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Cerebral amyloid angiopathy: early presentation in a patient with prior neurosurgical interventions. Case report

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Abstract

Background: Cerebral amyloid angiopathy (CAA) has classically been described as a disease of the elderly. Genetic predisposition has been linked to the APOE e3/e3 allele. Evidence suggests that brain insult in the form of injury, prior surgical intervention, or radiation can exacerbate the clearance of toxic proteins in patients susceptible to CAA.

Case: We describe a unique case of CAA in a 30-year-old male who had prior surgical interventions for spina bifida, Chiari malformation, and hydrocephalus as a child.

Conclusions: The case is used to teach important components regarding diagnosis, clinical suspicion, and highlight the need for further investigation regarding the emerging role of the glymphatic system and its role in clinical pathology.

Background

Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of amyloid fibrils along the walls of small to medium-sized arterial blood vessels (1). The pathogenesis of CAA remains unknown; however, in most cases of disease presentation, it is presumably caused by an irregular production or diminished clearance of amyloid beta protein (Aβ) (1). As a result, there is a significant buildup of Aβ protein levels, ultimately leading to its aggregation along the walls of small and medium sized leptomeningeal and cortical arteries (1). Impaired vasodilation and alteration in vascular reactivity have been

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identified as early markers of the disease (1). Collectively, these phenomena bring about oxidative stress, which further propagates the accumulation of Aβ (1). A study conducted by Yamada et al., investigating amyloid deposition in the brain of human subjects between the ages of 55 to 101 found that the incidence of amyloid deposition increases over time with advancing age. As such, CAA is considered a disease of the elderly (2). Little is known however if prior intracranial surgery can accelerate CAA in predisposed individuals.

Surgical intervention has the potential to damage healthy brain tissue and can lead to neuroinflammation, which has been postulated to accelerate amyloid pathology. Specifically, early surgical interventions can damage the blood-brain barrier (BBB), inhibit neurogenesis in the hippocampus, and lead to neural progenitor cell death. In patients without genetic predisposition for CAA, it has been postulated that the glymphatic system helps regulate neuroinflammation and clear toxic protein aggregates. In patients with APOE e3/3, this system may become overwhelmed with insult and result in malfunction (3). Additionally, vascular changes may involve early damage to vascular endothelial cells (3). A study conducted by Sugihara et al. employed immunohistochemistry to examine 123 autopsy brains from patients aged 30 to 59 (4). In their findings, Sugihara and colleagues report that the prevalence of cerebral Aβ deposits was two times higher in the patients who had received brain surgical interventions (27.8%) as compared to those who had not (14.8%) (4). Moreover, findings from this study also demonstrate that amyloid angiopathy was significantly more evident ($P < 0.05$) (4). This case report highlights a 30-year-old male who had early childhood surgical intervention for Spina bifida, Chiari malformation, and hydrocephalus who subsequently developed early onset CAA. We postulate potential mechanisms that may have contributed and warrant further investigation.

Case

This case report is of a 30-year-old male who had shunted hydrocephalus, Chiari decompression, spina bifida, seizures, and cerebral palsy. He presented originally at age 29 with a right frontoparietal hemorrhagic stroke with multiple other small intracranial hemorrhages including a left thalamic hemorrhage. He required a right decompressive hemicraniectomy with subsequent cranioplasty. Workup at that time for Col4a and aortopathy was negative. Diagnostic angiography was negative for vascular lesion. He was eventually discharged to rehab and made good clinical improvement with return to baseline functioning.

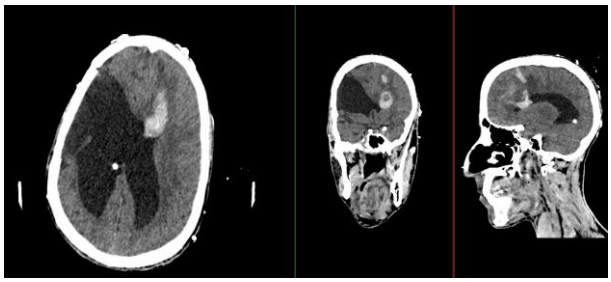

Figure 1. Prior encephalomalacia from previous right frontoparietal intraparenchymal hemorrhage. New acute left frontal hemorrhagic stroke.

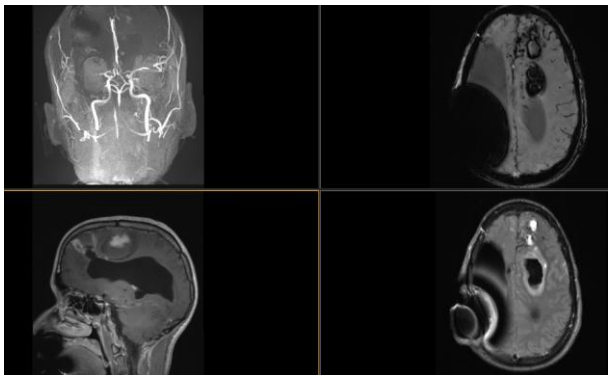

Figure 2. MRI/MRA consistent with cerebral amyloid angiography but not vasospasm. SWI imaging with classic presentation for CAA.

15 months after initial hemorrhage he developed symptoms of staring into space, right sided weakness, and aphasia. A left frontal intracranial hemorrhage was noted (Figure 1). Patient was admitted for further workup. Electroencephalography was done with abundant left frontal rhythmic delta activity but no seizures. Shunt tap was performed with no infectious or autoimmune etiology including negative findings for meningitis, JC virus, Varicella, fungal infection, malignancy panel, antiphospholipid battery, and ANCA. He was taken for diagnostic angiography where non-specific vasculopathy was noted. Magnetic Resonance Imaging with vasculitis protocol was done and concerning for CAA (Figure 2). Rheumatology was consulted and CT chest,

abdomen, and pelvis (CAP) was negative for vasculitis. Brain biopsy was completed and pathology was consistent with cerebral amyloid angiopathy and not acute vasculitis. APOE testing was positive for homozygous APOE e3/e3. He was discharged to long-term rehab and has been improving in strength and function. He remains non-verbal but is able to eat with assistance and smiles with family.

Discussion

CAA is associated with the accumulation of Aβ protein along the blood vessel walls in the brain. It is typically a disease presenting in elderly patients. Early-onset disease is generally associated with hereditary forms of CAA (5). However, history of prior brain surgery and/or radiation has also previously been shown to be associated with CAA in younger patients aged 30-59 (4). There are relatively few reported cases of biopsy-confirmed CAA years after initial surgical intervention. No cases have been associated with a specific childhood spina bifida, Chiari malformation, or shunted hydrocephalus. However, there has been documented vascular pathology after brain tumor radiation therapy that coincides with diagnostic criteria for cerebral amyloid angiopathy-related inflammation (CAA-RI), a subtype of CAA (6). Roongpiboonsopit et al. demonstrated evidence of cerebral microbleeds (CMBs) in 18/27 patients followed for a median of 4.1 years after craniospinal intervention (7). Five of these patients were children (median age 6.3 years). CMBs were primarily found in a lobar distribution which overlaps with the diagnostic criteria for CAA-RI, which suggests pathological and potentially functional similarity to CAA pathogenesis (6).

The exact correlation between history of prior cranial intervention and CAA remains unclear. A possible mechanism is decreased clearance of Aβ protein. Cerebral Aβ proteins are cleared through para-vascular pathways (8). The more recently discovered glymphatic system uses peri-vascular channels to facilitate excretion of central nervous system waste products, and has been suggested to play a direct role in Aβ protein clearance (9, 10). Early surgical intervention could theoretically impair lymphatic Aβ clearance, leading to an acceleration of CAA. McRobb et. al suggest another mechanism of early onset CAA is the downregulation of ADAM10, a protein that modulates the production of Aβ protein in the brain (11). Both of these topics warrant further investigation in pre-clinical studies with subsequent validation from clinical patient samples.

Conclusion

In summary, decreased clearance of Aβ protein by impaired glymphatic systems and downregulation of protein modulators may be a contributor to the pathogenesis of CAA and should be carefully considered in patients with APOE e3/e3 allele who had prior cranial interventions. Other sources of increased Aβ production should also be investigated.

List of Abbreviations: amyloid beta (Aβ), blood brain barrier (BBB), cerebral amyloid angiopathy (CAA), cerebral microbleeds (CMB), chest, abdomen, and pelvis (CAP)

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