Journal of Stroke and Cerebrovascular Diseases 34 (2025) 107969

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstroke

Case Report

Iatrogenic cerebral amyloid angiopathy: Two case reports to explore clinical heterogeneity and pathological patterns

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ARTICLE INFO

Keywords:
Case report
Iatrogenic cerebral amyloid angiopathy
Hemorrhagic stroke
Spontaneous intracerebral hemorrhage

ABSTRACT

Introduction: These case reports illustrate Iatrogenic Cerebral Amyloid Angiopathy (iCAA) due to neurosurgical procedures. Recent studies propose prion transmission during neurosurgery as a potential mechanism for β-amyloid seed implantation, linking neurosurgical history to the development of iCAA. The majority of reported cases in the literature have an unfavorable prognosis, with recurrence of intracerebral hemorrahge (ICH) and subsequent death during the first months of follow-up. There is no effective treatment for preventing the progression of the disease.

Results: a 41-year-old man with a previous history of left frontotemporal traumatic brain injury and subsequent neurosurgical intervention in childhood was admitted with an ICH leading to the diagnosis of iCAA. The patient's history of exposure, combined with imaging studies and neuropsychological assessments, supported the suspicion of iCAA. Confirmatory PET-CT scans revealed β-amyloid deposits in the cortical regions, aligning with the proposed criteria for iCAA. At the 2-year follow-up, the patient presents an NIHSS of 0 and a Modified Rankin Scale (mRS) of 1. The second case involved a 50-year-old man with a history of surgical treatment for Arnold-Chiari malformation, who developed transient neurological deficits and presented multiple ICH. The patient's history of neurosurgical intervention and the radiological and clinical features supported the diagnosis of probable iAAC. Despite a negative PET-CT result, CSF analysis provided evidence of ß-amyloid accumulation in the CNS. At the 6-year follow-up, the patient presented an NIHSS of 1(hemihypoesthesia) and mRS of 3.

Conclusion: iCAA is an emerging pathology probably driven by prion transmission of β-amyloid seed after neurosurgical interventions. It is important to suspect this condition in young patients with ICH and a history of neurosurgical procedure. Recognizing iCAA's clinical and radiological features is crucial for early identification. The diagnosis process is based on demonstrating the accumulation of β-amyloid protein in the central nervous system using PET-CT or cerebrospinal fluid (CSF) studies and also conducting genetics studies. As an evolving pathology without a clear pathophysiology and a potential divergent evolution between phenotypes, establishing standardized diagnostic criteria and a multicenter registry is imperative for a comprehensive understanding of iCAA.

Introduction

Iatrogenic cerebral amyloid angiopathy (iCAA) is a rare yet clinically significant condition that has recently garnered attention.[1–4] Recent studies propose prion transmission during neurosurgical interventions as a potential mechanism for transmitting β-amyloid seeds, capable of inducing iCAA decades after the procedure.[2–4] This fact suggests a connection between neurosurgical history and the development of iCAA, leading to intracerebral hemorrhages (ICH), particularly in young patients with a history of exposure.[5–7] UCL criteria had been proposed for

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https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107969
Received 13 May 2024; Received in revised form 16 August 2024; Accepted 25 August 2024
Available online 29 October 2024
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iCAA diagnosis[4]. The majority of reported cases have an unfavorable prognosis, with recurrence of ICH and subsequent death during the first months of follow-up.[4,7,8] There is no effective treatment for preventing the progression of the disease. The objective is to enhance the diagnostic process of iCAA by thoroughly examining these clinical cases, emphasizing the importance of confirming CNS accumulation of B-amyloid and conducting genetic studies for proper patient identification. Additionally, it contributes to the evidence supporting the existence of various clinical presentation phenotypes, characterized by a chronic disease course or late onset.[9]

Results

Brief report of case 1

The patient is a 41-year-old man with no allergies, married, and working as an illustrator who has been smoking 14 cigarettes per day since the age of 20, with no other known cardiovascular risk factors. He also has a history of left frontotemporal traumatic brain injury at the age of 3, which required neurosurgical intervention for the removal of a foreign body in 1983.

In the days leading up to admission to our center, he experienced a self-limiting episode of sensory disturbance, including paresthesias in the right arm with subsequent progression to the right hemifacial area and posterior hypoesthesia. Twenty-four hours later, he was admitted to the emergency department presenting focal seizures with secondary generalization.

A cranial CT revealed a left frontoparietal lobar hematoma (Fig. 1A), and CT angiography ruled out vascular abnormalities. The patient was hemodynamically stable and not feverish. Neurological examination revealed mild motor aphasia and right brachial hypoesthesia scoring 2 points on the NIHSS scale.

During the hospitalization, a comprehensive investigation was conducted for a young patient presenting with spontaneous ICH. A cerebral MRI revealed a left cortico-subcortical frontal lesion consistent with an acute hematoma, accompanied by mild vasogenic edema with subarachnoid hemorrhage (SAH) foci (Fig. 1B). No underlying focal lesions were identified. A complete cerebral angiography ruled out aneurysms, vascular malformations, and fistulas.

At the 1-month follow-up (Fig. 1C), a control cerebral MRI reported the emergence of new contralateral sulcal involvement with a convexity subarachnoid hemorrhage, prompting consideration of amyloid angiopathy. The follow-up MRI showed the appearance of new lesions indicative of CAA such as a right frontal microbledd and an extensive superficial hemosiderosis.

A neuropsychological study described a mild corticosubcortical frontal cognitive disorder with impaired attention, executive function alterations, and dysgraphia with difficulties in 3D drawings and color perception.

Given the patient's history of neurosurgical exposure with a dural graft, suspicion pointed towards iCAA. a PET-CT confirmed B-amyloid deposits at the cortical level affecting both frontal, temporal, and parietal lobes (Fig. 3A). CSF was not performed due to a positive amyloid-PET scan. After obtaining signed informed consent, whole-exome sequencing was performed, aided by Phenotype Ontology (HPO) terms to standardize clinical features and predict causative genes. No genetic variants associated with the clinical indication, including risk haplotypes, were detected. The ApoE genotype was E3/E3.

The patient meets the UCL proposed diagnostic criteria for probable iCAA.[3]

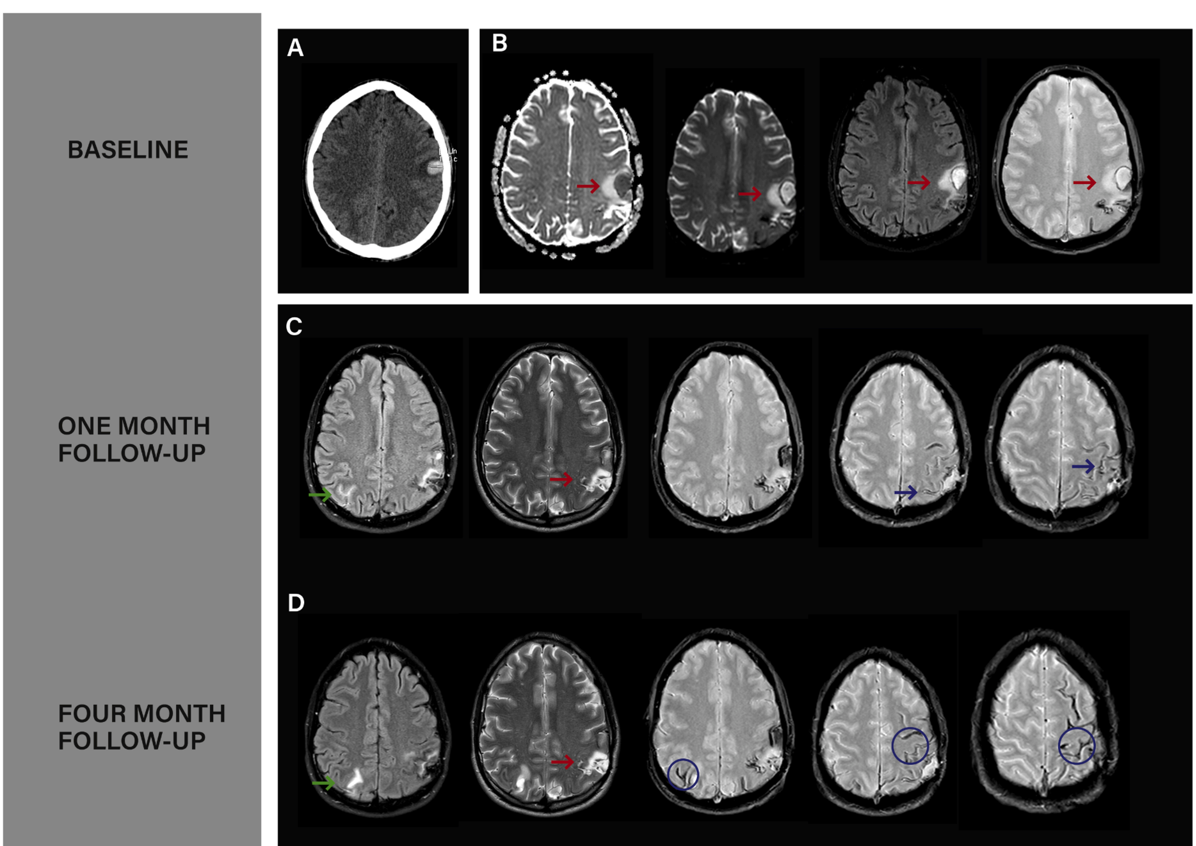

Fig. 1. Neuroimaging tests in case 1. A: Baseline brain CT: B. Baseline MRI. C: One month follow-up MRI. D: Four-month follow-up MRI.
Arrows in red show the intracerebral hemorrhage. Arrows in blue show cortical superficial siderosis. Arrows in green shows new subarachnoid hemorrhage. Circles in blue show new cortical superficial siderosis.

During the two-year follow-up period, the patient did not experience any new neurological focality nor cognitive decline. He presented an NIHSS of 0 and a Modified Rankin Scale of 1.

Brief report of case 2

A 50-year-old man with no known allergies, married, and actively employed, without any toxic habits or identified cardiovascular risk factors. He underwent surgical treatment for Arnold-Chiari malformation with secondary syringomyelia in 1989. It could not be verified whether a dural substitute, specifically Lyodura, was used.

At the age of 46, he developed clinical manifestations of right facial hemispasm, progressively worsening to daily episodes. Two years after this symptom onset, a cerebral MRI revealed multiple subcortical white matter lesions disproportionate to the patient's age (Fig. 2A). A follow-up MRI at 3 months showed evolving cerebral hemorrhagic lesions, predominantly in the cortico-subcortical junction, accompanied by signs of superficial hemosiderosis (Fig. 2B).

During the follow-up, the patient experienced resolution of facial hemispasm without additional motor or cognitive symptoms. Diagnostic tests included an angiogram, which ruled out vasculitis, aneurysms, fistulas, venous thrombosis, or other vascular malformations. Electromyography showed no abnormalities, and transthoracic cardiac ultrasound revealed a calcified aortic valve with dilation at the aortic root without any other findings. An electroencephalogram demonstrated a trace within normal limits, without epileptogenic characteristics. The thyroid and autoimmune profiles showed no abnormalities. Further investigations were conducted to exclude Fabry's disease and familial forms of cerebral amyloid angiopathy.

Four years after symptom onset, the patient was admitted to our Stroke Unit with motor deficits, left hemiparesis (NIHSS 7), secondary to a right frontoparietal intraparenchymal hematoma (Fig. 2C). A follow-up cerebral MRI revealed radiological progression with two subacute hematomas in the right parasagittal and right lateral frontal regions. Extensive superficial hemosiderosis predominantly in the bilateral convexity sulci, extending to the cerebellar folia with multiple microbleeds in the thalamic and periventricular region (Fig. 2D). Post-surgical occipital changes related to Chiari malformation with infratentorial superficial hemosiderosis associated.

Considering the patient's history of relevant neurosurgical procedures, and radiological and clinical characteristics, the patient could meet the UCL proposed diagnostic criteria for probable iCAA(3). To confirm ß-amyloid deposition in the central nervous system (CNS), a cerebral PET scan showed an absence of abnormal amyloid deposits in cortical regions (Fig. 3B). Despite the negative PET-CT result, a cerebrospinal fluid (CSF) study revealed increased Tau protein (486 pg/mL; normal range <385 pg/mL) with normal phosphorylated Tau (63 pg/mL; normal range <65 pg/mL) and decreased ß-amyloid 42 (289 pg/mL; normal range >600 pg/mL), consistent with ß-amyloid accumulation in the CNS.

After obtaining signed informed consent, whole-exome sequencing was performed, aided by Phenotype Ontology (HPO) terms to standardize clinical features and predict causative genes. No genetic variants associated with the clinical indication, including risk haplotypes, were

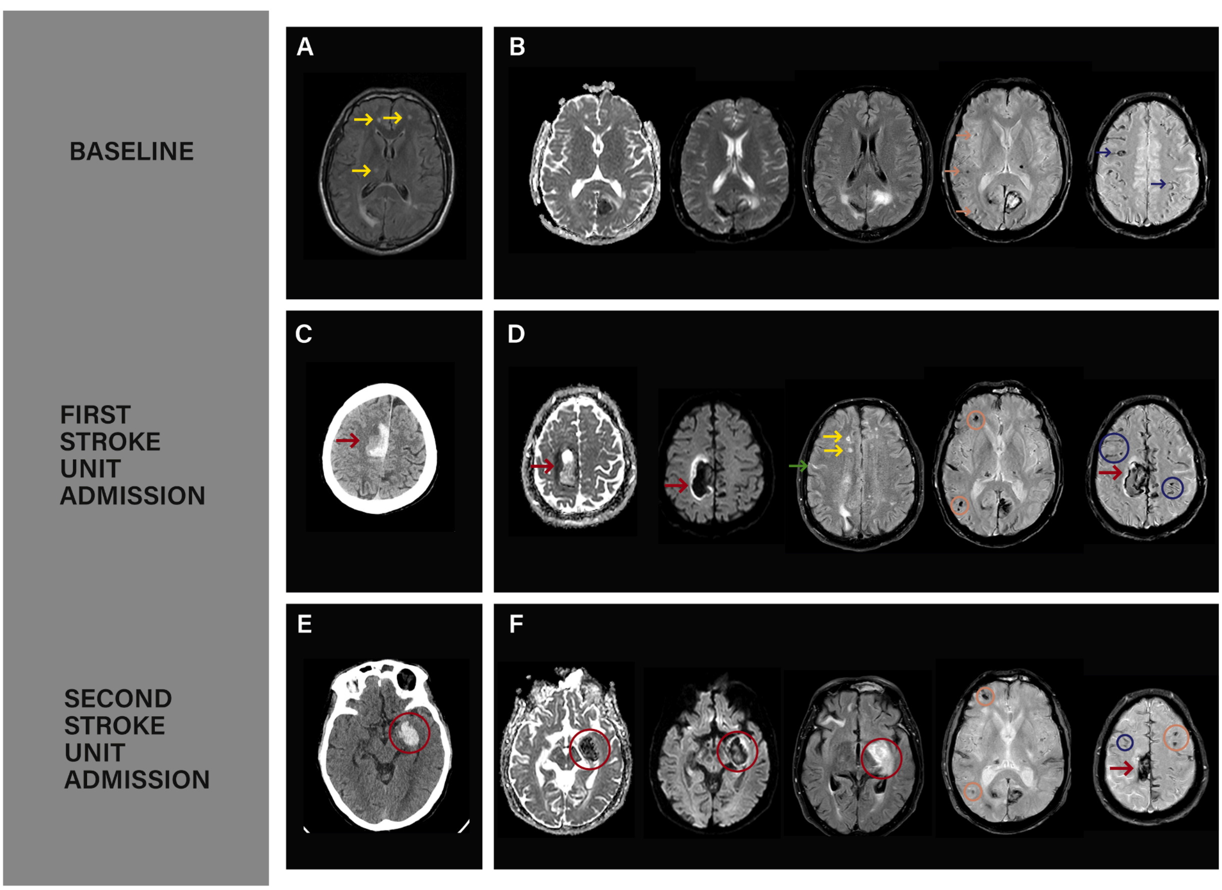

Fig. 2. Neuroimaging tests in case 2. A and B: Cerebral MRI before stroke. C: Brain CT at first Stroke Unit admission. D: MRI at first Stroke Unit admission. E: Brain CT at second Stroke Unit admission. F: MRI at second Stroke Unit admission.
Arrows in red show the intracerebral hemorrhage. Arrows in yellow show white matter hyperintensities. Arrows in orange show cerebral microbleeds. Arrow in green show new subarachnoid hemorrhage. Circles in red show new intracerebral hemorrhages. Circles in blue show new cortical superficial siderosis. Circles in orange show new cerebral microbleeds.

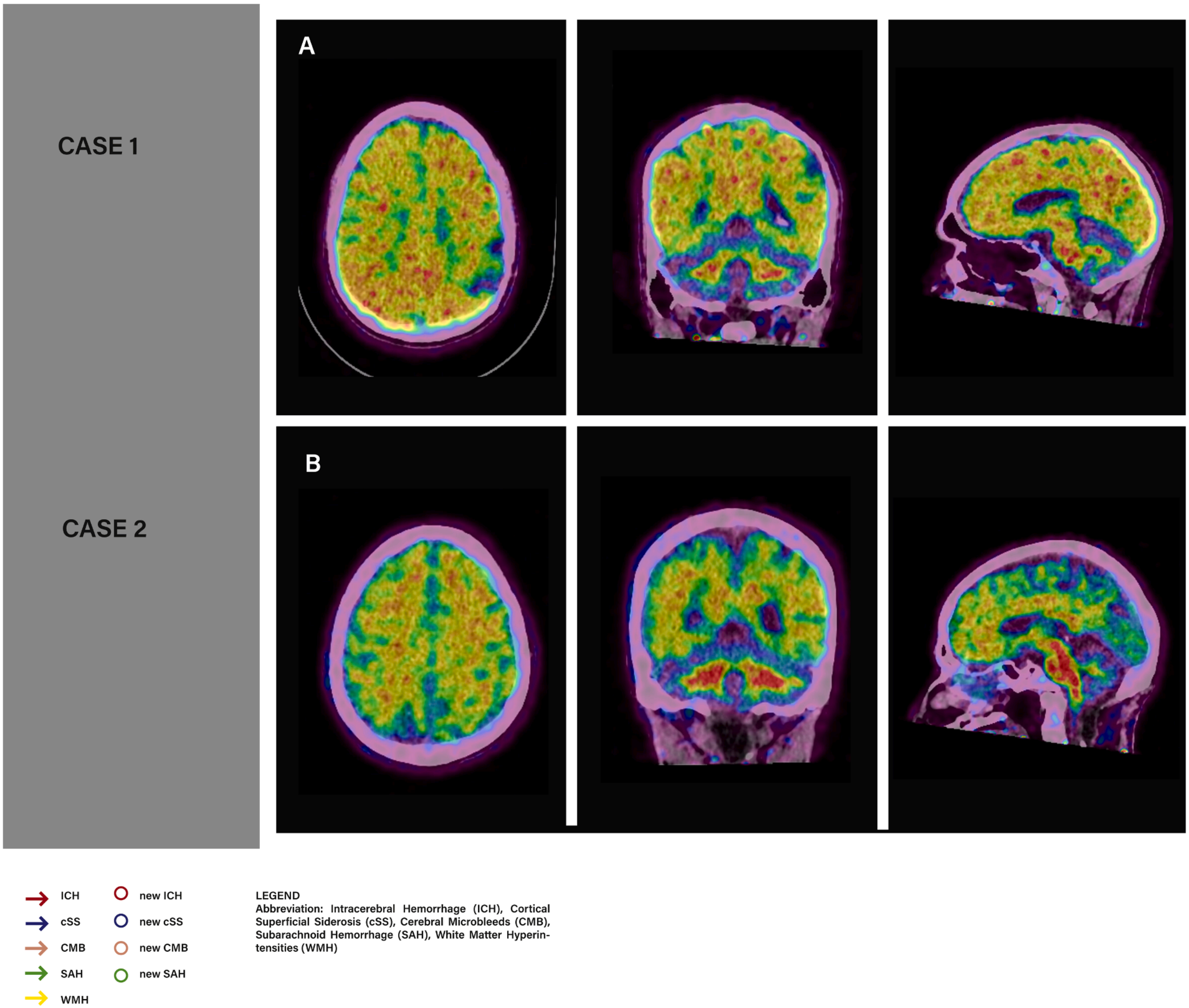

Fig. 3. A. PET-CT shows B-amyloid deposits at the cortical level affecting both frontal,temporal, and parietal lobes in case 1. B. Cerebral PET-CT shows an absence of abnormal amyloid deposits in cortical regions in case 2.

detected. The ApoE genotype was E3/E3.

During follow-up, the patient experienced new episodes of neurological deficits due to the occurrence of hemorrhagic lesions. An episode of right faciobrachial paresthesia and hypoesthesia lasting one hour coincided with the appearance of a small left frontal subarachnoid hemorrhage. Nine months after admission to the Stroke Unit, the patient was readmitted with a motor aphasia and brachial weakness secondary to a left temporal intracerebral hemorrhagic stroke (Fig. 2E). Follow-up MRI showed radiological features worsening (Fig. 3F), including an increase in the number of microbleeds, white matter lesions, greater superficial hemosiderosis, and focal subarachnoid hemorrhage.

The neuropsychological study showed anterograde amnesic deficits with impairment in executive and attentional functions. There was also significant anomia and bradypsychia.

Non-specific treatment was recommended due to the lack of evidence.

At the 6-year follow-up, the patient presented an NIHSS of 1 (hemihypoesthesia) and a Modified Rankin Scale of 3.

Discussion

Recent studies suggest that prion transmission during neurosurgical interventions may be a mechanism for transmitting β-amyloid seeds, potentially leading to iatrogenic cerebral amyloid angiopathy (iCAA) even decades later. This phenomenon is particularly significant in young patients with a history of such exposure, as illustrated by the cases presented. Therefore, iCAA should be considered in patients under 55 years old who experience early onset intracerebral hemorrhage (ICH) and have a history of neurosurgical intervention during childhood or adolescence, along with radiological and clinical features compatible with CAA (Fig. 4). Demonstrating the accumulation of β-amyloid protein in the central nervous system through PET-CT or cerebrospinal fluid (CSF) studies and genetics studies to rule out possible causes is crucial during the diagnosis process.

Proposed UCL diagnostic criteria for iatrogenic cerebral amyloid angiopathy (iCAA) should include[4]: (1) a history of neurosurgical procedures, (2) early-onset intracerebral hemorrhage in patients under 55 years of age, (3) radiological features consistent with CAA, such as microbleeds and white matter lesions, and (4) evidence of β-amyloid accumulation through advanced imaging or CSF analysis. Genetic studies to exclude other causes of amyloid angiopathy are also recommended.

Many reported cases of iCAA describe a progressive pathology with a poor short-term prognosis due to recurrent intracerebral hematomas, especially in young patients.[6,7] However, the cases presented in this article demonstrate a chronic disease course in two young patients, with some recurrences but good functional recovery. This underscores the potential variability in phenotypes that iCAA may present, including a chronic course with free-relapse periods.[1,9] iCAA is an emerging pathology with an increasing number of reported cases, yet its prevalence

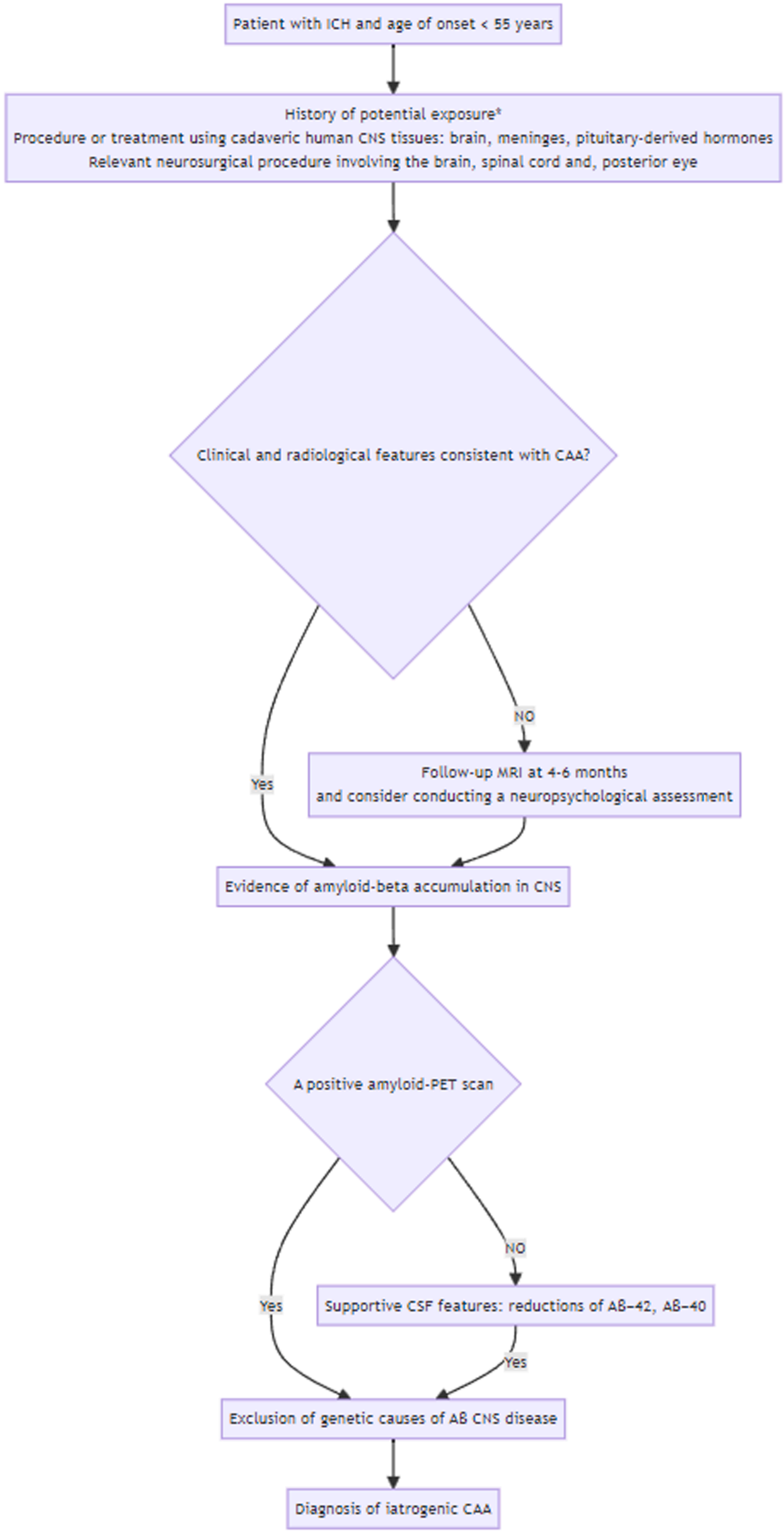

Fig. 4. Flow chart algorithm for iCAA diagnosis based on UCL proposed diagnostic criteria for iatrogenic cerebral amyloid angiopathy.

and natural history remain unknown. Establishing standardized diagnostic criteria and considering the creation of a multicenter registry is essential for increasing understanding of this condition.

Inclusion and ethics statement

This research complies with all pertinent ethical regulations, including CARE guidelines and the Declaration of Helsinki principles. The patients provided informed consent to participate in this case report.

Data availability

Neuroimaging, genetics, and medical data are available in this manuscript and its supplementary materials. Other clinical details and source files for the figures are available from the corresponding author upon reasonable request without sharing any sensitive patient data.

CRediT authorship contribution statement

Carla Vera-Cáceres: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Nerses Nersesyan:** Writing – review & editing, Data curation, Conceptualization. **Maria Obon:** Writing – review & editing, Validation, Supervision, Investigation, Data curation. **Mikel Terceño:** Writing – review & editing, Validation, Data curation, Conceptualization. **Joaquin Serena:** Validation, Supervision, Data curation, Conceptualization. **Juan Álvarez-Cienfuegos:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Data curation. **Tomàs Xuclà:** Writing – original draft, Formal analysis. **Saima Bashir:** Formal analysis, Data curation. **Yolanda Silva:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Authors declare no conflict of interest.

Acknowledgments

We would like to express our sincere gratitude to the patients who generously participated in this study. Their willingness to share their experiences and medical information has been invaluable to our research efforts.

We also thank the Department of Neuroradiology at our institution for their assistance in imaging procedures and data interpretation. Additionally, we acknowledge the Department of Genetics for its support in genetic analysis and interpretation. Furthermore, we are grateful to the Stroke Unit for their collaboration and expertise in managing the patients included in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2024.107969.

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