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ORIGINAL ARTICLE

Cerebrovascular pathology in cerebral amyloid angiopathy presenting as intracerebral haemorrhage

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Abstract

Cerebral amyloid angiopathy (CAA) is the second most common cause of non-traumatic intracerebral haemorrhage (ICH) accounting for 12–15% of lobar haemorrhages in the elderly. Definitive diagnosis of CAA requires histological evaluation. We aimed to evaluate the spectrum of cerebrovascular changes in CAA-related ICH. Between 2011 and 2015, biopsy-confirmed cases of CAA were retrieved and clinical, radiological and pathological features were reviewed. The spectrum of vascular alterations was evaluated and amyloid deposition was graded in accordance with the Greenberg and Vonsattel scale. Seven cases of sporadic CAA [5 males and 2 females] were diagnosed, none of whom were suspected to have CAA pre-operatively. Six presented with large intracerebral haematoma (ICH) requiring neurosurgical intervention (age range: 56–70 years) and one had episodic headache and multiple microhaemorrhages requiring a diagnostic brain biopsy (45 years). In the presence of large ICH, vascular amyloid deposits were of moderate to severe grade (grade 4 in 4, grades 2 and 3 in 1 case each) with predominant involvement of medium (200–500 μm) to large (> 500 μm) leptomeningeal vessels. Fibrinoid necrosis was noted in four. Two were hypertensive and on antiplatelet agents. β-Amyloid plaques were detected in two, one of whom had symptomatic dementia. MRI performed in 3 of 6 cases with ICH did not reveal any microhaemorrhages. Amyloid deposits in small (50–200 μm) to medium (200–500 μm) calibre intracortical vessels produced parenchymal microhemorrhages. Histopathological examination of ICH is essential for diagnosing CAA. The vascular calibre rather than grade of amyloid deposits dictates size of the bleed. Presence of co-morbidities such as antiplatelet agents may predispose to haemorrhage.

Keywords Amyloid deposits · Grade · Aβ · Lobar hematoma · Microhemorrhage

Introduction

Cerebral amyloid angiopathy (CAA) is characterized by the deposition of amyloid fibrils in the intracortical and leptomeningeal blood vessels. Among the various amyloid proteins described in humans, seven are associated with CAA and sporadic form of this disease is characterized by β-amyloid protein (Aβ) accumulation. Deposition of this

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congophilic material leads to progressive vasculopathy resulting in haemorrhage, infarct, or leukoencephalopathy. CAA most commonly presents as intracerebral haemorrhage (ICH) and CAA-related haemorrhages account for 5–20% of all spontaneous, non-traumatic cerebral haemorrhages in elderly subjects [1]. Boston criterion is utilized to diagnose CAA-related ICH clinically and includes "definite CAA" which requires a full post-mortem examination, "probable with supporting pathology" when there is biopsy-proven amyloid deposition, "probable" in the absence of biopsy or autopsy but presence of multiple lobar haemorrhages on MR imaging in patients over 55 years and "possible" CAA [2]. Lobar ICH in patients over the age of 55 years, when single is predictive of possible CAA. However, definitive diagnosis requires demonstration of amyloid in tissue obtained from biopsy or on autopsy particularly in the absence of multiple haemorrhages on imaging. Diagnosing this condition is essential as these individuals are prone to recurrent haemorrhages.

Here, we present a series of seven cases of sporadic CAA with intracerebral haematoma/microbleeds; none of whom were suspected to have an amyloid pathology prior to surgery/biopsy. The aim of the study was to evaluate the spectrum of vascular changes associated with CAA-related haemorrhages.

Materials and methods

From 2011 to 2015, the records maintained in the neuropathology archives were reviewed for cases of cerebral amyloid angiopathy. Among the 7003 surgical specimens received during this period, there were 77 cases (1.09%) of intracerebral haematomas (ICH). All cases of ICH were evaluated for vascular malformations/neoplasms/amyloid to determine the aetiology for ICH using Masson trichrome, elastic Van Gieson, Congo red stain and appropriate immunohistochemistry. Of these, seven cases were histopathologically proven to be CAA (9.1%).

Six patients (cases 1–6) presented with a large intracerebral hematoma causing mass effect requiring evacuation of the hematoma. They underwent craniotomy and evacuation of hematoma, which was sent for histological examination. Case 7 presented with longstanding headache, with neuroimaging features of microbleeds. The possibility of vasculitis or haemorrhagic metastasis was considered, and he underwent a diagnostic open brain biopsy.

The clinical and demographic details were obtained from the case records and analysed. Slides from all the cases were reviewed which included sections stained with haematoxylin and eosin and Masson's trichrome for delineating vascular alterations, Congo red stain and β-amyloid (indirect immunoperoxidase, clone: 6F/3D, 1:50 dilution, Leica Biosystems, Newcastle) for amyloid deposits. The cerebrovascular changes and the extent of Aβ deposition were graded in accordance with Greenberg and Vonsattel scale [3, 4] as given in Table 1. In addition, the type of bleed (fresh vs organizing) and the calibre of involved blood vessels were noted (large > 500 μm, medium 200–500 μm and small 50–200 μm in diameter). Radiological images were reviewed and any features to suggest amyloid pathology were looked for. The histopathological findings were correlated with clinical and radiological features.

Results

There were seven cases of CAA (M/F 5:2) and the age at presentation ranged from 45 to 70 years (mean age of 61 years). The clinical and demographic details are provided in Table 2. Six (cases 1 to 6) presented with solitary large intracerebral haematomas and features of raised intracranial tension. Acute onset headache was the presenting symptom in five cases (cases 1–5). In addition, case 1 (60-year-old female) also had memory and behavioural disturbances of 3 years duration. Two (cases 1 and 5) were hypertensive and had history of antiplatelet drug intake. Neuroimaging (CT scan in all and MRI in three cases 1, 3 and 5) revealed large intraparenchymal haematomas located in frontal lobe (3), temporoparietal (2) and basal ganglia (1) [Figs 1, 2 and 3]. Additional findings included diffuse cerebral atrophy (cases 1, 4 and 5), white matter changes (cases 1 and 3), subarachnoid haemorrhage (cases 3 and 6), sulcal haemorrhage (case 3), periventricular leukoaraiosis (case 4) and intraventricular haemorrhage (case 6). Three cases where MRI was available (cases 1, 3 and 5) failed to show microhaemorrhages. In all the six cases, there was evidence of intracranial mass effect which necessitated craniotomy and evacuation of haematoma.

Table 1 Greenberg and Vonsattel's histopathological grading of cerebral amyloid angiopathy (CAA) [3, 4]

Grade 1 "Mild"	Amyloid is restricted to the tunica media without significant destruction of smooth muscle cells.
Grade 2 "Moderate"	Tunica media completely replaced by amyloid and the vessel is thicker than normal.
Grade 3 "Severe"	Extensive amyloid deposition with focal vessel wall fragmentation, double barrelling of the vessel wall, microaneurysm formation and leakage of blood through the blood vessel wall.
Grade 4 "Severe"	Extensive amyloid deposition with fibrinoid necrosis and scarring.

Table 2 Clinical and neuroimaging findings of cerebral amyloid angiopathy presenting as intracerebral haemorrhage

Case	Age/sex	Clinical features	Co-morbidities	Imaging findings		Pre-operative diagnosis	Follow-up
				CT	MRI		
1	60/F	Acute onset headache since 1 m Memory and behavioural disturbances since 3 years	Hypertensive On antiplatelet drug	Left frontal haematoma Diffuse WM hypodensity	Diffuse cerebral atrophy	Tumour with bleed/organizing haematoma	6-year: progressive deterioration of memory and behavioural symptoms
2	56/M	Acute-onset headache	Nil	Left frontal haematoma	Not performed	Haematoma/AVM/ vasculitis	Not available
3	70/F	Acute-onset headache, vomiting and altered sensorium	Nil	Right frontal haematoma	Sulcal SAH in bilateral hemisphere. Diffuse WM hyperintensity	Haematoma	Lost to follow-up
4	69/M	Acute-onset headache, behavioural disturbance and Wernike's aphasia	Chronic smoker and alcoholic	Left temporoparietal haematoma Diffuse cerebral atrophy, periventricular leukoariosis	Not performed	Haematoma	2 months: persistent Wernicke's aphasia
5	67/M	Acute-onset headache and vomiting	Hypertensive TIA 4 years back On antiplatelet drug	Right temporoparietal haematoma	Post-op MRI: no white matter changes or microbleeds. Minimal atrophy	CVT	Lost to follow-up
6	60/M	Acute-onset hemiparesis, aphasia and altered sensorium	Nil	Left basal ganglion haematoma IVH, SAH	Not performed	Haematoma	Lost to follow-up
7	45/M	Chronic headache	Nil	–	Microbleeds in the supratentorial parenchyma at the corticomedullary junction	Vasculitis/haemorrhagic metastasis	1½ years: complete reduction in headache after pulse dose of methylprednisolone

AVM arteriovenous malformation, *CVA* cerebrovascular accident, *CVT* cerebral venous thrombosis, *IVH* intraventricular haemorrhage, *SAH* subarachnoid haemorrhage, *TIA* transient ischaemic attack, *WM* white matter

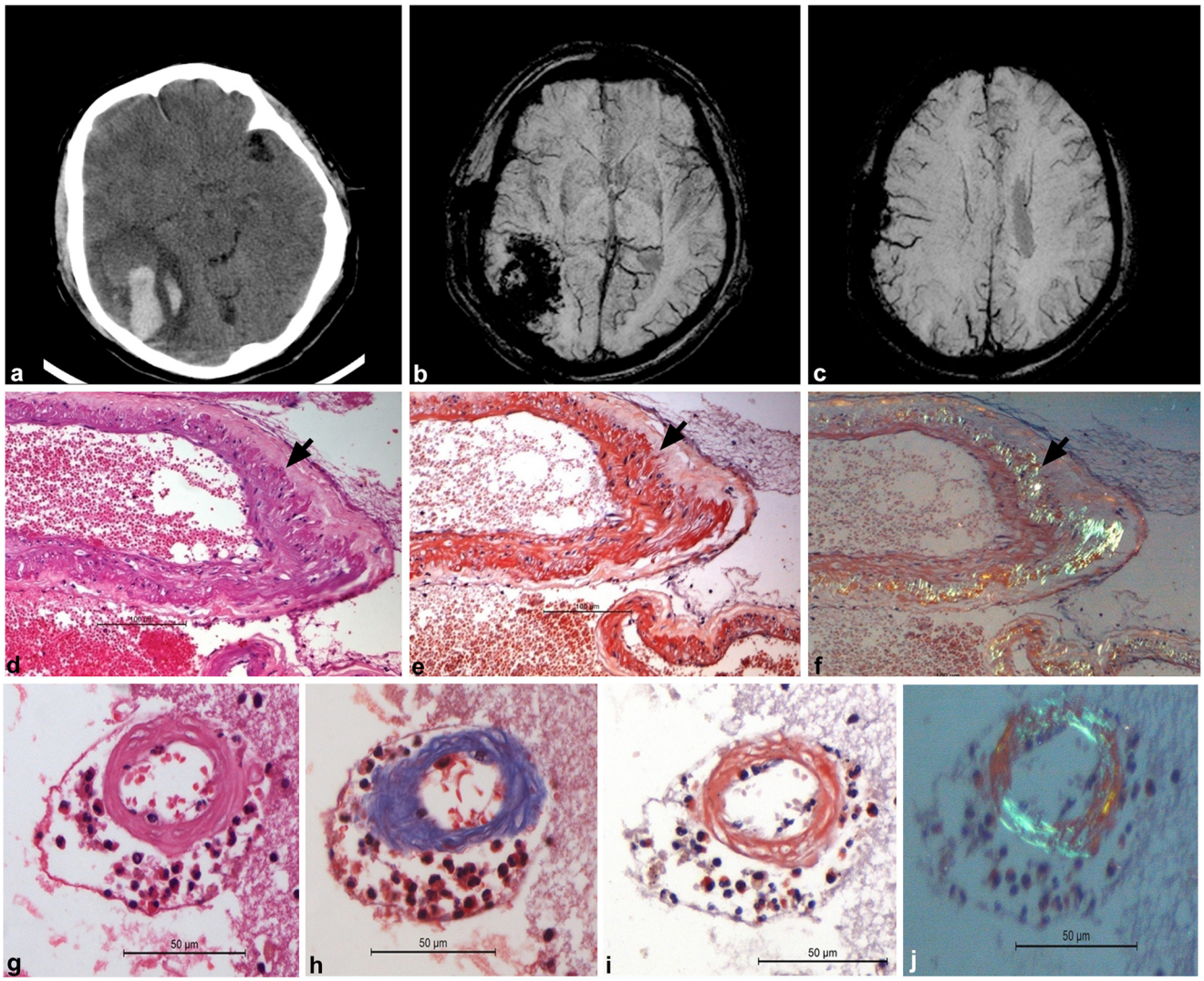

Fig. 1 (Case 5): A 67-year-old male presented with acute onset headache and vomiting. Axial CT reveals a large right temporoparietal hematoma (**a**). Post-operative axial SWI MR images show hemosiderin residue in the right temporoparietal region (**b**) without any evidence of macro or microhemorrhages in any other region (**b**, **c**). Histopathology reveals amyloid deposition in the outer aspect of tunica media of large calibre leptomeningeal blood vessel (arrows) (**d**–**f**) that are mahogany brown on Congo red stain (**e**) and show apple green birefringence (**f**). The intracortical small calibre blood vessel along the periphery of hematoma shows sclerosis (**g**, **h**) with complete replacement of the vessel wall by amyloid deposits (**i**) exhibiting apple green birefringence under polarizing light (**j**) [**d**, **g** haematoxylin and eosin; **h** Masson's trichrome; **e**, **f**, **i**, **j** Congo red. Scale bar—**d**, **e** 100 μm, **g**–**j** 50 μm. Magnification—**f** × 200]

Case 7 (45-year-old male) presented with hemicranial headache of 2 years duration that was episodic, with a frequency of 1–2 per week, lasting for 3–4 h per episode and relieved by analgesics. In the last 9 months, there was a change in the nature of headache in the form of occipital headache lasting for 7 h a day and not relieved by analgesics. MRI scan revealed multiple microbleeds at the corticomedullary junction of the supratentorial compartment. The possibilities of vasculitis or haemorrhagic metastasis were considered and a diagnostic brain biopsy was performed at another centre and the patient was referred to our institute. Repeat MRI performed 1 month after the diagnostic brain biopsy revealed multiple microbleeds on venobold sequence throughout the cortex also involving basal ganglia and midbrain. Patchy non-enhancing white matter hyperintensities were seen on FLAIR images without restrictive diffusion [Fig. 4]. MR angiography was normal. The patient was started on pulse dose of methylprednisolone, and at one and half years of follow-up, there was complete reduction in headache and he did not have cognitive impairment on examination.

None of the cases were suspected to have an underlying CAA aetiology pre-operatively. Other causes of intracerebral haemorrhage like antecedent head trauma, ischemic stroke, CNS tumour, vascular malformation, CNS vasculitis, blood dyscrasia and coagulopathy were absent in all of them.

Retrospectively, applying Boston criterion pre-operatively, cases 1–5 would have been classified as "possible CAA." Cases 6 and 7 would not have raised the suspicion of CAA

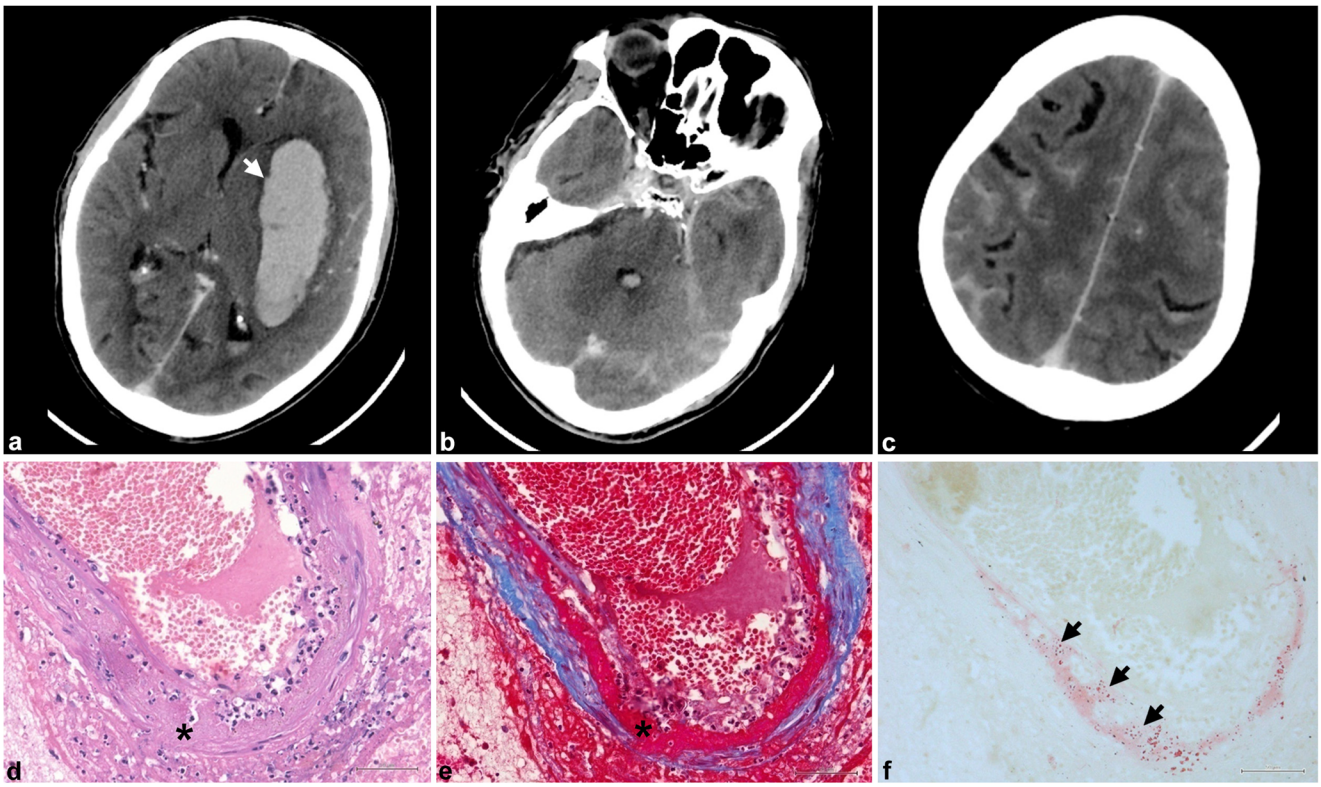

Fig. 2 (Case 6): A 60-year-old male presented with acute onset hemiparesis and aphasia. Axial CT sections showing left putaminal hematoma (arrow) with extension of blood into the ventricular system and subarachnoid space. Mass effect noted in the form of effaced left lateral ventricle and rightward midline shift (**a**–**c**). A large calibre leptomeningeal vessel shows fibrinoid necrosis of vessel wall (*) and extravasation of blood (**d**, **e**). Congo red stain exhibits amyloid deposition in the outer aspect of tunica media (**f**, arrows) [**d** haematoxylin and eosin, **e** Masson's trichrome, **f** Congo red. Scale bar—**d**–**f** 50 μm]

as the former presented with a basal ganglia bleed, and the latter occurred in a 45-year-old male.

Microscopically, cases presenting as large intracerebral haematoma (cases 1 to 6) exhibited amyloid deposits in large (> 500 μm) and medium (200–500 μm) calibre leptomeningeal blood vessels and in medium and small (50–200 μm) calibre superficial cortical blood vessels [Figs. 1 and 2]. Amyloid appeared as homogenous and eosinophilic material which with Congo red staining exhibited apple green birefringence and cross polarization under polarizing light [Fig. 1]. Full thickness involvement was seen in the small (50–200 μm) and medium (200–500 μm)-sized cortical and medium (200–500 μm)-sized leptomeningeal blood vessels, and the larger (> 500 μm) leptomeningeal blood vessels had abluminal deposition. Amyloid deposits were associated with fibrinoid necrosis and leakage of RBCs in four cases, double barrelling and microaneurysms in one each. Applying Greenberg and Vonsattel grading system [3, 4], these cases had moderate (grade 2) to severe (grade 3 to 4) degree of amyloid vasculopathy. Among them, grade 2 and 3 deposits were noted in cases on antiplatelet therapy. Immunohistochemistry for β-amyloid highlighted varying degrees of involvement within the same case with focal to circumferential deposits. Leakage of amyloid into the surrounding parenchyma was seen in smaller vessels following rupture. In addition to the vascular involvement, parenchymal β-amyloid plaques were noted in cases 1 and 3, of which the former had history of dementia and diffuse cerebral atrophy [Fig. 3].

Case 7 with microhaemorrhages had grade 4 amyloid deposits with predominant involvement of small intracortical blood vessels (50–200 μm), relatively sparing the larger leptomeningeal blood vessels (> 500 μm). Double barrelling and fibrinoid necrosis of blood vessel wall associated with leakage of RBCs were present [Fig. 4]. Interestingly, β-amyloid was seen leaking from some of the blood vessels into the perivascular areas. However, parenchymal amyloid plaques were absent.

The histopathological features of the cases are summarized in Table 3.

Discussion

CAA is the term used to describe pathological vascular changes characterised by amyloid deposition in the parenchymal and leptomeningeal blood vessels. Vascular amyloid deposit in the central nervous system was first described in 1909 by Gustav Oppenheim in association with the pathological changes of Alzheimer's disease [5]. Subsequently, clinical

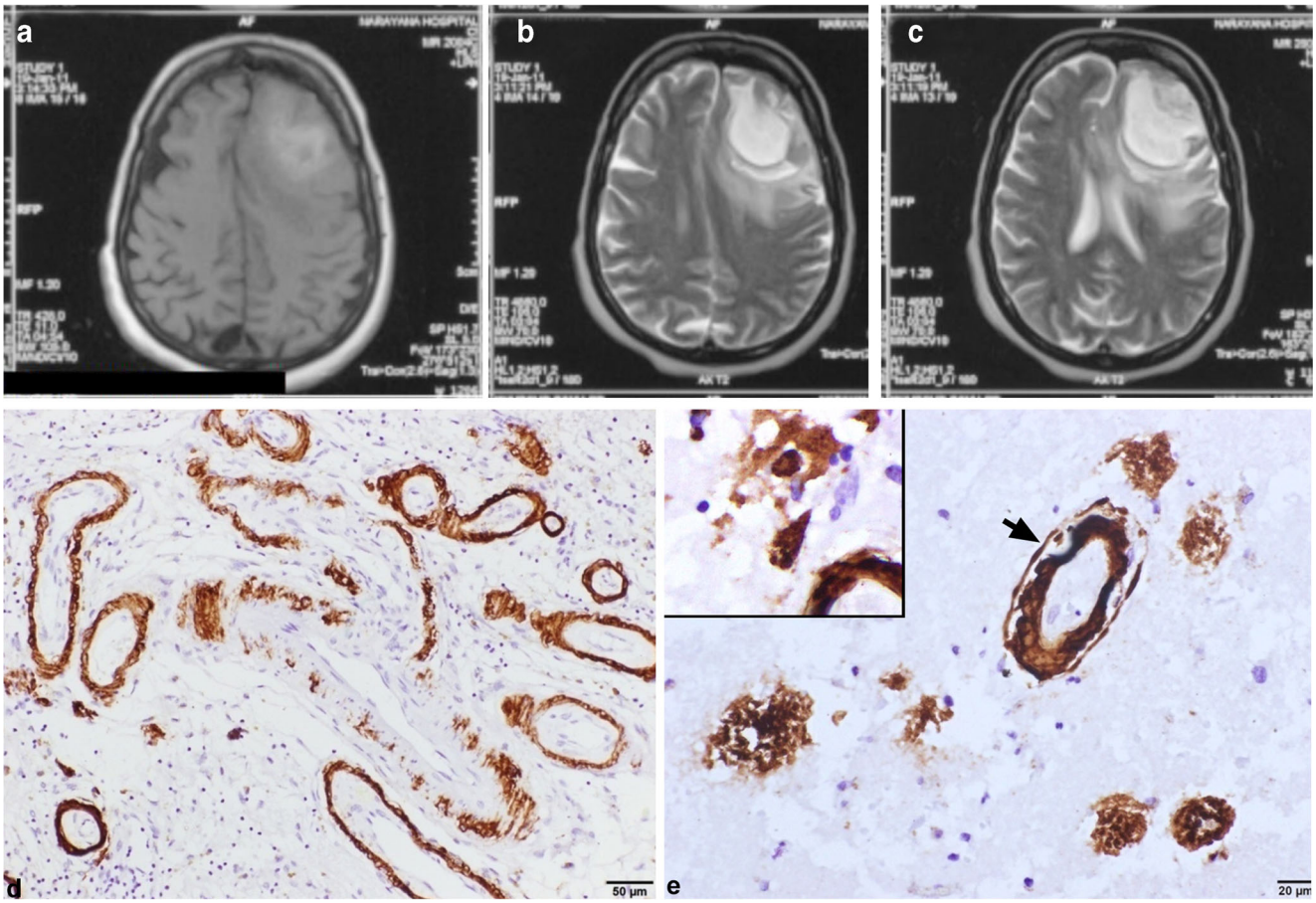

Fig. 3 (Case 1): A 60-year-old female with memory and behavioural disturbances presented with acute-onset headache. MR images show left frontal lesion heterogeneously hyperintense on T1 (**a**), hyperintense on T2 (**b**, **c**) with perilesional oedema and midline shift. Leptomeningeal large and medium calibre blood vessels (**d**) and smaller cortical vessels (**e**) reveal deposits of Aβ partially/completely replacing the media. Double barrelled appearance seen (arrow). Note multiple amyloid plaques (mature and immature). Inset shows a mature Aβ plaque [**d**, **e** Aβ immunoperoxidase. Scale bar—**d** 50 μm, **e** 20 μm]

and histological features of CAA was described in 1954 [6] and in 1979, Okazaki et al. established the relationship between CAA and lobar ICH [7].

Age is an important risk factor for sporadic CAA commonly affecting individuals over 60 years of age. The incidence of CAA increases with age: 2.3% in 65 to 74 year olds, 8.0% in 75 to 84 year olds and 12.1% in individuals over 85 years [3]. Familial forms of CAA have autosomal dominant mode of inheritance with early age of onset and severe clinical course [8]. All our cases were elderly except case 7 where CAA was found in a 45 year old. A detailed history failed to elicit any family history.

There are three hypotheses for the preferential deposition of amyloid in the blood vessels in CAA. The "neuronal or drainage hypothesis" suggests that amyloid deposition results from poor drainage of amyloid protein along the perivascular spaces. The "systemic hypothesis" proposes that receptor-mediated transport of systemic Aβ protein across the blood-brain barrier results in amyloid deposition. The "vessel wall hypothesis" suggests that Aβ protein is produced by smooth muscle cells in the tunica media of cerebral arteries. The drainage hypothesis is the most accepted theory [9].

Within the blood vessels, amyloid is deposited first in the abluminal portion of the tunica media and surrounds the smooth muscle cells. Progressive accumulation results in loss of smooth muscle cells and disruption of the vascular architecture resulting in double barrelling, microaneurysm formation, fibrinoid necrosis and perivascular leakage. Apart from the structural changes, soluble Aβ has been shown to act in a dose-dependent manner resulting in vasoconstriction, reduced resting cerebral blood flow, decreased response to endothelium-dependent vasodilators and impaired cerebral autoregulation. As the soluble Aβ accumulates as amyloid, these alterations become much more pronounced [10, 11]. Animal model studies have demonstrated Aβ deposition leads to anticoagulative microenvironment by mimicking inhibitors of the coagulation cascade or by inducing and activating tissue proteinases, like MMP-2 and MMP-9 [12, 13].

CAA-related ICH was noted in 20% of ICH cases in the Helsinki study [14] and 12% in the National Taiwan

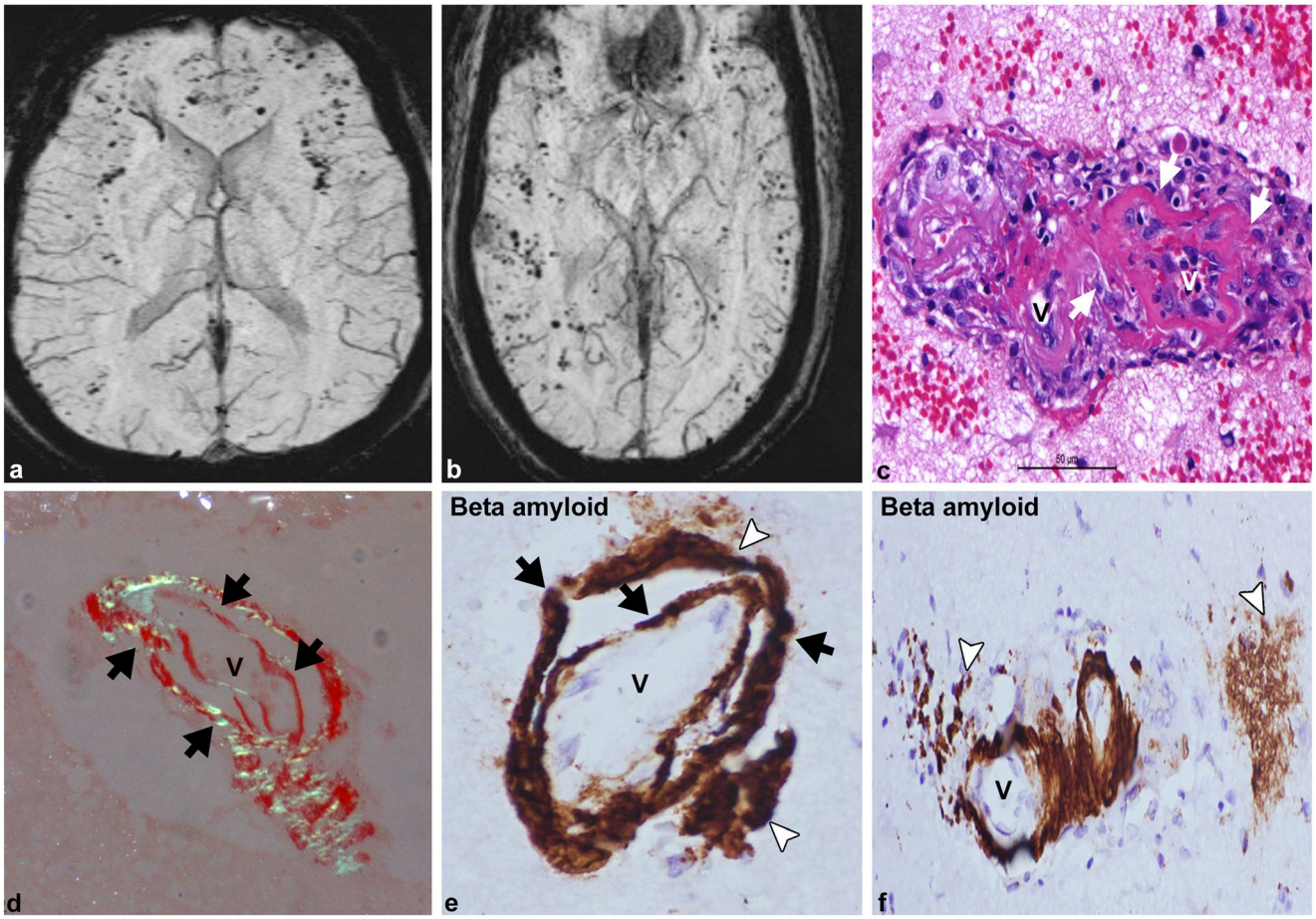

Fig. 4 (Case 7): A 45-year-old male with chronic headache since 2 years. MR images reveal multiple microhemorrhages throughout bilateral frontal, temporal and occipital lobes at grey white junction and corpus callosum (**a**, **b**). Histopathology reveals fibrinoid necrosis of vessel (v) wall (**c**, white arrows). Characteristic double barrelling seen with birefringent amyloid deposits of amyloid in media (**d**, **e** black arrow). Leakage of Aβ into the surrounding parenchyma is seen from the vessel wall (**e**, **f** arrowhead) [**c** haematoxylin eosin; **d** Congo red under polarized light, **e**, **f** Aβ immunoperoxidase. Magnification—**c**-**f** × 400]

University Hospital Stroke Registry [15] and was observed to be the second most common cause of ICH following hypertensive angiopathy. CAA-related ICHs are lobar, cortical, or cortico-subcortical in location and can extend to the subarachnoid space or ventricles [2]. Acute presentation is usually with headache and focal deficits compared to dementia and seizures in chronic forms [16]. In our series, CAA constituted 9.1% of ICH. The ICH was lobar, equally distributed between the frontal and the temporoparietal regions.

ICH was associated with moderate to high and not mild grade of amyloid deposits in the cerebral blood vessels and with fibrinoid necrosis [4, 17, 18]. In a study by Vonsattel et al. [4], fibrinoid necrosis was observed in 12 of 17 (71%) cases of CAA with haemorrhage. In cases without ICH, additional contributing factors for haemorrhages like head trauma and cerebral metastases with hypertension were noted. Vascular amyloid deposits and fibrinoid necrosis were found to be sensitive and specific marker for CAA-related haemorrhage [3]. Rupture of microaneurysms can also lead to haemorrhage. They are associated with severe CAA, with diffuse and uniform deposition of amyloid in contrast to moderate CAA, wherein the amyloid is segmental in distributed [4]. A previous reporting of three cases of CAA-related ICH noted severe grade of amyloid deposits involving leptomeningeal and superficial cortical blood vessels. In one of the cases in which an autopsy was performed, widespread vascular amyloid deposits were noted in cerebral hemispheres although haematoma was localized to occipital and frontal region, compared to milder deposits in brain stem and cerebellum [19].

All the cases in our series revealed moderate and severe grade of CAA irrespective of the clinical presentation (haematoma or microbleeds). Fibrinoid necrosis was present in five and microaneurysm in one case. Microbleeds were associated with amyloid deposits in small to medium parenchymal vessels in contrast to the leptomeningeal vessel

Table 3 Cerebrovascular pathology in cerebral amyloid angiopathy presenting as intracerebral haemorrhage

Case	Type of bleed	Vascular alterations						Grade of CAA [3, 4]	Aβ immunohistochemistry
		Type of vessels involved	Vascular thickening	Double barrelling	Fibrinoid necrosis	Microaneurysm	Leakage of blood through vessels		
1	Fresh and organizing haematoma	Leptomeningeal large-calibre vessels Few cortical medium calibre vessels	+	–	–	–	–	Grade 2	Vascular deposits and amyloid plaques
2	Fresh haematoma	Cortical medium-sized vessels (leptomeninges were not included in the biopsy)	+	–	+	–	–	Grade 4	Not available
3	Organizing haematoma	Predominantly leptomeningeal large- and medium-sized vessels Few cortical small-sized vessels	+	+	+	+	Ruptured veins	Grade 4	Vascular deposits and amyloid plaques
4	Fresh haematoma	Leptomeningeal large-calibre vessels Cortical medium- to small-calibre vessels	+	–	+	–	+ Acute inflammatory cells around necrosed blood vessels	Grade 4	Vascular deposits
5	Fresh haematoma	Leptomeningeal large- and medium-calibre vessels Cortical medium- and small-calibre vessels	+	–	–	–	Ruptured veins with neutrophilic infiltration in the subendothelium	Grade 3	Not available
6	Fresh haematoma	Only one arteriole included in the biopsy	+	–	+	–	+	Grade 4	Not available
7	Multiple microbleeds	Predominantly in cortical small- and medium-calibre vessels Leptomeningeal large- and medium-calibre vessels involved to a lesser degree	+	+	+	–	+	Grade 4	Vascular deposits with leakage into perivascular space

Calibre of vessels: large > 500 μm, medium 200–500 μm and small 50–200 μm in diameter

involvement in presence of large ICH. This observation suggests that the size of the haemorrhage is related to the calibre of vessels involved rather than the degree of amyloid deposits.

The incidence of amyloid plaques in CAA in our series was 28.6%, lower than that reported in the literature (50–82.35%) [4, 18]. Pathologically, CAA-related dementia is associated with cortical haemorrhages and/or infarctions, white matter destruction, or leukoencephalopathy [9]. In our series, case 1 with dementia exhibited infarction surrounding a nidus of amyloid-laden vessels. However, case 3 did not have clinically evident dementia despite the presence of amyloid plaques, suggesting contribution by other factors.

Radiologically, detection of amyloid proteins requires positron emission tomography using 11C-Pittsburgh Compound B (PiB) which can quantify the amyloid deposits and predict the risk of future haemorrhages [20]. Imaging features used to diagnose amyloid pathology include superficially located lobar haemorrhages with irregular borders and surrounding oedema [21], dilated Virchow-Robin spaces in white matter [22, 23] and microhaemorrhages [24].

Detection of microhaemorrhages is a very important clue in the diagnosis of amyloid angiopathy and is best detected by gradient-echo (GRE) sequence [25–27]. Microhaemorrhages preferentially occur in areas of concentrated amyloid deposits [28] and are predictive of risk for future symptomatic lobar ICH, recurrent bleeding, future cognitive impairment, loss of functional independence, or death [29, 30]. In our series, MRI in three of six cases failed to reveal this characteristic clue leading to misdiagnoses.

In addition to microhemorrhages, thrombolytic or anticoagulation and antiplatelet therapies also constitute a potential risk factor for ICH [31–33]. As sporadic CAA is a disease of elderly, co-occurrence of these is common. Two of our cases who were hypertensive and on antiplatelet therapy exhibited a lower grade (grade 2 and 3) of amyloid deposit and lacked fibrinoid necrosis. The contribution of these factors needs to be explored. The role of hypertension in CAA-related haemorrhage is debated [4, 34, 35]. The results of the PROGRESS trial revealed that a mean blood pressure reduction of 9/4 mmHg reduced the risk of future CAA-related ICH by about 77% [36] suggesting that hypertension plays an important role in amyloid-associated haemorrhages.

Diagnosing CAA is important as survivors of lobar haemorrhages have a higher risk of recurrence compared with deep ICH [37]. The predictors for poor post-operative outcome in CAA-related ICH include advanced age, CAA pathology severity and presence of intraventricular and subarachnoid haemorrhage [38].

Histopathological examination plays an essential role in establishing the diagnosis of CAA. As noted in this study, none of the cases of were suspected to have CAA pre-operatively.

Conclusion

Cerebral amyloid angiopathy is an important cause of intracerebral haemorrhage in elderly, and diagnosis requires histopathological examination. These haemorrhages are associated with moderate to severe grades of vascular amyloid deposits and fibrinoid necrosis. Presence of hypertension and antiplatelet/anticoagulant therapy appears to lower the threshold for haemorrhage in the affected blood vessels. An interesting observation in this study was that the calibre of vessels rather than the grade of amyloid deposits dictated the size of the bleed. Involvement of the large calibre leptomeningeal vessels was associated with intracerebral haematomas in contrast to the smaller cortical vasculature that produced microhaemorrhages.

Clinical diagnosis of CAA-induced haemorrhage is still a challenge particularly in the absence of microhemorrhages on neuroimaging. A high index of clinical suspicion and histopathological examination of the hematoma with surrounding cortical tissue and leptomeninges is essential for diagnosis.

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Authors' contributions Author 1, Rajalakshmi Poyuran, -analysed the cases; performed data collection, analysis and interpretation; drafted the manuscript and reviewed the literature.

Author 2, Anita Mahadevan, conceived and designed the study, performed data interpretation and analysis and critically reviewed and finalized the manuscript.

Authors 3 and 7, Arimappamagan Arivazhagan and K V L Narasinga Rao, are neurosurgeons who operated and managed the patients and performed clinical data acquisition, analysis and review of the manuscript with intellectual inputs.

Authors 4 and 8, Nandeesh BN and Yasha T Chickabasaviah, performed diagnosis of cases, data analysis and interpretation; reviewed the manuscript and provided inputs.

Author 5, Madhu Nagappa, is a neurologist who managed the patients, provided and interpreted clinical data, performed clinicopathological analysis and reviewed the manuscript with intellectual inputs.

Author 6, Jitender Saini, is a neuroradiologist who carried out neuroimaging studies, reviewed imaging findings and analysed and interpreted the neuroimaging data and reviewed the manuscript providing critical inputs.

All the authors gave final approval for publication and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Corresponding author takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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