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Clinical short communication

Cerebral amyloid angiopathy-related transient focal neurological episodes: A transient ischemic attack mimic with an increased risk of intracranial hemorrhage

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ABSTRACT

Background: Transient focal neurological episodes (TFNEs) are a recently recognized clinical presentation of cerebral amyloid angiopathy (CAA). Our aim was to describe the clinical and radiological features of a series of patients with AS.

Methods: We included 11 patients presenting with recurrent transient focal neurological symptoms and radiological features related to CAA.

Results: Mean age was 76,6 and 5 patients were women. All patients reported transient, stereotyped, and recurrent episodes (6 patients had > 10 episodes). Gradual spread of the symptoms was recorded in 9 patients. Initially, 3 patients were misdiagnosed as having recurrent transient ischemic attack (TIA), 6 as having seizures, and 2 as having both. Two patients were prescribed antiplatelet therapy. A cerebral MRI with T2* gradient-recalled echo sequence revealed cortical superficial siderosis (cSS) in 5 patients, cortical microbleeds in 1 patient, and both features in 5 cases. After a median follow-up of 36 months, intracranial hemorrhage (ICH) was recorded in 4 patients. All 4 had cSS in the previous cerebral MRI, and 1 was on antiplatelet therapy.

Conclusion: CAA-related TFNEs are an underdiagnosed entity, often mimicking TIA, seizures, or migraine aura. This misdiagnosis can lead to the prescription of antiplatelet or anticoagulant therapy, which increases the risk of ICH. Our results suggest that cSS might be a radiological marker that is closely related to an increased risk of bleeding. A T2* gradient-recalled echo MRI should be performed in elderly patients with transient focal neurological symptoms suggestive of CAA.

1. Introduction

Cerebral amyloid angiopathy (CAA) is an age-related small-vessel disease characterized by the deposition of amyloid beta in cortical and leptomeningeal vessels, mainly arteries and arterioles [1]. The prevalence of CAA increases with age, and the disease affects 20–40% of the elderly population according to various necropsy series [2]. This disorder is a major cause of spontaneous intracerebral hemorrhage (ICH) in the elderly and has been related to cognitive impairment [3]. Indeed, > 90% of patients with Alzheimer's disease present at least mild CAA [4].

Over the last few years, several neuroimaging markers related to CAA have been described, primarily cortical superficial siderosis (cSS) and cortical microbleeds (CMB) [5–8]. Both radiological features can be detected with blood-sensitive cerebral MRI sequences, such as T2* gradient-recalled echo (T2*GRE) [9]. cSS is defined as linear hemosiderin deposition in the superficial layers of the cortex and is considered the radiological manifestation of previous convexity subarachnoid hemorrhage. It is considered to be focal if 3 or fewer sulci are affected and diffuse or disseminate if the extension is greater. The presence of cSS has been closely associated with an increased risk of future lobar ICH in several case reports and series [10–14]. In the last years, this

Abbreviations: CAA, Cerebral amyloid angiopathy; ICH, intracerebral hemorrhage; cSS, cortical superficial siderosis; CMB, cortical microbleeds; T2*GRE, T2* gradient-recalled echo; TFNEs, transient focal neurological episodes; TIA, transient ischemic attack; HBP, high blood pressure; ACT, anticoagulante therapy; cSAH, cortical subaracnoid hemorrhage; APT, antiplatelet theraphy; AED, anti epilieptic drugs

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Table 1
Demographic characteristics and vascular risk factors of a series of patients with CAA-related TFNEs.

	Age	Sex	Vascular risk factors					Previous APT/ACT treatment	
			HBP	DL	Type 2 DM	Obesity	Smoking	APT	ACT
Case 1	65	Woman	No	No	No	No	No	No	No
Case 2	87	Man	Yes	Yes	No	No	No	Yes	No
Case 3	78	Woman	No	Yes	No	No	No	No	No
Case 4	70	Man	No	No	No	No	Yes (inactive)	No	No
Case 5	64	Man	Yes	Yes	No	No	Yes (inactive)	No	No
Case 6	76	Man	Yes	Yes	No	Yes	Yes (inactive)	No	No
Case 7	78	Man	Yes	No	No	No	No	No	No
Case 8	84	Man	Yes	No	No	No	Yes (inactive)	Yes	No
Case 9	65	Woman	Yes	Yes	No	No	No	No	No
Case 10	68	Woman	No	Yes	No	No	No	No	No
Case 11	81	Woman	Yes	Yes	No	No	No	No	No
Mean (Range)	76,6 (66–89)								
N (%)		M 6 (54,5) W 5 (45,5)	7 (63,6)	7 (63,6)	0 (0)	1 (9,1)	4 (36,4)	2 (18,2)	0 (0)

CAA: cerebral amyloid angiopathy; TFNEs: transient focal neurological episodes; HBP: High blood pressure; DL: dyslipidaemia; DM: Diabetes Mellitus; APT: antiplatelet therapy; ACT: anticoagulant therapy; M: man; W: woman.

radiological sign has been proposed as part of the Boston Criteria for CAA (modified Boston Criteria for CAA) [15]. On the other hand, microbleeds are defined as small hypointense images that have a diameter of < 10 mm in blood-sensitive MRI sequences [16]. In CAA, microbleeds are typically localized in lobar regions, especially in the occipital lobes [17,18].

A novel clinical entity associated with CMB and cSS known as CAA-related transient focal neurological episodes (TFNEs) was recently proposed [19]. CAA-related TFNEs, also referred to as "amyloid spells" consist in brief, recurrent, and stereotyped transient focal neurological symptoms. They usually last < 30 min and frequently have a spreading onset, which corresponds to the cortical representation of the radiological lesion. In several publications, symptoms have been classified as positive and negative [5,6,20]. These episodes are often misdiagnosed as other, more common clinical entities, such as transient ischemic attacks (TIA), epileptic seizures, and migraine aura [21].

Our aim is to describe the clinical features, neuroimaging findings, and risk of future ICH after follow-up in a series of patients with CAA-related TFNEs.

2. Methods

We retrospectively analyzed a series of patients admitted to the Stroke Unit of Hospital General Universitario Gregorio Marañón between 2014 and 2018 which fulfilled the following criteria:

- Transient focal neurological symptoms with clinical characteristics suggestive of CAA-related TFNEs: recurrent, fully resolved (< 24 h), stereotyped, and/or spreading onset episodes.
- Age over 55 years according to the cut-off point established in the classic and modified Boston criteria for diagnosis of CAA [15,22].
- Cerebral MRI with T2*GRE sequences revealing radiological findings suggestive of CAA, including cSS and CMB.
- Not known alternative explanation other than CAA (eg, structural brain lesion, atrial fibrillation, extracranial or intracranial stenosis).

We recorded the baseline characteristics of the patients including demographic data, vascular risk factors, previous treatment, symptoms of the attacks, neuroimaging findings, and initial treatment. All patients underwent laboratory exams, which included complete blood count, prothrombin and activated partial thromboplastin time and biochemistry tests that included glucose, sodium, potassium, liver and kidney function tests, lipid profile, thyroid hormones levels and glycosylated hemoglobin. The supraaortic and intracranial arteries were evaluated by CT angiography and/or carotid and transcranial ultrasonography to rule out large vessel abnormalities. In all patients a transthoracic echocardiogram was done to exclude structural cardiac disease and a 12-lead ECG and 24-h cardiac telemetry was available to detect cardiac arrhythmias. Also, some patients underwent a 20-min interictal electroencephalogram.

Cerebral MRI was at 1.5 T field strength and included T1-weighted, T2-weighted, fluid-attenuated inversion recovery, diffusion-weighted, and T2*-GRE sequences. In some patients a magnetic resonance angiography was also available. All cerebral MRI were evaluated by expert Neuroradiologists. Small vessel disease was defined as the presence of white matter T2 hyperintense lesions and was quantified by the simplified Fazekas rating scale from 0 to 3 [23]. New ICH was defined as a symptomatic stroke syndrome associated with imaging evidence of a corresponding ICH > 5 mm in diameter, according to previous reports [24].

Follow-up data on recurrences, development of ICH, and changes in therapy were obtained from on-site medical visits. Patients were evaluated in Neurology Clinics every 6 months approximately.

3. Results

3.1. Baseline characteristics

A total of 11 patients were included. Mean age was 76,6 years (range, 66–89 years). Six patients were men and 5 women. Seven patients had high blood pressure (HBP), 7 had dyslipidemia, 4 were former smokers, none were diabetic, and 1 was obese. No patients were diagnosed with atrial fibrillation or ischemic heart disease. No patients had a previous history of spontaneous ICH. Two patients were prescribed antiplatelet drugs at symptom onset, and none started anticoagulant therapy (ACT). (Table 1).

3.2. Clinical characteristics, symptoms and signs of the episodes

All patients reported transient focal neurologic episodes with a maximum duration of 30 min and a minimal duration of seconds. Ten of 11 patients presented stereotyped and recurrent episodes. Of note, 6 patients experienced > 10 recurrences. Nine patients reported transient paresthesia with or without numbness, which was the most frequent symptom. In all cases, sensory symptoms affected the perioral region and upper limbs and had a gradual spreading onset. Furthermore, 6 patients experienced focal weakness, 4 aphasia, 3 dysarthria, and 1 a drop attack. Most patients (8 of 11) presented with a combination of

Table 2
Clinical features in a series of patients with CAA-related TFNEs.

	Semiology of the attacks							
	Self- limiting	Stereotyped	Recurrent	Course of recurrence	Symptoms	Spreading	Min. duration (min)	Max. duration (min)
Case 1	Yes	Yes	Yes (> 10)	Over several months	Paresthesia Numbness Aphasia	Yes	5	15
Case 2	Yes	Yes	Yes (> 10)	Over several months	Paresthesia Numbness Focal weakness	Yes	10	10
Case 3	Yes	Yes	Yes (> 10)	Over several months	Paresthesia Focal weakness Dysartira	Yes	10	15
Case 4	Yes	No	No	Over a day	Drop Attack	No	seconds	seconds
Case 5	Yes	Yes	Yes (2–5)	Over a week	Aphasia	No	5	5
Case 6	Yes	Yes	Yes (5–10)	Over several months	Paresthesia Numbness Focal weakness Aphasia	Yes	5	30
Case 7	Yes	Yes	Yes (> 10)	Over several weeks	Paresthesia Focal weakness Aphasia	Yes	5	10
Case 8	Yes	Yes	Yes (5–10)	Over a week	Paresthesia Focal weakness	Yes	5	10
Case 9	Yes	Yes	Yes (> 10)	Over several months	Paresthesia Numbness	Yes	2	3
Case 10	Yes	Yes	Yes (> 10)	Over several months	Paresthesia Dysarthria	Yes	5	20
Case 11	Yes	Yes	Yes (5–10)	Over several months	Paresthesia Focal weakness Dysarthria	Yes	5	30
Median (IQ range)							5 (5–5)	10 (5–20)
N (%)	11 (100)	10 (90,9)	10 (90,9)			9 (81,8)		

CAA: cerebral amyloid angiopathy; TFNEs: transient focal neurological episodes; IQ: interquartilic; Min: minimal; Max: maximal.

these symptoms instead of a single symptom isolated. Regarding the clinical course of the events, 7 patients reported recurrences over several months which tend to present in clusters on a single day, one patient experienced recurrences over several weeks, 2 patients experienced recurrences over a single week and only one patient experienced a unique episode with no recurrences (Table 2).

3.3. Neuroimaging findings and other complementary studies

A cerebral MRI with T2*GRE sequence revealed cSS in 10 of 11 patients, thus making this finding the most frequent feature. cSS was disseminated in all cases (> 3 sulci affected). Six cases had CMB, which were multiple in most cases. 5 patients had the combination of both radiological features. All patients showed white matter hyperintensities which were graded as “low” in 6 cases, “moderate” in 3 cases and “severe” in 2 cases (Table 3 and Fig. 1). 4 patients (cases 5,6, 8 and 10) presented with acute convexity subarachnoid hemorrhage (cSAH) on CT at the time of hospital admission. These 4 patients showed disseminated cSS on MRI.

All patients underwent a vascular study, which included an extra and intracranial ultrasound examination or CT angiography, transthoracic echocardiogram, and 24 h ECG telemetry. The results of the vascular study were normal in every case, except for the finding of diffuse carotid atheromatosis without significant stenosis in 2 patients. Eight patients underwent a 20-min interictal electroencephalogram, which did not show epileptiform activity. In 3 cases, focal slowness contralateral to the symptomatic side was detected without any other abnormality.

3.4. Initial diagnosis and clinical course

Initially, 3 patients were misdiagnosed as having recurrent TIA, 6 as having seizures, and 2 as having both. As for initial treatment, 3 patients were prescribed antiplatelet therapy (APT), 4 patients started on anti-epileptic drugs (AED), and 1 patient was prescribed both treatments. Three patients were not prescribed any specific treatment for the attacks (Table 3).

After a median follow-up of 36 months (interquartile range 12–48 months), 4 of 10 patients developed a spontaneous symptomatic lobar ICH. MRI revealed that all 4 cases had cSS (cases 1, 2, 3 and 9), and 2 also had CMB (Figs. 1 and 2). One of these patients was on 100 mg of aspirin daily when the ICH occurred.

The median delay from the onset of the first episode to the final diagnosis of CAA-related TFNE was 9 months (interquartile range, 1–24 months). The diagnosis of CAA-related TFNE was only suspected after the first episode in 9 of 11 patients. In 3 of the 4 cases with CAA-related ICH, the diagnosis of TFNE was only confirmed when the bleeding took place. The final diagnosis was probable CAA for cases 1, 2, 3 and 9 and possible CAA for cases 5, 6, 7, 8, 10 and 11 according to the modified Boston Criteria. Case 4 did not achieve the diagnosis of probable/possible CAA according to these criteria, but it was included as CAA was highly suspected (Table 3).

Regarding symptomatic treatment, two patients were prescribed topiramate which was not effective to fully control the recurrences. No patient was restarted on APT after the diagnose of possible/probable CAA was done.

4. Discussion

Our results reveal that CAA-related TFNEs are an underdiagnosed clinical entity that often mimics TIA or seizures [21]. However, these episodes have inherent clinical characteristics that may be taken into consideration in the differential diagnosis with other, more common entities. In this series, most patients experienced brief, recurrent, and stereotyped transient focal neurological events lasting < 30 min. Notably, more than half of the patients (6 of 11) reported > 10 episodes,

Table 3
Neuroimaging findings, initial diagnosis, initial treatment, final diagnosis and clinical course in a series of patients with CAA-related TFNEs.

	MRI features			Initial diagnosis		Initial treatment		Final diagnosis		Clinical course	
	cSS (focal/ disseminated)	CMB (number)	WMH severity	TIA	ES	APT	AED	Possible/ probable CAA	Delay time (months)	ICH	Timing ICH (months after first TFNEs)
Case 1	Yes (disseminated)	No	1	No	Yes	No	Yes	Probable CAA	72	Yes	72
Case 2	Yes (disseminated)	Yes (3)	3	Yes	No	Yes	No	Probable CAA	9	Yes	25
Case 3	Yes (disseminated)	No	2	No	Yes	No	Yes	Probable CAA	48	Yes	48
Case 4	No	Yes (multiple)	2	Yes	No	Yes	No	–	24	No	–
Case 5	Yes (disseminated)	No	1	No	Yes	No	No	Possible CCA	10	No	–
Case 6	Yes (disseminated)	No	1	No	Yes	No	No	Possible CCA	9	No	–
Case 7	Yes (disseminated)	Yes (multiple)	3	Yes	Yes	Yes	Yes	Possible CCA	0	No	–
Case 8	Yes (disseminated)	Yes (multiple)	1	No	Yes	No	Yes	Possible CCA	0	No	–
Case 9	Yes (disseminated)	Yes (3)	1	Yes	Yes	Yes	No	Probable CAA	24	Yes	24
Case 10	Yes (disseminated)	No	1	No	Yes	No	Yes	Possible CCA	2	No	–
Case 11	Yes (disseminated)	Yes (multiple)	2	Yes	No	No	No	Possible CCA	1	No	–
Median (IQ range)			1 (1–2)						9 (1–24)		36,5 (24,5–60)
N (%)	10 (90,9)	6 (54,5)		5 (45,5)	8 (72,7)	4 (36,4)	5 (45,5)			4 (36,4)	

CAA: cerebral amyloid angiopathy; TFNEs: transient focal neurological episodes; IQ: interquartilic; cSS: cortical superficial siderosis; CMB: cortical microbleeds; TIA: transient ischaemic attack; ES: epileptic seizure; AED: antiepileptic drug; ICH: intracerebral hemorrhage.

thus reflecting a strong tendency towards recurrence. Most patients (7 of 11) experienced recurrences over several months which tend to present in clusters on a single day. Consistent with previous reports, gradually spreading paresthesia was the most common symptom observed [6,9,19–21]. This "aura-like" presentation may be especially helpful in the differential diagnosis with TIA. Nevertheless, other reported symptoms include focal weakness, numbness, dysarthria, aphasia, and drop attack. Neither visual symptoms nor limb-jerking episodes were recorded in this series. In several publications, it has been hypothesized that positive symptoms emerge from cortical spreading depression as a result of the irritant effect of hemosiderin, while negative symptoms may result from cerebral vasospasm following amyloid deposition [5,6,20]. However, the origin of negative symptoms is still not completely understood. Some studies have described a high

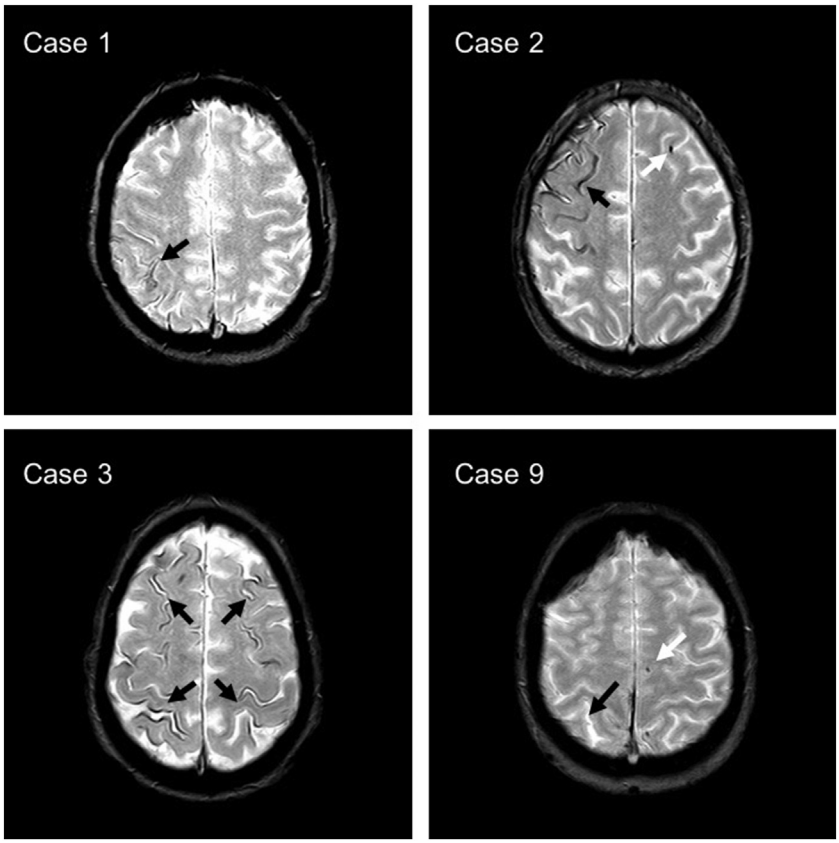

Fig. 1. T2* gradient-recalled echo cerebral MRI of patients 1, 2, 3, and 9 showing cortical superficial siderosis (black arrows) and cortical microbleeds (white arrows).

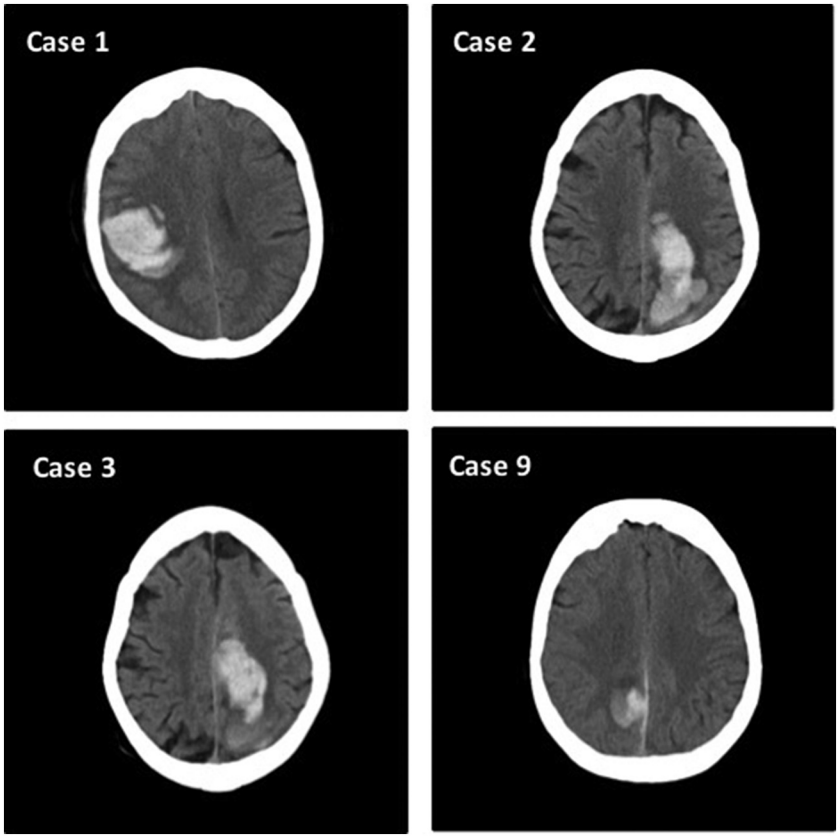

Fig. 2. CT scans of patients 1, 2, 3, and 9 showing a lobar hyperdense lesion suggestive of CAA-related intracerebral hemorrhage.

prevalence of DWI-positive lesions on MRI near cSAH or cSS in CAA suspected patients, which etiopathogenesis has not been well established [24,25]. Spreading depolarization can cause ischemia and hypothetically this could lead to positive neurological symptoms followed by negative ones. Therefore, spreading depolarization could be the mechanism causing both type of clinical phenomena. In our and other series, most cases presented with a combination of these symptoms rather than a single, isolated symptom [26]. Thus, in elderly patients presenting with these characteristic clinical features, the diagnosis of CAA-related TFNEs should be suspected.

Several radiological features related to CAA can be detected on cerebral MRI with the T2*GRE sequence, including CMB and cSS [9]. cSS was the most common neuroimaging finding in this series (10 of 11 patients) and is the radiological marker most commonly associated with an increased risk of ICH according to several studies [10,11,27]. CMB, whether isolated or in combination with cSS, were detected in a lower number of cases in this series (6 of 11 patients). A previous retrospective cohort study including CAA patients with and without TFNE found that cSS was significantly more common in patients with CAA-related TFNEs than in those without [26]. Our results show that CAA-related TFNEs are related more to the presence of cSS in MRI and may represent the clinical manifestation of this radiological feature.

Of note, the median delay between symptom onset and definitive diagnosis of CAA-related TFNEs was almost 1 year (9 months). In 3 of 4 patients who developed CAA-related ICH, the diagnosis of CAA-related TFNEs was retrospectively obtained when the bleeding occurred after widely reviewing the past medical history and previous cerebral MRI, thus indicating that CAA-related TFNEs are a remarkably underdiagnosed clinical entity in clinical practice [21,26]. The misdiagnosis of CAA-related TFNEs as TIA can lead to the prescription of ATP or anticoagulant therapy, which may increase the risk of ICH and worsen the functional clinical course in cases of symptomatic ICH [12,28]. In our series, 4 patients were initially prescribed APT, and 1 of them was on ATP when the ICH occurred.

After a median follow-up period of 36 months, a high proportion of patients (4 of 11) experienced a CAA-related ICH. In 3 of these 4 cases, the lobar hemorrhage was contralateral to the TFNEs symptom's side and ipsilateral to the hemisphere with more cSS in the previous MRI. Interestingly, all 4 cases had cSS—whether isolated or in combination with CMB—in the previous cerebral MRI. Several case reports and series have associated cSS with a significantly increased risk of bleeding [26,29]. A previous study suggests that the presence of cSS is closely associated with a hemorrhagic phenotype of CAA, whereas a lower presence of cSS is associated with a non-hemorrhagic form, with a predominance of cognitive impairment [30]. Our results confirm that the combination of CAA-related TFNEs and cSS is associated with an increased risk of ICH.

Recently, an observational study which included a pooled analysis of several cohorts has related acute non-traumatic cSAH due to suspect CAA with a high risk of future ICH [31]. In this series four patients presented with a cSAH on admission, but neither of these cases has suffered a ICH during the follow-up.

This case series has several limitations based on its design and low number of patients included. However, this report shows that CAA-related TFNEs is an underdiagnosed clinical entity that often mimics TIA and seizures. Diagnostic delay can lead to the prescription of inappropriate therapies such as APT or anticoagulants, which increase the risk of ICH, Our results suggest that the combination of CAA-related TFNEs and cSS might be closely associated with an increased risk of bleeding. Therefore, in elderly patients with transient focal neurological symptoms compatible with CAA-related TFNEs, a T2*GRE MRI should be performed to investigate radiological signs related to CAA. Lastly, clinicians should recommend strict control of modifiable risk factors for ICH, such as high blood pressure and smoking, and discontinue or avoid administering antiplatelet or anticoagulant drugs, which can increase the risk of bleeding.

Declaration of Competing Interest

All authors declare there is no conflict of interest.

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