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Chapter 4

Cerebral Amyloid Angiopathy

Vikas Chaudhary, Shahina Bano,
Sachchidanand Yadav, Umesh Chandra Garga and
Sachin Kumar Singh

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1. Introduction

Cerebral amyloid angiopathy (CAA) is an important but under-recognized cause of spontaneous intracranial hemorrhage (ICH) in the normotensive individuals. [1] Both sporadic and hereditary forms may occur. Hereditary form of CAA is seen at a younger age, as early as the third decade; in contrast, the sporadic form is more common in elderly and increases in both prevalence and severity with increasing age. CAA results from deposition of β-amyloid protein in small and medium sized cortical, subcortical, and leptomeningeal vessels. This deposition is responsible for the wide spectrum of clinical symptoms and neuroimaging findings. [1,2] CAA is not associated with the presence of systemic amyloidosis. [3] Majority of cases of CAA are asymptomatic. However, symptomatic patient may present with sudden neurological deficit due to transient ischemic attack, progressive cognitive decline, or potentially devastating intracranial hemorrhage. [3,4] Computed tomography is the imaging modality of choice for evaluation of suspected acute intracranial hemorrhage. Magnetic resonance imaging is a sensitive technique for identifying microhemorrhages, microangiopathy-related ischemic changes and assessment of disease progression. The early and accurate diagnosis of CAA is important because of the likely implication it has on future management targeted to reduce the risk of recurrent hemorrhage. In this chapter our emphasis will be on the complex pathophysiology, important clinical and radiological features and the role of imaging in secondary prevention of CAA related ICH. [1,3,4]

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2. Pathophysiology

CAA is characterized by deposition of β-amyloid protein in media and adventitia of small and medium-sized cortical, subcortical, and leptomeningeal vessels, with sparing of similar-sized vessels in the deep white matter. [2] The complex structural changes in the vessel wall related to β-amyloid deposition include endothelial dysfunction, loss of smooth muscle cells, fibrinoid necrosis, vessel wall fragmentation (fragile vessel) and microaneurysm formation. All these factors predispose the patient to repeated episodes of blood vessel leakage and frank hemorrhages in response to sudden increase in blood pressure or minor trauma. [3,4] CAA related inflammation (termed as cerebral amyloid angitis or cerebral amyloid inflammatory vasculopathy) is typically perivascular and may be associated with frank vasculitis. β-amyloid deposition causes vessel wall thickening and subsequent luminal narrowing leading to ischemic changes. [2] The deposition may also impair the perivascular drainage, leading to dilatation of perivascular spaces (also known as Virchow Robin spaces) within the lobar region and in deep cerebral white matter. The enlarged perivascular spaces, a potential useful neuroimaging marker of CAA, can reach several millimeters in diameter and may be visible on brain imaging. [5,6] Histologically, β-amyloid deposits stained with Congo red show classic yellow-green birefringence under polarized light. [3]

3. Clinical spectrum

In general, hereditary form of CAA has an earlier onset and more severe clinical manifestations than sporadic CAA. Symptomatic CAA has variable clinical presentations, which include sudden neurologic deficit (stroke) related to acute ICH, TIA-like symptoms, cognitive impairment and dementia. [7]

The most common presentation of CAA is the development of a sudden neurological deficit secondary to an acute ICH. Specific clinical symptoms and signs depend on both the size and location of the ICH. CAA can have similar presentation as acute ICH related to other causes: headache, nausea and vomiting, loss of consciousness, focal neurological deficits and seizures. [8]

Transient-ischemic attack (TIA) like symptoms also termed as "amyloid spells" is the next most commonly described presentation. The spells are typically brief (<30mts) and are characterized by recurrent, stereotyped episodes of 'positive' spreading sensory symptoms (paraesthesias). The spells are related to hemorrhagic components of CAA, for example cortical microbleeds (CMBs), cortical subarachnoid hemorrhage (cSAH), or cortical superficial siderosis. [4,9]

The prevalence of CAA is significantly higher in demented patients (due to Alzheimer disease) compared to non-demented patients. CAA-related dementia is slowly progressive, similar to that seen in patients with Alzheimer disease. [10] CAA is also the direct cause of cognitive impairment that progresses rapidly over the course of a few weeks. These patients may present with confusion and disorientation. [3]

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4. Neuroimaging correlates of CAA

The Boston criteria (table 1) was first proposed in 1990 in order to standardize the diagnosis of cerebral amyloid angiopathy. They comprise of combined clinical, imaging and pathological parameters. [11]

Definite CAA
Full postmortem examination demonstrating:
-Lobar, cortical, or corticosubcortical hemorrhage
-Severe CAA with vasculopathy
-Absence of other diagnostic lesion
Probable CAA with supporting pathology
Clinical data and pathologic tissue demonstrating:
-Lobar, cortical, or corticosubcortical hemorrhage
-Some degree of CAA in specimen
-Absence of other diagnostic lesion
Probable CAA
Clinical data and MRI or CT demonstrating:
-Multiple hemorrhages restricted to lobar, cortical, or corticosubcortical regions
-Age more than 55 years
-Absence of other cause of hemorrhage
Possible CAA
Clinical data and MRI or CT demonstrating:
-Single lobar, cortical, or corticosubcortical hemorrhage
-Age more than 55 years
-Absence of other cause of hemorrhage
CAA: Cerebral amyloid angiopathy

Table 1. Boston criteria for diagnosis of CAA-related hemorrhage

Recognition of the imaging findings of CAA is important for correct diagnosis. The important imaging correlates of CAA include: (i) large intracranial hemorrhages (ICHs), (ii) cerebral microbleeds (CMBs), (iii) convexity subarachnoid hemorrhages (cSAH), (iv) cortical superficial siderosis, (v) white matter changes (leukoaraiosis), and (vi) prominent VRSs.

The majority of ICHs (>75%) in elderly are spontaneous due to rupture of small arteries affected by either of the two processes; the hypertensive arteriopathy or CAA. Distribution of ICH reflects the underlying microangiopathy. Hypertensive arteriopathy is characterized by lipohyalinosis and fibrinoid necrosis of lenticulostriate perforators located in deep gray nuclei (i. e. basal ganglia, thalami) and infratentorial location (i. e. pons). In contrast, CAA related ICH is preferentially lobar (any lobe may be involved); less commonly involves the cerebellum and rarely the deep nuclei or the brainstem. [12] CAA-related ICH represents 2% of all ICH and is an important cause of hemorrhage in normotensive elderly patients without trauma.

Nonenhanced CT helps to exclude the presence or absence of an acute ICH and provides information regarding the location, size, shape and extension of ICH (Figure 1). MR imaging is most sensitive for detection of chronic hemorrhages in suspected cases of CAA. After ICH, hemosiderin remains stored within the macrophages, leads to focal dephasing of the MR signal, and causes hemosiderin-containing areas to appear dark on T2-weighted spin-echo sequences. This effect may be further enhanced by the use of imaging techniques with high sensitivity for differences in magnetic susceptibility, such as the T2*-weighted gradient-echo (GRE) sequence (Figure 2). The susceptibility-weighted imaging (SWI) has been found to be more sensitive than conventional GRE techniques for the detection of blood products. [13,14,15]

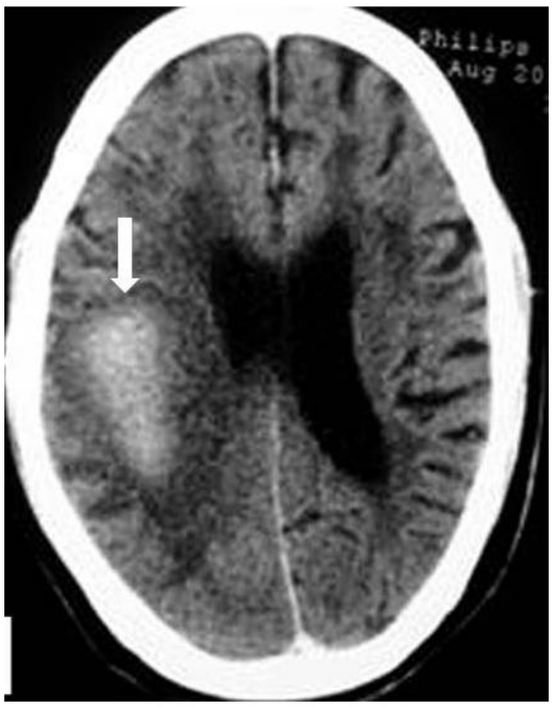

Figure 1. Plain axial CT image of a 66-year-old normotensive male reveals a large, right parietal lobe, hyperdense, subacute hemorrhage (arrow) causing mass effect in form of effacement of adjacent sulci and compression of posterior part of the body of ipsilateral lateral ventricle. Diffuse periventricular white matter hypodensities (leukoaraiosis) is also noted.

The hemorrhage is typically lobar and cortical-subcortical in distribution; it generally spares the deep white matter, basal ganglia and the brainstem. Symptomatic ICH is large (>5mm), while microhemorrhages (<5mm) are often clinically silent. CAA-related macrohemorrhages typically exhibit irregular borders (Figure 1) and may be associated with subarachnoid hemorrhage, subdural hemorrhage, or, less commonly, intraventricular hemorrhage. CMBs are small, well demarcated; rounded lesions not detected on conventional MRI (Figure 2). The presence of chronic cortical-subcortical microhemorrhages in association with large ICH increases the probability of CAA (Figure 3). Multiplicity and recurrence of ICH further favors CAA. [16,17]

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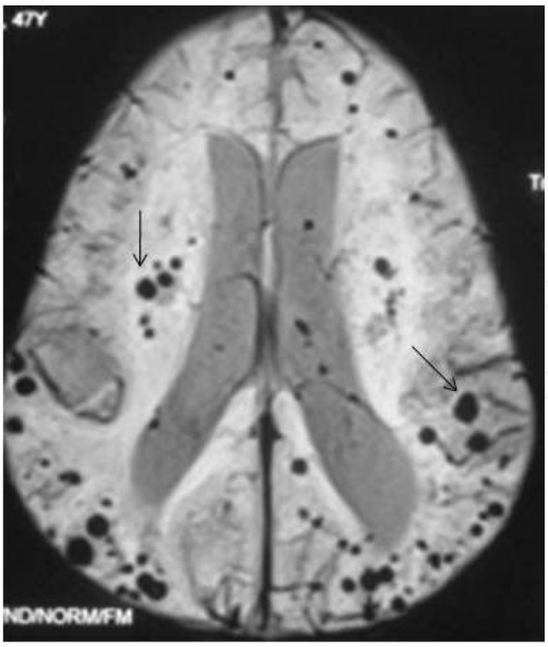

Figure 2. T2*-weighted gradient-echo MR image of a 62-year-old male patient shows diffuse and small multifocal hemosiderin deposits (chronic microhemorrhages) in corticosubcortical location of both the cerebral hemispheres, seen as signal void areas (blooming) (arrows).

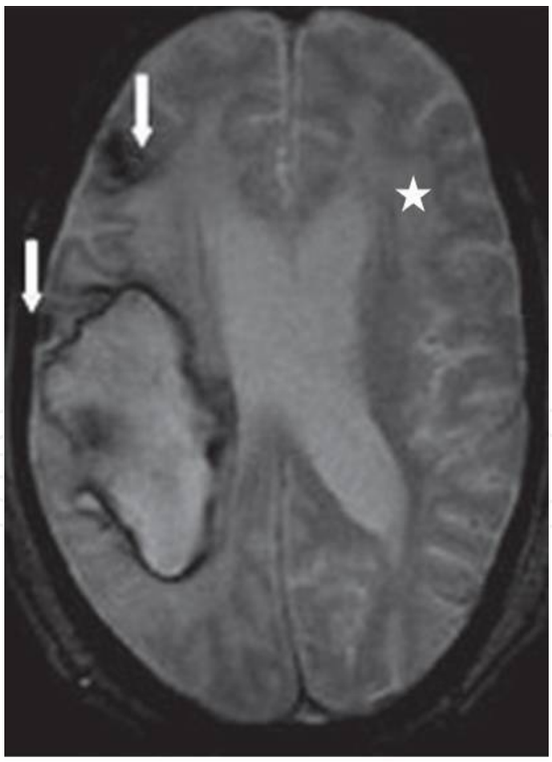

Figure 3. T2*-weighted gradient-echo MR image of same patient as in figure 1, demonstrates a large right parietal hematoma in association with multiple chronic cortical-subcortical microhemorrhages (arrows) and periventricular white matter abnormality (asterisk), thus increasing the probability of CAA.

Chronic subarachnoid hemorrhage (cSAH) and superficial siderosis are quite characteristic of CAA. cSAH often results from lobar ICH extending to the cortical surface (Figure 4). Cortical superficial siderosis describes hemosiderin deposition in the superficial layers of the cerebral cortex and may follow repeated episodes of bleeding in the subarachnoid space. On T2*-weighted GRE sequence, cortical superficial siderosis shows a characteristic gyriform pattern of hypointense signal. [18]

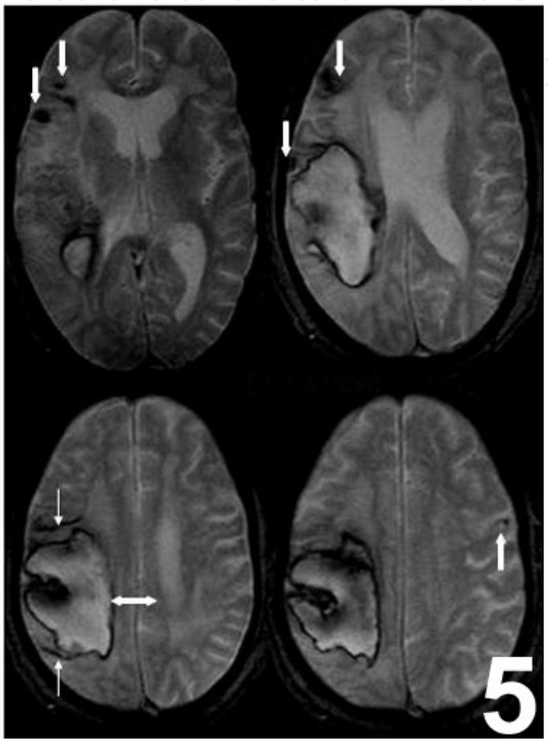

Figure 4. T2*-weighted gradient-echo MR image of same patient as in figure 1, shows two linear areas of signal void (thin arrows) in the vicinity of large primary lobar hemorrhage (thick arrow) suggest chronic subarachnoid hemorrhage and cortical superficial hemosiderosis.

MRI is also sensitive for identifying CAA-related inflammation and ischemic changes and assessment of disease progression. [19] Leukoaraiosis, a radiological term which describes imaging changes in deep cerebral white matter, is a nonspecific finding seen in patients with CAA and can be due to demyelination, infarction or edema. On imaging, leukoaraiosis appears as patchy or confluent, CT hypodense or T2/FLAIR (fluid attenuated inversion recovery) hyperintense white matter abnormality with or without sparing of subcortical U fibers (Figure 5). Leukoaraiosis with sparing of U fibers is secondary to ischemic white matter damage and is seen in association with long standing dementia; whereas, white matter changes that extend to involve the U fibers are common in patients with subacute cognitive decline and are associated with mass effect due to inflammatory edema. [20,21] White matter changes in CAA increases over time and is an important contributor to overall disease burden. The CAA should be considered in the broad differential diagnosis of leukoencephalopathy especially if associated with progressive dementia or cognitive impairment. [13]

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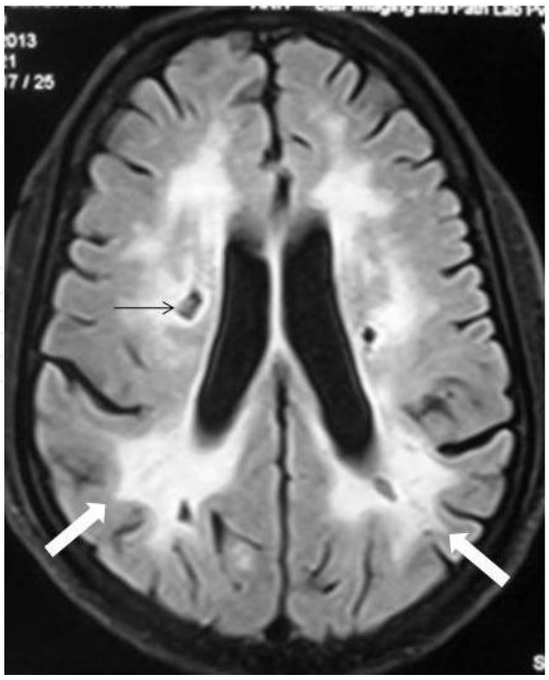

Figure 5. Axial MRI (FLAIR sequence) of the same patient as in figure 2, demonstrates bilateral symmetrical, confluent, supratentorial periventricular white matter hyperintensity with involvement of posterior subcortical U fibers (thick arrows). Also note dilated perivascular spaces (Virchow Robin spaces) in deep cerebral white matter (thin arrow).

5. Management prospect and prognosis

Currently, there is no treatment to halt or reverse β-amyloid deposition. Thus, attention is directed instead to the prevention of adverse outcomes associated with CAA, such as recurrent hemorrhages or progressive dementia. In this context, MRI may help in selecting patients for different types of secondary prevention of stroke. MR evidence of higher number of chronic microbleeds on baseline GRE MR images are predictive of a greater risk of recurrent hemorrhage and future cognitive impairment. A routine use of GRE MRI sequence is suggested to detect microbleeds in older people to avoid potentially dangerous anticoagulant or antiplatelet therapy. [22]

The role of neurosurgery in ICH remains to be defined clearly. However, hematoma evacuation appears relatively safe in patients <75 years of age without intraventricular extension. [23] For future treatment of CAA, it is important to identify patients early in the course of disease before ICH or dementia occurs, to allow the use of disease modifying therapies. [24] Tramiprosate has been found to be a safe treatment option for patients with suspected CAA. Tramiprosate is an ionic compound that binds with soluble β-amyloid, interferes with the amyloid cascade and delays or inhibits the progression of CAA. [25]

6. Summary

- Cerebral amyloid angiopathy (CAA) is an important cause of spontaneous cortical-subcortical intracranial hemorrhage in the normotensive elderly.
- Leukoencephalopathy in conjunction with acute or chronic ICH in a cortical-subcortical location increases the diagnostic specificity for CAA.
- Computed tomography is the imaging study of choice for evaluation of suspected acute cortical hemorrhage.
- MRI is best suited for identification of chronic cortical-subcortical hemorrhages, ischemic sequelae of the disease and assessment of disease progression.
- The burden of asymptomatic cerebral microhemorrhages detectable by GRE MRI in patients with CAA is a good predictor of hemorrhage recurrence, and therefore highlights the importance of secondary prevention in CAA-related PICH.

Author details

Vikas Chaudhary[1*], Shahina Bano[2], Sachchidanand Yadav[2], Umesh Chandra Garga[2] and Sachin Kumar Singh[3]

*Address all correspondence to: dr_vikaschaudhary@yahoo.com

1 Department of Radiodiagnosis, Employees' State Insurance Corporation (ESIC) Model Hospital, Gurgaon, Haryana, India

2 Department of Radiodiagnosis, PGIMER, Dr. Ram Manohar Lohia (RML) Hospital, India

3 Department of Radiodiagnosis, Jawahar Lal Nehru (JLN) Medical College, Bhagalpur, Bihar, India

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