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Case Report

Cerebral amyloid angiopathy related inflammation: An under recognized but treatable complication of cerebral amyloid angiopathy ☆

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ABSTRACT

Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a subset of cerebral amyloid angiopathy (CAA) causing a reversible encephalopathy characterized by seizures and focal neurological deficit. Previously, biopsy was required to make this diagnosis, distinct radiological features have allowed development for clinicoradiological criteria to assist in diagnosis. CAA-ri is an important condition to recognize as patients respond to high dose corticosteroids with significant resolution of symptoms. A 79-year-old woman presents with new onset seizures and delirium with prior history of mild cognitive impairment. An initial computed tomography (CT) brain demonstrated vasogenic oedema in the right temporal lobe, and magnetic resonance imaging (MRI) showed bilateral subcortical white matter change and multiple microhemorrhages. The MRI findings were suggestive of cerebral amyloid angiopathy. Cerebrospinal fluid analysis demonstrated raised protein and oligoclonal bands. A thorough septic and autoimmune screen demonstrated no abnormality. Following a multidisciplinary discussion, a diagnosis of CAA-ri was made. She was commenced on dexamethasone and her delirium improved. CAA-ri is an important diagnostic consideration in an elderly patient who presents with new seizures. Clinicoradiological criteria are useful diagnostic tools and may avoid the need for invasive histopathological diagnosis.

Introduction

Cerebral amyloid angiopathy (CAA) is a disorder of the elderly in which amyloid peptides are deposited in the walls of cerebral arteries leading to micro and macrohemorrhages, and eventually dementia. Cerebral amyloid angiopathy-related inflammation (CAA-ri) is an increasingly recognized subset of CAA, described as a reversible encephalopathy with imaging features of inflammation and oedema.

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CAA-ri is an important diagnostic consideration in an elderly patient who presents with new seizures. Other common symptoms include delirium, headaches and other focal neurological deficits. Reported incidence is approximately 0.13 in 100,000 but the condition is likely to be underdiagnosed and the true incidence is probably higher. Clinicoradiological criteria are useful diagnostic tools, avoiding the need for histopathological examination. CAA-ri is an important condition to recognize as patients respond to high dose corticosteroids with significant resolution of symptoms.

Case presentation

A 79-year-old woman presented with delirium which developed over several days. She had a 3-year history of mild cognitive impairment, and lived at home with her husband and daughter prior to her hospital admission. Her medical history was also significant for major depressive disorder, which had required multiple antipsychotics and electroconvulsive therapy, osteoporosis and a colorectal carcinoma with hemicolectomy.

There was no history of febrile illness or symptoms to suggest an infection. There was no evidence of urinary retention or constipation. She did not complain of chronic pain and her medications had not been recently changed. We could not elicit a history of headache or focal neurological deficit. She had been found confused and drowsy by her family at home, and was admitted for investigation for investigation of delirium. Initial CT Brain showed no evidence of an acute ischemic or hemorrhagic event.

During her admission she was observed to have three generalized tonic clonic seizures.

Clinical findings

On physical examination, she was obtunded, with a Glasgow Coma Scale (GCS) score of E4V2M6. Her blood pressure was 173/101 mm Hg and she was afebrile. Tone and power of her limbs were normal, with brisk deep tendon reflexes. She had no cranial nerve abnormality or cerebellar dysfunction. Her neck was supple on examination with no evidence of meningeal irritation.

Diagnostic assessment

Blood counts showed normal hemoglobin and a white cell count of 12 × 109/dL with neutrophilia, and C-reactive protein of 4 mg/L. Serum electrolytes, calcium, liver function, thyroid function, B12 and folate were normal. Flow cytometry, ANCA, antineuronal, anti-VGK and GKC antibodies were negative. Lumbar puncture demonstrated increased protein 0.97 g/L with no white cells in the cerebrospinal fluid (CSF). CSF cytology was negative. PCR for VZV and HSV was similarly negative. Further CSF analysis for protein 14-3-3, anti-VGKC, treponema pallidum, JC virus and anti-NMDA-R was negative. EEG showed theta-slowing without evidence of nonconvulsive status epilepticus.

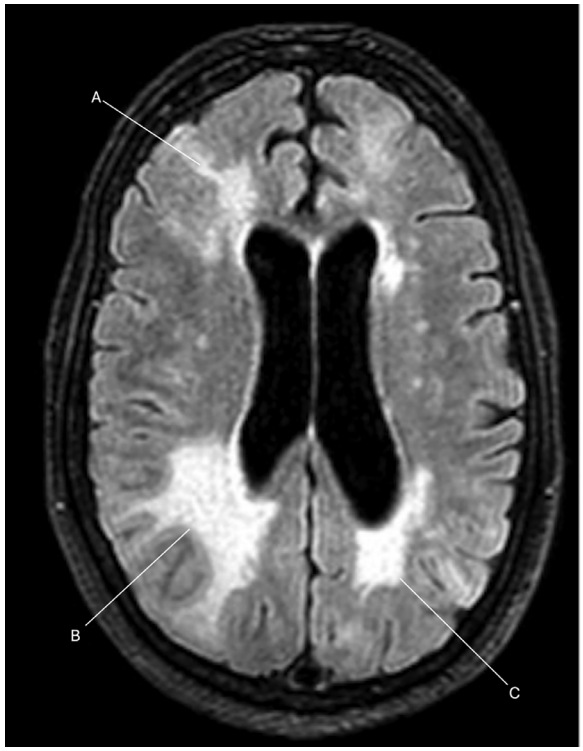

Fig. 1 – FLAIR demonstrating subcortical white matter hyperintensity to right frontal (A) and temporo-parietal (B) and left parietal regions (C), with vasogenic oedema and sulcal effacement.

Magnetic resonance imaging (MRI) of the brain demonstrated subcortical white matter hyperintensity in the right frontal (A) and temporo-parietal (B) and left parietal regions (C), with vasogenic oedema and sulcal effacement on FLAIR (Fig. 1). There were corresponding cerebral microbleeds at the corticomedullary junction on SWI (Fig. 2).

The important differential diagnoses are infective causes, autoimmune causes and malignancy. Infective causes were ruled out based on negative CSF and cultures, and negative auto-antibodies and cytology. The imaging features were not suggestive of malignancy.

Following neuroradiology review, a diagnosis of CAA-ri was made. The diagnosis was based on the clinical presentation and characteristic imaging findings of inflammation and CAA shown in the accompanying figures, and supported by clinicoradiologic diagnostic criteria [1].

Therapeutic intervention

Acyclovir and antibiotics were commenced to treat a suspected infection, based on the clinical presentation. These were ceased following the lumbar puncture results. Dexamethasone was commenced on admission at 4 mg 3 times per day for 2 weeks and weaned. Sodium valproate was continued.

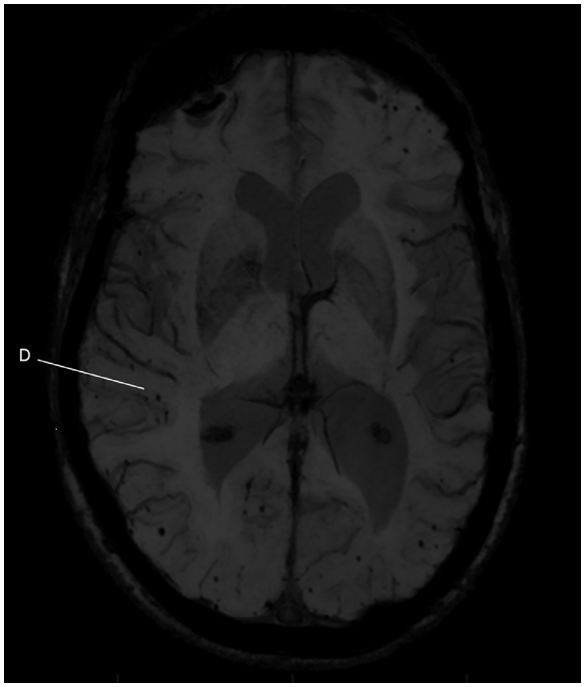

Fig. 2 – SWI demonstrating cerebral microbleeds at the corticomedullary junction (D).

Follow-up and outcomes

Prior to commencing dexamethasone the patient had been confused, agitated and disorientated, requiring constant supervision, redirection and assistance. After commencement of dexamethasone there was progressive improvement in cognitive state, with the patient becoming alert, interactive, able to follow simple commands and was less agitated. After 2 weeks of dexamethasone there had been good clinical improvement and she was discharged to inpatient rehabilitation with a plan to slowly wean the dexamethasone and repeat an MRI. During her inpatient rehabilitation stay she had some ongoing improvement in her delirium. She had no further seizures and was ultimately discharge to an aged care facility.

The patient was transferred to an in-patient rehabilitation unit with significant cognitive improvement at follow-up.

Discussion

CAA is a well described entity characterized by amyloid beta (Aβ) deposition in small and medium-sized blood vessels of the cerebral cortex, leading to lobar micro/macro hemorrhage, and transient or permanent focal neurological episodes [2]. CAA-ri is a rare subtype of CAA, with an estimated incidence of 0.13 per 100,000 [3]. The condition is likely under recognized and may, as a result, be more common [4]. The mean age of onset is in the seventh decade of life, at least a decade earlier than CAA. APOE4 homozygosity has been identified as a risk factor, and was identified in 76.9% of cases in 1 case series [4]. The predisposition is attributed to the proinflammatory response to increased Aβ deposition that this genotype predisposes to [4]. CAA-ri may present with subacute cognitive decline, seen in 48% of cases, seizures (33%) or headaches (33%) or transient behavioral disturbance (27%), and less frequently with focal neurologic deficit [5].

Lumbar puncture typically shows increased CSF protein (80%) and pleocytosis (44%) with an absence of oligoclonal bands generally [5]. CSF amyloid beta antibodies are raised during acute attacks and progressively decrease with treatment [6–8]. This supports the hypothesis of an inflammatory role of Aβ deposition, predisposed by APOE4 genotype. This hypothesis is further supported by similar imaging findings in cases of aseptic meningoencephalitis observed following experimental vaccination to Aβ and Aβ monoclonal antibodies [9,10]. There are no confirmatory blood investigations in CAA-ri but there is a role of blood investigations in ruling out differential diagnoses.

Imaging studies are sufficient to make a diagnosis of CAA-ri as part of clinicoradiological criteria, which have been validated with high sensitivity and excellent specificity [11,12]. MRI demonstrates patchy or confluent T2 weighted white matter hyperintensity in a generally asymmetric pattern [1]. Striking radiological features of vasogenic edema in the frontal and temporal lobes, involving the subcortical white matter, have also been described. They are often multifocal and involve both hemispheres in 30% of patients. Cortical involvement can occur and accounts for seizures in these patients. While typical features of CAA, based on the Boston criteria, are commonly identified, there is a higher incidence of cerebral microbleeds and altered distribution in patients with CAA-ri [13]. There may be gadolinium enhancement of either parenchyma or leptomeninges, more commonly in amyloid-beta related angiitis. Isolated leptomeningeal enhancement has been occasionally identified in cases that do not fulfil clinicoradiologic criteria [11]. Amyloid positron emitted topography (PET) may further aid in clarifying the diagnosis in these cases [14].

Diagnosis of CAA-ri has traditionally relied on pathological confirmation, though this is invasive and may increase morbidity. Histopathology is characterized by amyloid deposition, inflammatory infiltration by lymphocytes, eosinophils and multinucleated giant cells, with pathologic features of both CAA and vasculitis [1]. Two pathological subtypes have been identified; inflammatory CAA, defined by lack of destructive perivascular inflammation, and amyloid-beta-related angiitis (ABRA), defined by transmural or intramural inflammation. This distinction may assist in treatment, as ABRA is more likely to require combination immunosuppression compared to inflammatory CAA (33% vs 12.8%).

While there are no clear imaging features to help differentiate these 2 distinct entities, there has been an association between gadolinium enhancement and ABRA [15]. As pathological diagnosis is highly invasive and not always available, Chung et al [16] developed diagnostic criteria for probable CAA-ri based on clinical and radiological features, which were applied in our case. This consists of clinical features of subacute change in mental state, headache, focal neurology or seizures, in patients with radiological features of CAA based on the Boston criteria, aged 40 or older and with unifocal or multifocal white matter hyperintensity where an alternate ex-

planation is not apparent. Clinical application of the criteria has been validated with 82% sensitivity and 97% specificity [17].

CAA-ri has an effective response to empirical corticosteroids, with 24-month follow up demonstrating nil or minimal disability, albeit with a risk of relapse [5]. In one study conducted over 2.7 years, this cumulative risk was 40% for 1 relapse, 21% for multiple relapses, and a 75% reduced relapse rate in those on ongoing immunosuppressant therapy [17]. For this reason, various steroid-sparing regimens have been attempted including cyclophosphamide and mycophenolate. Follow up MRIs with volumetric analysis have demonstrated correlating reductions in T2 hyperintensities in patients responding to treatment. Kinnecom et al [4] demonstrated an average 78% reduction in lesion size based on longitudinal MRI analyses. Radiological response is more likely in patients on immunosuppressant [17]. Relapses are classically associated by radiological relapse at the same sites as the first flare [4].

In 1 study, 60% of treated patients with CAA-ri reported recovery without relapse [4]. Further studies are needed to compare outcome in treated versus control patients or patients with CAA without CAA-ri.

Conclusion

CAA-ri is likely to be an under recognized but highly treatable complication of CAA. While this may present as subacute cognitive impairment, other presentations include focal neurological deficits or seizures. Increasing use of MRI has improved the diagnosis of such patients. Clinicoradiological criteria offer a less invasive alternative to the previous gold-standard pathological diagnosis, and assist in diagnosis with high sensitivity and specificity. Accurate diagnosis allows directed therapy with high rates of remission and low relapse rates.

Patient consent

Written informed consent was obtained from the patient's next-of-kin and can be provided upon request.

REFERENCES

[1] Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. Ann Neurol 2004;55:250–6.

[2] Shah F, Yazdani S, l'anson M, et al. Cerebral amyloid angiopathy: an underdiagnosed cause of recurrent neurological synptoms. BMJ Case Reports CP 2021;14:e235949.

[3] Sakai K, Ueda M, Fukushima W, Tamaoka A, Shoji M, Ando Y, et al. Nationwide survey on cerebral amyloid angiopathy in Japan. Eur J Neurol 2019;26:1487–93. doi:10.1111/ene.14031.

[4] Kinnecom C, Lev MH, et al. Course of cerebral amyloid angiopathy-related inflammation. Neurology 2007;;68(17):1411-1416.

[5] Corovic A, Kelly S, Markus HS. Cerebral amyloid angiopathy associated with inflammation: a systematic review of clinical and imaging features and outcome. Int J Stroke 2018;13:257–67. doi:10.1177/1747493017741569.

[6] DiFrancesco JC, Longoni M, Piazza F. Anti-Abeta autoantibodies in amyloid related imaging abnormalities (ARIA): candidate biomarker for immunotherapy in Alzheimer's disease and cerebral amyloid angiopathy. Front Neurol 2015;6:207. doi:10.3389/fneur.2015. 00207.

[7] Salvarani C, Hunder GG, Morris JM, Brown RD, Christianson T, Giannini C. Ab-related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. Neurology 2013;81:1596–603. doi:10.1212/WNL.0b013e3182a9f545.

[8] Piazza F, Greenberg SM, Savoiardo M, Gardinetti M, Chiapparini L, Raicher I, et al. Anti-amyloid beta autoantibodies in cerebral amyloid angiopathy-related inflammation: implications for amyloid-modify- ing therapies. Ann Neurol 2013;73:449–58. doi:10.1002/ana.23857.

[9] Ferrer I, Boada Rovira M, Sanchez Guerra ML, Rey MJ, Costa-Jussa F. Neuropathology and pathogenesis of encephalitis following amyloid-beta immunization in Alzheimer's disease. Brain Pathol 2004;14:11–20.

[10] Sperling RA, Jack Jr CR, Black SE, Frosch MP, Greenberg SM, Hyman BT, et al. Amyloid-related imaging abnormalities in amyloid-modifying therapeutic trials: recommendations from the Alzheimer's Association Research Roundtable Workgroup. Alzheimers Dement 2011;7(4):367–85. doi:10.1016/j.jalz.2011.05.2351.

[11] Coulette S, Renard D, Lehmann S, Raposo N, Arquizan C, Charif M, et al. A clinico-radiological study of cerebral amyloid angiopathy-related inflammation. Cerebrovasc Dis 2019. doi:10.1159/000502832.

[12] Auriel E, Charidimou A, Gurol ME, Ni J, Van Etten ES, Martinez- Ramirez S, et al. Validation of clinicoradiological criteria for the diagnosis of cerebral amyloid angiopathy-related inflammation. JAMA Neurol 2016;73:197–202. doi:10.1001/jamaneurol.2015.4078.

[13] Renard D, Tatu L, Collombier L, Wacongne A, Ayrignac X, Charif M, et al. Cerebral amyloid angiopathy and cerebral amyloid angiopathy-related inflammation: comparison of hemorrhagic and DWI MRI features. J Alzheimers Dis 2018;64:1113–21. doi:10.3233/JAD-180269.

[14] Carmona-Iragui M, Fernández-Arcos A, Alcolea D, Piazza F, Morenas-Rodriguez E, Antón-Aguirre S, et al. Cerebrospinal fluid anti-amyloid-b autoantibodies and amyloid PET in cerebral amyloid angiopathy-related inflammation. J Alzheimers Dis 2016;50:1–7. doi:10.3233/jad-150614.

[15] Chu S, Xu F, Su Y, Chen H, Cheng X. Cerebral amyloid angiopathy (CAA)-related inflammation: comparison of inflammatory CAA and amyloid-beta-related angiitis. J Alzheimers Dis 2016;51:525–32. doi:10.3233/JAD-151036.

[16] Chung KK, Anderson NE, Hutchinson D, Synek B, Barber PA. Cerebral amyloid angiopathy related inflammation: three case reports and a review. J Neurol Neurosurg Psychiatry 2011;82(1):20–6.

[17] Regenhart RW, Thon JM, Das AS, Thon OR, Charidimou A, Viswanathan A, et al. Association Between Immunosuppressive treatment and outcomes of cerebral amyloid angiopathy–related inflammation. JAMA Neurol 2020;77(10):1261–9.