Biopsy Proven Cerebral Amyloid Related Inflammation Causing Vasogenic Edema with Midline Shift

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The authors confirm contribution to the paper as follows: Kelly performed literature review, interpretation, and analysis. The manuscript preparation was conducted by Kelly and Spirnak. Dedekam guided and supervised the project. All authors reviewed and approved the final version of the manuscript.

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HUMAN AND ANIMAL RIGHTS
No experiments were performed on human or animal experiments.

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ABSTRACT

Cerebral amyloid angiopathy related inflammation is a rare condition that can present with rapid cognitive impairment, seizures, and headaches. Imaging typically shows the underlying microbleeds and signs of inflammation; however, a brain biopsy is needed for a definitive diagnosis. Once diagnosed, treatment tends to be immunosuppression. Here, we present a severe case confirmed with brain biopsy with classic imaging of this infrequently seen condition.

CASE REPORT

BACKGROUND

Cerebral amyloid angiopathy related inflammation (CAAri) is a rare but treatable rapidly progressive dementia. With the rarity of this disease, this patient's presentation provides exposure to classic clinical symptoms of CAAri and its associated radiographic features. Additionally, this case exemplifies the reversibility of symptoms and radiographic changes that can come with appropriate treatment. Given its therapeutic potential, this case demonstrates that it is imperative to readily keep this condition's clinical presentation and radiographic features in consideration.

CASE REPORT

68-year-old female without significant past medical history presented to the hospital for rapid decline in cognition. For one week prior to hospital presentation, the patient noticed difficulty with simple mathematical calculations, such as trouble determining the tip at a restaurant. She also noticed mild disequilibrium for the week preceding hospital presentation. She then began to have a new, severe headache, visual hallucinations, and confusion to the point of getting lost in her own house. This confusion concerned the patient enough for her to seek medical care by ambulance.

Imaging Findings

CT head on admission was notable for vasogenic edema in the right temporal and parietal lobes.

Axial post-contrast T2 FLAIR images (A and B) shows extensive vasogenic edema with cortical involvement affecting the right temporal, parietal and occipital lobes, causing 8 mm of leftward midline shift. Axial GRE (C) shows scattered cortical/

subcortical microhemorrhages. Axial post-contrast T2 FLAIR (D) shows marked improvement in edema with mild residual edema in the right occipital lobe following treatment.

Management

Serum labs were unremarkable for infectious or inflammatory causes. CSF studies were consistent with an inflammatory process with elevated protein and negative cultures, polymerase chain reaction (PCR) test, and cytology. Electroencephalogram (EEG) was without seizure or epileptiform discharges. She underwent brain biopsy that showed fibrinoid vasculopathy, perivascular inflammation, and hemosiderin deposition. The patient's symptoms rapidly improved following the first dose of immunosuppressing treatment with steroids. Her clinical presentation, radiographic findings, neuropathologic findings, and robust response to immunosuppression were consistent with a diagnosis of cerebral amyloid angiopathy related inflammation. She had no neurologic deficits on examination upon discharge. She was advised to avoid anticoagulation of anti-platelet agents unless a strong indication arose. Normotension was recommended.

Follow Up

She continued to have mild word finding difficulty, calculation problems, and misplaced items more frequently but was able to return fully to her activities of retired life. Though her imaging findings greatly improved, her imaging did not return to normal. Given this, patient was treated with a week of steroid infusions and longer-term cyclophosphamide. This immunosuppression was discontinued after 3 months due to radiographic stability and intolerable medication side effects of urinary urgency and diarrhea.

DISCUSSION

Cerebral amyloid angiopathy related inflammation (CAAri) is a rare condition caused by an inflammatory response to amyloid protein deposition in the walls of cerebral blood vessels. The prevalence is about 30 cases per 100,000 people [1]. It is also known as congophilic amyloid angiopathy or amyloid-β-related angiitis. Diagnostic criteria for this disease process were introduced in 2010 and validated in 2016 [2].

Etiology & demographics

The condition tends to affect patients in their 5th to 6th decade of life [1]. A diagnostic criterion is that the patient is equal to or greater than 40 years old [2]. A retrospective study of 15 patients showed a range of ages from 40-90 years old with 7:8 male to female ratio [3].

The etiology and pathogenesis of CAAri is not known. It is suspected that CAAri results from an autoimmune reaction to the amyloid protein deposition within the cerebral blood vessels' walls [2]. This immune response is supported by the condition's robust response to immunosuppression with steroids. Additionally, a case series evidenced elevated anti-Aβ autoantibodies in the CSF of patients during their acute symptomatic presentation with these antibody levels reducing following remission of disease also suggesting an autoimmune etiology [2].

Clinical & imaging findings

Clinically, patients with CAAri have rapidly progressive dementia with other neurologic features. Patients typically present with an acute to subacute onset of headache, cognitive decline, seizure, behavior change, and focal neurologic deficit. Absence of neoplastic, infectious, or other cause is a component of the diagnostic criteria. Radiographically, the diagnostic criteria include specific brain MRI features. These features include cerebral hemorrhagic lesions (micro- or macro-bleeds, or superficial siderosis) and T2-weighted or FLAIR sequence findings of unifocal or multifocal, asymmetric, cortico-subcortical white matter hyperintensities [2, 4]. Though cerebrospinal fluid (CSF) studies are not required to diagnose CAAri, consistent CSF findings are pleocytosis, high concentrations of anti- Aβ autoantibodies, and absence of neoplastic or infectious characteristics [2]. Definite diagnosis requires supporting neuropathologic evidence [2]. Histopathological features of the affected brain region in CAAri are intramural or perivascular inflammation and amyloid deposits in blood vessel walls [1].

Treatment & prognosis

There are no standard treatment recommendations; however, most patients are treated with immunosuppression, typically with a pulse of high-dose steroids [1, 2, 4]. Some consider cytostatic agents like we did with our patient [4, 5]. The end goal to immunosuppressive treatment is not clear whether clinical remission is sufficient or if radiographic resolution is needed as well. Patients typically do well with over 80% clinically improving and 13% remaining clinically stable with improvement being more likely if treated with immunosuppression [7]. Some patients do spontaneously achieve clinical and radiographic remission without treatment [2, 7]. Though CAAri is thought to be steroid responsive and reversible, not all patients improve. Mortality rates vary but are seen to be as high as 10% [1]. Some patients can have relapses following cessation of treatment [1, 3]. Due to the risk of spontaneous hemorrhage with the underlying amyloid deposition in the blood vessel walls, it is recommended to balance risks and benefits when considering use of anticoagulants and antiplatelets for other indications [8]. Additionally, because of this risk for spontaneous hemorrhage, normotension is recommended [8].

Differential Diagnosis

The differential diagnosis for a patient presenting with features of CAAri includes vasculitis, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), infiltrating glioma, neurosarcoidosis, autoimmune encephalitis, and reversible

cerebral vasoconstrictive syndrome (RCVS) [1, 2, 4]. The CAAri diagnostic criteria facilitate delineation of the appropriate diagnosis with an 82% and 97% sensitivity and specificity, respectively, for probable disease [6]. Biopsy of the affected region can solidify the diagnosis definitively.

TEACHING POINT

The radiographic features required for diagnosis of "probable" CAAri include characteristic cerebral hemorrhagic and white matter lesions. Hemorrhagic lesions include microbleeds, macrobleeds, or superficial siderosis; which are best demonstrated as signal loss on T2*-weighted sequences. White matter lesions include asymmetric areas of white matter T2/FLAIR hyperintensity, which extend to the subcortical white matter. Of note, the presence of symmetric white matter lesions extending to the subcortical white matter would only meet criteria for "possible" CAAri.

Typical clinical and radiographic presentation can suggest a diagnosis of probable CAAri with high sensitivity and specificity; however, neuro-histopathologic evidence is required for definite diagnosis (Summary Table).

QUESTIONS

Question 1: Which of the following would not be a symptom/sign of CAAri?

1. Cognitive decline
2. Headaches
3. Seizures
4. Behavior change
5. Fasciculations (applies)

Explanation for question 1 [Patients typically present with an acute to subacute onset of headache, cognitive decline, seizure, behavior change, and focal neurologic deficit.] Lower motor neuron or peripheral neurologic signs would not be expected.

Question 2: What treatments are considered for CAAri?

1. Immunosuppression (applies)
2. Anticoagulation
3. Antiplatelet agents
4. Normotension (applies)
5. Monitoring and supportive care (applies)

Explanation for question 2

1. Immunosuppression [most patients are treated with immunosuppression, typically with a pulse of high-dose steroids]
2. Anticoagulation [Due to the risk of spontaneous hemorrhage with the underlying amyloid deposition in the blood vessel walls, it is recommended to balance risks and benefits when considering use of anticoagulants and antiplatelets for other indications]
3. Antiplatelet agents [Due to the risk of spontaneous hemorrhage with the underlying amyloid deposition in the blood vessel walls, it is recommended to balance risks and benefits when considering use of anticoagulants and antiplatelets for other indications]
4. Normotension [Additionally, because of this risk for spontaneous hemorrhage, normotension is recommended]
5. Monitoring and supportive care [Some patients do spontaneously achieve clinical and radiographic remission without treatment]

Question 3: How can CAAri be definitively diagnosed?

1. CAAri is diagnosed clinically
2. CAAri is diagnosed by radiographic features
3. CAAri is diagnosed by EEG findings
4. CAAri is diagnosed with brain biopsy (applies)
5. CAAri is diagnosed by its steroid responsiveness

Explanation for question 3

[neuro-histopathologic evidence is required for definite diagnosis]

Question 4: What are radiographic features found in CAAri?

1. Micro-bleeds (applies)
2. Macro-bleeds (applies)
3. Superficial siderosis (applies)
4. Unifocal cortico-subcortical white matter hyperintensities (applies)
5. Multifocal cortico-subcortical white matter hyperintensities (applies)

Explanation for question 4

[Radiographically…features include cerebral hemorrhagic lesions (micro- or macro-bleeds, or superficial siderosis) and T2-weighted or FLAIR sequence findings of unifocal or multifocal, asymmetric, cortico-subcortical white matter hyperintensities]

Question 5: The underlying etiology of CAAri is?

1. The complete understanding of the etiology of CAAri is unknown (applies)
2. Autoimmune (applies)
3. Neoplastic
4. Vascular (applies)
5. Metabolic

Explanation for question 5

1. The complete understanding of the etiology of CAAri is unknown [The etiology and pathogenesis of CAAri is not known]
2. Autoimmune [It is suspected that CAAri results from an autoimmune reaction to the amyloid protein deposition within the cerebral blood vessels' walls [2]. This immune response is supported by the condition's robust response to immunosuppression with steroids. Additionally, a case series evidenced elevated anti-Aβ autoantibodies in the CSF of patients during their acute symptomatic presentation with these antibody levels reducing following remission of disease also suggesting an autoimmune etiology]
3. Neoplastic [It is suspected that CAAri results from an autoimmune reaction to the amyloid protein deposition within the cerebral blood vessels' walls]
4. Vascular [It is suspected that CAAri results from an

autoimmune reaction to the amyloid protein deposition within the cerebral blood vessels' walls]

5. Metabolic [It is suspected that CAAri results from an autoimmune reaction to the amyloid protein deposition within the cerebral blood vessels' walls]

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FIGURES

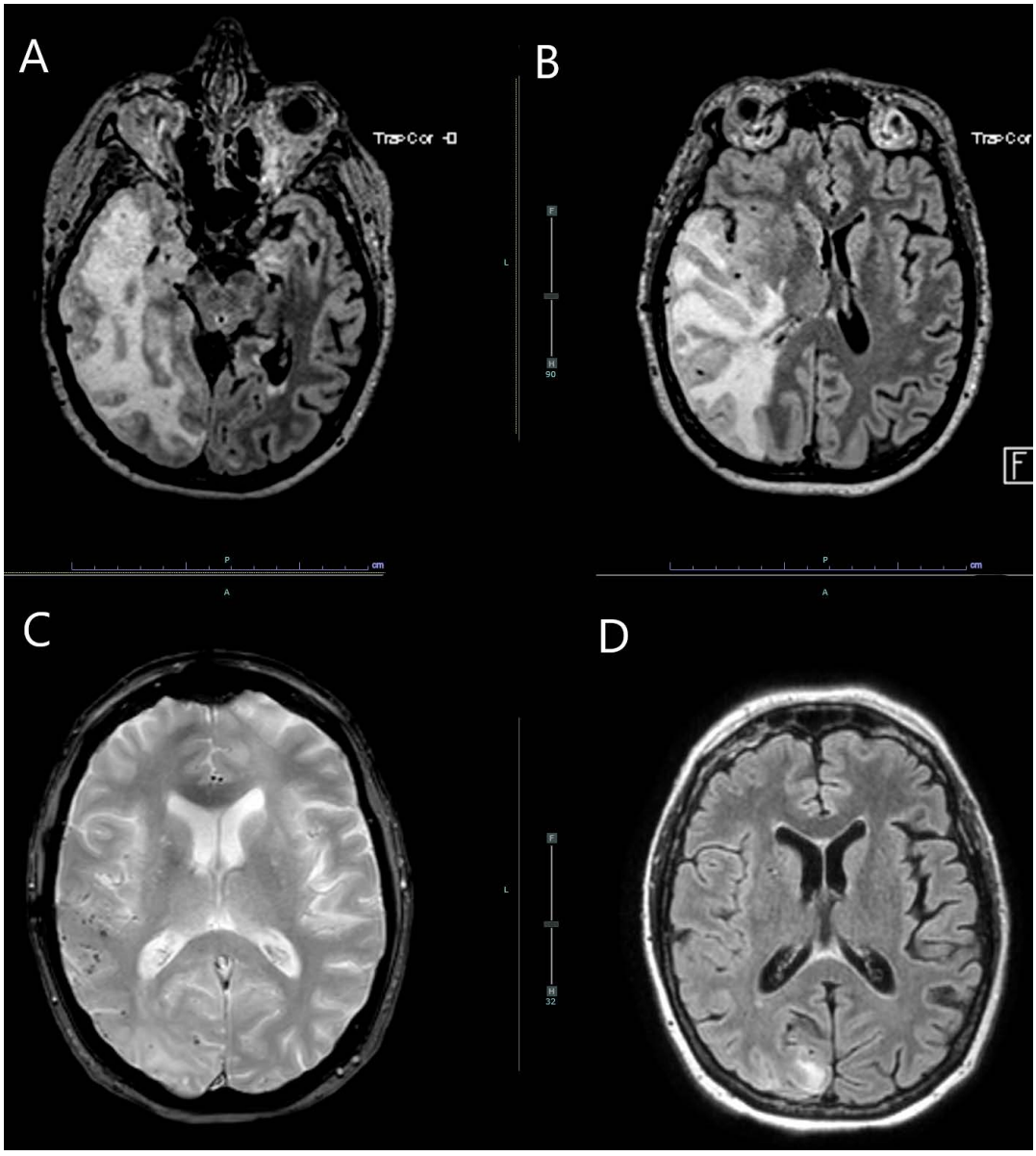

Figure 1: Axial post-contrast T2 FLAIR images (A and B) showing extensive vasogenic edema with cortical involvement affecting the right temporal, parietal and occipital lobes, causing 8 mm of leftward midline shift. Axial GRE (C) shows scattered cortical/subcortical microhemorrhages. Axial post-contrast T2 FLAIR (D) shows marked improvement in edema with mild residual edema in the right occipital lobe following treatment.

Summary table

Etiology	Unknown but thought to be autoimmune
Incidence	30 cases per 100,000 people
Gender ratio	7:8 male to female ratio
Age predilection	5th to 6th decade of life
Risk factors	ApoE genotype
Treatment	Immunosuppression
Prognosis	Good
Imaging findings	-Cerebral hemorrhagic lesions that can be microbleeds or macrobleeds or superficial siderosis -T2-weighted or FLAIR sequence findings of unifocal or multifocal, asymmetric, cortico-subcortical white matter hyperintensities

KEYWORDS

Amyloid; Cerebral amyloid angiopathy related inflammation; Rapidly progressive dementia; Cortical microbleeds; Superficial siderosis; Steroid responsive encephalopathy; Brain biopsy

ABBREVIATIONS

CAARI = Cerebral Amyloid Angiopathy Related Inflammation
CSF = Cerebro Spinal Fluid
EEG = Electro Encephalo Gram
MRI = Magnetic Resonance Imaging
PCR = Polymerase Chain Reaction
PRES = Posterior Reversible Encephalopathy Syndrome
PML = Progressive Multifocal Leukoencephalopathy
RCVS = Reversible Cerebro-Vasoconstrictive Syndrome

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