

Cerebral Amyloid Angiopathy (CAA)-Related Inflammation: Comparison of Inflammatory CAA and Amyloid- β -Related Angiitis

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Abstract. Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a relatively rare syndrome of reversible encephalopathy and could be divided into two subtypes of inflammatory CAA (ICAA) and amyloid- β -related angiitis (ABRA) according to histopathology. We present a case of pathologically proved ABRA with partial seizures and headache, and a focal lesion in the right temporal lobes on magnetic resonance imaging. Summarized from previous 139 ABRA and ICAA cases, ABRA is preferred when the lesion is enhanced on MRI and requires combination drug therapy, while ICAA is highly suspected with ApoE genotype of $\epsilon 4/\epsilon 4$. More clinical markers for diagnosis of CAA-ri warrant further researches.

Keywords: Amyloid- β -related angiitis, cerebral amyloid angiopathy, cerebral amyloid angiopathy-related inflammation, inflammatory cerebral amyloid angiopathy

INTRODUCTION

Cerebral amyloid angiopathy (CAA) refers to the deposition of amyloid- β in the media and adventitia of small- and medium-sized arteries (and less frequently, veins) of the cerebral cortex and the leptomeninges [1]. The common presentation is spontaneous cerebral lobar hemorrhage

occurring in elderly patients with normal blood pressure [2]. Cerebral amyloid angiopathy-related inflammation (CAA-ri) is a relatively rare syndrome of CAA characterized clinically by acute or subacute encephalopathy, focal neurologic signs, headache, and seizures, and radiographically by asymmetric hyperintensities on T2-weighted or fluid attenuated inversion recovery (FLAIR) images [3]. Histopathology of the brain biopsy makes a definite diagnosis. CAA-ri includes two pathological subtypes: perivascular cuffing (inflammatory CAA, ICAA) and transmural or intramural inflammation (amyloid- β -related angiitis, ABRA) of vessels with amyloid deposition [4]. To date, several reviews

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on CAA-ri cases have been published, but none of them focused on the comparison between ICAA and ABRA. Herein, we report a patient with pathologically confirmed ABRA who complained of seizures and presented as a focal lesion of T2-hyperintensity without enhancement on magnetic resonance imaging (MRI), and summarize clinical characteristics of total 100 ABRA cases and 39 ICAA cases.

Case report

A 63-year-old left-handed male presented with a simple partial seizure in both upper limbs in 2008. He experienced another similar seizure and began to feel headache in the right temporal region two months before admission. He had no history of smoking, diabetes, hypertension, or exposure to toxic chemicals or drugs. The patient had a history of drinking with a

quantity of 100 grams of spirits per day. No hereditary diseases, tumors, or immunological diseases were recorded in his family. At admission his blood pressure was 120/80 mmHg. Physical examination was unremarkable. Laboratory tests at admission were all within normal limits.

MRI demonstrated an infiltrating lesion in the right temporal lobes with involvement of gray and white matter. The lesion was characterized by slightly hypointense on T1-weighted images (Fig. 1A) and heterogeneously hyperintense on FLAIR and T2-weighted images (Fig. 1B, D). No abnormal contrast enhancement or obvious intracranial hemorrhage sign was identified (Fig. 1C). MRI findings were judged to be consistent with inflammation. The possibility of low-grade glioma could not be ruled out.

On August 10, 2011, the patient underwent excision of the right temporal lesion. During the surgery,

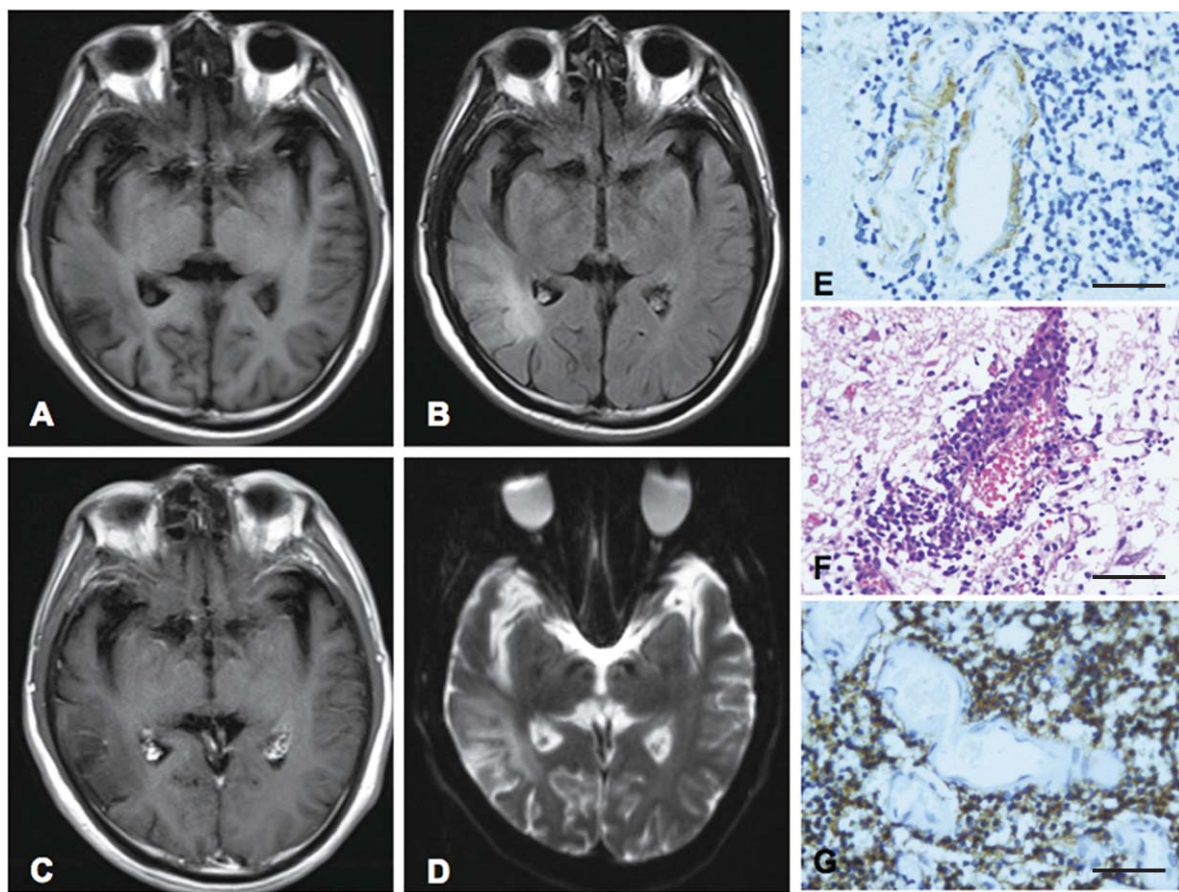


Fig. 1. A) The lesion in the right temporal white matter shows slightly hypointense on T1WI. B, D) The lesion shows heterogeneously hyperintense on FLAIR and T2WI. C) No abnormal contrast enhancement was identified. Histopathology was shown in Fig. 1E–G. Bar: 25 μ m. E) Immunohistochemical staining ($\times 400$) for amyloid- β showing moderate to severe deposition of amyloid in the cerebral vessel walls. F) Perivascular cuffing with lymphocytes infiltration, fibrinoid necrosis and erythrocyte extravasation (Hematoxylin-eosin staining $\times 400$). G) LCA positive lymphocytes around the cerebral vessels (immunohistochemical staining $\times 400$).

the macroscopic abnormal brain tissue in the right temporal lobe was excised. A histopathologic examination of the surgery specimen revealed moderate to severe deposition of amyloid- β in the cerebral vessel walls (Fig. 1E). The vessel wall was infiltrated and destructed by lymphocytes, with erythrocyte extravasation (Fig. 1F). LCA positive lymphocytes were around the cerebral vessels (Fig. 1G). The pathological diagnosis was ABRA. Due to some social factors, the patient did not receive immunosuppressant therapy and was discharged from the hospital after recovery from the surgery with modified Rankin scale (mRS) score of 1, without further examinations of susceptibility weighted imaging (SWI), ApoE genotype, cerebrospinal fluid (CSF), or detailed cognitive tests. He felt slight headache in the right temporal region occasionally and remained seizures free 4 years after surgery. Intact gross cognition was found through telephone follow-up, with Mini-Mental State Examination (MMSE) testing the ability of orientation, registration, attention, calculation, recall, and repetition.

METHODS

Search strategy

We carefully searched articles published in English from the PubMed and Cochrane Library databases from 1987 to July 2015. The following terms were used as keywords: “cerebral amyloid angiopathy AND inflamm*”, “amyloid beta AND angiitis”, “cerebral amyloid angiitis”, “granulomatous angiitis AND cerebral amyloid angiopathy”, “primary angiitis of the CNS AND cerebral amyloid angiopathy”, “giant cell arteritis AND cerebral amyloid angiopathy”. By hand screening references of literature reviews on this subject, we also identified the additional citations. For repeated cases in different articles, preference was given to the one with more comprehensive clinical data. The flow chart of the review was showed in Fig. 2.

Study selection

We selected all types of case reports and cohort studies with pathologically proven CAA-ri. Clinical information was extracted from each article as followings: pathological subtypes (ABRA or ICAA), age, gender, past history, clinical manifestations, ApoE genotype, MRI findings (imaging features, location of lesions, enhancement, and

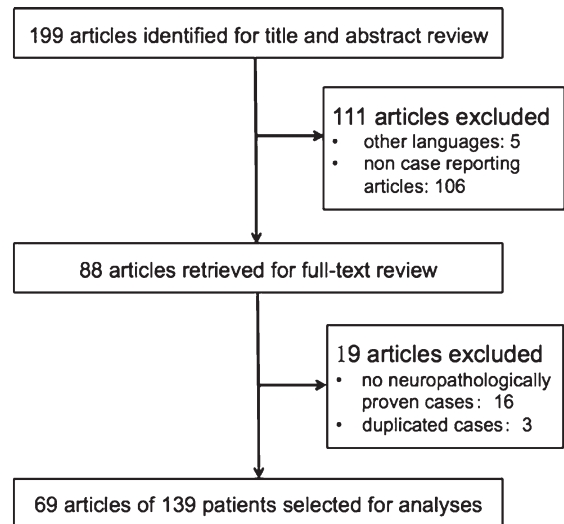


Fig. 2. Flow chart of articles selection process.

cerebral microbleeds on SWI), other examinations, CSF results, treatment strategy, responses to therapy, and outcomes showing as mRS scores. Two reviewers (S Chu and Y Su) independently did the data extraction and if there was a disagreement about the classification, a third reviewer (X Cheng) was consulted.

Statistical analyses

We divided all the patients into two groups of ABRA and ICAA and compared their differences of clinical data. Continuous data were presented as median. Categorical data were presented as number and percentage of patients.

RESULTS

Here we summarized clinical data of 170 patients with probable or definite CAA-ri including ours. We carefully categorized the 139 pathologically confirmed cases into two subtypes of ABRA and ICAA, and compared the clinical data, trying to find specific features of either subtype except for pathological findings (Table 1) [3–5, 7–73].

A total of 100 ABRA and 39 ICAA patients were included in this review. There were almost no differences in baseline characteristics of age (67.2 years and 67.3 years of each group) and gender. The past history of cerebral vascular diseases was similar in ABRA (16.7%) and ICAA (18.2%) patients. Previous history of headache and tumor was only found in

Table 1
Comparison of clinical features, imaging findings and cerebral spinal fluid (CSF) results between amyloid- β related angiitis (ABRA) and inflammatory cerebral amyloid angiopathy (ICAA)

	ABRA	ICAA
No.	100	39
Age	67.2	67.3
Gender, female	49/100 (49.0)	15/39 (38.5)
ApoE genotype		
$\epsilon 4/\epsilon 4$	0/4 (0)	13/17 (76.5)
$\epsilon 3/\epsilon 3$	2/4 (50.0)	1/17 (5.9)
$\epsilon 2/\epsilon 3$	2/4 (50.0)	3/17 (17.6)
Past history		
Headache	2/24 (8.3)	0/11 (0)
Tumor	6/24 (25)	0/11 (0)
Dementia	2/24 (8.3)	4/11 (36.4)
Cerebral vascular diseases	4/24 (16.7)	2/11 (18.2)
Clinical manifestations		
Headache	39/100 (39.0)	12/39 (30.8)
Confusion	26/100 (26.0)	7/39 (17.9)
Cognitive decline and/or behavioral changes	55/100 (55.0)	25/39 (64.1)
Focal neurological deficits	31/100 (31.0)	11/39 (28.2)
Seizures	35/100 (35.0)	25/39 (64.1)
Visual symptoms (any type)	20/100 (20.0)	9/39 (23.1)
Gait abnormalities	11/100 (11.0)	6/39 (15.4)
Higher brain dysfunction	9/100 (9.0)	5/39 (12.8)
Treatment		
Steroids alone	31/100 (31.0)	24/39 (61.5)
Steroids + cyclophosphamide	26/100 (26.0)	5/39 (12.8)
Steroids + cyclophosphamide, then azathioprine	7/100 (7.0)	0/39 (0)
No therapy	12/100 (12.0)	10/39 (25.6)
Reponses to therapy		
Improvement without relapse	46/75 (61.3)	25/39 (64.1)
Improvement with relapse	16/75 (21.3)	10/39 (25.6)
Deterioration	13/75 (17.3)	4/39 (10.3)
Outcomes		
mRS 0–3	49/83 (59.0)	14/26 (53.8)
mRS 4–5	15/83 (18.1)	6/26 (23.1)
Death	19/83 (22.9)	6/26 (23.1)
MRI Imaging features		
T2 hyperintensities	77/100 (77.0)	31/39 (79.5)
Strictly leptomeningeal enhancement	9/100 (9.0)	4/39 (10.3)
Lobar hemorrhage	2/100 (2.0)	1/39 (2.6)
Location of lesions		
Bilateral	21/46 (45.7)	21/28 (75.0)
Left	8/46 (17.4)	2/28 (7.1)
Right	17/46 (37.0)	5/28 (17.9)
Enhancement on MRI	44/66 (66.7)	10/32 (31.3)
Meningeal	37/66 (56.1)	9/32 (28.1)
Intracerebral	7/66 (10.6)	2/32 (6.3)
Cerebral microbleeds on SWI	13/14 (92.9)	20/21 (95.2)
Angiography abnormalities	1/13 (7.7)	1/5 (20.0)
^{11}C -PiB PET showing amyloid- β deposition	0/1 (0)	2/2 (100.0)
EEG		
Epileptiform abnormalities	1/6 (16.7)	5/25 (20.0)
Slow activities	4/6 (66.7)	19/25 (76.0)
CSF		
Protein >450 mg/L	52/66 (78.8)	10/16 (62.5)
WBC pleocytosis	22/66 (33.3)	4/16 (25.0)
Lymphocytic pleocytosis	13/66 (19.7)	1/16 (6.3)

mRS, modified Rankin Scale; MRI, magnetic resonance imaging; SWI, susceptibility weighted imaging; EEG, electroencephalogram. Continuous data are presented as median. Categorical data are presented as number and percentage of patients.

ABRA (8.3% and 25%), while history of dementia was more common in ICAA compared with ABRA (36.4% versus 8.3%). Among the most common clinical manifestations in CAA-ri patients, it seemed that only seizure had a tendency for ICAA (64.1% versus 35.0%). Others including cognitive decline and/or behavioral changes, headache, focal neurological deficits, confusion, visual symptoms, gait abnormalities, and higher brain dysfunction showed no differences between ICAA and ABRA.

ICAA showed a preference for ApoE genotype of $\epsilon 4/\epsilon 4$ (76.5%), while ABRA of $\epsilon 3/\epsilon 3$ and $\epsilon 2/\epsilon 3$. The CSF results manifested as inflammatory changes with elevated protein levels (78.8% in ABRA versus 62.5% in ICAA) and lymphocytic pleocytosis (19.7% in ABRA versus 6.3% in ICAA).

The general presentation of the initial MRI since symptoms was bilateral asymmetric subcortical focal or diffuse lesions of T2 hyperintensity (77.0% in ABRA versus 79.5% in ICAA), with or without vasogenic edema or mass effect, in the temporal, occipital, and frontal lobes. Multiple cerebral microbleeds (CMBs) existed in 94.3% of 35 CAA-ri patients undergoing T2-weighted gradient echo (T2-GRE) or SWI, while the cortical superficial siderosis (cSS) was found in 3 cases. The findings of CMBs and cSS in two subtypes were quite similar. Gadolinium contrast enhancement on MRI was found in 66.7% of ABRA and 31.3% of ICAA, because of the less involvement of vessel walls in ICAA than ABRA.

Steroids were used in 78.0% of ABRA and 74.4% of ICAA. More than half of the patients could return to independency for daily life both in groups of ABRA (59.0%) and ICAA (53.8%). The combination therapy with steroids and immunosuppressant drugs was more needed in patients with ABRA (33.0%) than in those with ICAA (12.8%), leading to the similar proportions of improvement and status of mRS ≤ 3 .

DISCUSSION

CAA-ri involves the coexistence of vascular amyloid deposition and inflammatory infiltration by lymphocytes, eosinophils, and multinucleated giant cells, leading to clinical and imaging features of both CAA and central nervous system vasculitis and a good response to corticosteroid [3].

The typical symptoms of CAA-ri at presentation include acute or subacute headache, cognitive decline and/or behavioral changes, seizures, and focal neu-

rological deficits [1]. As a non-invasive method, MRI is the first and the most important examination in suspected cases of CAA-ri. The imaging criteria for CAA-ri proposed by Chung et al. included two aspects: 1) patchy or confluent T2 or FLAIR hyperintensities which were usually asymmetric, with or without mass effect and with or without leptomeningeal or parenchymal enhancement; 2) evidence of pre-existing CAA on SWI of multiple cortical and subcortical hemorrhages or microhemorrhages and/or recent or past lobar hemorrhage [4]. Amyloid deposition and related inflammatory factors within the vascular walls contributed to hypoperfusion to vulnerable areas of white matter and led to the imaging changes on MRI. Since lobar hemorrhage is not that common in patients with CAA-ri, these two radiographic markers of CMBs and cSS for CAA are greatly helpful to make a diagnosis without brain biopsy. Other MRI images include strictly leptomeningeal enhancement (13 cases), lobar hemorrhage (3 cases), multiple infarcts with multifocal attenuation of intracranial vessels (1 case), and significant mass effect of the entire right hemisphere (1 case). These findings suggested that the diagnosis of CAA-ri could not be excluded even without characteristic T2-hyperintensities.

The definite diagnosis of CAA-ri still requires biopsy. According to the pathology, CAA-ri could be divided into two subtypes. ICAA is perivascular infiltration around the vessel wall, and ABRA is characterized by transmural and intramural inflammation, often with granulomas formation [5]. Recently, some have proposed ABRA as a subset of primary central nervous system vasculitis (PCNSV) other than CAA. ABRA was detected in approximately 30% of PCNSV and featured prominent contrast enhancement on MRI, showing rapid clinical improvement and resolution of MRI lesions with response to corticosteroid [6]. Clinicians have noted the clinical differences between ICAA and ABRA, however, without basis on data.

From our review of a total of 139 pathologically proved patients, there are some possible non-invasive markers for distinguishing ABRA from ICAA. The ApoE genotype of $\epsilon 4$ allele was considered to promote A β deposition on the vessel wall [73], and it was much more likely to be found in ICAA. But only 4 ABRA cases (4%) were tested for ApoE genotype, so more data are needed for confirmation of the difference.

Gadolinium contrast enhancement on MRI, especially the meningeal enhancement, could be a

potential imaging marker for the differential diagnosis of ABRA and ICAA. However, a previous review of literature and our case showed an absence of enhancement on MRI images [5]. It means that the blood-brain barrier had remained intact, possibly indicating a lack of capillary involvement by the amyloid process. These differences might be attributed to the extent of involvement and severity of destruction to the vessel wall from inflammation. To our knowledge, not only for diagnosis, contrast enhancement could be a predictor for prognosis of CAA-ri. One review of 39 cases suggested a mortality of 5.3% among 19 patients in leptomeningeal status versus 35% among 20 without enhancement [38].

The past history of headache, tumor, dementia, and the clinical presentation of seizures have shown some differences between the two groups. Considering that these were relatively non-specific manifestations and complete previous history was recorded in less than a quarter of all patients, we did not regard these findings as differential markers. Some new CSF biomarkers such as A β 40, A β 42, tau, P-181 tau, IL-6/8 and anti-A β autoantibodies have been used for the auxiliary diagnosis of CAA-ri to avoid an invasive procedure such as brain biopsy [56]. But with only 5 reported cases of all CAA-ri patients, one could not estimate its diagnosis and differential diagnosis value.

Corticosteroid pulse therapy is the first choice for CAA-ri cases. The addition of cyclophosphamide and azathioprine could be salvage therapy for steroid-resistant patients. While in our case, the patient underwent excision of the right temporal lesion due to the suspicion of glioma. In summary, among 139 CAA-ri cases including ours, 4 patients received excision of the intracranial lesion, with 2 of total improvement and 2 of death after surgery. In consideration of good responses to steroids therapy, brain biopsy was recommended first for the diagnosis, not for the treatment.

Since CAA-ri is a rare disease, our literature review is limited by the small number of cases and incomplete clinical data available for comparison, and selection bias. The relative fragile data from articles identified most of which are case reports, make statistical results imprecise. Further large cohort studies are needed.

CONCLUSION

As one of the most important features for diagnosis, asymmetric T2 hyperintensities, meningeal

enhancement, multiple CMBs and cSS are imaging markers for CAA-ri. Although the therapy strategies differ, it is difficult to separate ABRA from ICAA only with clinical and imaging information. Enhancement on MRI might be a contributory factor for ABRA and ApoE ϵ 4/ ϵ 4 for ICAA. Further investigations are needed to confirm the relationship between clinical findings and diagnosis and prognosis.

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