Cerebral amyloid angiopathy - Intracerebral haemorrhage pattern indicating small vessel disease

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Learning objectives

Cerebral amyloid angiopathy (CAA) related bleedings are an important cause of primary intracerebral hemorrhage (ICH). It is essential that radiologists are able to differentiate as many of the causes of ICH as possible. Our objective is to achieve a comprehensive overview of CAA related bleedings by addressing the following focus points:

• Illustrate the radiological and clinical features of cerebral amyloid angiopathy (CAA) related hemorrhages
• Demonstrate the usual appearance of CAA bleeds on CT
• Highlight the role of MRI in microbleed detection
• Emphasize the effectiveness of the Boston Diagnostic Criteria and the power of combined imaging in CAA differential diagnostics

Background

While cerebral amyloid angiopathy is a relatively common cause of non-traumatic intracerebral hemorrhage in the elderly (12-15% of hemorrhages above the age of 60) [1], it still remains under-diagnosed. It is probably because on the one hand CAA only makes up 2% of all ICH [2], and on the other CAA bleeds lack explicit clinical or imaging features. However, certain imaging clues together with the clinical data can be suggestive for CAA.

In the following section we aim to lay out an overview on the ways our understanding of the disease has evolved.

A. History of CAA

1907 Alzheimer - deposition of a "peculiar and difficult to stain" substance in intracranial vessels [1]

1909 Oppenheim - amyloid = "starch like" substance. Falsely believed to be iodine containing fatty- or carbohydrate deposit.

Now known, amyloid appears in many diseases, and it is an irregularly folded superoxidized #-structure protein derivate. /CAA related amyloid is not deposited in extracerebral organs and should not be confused with systemic amyloidosis./

1979 Okazaki - association of dementia and lobar hemorrhage [1]
**1990s** Boston Diagnostic Criteria - international categorization tool of CAA related hemorrhages

**2012 Molecular imaging** of Alzheimer's disease (AD); #-amyloid specific radiopharmaceuticals - (florbetapir F18) might provide future insight for more subtle, less severe forms of the disease [3]

### B. Pathophysiology

- #-amyloid protein deposition in **small-** and **middle size** cerebral vessels in **cortical and subcortical** localization
- recurring hemorrhages

**Familial** (extremely rare)
- Dutch, Icelandic, Italian etc. families

**Sporadic**
- non-dementia, elderly - demonstrated in 20-40% of patients' vessels
- dementia, elderly (A#42 protein) - 50-60% show CAA in vessels
- Alzheimer's disease associated (A#40 protein) - CAA found in 80-90% of patient's vessels. [4]

**Note:** only 40% of CAA patients show AD at autopsy. The two diseases are overlapping **but not directly linked!** [2]

### C. Clinical appearance

- intracranial hemorrhage- consequent neurologic deficit
- transient focal neurologic episodes (TIA-like attacks) **amyloid spell**
- slowly progressing **dementia** (25-40%) [4]
- rapid neurologic and **cognitive impairment**

**Age related prevalence** (Table 1 on page 4)

- age is a very important differential diagnostic factor for CAA related hemorrhage
- incidence rapidly increases over 55 years
- over 70 years CAA is the most common cause of ICH

**Interesting to know:** despite the seemingly high prevalence, only a small portion (5.6%) of CAA patients actually develop bleeding! [5]
**Table 1:** Incidence cerebral amyloid angiopathy by various age groups. (Reproduced with permission from Yamada M)
In order to demonstrate the typical features of CAA related cerebral hemorrhage we have browsed through our department's database for CAA related and other types of bleedings. Finally, 24 patients with intracranial hemorrhage were selected out of which 8 were suggestive of or proved to be CAA related bleedings.

These CAA patients all showed intracerebral hemorrhage on CT and all were older than 65 years (average 75 years). Female to male ratio was 6:2. The hemorrhage was often extended, multilocular (involved 3 lobes on average) and was always situated cortico-subcortically. At times the hemorrhage showed subdural or subarachnoid propagation or appeared cystic with fluid-fluid levels. Intraventricular bleeding was rare. When performed, MRI scans detected multiplex microbleeds in a cortico-subcortical localization. The patient data and radiological images were also categorized according to the Boston Criteria.

We classified various clinical and imaging features according to how likely predictors they were for CAA. Table 2 on page 7

In the following part we illustrate these findings to highlight the differential diagnostic clues of CAA related bleeding.

**Sample case Fig. 1 on page 7**

**Main clues identifiable on imaging:**

- lobar hemorrhage defined as: superficially localized bleeding affecting the cortico-subcortical border [6]
- multilocular / multiplex bleeding
- cascade like pattern - multiple ages of hemorrhage indicating slow/steady or rapid/repetitive hemorrhage
- subdural or subarachnoid propagation of the bleeding
- fluid-fluid levels indicating cystic, cavitated damage
- microhemorrhages detectable on MR
- leukoencephalopathy
- atrophy

**Boston Diagnostic Criteria** [7]

**A. Histologic sample available - pathology based diagnosis**

1. **Definite CAA**
• post-mortem histological examination performed Fig. 2 on page 8
• gold standard: 100% sensitivity

2. Probable CAA with pathologic evidence

• some CAA on pathologic specimen (hematoma, biopsy)
• 67% sensitivity [8]
• increased risk of bleeding
• neurosurgical intervention is often not indicated -> lack of surgical sample -> radiolological image and clinical data remain diagnostic clues

B. Histologic sample not available - imaging feature based diagnosis

3. Probable CAA, based on radiological and clinical data

• multiplex lobar hemorrhage
• age >55 (dementia)
• lack of other cause

Knudsten et al: compared to the post-mortem examination of patients of this "probable" category the radio-clinical image provides a 100% diagnostic accuracy. [9]

Differential diagnostic examples:

• Hemorrhage localization: cortico-subcortical (lobar) vs. basal ganglia (hypertensive) hemorrhage Fig. 3 on page 9
• Hemorrhage localization: cortico-subcortical vs. cortical bleeding Fig. 4 on page 10
• Multiplex / multilocular hemorrhages Fig. 5 on page 11
• Multiplex / multilocular hemorrhage + subdural / subarachnoid propagation Fig. 6 on page 12
• Influence of patient age and clinical history Fig. 7 on page 13

4. Possible CAA, based on radiological and clinical data

• unilocular hemorrhage
• age >55
• lack of other cause

Knudsten et al: compared to the postmortem examination of patients of this "possible" category the radio-clinical image provides a 62% diagnostic accuracy. [9]
Differential diagnostic examples of unilocular hemorrhage:

- Possible CAA Fig. 8 on page 14
- CAA ruled out by imaging Fig. 9 on page 15
- Microbleed detection with GRE MR Fig. 10 on page 16

Microhemorrhage (bleedings <5mm) are readily detectable on GRE sequences. Hemosiderin around these small bleedings cause magnetic field inhomogeneities, and on sequences which are more prone to magnetic susceptibility microbleeds appear as hypointensities. In fact, MR is so sensitive that microhemorrhages in non-symptomatic dementia patients could be used for the screening of CAA. [10]

- MRI microhemorrhage detection, non-CAA cause. Fig. 11 on page 16
- Most common localisation of unilocular bleeding - the occipital lobe Table 3 on page 17 Possible CAA. Fig. 12 on page 18

Images for this section:

![Table 2: Clinical and imaging predictor features for CAA.](image)

Table 2: Clinical and imaging predictor features for CAA.
Fig. 1: Sample case of CAA. 66 year-old male patient with sudden collapse left sided hemiplegia and homonymous hemianopsia. A, Non-enhanced CT scan at admission showed extensive, right cortico-subcortical hemorrhage in the fronto-parieto-occipital region. B, 5 days postictal MR, axial FLAIR showed small, perifocal edema, slight leukoencephalopathy, old vascular lesions and cortical atrophy. C-E, axial GRE MR revealed multiple microhemorrhages bilaterally cortico-subcortically. F, Progression, 7th postictal day, non-enhanced CT exam revealed subarachnoid propagation of the bleeding (arrow). Patient's autopsy confirmed CAA. (Boston 1)
Fig. 2: #-amyloid immunohistochemical staining, hematoxylin background stain. #-amyloid deposition in the leptomeningeal vessels in the cortical area adjacent to the hemorrhage. Histological diagnosis - cerebral amyloid angiopathy.
Fig. 3: CAA differential diagnostics 1. Hemorrhage localization: cortico-subcortical (lobar) vs. basal ganglia (hypertensive) hemorrhage. A, 83 year-old female patient with left upper limb paresis, motor aphasia and left facial paresis. Non-enhanced CT showed right, multilocular, cascade like cortico-subcortical hemorrhage in the fronto-parieto-occipital region. No autopsy was performed, suspected for CAA (Boston 3). B-D, Non-enhanced CT scans: hypertensive hemorrhage pattern (deep, basal ganglia bleeding). B, 47 year-old female, extensive right thalamic hemorrhage with intraventricular propagation. C, 58 year-old male, left lentiform nucleus bleeding. D, 60 year-old female right thalamic hemorrhagic stroke.
Fig. 4: CAA differential diagnostics 2. Hemorrhage localization: cortico-subcortical vs. cortical bleeding. A, Non-enhanced CT of 72 year-old demential female patient. Extensive right fronto-parietal lobar hemorrhage, suspected for CAA (Boston 3). B, 88 year-old male patient, non-enhanced CT shows extensive right temporo-parietal cortical hyperdensity. C, corresponding MR axial FLAIR image shows hypointense cortex and edema (GRE confirmed hemorrhage). Phase contrast series (not shown) confirmed thrombosis of the right sigmoid and transverse sinuses. Cortical bleeding was proven to be the subsequent complication of venous infarct. D-E, Non-enhanced CT examination. 64 year-old male patient admitted for subacute extensive left MCA infarct (D), 14 day postictal non-enhanced control CT scan (E) taken after worsening of clinical symptoms. Ribbon-like cortical hemorrhage confirmed hemorrhagic transformation of the ischemic infarct.
Fig. 5: CAA differential diagnostics 3. Multiplex / multilocular hemorrhages. A-B, 77 year-old female patient. Multiple extensive, "cascade"-like cortico-subcortical hemorrhage in the right fronto-temporo-parieto-occipital region, subdural bleeding was also visible. No autopsy, suspected for CAA (Boston 3). C-E, 61 year-old male patient. Atypical, massive right hemispheric hemorrhage. Proposed mechanism of bleeding: primary hypertensive bleeding originating from the left lentiform nucleus with consequential cerebral venous compression and hemorrhagic venous infarct in the temporal lobe.
Fig. 6: CAA differential diagnostics 4. Multiplex / multilocular hemorrhage + subdural / subarachnoid propagation. A-B, Non-enhanced CT exam of 81 year-old female patient. Extended right temporo-parieto-occipital lobar hemorrhage with subdural and subarachnoid bleeding. Histological diagnosis confirmed CAA (Boston 1). C-D, 66 year-old male, severe head trauma, non-enhanced CT scans. Hemorrhagic contusions in the right frontal and left parietal lobes with subdural and subarachnoid bleeding components.
Fig. 7: CAA differential diagnostics 5. Influence of patient age and clinical history. A, Sagittal reformatted and axial non-enhanced CT scan of a 90 year-old female patient. Massive, left hemispheric hemorrhage with significant mass effect and intraventricular propagation. Patient's age raised the possibility for CAA, but was ruled out by autopsy. Diagnosis: hypertensive bleeding. B, 72 year-old, demential female (also shown on fig.3) Axial and reformatted coronal and sagittal CT scans. Extensive right hemispheric hemorrhage with fluid-fluid levels. Lobar appearance, multilocularity, known dementia and patient's age suggested CAA. No other cause was found, autopsy not available (Boston 3). C. Axial and reformatted coronal non-enhanced CT images of a 68 year-old alcoholic male. Extensive left cortico-subcortical bleeding and intraventricular propagation are visible. Clinically, severe hepatic toxicity. Autopsy ruled out CAA, cause is hypertension. D. 81 year-old massive left hemispheric hemorrhage with distinct fluid-fluid levels creating cystic/cavitated appearance, severe mass effect. Known prosthentic cardiac valve implant. No further examination or clinical data available. Hemorrhagic tumor or coagulopathy are most likely, however, imaging data and clinical information are not conclusive.
Fig. 8: CAA differential diagnostics 6. Unilocular cortico-subcortical hemorrhage - possible CAA. A, 79 year-old female patient: admitted for drowsiness, headache, speech impairment, senso-motor aphasia. Non-enhanced CT showed atypical, cortico-subcortical bleeding in the left parieto-occipital junction. Subsequent control CT examinations (B,C) showed regression, the symptoms regressed. Clinically suspected for CAA (Boston 4).

Fig. 9: CAA differential diagnostics 7. Unilocular cortico-subcortical hemorrhage - non-CAA cause proven. A. 19 year-old female, atypical, right parasagittal frontal hemorrhage. CTA (below) revealed vascular malformation. B. Non-enhanced CT of 23 year-old male patient, left frontal parasagittal hemorrhage with ventricular propagation. 3D TOF MRA (below) confirmed AVM, with the pericallosal artery as the feeding vessel. C. 66 year-old female after acute myocardial infarction. CT scan revealed left occipital hemorrhagic
stroke, cardiac source of the embolism confirmed by echocardiography. Control CT shows regression of the bleeding. D. 51 year-old female patient, first partial seizure of her life. Non-enhanced sagittal and coronal reformatted CT scans revealed right cortical hemorrhage and parasagittal hyperdense lesion, right lateral ventricle compression. Sagittal and coronal contrast enhanced T1W MR revealed multifocal enhancing mass. Biopsy proved glioblastoma multiforme.

**Fig. 10:** CAA differential diagnostics 8. Unilocular cortico-subcortical hemorrhage. MRI: microhemorrhage detection with GRE. A, Non-enhanced CT scan of 60 year-old male patient. Left sided atypical parieto-occipital, cortico-subcortical bleeding. B, Axial FLAIR scan showed perifocal edema and slight leukoencephalopathy, cortical atrophy. C, GRE MR revealed multiple microhemorrhages cortico-subcortically with occipital lobe dominance. E-F, Magnified GRE images of microbleeds. Patient's symptoms and the bleeding regressed, no biopsy. Possible CAA (Boston 4).
**Fig. 11:** CAA differential diagnostics 9. MRI microhemorrhage detection, non-CAA cause. A1, 24 year-old female patient. Non-enhanced CT revealed a right frontal white matter hyperdense lesion, atypical bleeding suspected. A2-A3, Consequent MR examination axial FLAIR and GRE images confirmed multiple hypointense microbleeds with semioval center dominancy. Cavernous hemangiomas. B. Axial GRE MR showing microhemorrhages in the left thalamus and caudate nucleus. Hypertensive microbleeds.
Table 3: Distribution of cerebral amyloid angiopathy affected vessels by anatomic regions in 70 patients with CAA. (Reproduced with permission from Yamada M)
**Fig. 12:** CAA differential diagnostics 10. Unilocal bleeding occipital lobe involvement, other causes ruled out - possible CAA. A-B, Non-enhanced CT scans of 81 year-old female patient. Left occipital cortico-subcortical hemorrhage. B, Different hyperdensities indicate multiphase bleeding. C-D, 5 days postictal MR ruled out tumor or vascular malformation. On FLAIR (C) extensive leukoencephalopathy and small lacunar infarcts are also visible. D, GRE confirmed blood, with intraventricular propagations. Clinically CAA is suspected (Boston 4).
Conclusion

CAA related bleedings represent only a small observable part of the disease. Ageing populations and the high prevalence of CAA in the elderly seem to result in the rise in the total number of cases. At the moment postmortem examination is still the gold standard for the diagnosis. We have shown that CT scans are appropriate to assess the more characteristic forms of CAA macrohemorrhages: multilocular, cortico-subcortically localized, cascade like bleeding. However, when only atypical unilocular bleeding is present CT scans alone are not suitable for complete differential diagnosis. In these situations - or in case of asymptomatic patients - MR provides additional information by microbleed detection with GRE (or T2*GRE) sequence. Because CAA related bleedings are not image specific clinical information should always be considered in the assessment. The Boston Criteria serve as a simple and effective categorization tool for this purpose.

At the moment early detection, effective treatment and prevention of the disease are still limited. The routine use of MRI is recommended, while molecular imaging might provide future diagnostic opportunities.

References

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5. Yamada M, Cerebral amyloid angiopathy: An overview Neuropathology 2000; 1, 8-22

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