Cerebral Amyloid Angiopathy -Related Inflammation (CAA-ri): Is Steroid/Imunosuppressive Therapy Beneficial?

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Abstract

Background: Cerebral amyloid angiopathy (CAA) is an important cause of intracerebral hemorrhage. Brain amyloid-related imaging abnormalities (ARIA) can be classified into two groups; those with edema or sulcal effacement (ARIA-E) and those with cerebral microbleeds or small hemorrhages (ARIA-H). There is an aggressive form of CAA, called CAA-related inflammation (CAA-ri) which is characterized by vascular or perivascular inflammation. Current treatment guidelines do not recommend routine use of steroids for intraparenchymal hemorrhage.

Methods: We describe the clinical course, radiologic and pathologic findings of a 78-year-old man with recurrent intracerebral hemorrhage. Diagnostic studies included CT and MRI-scans of the brain, histopathology studies and autopsy.

Results: The patient was diagnosed with a vasculitic form of amyloid angiopathy. Treatment with steroids resulted in clinical and radiological improvement.

Conclusions: There might be a benefit of steroid or other immunosuppressive therapy in some patients with recurrent lobar hemorrhage related to CAA. Patients demonstrating edema out of proportion to the size of hematoma and extension of edema to the subcortical U fibers on imaging studies due to underlying vasculitis or CAA-ri may be candidates for such therapeutic interventions.

Keywords: Intracerebral Hemorrhage; Amyloid Angiopathy; Vasculitis; Amyloid Associated Angiitis; CAA-Related Inflammation; Steroid and Immunosuppressive Therapy

Introduction

Cerebral Amyloid Angiopathy (CAA) is an important cause of intracerebral hemorrhage resulting from the deposition of amyloid protein in the walls of small and medium sized cortical and leptomeningeal arteries [1]. It was first observed by Oppenheim in 1909 [2] and formally described by Scholz in 1938[3]. The incidence of CAA is 20/100,000 in persons more than 60 years of age, and there is no difference in occurrence between genders. CAA accounts for up to 10-15% of cerebral hemorrhages in the elderly [4]. There are two different types of CAA; sporadic- and familial forms. The sporadic type of CAA is more common than the familial type and mostly results from the deposition of Aβ peptide in the vessel wall, resulting from cleavage of amyloid precursor protein (APP) by β and γ-secretases [5]. Deposition of these amyloid proteins into the cerebrovasculature is associated with heat shock proteins that trigger release of IL-8, leading to a cerebral inflammatory reaction [6]. Amyloid proteins may also trigger activation of the complement system, alteration of blood-brain barrier permeability, oxidative stress, formation of ion-like channels, and cell toxicity [7,8]. Though the pathogenesis is not fully understood, it is thought that these changes weaken the vessel wall, increasing susceptibility to rupture and hemorrhage [6,9]. The pattern of cerebral hemorrhage on brain imaging studies and histopathological findings are of importance in the diagnosis of CAA.

Case Description

A 78-year-old man with a history of right parietal intracerebral hemorrhage three years ago, and multiple transient ischemic attacks, presented with confusion and bilateral temporo-occipital headache associated with nausea and multiple episodes of vomiting within 24 hours of his admission to the emergency department (ED). There was no history of hypertension, fall, recent sickness or travel. He was not on anti-platelet or anticoagulation therapy.

Upon physical examination, vital signs were normal, except a mildly elevated blood pressure (157/82 mm Hg). The patient was alert and oriented to time, place and person. He had a left visual field defect and sensory neglect. There was no gaze preference, aphasia or any focal motor deficit.

A brain CT scan in the ED showed large right parieto-temporal hematoma (Figure 1A). The patient was admitted to the stroke unit and was closely monitored. His blood pressure was treated to a level of ≤ 140 mm Hg. Phenytoin was administered to prevent seizure spells. We performed magnetic resonance imaging (MRI) and conventional cerebral angiography on the patient to rule out underlying arteriovenous malformation, dural arteriovenous fistula and other structural causes of brain bleeding. The cerebral angiography was unremarkable. However, the MRI brain showed surrounding edema out of proportion to the size of the hematoma.

Figure 1A: CT scan brain showing large right parieto-temporal and right subdural hematoma.
During the next several days, the patient clinically deteriorated and became more confused, lethargic, less responsive to verbal requests and developed left hemiparesis. A repeat CT brain study showed expansion of the right parietal hematoma with increasing edema and midline shift (Figure 1B). The edema extended out to subcortical U-fibers. He was treated with 3% saline (goal sodium level between 145-150 mEq/L) and methyl prednisolone 150 mg IV every 8 hours. The patient clinically improved within the next 48 hours. There was some radiological improvement as the edema and midline shift decreased from the prior CT brain study without any significant change in hematoma size (Figure 1C). Steroid treatment was stopped after 3 days, and 3% saline was continued. The patient again deteriorated clinically and repeat CT brain again showed worsening of edema and midline shift following discontinuation of steroid therapy. The patient was started on mannitol, underwent emergent intubation and, then had a craniotomy to evacuate the hematoma. Brain tissue samples were taken for histopathological diagnosis. His condition did not improve after hematoma evacuation, and brain CT scan showed resolution of the right parietal hematoma, but a new left parietal hematoma had formed. The patient was extubated per family wishes, “comfort care” was administered, and he died a few hours later. The family agreed to a limited autopsy (brain only). There was deposition of amyloid in the walls of cortical blood vessels and white matter without any significant typical Alzheimer’s disease plaques. 2A- H & E stain; 2B- Congo red stain.

Discussion

Our case is an example of CAA with lobar intracerebral hemorrhage and surrounding edema that is out of proportion to the size of the hematoma and is responsive to steroid therapy. In clinical practice, the clinical and radiological findings are atypical for a case of intracranial bleed due to amyloid angiopathy without inflammation as there was no early expansion of intracerebral hematoma, yet the patient clinically deteriorated over the course of two weeks. Patients with intraparenchymal hemorrhage typically worsen clinically in the 24-36 hours after the ictus. Furthermore, our patient responded to steroid therapy, and then his condition deteriorated when steroid therapy was discontinued. Modern management guidelines do not recommend routine use of steroids for intraparenchymal hemorrhage, and thus, steroid administration is no longer a common practice when there is brain hemorrhage. The radiological findings in this case were suggestive of vasogenic edema which served as rationale for a short course of steroid therapy. Vasogenic findings in this case were supportive of vasogenic edema which served as rationale for a short course of steroid therapy. Vasogenic edema of the magnitude in this case was most likely due to underlying vasculitis which has been described in cases of CAA [10,11]. However, there was no evidence of vasculitis on brain autopsy. It is possible the vasculitis was missed as high dose methyl prednisolone was administered and may have ablated such findings, or it was overlooked in the brain necropsy sampling procedure.

Another interesting radiological feature of our case was the interval worsening of white matter brain lesions (WML) on the brain MRI scan three years after our patient had his first intracerebral bleed in the right parietal region. WML, a common finding in CAA, are clinically relevant but often neglected in the differential diagnosis, and may be associated with intracerebral hemorrhage [12]. CAA with WML has also been associated with vasculitis and the progression of these WML might serve as a marker of CAA [12].

Figure 1B: CT brain showing the expansion of right parietal hematoma with increasing surrounding edema and midline shift.

Figure 1C: CT brain showing interval decrease in edema and midline shift from the last CT brain (Figure 8) without any significant change in hematoma size.

Figure 2: Histopathology showing the deposition of amyloid in the wall of cortical blood vessels and white matter without any typical Alzheimer’s disease plaques. 2A- H & E stain; 2B- Congo red stain.
vascular or perivascular inflammation. Our patient displayed typical manifestations of CAA-ri which may include rapid and progressive cognitive decline, focal neurological deficits, and seizure. Like ARIA, CAA-ri typically resolves spontaneously or with steroid therapy. Recently, it has been shown that in CAA-ri patients, cerebrospinal fluid amyloid beta antibodies increase with symptomatic CAA-ri, but decrease with clinical and neuroimaging remission of CAA-ri, and are not elevated in sporadic CAA without inflammation [16]. Administration of oral corticosteroids has been shown to significantly decrease levels of anti-β 42 antibody in CSF along with improvement in clinical symptoms [6]. This biomarker may prove important in future management of patients such as our patient who may have had CAA-ri.

In summary, we provided the clinical findings and course of disease of an elderly patient with a past history of lobar brain hemorrhage and recent history of recurrent lobar brain hemorrhages. Brain imaging showed evidence of past cerebral microbleeds and extension of edema to the U-fibers surrounding the acute brain hemorrhage. In addition, the patients' edema was out of proportion to the size of hematoma. In such clinical circumstances, one may consider underlying vasculitis or CAA-ri, and in these cases steroids or other immunotherapy may be of benefit.

Author Contributions

Dr. Farooq was involved in the patient care and wrote the first draft of the manuscript. He also revised this manuscript after the critique by Dr. Gorelick. Dr. Gorelick was involved in drafting and critiquing the manuscript and developing a plan for revision. Jonathan Zande was involved in revision of the manuscript.

Ethical Approval

This manuscript/case report was considered by the Mercy Health, Saint Mary’s Health Care IRB and was determined to be exempt from IRB review.

References