotein E (ApoE) gene; A β , amyloid-beta; CAA, cerebral amyloid angiopathy; CAA-RI, CAA-related inflammation; CMB, cerebral microbleed; CMT, Crossmon's modified Mallory's trichrome; cSAH, convexity subarachnoid hemorrhage; cSS, cortical superficial siderosis; CT, computed tomography; ICH, intracerebral hemorrhage; IVT, intravenous thrombolysis; MNGC, multinucleated giant cell; MRI, magnetic resonance imaging; WM, white matter.

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1 | Introduction

Intravenous thrombolysis (IVT) in acute ischemic stroke (AIS) is relatively safe, with a 3%–8% risk for symptomatic and ~2% for fatal intracerebral hemorrhage (ICH). The decision-making on IVT is generally based on computed tomography (CT) as the most time-efficient modality. However, CT cannot detect chronic hemorrhagic alterations, including cerebral microbleeds (CMBs) and cortical superficial siderosis (cSS), which indicate conditions with potential risk for IVT-ICHs, such as cerebral amyloid angiopathy (CAA) [1–3]. These can be visualized by hemosiderin-sensitive magnetic resonance imaging (MRI) sequences, such as T2*-gradient echo (GRE) and susceptibility-weighted imaging (SWI).

Sporadic CAA is characterized by amyloid- β ($A\beta$) deposition primarily in leptomeningeal/cortical arterioles, affecting up to 25% of the elderly at moderate-to-severe degree [3]. Alzheimer's disease (AD) is frequently concomitant, with the $\epsilon 4$ allele of apolipoprotein E (*ApoE*) gene (*ApoE*) being considered a mutual risk. Hallmark MRI features are strictly lobar hemorrhages, including CMB, convexity subarachnoid hemorrhage (cSAH), cSS, and ICH, enabling *probable CAA* diagnosis [1]. Typical symptoms include ICH-associated signs, dementia, and transient focal neurological episodes characteristically due to corresponding cSAH/cSS (a.k.a. “amyloid spells”) [4]. Additionally, CAA can rarely manifest in subacute encephalopathy in a clinical-radiological syndrome termed *CAA-related inflammation* (CAA-RI). Two histopathological subtypes are distinguished: (1) transmural CAA-RI (a.k.a. $A\beta$ -related angitis (ABRA) or vasculitic CAA-RI) and (2) perivascular CAA-RI (a.k.a. non-vasculitic CAA-RI), which are characterized by transmural and perivascular-only lymphomonocytic inflammatory infiltration of CAA vessels, respectively, with or without multinucleated giant cells (MNGCs) [5]. Irrespective of histopathological subtype, radiologically CAA-RI typically presents with asymmetric confluent white matter (WM) edema accompanying CAA-compatible hemorrhages (*probable CAA-RI*). Recently, leptomeningeal enhancement and sulcal non-nulling on FLAIR were proposed to be incorporated into the criteria as alternative CAA-RI presentations [5, 6].

Here, we present a case of a fatal IVT-associated ICH, with an unexpected neuropathological finding of ABRA, the second in the literature. The detailed neuropathological analysis highlighted the role of phagocytosis of vascular $A\beta$ in the pathogenesis. The CARE guidelines were followed.

2 | Clinical Summary

The 65-year-old woman was admitted with a 45-min history of sudden-onset left-hemispheric symptoms (right-sided tingling, soon followed by right-sided weakness and slurred speech; the time-line of the clinical course is presented in [Supporting Information](#), File 1). Her history included mild hypertension and insulin resistance, requiring no medication after lifestyle change. She experienced subjective memory impairment in the preceding months, and dull headache in the days before admission, felt similar to her habitual headaches. She suffered no head

trauma. The family history included dementia (mother) and a disabling stroke (aunt).

The neurological examination revealed dysarthria, right-sided central facial palsy, moderate hemiparesis, hemiparesthesia, hemihyesthesia, and hyperreflexia. The blood pressure was 157/101 mmHg. Blood glucose and clotting parameters were normal. A cranial/carotid CT angiography was unrevealing (Figure 1A). Without evident contraindication and assuming AIS, IVT was initiated, 80 min after onset, with a 34-min door-to-needle time. Ten minutes later, she had a headache, and at 20 min, she vomited and developed somnolence, gaze deviation to the left, global aphasia, and hemiplegia. Alteplase was stopped. An urgent CT scan demonstrated a huge left frontal-parietal ICH, with subarachnoid extensions and finger-like projections (Figure 1B). The blood pressure was constantly within the recommended range. Despite osmotic therapy, the patient rapidly developed a coma and required mechanical ventilation. A third CT scan revealed enlarged ICH, edema, and tonsillar herniation. Repeated neurosurgical consultations did not recommend surgery. Two days later, brain death was determined.

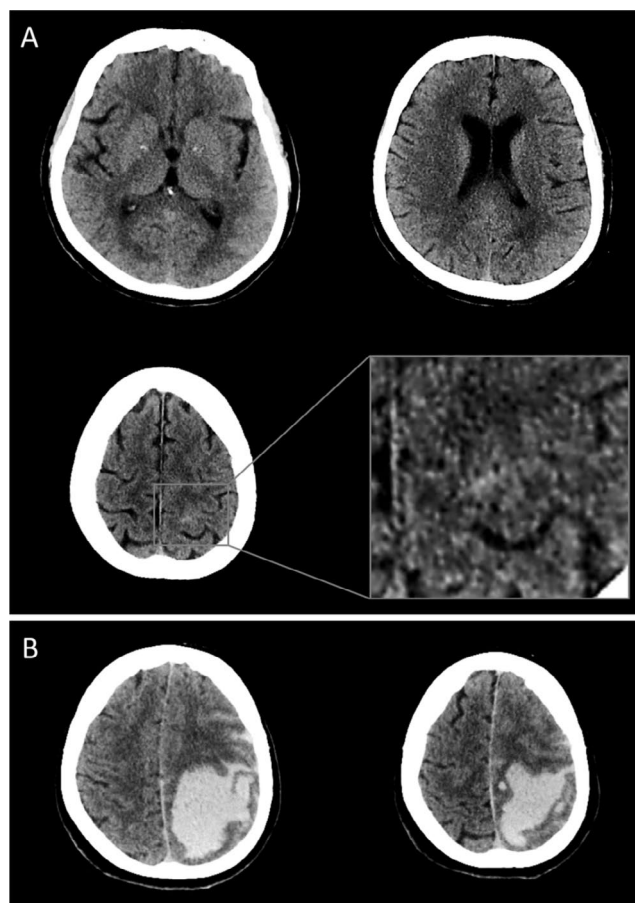


FIGURE 1 | Radiological presentation. Initial cranial CT scan demonstrates moderate periventricular and deep white matter lucencies indicative of small vessel disease (A), with a tiny sulcal hyperdensity noted during retrospective evaluation (inlet of A). Urgent follow-up CT scan after IVT demonstrates a large frontal-parietal ICH with subarachnoid extensions and finger-like projections (B).

Due to the surprisingly progressive IVT-associated ICH morphologically resembling CAA-related ICHs (simplified Edinburgh criteria: *CAA high probability* [7]), a re-evaluation of initial imaging was performed for amyloid-related abnormalities. No asymmetric edema was noted; however, a subtle sulcal hyperdensity was suspected left centrally, raising the suspicion of cSAH (Figure 1A). Neuropathological and molecular genetic work-up was initiated.

3 | Pathological Findings and Molecular Genetic Findings

After fixation in formaldehyde for 2.5 weeks, the brain weighed 1350 g. One-mm-thick subarachnoid hemorrhage was observed overlying the left hemisphere. Both hemispheres were swollen. In the deep WM of the left middle frontal gyrus, fresh colliquation was observed (30×20×20 mm). Dorsally to this, a blood-filled cavity was seen (90×85×65 mm). The hippocampi were notable for slight meningeal thickening. The basal ganglia were unremarkable. The cerebellum and brainstem showed congestion with secondary stripe-like hemorrhages. Methods related to histopathology are summarized in [Supporting Information, File 2](#).

Surrounding the frontal ICH margin, leptomeningeal/cortical vessels contained congophilic amyloid with apple-green birefringence, confirmed to be A β , consistent with CAA (Figure 2A,B). The double-barrel formations and extensive fibrinoid necrosis rendered the severity to be Vonsattel grade 4 (Figure 2C–E); the extension was Love grade 2 and 3 in the parenchyma and leptomeninges, respectively. The capillary involvement yielded Thal CAA Type 1 (Figure 2F). The small emolition in the middle frontal gyrus was consistent with acute infarct; however, the ICH impeded the etiological evaluation of territories corresponding to the initial symptoms. No evident ruptured vessels [8] or Prussian blue-positive siderophages indicating prior hemorrhage were noted. The erythrocyte-filled subarachnoid space contained slight non-specific mononuclear inflammatory infiltration not associated with vessels, with only 1 CAA vessel demonstrating perivascular cuffing (Figure 2G).

In the right collateral sulcus, many leptomeningeal CAA vessels and some of their perforators were associated with overt perivascular and transmural inflammation, comprising predominantly CD4-positive and CD8-positive T lymphocytes, few CD20-positive B lymphocytes, and abundant CD68-positive microglia/macrophages, consistent with ABRA (Figure 2H–V, [Supporting Information, File 3](#)). Many inflammatory cells showed intracytoplasmic A β positivity, including perivascular MNGCs (identified as CD68+ macrophages), indicating phagocytosis (Figure 2I–L). Notably, vascular A β positivity here was remarkably pale. In fact, the most severely vasculitic vessels showed minimal-to-no A β positivity but were associated with perivascular/intramural cells with intracytoplasmic A β , occasionally in a pattern almost indistinguishable from CD68 positivity, suggesting phagocytosis of vascular A β (Figure 2N,R,U,V). The subarachnoid infiltrate also contained a few scattered erythrocytes with occasional single siderophages suggesting erythrocyte extravasation but

no overt hemorrhage. Numerous diffuse and a few dense core A β plaques were noted but with only occasional neurofibrillary tangles in the entorhinal cortex but not in the hippocampus (Braak stage 1/2), excluding AD. The hippocampus proper was affected by mild-to-moderate CAA. The deep subcortical WM was devoid of CAA. The basal ganglia showed mild arteriosclerosis (with occasional single perivascular siderophages) but no CAA.

Restriction fragment length polymorphism analysis of *ApoE* revealed an $\epsilon 3/\epsilon 3$ genotype.

4 | Discussion

This is the second report on the sequelae of IVT applied for suspected AIS in a patient with ABRA at autopsy, preceded by a report on a 55-year-old man with multiple IVT-ICHs, likewise without clinical-radiological hints of CAA-RI [9].

CAA-RI (including its vasculitic subtype, ABRA) is a rare inflammatory CAA manifestation, typically presenting with cognitive/behavioral changes, headache, focal neurological deficits, and/or seizures, predominantly in association with asymmetric confluent WM edema and CAA-compatible hemorrhagic alterations. However, alternative (strictly leptomeningeal) presentations have been highlighted in recent extended criteria [5, 6]. Most recently, a study found association between cSAH-related spells and corresponding leptomeningeal enhancement in cases without WM edema, suggesting a causal link between cSAH and leptomeningeal CAA-RI [10]. The diagnostic relevance of CAA-RI is established by its propensity to respond to immunosuppression (>80%). Without MRI, it is unclear whether our patient would have met *probable CAA-RI* by existing criteria; however, apparent confluent edema was absent. Though CAA was suspected based on ICH morphology, CAA-RI was not suspected until histopathological work-up. Speculatively, the recent memory complaints and headache might be discussed as correlates of CAA-RI, but these were not bothersome enough to prompt seeking medical help. The mean 10 years earlier presentation of CAA-RI (67 years) compared to that of the first CAA-related ICH fits with the age of our case [2, 5]. The majority of CAA-RI cases have *ApoE*- $\epsilon 4/\epsilon 4$ genotype [5], which was, however, not present.

The risk for lobar ICHs posed by CAA, especially with concomitant antithrombotics, has long been recognized [2]. Additionally, increasing evidence links IVT-ICHs to CAA. Early clinical evidence linking pathology-verified CAA to IVT-ICHs came from acute myocardial infarction cases; however, the concomitant heparinization obscured the interpretation [11]. More recently, three cases suffering ICH(s) after IVT used for AIS have been reported with definite (autopsy-verified) CAA, 1 with ABRA ([Supporting Information, File 4](#)) [9, 12, 13]. Systematically, a 13.3% (2/15) prevalence of symptomatic IVT-ICHs was found in AIS cases with *probable CAA* on pretreatment MRI (higher than in unselected populations), with invariable fatality [14]. Similarly, 53.8% (7/13) of AIS cases with IVT-associated lobar remote parenchymal hemorrhage had strictly lobar (CAA-compatible) CMBs on post-treatment MRI, versus 3.0% in those

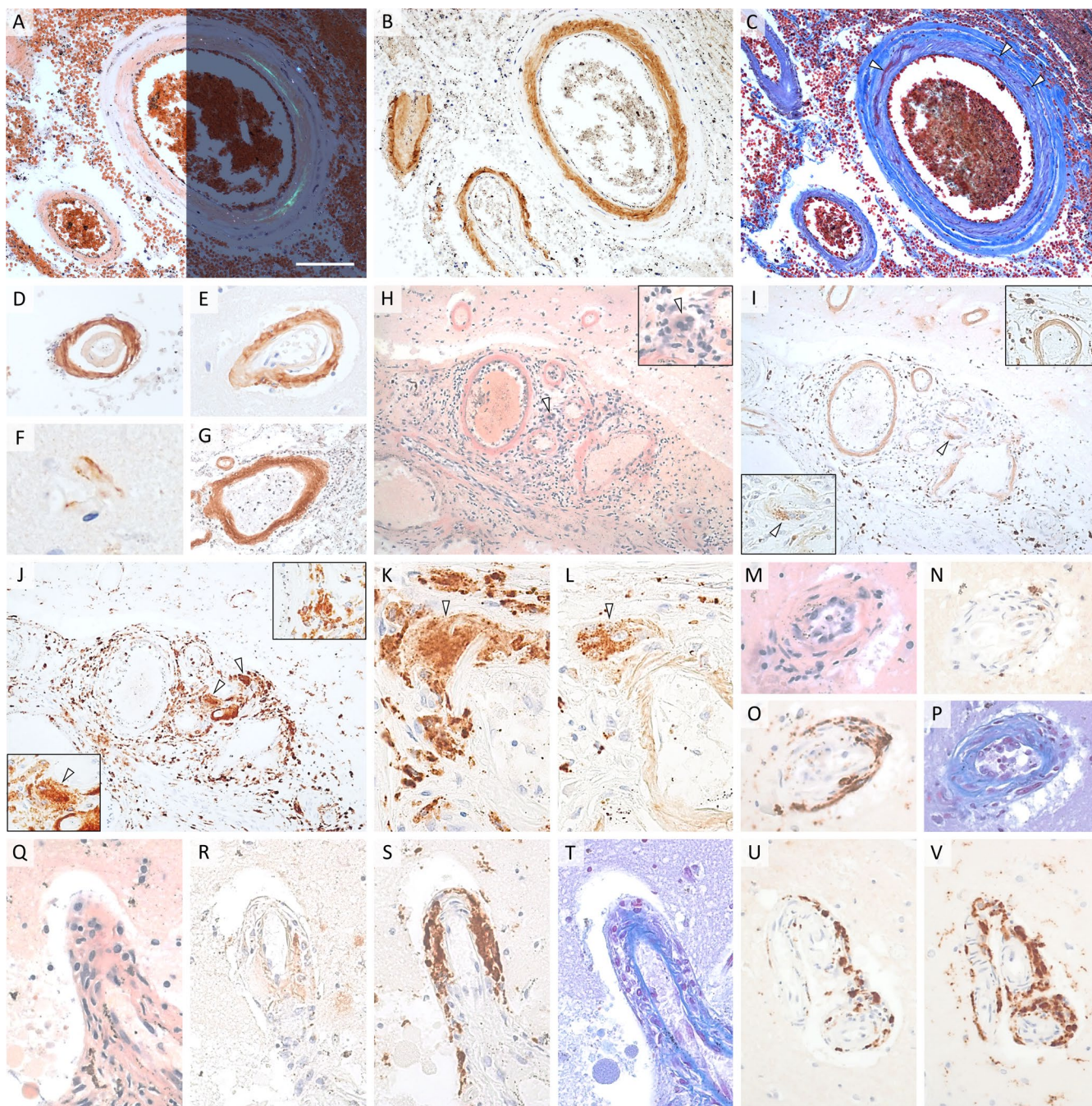


FIGURE 2 | Neuropathological presentation. Frontal vessels near the ICH display congophilic CAA, with apple-green birefringence under the polarized microscope (A) and A β immunopositivity (B). Fibrinoid necrosis (Vonsattel grade 4, C). Double-barrel formations in the leptomeninges (D) and parenchyma (E). Capillary involvement (Thal CAA Type 1, F). A single vessel shows perivascular mononuclear cuffing in this region (G). Massive inflammatory infiltrate encompasses CAA vessels in the collateral sulcus and adjacent cortices (H–V), comprising several lymphocytes, with abundant CD68-positive microglia/macrophages (J, K, O, S, V). Many cells contain intracytoplasmic A β (I, L, N, U). MNGCs (arrows in H–L), often with intracytoplasmic A β (arrows in I and L). Intramural involvement (M–V), consistent with ABRA. Remarkably paler vascular A β positivity in the inflamed area (I, L, R) compared to frontal CAA (B, D, E, G). Vessels with the most severe vasculitis demonstrate extremely pale (R) or minimal-to-no vascular A β positivity (N, U), but are associated with various amount of cells with intracytoplasmic A β (N, U), occasionally in a pattern almost indistinguishable from CD68 positivity (U, V), reflecting phagocytosis of vascular A β . Congo red: (A), (H), (M), (Q); anti-A β antibody: (B), (D–G), (I), (L), (N), (R), (U); Crossman's modified Mallory's trichrome: (C), (P), (T); anti-CD68 antibody: (J, K), (O), (S), (V). Scale bar in (A) represents 100 μ m in (A–C), 65 μ m in (D, M–P, U, V), 55 μ m in (E, Q–T), 20 μ m in (F), 145 μ m in (G–J), and 35 μ m in (K, L).

without hemorrhage [15]. Correspondingly, significantly higher cortical Pittsburgh compound B retention was reported in patients with versus those without parenchymal hemorrhage after IVT [16]. Systematic autopsy data are lacking.

Though an increased risk for hemorrhage formation posed by CAA-RI in particular has only recently been supported by systematic analysis [5], a medicolegal autopsy case was reported with ABRA as a proposed etiology underlying fatal multiple

lobar spontaneous ICHs [17]. Similarly to our case, the authors reported the paucity of A β in severely vasculitic vessels and the presence of phagocytosed A β in MNGCs [17]. Phagocytosed A β in microglia, macrophages, or MNGCs is frequently described in CAA-RI (reviewed in [5, 18]). Remarkably, this seemingly inverse relationship between vascular A β load and vasculitic severity has also been noted by a few reports [5, 17, 19], most of them also observing phagocytosed A β [5, 17], in the above case with concomitant ICH [17]. These together with our corroborating observations imply a possible role of phagocytic A β clearance in hemorrhage formation in CAA-RI.

Our case expands the knowledge on the potential complications of CAA/CAA-RI; however, the etiology underlying her initial symptoms is a dilemma, as faced before [13]. Indeed, the ICH-associated destruction precluded the verification of primary ischemia. Additionally, CAA can present with “amyloid spell”, often with corresponding cSAH. From this respect, we cannot exclude that the identified vague sulcal hyperdensity had etiological relevance, especially in light of the recently proposed link between cSAH and leptomeningeal CAA-RI [10]; however, it was not considered hemorrhage by radiologists/neurologists during acute care, and might have required confirmatory MRI. Finally, the symptoms could be related to CAA-RI itself.

This case study has several learning points and peculiarities: (a) it confirms CAA/CAA-RI to be a risk for IVT-ICH, implying the additive role of inflammation; (b) reports the second ABRA case in this scenario; (c) strongly implicates the role of vascular A β phagocytosis; (d) confirms that CAA-RI may present without prominent edema; (e) highlights that CAA/CAA-RI-related focal deficits (including amyloid spells) can be potential AIS mimics within the IVT time window, suggesting their consideration in the differential diagnosis; and (f) urges for rigorous analysis of pre-IVT CT scans for even subtle sulcal hyperdensities suggesting cSAH/amyloid spell in elderly patients, prompting consideration of MRI at the slightest suspicion.

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Disclosure

L.S. received speaker's honoraria from Biogen and conference registration fees from Bayer, Biogen, Gedeon Richter Plc., Sandoz, and Sanofi-Genzyme.

Ethics Statement

The study and the publication of the case were approved by local Ethical Committee (44/2016, 22/2021).

Consent

The next-of-kin provided informed consent to the genetic analysis and publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

References

1. A. Charidimou, G. Boulouis, M. P. Frosch, et al., “The Boston Criteria Version 2.0 for Cerebral Amyloid Angiopathy: A Multicentre, Retrospective, MRI-Neuropathology Diagnostic Accuracy Study,” *Lancet Neurology* 21 (2022): 714–725.
2. B. Fakan, Z. Reisz, D. Zadori, L. Vecsei, P. Klivenyi, and L. Szalardy, “Predictors of Localization, Outcome, and Etiology of Spontaneous Intracerebral Hemorrhages: Focus on Cerebral Amyloid Angiopathy,” *Journal of Neural Transmission* 127 (2020): 963–972.
3. L. Jakel, A. M. De Kort, C. J. M. Klijn, F. Schreuder, and M. M. Verbeek, “Prevalence of Cerebral Amyloid Angiopathy: A Systematic Review and Meta-Analysis,” *Alzheimer's & Dementia* 18 (2022): 10–28.
4. A. Charidimou, A. Peeters, Z. Fox, et al., “Spectrum of Transient Focal Neurological Episodes in Cerebral Amyloid Angiopathy: Multicentre Magnetic Resonance Imaging Cohort Study and Meta-Analysis,” *Stroke* 43 (2012): 2324–2330.
5. L. Szalardy, B. Fakan, R. Maszlag-Torok, et al., “Identifying Diagnostic and Prognostic Factors in Cerebral Amyloid Angiopathy-Related Inflammation: A Systematic Analysis of Published and Seven New Cases,” *Neuropathology and Applied Neurobiology* 50 (2024): e12946.
6. A. Charidimou, “Diagnosing Cerebral Amyloid Angiopathy-Related Inflammation,” *Neurology* 103 (2024): e209647.
7. M. A. Rodrigues, N. Samarasekera, C. Lerpiniere, et al., “The Edinburgh CT and Genetic Diagnostic Criteria for Lobar Intracerebral Haemorrhage Associated With Cerebral Amyloid Angiopathy: Model Development and Diagnostic Test Accuracy Study,” *Lancet Neurology* 17 (2018): 232–240.
8. S. Takeda, K. Hinokuma, K. Yamazaki, et al., “The Hemorrhage Caused by Sporadic-Type Cerebral Amyloid Angiopathy Occurs Primarily in the Cerebral Sulci,” *Neuropathology* 32 (2012): 38–43.
9. Z. Reisz, C. Troakes, L. K. Sztrihai, and I. Bodi, “Fatal Thrombolysis-Related Intracerebral Haemorrhage Associated With Amyloid-Beta-Related Angiitis in a Middle-Aged Patient - Case Report and Literature Review,” *BMC Neurology* 22 (2022): 500.
10. A. Sellimi, L. Panteleienko, D. Mallon, et al., “Inflammation in Cerebral Amyloid Angiopathy-Related Transient Focal Neurological Episodes,” *Annals of Neurology* 97 (2025): 475–482.
11. M. O. McCarron and J. A. Nicoll, “Cerebral Amyloid Angiopathy and Thrombolysis-Related Intracerebral Haemorrhage,” *Lancet Neurology* 3, no. 8 (2004): 484–492.
12. R. J. Felling, R. Faigle, C. Y. Ho, R. H. Llinas, and V. C. Urrutia, “Cerebral Amyloid Angiopathy: A Hidden Risk for IV Thrombolysis?,” *Journal of Neurology and Translational Neuroscience* 2, no. 1 (2014): 1034.
13. O. S. Mattila, T. Sairanen, E. Laakso, A. Paetau, M. Tanskanen, and P. J. Lindsberg, “Cerebral Amyloid Angiopathy Related Hemorrhage After Stroke Thrombolysis: Case Report and Literature Review,” *Neuropathology* 35 (2015): 70–74.
14. A. Leonte, S. Laurent-Chabalier, A. Wacogne, et al., “Brain Hemorrhage on 24h-CT and Functional Outcome in Stroke Patients With Cerebral Amyloid Angiopathy Features on Pre-Thrombolysis MRI Treated With Intravenous Thrombolysis: A Case Series,” *Journal of Stroke and Cerebrovascular Diseases* 32 (2023): 106907.
15. L. Prats-Sanchez, A. Martinez-Domeno, P. Camps-Renom, et al., “Risk Factors Are Different for Deep and Lobar Remote Hemorrhages After Intravenous Thrombolysis,” *PLoS One* 12 (2017): e0178284.

16. J. V. Ly, C. C. Rowe, V. L. Villemagne, et al., "Cerebral Beta-Amyloid Detected by Pittsburgh Compound B Positron Emission Topography Predisposes to Recombinant Tissue Plasminogen Activator-Related Hemorrhage," *Annals of Neurology* 68 (2010): 959–962.
17. S. Ichimata, Y. Hata, K. Yoshida, and N. Nishida, "Autopsy of a Multiple Lobar Hemorrhage Case With Amyloid-Beta-Related Angiitis," *Neuropathology* 40 (2020): 280–286.
18. K. Sakai and M. Yamada, "Cerebral Amyloid Angiopathy-Related Inflammation and Dementia," *Clinical and Experimental Neuroimmunology* 12 (2021): 101–106.
19. K. Sakai, S. Hayashi, K. Sanpei, M. Yamada, and H. Takahashi, "Multiple Cerebral Infarcts With a Few Vasculitic Lesions in the Chronic Stage of Cerebral Amyloid Angiopathy-Related Inflammation," *Neuropathology* 32 (2012): 551–556.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.