Neuropsychological effects of cerebral amyloid angiopathy

Matthew Schrag MD, PhD; Howard Kirshner MD
Affiliation: Vanderbilt University School of Medicine, Dept of Neurology, Nashville, TN

Contact information:
        Address - 1301 Medical Center Dr, TVC Neurology Suite, Nashville TN 37232
        E-mail: matthew.schrag@vanderbilt.edu and howard.kirshner@vanaderbilt.edu

ABSTRACT
        Cerebral amyloid angiopathy is a condition of the cerebral arterioles and to a lesser extent capillaries and veins, wherein beta-amyloid is deposited. In arterioles, this preferentially targets vascular smooth muscle cells and in the later stages undermines the stability of the vessel. This condition is frequently co-morbid with Alzheimer's disease and its role in cognitive impairment and dementia is a topic of considerable recent research. This article reviews recent literature which confirms that CAA independently contributes to cognitive impairment by potentiating the neurodegeneration of Alzheimer's disease, by predisposing to microhemorrhagic and microischemic injury to the brain parenchyma, and by interfering with the autoregulation of CNS blood flow. In this review, we discuss the clinical presentation of cerebral amyloid angiopathy, with a focus on the neuropsychological manifestations of this vasculopathy.

Introduction
        Cerebral amyloid angiopathy (CAA) was largely a finding in pathological specimens at autopsy until the mid-1990s, but since then it has gradually become a widely recognized and important clinical entity. This disease is closely associated with Alzheimer's disease and is produced by vascular deposition of the same beta-amyloid peptide that produces the classical plaques in the parenchyma of patients with Alzheimer's dementia [1]. However, CAA may also occur independently of Alzheimer's disease, and it is an important cause of hemorrhagic stroke, subarachnoid hemorrhage, and focal epilepsy in the elderly. Recent research has suggested that among patient with Alzheimer's disease, the contribution of CAA to cognitive decline appears to be independent of parenchymal amyloidosis [2]. Finally, a CAA-associated angiitis which has been termed CAA-related inflammation or CAARI is an important, although rare, clinical presentation of CAA. In this syndrome, an aggressive autoimmune reaction against beta-amyloid in the CNS vasculature leads to acute or subacute inflammation or "CAARI" (cerebral amyloid angiopathy related inflammation". This syndrome was reproduced by vaccinations against the beta-amyloid peptide in a clinical trial to treat Alzheimer's disease (termed amyloid-related imaging abnormality (ARIA), but it is indistinguishable from CAARI) [3]. This reaction clarified that CAA is an important variable which may affect how patients with Alzheimer's disease respond to treatment. For these reasons, we felt it was important to review the pathophysiology and clinical presentation of CAA, with emphasis on the cognitive aspects of the disorder.

Pathophysiology
        It is becoming clear that one of the major mechanisms of clearing beta-amyloid from the brain involves active transport of the peptide by microglia to the perivascular space, where it crosses into the peripheral circulation [4]. Cerebral amyloid angiopathy is caused by the deposition of the beta-amyloid peptide in cerebral microvessels. This preferentially involves arterioles in the leptomeninges and cortical gray matter, although cortical capillaries and veins may be variably involved [1]. A mild degree of cerebral amyloid angiopathy is probably physiologic, representing this efflux of beta-amyloid from the brain via the perivascular clearance route. However, deposits of beta-amyloid may

accumulate along the basement membranes and in the vascular smooth muscle layer of arterioles, resulting in the death of vascular smooth muscle cells. This initiates a cascade of effects, both locally at injured vessels and within adjacent parenchyma.

There are at least two pathways contributing to the loss of vessel integrity in CAA: 1) lytic injury secondary to late complement activation, and 2) connective tissue remodeling secondary to matrix metalloproteinase activity. Parenchymal beta-amyloid binds and activates the classical complement pathway and binds to C3b, but because the parenchyma is deficient in late complement elements there is little lytic injury around parenchymal plaques. Vascular smooth muscle, however, secretes all of the elements of the complement cascade, including the late complement, so when the beta-amyloid/C3b complex is transported to the vessel, it activates the membrane attack complex, leading to lytic injury to the smooth muscle and other vascular elements [5,6,7]. Changes in complement levels may also be detected peripherally, suggesting that there is extensive activation of this pathway [8]. Matrix metalloproteinases are activated in CAA-affected vessels and in the surrounding parenchyma (MMP-2 in particular). These enzymes break down and remodel the basement membranes and other connective tissue elements [9]. Cumulatively, these processes undermine both the ability of the arteriole to autoregulate blood flow, and ultimately the fundamental structural integrity of the vessel.

There is diverse parenchymal injury secondary to this vascular dysfunction. The loss of vessel integrity leads to microhemorrhages and microinfarcts. The hemorrhagic changes unleash a cascade including induction of heme oxygenase, biliverdin reductase, and ultimately leading to local oxidative injury secondary to free-iron induced reactive oxygen species [10,11]. Additionally, there are perivascular T-cell infiltrates in the vessels around microhemorrhages which may carry the inflammatory milieu a larger distance than would be affected by the microhemorrhage alone. More broadly, vessels affected by CAA are surrounded by microglia/macrophages, suggestive of extensive inflammation which is unlikely to be restricted to the vasculature.Vascular smooth muscle cells then deteriorate [5,12]. The full impact of the loss of autoregulation on the function of parenchyma is not yet fully understood, but is likely to be of substantial importance. On neuroimaging, extensive white matter disease is an invariable finding in the setting of CAA, despite the observation that beta-amyloid deposition is largely restricted to the cortical ribbon and leptomeninges [13]. It is likely that white matter dysfunction is at least in part related to impaired autoregulation.

Clinical presentations of CAA

There are three common clinical presentations of CAA which may occur independently or together: 1) progressive cognitive impairment, 2) transient neurological spells (so-called "amyloid spells"), and 3) sudden focal neurological deficits related to intracerebral hemorrhage. CAA is present to some degree in nearly all brains meeting criteria for Alzheimer's disease, although moderate to severe CAA (which can be detected clinically) is present in about 30% of cases of Alzheimer's disease. About 10-20% of cases of moderate and severe CAA have no parenchymal
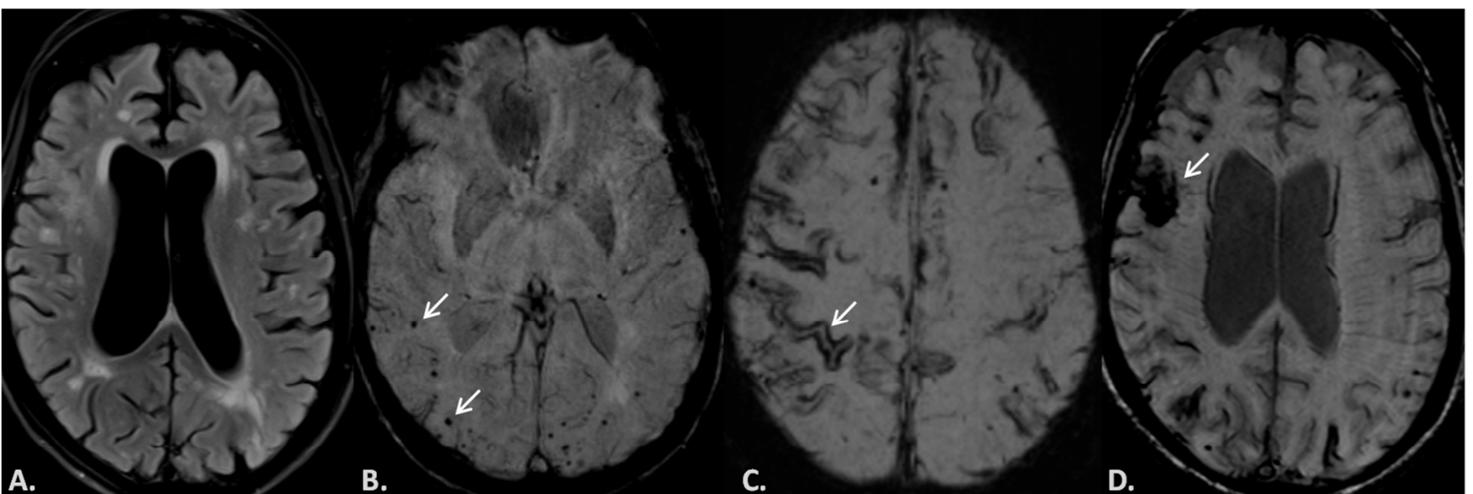

Figure 1: Neuroimaging features of cerebral amyloid angiopathy. A. Extensive white matter hyperintensity on T2 weighted or FLAIR sequences is a consistent but non-specific feature of cerebral amyloid anigopathy. B. Multiple microhemorrhages on susceptibility weighted imaging at the junction of the grey and white matter help to clinically establish the diagnosis of cerebral amyloid angiopathy and are related to cognitive dysfunction. C. Superficial siderosis is present in a minority of patients with cerebral amyloid angiopathy and may form a distinctive "tram track" sign, parallel outlines of the sulci as at the arrow. This finding is closely associated with "amyloid spells" and may predict the site of future intracerebral hemorrhage. D. Intracerebral hemorrhage from cerebral amyloid angiopathy is most common in the frontal lobes. After a symptomatic hemorrhage, patients are at high risk for recurrent hemorrhages.

pathology of AD [14-16]. Despite the high rate of comorbidity, the contribution of CAA to cognitive impairment is, at least in part, independent of the parenchymal AD pathology.

"Amyloid spells" are poorly understood, and they are often diagnosed as transient ischemic attacks (TIAs). A recent study suggested that TIAs or amyloid spells were often the earliest clinical sign of CAA [17]. This phenomenon is most closely associated with the neuroimaging finding of superifical siderosis on susceptibility-weighted sequences on MRI (see figure 1) [18]. This is most likely a focal epileptiform process, although others have suggested it is related to cortical spreading depression [19]. A definitive approach to managing these spells has not yet been presented, and it is doubtful that aggressive antiepileptic treatment of spells which are not explicitly epileptic in origin carries any benefit. The impact of these spells on prognosis from a cognitive or hemorrhagic standpoint is also not fully understood, although clearly areas of superficial siderosis are at risk for subsequent symptomatic hemorrhage [20].
The most dramatic and immediately life-threatening clinical presentation of CAA is spontaneous intracerebral hemorrhage in the elderly. These hemorrhages tend to be lobar in location, and if the patient survives, there is a high rate of subsequent re-hemorrhage [21]. Hemorrhages in CAA usually occur near the cortical-subcortical junction and can extend both into the brain parenchyma and into the subarachnoid space. Not surprisingly, intracerebral hemorrhage may leave patients with focal neurological deficits, or cognitive deficits which are less typical of AD. The most common site of symptomatic hemorrhage is the frontal lobes (despite CAA typically being more severe in the parietal and occipital lobes) and this may lead to dysexecutive syndromes which are atypical of Alzheimer's disease [22]. Moreover, epilepsy is more common after this sort of focal injury. CAA appears to be more common in Hispanic populations [17]. The strongest genetic risk alleles associated with sporadic CAA are complement receptor 1 (CR1) and ApoE epsilon 4 [23]. The association of complement receptor 1 (CR1) with the risk of developing CAA further strengthens the association between CAA and the complement cascade.

Neuropsychological profile of CAA

There is no neuropsychological correlate for mild CAA, which may suggest that mild CAA represents physiologic beta-amyloid clearance, rather than a pathological process. Moderate and severe CAA correlate most profoundly with decreased perceptual speed and less prominently with deficits in perceptual memory [24]. These findings remain significant after correction for co-morbid parenchymal AD and Lewy body pathologies, supporting the argument that CAA independently contributes to cognitive impairment. In the largest study on the topic, CAA (confirmed at autopsy) independently contributed to cognitive impairment and increased the risk for AD [2]. This important study confirmed the association with perceptual speed and episodic memory and further identified impairment in semantic memory and global cognition attributable to CAA pathology. Curiously, this study found no cognitive correlate to capillary CAA. While venous and capillary CAA have been observed in neuropathological samples, it is not clear what role if any they play in cognitive impairment.

Decreased perceptual speed is often viewed as a correlate to white matter injury and is observed to a degree as a feature of normal aging [25]. White matter hyperintensities are an invariable albeit non-specific feature of CAA; these occur with normal aging, and especially with vascular risk factors, but they are generally much more severe in CAA than in normal aging [26]. This is probably a manifestation of impaired cerebral autoregulation and vessel wall destabilization. A recent study found that cognitively normal subjects with suspected CAA, based on the presence of cortical microhemorrhages, had dramatically reduced cerebral blood flow (25 percent less than controls on global measures and even greater reductions focally in the parietal lobes and pre-cuneus area) [27]. Combined with the observed reduction in arteriolar vasoreactivity in CAA, this is strong evidence that white matter disease in CAA is largely related to hypoperfusion [28]. Neuropathologically, these white matter hyperintensities appear to be related to perivascular space widening, spongiosis and demyelination of the white matter, located most prominently around distal territories of perforating arterioles [29]. Microinfarcts have also been frequently observed in severe CAA, but they are virtually absent in mild CAA. These infarcts are distributed throughout the grey and white matter, and their presence is independent of ApoE status, other vascular risk factors, and Alzheimer's pathology, suggesting that they are likely related to the underlying beta-amyloid vasculopathy [30,31]. An independent contribution of these microinfarcts to cognitive impairment has not yet been reported, but given the extent of this pathology, it is likely that they are relevant. Even in typical Alzheimer's disease, the presence of even a few small infarctions seems to lower the threshold for the symptomatic presentation of the dementia [32-35].

Cognitive impact of cerebral microhemorrhages

Cerebral microhemorrhages can be detected with MRI using gradient echo T2* or the more sensitive susceptibility weighted imaging, both of which detect the presence of iron. Any paramagnetic material in the brain causes a magnetic dipole around the focus, thereby dephasing the image or making it appear dark. Signal voids 1-10mm in diameter in the brain parenchyma which can be separated from end-on vessels or areas of calcification are generally interpreted as cerebral microhemorrhages. It should be noted that the apparent size of microhemorrhages is overestimated by these techniques, an effect termed "blooming artifact" [36]. Cerebral microhemorrhages may be caused by a number of vasculopathies, including hypertension, infection (such as bacterial endocarditis), and genetic causes; they are most commonly associated with CAA when they occur in a lobar distribution (sparing the basal ganglia, pons and usually the cerebellum, locations much more typical of microhemorrhages associated with hypertension) in elderly patients [37]. Microhemorrhages in a cortical/lobar distribution appear to affect cognition and the risk of subsequent cognitive decline, while deep and infratentorial microhemorrhages are not definitively related to cognition [38-40]. For this reason, studies which did not discriminate based on the distribution of microhemorrhages have generally not detected cognitive sequelae from microhemorrhages [41]. The correlation of cortical cerebral microhemorrhagess with cognitive impairment and CAA on neuropathology has been robust, and microhemorrhages on MRI have become a clinical surrogate marker of CAA.

CAA related inflammation

CAA related inflammation is a treatable cerebral vasculitis occurring in the context of severe CAA. Patients with this vasculitis are usually younger than typical patients with CAA and are often homozygous for APOE e4. Patients with this variant of CAA typically present with rapidly progressive dementia accompanied by headaches, seizures and/or focal neurological symptoms. On imaging, they usually have an asymmetric pattern of lobar/cortical microhemorrhages with vasogenic edema in the areas most severely affected. Early recognition of this syndrome and prompt treatment with high-dose corticosteroids and/or cyclophosphamide typically produces a good outcome. The underlying edema usually resolves, although the microhemorrhages are permanent. A minority of patients progress despite treatment and a minority of patients have more than one episode [42,43].

The long-term cognitive outcome of CAA-RI is not yet clear. Some patients appear to have complete remission of symptoms, while others have progressive cognitive decline which may be related to an underlying neurodegenerative disease. The literature describing this syndrome uses a variety of terms – CAA related inflammation (CAARI), amyloid-beta related angiitis (ABRA), and amyloid-related imaging abnormalities (ARIA). From a practical point of view, these syndromes are clinically indistinguishable. CAA-related inflammation, despite its rarity, is clinically important because it is treatable if recognized early. Additionally, it may represent the most severe spectrum of beta-amyloid associated blood vessel diseases and give some insight into the mechanism(s) of immunological damage to the vessels in this vasculopathy.

Concluding remarks

Moderate and severe beta-amyloid deposition in cerebral arterioles is associated with decreased perceptual speed, impaired memory, and global cognition, and this association appears to be independent of comorbid neuropathologies. Mild CAA and capillary CAA have no clear neuropsychiatric correlates, suggesting they are either physiologic or pre-clinical conditions. It is becoming clear that CAA is an important variable in the pathophysiology of AD.

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