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Cerebral Amyloid Angiopathy Related Inflammation

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Abstract

Cerebral amyloid angiopathy related inflammation (CAA-ri) is an increasingly recognized and rare cause of reversible encephalopathy, affecting a subset of patients with cerebral amyloid angiopathy. We describe 5 cases of probable CAA-ri that presented to 3 different hospitals in Ireland. A wide spectrum of presenting symptoms was seen ranging from episodic sensory disturbances to severe presentations with tonic-clonic seizures and encephalopathy. Magnetic Resonance Imaging (MRI) is essential to enable prompt diagnosis and must include a blood sensitive sequence such as gradient echo (GRE) or in particular, susceptibility weighted imaging (SWI). It is important for clinicians to be aware of this condition, as prompt treatment with immunosuppression is usually associated with rapid clinical improvement in the majority of patients.

Introduction

Cerebral amyloid angiopathy related inflammation (CAA-ri) is an increasingly recognized and rare cause of reversible encephalopathy, affecting a subset of patients with cerebral amyloid angiopathy (CAA).[1] In CAA, amyloid A-beta peptides are deposited in the walls of small arteries, arterioles and capillaries supplying the cortex, subcortex and leptomeninges.[1] CAA classically presents clinically with lobar intracranial haemorrhage. Other presentations include 'amyloid spells', (a transient ischemic attack mimic), chronic cognitive impairment and convexal sub-arachnoid haemorrhage. In CAA-ri, amyloid A-beta depositions are associated with peri-vascular inflammation and oedema.[1] It can present with acute/ sub-acute encephalopathy, headaches, seizures and focal neurological signs.[2] Magnetic resonance imaging (MRI) reveals T2 hyperintense lesions in the cortex and subcortical white matter suggestive of cerebral oedema. Brain biopsy demonstrates perivascular inflammation and the presence of multinucleate giant cells. CAA-ri is associated with presence of the apolipoprotein E4/E4 genotype.[1]

We describe 5 cases of CAA-ri that presented to 3 different hospitals in Ireland, illustrating the heterogeneity in the presentation of this condition.

Case 1

An 82-year-old man was found obtunded in his house having been unresponsive to messages from his son for a period of several days. At presentation he was alert but disorientated and restless. Speech was slow and hesitant with neurological examination otherwise unremarkable. Blood pressure was normal. Non-contrast CT brain showed asymmetrical vasogenic oedema involving bilateral temporal, parietal and occipital lobes. Contrast enhanced MRI brain demonstrated multifocal areas of T2-weighted Fluid Attenuated Inversion Recovery (T2-FLAIR) hyperintensities affecting cortical and subcortical white matter regions without enhancement. Blood sensitive susceptibility weighted imaging (SWI) sequences revealed bilateral multiple cortical punctuate hypointensities consistent with microhemorrhages sparing the basal ganglia bilaterally. Work up including CSF analysis was otherwise unrevealing.

Initial treatment included empirical cover for viral encephalitis and anticonvulsant therapy, as there was a clinical suspicion of unwitnessed seizure activity. In view of his presentation and radiological features, a presumptive diagnosis of CAA-ri was made. He was commenced on a 6-week tapering course of oral prednisone 30mg. Follow up MRI 6 weeks later revealed complete resolution of the white matter hyperintensities. At outpatient review, he was asymptomatic and living independently. Folstein Mini Mental State Examination Score was 24/30.

Case 2

A 67-year-old lady was admitted electively to hospital in October 2017 for neoadjuvant chemotherapy with weekly carboplatin and taxol for locally advanced oesophageal squamous cell cancer. A few weeks following completion of the chemotherapy she developed 2 generalized tonic-clonic seizures at home and was readmitted to the hospital. She was encephalopathic on admission. Lumbar puncture excluded viral encephalitis. The suspected diagnosis at the time was Posterior Reversible Encephalopathy Syndrome (PRES) secondary to chemotherapy. MRI brain at the time showed bilateral T2 FLAIR hyperintensities (Figure 1a). She had no further seizures after admission, however she deteriorated rapidly requiring parenteral nutrition. She was managed with supportive care. Repeat MRI brain in January 2018 showed significant progression of the T2 FLAIR hyperintensities (Figure 1b). SWI sequences showed associated micro-bleeds. This raised a suspicion for CAA-ri and she was commenced on a course of oral steroids.

She was readmitted in February 2018 from an outpatient rehabilitation facility with clinical deterioration in her symptoms despite improvement in the T2 FLAIR hyperintesities on MRI brain. Steroids were reinstated. Repeat MRI brain in March 2018 showed interval improvement in T2 FLAIR hyperintensities (Figure 1c). SWI sequence showed the presence of new microbleeds (Figure 1d).

She was well when reviewed in July 2018 and she was weaned off the anti-epileptics, Levetiracetam and Lamotrogine. Prednisolone was weaned down to a maintenance dose of 10mg every day. In October 2018, she had a generalized tonic-clonic seizure at home. MRI brain showed prominent post contrast vascular enhancement in bilateral occipital lobes. She was recommenced on 40mg oral prednisolone and improved significantly. Levetiracetam was recommenced. She was commenced on azathioprine 2mg per kilogram as a steroid-sparing agent in January 2019. MRI brain in April 2019 is stable with no new T2 hyperintensities (Figure 1e). She remains well.

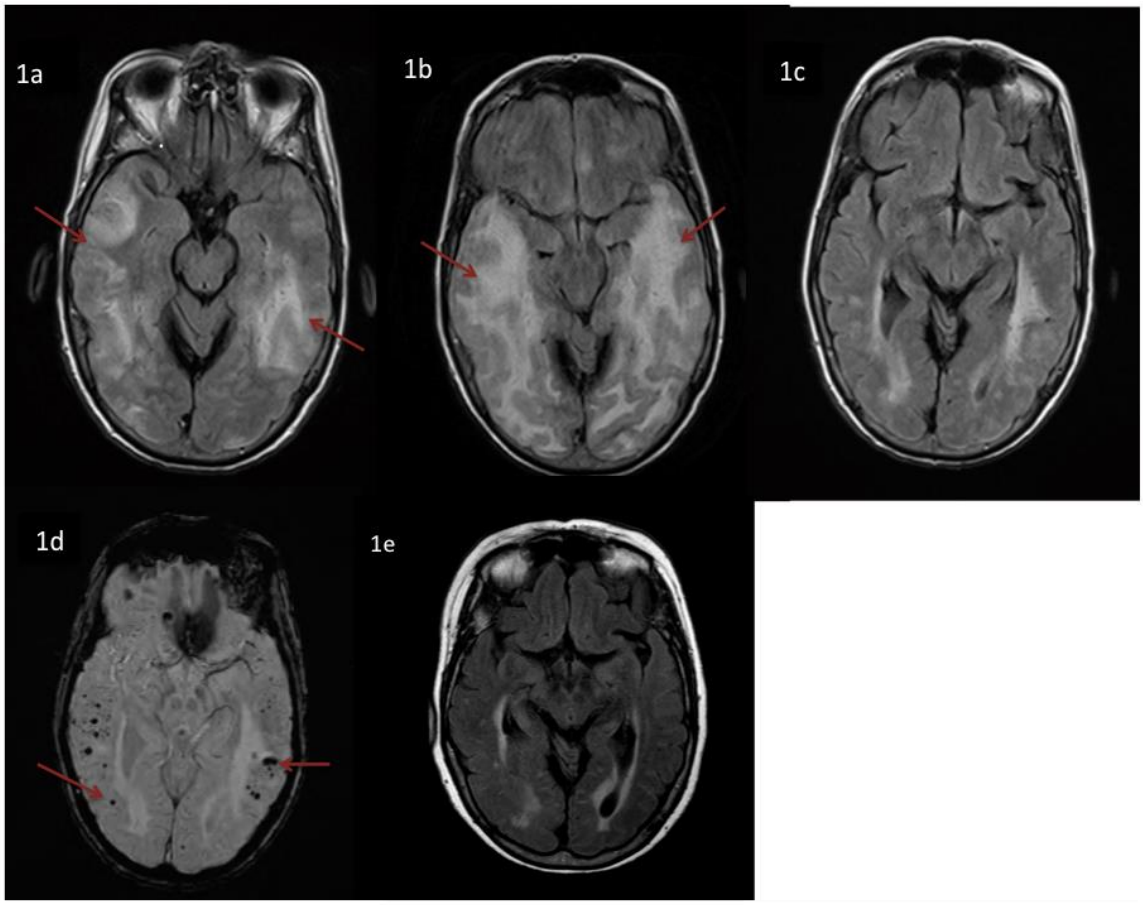

Figure 1a: Axial T2 FLAIR MRI brain in December 2018 showing bi-temporal and parietal hyper-intensities.
Figure 1b: Axial T2 FLAIR MRI brain in January 2018 with extensive bilateral white matter hyper-intensities.
Figure 1c: Axial T2 FLAIR MRI brain in March 2018 showing improvement in bilateral white matter hyperintensities.
Figure 1d: Axial SWI sequence in March 2018 showing numerous punctuate hypointense lesions, which are consistent with macro and microhaemorrhages.
Figure 1e: Axial T2 FLAIR MRI brain in April 2019 showing improvement in white matter hyperintensities.

Case 3

In 2013, a 56-year-old man presented with intermittent paraesthesia and numbness on the right side of the chin, which had been present for one year. He had a past history of hypertension, hypercholestrolaemia and a head injury 16 years ago. His family history was significant for Alzheimer's disease in his father and intra-cranial hemorrhage in his paternal aunt. MRI brain showed subcortical T2 FLAIR white matter hyperintensities in both temporal and parietal lobes (Figure 2a). The changes were initially thought to be secondary to the prior head injury. However, clinically isolated syndrome remained within the differential.

He was reviewed in clinic following a repeat MRI brain in 2014, which showed extensive T2 FLAIR white matter hyper-intensities (Figure 2b). He was minimally symptomatic, and his Montreal Cognitive Assessment test score was 29/30. Repeat MRI brain with contrast showed a persistent large area of T2 hyperintense signal in the left temporal lobe and to a lesser extent in the left parietal lobe, with no post-contrast enhancement. There were no oligoclonal bands detected on lumbar puncture.

These findings were most consistent with a diagnosis of probable tumefactive cerebral amyloid angiopathy. Aspirin for primary prevention was discontinued to reduce risk of intra-cranial haemorrhage.

Repeat MRI brain in May 2015 showed a new area of tumefactive change in the right frontal lobe (Figure 2c). MR angiography was normal. He was treated with intravenous methylprednisolone 1-gram daily for 5 days following the MRI brain and then switched to oral prednisolone. Repeat MRI brain in September 2015 (Figure 2d) showed resolution of the lesion in the right frontal lobe. Steroids were then tapered down over a few weeks and stopped.

MRI brain in September 2017 (Figure 2e) showed significant interval progression of the subcortical white matter T2 FLAIR hyperintensities in the left frontal lobe. He was recommenced on prednisolone 30mg, which was then tapered over 3 months. MRI brain in October 2017 (Figure 2f) showed resolution of the tumefactive change in the left frontal lobe. He has remained clinically and radiologically stable since 2017. MRI imaging in 2018 showed improvement in the FLAIR hyperintensities and stable florid bilateral microbleeds on SWI sequence.

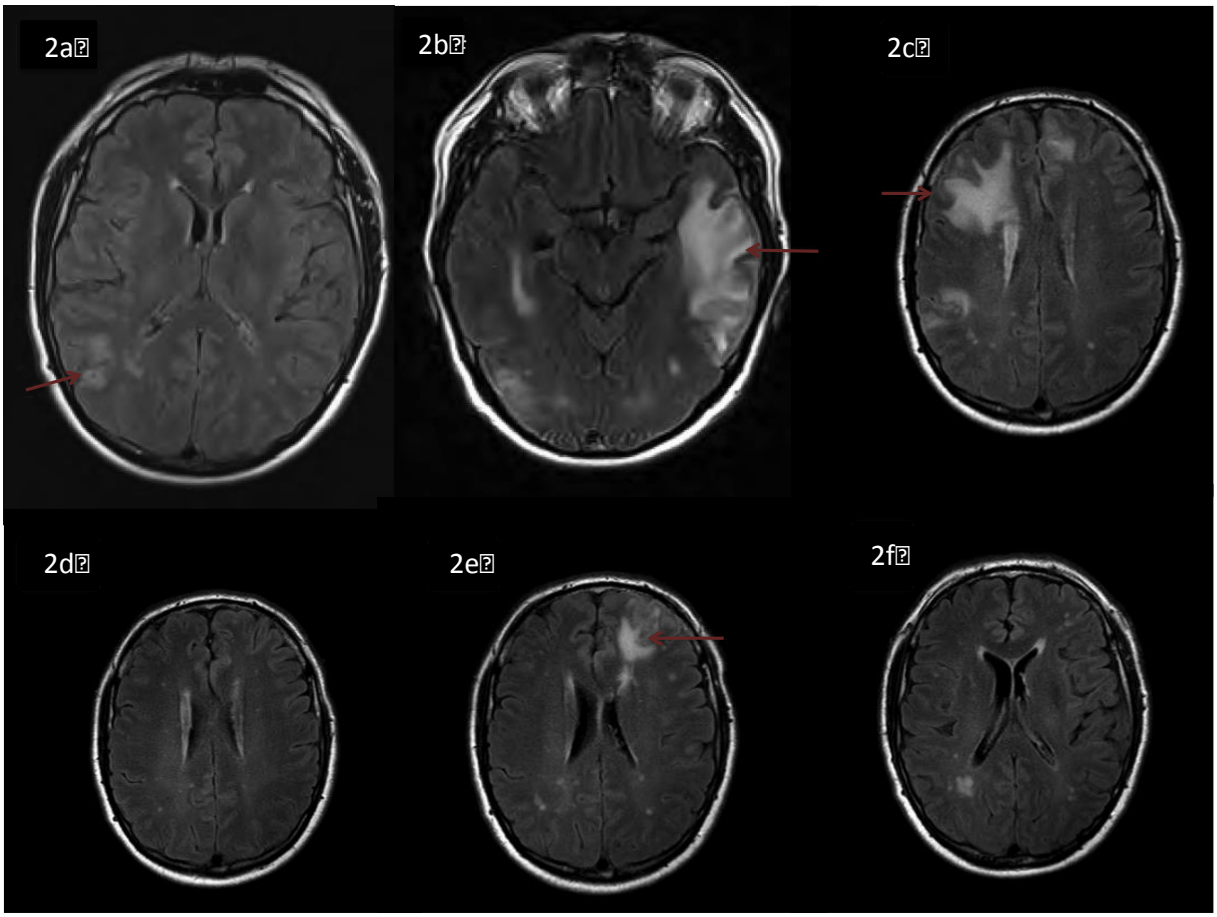

Figure 2a: Axial T2 FLAIR MRI brain in 2013 showing subcortical white matter hyperintensities.
Figure 2b: Axial T2 FLAIR MRI brain in 2014 showing extensive bilateral white matter hyperintensities.
Figure 2c: Axial T2 FLAIR MRI brain in May 2015 showing a new area of tumefactive change in the right frontal lobe.
Figure 2d: Axial T2 FLAIR MRI brain in September 2015 showing resolution of area of tumefactive change in the right frontal lobe following treatment with steroids.
Figure 2e: Axial T2 FLAIR MRI brain in September 2017 showing progression of left frontal hyperintense area.
Figure 2f: Axial T2 FLAIR MRI brain in October 2017 showed resolution of tumefactive change in left frontal lobe.

Case 4

An 84-year-old female was brought to hospital following acute onset of headache, confusion and left sided weakness. On admission she was normotensive with a Glasgow Coma Scale of 12/15. There was evidence of left sided hemiparesis, left sided hemianopia and left sided neglect.

Non-contrast CT brain showed asymmetrical vasogenic oedema involving bilateral occipital lobes with a 5mm hyperdense area in the right occipital lobe (Figure 3a). Contrast enhanced MRI brain demonstrated multifocal areas of T2 hyperintensities most marked in the occipital regions. (Figure 3b). Blood sensitive SWI sequences revealed bilateral, multiple, small punctuate hypointensities consistent with micro-hemorrhages (Figure 3c). Investigations including CSF analysis was otherwise unrevealing.

A presumptive diagnosis of CAA-ri was made. She was commenced on a 6-week tapering course of oral prednisone 30mg. Follow up MRI 6 weeks later revealed partial resolution of the white matter hyperintensities, and steroids were tapered to 5mg maintenance dose (Figure 3d). A Further MRI with gradient echo (GRE) 6 months from the previous scan revealed resolution of white matter hyperintensities. At outpatient review, she was asymptomatic and independent in all activities of daily living. Her blood pressure was controlled on therapy and her Folstein Mini Mental State Examination score was 25/30.

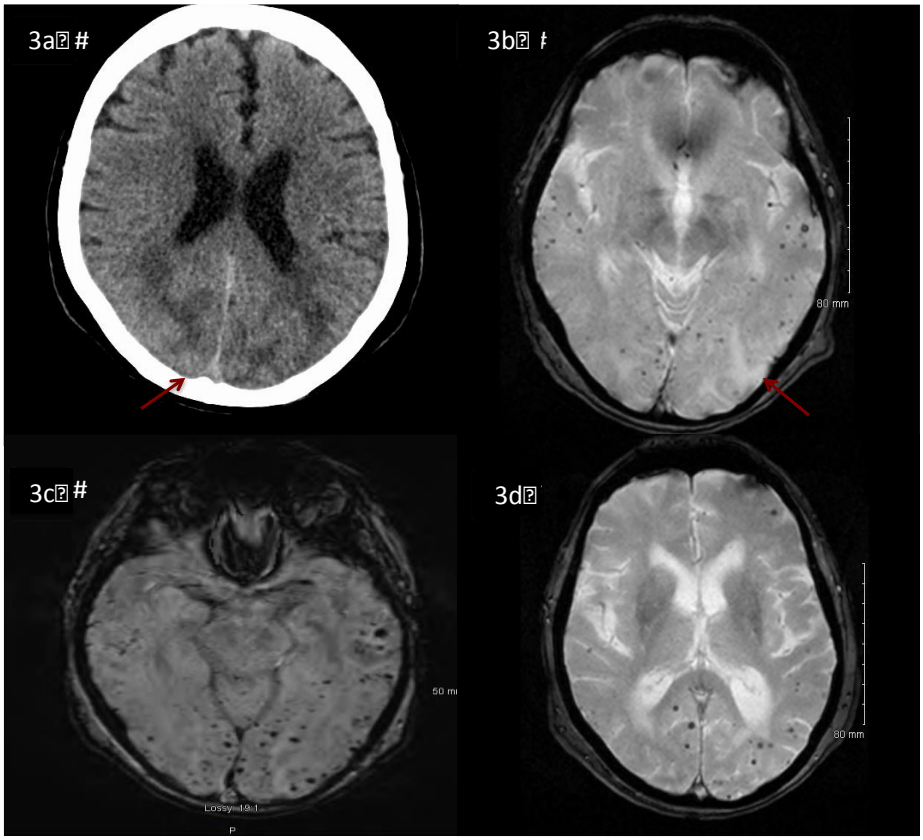

Figure 3a: Non-contrast axial CT brain showing asymmetrical vasogenic oedema involving bilateral occipital lobes with a 5mm hyperdense area in right occipital lobe .
Figure 3b: Axial T2 MRI brain showing hyperintense areas involving cortical and subcortical regions predominantly on the left parieto-occipital area.
Figure 3c: Axial SWI image showing multiple, punctate hypointense cortical lesions due to micro-hemorrhages.
Figure 3d: Axial T2 MRI Brain at 6-weeks interval following steroid therapy. There is remarkable regression of hyperintensities, consistent

Case 5

An 87-year-old woman experienced an episode of transient left-sided visual loss. Her symptoms resolved fully within fifteen minutes. She was orientated to place and time and could give a good account of preceding events. However, during her admission it became clear that she had difficulty recalling information from one day to the next. Her Montreal Cognitive Assessment (MoCA) was 19/30.

Non-contrast CT brain demonstrated a rounded hyperdensity in the right occipital lobe consistent with acute intraparenchymal haemorrhage (Figure 4a). Multiple smaller punctate hyperdensities, suggestive of subarachnoid haemorrhage was also seen. Contrast enhanced MRI brain demonstrated confluent periventricular and occipital T2-FLAIR hyperintensities (Figure 4b). SWI sequences demonstrated multiple microhaemorrhages throughout the brain, most numerous in the occipital lobes bilaterally (Figure 4d). Superficial siderosis overlying the cerebellar folia was also seen (Figure 4c).

These findings were consistent with probable CAA-ri. The patient was treated with intravenous methylprednisolone for five days and subsequently with a gradually tapering dose of oral prednisolone 30mg to a maintenance dose of 5mg. A repeat MRI brain performed seven days after steroid treatment demonstrated a modest reduction in the extent of subcortical oedema. Her MoCA score improved to 23/30. She continues to live independently with home supports.

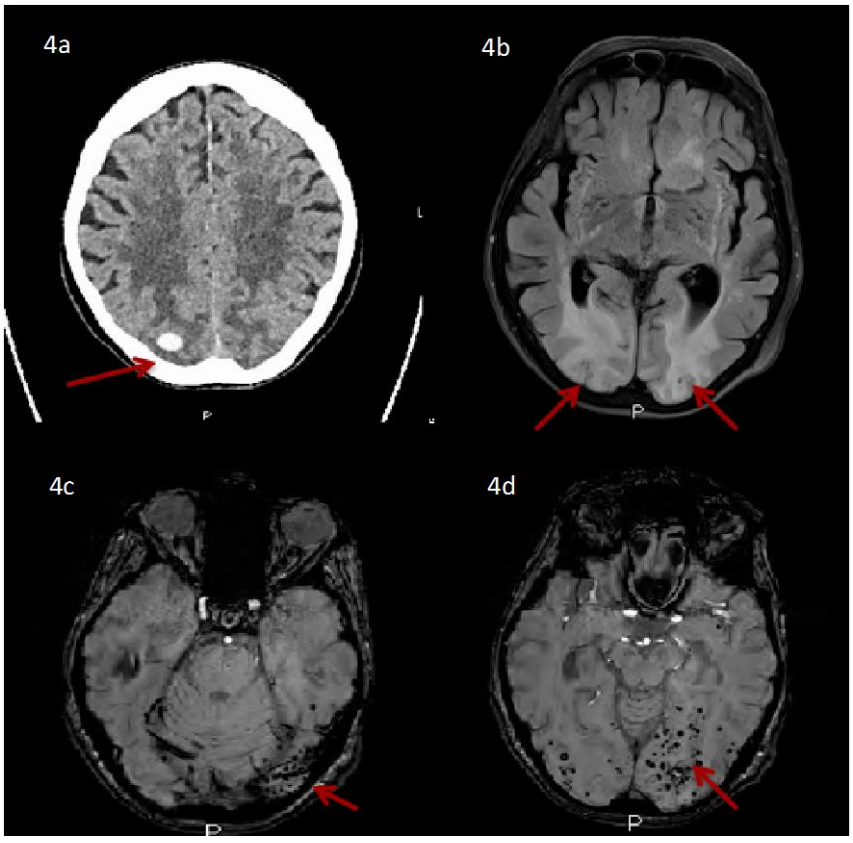

Figure 4a: Non-contrast axial CT brain showing rounded hyperintensity consistent with acute intraparenchymal haemorrhage in the right occipital lobe .
Figure 4b: Axial T2-FLAIR MRI brain showing diffuse subcortical hyperintensity consistent with vasogenic odema.
Figure 4c: Axial SWI image showing multiple, multiple punctate microhaemorrhages and linear hypodensity overlying the cerebellar folia consistent with superficial siderosis.
Figure 4d: Axial SWI image demonstrating many microhaemorrhages thoughout the occipital lobes bilaterally.

Discussion

Inflammatory cerebral amyloid angiopathy includes two entities with similar clinical and imaging features: amyloid beta related angitis (ABRA) and CAA-ri.[3] Inflammatory CAA is associated with a marked inflammatory response on both pathologic examination and imaging in comparison to typical CAA. ABRA is characterized on pathologic examination by vasculitis with intra-mural granulomas and regions of vessel wall destruction. In comparison, CAA-ri is characterized by perivascular inflammation and edematous gyri at autopsy.[3] It is not yet clear whether ABRA and CAA-ri are the same or separate conditions.[4]

Chung et al. proposed a clinical diagnostic criterion for probable CAA-ri to avoid histopathological confirmation with brain biopsy.[5] Auriel et al. modified Chung et al.'s criteria and created a clinical criterion for probable and possible CAA-ri.[6] They demonstrated the probable criteria had a sensitivity and specificity of 82% and 97% respectively for CAA-ri.[6] Auriel et al.'s modified criteria for probable CAA-ri suggests that CAA-ri should be considered in patients presenting (1) aged 40 years or older; (2) with at least one of the following symptoms: headache, decrease in consciousness, behavioural change, focal neurological signs and seizures whereby the presentation is not directly attributable to an acute intracranial haemorrhage ; (3) MRI showing unifocal or multifocal white matter hyperintensities that are asymmetric and extend to the subcortical white matter; (4) presence of one of more of the following: corticosubcortical haemorrhagic lesions, cerebral macrobleed, cerebral microbleed, or cortical superficial siderosis; (6) absence of neoplastic, infectious or other cause.[6] Definite diagnosis of CAA-ri requires brain biopsy.[7]

We report 5 cases of probable CAA-ri presenting with symptoms as mild as a numb chin, to symptoms as severe as tonic clonic seizures and encephalopathy. Our cases highlight the importance of neuroimaging, in particular obtaining SWI or GRE sequences, to assess for the presence of pre-existing microbleeds due to cerebral amyloid angiopathy. Tiny haemorrhages may only be seen on these sequence and not seen on T1 or T2 MRI sequences or on CT. The radiological findings of white matter hyperintesities with co-existent microbleeds enabled us to diagnose probable CAA-ri in all 5 cases. Microbleeds are present in almost 90% of patients with CAA-ri.[8] Leptomeningeal enhancement seen only in the oedematous region is another common finding in CAA-ri. [3,4] Case 2 and 3 highlight the need for frequent imaging to assess for any radiological signs of recurrence, since clinical features might not always be apparent. Case 3 and 5 highlights the dissociation between the mild clinical features and striking radiological abnormalities, a finding that has been reported previously.[9] Case 3 also highlights the importance of being aware of tumefactive cerebral amyloid angiopathy, which is often mistaken for a brain tumour.[10]

The 5 cases showed marked response to therapy with steroids, consistent with existing literature .[11] It is important to note that patients with CAA-ri can relapse when treatment with steroids is stopped, such as in case 2, whilst spontaneous remission can also occur.[12] Kinnecom et al, demonstrated in their study that 7 out of 12 patient had monophasic improvement with immunosuppressive therapy, while 3 out of 12 had initial improvement followed by symptomatic relapse while 2 out of 12 had no evident response to treatment. [13] A systematic review showed that 49 out of 85 patients improved with immunosuppressive therapy, while 12 remained the same and 24 deteriorated further. This study also showed that there was no difference in functional outcome between those patients treated with steroids alone in comparison with those treated with cytotoxic agents in combination with corticosteroids.[14] A recent study has demonstrated that immunosuppressive therapy is associated with clinical and radiological improvement of the presenting disease episode and reduced risk of subsequent recurrent disease flare over a median 2.7 year follow up period. [15]

It is important to be cognizant of other potential conditions that can present with similar clinical presentations and white matter hyperintesities on MRI brain including: posterior reversible encephalopathy syndrome, primary CNS vasculitis, primary CNS neoplasm, CNS lymphoma, acute disseminated encephalomyelitis, infections including progressive multifocal leukoencephalopathy.[3,4] The imaging findings in primary CNS vasculitis and CNS lymphoma can both improve with steroid therapy. In patients with CNS lymphoma, initiation of corticosteroid therapy prior to biopsy can obscure the histological diagnosis of primary CNS lymphoma.

Amyloid related imaging abnormalities (ARIA) represent the major side effect of amyloid-beta immunotherapy e.g. bapineuzumab for Alzheimer's disease. Interestingly imaging findings noted in ARIA consisting of ARIA-E (MRI evidence of vasogenic edema or sulcal effusios on FLAIR) and ARIA-H (MRI evidence of haemosiderin deposition suggestive of microhaemorrhages and superficial siderosis on T2 weighted GRE or SWI) are similar to the imaging findings noted in CAA-ri and ABRA.[16] Furthermore apoE e4/e4 genotype might potentiate the inflammatory response in all three conditions. [4,7,16] The similarities between ARIA and inflammatory CAA has lead to the suggestion that immunotherapy related vasogenic edema is a treatment induced counterpart to spontaneous inflammatory CAA.[15] Autoantibodies against amyloid-beta 1-40 and 1-42 forms have been shown to be elevated in CSF of patients with ABRA, CAA-ri and ARIA. These finding has given interest to whether amyloid beta autoantibodies could be a potential biomarker for inflammatory CAA.[4,16,17] The patients in our case series did not have CSF testing for amyloid beta 1-40 and 1-42.

In summary, our cases highlight the need to be aware of this condition, which can present with diverse symptoms ranging from mild to severe symptoms such as seizures and cognitive dysfunction. This is an important condition for clinicians involved in acute medical care to be aware of in order to diagnose and treat it appropriately. Brain MRI imaging to include either GRE or SWI sequences is essential and means that invasive brain biopsy can be avoided through recognition of the characteristic imaging findings. Prompt treatment with immunosuppression can improve symptoms in the majority of patients.

Declaration of Conflicts of Interest:

The authors have no conflicts of interest to declare.

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