

# Cerebral Amyloid Angiopathy Associated with Inflammation: Report of 3 Cases and Systematic Review

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**Introduction:** Cerebral amyloid angiopathy associated with inflammatory process (CAA-I) is a rare potentially treatable encephalopathy, characterized by an inflammatory response to vascular deposits of  $\beta$ -amyloid. We aimed to describe 3 clinical cases and perform a systematic review of all neuropathologically proved CAA-I case reports to describe its clinical and pathologic features and outcome under different treatments. **Methods:** We searched PubMed and Cochrane Library and screened references of included studies and review articles for additional citations. Outcome was classified at the last available follow-up by the modified Rankin Scale (mRS). **Results:** A total of 67 publications, reporting on 155 patients, were included. Mean age was 66.9 years, and 53.5% were men. The most common clinical presentation was cognitive dysfunction (48.0%) followed by headaches (38.7%), seizures (36.7%), and pyramidal signs (20.0%). Perivascular and vasculitic inflammation with granuloma was the most common pathologic pattern (27.5%). Eighty-six percent were treated with corticosteroids and 33.9% with cyclophosphamide. Forty-two percent regained independence (mRS score 0-2), whereas 20.5% were left with a severe handicap (mRS score 3-5) and 37.5% died. There were no statistically significant differences in outcome between patients treated with therapy with corticosteroids alone comparing with those treated with combination corticosteroids with cytostatic agents. **Conclusions:** The most common clinical manifestation of CAA-I was cognitive dysfunction. The functional outcome was unfavorable in the majority of the patients, with death or severe disability in almost two third of the cases, despite treatment. No differences in outcome could be detected between patients treated with corticosteroids versus patients treated with cytostatics, combined with corticosteroids. **Key Words:** Cerebral amyloid angiopathy—related inflammation—amyloid angiopathy—cerebral vasculitis—steroids—cytostatics—brain biopsy.

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## Introduction

Cerebral amyloid angiopathy (CAA) is associated with intracerebral hemorrhage in the elderly population, dementia, small cerebral infarctions,<sup>1</sup> and less frequently to an inflammatory response to vascular deposits of  $\beta$ -amyloid.<sup>2,3</sup>

In the last decades, a few case reports described a subset of patients with CAA exhibiting headaches, seizures, cognitive impairment, and white matter lesions with or without gadolinium enhancement. These patients had neuropathologic evidence of a CAA-associated vascular inflammatory process (CAA-I), potentially responsive to immunosuppression. This condition has been categorized into 2 groups accordingly to pathologic findings: cerebral amyloid angiopathy-related inflammation (CAA-ri), which is characterized by perivascular inflammatory infiltration and amyloid  $\beta$ -related angiitis (ABRA) that is distinguished from the former by the presence of severe vasculitic transmural inflammation with or without granuloma formation.<sup>4-6</sup> Although several reports described the clinical picture associated with CAA-I, its outcome and effect of treatments have received less attention.

We aimed to present 3 clinicopathologic cases of CAA-I and a systematic review of all neuropathologically proven CAA-I case reports (either CAA-ri or ABRA) to describe its clinical and pathologic features, outcome, and effect of immunosuppressive treatments.

## Case Reports

### *Patient 1*

A 63-year-old male patient with a medical history of hypertension, diabetes mellitus type 2, and ischemic cardiomyopathy was admitted to our department with a 2-month history of mild left parietal headache, slight memory complaints, gait unsteadiness, and bilateral photopsias with 1 week of duration. On admission, bilateral dysmetria in finger-to-nose test was observed. His brain computed tomographic (CT) scan showed bilateral cortico-subcortical temporo-occipital hypodensities, and brain magnetic resonance imaging (MRI) (Fig 1, A,B) revealed extensive temporo-occipital vasogenic edema without contrast enhancement, with bilateral cortico-subcortical hemorrhagic component and diffuse microbleeds. Blood analysis including erythrocyte sedimentation rate, C-reactive protein, autoimmunity, serum protein electrophoresis, angiotensin-converting enzyme, and adenosine deaminase were normal. Carotid triplex scan and transcranial Doppler revealed a left internal carotid 30% stenosis. Electroencephalogram was unremarkable. After admission, he developed transient visual hallucinations and was treated with valproic acid 500 mg twice a day. He remained normotensive and was discharged with the diagnosis of probable CAA-I. Three days later, he was readmitted because of worsening of

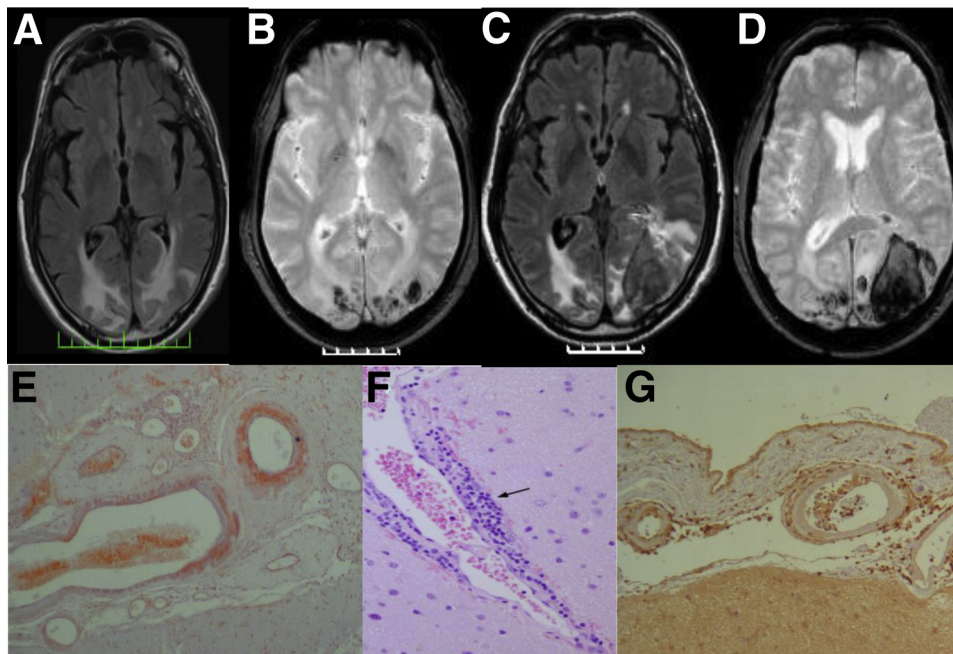
headaches, psychomotor slowing, spatial and temporal disorientation, right homonymous hemianopsia, and right optic ataxia. Brain MRI (Fig 1, C,D) revealed a left cortico-subcortical temporo-occipital hemorrhage. Conventional cerebral angiography was normal. An open right occipital cerebral biopsy (Fig 1, E-G) showed mononuclear, mainly T lymphocytes, perivascular inflammatory infiltration associated with vascular deposition of  $\beta$ -amyloid, establishing the diagnosis of CAA-I, subtype CAA-ri. The patient was started on methylprednisolone 1 g/d for 5 days followed by prednisolone 60 mg/d. At the end of the second month of corticosteroid therapy, there was a deterioration of cognition and changes in personality and behavior. Monthly intravenous cyclophosphamide was started. There was a slight behavioral improvement, but he remained demented and dependent with an mRS score 4 after 20 months of follow-up.

### *Patient 2*

A 79-year-old male patient with a history of hypertension and Alzheimer dementia with 2 years of duration treated with donepezil and perindopril presented to the Emergency Room because of progressive left hemiparesis. On neurologic examination, a grade 4 left hemiparesis was confirmed. He scored 10 on the Mini-Mental State Examination, showing temporal and spatial disorientation, memory, attention, and executive deficits. Brain CT scan showed a right frontal hypodensity. Brain MRI (Fig 2, A,B) revealed extensive right fronto-parieto-occipital vasogenic edema without gadolinium enhancement and disperse microbleeds mainly in the right hemisphere. An open right parietal cerebral biopsy (Fig 2, E-G) was performed and disclosed senile plaques, vascular deposition of  $\beta$ -amyloid surrounded by perivascular predominantly T-lymphocytic inflammatory infiltrate consistent with CAA-I, subtype CAA-ri. The genotype of apolipoprotein E (APOE) was  $\epsilon 3/\epsilon 3$ . He was initially treated with dexamethasone 5 mg/d for 5 days followed by methylprednisolone 1 g/d for 5 days and then prednisolone 60 mg/d with a slow taper down to 40 mg/d. After 1 month of steroid therapy, hemiparesis recovered, and there was an improvement of cognitive dysfunction (MMSE score 14), especially in executive functions. The 1-month follow-up brain MRI showed an impressive reduction of vasogenic edema (Fig 2, C,D). Unfortunately, 12 months after the diagnosis, he had sudden dyspnea followed by cardiopulmonary arrest and died in another hospital.

### *Patient 3*

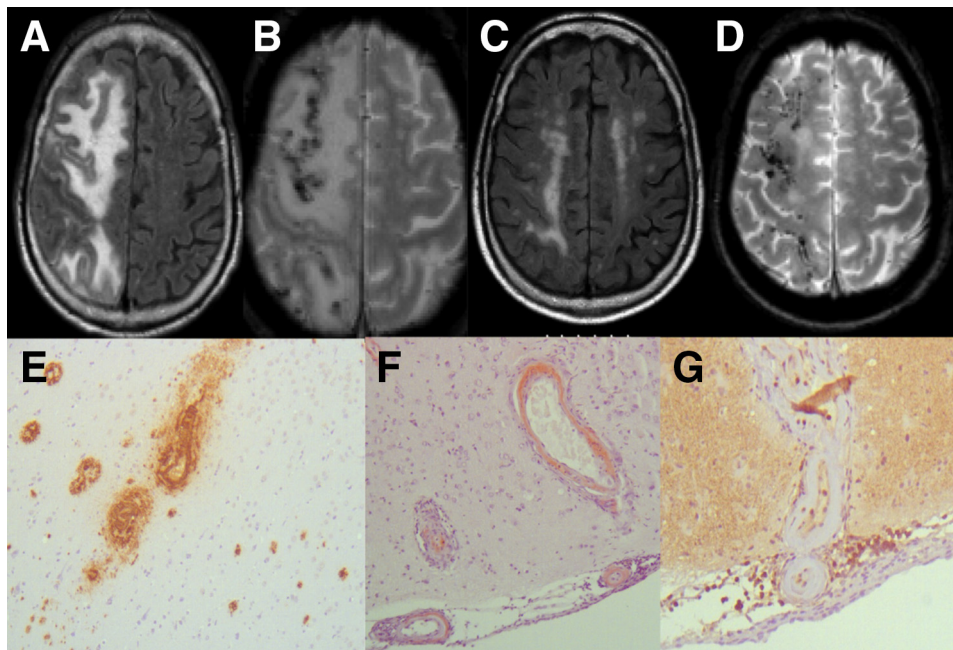
A 70-year-old male patient with hypertension, ischemic heart disease, and an 8-year history of Alzheimer disease presented to the emergency room because of a generalized tonic-clonic seizure. Neurologic examination revealed global aphasia, right homonymous hemianopia,



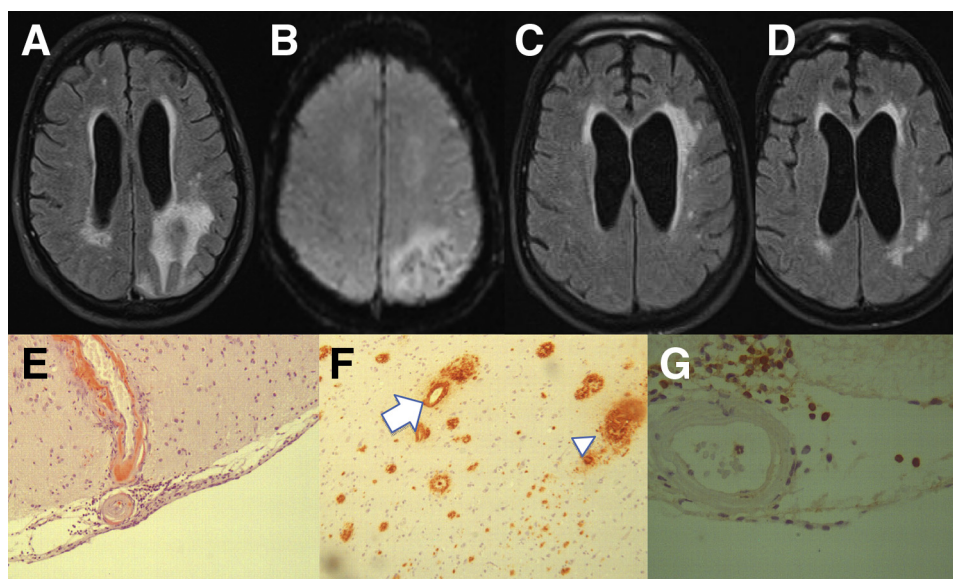
**Figure 1.** Patient 1—imaging findings: fluid-attenuated inversion-recovery (FLAIR) (A) and T2\*-weighted gradient-echo (B) brain magnetic resonance imaging (MRI) performed at first admission showed symmetric posterior vasogenic edema in temporo-occipital region with hemorrhagic component and disperse microbleeds; FLAIR (C) and T2\*-weighted gradient-echo (D) brain MRI performed at second admission revealed a left temporo-occipital hemorrhage. Pathologic findings: (E) vascular  $\beta$ -amyloid deposition in leptomeningeal and parenchymal vessels (Congo red staining, original magnification  $\times 4$ ) surrounded by (F and G) perivascular lymphocytic inflammatory infiltration (arrow) (hematoxylin and eosin, original magnification  $\times 20$ ; CD3 antibody staining, original magnification  $\times 10$ , respectively).

right-sided spasticity and hyper-reflexia, and bilateral Babinski sign. Blood analyses showed an elevated erythrocyte sedimentation rate of 43 mm/h and a rheumatoid factor of 981 IU/mL (normal  $\leq 15$  IU/mL). Electroence-

phalogram only revealed slowing of the background activity. Brain CT scan disclosed left parieto-occipital hypodensity, and brain MRI (Fig 3, A,B) showed subcortical digitiform left parieto-occipital vasogenic edema without



**Figure 2.** Patient 2—imaging findings: fluid-attenuated inversion-recovery (FLAIR) (A) and T2\*-weighted gradient-echo (B) brain magnetic resonance imaging (MRI) performed before treatment; dramatic reduction of vasogenic edema can be observed in FLAIR MRI (C) after immunosuppressive treatment and T2\*-weighted gradient-echo imaging (D). Pathologic findings: (E and F) amyloid deposition in cerebral parenchymal and leptomeningeal vascular walls (A $\beta$ 4, original magnification  $\times 10$ ; Congo red staining, original magnification  $\times 10$ , respectively); (G) leptomeningeal perivascular infiltration of lymphocytic inflammatory cells (CD3 staining, original magnification  $\times 10$ ).



**Figure 3.** Patient 3—*imagingologic findings: fluid-attenuated inversion-recovery (FLAIR) (A) and T2\*-weighted gradient-echo (B) brain magnetic resonance imaging (MRI) performed before treatment; marked contraction of vasogenic edema can be observed in FLAIR MRI (C and D) 1 month after immunosuppressive treatment. Pathologic findings: (E) amyloid deposition on parenchymal and leptomeningeal vascular walls (Congo red staining, original magnification  $\times 10$ ); (F) vessel wall (arrow) and several amyloid plaques (arrowhead) (immunohistochemistry A $\beta$ 4, original magnification  $\times 10$ ); (G) perivascular inflammatory T3 lymphocytes and a vessel with amyloid deposit (CD3 staining, original magnification  $\times 40$ ).*

gadolinium enhancement and intralésional microbleeds. Cerebrospinal fluid (CSF) analysis documented an elevated protein concentration (77 mg/dL) with normal glucose and cell count. An open left parietal brain biopsy (Fig 3, E-G) was performed and revealed vascular deposition of  $\beta$ -amyloid, surrounded by perivascular inflammatory infiltrate, confirming the diagnosis of CAA-I, subtype CAA-ri. The patient was started on dexamethasone 8 mg/d followed by a slow taper down. After 1 month, he showed improvement of both clinical and MR findings (Fig 3, C,D). However, over the next months, there was a progressive clinical worsening. The patient was severely disabled and bedridden (mRS score of 5) after 18 months of follow-up.

## Methods

The Meta-analysis of Observational Studies in Epidemiology guidelines<sup>7</sup> were followed to perform and report this systematic review.

## Sources

Potentially eligible studies were identified by 2 authors (A.C.C. and C.S.) through electronic search of bibliographic databases including Pubmed and Cochrane Library from inception to April 2014. We also performed extensive hand searching by screening references of included studies and review articles for additional citations.

The following search terms were used: cerebral amyloid angiopathy AND inflammation, amyloid- $\beta$ -related

angiitis; angiitis AND  $\beta$ -amyloid; cerebral amyloid angiopathy AND granulomatous angiitis; primary CNS angiitis AND cerebral amyloid angiopathy; cerebral amyloid inflammatory vasculopathy; cerebral amyloid angiitis; cerebral amyloid angiopathy associated with inflammation; and giant cell arteritis AND cerebral amyloid angiopathy.

We screened titles, key words, and abstracts retrieved from electronic searches and obtained potentially suitable reports for further evaluation. In cases of unclear or missing information, an attempt to contact the authors was done.

## Study Selection

### Eligibility Criteria

We included only neuropathologically proven CAA-I case reports. All types of observational studies, case reports, and case series were considered, irrespective of language. The data extracted from the publications written in languages other than English, French, Portuguese, and Spanish were done through the abstract and through contact with the authors. If this was not possible, the article was excluded.

### Data Collection Process

Bibliographic screening and data extraction were done independently by 2 authors (A.C.C. and C.S.). Doubts and disagreements were solved by consensus, and if consensus was not reached, a third author (J.F.) was consulted. We extracted information regarding

characteristics of participants including age, gender, clinical manifestations (headaches, focal signs, seizures, and altered mental functions) and findings on brain MRI (white matter abnormalities, microbleeds, edema, gadolinium enhancement, and changes on diffusion-weighted sequences). Although brain computed tomographic scan result was available for most patients, we decided to evaluate only MRI because of its increase sensitivity over CT scan in the current disease setting. Cerebrospinal fluid (cells and proteins), serum (erythrocyte sedimentation rate and C-reactive protein) analysis, and neuropathologic findings (vasculitic and perivascular patterns and granuloma) were also extracted. Clinical features were grouped into 3 patterns: coma/encephalopathy (defined by altered mental state, with or without focal signs, with or without seizures), multifocal (defined by >1 focal sign with or without focal seizures), and unifocal (defined by 1 focal sign with or without focal seizures) presentations. We further classified the clinical manifestations according to its time course as acute ( $\leq 2$  days), subacute (3-30 days), and chronic ( $\geq 30$  days). Regarding pharmacologic interventions, we considered therapy with corticosteroids and/or cytostatics (cyclophosphamide, mycophenolate mofetil, azathioprine, methotrexate, and nonspecified).

### Outcomes

We analyzed the following outcomes: (1) clinical improvement with treatment, defined as the proportion of patients who clinically improved with immunosuppressive treatment, based on author's report; (2) clinical outcome at last available follow-up evaluated by the modified Rankin Scale (mRS) (grade  $\leq 2$  if independent, 3-5 if dependent, and 6 if dead); and (3) the time (months) to death or dependency (mRS score 3-5).

### Statistical Analyses

We analyzed the relationship between outcomes and (a) clinical presentation patterns, (b) neuropathologic patterns, and (c) treatments. We report frequencies, percentage, means (for continuous variables), and medians. Comparisons were performed using the chi-square test, with continuity correction or the Fisher's exact test, when indicated. A *P* value less than .05 was considered statistically significant.

### Systematic Review

The electronic database and hand searches produced a total of 207 publications. After the application of inclusion and exclusion criteria, 67 publications were included. One German and 2 Japanese publications<sup>8-10</sup> were excluded. Figure 4 shows the flow chart of the search. A total of 155 patients were included: 152 patients from 67 publications<sup>4,6,11-72</sup> and 3 reported earlier (Supplemental Table 1).

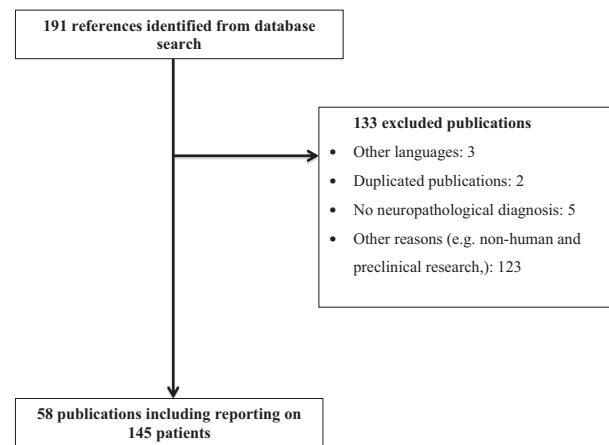


Figure 4. Flow chart of literature search and results.

### Clinical Manifestations

The mean age of the initial neurologic manifestation was 66.9 years (median 69; range 42-86 years) and 53.9% (n = 83) were men. Information on the clinical manifestations was available in 96.7% (n = 150) of the patients. The most common clinical features were cognitive dysfunction (48.0%, n = 72), headaches (38.7%, n = 58; 15.5% bilateral, 5.2% unilateral), seizures (36.7%, n = 55), monoparesis/hemiparesis (20.0%, n = 30), confusional syndrome (18.0%, n = 27), aphasia (16.7%, n = 25), visual field defect (14.7%, n = 22), altered level of consciousness (12.7%, n = 19), personality/behavior disorder (12.0%, n = 18), dementia (9.3%, n = 14), ataxia (7.3%, n = 11), gait disturbance (7.3%, n = 11), neglect (6.0%, n = 9), hallucinations (5.3%, n = 8), dysarthria (4.7%, n = 7), and sensory defect (2.0%, n = 3). The majority of these clinical manifestations (data available in 78 patients) had a chronic (65.4%, n = 51), followed by subacute course (24.4%, n = 19) and acute presentation (10.3%, n = 8) of patients.

These clinical features could be grouped in 3 major patterns: 46.0% (n = 52 of 113) had encephalopathy/coma pattern, 34.5% (n = 39 of 113) had multifocal pattern, and 19.5% (n = 22 of 113) had unifocal pattern.

### Ancillary Procedures

Sixty percent (9 of 15 with available results) of patients had increased C-reactive protein with average values of 3.0 mg/dL (0.3-12.5 mg/dL; median 1.15 mg/dL) and 37.5% (27 of 72 with available results) had increased erythrocyte sedimentation rate with an average of 36.8 mm/h (12-116 mm/h; median 35 mm/h).

Regarding CSF examination, 84.8% (78 of 92 with available results) had at least 1 abnormality: pleocytosis in 67.4% (n = 62) and increase of protein content in 66.3% (n = 61) of patients.

Regarding MRI, 96.6% (86 of 89 with available results) of patients had white matter changes, with gadolinium enhancement in 63.6% (56 of 88 with available results)

of patients. Other abnormal findings included edema in 53.5% (38 of 71 with available results), microbleeds in 41.2% (28 of 68 with available results), and diffusion-weighted image changes in 24.2% (16 of 66 with available results) of patients.

Results of APOE genotype were available for 26 patients with the following distribution:  $\epsilon 4/\epsilon 4$  seen in 61.5% ( $n = 16$ ),  $\epsilon 2/\epsilon 3$  (19.2%,  $n = 5$ ),  $\epsilon 2/\epsilon 4$  (3.8%,  $n = 1$ ), and  $\epsilon 3/\epsilon 3$  (15.4%,  $n = 4$ ), which was seen in one of the presented cases (patient 2).

### Neuropathologic Findings

As stated earlier, only neuropathologically proven cases of CAA-I were included in this systematic review (Fig 4). All patients had vascular amyloid deposition, which was accompanied by perivascular and/or vasculitic inflammatory changes with or without granuloma formation. The report of neuropathologic pattern was available in 142 patients. The most common neuropathologic pattern was perivascular and vasculitic inflammation with granuloma (27.5%,  $n = 39$ ). This was followed by perivascular and vasculitic inflammatory pattern without granuloma (22.5%,  $n = 32$ ), perivascular inflammation with granuloma (20.4%,  $n = 29$ ), perivascular inflammatory pattern (14.1%,  $n = 20$ ), vasculitic inflammation with granuloma (12.7%,  $n = 18$ ), and vasculitic inflammation alone (2.8%,  $n = 4$ ). Of this, 35.2% ( $n = 50$ ) of the cases had an ABRA pattern (vasculitic inflammation with or without granuloma), 14.8% ( $n = 21$ ) had a CAA-ri pattern (perivascular inflammation with or without granuloma), and 50% ( $n = 71$ ) of the cases had an overlap between CAA-ri and ABRA patterns.

### Treatment

Information on therapeutic interventions was available for 78.0% ( $n = 121$ ) of the cases. The most common offered treatment was steroid therapy (86.8%,  $n = 105$ ) with a wide range of prescription schemes, such as one to several pulse corticosteroid therapy, one pulse corticosteroid therapy followed by high doses of prednisolone, and high doses of prednisolone followed by slow taper. The second most frequent treatment was cyclophosphamide, which was administered in 33.9% of patients ( $n = 41$ ), followed by azathioprine (5.0%,  $n = 6$ ) and mycophenolate mofetil (5.0%,  $n = 6$ ). Other cytostatics were given in 2.5% ( $n = 3$ ) including methotrexate ( $n = 1$ ). Only 13 (10.2%) patients did not receive pharmacologic treatment. Of these, 5 received surgical treatment including "tumor" resection and CSF shunt.

### Outcomes

As stated earlier, we choose as main outcome to evaluate treatment of the proportion of patients who clinically improved with immunosuppressive drugs, accordingly

to the authors' report. Information regarding the response to treatment was available in 98 (63.2%) patients. From this group of patients, 85 patients were treated with immunosuppressive treatment: more than half (57.6%,  $n = 49$ ) showed clinical improvement, the remaining maintained the same clinical status (14.1%,  $n = 12$ ), or even deteriorated further (28.2%,  $n = 24$ ). On the other hand, 13 patients were not treated with immunosuppressive scheme, and from this, 4 (30.8%) showed improvement and the other 8 (61.5%) patients further deteriorated.

Information regarding functional outcome was only available in 88 patients (56.7%). The outcome differed widely among these patients: 42.0% ( $n = 37$ ) regained independence (mRS score 0-2), 37.5% ( $n = 33$ ) died (mRS score 6), and the remaining patients (20.5%,  $n = 18$ ) were left dependent (mRS score 4-5). The mean follow-up was 21.06 months (range 10-156 months). The mean time to death or dependency was 13.7 months.

There were no association between neuropathologic subtypes ABRA and CAA-ri and clinical presentation (encephalopathy/coma versus multifocal or unifocal presentation;  $P = .39$ ).

There were no statistically significant results or trends between proportion of death or dependency in patients with encephalopathic/coma presentation versus patients with less severe manifestations including multifocal/unifocal presentations (for mRS score 3-6  $P = .10$  and for mRS score 6  $P = .09$ ). There were no statistically significant association between neuropathologic patterns, namely those with perivascular infiltrates or those with vasculitis features and outcome.

There were no statistically significant differences or trends on functional outcome between patients treated with corticosteroids alone comparing with those treated with cytostatic agents in combination with corticosteroids (for mRS score 3-6  $P = .70$  and for mRS score 6  $P = .15$ ).

## Discussion

This systematic review could collect a large sample of neuropathologically proven CAA-I cases, reporting the clinical picture of this entity, treatment, and outcome. Although we extracted and collected the maximum information available from these retrospective and observational studies, many of the reported data done in our review were performed in a low number of cases, mainly blood analysis, APOE genotype, and MRI. In these cases, conclusions should be done carefully.

The mean age of the first clinical manifestation was 66.9 years, which fits within previously reported values.<sup>6,24,53</sup> We highlight the slight male predominance (53.5%). As stated in other studies,<sup>6,17,24,53</sup> the most common clinical presentation of CAA-I was cognitive dysfunction including memory loss, apraxia, executive dysfunction, and judgment impairment, ultimately

leading to severe dementia and behavior disturbances. Two of our patients (cases 2 and 3) also had Alzheimer disease. This finding is not surprising because CAA is found in about 80% patients with Alzheimer disease. Some publications<sup>4,6,12,62</sup> suggested that CAA-I has predominantly an acute or subacute presentation; however, none of these studies have specified the used classification. Our results do not confirm this allegation because in our study 64.8% of patients had a chronic course (>30 days).

We cannot find any differences between the 2 neuropathologic subtypes, CAA-ri and ABRA, in terms of clinical presentation and outcome. This reinforces the concept that CAA-ri and ABRA represent a spectrum of the same disease—CAA-I—with similar clinical presentation and course.

Altogether with 2 reported patients by Piazza et al<sup>68</sup> and our patient 2, there are 3 reported APOE  $\epsilon 3/\epsilon 3$  genotypes. This finding suggests that mechanisms other than the proinflammatory role of APOE  $\epsilon 4$  may also be involved in the pathogenesis of CAA-I.

We found a low incidence (41.2%) of microbleeds detected in MRI. Because microbleeds have been linked to CAA and Alzheimer disease,<sup>73</sup> we would expect a much higher incidence of microbleeds in CAA-I population. The gradient-echo T2\*-weighted MRI in 3T has the highest sensitivity<sup>74</sup> for detection of microbleeds. It is possible that this MRI sequence was not used systematically, decreasing the likelihood of detecting microbleeds. An alternative possibility is that microbleeds are not present because of the early and acute inflammatory process.

We emphasize the high prevalence of granuloma formation in this review. This finding may be biased because patients with granulomatous inflammation and “tumor-like” lesions could have a more dramatic clinical presentation and, therefore, would be more likely to be biopsied.

Kinnecom et al<sup>4</sup> and Chung et al<sup>53</sup> suggested that in the context of typical clinical and radiologic picture, the diagnosis of CAA-ri could be done without biopsy and the latter proposed diagnostic criteria for probable CAA-ri. We also advocate that some patients, specially the elderly and those with several co-morbidities, may not need a cerebral biopsy and may be treated with immunosuppression without the histologic diagnosis.

The presence of increased levels of anti- $\beta$  1-40 and 1-42 autoantibodies in blood<sup>52</sup> and in CSF<sup>68,75</sup> in patients with CAA-ri has been shown. The presence of these autoantibodies suggest an autoimmune basis of CAA-ri<sup>68</sup> and, therefore, an argument to initiate immunosuppressive treatment. Moreover, they may also improve diagnostic accuracy in cases when the biopsy cannot be done and may also serve as a biomarker for monitorization of therapeutic response.<sup>52,68</sup>

Although CAA-I has been labeled as a potentially treatable condition, the long-term efficacy of immunosuppression has not been evaluated. Despite the fact that there

were no statistically significant differences between patients treated with corticosteroids alone compared with those treated with cytostatic agents alone or in combination with corticosteroids, more than a half of patients treated with these drugs improved. However, these results may be biased because of the small sample size, the various definition of improvement, and the unblind assessment of outcome and short follow-up.

There was an increase in reports of CAA-I cases in the last years. This may be most probably associated with an increased recognition of the disease. Nonetheless, we cannot exclude an increase of incidence of this entity in the last years.

More recently, a new entity, amyloid-related imaging abnormalities (ARIAs), has received more attention. It was observed during clinical trials with Alzheimer patients with monoclonal antibodies with other amyloid-modifying therapies and represents vasogenic edema, either focal or confluent, visible in fluid-attenuated inversion-recovery sequences and/or sulcal effusion (ARIA-E), and hemorrhagic findings (ARIA-H) including microhemorrhages and superficial siderosis evident in T2\*-weighted gradient-echo images.<sup>68,76</sup> It is apparent the parallelism between ARIA with CAA-ri and ABRA. However, in ARIA, the clinical picture tends to be more acute, starting within 1 month after the beginning of the treatment.<sup>76</sup> As with CAA-ri and ABRA, imagiologic abnormalities are seen more frequently in patients with APOE  $\epsilon 4$ .<sup>76</sup>

Our systematic review has several limitations: (1) because this is a retrospective study, some of the data might be fragile because of implicit limitations of these type of analysis, (2) CAA-I is a rare disease with only 155 neuropathologically proven reported cases, which make statistical inferences imprecise, (3) treatment allocation was nonrandomized and evaluation was not blinded to treatment modality, (4) most of the reports have a short follow-up, and (5) a considerable amount of reports have incomplete published data.

In summary, we showed that the typical presentation of CAA-I includes cognitive dysfunction, headaches, and seizures with a mean age of 67 years. These patients have characteristic imagiologic findings with white matter changes with or without gadolinium enhancement. The most frequent histologic pattern is perivascular and vasculitic inflammation with granuloma formation. Despite the fact that more than half of the patients improved with immunosuppression, the outcome was unfavorable in the majority of the patients, with death or dependency in almost 60% of patients.

### Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2015.04.015>.

## References

1. Olichney JM, Hansen LA, Hofstetter CR, et al. Cerebral infarction in Alzheimer's disease is associated with severe amyloid angiopathy and hypertension. *Arch Neurol* 1995;52:702-708.
2. Ringheim GE, Conant K. Neurodegenerative disease and the neuroimmune axis (Alzheimer's and Parkinson's disease, and viral infections). *J Neuroimmunol* 2004;147:43-49.
3. Schenk D. Amyloid- $\beta$  immunotherapy for Alzheimer's disease: the end of the beginning. *Nat Rev Neurosci* 2002;3:821-824.
4. Kinnecom C, Lev MH, Wendel L, et al. Course of cerebral amyloid angiopathy-related inflammation. *Neurology* 2007;68:1411-1416.
5. Eng JA, Frosch MP, Choi K, et al. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. *Ann Neurol* 2004;55:250-256.
6. Scolding N, Joseph F, Kirby PA, et al. A $\beta$ -related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Brain* 2005;128 (pt 3):500-515.
7. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008-2012.
8. Preusse S, Vogelgesang S, Block F. Cerebral amyloid angiopathy with associated vasculitis. *Nervenarzt* 2011;82:1615-1619.
9. Lettau M, Ludescher B, Bornemann A. A rare form of cerebral vasculitis: amyloid beta peptide associated angiitis. *Rofa* 2010;182:276-277.
10. Yamazaki T, Okamoto K, Hirai S, et al. A case of cerebral amyloid angiopathy associated with granulomatous angiitis of the central nervous system. *Rinsho Shinkeigaku* 1988;28:1164-1170.
11. Anders KH, Wang ZZ, Kornfeld M, et al. Giant cell arteritis in association with cerebral amyloid angiopathy: immunohistochemical and molecular studies. *Hum Pathol* 1997;28:1237-1246.
12. Fountain NB, Eberhard DA. Primary angiitis of the central nervous system associated with cerebral amyloid angiopathy: report of two cases and review of the literature. *Neurology* 1996;46:190-197.
13. Ginsberg L, Geddes J, Valentine A. Amyloid angiopathy and granulomatous angiitis of the central nervous system: a case responding to corticosteroid treatment. *J Neurol* 1988;235:438-440.
14. Harkness KAC, Coles A, Pohl U, et al. Rapidly reversible dementia in cerebral amyloid inflammatory vasculopathy. *Eur J Neurol* 2004;11:59-62.
15. Marotti JD, Savitz SI, Kim W-K, et al. Cerebral amyloid angiitis processing to generalized angiitis and leukoencephalitis. *Neuropathol Appl Neurobiol* 2007;33:475-479.
16. Murphy MN, Sima AA. Cerebral amyloid angiopathy associated with giant cell arteritis: a case report. *Stroke* 1985;16:514-517.
17. Salvarani C, Brown RD, Calamia KT, et al. Primary central nervous system vasculitis: comparison of patients with and without cerebral amyloid angiopathy. *Rheumatology (Oxford)* 2008;47:1671-1677.
18. Reid AH, Maloney AF. Giant cell arteritis and arteriolitis associated with amyloid angiopathy in an elderly mongol. *Acta Neuropathol* 1974;27:131-137.
19. Shintaku M, Osawa K, Toki J, et al. A case of granulomatous angiitis of the central nervous system associated with amyloid angiopathy. *Acta Neuropathol (Berl)* 1986;70:340-342.
20. Briceno CE, Resch L, Bernstein M. Cerebral amyloid angiopathy presenting as a mass lesion. *Stroke* 1987;18:234-239.
21. Powers JM, Stein BM, Torres RA. Sporadic cerebral amyloid angiopathy with giant cell reaction. *Acta Neuropathol* 1990;81:95-98.
22. Coz PL, Mikol J, Ferrand J, et al. Granulomatous angiitis and cerebral amyloid angiopathy presenting as a mass lesion. *Neuropathol Appl Neurobiol* 1991;17:149-155.
23. Mandybur TL, Balko G. Cerebral amyloid angiopathy with granulomatous angiitis ameliorated by steroid-cytosan treatment. *Clin Neuropharmacol* 1992;15:241-247.
24. Fountain NB, Lopes MB. Control of primary angiitis of the CNS associated with cerebral amyloid angiopathy by cyclophosphamide alone. *Neurology* 1999;52:660-662.
25. Scully RE, Mark EJ, McNeely WF, et al. Case records of the Massachusetts General Hospital, weekly clinicopathological exercises, case 10-2000. *N Engl J Med* 2000;342:957-965.
26. Streichenberger N, Girard-Madoux P, Verejan I, et al. Giant cell angiitis of the central nervous system with amyloid angiopathy. A case report and review of the literature. *Clin Exp Pathol* 1999;47:311-317.
27. Brotman D, Eberhart CG, Burger PC, et al. Primary angiitis and Alzheimer's disease: clinically and pathologically evident in a single patient. *J Rheumatol* 2000;27:2935-2937.
28. Tamargo RJ, Connolly ES, McKhann GM, et al. Clinicopathological review: primary angiitis of the central nervous system in association with cerebral amyloid angiopathy. *Neurosurgery* 2003;53:136-143.
29. Schwab P, Lidov HG, Schwartz RB, et al. Cerebral amyloid angiopathy associated with primary angiitis of the central nervous system: report of 2 cases and review of the literature. *Arthritis Rheum* 2003;49:421-427.
30. Jacobs DA, Liu GT, Nelson PT, et al. Primary central nervous system angiitis, amyloid angiopathy, and Alzheimer's pathology presenting with Balint's syndrome. *Surv Ophthalmol* 2004;49:454-459.
31. McHugh JC, Ryan AM, Lynch T, et al. Steroid-responsive recurrent encephalopathy in a patient with cerebral amyloid angiopathy. *Cerebrovasc Dis* 2007;23:66-69.
32. Amick A, Joseph J, Silvestri N, et al. Amyloid- $\beta$ -related angiitis: a rare cause of recurrent transient neurological symptoms. *Nat Clin Pract Neurol* 2008;4:279-283.
33. Hashizume Y, Yoshida M, Suzuki E, et al. A 65-year-old man with headaches and left homonymous hemianopsia. *Neuropathology* 2004;24:350-353.
34. Mikolaenko I, Mikolaenko I, Conner MG, et al. A 50-year-old man with acute-onset generalized seizure. *Arch Pathol Lab Med* 2006;130:5-7.
35. Oh U, Gupta R, Krakauer JW, et al. Reversible leukoencephalopathy associated with cerebral amyloid angiopathy. *Neurology* 2004;62:494-497.
36. Safriel Y, Sze G, Westmark K, et al. MR spectroscopy in the diagnosis of cerebral amyloid angiopathy presenting as a brain tumor. *Am J Neuroradiol* 2004;25:1705-1708.
37. Oide T, Tokuda T, Takei Y, et al. Serial CT and MRI findings in a patient with isolated angiitis of the central nervous system associated with cerebral amyloid angiopathy. *Amyloid* 2002;9:256-262.
38. Machida K, Tojo K, Naito K-S, et al. Cortical petechial hemorrhage, subarachnoid hemorrhage and corticosteroid-responsive leukoencephalopathy in a



- patient with cerebral amyloid angiopathy. *Amyloid* 2008;15:60-64.
39. Greenberg SM, Parisi JE, Keegan BM. A 63-year-old man with headaches and behavioral deterioration. *Neurology* 2007;68:782-787.
  40. Wong SH, Robbins PD, Knuckey NW, et al. Cerebral amyloid angiopathy presenting with vasculitic pathology. *J Clin Neurosci* 2006;13:291-294.
  41. Takeda A, Tatsumi S, Yamashita M, et al. Granulomatous angiitis of the CNS associated with cerebral amyloid angiopathy: an autopsied case with widespread involvement. *Brain Nerve* 2007;59:537-543.
  42. Rigby H, Easton A, Bhan V. Amyloid  $\beta$ -related angiitis of the central nervous system: report of 3 cases. *Can J Neurol Sci* 2011;38:626-630.
  43. Morishige M, Abe T, Kamida T, et al. Cerebral vasculitis associated with amyloid angiopathy: case report. *Neurol Med Chir* 2010;50:336-338.
  44. Weiss SA, Pisapia D, Mayer SA, et al. Amyloid  $\beta$ -related angiitis causing coma responsive to immunosuppression. *Case Rep Pathol* 2012;2012:678746.
  45. Makol A, Parisi JE, Petty GW, et al. A 60-year-old woman with headache, confusion, and hallucinations. *Arthritis Care Res* 2011;63:1486-1494.
  46. Luppe S, Betmouni S, Scolding N, et al. Cerebral amyloid angiopathy related vasculitis: successful treatment with azathioprine. *J Neurol* 2010;257:2103-2105.
  47. Sakaguchi H, Ueda A, Kosaka T, et al. Cerebral amyloid angiopathy-related inflammation presenting with steroid-responsive higher brain dysfunction: case report and review of the literature. *J Neuroinflammation* 2011;8:116.
  48. Szpak GM, Lewandowska E, Sliwinska A, et al. Inflammatory cerebral amyloid angiopathy: the overlap of perivascular (PAN-like) with vasculitic (A $\beta$ -related angiitis) form: an autopsy case. *Folia Neuropathol* 2011;49:335-347.
  49. Tschampa HJ, Niehusmann P, Marek M, et al. MRI in amyloid beta-related brain angiitis. *Neurology* 2009;73:247.
  50. Ghavanini AA, Munoz DG. Primary angiitis associated with amyloid angiopathy. *Arch Neurol* 2011;68:1202-1203.
  51. Kurian M, Burkhardt K, Assal F, et al. Amyloid plaques and intraneuronal tau inclusions in A-beta-related angiitis (ABRA). *Neuropathol Appl Neurobiol* 2012;38:391-394.
  52. Hermann DM, Keyvani K, van de Nes J, et al. Brain-reactive  $\beta$ -amyloid antibodies in primary CNS angiitis with cerebral amyloid angiopathy. *Neurology* 2011;77:503-505.
  53. Chung KK, Anderson NE, Hutchinson D, et al. Cerebral amyloid angiopathy related inflammation: three case reports and a review. *J Neurol Neurosurg Psychiatry* 2011;82:20-26.
  54. Kloppenborg RP, Richard E, Sprengers ME, et al. Steroid responsive encephalopathy in cerebral amyloid angiopathy: a case report and review of evidence for immunosuppressive treatment. *J Neuroinflammation* 2010;7:18.
  55. Kimura A, Sakurai T, Yoshikura N, et al. Corticosteroid therapy in a patient with cerebral amyloid angiopathy-related inflammation. *J Neuroinflammation* 2013;10:39.
  56. Annweiler C, Paccalin M, Berrut G, et al. Association of angiitis of central nervous system, cerebral amyloid angiopathy, and Alzheimer's disease: report of an autopsy case. *Vasc Health Risk Manage* 2008;4:1471-1474.
  57. Melzer N, Harder A, Gross CC, et al. CD4(+) T cells predominate in cerebrospinal fluid and leptomeningeal and parenchymal infiltrates in cerebral amyloid  $\beta$ -related angiitis. *Arch Neurol* 2012;69:773-777.
  58. Porter M, Newey CR, Toth G. Teaching NeuroImages: treatment-resistant rapidly progressive amyloid  $\beta$ -related angiitis. *Neurology* 2013;80:e187-e188.
  59. Bogner S, Bernreuther C, Matschke J, et al. Immune activation in amyloid- $\beta$ -related angiitis correlates with decreased parenchymal amyloid- $\beta$  plaque load. *Neurodegener Dis* 2013;13:38-44.
  60. Sakai K, Hayashi S, Sanpei K, et al. Multiple cerebral infarcts with a few vasculitic lesions in the chronic stage of cerebral amyloid angiopathy-related inflammation. *Neuropathology* 2012;32:551-556.
  61. Probst A, Ulrich J. Amyloid angiopathy combined with granulomatous angiitis of the central nervous system: report of two patients. *Clin Neuropathol* 1985;4:250-259.
  62. Salvarani C, Hunder GG, Morris JM, et al. A $\beta$ -related angiitis: comparison with CAA without inflammation and primary CNS vasculitis. *Neurology* 2013;81:1-8.
  63. Nouh A, Borys E, Gierut AK, et al. Amyloid-beta related angiitis of the central nervous system: case report and topic review. *Front Neurol* 2014;5:13.
  64. Hosoi Y, Uchiyama T, Yoshida M, et al. A case of cerebral amyloid angiopathy with reversible white matter lesions and multiple cerebral microbleeds. *Rinsho Shinkeigaku* 2012;52:90-95.
  65. Martucci M, Sarria S, Toledo M, et al. Cerebral amyloid angiopathy-related inflammation: imaging findings and clinical outcome. *Diagnostic Neuroradiol* 2014;56:283-289.
  66. Ishii M, Lavi E, Kamel H, et al. Amyloid  $\beta$ -related central nervous system angiitis presenting with an isolated seizure. *Neurohospitalist* 2014;4:86-89.
  67. Child ND, Flanagan EP, Keegan BM, et al. Amyloid- $\beta$ -related angiitis presenting as a uveomeningeal syndrome. *Neurology* 2013;81:1796-1798.
  68. Piazza F, Greenberg SM, Savoirdo M, et al. Anti-amyloid  $\beta$  autoantibodies in cerebral amyloid angiopathy-related inflammation: implications for amyloid-modifying therapies. *Ann Neurol* 2013;73:449-458.
  69. Danve A, Grafe M, Deodhar A. Amyloid beta-related angiitis—a case report and comprehensive review of literature of 94 cases. *Semin Arthritis Rheum* 2014;44:86-92.
  70. Sengoku R, Matsushima S, Murakami Y, et al. 11C-PiB PET imaging of encephalopathy associated with cerebral amyloid angiopathy. *Intern Med* 2014;53:1997-2000.
  71. Ryan NS, Lashley T, Revesz T, et al. Spontaneous ARIA (amyloid-related imaging abnormalities) and cerebral amyloid angiopathy related inflammation in presenilin 1-associated familial Alzheimer's disease. *J Alzheimers Dis* 2015;44:1069-1074.
  72. Boncoraglio GB, Piazza F, Savoirdo M, et al. Prodromal Alzheimer's disease presenting as cerebral amyloid angiopathy-related inflammation with spontaneous amyloid-related imaging abnormalities and high cerebrospinal fluid anti-A $\beta$  autoantibodies. *J Alzheimers Dis* 2015;45:363-367.
  73. Cordonnier C. Brain microbleeds. *Pract Neurol* 2010;10:94-100.
  74. Kato H, Izumiyama M, Izumiyama K, et al. Silent cerebral microbleeds on T2\*-weighted MRI: correlation with stroke subtype, stroke recurrence, and leukoaraiosis. *Stroke* 2002;33:1536-1540.

75. DiFrancesco JC, Brioschi M, Brighina L, et al. Anti-A $\beta$  autoantibodies in the CSF of a patient with CAA-related inflammation: a case report. *Neurology* 2011; 76:842-844.
76. Sperling R, Salloway S, Brooks DJ, et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. *Lancet Neurol* 2012;11:241-249.