


# Recurrent intracerebral haemorrhages as main manifestations in cerebral amyloid angiopathy-related inflammation

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## SUMMARY

Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a relatively rare and treatable subtype of CAA. We have herein reported a case of CAA-ri with repeated recurrent lobar haemorrhages within a short time as the main manifestations and effectively treated with immunosuppressive therapy. Our case expanded the clinical spectrum of CAA-ri and indicated that leptomenigeal inflammation might be a trigger and bleeding source for recurrent haemorrhage in CAA.

## BACKGROUND

Cerebral amyloid angiopathy (CAA) is a progressive small vessel disease due to  $\beta$ -amyloid deposition in leptomenigeal and cortical arterioles and presents with recurrent lobar intracerebral haemorrhages (ICH) and cognitive decline in the elderly.<sup>1</sup> CAA-related inflammation (CAA-ri) is a relatively rare subtype pathologically featured by perivascular or transmural inflammation of amyloid-deposited vessels. The common characteristics are rapidly progressive dementia, seizures and headaches, and unifocal or multifocal white matter hyperintensities on T2-weighted sequences as well as cortical or subcortical haemorrhagic lesions.<sup>2</sup> Identification of rare clinical manifestations including parkinsonism, stroke-like episodes and so on<sup>3,4</sup> and early diagnosis of CAA-ri have important clinical significance since it shows good response to immunosuppressive treatment.<sup>5</sup>

Here, we describe a patient of CAA-ri with repeated recurrent lobar ICH within a short time as the main manifestations and effectively treated with methylprednisolone pulse therapy to avoid ICH recurrence.

## CASE PRESENTATION

An old woman in her 60s experienced sudden left limb weakness, two episodes of severe headache and progressive cognitive impairment within 1 month. Serial brain CT scans revealed three sequential ICH lesions in the right parietal, left frontal and left temporal lobes. No significant personal or family

history was present. The relatives also denied obvious symptoms of headache, behavioural change or cognitive impairment for the patient before the first ICH event.

## INVESTIGATIONS

On neurological examination, she was conscious and alert but was not able to answer even her name or age. The left limb muscle strength was grade II and left Babinski sign was positive. Apolipoprotein E genotype was  $\epsilon 2/\epsilon 3$ . Screening for serum autoimmune antibody was negative. There were normal white cell count, glucose and protein levels in the cerebrospinal fluid. Brain MRI showed diffuse asymmetric white matter hyperintensities mainly in bilateral frontal and left temporal lobes beyond ICH lesions on T2-weighted images, and haemorrhage, cerebral microbleeds and superficial siderosis on susceptibility weighted images. 18F-florbetapir positron emission tomography (PET) showed diffuse amyloid deposition in cerebral lobes (figure 1A–F).

## DIFFERENTIAL DIAGNOSIS

Brain biopsy of the left temporal lobe was performed. Histopathological examination revealed perivascular cuffing with CD5 positive T lymphocytes infiltration and fibrinoid necrosis, and severe amyloid-beta deposition in leptomenigeal vessels (figure 2). The pathological diagnosis was CAA-ri.

## TREATMENT

The patient received methylprednisolone pulse therapy and slow tapering to oral prednisone.

## OUTCOME AND FOLLOW-UP

She had cognitive improvement manifested by answering simple questions correctly, and also radiographic improvement with white matter lesion regression in left temporal and

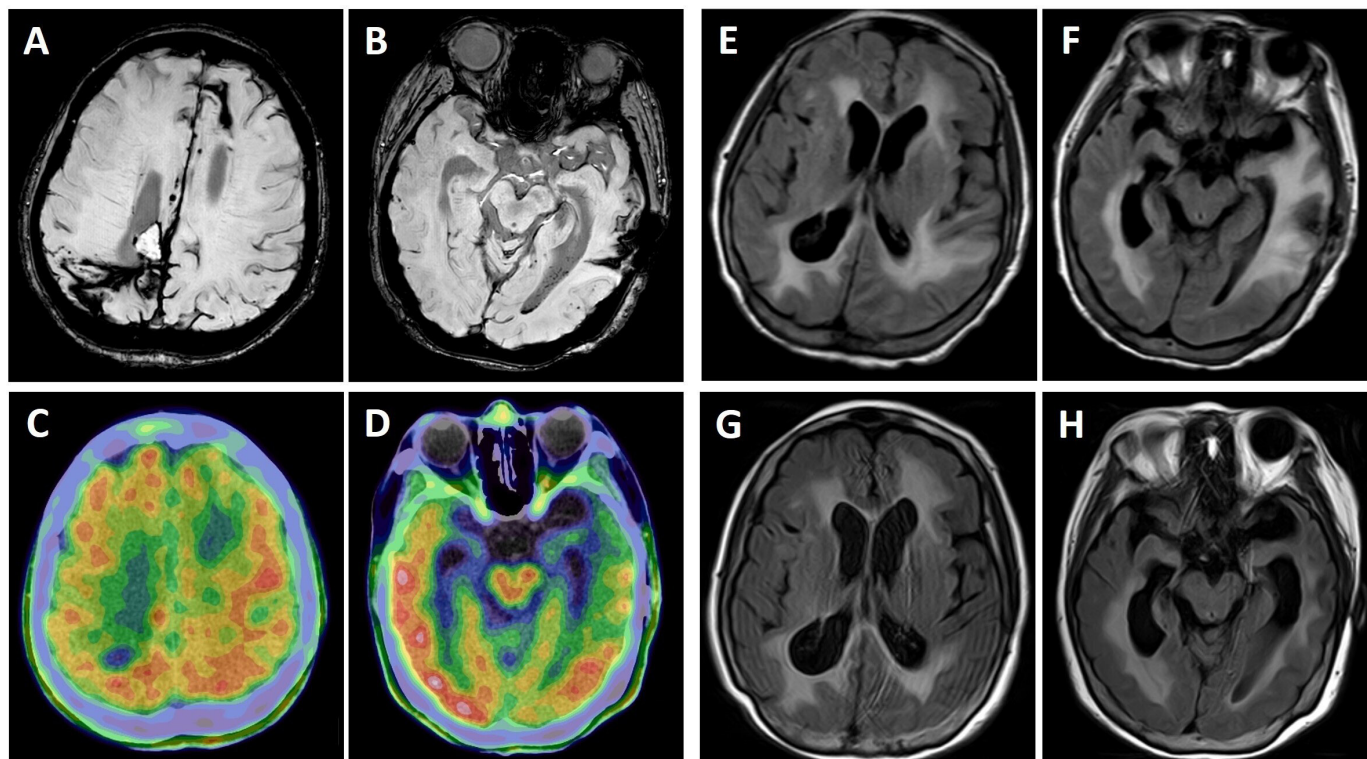


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**Figure 1** Neuroimaging features of CAA-ri. Susceptibility-weighted imaging showed multiple cerebral macrobleeds, microbleeds and superficial siderosis (A–B).  $^{18}\text{F}$ -florbetapir positron emission tomography revealed higher tracer retention (red) representing diffuse amyloid deposition in cerebral lobes (C–D). Baseline brain MRI showed asymmetric white matter hyperintensities beyond ICH lesions on T2-weighted images (E–F). White matter lesions in left temporal and parietal lobes resolved after corticosteroid therapy (G–H). CAA-ri, cerebral amyloid angiopathy-related inflammation; ICH, intracerebral haemorrhage.

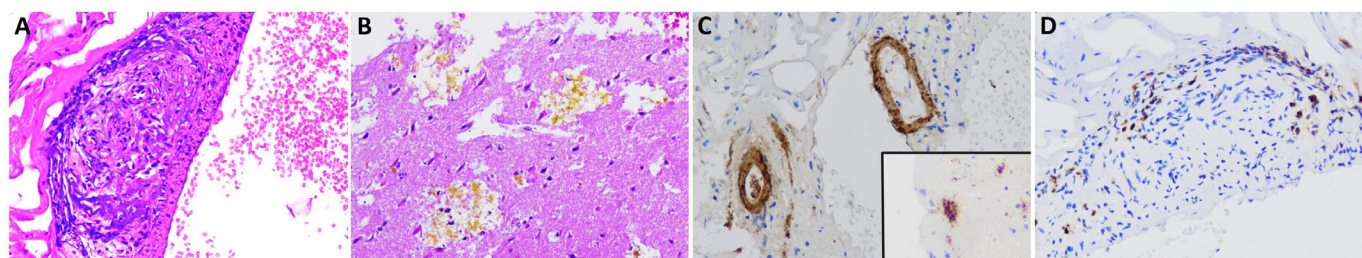
parietal lobes at discharge (figure 1G–H). There was no ICH recurrence after 1-year follow-up.

## DISCUSSION

The clinicrodiologic criteria of CAA-ri emphasised that the presentation and white matter lesions were not directly attributable to acute ICH events.<sup>2</sup> Our case was easily misdiagnosed with pure CAA-ICH which lacked effective therapy to prevent ICH recurrence. From previous prospective studies, the median delay to the first recurrent ICH in cases with CAA-ICH was 19.5 months

(IQR 2.4–44.5 months) in an American cohort and 10.0 months (IQR 7.0–43.5 months) in our cohort.<sup>6,7</sup> In our case, asymmetric white matter hyperintensities beyond ICH regions and three recurrent ICH events within 1 month raised the possibility of CAA-ri, and the final diagnosis was made by amyloid PET and pathological findings.

The history of past ICH existed in about one-third of patients with CAA-ri in a multicentre cohort study.<sup>8</sup> However, there are few reports of CAA-ri with recurrent haemorrhages as the main manifestations.<sup>9</sup> In our case,



**Figure 2** Histological and immunohistochemical features of biopsy specimen. Biopsy of the left temporal cortex. H&E staining showed perivascular cuffing with lymphocytes infiltration and fibrinoid necrosis (A), as well as haemosiderin deposition (B). Immunohistochemical staining for amyloid-beta showed severe amyloid deposition in leptomeningeal vessels and diffuse amyloid plaques (inset) (C). Immunohistochemical staining for CD5 showed that leptomeningeal inflammation was mainly composed of T lymphocytes (D). Original magnification  $\times 400$ .

the severe and diffuse amyloid deposition beyond clearance capacity (revealed by PET and pathology) could induce severe small vessel destruction and immune response (revealed by pathology). Fibrinoid necrosis in leptomeningeal vessels caused by inflammatory processes including downstream microglial activation might be a trigger and bleeding source for recurrent lobar ICH in CAA.<sup>10</sup> This finding might share a potential common mechanism for the relatively high co-occurrence of amyloid-related imaging abnormalities-oedema and haemorrhage in the use of anti-amyloid antibodies. It indicated that the diagnosis of CAA-ri should be considered when a case presented with repeated lobar ICH especially within a short time.

Immunosuppressive treatment was reported to be associated with clinicoradiologic improvement and decreased likelihood of CAA-ri relapse.<sup>5</sup> Slow oral tapering off after high-dose corticosteroid therapy was likely to further reduce the risk of CAA-ri recurrence.<sup>8</sup> The recurrent ICH events in our case were successfully stopped by methylprednisolone pulse and slow tapering therapy with 1-year follow-up, while its long-term effectiveness remained to be verified.

### Learning points

- ⇒ Recurrent lobar intracerebral haemorrhage (ICH) can be main manifestations of cerebral amyloid angiopathy-related inflammation (CAA-ri).
- ⇒ The diagnosis of CAA-ri should be considered when a case presented with repeated lobar ICH within a short time, especially with asymmetric white matter hyperintensities beyond ICH regions.
- ⇒ Immunosuppressive therapy is the first-line treatment for CAA-ri and may be effective in preventing CAA-ri-related ICH recurrence.

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