Cerebral Amyloid Angiopathy (CAA)
Emerging Concepts
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Disclaimer
• I have no actual or potential conflict of interest in relation to this program/presentation.

Objectives
• Following this presentation the learner will be able to:
  – Explain (3) characteristics of sporadic CAA
  – List (3) symptoms associated with cerebral lobar hemorrhage associated with CAA
  – Discuss (3) treatment strategies to manage CAA
Amyloid
What is it?

- Amyloids are aggregates of proteins that become folded into a shape that allows many copies of that protein to stick together.
- In the human body, amyloids are usually unhealthy developments.
- Disrupt the healthy function of nearby tissues and organs.

However;

- Kumar et al. showed that Amyloid-β peptide/protein (Aβ) is a natural antibiotic that protects the brain from infection.
- Most surprisingly, Aβ aggregates trap and imprison bacterial pathogens.
- Aβ expression protects against fungal and bacterial infections. Science Translational Medicine 25 May 2016: 8(340) ra72

Low amounts of Aβ could work as antioxidants
Relationship of Amyloid & Cholesterol

- The brain contains ~25% of the body’s total cholesterol...of which 70% is found in the myelin sheaths. (Speed and accuracy of neural transmission)
- Cholesterol has been found to bind both Aβ and its precursor protein (APP), suggesting another rationale for high cholesterol levels being deleterious. - *Alzheimers Res Ther.* 2013; 5(2): 8.

Cholesterol is required everywhere; in the brain as an antioxidant &
- an electrical insulator (to prevent ion leakage),
- as a structural scaffold for the neural network,
- functional component of all membranes.
- Cholesterol is also utilized in synaptic delivery of the neurotransmitters.
- It also plays an important role in the formation and functioning of synapses in the brain.

Cholesterol is needed to make hormones
- and neurotransmitters which brain cells use to communicate with each other.
- Cholesterol is an antioxidant that:
  - protects against cancer,
  - plays a critical role in the production of vitamin D,
  - vital in keeping cell membranes firm and preventing them from becoming porous.
Back to Aβ - byproduct of Aβ precursor protein (APP) and cholesterol

- High levels of LDL cholesterol and low levels of HDL cholesterol were linked to having more amyloid in the brain.
- Extracellular APP fragments can associate into plaques around neurons and cause degeneration and death in surrounding cells.

Amyloid-β (Aβ) pathology is known to

- promote chronic inflammatory responses in the brain.
- It was thought previously that Aβ was associated only with Alzheimer’s Disease (AD) & Down syndrome.
  - However, studies have shown its involvement in many other neurological disorders.

Aβ deposition

is most often seen in the context of cognitive impairment due to AD.

- Cerebral amyloid angiopathy (CAA) is characterized by Aβ deposition along the walls of the cerebral vasculature, which includes arteries, arterioles, veins and less often capillaries.
  - The amyloid that causes CAA does not affect organs outside of the brain and spinal cord, while the amyloid deposits that damage the kidneys, heart, or other organs in the body very rarely have any impact on the brain.
Cerebral Amyloid Angiopathy (CAA)

• Although generally unrecognized during life, the presence of CAA pathology is common in the elderly.
• Estimates of the prevalence of CAA from autopsy series are:
  • 10% to 50% in the general elderly population, increasing with age, and
  • 80% in subjects with pathological features of Alzheimer disease (AD).
• The most common form of dementia is AD which presently affects over 35 million individuals globally, and is predicted to affect 115 million people worldwide by 2050.

CAA

• is defined as the deposition of Aβ peptide within leptomeningial and cortical vessels, likely reflecting an imbalance between Aβ production and clearance.
• Amyloid buildup triggers a series of destructive alterations in the cerebral vascular architecture, leading to a spectrum of neurological events including
  • lobar intracerebral hemorrhage (ICH),
  • brain ischemia and
  • cognitive decline.
• Neuroimaging has taken a central role in defining CAA.

CAA is a common process

• in aging and usually harmless.
• However in severe CAA, the Aβ protein deposits cause the blood vessel walls to crack, blood can leak out and damage the brain.
• Spontaneous (ICH), defined as non-traumatic bleeding into the brain tissue, is the second most common subtype of stroke, with 5.3 million cases and over 3 million deaths reported worldwide in 2010.
  • Case fatality is extremely high (reaching approximately 60 % at 1 year post event).
  • Only 20 % of patients who survive are independent within 6 months.
• Factors such as chronic hypertension, CEREBRAL AMYLOID ANGIOPATHY, and anticoagulation are commonly associated with ICH.
Both sporadic and hereditary forms of CAA may occur.

- Hereditary form of CAA is seen at a younger age, as early as the third decade; in contrast,
- Sporadic form is more common in elderly and increases in both prevalence and severity with increasing age. Ann Clin Transl Neurol. 2016 Jan; 3(6): 455-462.

Prevalence of CAA increases with aging, but often remains clinically silent

Healthy individuals have Aβ levels in their plasma and cerebrospinal fluid (CSF).

- Aβ proteins are doing their damage over many years, even decades, before signs/symptoms appear.
- Cerebrovascular amyloid is present in approximately 40% of elderly and 80% or more in AD patients. Int J Mol Sci. 2016 Mar; 17(3): 338.
Can Amyloid be prevented?

- Our bodies make several proteins that can cause amyloidosis.
- Amyloidosis is a disease that leads to the buildup of protein in vital organs, which causes these organs to become damaged.
- It’s important to know the exact amyloid protein causing the disease.
- The outlook depends on the form of amyloidosis and its response to treatment.

Cerebrovascular Aβ deposits accompany functional and pathological changes

- in cerebral blood vessels:
  - CAA-associated vasculopathies lead to development of:
    - hemorrhagic lesions,
    - cortical micro-hemorrhage,
    - focal convexity subarachnoid hemorrhage (SAH),
    - ischemic lesions (cortical infarction and ischemic changes of the white matter),
Risk Factors for Intracerebral Hemorrhage (ICH)

- Hypertension
- CEREBRAL AMYLOID ANGIOPATHY
- ADVANCED AGE
- Anticoagulation intensity
- Leukoaraiosis or white matter disease
- Prior stroke or ICH
- Hematologic abnormalities
- Chronic kidney disease
- Trauma and falls
- Aneurysm/vascular malformations
- Alcohol consumption
- Drug abuse
- Low cholesterol

According to the “Global Burden of Diseases, Injuries, and Risk Factors” report, there were 5.3 million cases and over 3.0 million deaths secondary to ICH worldwide in 2010.

- The case-fatality rate ranges from 35% at 7 days to 59% at 1 year.
- Half of fatal cases occur in the first 48 hours after presentation.

Survivors are often left with severe disability, with less than 40% of patients regaining functional independence.

Given increasing life expectancies and the effective control of hypertension, CAA is common.

- The incidence of Cerebral Lobar Hemorrhage (CLH) has exhibited an increasing trend.
  - CLH is the most common clinical manifestation of CAA.
- CAA-related CLH usually involves more than one lobe, and survivors of a first hemorrhage commonly experience recurrence.
The Boston criteria (CAA diagnosis)

- was first proposed in 1990 in order to standardize the diagnosis of CAA.
- The criteria are comprised of
  - clinical, 
  - imaging and 
  - pathological parameters.

The Boston criteria are divided into four tiers:

- **Definite CAA**: 
  - full post-mortem examination reveals lobar, cortical, or cortical/subcortical hemorrhage and pathological evidence of severe cerebral amyloid angiopathy
- **Probable CAA with supporting pathological evidence**: 
  - clinical data and pathological tissue (evacuated hematoma or cortical biopsy specimen) demonstrate a hemorrhage as mentioned above and some degree of vascular amyloid deposition doesn’t have to be post-mortem
- **Probable CAA**: 
  - pathological confirmation not required
  - patient older than 55 years
    - appropriate clinical history
    - MRI findings demonstrate multiple hemorrhages of varying sizes/ages with no other explanation
- **Possible CAA**: 
  - patient older than 55 years
  - appropriate clinical history
  - MRI findings reveal a single lobar, cortical, or cortical/subcortical hemorrhage without another cause, multiple hemorrhages with a possible but not a definite cause, or some hemorrhage in an atypical location

CLH

- According to Boston criteria a probable diagnosis of CAA is made in elderly patients with at least two acute or chronic lobar hemorrhagic lesions without any other definite cause of intracerebral hemorrhage like prior trauma, ischemic stroke, CNS tumor, vascular malformation, or bleeding diathesis.

Critical Care201620:272
Patients with ICH

- usually experience stroke-like symptoms with an abrupt or sudden clinical onset, accompanied with focal neurological deficits.
  - Large hematomas usually lead to a decreased level of consciousness as a result of increased intracranial pressure (ICP).
- It is clinically difficult to distinguish an ICH from an ischemic stroke at the bedside, but headache, nausea, vomiting, and depressed level of consciousness should raise the suspicion for a hemorrhagic event compared to ischemic stroke.
- In about 25% of patients who are initially alert, deterioration in the level of consciousness occurs in the first 24 hours. - The Neurohospitalist, (2011) 1(3), 148–159

Following initial vessel rupture

- the hematoma causes direct mechanical injury to the brain parenchyma and surrounding blood vessels.
  - Perihematomal edema develops within the first 3 hours from symptom onset and peaks between 10 to 20 days.
- Next, blood and plasma products cause secondary injury processes including:
  - an inflammatory response,
  - activation of the coagulation cascade, and
  - iron deposition from hemoglobin degradation.
- The collective effect is further degradation of BBB integrity, extracellular matrix breakdown and worsening of cerebral edema.

Etiology CAA & ICH.

(A) Ganglionic/deep versus (B) lobar ICH.

A. Supratentorial, intracerebral (intraparenchymal) hemorrhage which originated within the right thalamus and extends into the right lateral ventricle. Etiology hypertension.

B. Supratentorial right hemisphere large right lobar hematoma with mass effect, cerebral edema, and midline shift. Heterogeneous hematoma suggestive of blood in different stages.
Intracerebral hemorrhage (ICH)

- is not a monophasic event that stops promptly.
  - The hematoma continues to expand for up to 6 hours in non-coagulopathic ICH and up to 24 hours in coagulopathic ICH.
- Peri-hematomal edema peaks at 72 hours and usually persists for 5 days, although it has been reported for up to 2 weeks.

The 1-month ICH case fatality rate

- is approximately 40%, rising to 55% in 1 year.
- The 10-year survival rate is estimated at 20–25%.
- Despite advances in therapy, survival rates have not improved in the last decades.
- The rate of functional independence after ICH at one year varies from 12% to 39%.

Estimating the volume of the ICH is important as larger hematomas have a poorer prognosis.

Stroke; a Journal of Cerebral Circulation, 45(8), 2280–2285.
CAA is regarded as a disease of aging;

- the proportion of ICH cases in older people that are causally linked to CAA is unclear, but recent estimates place that number as high as 50%.

- Besides hypertension, cerebrovascular amyloid deposition (i.e., CAA) is associated with ICH in older patients. Critical Care 2016; 20:272

The most common cause of ICH in the elderly is CAA

- and recurrence is common; yet, there are no treatments for the prevention of CAA-related ICH.
  - CAA was described as a cause of normotensive cerebral hemorrhage in older individuals.

- CAA is the second most frequent cause of ICH after hypertensive vasculopathy.
  - The incidence of CAA related ICH has increased overall and this is most likely due to increasingly aging populations, in which CAA is prevalent. Austin J Cerebrovasc Dis & Stroke. 2015;11(1): 1033.

- Aβ deposition can obliterate the vessel lumen, leading to ischemia (stroke). Int J Mol Sci. 2016 Mar; 17(3): 338.

The hemorrhage is typically lobar and cortical-subcortical

- in distribution; it generally spares the deep white matter, basal ganglia and the brainstem.

- Symptomatic ICH is large (>5mm), while micro-hemorrhages (<5mm) are often clinically silent.
In total, 3257 participants (54.7% women; mean age 59.6 years) completed baseline and follow-up testing.

- Microbleeds (MB’s) were prevalent in 15.3% of the cohort (17.8% 60-69 years, 38.3% ≥80 years), associated with cognitive decline.
- Specifically, lobar MB’s were associated with a decline in executive function, information processing, and memory function. JAMA Neurol. 2016

CAA

- is an important cause of cognitive impairment and spontaneous & recurrent (ICH) in the elderly.
- The most common presentation of CAA is the development of a SUDDEN NEUROLOGICAL DEFICIT secondary to an acute ICH. Radiographics. 2016 Jul-Aug;36(4):1147-63.
- A hematoma volume of 30 ml represents a cutoff point for increased mortality and worse functional outcome. Critical Care 2016;20:272

The symptoms of CAA-related CLH include

- sudden onset of headache
- sudden onset of neurological symptoms:
  - limb weakness
  - sensory loss
  - visual
  - language changes (symptoms depend on the lobe involved)
  - decreased consciousness
  - nausea; and vomiting
- CAA-related CLH is often accompanied by subarachnoid hemorrhage (SAH), cervical rigidity, and positive meningeal irritation. Journal of Korean Neurosurgical Society, 58(1), 30–35
A large heterogeneous IPH/ICH/CLH in right posterior-temporal lobe

• Survival curves of the 2 groups for occurrence of intracerebral hemorrhage (ICH; A)
• And death (B).
MB indicates microbleed.
Stroke; a Journal of Cerebral Circulation, 45(8), 2280–2285.

CAA-related hemorrhages
• typically occur in the cortical lobes, frequently break into the subarachnoid space between the brain and membrane (meninges), and often occur at night.
• Hypertensive hemorrhages usually occur deep in the brain, break into the ventricle or deep brain cavity, and normally occur in daytime.
Journal of Korean Neurosurgical Society, 58(1), 30–35
CAA:

- Focal neurological deficits,
  - disturbances of consciousness,
  - progressive cognitive decline,
  - dementia, and
- death can occur as a consequence of these vascular mechanisms.

International Journal of Molecular Sciences, 17(3), 338.

- An 85-year-old woman with no prior stroke, who presented with cognitive symptoms, after finding of multiple isolated lobar MB on MRI (white arrows, A).
- Four months later, the patient presented to the emergency department with acutely altered mental status.
- Her head CT showed a right-sided posterior lobar ICH with ventricular extension (black arrow, B).

Stroke; a Journal of Cerebral Circulation, 45(8), 2280–2285.

Non-enhanced head/brain CT helps to identify the presence or absence

- of an acute ICH
- Provides information regarding the location, size, shape and extension of ICH.
- MRI is most sensitive for detection of chronic hemorrhages in suspected cases of CAA.
CAA is patho-physiologically related to both cerebrovascular disorders and dementia

- CAA is commonly found in AD, with a prevalence of more than 80%.
- On the other hand, a relatively small subset of patients with symptomatic CAA-related ICH present with dementia/AD at onset of ICH, suggesting vascular-dominant distribution of amyloid deposition in the brain.

Five independent predictors of 30-day mortality

- were identified and used to build the score:
  - level of consciousness according to the GCS;
  - age;
  - ICH volume;
  - IVH; and
  - infra-tentorial location of ICH.
- The GCS at the time of transfer from the ED to the ICU (or to the operating room) was found to be the strongest independent predictor of 30-day mortality, and consequently given the heaviest weight in the score. Critical Care 2016:20:272

There is increasing evidence that CAA could be a risk factor for ICH

- in thrombolytic therapies for acute myocardial infarction, pulmonary embolism, or ischemic stroke, and in warfarin/anticoagulation therapies.
- The use of anti-platelet drugs such as aspirin was related to the presence of microbleeds, and to strictly lobar microhemorrhages suggestive of CAA. Front. Neurol., 25 April 2012
The role of neurosurgery in ICH remains to be defined clearly.

- However, (CLH/ICH) hematoma evacuation appears relatively safe in patients <75 years of age without intraventricular extension.
- For future treatment of CAA, it is important to identify patients early in the course of disease before ICH or dementia occurs, to allow the use of disease modifying therapies. Critical Care 2016:20.272

Cortical Superficial Siderosis

- characteristic of CAA.
- Cortical superficial siderosis describes hemosiderin deposition in the superficial layers of the cerebral cortex and may follow repeated episodes of bleeding in the subarachnoid space. Critical Care 2016:20.272

Sporadic Cerebral Amyloid Angiopathy

Lobar ICH, the distribution of CMs in cerebral amyloid angiopathy show a posterior cortical predominance (favoring the temporal and occipital lobes). They also tend to cluster in the same lobe in patients with multiple lesions. Blood-sensitive MRI sequences are also important to detect superficial cortical siderosis and subarachnoid hemorrhage, which are additional markers of sporadic CAA.
Cerebral amyloid angiopathy-related inflammation (CAA-ri)

- presents with
  - cognitive decline,
  - headaches, and
  - seizures
- rather than the chronic dementia or hemorrhagic strokes classically associated with CAA.
- The mean age at onset is ~ 68y; significantly younger than for hemorrhagic CAA.

In addition to CLH,

- dementia and AD are other diseases that are closely linked to CAA.
- In a large study, one-third of the patients with pathologically confirmed CAA had a history of dementia. *Journal of Korean Neurosurgical Society, 58(1), 30–35*

The prevalence of CAA is significantly higher

- in demented patients (due to AD) compared to non-demented patients.
- Dementia, psychiatric symptoms, transient neurological dysfunction, and recurrent and/or multiple cerebral lobar hemorrhage (CLH) are the clinical features of this disorder. *Journal of Korean Neurosurgical Society, 58(1), 30–35*
Transient-ischemic attack (TIA)

- Like symptoms also termed as “amyloid spells” is the next most commonly described presentation.
- The spells are typically brief (<30 mts) and are characterized by recurrent, stereotyped episodes of ‘positive’ spreading sensory symptoms (paraesthesias).
- The spells are related to hemorrhagic components of CAA - cortical microbleeds (CMB)

CAA Prognosis:

- The prognosis for most CAA patients is poor:
  - 20% to 90% of patients die from the onset of bleeding or its complications, which include bleeding progression, cerebral edema-induced brain hernia, epilepsy, and infections, such as pneumonia.
  - Most survivors have neurological deficits that are secondary to the lobar hemorrhage as well as an increased risk of recurrent bleeding, epilepsy, and dementia.
  - Elderly patients and patients suffering from heavy bleeding or short-term recurrent bleeding have the worst prognosis. *Journal of Korean Neurosurgical Society, 58(1), 30–35*

Currently, there is no treatment to halt or reverse β-amyloid deposition.

- Attention is directed to the prevention of adverse outcomes associated with CAA, such as recurrent hemorrhages or progressive dementia.
- MRI may help in selecting patients for different types of secondary prevention of stroke.
- MR evidence of higher number of chronic MB’s are predictive of a greater risk of recurrent hemorrhage and future cognitive impairment.
- Routine use of MRI is suggested to detect MB’s in older people to avoid potentially dangerous anticoagulant or antiplatelet therapy.
Tramiprosate has been found to be a safe treatment option for patients with suspected CAA.

- Tramiprosate is an ionic compound that binds with soluble β-amyloid, interferes with the amyloid cascade and delays or inhibits the progression of CAA.

Summary

- Cerebral amyloid angiopathy (CAA) is an important cause of spontaneous cortical/subcortical ICH in the normotensive elderly.
- CT is the imaging study of choice for evaluation of suspected acute cortical hemorrhage.
- MRI is best suited for identification of chronic cortical-subcortical hemorrhages, ischemic sequelae of the disease and assessment of disease progression.
- The burden of asymptomatic cerebral MB's detectable by MRI in patients with CAA is a good predictor of hemorrhage recurrence, and highlights the importance of secondary prevention in CAA-related ICH.

Summary

- CAA is not associated with the presence of systemic amyloidosis.
- Majority of cases of CAA are asymptomatic.
- However, symptomatic patient may present with sudden neurological deficit due to transient ischemic attack, progressive cognitive decline, or potentially devastating intracranial hemorrhage.
CAA relationship to AD

• Alzheimer’s disease pathology is clearly associated with CAA.
• Recent studies have shown that more than 90% of patients with clinical AD have some degree of CAA.
• However, it has also been shown that 30% of all people with CAA have no additional Alzheimer’s pathology (usually younger patients).

CAA is a cerebrovascular disorder with a high risk of cognitive impairment.

• Even though disease-modifying treatments for CAA are not available, supportive care and, in patients with recent ICH, cognitive rehab may maximize function and enhance recovery.
• Patients clinically diagnosed with CAA frequently have cognitive impairment with relatively preserved episodic memory that would be unusual for AD. Stroke. 2016;47:2010-2016.

Objectives Revisited:

• Explain (3) characteristics of sporadic CAA:
  • Promote chronic inflammatory responses in the brain
  • Extracellular APP fragments can associate into plaques around neurons and cause degeneration and death in surrounding cells
  • Apolipoprotein deposits cause the blood vessel walls to crack, blood can leak out and damage the brain.
• List (3) symptoms associated with cerebral lobar hemorrhage associated with CAA:
  sudden onset of headache
  • sudden onset of neurological symptoms, such as
  • body weakness
  • sensory loss
  • visual
  • language changes (symptoms depend on the lobe involved)
  • decreased consciousness
  • nausea and vomiting
• Discuss (3) treatment strategies to manage CAA:
  • Cognitive Rehabilitation
  • Avoidance of aspirin/anticoagulants (especially with evidence of lobar hemorrhage)
  • Avoidance of head trauma
  • Surgical (ICH) Hematoma evacuation
  • Management of Blood Pressure and Intracranial Pressure
  • Provocative head atherectomy
  • Possible steroids/polyphosphonate for vasculitis. medscape.com/article/1062730-overview
References