geliş tarihi/received date 24/02/2009 • kabul ediliş tarihi/accepted date 05/03/2009

Cerebral Amyloid Angiopathy*

Serebral Amiloid Anjiyopati*

Mahmut Edip Gürol

Iowa Üniversitesi Carver Tıp Fakültesi, Nöroloji Bölümü, Iowa City, Iowa, Amerika Birleşik Devletleri

* Presented in part at the 44th Annual National Neurology Congress of the Turkish Neurological Society, Antalya, Turkey (Bu çalışmanın bir kısmı, Türk Nöroloji Derneği tarafından düzenlenen 44. Ulusal Nöroloji Kongresinde sunulmuştur).

Turk Norol Derg 2009; 15: 1-9

ÖZET

Serebral amiloid anjiyopati (SAA) amiloid-beta (Aβ) peptidlerinin leptomeningeal arterler, arteriyoller ve de venüllerin duvarında birikimi ile tanımlanan bir hastalıktır. Bu patolojik değişikliklerin ilk defa 1909 yılında tanımlanmış olmasına rağmen, SAA'nın klinik-radyolojik belirtileri, nörobiyolojisi ve de doğal seyri ile ilgili bilgilerimizin çoğu son 30 yılda yapılan araştırmalardan kazanılabilmiştir. SAA ile diğer sistemik/viseral amiloidozlar arasında belirgin bağlantı gösterilememiştir. Hipertansiyon dahil klasik damarsal risk faktörlerinin de SAA patogenezinde rolü saptanmamıştır. SAA yaşlı insanlardaki spontan ve antikoagülana bağlı lober intraserebral kanamaların en sık görülen sebebidir. Bu patoloji aynı zamanda, yine lober bölgelerde, manyetik rezonans gradyen eko (MRI-GRE) sekanslarında küçük noktasal siyah "susceptibility" artefaktları olarak görülüp serebral mikrokanama (SMK) diye adlandırılan lezyonlara da neden olmaktadır. SMK sayısı hastalık ağırlığının önemli bir işareti ve de SAA için kötüleşme prediktörüdür. Amiloid anjiyopati aynı zamanda iskemik mikrovasküler ak madde hastalığının ve derin infarktların da sıkça rastlanan bir nedenidir. Bahsedilen ak madde hastalığı kavramı bilgisayarlı tomografide koyu, "fluid attenuated inversion recovery (FLAIR)" manyetik rezonansta parlak gözüken, subkortikal ve periventriküler ak maddede infarkta ilerlememiş değişiklikleri tanımlamak için kullanılmaktadır. SAA'ya bağlı damarsal işlev bozukluğu ve de bunun hemorajik ve iskemik komplikasyonları yaşlılarda vasküler bilişsel bozukluğun önemli nedenlerindendir. Bu bağımsız etkinin senil plaklar ve nörofibriler yumaklar gibi Alzheimer patolojisi ile sinerjistik olarak etkileşimde bulunduğu gösterilmiştir. SAA tanısının hasta hayatta iken güvenli şekilde konabilmesi için klinik-radyolojik tanı kriterleri geliştirilmiş ve de bunların validasyonu yapılmıştır. Boston kriterlerine göre, 55 yaş ve üzerindeki bir hastada, beynin lober, kortikal veya kortikosubkortikal alanlarına sınırlı (serebellar kanamalar kabul edilmektedir), başka bir altta yatan etyoloji ile açıklanamayan çok sayıda büyük veya mikrokanamanın varlığında tanı "probable" (muhtemel) SAA, aynı şartlarda tek bir kanamanın varlığında ise tanı "possible" (olası) SAA şeklinde konulmaktadır. Şu anki tedavi ilkelerine göre SAA ile bağlantılı intraserebral kanamadan şüphelenilen hastalarda nonvalvüler atriyal fibrilasyon varlığında antikoagülasyon, ciddi kanama riski nedeniyle önerilmemektedir.

Anahtar Kelimeler: Serebral amiloid anjiyopati, serebral kanama, kognitif bozukluk, manyetik rezonans görüntüleme.

ABSTRACT

Cerebral Amyloid Angiopathy

Mahmut Edip Gürol

Department of Neurology, Carver College of Medicine, University of Iowa, Iowa City, Iowa, United State of America

Cerebral amyloid angiopathy (CAA) is characterized by the accumulation of amyloid beta-peptides (Aβ) in the walls of leptomeningeal arteries, arterioles, and veins. Despite the fact that these pathological changes were first described in 1909, major advancement in our understanding of the clinicoradiological manifestations, neurobiology, and course of CAA has occurred only during the last 30 years. No significant associations have been shown between CAA and other systemic/visceral amyloidoses or vascular risk factors, including hypertension. CAA is well known as the most common cause of spontaneous and anticoagulant-related lobar parenchymal ICH in the elderly. It also causes lobar cerebral microbleeds (CMBs), small dot-like dark susceptibility artifacts visible with gradient recalled echo (GRE)-magnetic resonance imaging (MRI). CMBs are important markers of disease severity and predictors of CAA progression. Amyloid angiopathy is also a common cause of ischemic microvascular white matter disease (WMD) and deep cerebral infarctions. Such WMD is defined as subcortical and periventricular white matter changes without obvious infarction, as well as a dark appearance on computerized tomography (CT) and a bright appearance on fluid attenuated inversion recovery (FLAIR)-MRI. CAA-related vascular dysfunction, with its hemorrhagic and ischemic complications, is a recognized contributor to vascular cognitive impairment in the elderly, an independent effect that is synergistically increased by Alzheimer pathologies, such as plaques and tangles. A set of clinicoradiological criteria was established for the accurate diagnosis of CAA. According to the Boston Criteria, patients aged 55 years and older with multiple hemorrhages (on CT or GRE-MRI) restricted to the lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) are diagnosed as probable CAA when no other etiology is found; a single hemorrhage in the same region is classified as possible CAA. Current guidelines recommend that patients with non-valvular atrial fibrillation suspected to have CAA-related ICH not be offered long-term anticoagulation therapy because of the significant risk of rebleeding.

Key Words: Cerebral amyloid angiopathy, cerebral hemorrhage, cognitive impairment, magnetic resonance imaging.

Cerebral amyloid angiopathy (CAA) is caused by the accumulation of amyloid beta-peptides (Aβ) in the walls of leptomeningeal vessels and is the most common cause of lobar intracerebral hemorrhage (ICH) in patients over 55 years of age. These fibrillar proteins are similar to the predominant constituents of the senile plaques observed in Alzheimer's disease (AD); plaque amyloid is primarily comprised of the Aβ-42 species, which has a carboxyl terminus at amino acid position 42, and vascular amyloid primarily consist of the Aβ-40 species, which terminates at position 40 (1). Gustav Oppenheim published the first histopathological description of the vascular abnormalities recognizable as vascular-amyloid depositions in 1909, just 2 years after the original clinical-pathological report of a demented patient by Alzheimer. Despite this early recognition, it took another 3 decades for the first article with a primary focus on cerebrovascular amyloid deposition to appear in the medical literature; the first influential paper on the association between CAA and ICH was published in 1979 (2). The use of magnetic resonance imaging (MRI) methods that can detect cerebral microbleeds (CMBs, susceptibility artifacts ≤ 5 mm in diameter) and the subsequent validation of clinicoradiological criteria made the diagnosis of CAA in living patients possible, significantly increasing the pace of clinical research in CAA during the last 2 decades (3,4). There is now unequivocal evidence that CAA-related vasculopathy not only causes lobar ICH, but also ischemic microvascular white matter disease (WMD), thereby contributing to vascular cognitive impairment in elderly patients. Transgenic mouse models have been developed with mutations in genes related to AD and CAA, furthering our understanding of the etiology and evolution of these related conditions. This review focuses on the clinical, physiopathological, and radiological features of CAA, with a particular emphasis on its independent contribution to the risk of WMD and dementia in the elderly.

PATHOPHYSIOLOGY

Microscopically, deposition of an amorphous, intensely eosinophilic material results in characteristic acellular thickening of the walls of small- and medium-sized leptomeningeal arteries (including arterioles) and veins. The amyloid-laden vessels have a rather characteristic appearance, even with routine hematoxylin and eosin staining, but the "apple-green" birefringence of the sections stained with Congo red viewed under polarized light is still cited as the classical pathological hallmark of CAA (5). Immunohistochemistry is increasingly used to identify amyloid deposition in the brain (Figure 1). This selective staining showed that antibodies to the Aβ 1- to 40-amino acid peptide (Aβ-40) more effectively label microvessels, whereas anti-Aβ-42 antibodies preferentially bind senile plaques of AD (6). This finding shows that pathogenic molecules involved in ce-

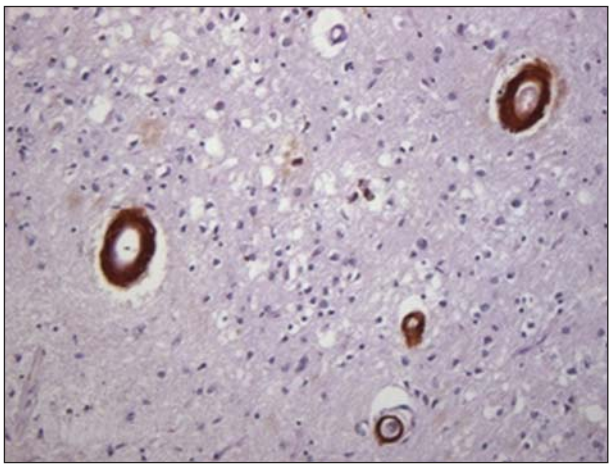

Figure 1. Aβ immunohistochemistry shows the replacement of many arteriolar walls by Aβ-immunoreactive material.

rebral parenchymal and vascular amyloid deposits-albeit closely related-are different. In CAA, amyloid infiltrates the media and adventitia of small- to medium-sized leptomeningeal and superficial cortical vessels, resulting in effacement of the vessel wall, sometimes to the point that its identification as arterial or venous is impossible. Affected vessels might show a distinctive "double-barrel" appearance. These vessels might undergo fibrinoid degeneration or necrosis, as well as segmental dilation with microaneurysm formation, leading to vessel rupture and hemorrhage. No significant relationship between CAA and other systemic/visceral amyloidoses has been reported.

The sequence of events that triggers the deposition of cerebrovascular amyloid, the determinants of its distribution and progression, and the mechanisms of blood vessel injury are not well understood. More than 10 different amyloid peptides are known to accumulate in cerebral parenchyma and vessels, but Aβ-related CAA is the most common form observed in AD and CAA (7); therefore, Aβ is thought to be detrimental to vessel structure and function. Aβ is generated by the sequential proteolytic processing of a transmembrane protein-amyloid-β precursor protein (APP); the enzymes involved are β-secretase (BACE) and the γ-secretase/presenilin complex (8). Based on animal models, vascular amyloid appears most likely to be of neuronal origin, but the hematogenous and vessel wall hypotheses cannot be completely refuted (9).

Some genetic factors have been associated with early onset and familial types of CAA. A number of mutations located within the Aβ sequence or at the β- and γ-secretase cleavage sites can cause familial Aβ-CAA, such as the Dutch, Iowa, Italian, and Arctic types, or familial AD with prominent Aβ-CAA pathology (10). Even in the exceedingly more common form-sporadic CAA with clinical presentation 20 years later than in hereditary forms-a significant association between the presence of the APOE epsilon 2 (ε2) or epsilon 4 (ε4) alleles and greater risk of CAA-related hemorrhage was observed when compared to people that had only the common APOE epsilon 3 (ε3) allele (11,12). The APOE ε4 allele has been associated with increased Aβ deposition, whereas APOE ε2 is associated with vessel pathology, such as cracking and necrosis that predispose to rupture; these associations further support a mechanistic link between APOE ε allele carrier status and vessel pathology in CAA (13,14). Regarding the accumulation of Aβ in vessel walls, both increased production and decreased degradation have been proposed as potential culprits.

Currently, observations from transgenic mice models support the hypothesis that impaired interstitial fluid drainage results in decreased Aβ clearance, thereby promoting Aβ aggregation and vascular deposition. A detailed discussion of the proposed mechanisms of Aβ-related vascular injury is beyond the scope of this review, but the aforementioned genetic factors in combination with acquired factors, such as age-related degenerative changes, minor trauma, and focal amyloid accumulation, appear to promote vascular toxicity of the Aβ, triggering the pathological cascade that ultimately results in the clinical manifestations of CAA.

Autopsy series report a propensity for severe CAA pathology to involve the parieto-occipital regions (5). These data are supported by advanced radiological studies that report more lobar bleeds and significant retention of an in vivo amyloid-labeling agent (Pittsburgh Compound B) in the posterior regions of the brains of patients with CAA (15,16).

EPIDEMIOLOGY

Inconsistencies in the definition of CAA in postmortem pathologic case series make it difficult to compare its prevalence across studies, but there is unequivocal evidence showing that both the prevalence of CAA pathology and the incidence of its clinical manifestations increase with age. In a large autopsy series consisting of 784 consecutive postmortem brain pathology studies, the prevalence of moderate to severe CAA was 2.3% among patients aged 65-74 years, 8% among those 75-84 years, and 12.1% among those over 85 years (17). In a series of 400 consecutive autopsies from Japan, CAA of any grade was observed in at least one section in 91 cases (22.8%) and was strongly correlated with age. The presence of CAA did not correlate with blood pressure nor with the severity of cerebral atherosclerosis, a finding replicated in most subsequent studies (18). Another study that compared the frequency of CAA pathology in AD patients and age-matched controls reported a significantly higher rate in AD patients (94.1% vs. 33.3%) (19).

CLINICORADIOLOGICAL FEATURES and DIAGNOSTIC CRITERIA

Lobar Intracerebral Hemorrhage (ICH)

Spontaneous cortical and corticosubcortical (lobar) ICH is the clinical hallmark and a dreaded consequence of CAA. CAA is also an important cause of warfarin-associated lobar ICH in the elderly (20). The worldwide annual incidence of primary ICH is 30-52/100.000 (21,22). Recent population-based studies showed an increase in antithrombotic-associated bleeds and lobar hemorrhages, possibly related to CAA in the aging population-further evidence of the importance of CAA as a public health problem (23,24). The annual age- and sex-adjusted lobar ICH incidence rate was 9.0/100.000, yielding a deep to lobar ratio of 2.3:1, but it should be remembered that other rare etiologies such as vascular malformation might also cause lobar ICH (22). Advanced age, again, represents the strongest risk factor for CAA-related ICH, whereas gender does not appear to play a significant role. In a clinicopathologic series of 107 patients with sporadic CAA-related ICH (mean age: 72 years) compiled by Vinters, the frequency of high blood pressure was 31.8% (5). This rate is low compared to the > 50% prevalence of hypertension among Americans aged 65 years and older, and hypertension has not been shown to be a significant risk factor for CAA-related ICH (25).

APOE ε4 and ε2 allele carrier status as a risk factor for increased vascular Aβ accumulation and for vessel pathology resulting in rupture were discussed in the Pathophysiology section (13,14). The APOE ε2 allele was overrepresented among patients with warfarin-associated lobar hemorrhage and there is strong evidence suggesting that CAA is an important cause of anticoagulant-related lobar ICH in the elderly (20). The recognition of this association and the high rate of ICH recurrence in CAA have led to a change in recommendations regarding long-term anticoagulation as a secondary prevention strategy (26). While antiplatelets can be resumed in survivors of both deep and lobar ICH without a major increase in the risk of recurrent bleeds, it is recommended that survivors of suspected CAA-related ICH with non-valvular atrial fibrillation not be offered long-term anticoagulation (27,28). Current guidelines do not recommend routine genetic testing or MRI screening in an attempt to identify asymptomatic CAA before starting long-term anticoagulation therapy (29).

CAA-related hemorrhages are located in the cortical and corticosubcortical regions of the brain, which are also the most common sites of vascular amyloid deposition. A gradient-echo MRI-based study of 59 patients with probable CAA reported that hemorrhages are more likely to occur in the temporal and occipital lobes, and that they tend to recur in areas of prior hemorrhage, regardless of lobe, suggesting that regional differences within the brain play a role in the development of CAA-related hemorrhages. The cerebellum might contain some vascular amyloid and was reported to occasionally show CAA-related ICH. The pons is not a site associated with CAA-related ICH and it is critically important to remember that deep seated hematomas-whether in the basal ganglia/thalamus or in brainstem-are typically not associated with CAA pathology (30).

Clinically, acute CAA-related lobar ICH is not significantly different than other types of ICH. The size and location of the bleed, together with the clinical severity in the acute phase, determine the outcome. Any anticoagulation should be rapidly reversed and other aspects of ancillary care should be provided according to current guidelines (31). Cerebellar hemorrhages should be treated, with particular attention to the mass effect and impending risk of ventricular outflow obstruction, and increased intracranial pressure that might result in herniation unless treated with decompressive surgery (32). Based on the existing data, small differences between lobar and deep ICH might exist in terms of clinical course and treatment response. Patients with a small lobar ICH might be at greater risk of immediate seizure and their bleeds are more likely to extend into the subarachnoid space than into the ventricles (33). Despite the fact that early surgical intervention did not show any significant benefit in ICH patients overall, a meta-analysis of 293 patients with lobar hemorrhage included in 3 randomized trials suggest that a better outcome is obtained with early surgery in lobar ICH cases (34). The Surgical Trial in Intracerebral Hemorrhage II (STICH II) is currently underway in an effort to compare the benefit of surgery within 48 hours to initial conservative management in patients with spontaneous ICH located within 1 cm of the cortical surface. If this ongoing study confirms the beneficial effect reported in the meta-analysis, surgical evacuation might become an important acute treatment option for CAA-related lobar ICH patients (34).

The course of the disease is characterized by recurrent lobar hemorrhages, with a 2-year cumulative recurrence rate of 21% in a cohort of 71 consecutive survivors of lobar ICH (35). Molecules that can interfere with the pathogenic Aβ cascade have been tested in preliminary studies, but currently there is no treatment that can halt the progression of the pathology or its clinical course.

Rare Clinical Manifestations

Transient neurological symptoms constitute a rare, but known entity in CAA. Such patients describe spells consisting of negative (weakness, numbness) or positive (paresthesias) symptoms of short (seconds-to-minutes) duration that can spread smoothly over contiguous body

parts (36). These episodes are thought to originate from epileptic activity or spreading depression of the cortex surrounding small hemorrhages. As these spells are mostly recurrent and stereotypical, transient ischemic attacks should be a part of the differential diagnosis and these patients should undergo vascular imaging to rule out proximal vessel stenosis. Performing and carefully reviewing GRE-MRI is important for identifying a corresponding superficial bleed in order to avoid antithrombotic treatments that might be hazardous in the presence of CAA.

A number of case reports describe patients that presented with subacute cognitive/behavioral changes, seizures, headache, and focal neurological deficits. These patients also had significant white matter hyperintensities (WMH) on T2-weighted MRI and cerebrospinal fluid exams, indicating ongoing inflammation in the absence of infection. Two closely related categories, both associated with severe CAA pathology, were identified upon neuropathologic evaluation:

1. Aβ-related angiitis that often shows granulomatous, angiodestructive inflammation and meningeal lymphocytosis (37), and

2. CAA-related perivascular inflammation with multinucleated giant cells, but no angiographic or pathologic evidence of vasculitis (38). The recognition of these clinicopathological entities is important, as they might respond favorably to immunosuppressive treatment.

Radiological Features and Diagnostic Criteria

Brain CT is fast, widely available, and accurate in the early diagnosis of ICH. Nevertheless, MRI outperformed CT in emergency assessment of patients with most types of suspected acute strokes, and both modalities performed similarly in the detection of acute intracranial hemorrhage (39). GRE-MRI revolutionized clinical practice and research involving CAA patients by virtue of its ability to show both acute (deoxyhemoglobin-containing) and old (hemosiderin-containing) bleeds as strong hypointense areas. GRE sequences are ideal for demonstrating microbleeds that may not be seen with other imaging studies. CMBs are small dot-like hypointense lesions ≤ 5 mm in diameter that represent hemosiderin deposition from tiny (mostly subclinical) blood leaks (Figure 2A). A detailed field guide for accurate detection and interpretation of CMBs was recently published (40). Furthermore, the Stroke Diagnostics and Therapeutics Branch of the National Institute of Neurological Disorders and Stroke has an interactive website dedicated to the interpretation of GRE-MRI in acute stroke patients, and includes examples of hemorrhage mimics and other GRE findings, as well as self-assessment tools (http://gre.ninds.nih.gov/). CMBs proved to be an important predictor of clinical and radiological deterioration in CAA patients. Microhemorrhages are common in patients with CAA-related symptomatic ICH and their lobar distribution is similar to that of macrobleeds. Greater number of hemorrhages at baseline is predictive of an increased risk of subsequent cognitive impairment, loss of independence, or death among patients not previously demented/dependent, as well as the risk of future symptomatic ICH (26).

One of the key achievements in CAA research has been the development and validation of a set of criteria that allows this diagnosis to be made in living patients (4). According to the Boston Criteria, patients aged 55 years and older with multiple hemorrhages (on CT or MRI-GRE) restricted to the lobar, cortical, or corticosubcortical regions (cerebellar hemorrhage allowed) are diagnosed as probable CAA when no other etiology is found; a single hemorrhage in the same setting is classified as possible CAA (4). The criteria do not specifically state the minimum imaging requirements to exclude other underlying pathologies (i.e., vascular malformations, tumor, hemorrhagic infarction), but most lobar ICH patients in the United States undergo brain MRI that includes GRE, diffusion-weighted, and post contrast T1-weighted sequences. If ≥ 2 micro- or macrobleeds are found in a patient over 65 years, without clinical or radiological suspicion of an alternative etiology, the diagnosis of probable CAA is generally made. Among younger patients, in those with single lobar bleeds and in all patients that raise suspicion of a different underlying pathology, further imaging and diagnostic testing is performed. Advanced testing is tailored according to the individual patient's presentation and might include non-invasive imaging, such as MR angiography or CT angiography, or invasive tests, such as cerebral angiography, lumbar puncture, and in rare cases a brain biopsy. A clinicopathological correlation study was performed with 39 patients that had a clinical diagnosis of probable or possible CAA and full postmortem pathological assessment (4). All 13 patients diagnosed with probable CAA according to Boston Criteria had significant amyloid angiopathy on pathological evaluation, indicating a very high specificity of the probable category. Among the 26 patients with the diagnosis of possible CAA, 16 (61%) were pathologically confirmed as having severe CAA, suggesting a fair specificity for this category (4). Boston Criteria has made it possible to enroll well-characterized CAA patient populations into clinical studies, thereby facilitating advances in our understanding of the clinical, radiological, and physiopathological correlates, as well as the course of this condition in humans.

Amyloid Angiopathy-Related Vascular Dysfunction and Ischemic Manifestations

An association between hereditary CAA and cognitive impairment has been reported in the few familial forms of CAA (41). Clinical observations suggesting such an associ-

ation between the much more common sporadic forms of CAA and cognitive impairment also exist, but have only recently been tested in prospectively identified cohorts that underwent standardized cognitive testing and imaging studies. Advances in MR imaging and analysis methods have also made it possible to investigate the association between CAA and WMD that appears in subcortical and periventricular brain regions as bright lesions with T2/FLAIR MRI sequences (Figure 2B,2C).

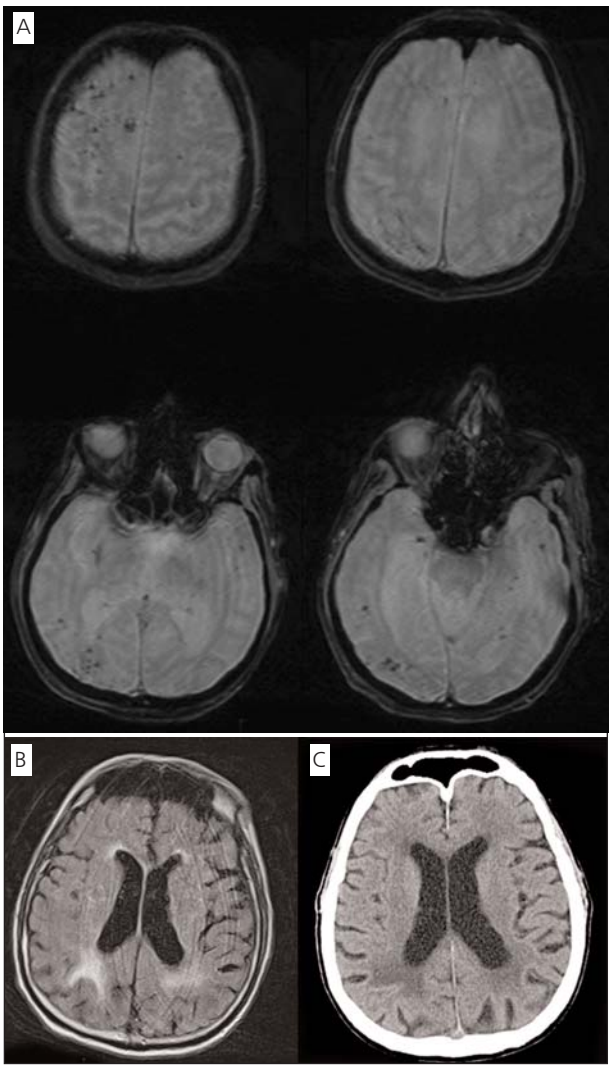

Figure 2. Radiological images of a 92-year-old patient that presented with predominantly executive dysfunction of 2-3-year duration. This patient did not have any symptomatic ICH and autopsy confirmed the diagnosis of CAA. Microhemorrhages clustered mostly in the right frontal and right temporooccipital regions are seen on GRE-MRI **(A)**. Part or all of some deep structures, such as the basal ganglia, might appear dark on GRE-MRI because of their iron content; this artifactual appearance should not be confused with bleeds. FLAIR-MRI **(B)** and head CT **(C)** show a moderate degree of white matter change, predominantly in the posterior periventricular regions.

Two population-based autopsy series suggested that the presence of CAA pathology might be independently associated with the risk of dementia, even after adjusting for age and markers of concomitant AD pathology, such as plaque and tangle counts (42,43). These studies included unselected community-dwelling elderly individuals with a mean age at death of 85 years. The presence of hemorrhages did not account for the increased risk of dementia found in patients with CAA pathology, but only a few of them had brain bleeds. The potential factors that might mediate such a link might be the direct effects of critically located cerebral macro- or microhemorrhages, cortical or subcortical infarcts, and widespread WMD that result in disruption of neural tracts.

In a study that assessed the relationships between white matter lesions, cognitive impairment, and other clinical markers of disease severity in a CAA cohort, WMD was a frequent finding on brain imaging (found in 77%, severe in 32%). WMD was associated with GRE-MRI hemorrhage counts and with the risk of recurrent ICH. Patients with cognitive impairment prior to their index ICH were more likely to have severe WMD on CT and advanced periventricular WMH on MRI, even after adjusting for age (44). The view that advanced CAA can induce clinically important vascular dysfunction that might ultimately result in white matter ischemia became an intriguing hypothesis for the association between CAA, WMD, and cognitive impairment, and fueled further clinical and laboratory research (45).

Using sensitive quantitative methods to measure white matter hyperintensities (WMH), we have found that CAA patients had almost twice the WMH volume that AD patients and individuals with mild cognitive impairment (MCI) had (1). This association is even more striking in view of the data showing increased WMD in AD patients when compared to non-demented age-matched controls, which suggests that CAA pathology may contribute independently to ischemic changes in white matter (46). Our group also noted an average 18% annual increase in WMH volume in CAA patients and that there was an independent association between the rate of progression and the presence of cognitive impairment (47). The anatomic distribution of WMD in patients with advanced CAA was compared to that of healthy controls using diffusion tensor imaging (DTI). Fractional anisotropy (FA), calculated from DTI, is a measure of the directional diffusivity of water, and it is thought to represent white matter integrity. FA was reduced in CAA, specifically in temporal white matter and in the splenium of the corpus callosum, suggesting that advanced CAA could be associated with a characteristic pattern of regional brain tissue degeneration (48). Another very recent study identified small areas of restricted diffusion (acute silent infarcts) in

12 of 78 subjects (15%) with CAA versus 0 of 55 AD/MCI subjects, further supporting the view that CAA causes ischemic lesions in addition to ICH (49).

Several studies directly addressed the unexplained issue of the mechanism of vascular dysfunction in CAA. Plasma Aβ-40 concentration (but not Aβ-42 level) was found to be independently associated with WMH volume in individuals with CAA, AD, and MCI (1). Aβ-40 peptide is the soluble form most commonly found in vessel walls, whereas Aβ-42 is primarily observed in parenchymal plaques in AD. In a transgenic mouse model Aβ-40 (but not Aβ-42) applied to the mouse cortex blunted the physiological increase in cerebral blood flow that normally results from pharmacological (acetylcholine, bradykinin, or calcium ionophore) and physiological (sensory stimulation) stimuli (50,51). Accumulation of Aβ-40 deposits in the walls of leptomeningeal vessels in CAA patients might result in ischemia in the territory of the distal end arteries running to the deep white matter, presumably via similar mechanisms. A recent study used transcranial Doppler ultrasound to compare cerebral vascular reactivity (VR) in patients with CAA to healthy age-matched controls. Patients with CAA showed significantly decreased VR in the posterior cerebral arteries in response to visual stimulation, possibly reflecting an occipital predilection of the pathology (52). In summary, there is now ample data from both human and animal studies that support the theory that CAA-induced vascular dysfunction is a cause of ischemic microvascular white matter damage in the elderly. CAA and CAA-related WMD appear to contribute independently to cognitive impairment in the elderly, giving CAA a high priority in dementia as well as in stroke research.

THE FUTURE

One of the limitations of studying Aβ in humans, until recently, has been the lack of in vivo markers of Aβ; therefore, quantitative studies have had to rely on autopsies. The development of positron emission tomography (PET) ligands that can bind to Aβ deposits has revolutionized research in CAA and AD. Pittsburgh compound B (PiB) is one of these molecules, a derivative of Congo red with a carbon 11 atom attached. The binding is increased most prominently in the frontal cortex in AD and the occipital cortex in CAA (16,53). PiB-PET detection of vascular Aβ can serve as a method for identifying the location and extent of CAA in living subjects. PiB might become an invaluable marker of disease severity, disease progression, and treatment response if ongoing studies prove its correlation with these measures. In a 42-year-old man with subtle clinical signs of Iowa-type hereditary CAA, we observed elevated PiB retention, selectively in the occipital cortex, sparing regions typically labeled in AD (54). This finding strongly suggests that PiB-PET can non-invasively detect isolated CAA prior to overt signs of hemorrhagic/ischemic brain damage and can potentially help in the identification and stratification of pre-symptomatic patients for enrollment in clinical studies.

Recent studies using in vivo kinetic measurements via multiphoton imaging in transgenic mouse models provided some insight into the initial vessel involvement and propagation of CAA. The earliest appearance of CAA was observed in leptomeningeal arteries as multifocal deposits of band-like Aβ. Over subsequent imaging sessions, these deposits grew locally and new bands appeared in different segments (additional initiation events). During the early phases of CAA development, the overall pathology burden progressed at a consistent rate, raising hopes that this model is amenable to investigations of therapeutic interventions (55).

CONCLUSIONS

Following rather slow but constant progress in the understanding of CAA during the 7 decades following its initial description, there has been a huge increase in research into its cause, genetic associations, disease mechanisms, clinical manifestations, and natural course. We now have a validated set of clinicoradiological criteria that allows accurate diagnosis of CAA in living patients. CAA is well established as the most common cause of lobar parenchymal macro- and microbleeds in the elderly, but also as a common cause of ischemic microvascular white matter injury and deep cerebral infarctions. CAA-related vascular dysfunction, with its hemorrhagic and ischemic complications, is a recognized cause and/or contributor to vascular cognitive impairment in the elderly, an independent effect that is synergistically increased by Alzheimer pathologies, such as plaques and tangles. There is currently no treatment that is proven to stop the progression of CAA, but research has shown a number of relevant therapeutic targets as well as new radiological markers of disease severity and progression that will be useful when potential treatments are ready to be tested in clinical trials.

REFERENCES

1. *Gurol ME, Irizarry MC, Smith EE, Raju S, Diaz-Arrastia R, Bottiglieri T, et al. Plasma beta-amyloid and white matter lesions in AD, MCI, and cerebral amyloid angiopathy. Neurology 2006;66:23-29.*
2. *Smith EE, Eichler F. Cerebral amyloid angiopathy and lobar intracerebral hemorrhage. Arch Neurol 2006;63:148-151.*
3. *Greenberg SM, Finklestein SP, Schaefer PW. Petechial hemorrhages accompanying lobar hemorrhage: Detection by gradient-echo MRI. Neurology 1996;46:1751-1754.*
4. *Knudsen KA, Rosand J, Karluk D, Greenberg SM. Clinical diagnosis of cerebral amyloid angiopathy: Validation of the Boston criteria. Neurology 2001;56:537-9.*

5. *Vinters HV. Cerebral amyloid angiopathy. A critical review. Stroke 1987;18:311-24.*
6. *Verbeek MM, De Waal RMW, Vinters HV. Cerebral amyloid angiopathy in Alzheimer's disease and related disorders. Dordrecht; London: Kluwer Academic, 2000.*
7. *Revesz T, Holton JL, Lashley T, Plant G, Rostagno A, Ghiso J, et al. Sporadic and familial cerebral amyloid angiopathies. Brain Pathol 2002;12:343-57.*
8. *De Strooper B. Aph-1, Pen-2, and Nicastrin with Presenilin generate an active gamma-Secretase complex. Neuron 2003;38:9-12.*
9. *Herzig MC, Van Nostrand WE, Jucker M. Mechanism of cerebral beta-amyloid angiopathy: Murine and cellular models. Brain Pathol 2006;16:40-54.*
10. *Zhang-Nunes SX, Maat-Schieman ML, van Duinen SG, Roos RA, Frosch MP, Greenberg SM. The cerebral beta-amyloid angiopathies: Hereditary and sporadic. Brain Pathol 2006;16:30-9.*
11. *Greenberg SM, Briggs ME, Hyman BT, Kokoris GJ, Takis C, Kanter DS, et al. Apolipoprotein E epsilon 4 is associated with the presence and earlier onset of hemorrhage in cerebral amyloid angiopathy. Stroke 1996;27:1333-7.*
12. *Nicoll JA, Burnett C, Love S, Graham DI, Ironside JW, Vinters HV. High frequency of apolipoprotein E epsilon 2 in patients with cerebral hemorrhage due to cerebral amyloid angiopathy. Ann Neurol 1996;39:682-3.*
13. *Schmechel DE, Saunders AM, Strittmatter WJ, Crain BJ, Hulette CM, Joo SH, et al. Increased amyloid beta-peptide deposition in cerebral cortex as a consequence of apolipoprotein E genotype in late-onset Alzheimer disease. Proc Natl Acad Sci U S A 1993;90:9649-53.*
14. *Greenberg SM, Vonsattel JP, Segal AZ, Chiu RI, Clatworthy AE, Liao A, et al. Association of apolipoprotein E epsilon2 and vasculopathy in cerebral amyloid angiopathy. Neurology 1998;50:961-5.*
15. *Rosand J, Muzikansky A, Kumar A, Wisco JJ, Smith EE, Betensky RA, et al. Spatial clustering of hemorrhages in probable cerebral amyloid angiopathy. Ann Neurol 2005;58:459-62.*
16. *Johnson KA, Gregas M, Becker JA, Kinnecom C, Salat DH, Moran EK, et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. Ann Neurol 2007;62:229-34.*
17. *Greenberg SM, Vonsattel JP. Diagnosis of cerebral amyloid angiopathy. Sensitivity and specificity of cortical biopsy. Stroke 1997;28:1418-22.*
18. *Masuda J, Tanaka K, Ueda K, Omae T. Autopsy study of incidence and distribution of cerebral amyloid angiopathy in Hisayama, Japan. Stroke 1988;19:205-10.*
19. *Jellinger KA, Attems J. Prevalence and pathogenic role of cerebrovascular lesions in Alzheimer disease. J Neurol Sci 2005;229-230:37-41.*
20. *Rosand J, Hylek EM, O'Donnell HC, Greenberg SM. Warfarin-associated hemorrhage and cerebral amyloid angiopathy: a genetic and pathologic study. Neurology 2000;55:947-51.*
21. *Inagawa T. Risk factors for primary intracerebral hemorrhage in patients in Izumo City, Japan. Neurosurg Rev 2007;30:225-234; discussion 234.*
22. *Labovitz DL, Halim A, Boden-Albala B, Hauser WA, Sacco RL. The incidence of deep and lobar intracerebral hemorrhage in whites, blacks, and Hispanics. Neurology 2005;65:518-22.*
23. *Flaherty ML, Kissela B, Woo D, Kleindorfer D, Alwell K, Sekar P, et al. The increasing incidence of anticoagulant-associated intracerebral hemorrhage. Neurology 2007;68:116-21.*
24. *Lovelock CE, Molyneux AJ, Rothwell PM. Change in incidence and aetiology of intracerebral haemorrhage in Oxfordshire, UK, between 1981 and 2006: a population-based study. Lancet Neurol 2007;6:487-93.*
25. *Pickering TG, Hall JE, Appel LJ, Falkner BE, Graves J, Hill MN, et al; Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Recommendations for blood pressure measurement in humans and experimental animals: Part 1: Blood pressure measurement in humans: A statement for professionals from the Subcommittee of Professional and Public Education of the American Heart Association Council on High Blood Pressure Research. Hypertension 2005;45:142-61.*
26. *Greenberg SM, Eng JA, Ning M, Smith EE, Rosand J. Hemorrhage burden predicts recurrent intracerebral hemorrhage after lobar hemorrhage. Stroke 2004;35:1415-20.*
27. *Viswanathan A, Rakich SM, Engel C, Snider R, Rosand J, Greenberg SM, et al. Antiplatelet use after intracerebral hemorrhage. Neurology 2006;66:206-9.*
28. *Eckman MH, Rosand J, Knudsen KA, Singer DE, Greenberg SM. Can patients be anticoagulated after intracerebral hemorrhage? A decision analysis. Stroke 2003;34:1710-6.*
29. *Eckman MH, Wong LK, Soo YO, Lam W, Yang SR, Greenberg SM, et al. Patient-specific decision-making for warfarin therapy in nonvalvular atrial fibrillation: How will screening with genetics and imaging help? Stroke 2008;39:3308-15.*
30. *Kyriakides T, Silbert PL, Kakulas BA. Cerebral amyloid angiopathy and intracerebral hemorrhage with special reference to the pons. Clin Neuropathol 1994;13:71-6.*
31. *Gurol ME, Greenberg SM. Management of intracerebral hemorrhage. Curr Atheroscler Rep 2008;10:324-31.*
32. *Gurol ME, St Louis EK. Treatment of cerebellar masses. Curr Treat Options Neurol 2008;10:138-50.*
33. *Passero S, Rocchi R, Rossi S, Ulivelli M, Vatti G. Seizures after spontaneous supratentorial intracerebral hemorrhage. Epilepsia 2002;43:1175-80.*
34. *Mendelow AD, Unterberg A. Surgical treatment of intracerebral haemorrhage. Curr Opin Crit Care 2007;13:169-74.*
35. *O'Donnell HC, Rosand J, Knudsen KA, Furie KL, Segal AZ, Chiu RI, et al. Apolipoprotein E genotype and the risk of recurrent lobar intracerebral hemorrhage. N Engl J Med 2000;342:240-5.*
36. *Greenberg SM, Vonsattel JP, Stakes JW, Gruber M, Finklestein SP. The clinical spectrum of cerebral amyloid angiopathy: Presentations without lobar hemorrhage. Neurology 1993;43: 2073-9.*
37. *Scolding NJ, Joseph F, Kirby PA, Mazanti I, Gray F, Mikol J, et al. Abeta-related angiitis: Primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. Brain 2005;128:500-15.*
38. *Eng JA, Frosch MP, Choi K, Rebeck GW, Greenberg SM. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. Ann Neurol 2004;55:250-6.*
39. *Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, et al. Magnetic resonance imaging and computed tomography in emergency assessment of patients with sus-*

pected acute stroke: A prospective comparison. Lancet 2007;369:293-8.

40. *Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Salman RA, Warach S, et al; Microbleed Study Group. Cerebral microbleeds: A guide to detection and interpretation. The Lancet Neurology 2009;8:165-74.*
41. *Natte R, Maat-Schieman ML, Haan J, Bornebroek M, Roos RA, van Duinen SG. Dementia in hereditary cerebral hemorrhage with amyloidosis-Dutch type is associated with cerebral amyloid angiopathy but is independent of plaques and neurofibrillary tangles. Ann Neurol 2001;50:765-72.*
42. *Pathological correlates of late-onset dementia in a multicentre, community-based population in England and Wales. Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS). Lancet 2001;357:169-75.*
43. *Pfeifer LA, White LR, Ross GW, Petrovitch H, Launer LJ. Cerebral amyloid angiopathy and cognitive function: The HAAS autopsy study. Neurology 2002;58:1629-34.*
44. *Smith EE, Gurol ME, Eng JA, et al. White matter lesions, cognition, and recurrent hemorrhage in lobar intracerebral hemorrhage. Neurology 2004;63:1606-12.*
45. *Greenberg SM, Gurol ME, Rosand J, Smith EE. Amyloid angiopathy-related vascular cognitive impairment. Stroke 2004;35:2616-9.*
46. *Fisher CM. Binswanger's encephalopathy: A review. J Neurol 1989;236:65-79.*
47. *Chen YW, Gurol ME, Rosand J, Viswanathan A, Rakich SM, Groover TR, et al. Progression of white matter lesions and hemorrhages in cerebral amyloid angiopathy. Neurology 2006;67:83-7.*
48. *Salat DH, Smith EE, Tuch DS, Benner T, Pappu V, Schwab KM, et al. White matter alterations in cerebral amyloid angiopathy measured by diffusion tensor imaging. Stroke 2006;37:1759-64.*
49. *Kimberly WT, Gilson A, Rost NS, et al. Silent Ischemic Infarcts are Associated with Increased Hemorrhage Burden in Cerebral Amyloid Angiopathy. Neurology 2009;in press.*
50. *Niwa K, Carlson GA, Iadecola C. Exogenous A beta1-40 reproduces cerebrovascular alterations resulting from amyloid precursor protein overexpression in mice. J Cereb Blood Flow Metab 2000;20:1659-68.*
51. *Niwa K, Younkin L, Ebeling C, Turner SK, Westaway D, Younkin S, et al. Abeta 1-40-related reduction in functional hyperemia in mouse neocortex during somatosensory activation. Proc Natl Acad Sci U S A 2000;97:9735-40.*
52. *Smith EE, Vijayappa M, Lima F, Delgado P, Wendell L, Rosand J, et al. Impaired visual evoked flow velocity response in cerebral amyloid angiopathy. Neurology 2008;71:1424-30.*
53. *Klunk WE, Engler H, Nordberg A, Wang Y, Blomqvist G, Holt DP, et al. Imaging brain amyloid in Alzheimer's disease with Pittsburgh Compound-B. Ann Neurol 2004;55:306-19.*
54. *Greenberg SM, Grabowski T, Gurol ME, Skehan ME, Nandigam RN, Becker JA, et al. Detection of isolated cerebrovascular beta-amyloid with Pittsburgh compound B. Ann Neurol 2008;64:587-91.*
55. *Robbins EM, Betensky RA, Domnitz SB, Purcell SM, Garcia-Alloza M, Greenberg C, et al. Kinetics of cerebral amyloid angiopathy progression in a transgenic mouse model of Alzheimer disease. J Neurosci 2006;26:365-71.*

Yazışma Adresi/Address for Correspondence

Mahmut Edip Gürol, MD

Department of Neurology
University of Iowa
200 Hawkins Drive
Iowa City, Iowa/USA 52242

E-posta: egurol@yahoo.com