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Cerebral Manifestations of Amyloidosis: questions of early diagnosis and therapy

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ABSTRACT

Background. Cerebral amyloid angiopathy (CAA) is the generally accepted term used to define amyloid deposits in the walls of leptomeningeal and cortical arteries of medium and small diameter, arterioles, less often capillaries and veins. Cerebral amyloid angiopathy is an important cause of cerebral haemorrhage, although it can also lead to ischemic infarction and dementia. Patients with CAA may have a wide clinical spectrum, including cognitive decline, lobar intracranial haemorrhage, and transient focal neurological episodes (recurrent, stereotyped, transient episodes of smoothly spreading paresthesia's, numbness, or weakness, usually lasting seconds to minutes, usually resolving within a similar period).

Keywords: Cerebral amyloid angiopathy, Alzheimer's disease, intracranial haemorrhage, MRI

INTRODUCTION

Cerebral amyloid angiopathy (CAA) is a type of cerebrovascular disorder characterized by the accumulation of beta-amyloid peptides in leptomeninges and small/medium cerebral blood vessels.

Amyloid deposition leads to vascular fragility, which can manifest as lobar intracerebral haemorrhage (ICH). It can also present with cognitive impairment, occasional microbleeds, hemosiderosis, inflammatory leukoencephalopathy,

Alzheimer's disease, or transient neurological symptoms. [1, 2, 3]

It may occur in certain familial syndromes or may occur sporadically.

Diagnosis is primarily based on a combination of clinical, pathological, and radiographic findings.

However, a definitive diagnosis requires a postmortem examination of the brain. There are currently no disease-modifying therapies.

The prognosis depends on the characteristics of CAA, with worse outcomes in patients with large hematomas and the elderly. [11]

Purpose of the work: to summarize the available literature data on the prevalence, causes and pathogenesis of cerebral amyloid angiopathy.

MATERIALS AND METHODS

We conducted a literature review of scientific papers over the past 20 years, using the resources of the PubMed and eLIBRARY search engines, for the above keywords.

For this meta-analysis, we used articles containing an evidence-based experimental and clinical base on the

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most recent issues related to the epidemiology, aetiology and pathogenesis of Cerebral amyloid angiopathy.

MAIN PART

Epidemiology. The true incidence and prevalence of cerebral amyloid angiopathy (CAA) are difficult to determine since definite CAA is a pathological diagnosis that is usually made post-mortem.

However, estimates can be made based on the autopsy series and the incidence of croupous intracranial haemorrhage (ICH). A series of 400 autopsies revealed signs of CAA in the brains of 18.3% of men and 28% of women aged 40–90 years.

In another autopsy study of 1079 patients with a mean age at death of 89.7 years, the prevalence of moderate to severe CAA was 36%.

In a series of 117 patients with confirmed AD, 83% had signs of CAA.

The prevalence of CAA increases with age; some autopsy series found CAA in 5% of people in their seventh decade, but in 50% of people over 90 years of age. In patients with Alzheimer's disease (AD), the incidence in several studies and meta-analyses ranged from 80% to 90%.

A systematic review of four population-based studies found that 55–59% of patients with dementia have CAA compared with 28–38% of patients without dementia. [13, 14, 15, 16]

It is estimated that CAA accounts for up to 15% of all ICH in patients over 60 years of age and up to half of non-traumatic lobar ICH in patients over 70 years of age (approximately 15–20 cases per 100,000 people annually). CAA and CAA-associated bleeding are especially common in older adults with AD and Down's syndrome.

The exact aetiology of cerebral amyloid angiopathy is not fully understood. CAA is characterized by the deposition of congophilic material (amyloid beta peptide) in the leptomeningeal membranes and small to medium cerebral blood vessels.

This deposit weakens the walls of blood vessels, making them prone to bleeding. CAA may occur in certain familial syndromes or sporadically. [11,14,15,16]

Cerebral amyloid angiopathy (CAA) is the result of the deposition of amyloidogenic protein in the cortical and leptomeningeal vessels.

The most common type of CAA is caused by the beta-amyloid protein (Abeta), which is particularly associated with Alzheimer's disease (AD).

Excessive production of Abeta-CAA can be caused by several mutations in the Abeta precursor protein and presenilin genes.

The origin of Abeta in CAA is probably related to neurons, although it cannot be ruled out that the source is cerebrovascular cells or the circulation.

Despite apparent similarities, the pathogenesis of CAA appears to differ from that of senile plaques in several ways, including the mechanism of Abeta-induced cellular toxicity, the extent of the inflammatory response, and the role of oxidative stress.

Thus, therapeutic strategies in AD should, at least in part, also target CAA. Moreover, CAAs and cerebrovascular diseases (CVDs) may set a lower threshold for AD-like changes to cause dementia and may even cause dementia itself, as patients with AD and CAAs and/or CVCs have more cognitive impairment than patients with only AD. In conclusion, the exact impact of CAA on AD or dementia remains unclear, however, its role may have been underestimated in the past and more extensive studies of in vitro and in vivo models of CAA will be required to elucidate the importance of CAA-specific approaches to developing intervention strategies in AD. [12]

Over the past 5 years, there has been a rapid increase in publications and research in this area with the development of new disease biomarkers due to advances in MRI, amyloid positron emission tomography, and cerebrospinal fluid biomarker analysis.

The inadvertent development of CAA, a similar pathology, in patients treated with beta-amyloid immunotherapy for Alzheimer's disease, has highlighted the importance of establishing how and why CAA develops; without this information, the use of these treatments may be unnecessarily restricted.

Our understanding of the clinical and radiological spectrum of CAA continues to evolve, and there is new information about the independent impact of CAA on cognitive function in the context of ageing and intracerebral haemorrhage, as well as in Alzheimer's disease and other dementias. [2]

DIAGNOSIS OF CAA

While direct visualization of vascular amyloid-β in CAA requires a brain biopsy or autopsy, a set of clinical and MRI-based diagnostic criteria called the (modified) Boston criteria has been validated for the diagnosis of CAA without the need to obtain brain tissue.

These criteria indicate that the presence of cortical hemorrhagic lesions, including lobar intracranial haemorrhages, strictly cortical cerebral microbleeds, and/or superficial siderosis without the presence of deeper haemorrhages in patients older than 55 years, is highly sensitive and specific for CAA. Cerebral microbleeds and superficial siderosis can be observed with gradient echo and susceptibility-weighted MRI sequences (Figure 1).

Cerebral microbleeds are more often found in the posterior regions of the brain, but they can be seen anywhere in the cortex in the presence of CAA. Recent work has also demonstrated that the presence of severely superficial cerebellar microbleeds is associated with CAA. [10]

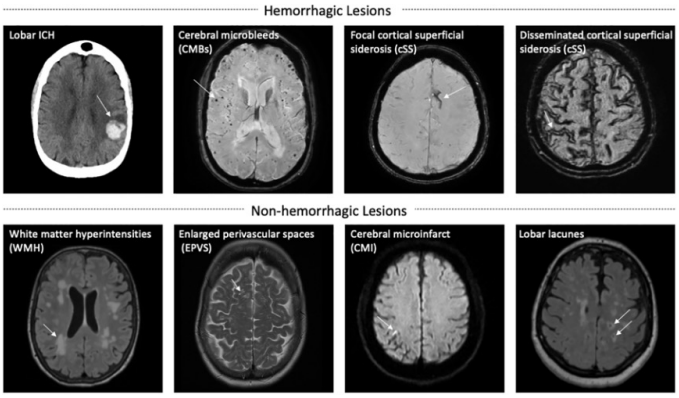

Figure 1. Cerebral microbleeds and superficial siderosis can be observed with gradient echo and susceptibility-weighted MRI sequences.

A key diagnostic category for clinical practice and research is probably CAA, the highest level of diagnostic certainty currently achievable without obtaining brain tissue. In the first formulation (original Boston criteria), probable CAA entailed neuroimaging demonstration of multiple (i.e., 2 or more) haemorrhages limited to lobar areas of the brain, 2, 3 defined as the cerebral cortex, cortico-subcortical (grey-white) junction, and subcortical White spots matter. In 2010, a modification of the cortical sulcus blood count (cortical superficial siderosis, cSS) as one additional hemorrhagic lesion (modified Boston criteria) was proposed and approved. The most recent version of the criteria is known as the modified Boston criteria. [4]

The modified Boston CAA3 criteria are based on the number and location of haemorrhages detected by T2*-weighted MRI, which requires the presence of multiple strictly lobar foci of intracerebral haemorrhage, micro bleeding, or cortical superficial siderosis. In the new criteria, probable CAA is now defined as either the presence of two strictly lobar hemorrhagic lesions (intracerebral hemorrhage, microbleeds, or superficial cortical siderosis) or the presence of one strictly lobar hemorrhagic lesion plus at least one white matter characteristic. [5]

Pathological studies have shown that lobar intracranial haemorrhage in the elderly is usually associated with CAA. Patients with a previous CAA-related intracranial haemorrhage had an almost 5-fold risk of recurrent intracranial haemorrhage compared with patients with a deep hypertension-related intracranial haemorrhage. In addition, the risk of intracranial haemorrhage is higher in patients receiving anticoagulants. Warfarin-associated intracranial haemorrhage has a poor outcome even with anticoagulant withdrawal, resulting in >70% of patients becoming disabled or dying. Improved blood pressure control in young people reduced the incidence of intracranial haemorrhage; however, there is an increased proportion of lobar intracranial haemorrhage in older people receiving antithrombotic drugs, probably due to an increase in the frequency and severity of CAA with age. [5]

CAA is a small vessel disease that leads to lobar intracranial hemorrhage, and cognitive impairment in the elderly. There is a growing number of studies providing biomarkers for the diagnosis of CAA and for predicting the risk of primary and recurrent lobar intracranial haemorrhage. The availability of non-anticoagulant stroke prevention strategies has enabled physicians to avoid the need for lifelong anticoagulation, even in patients with non-valvular atrial fibrillation. Despite these promising advances in the prevention of ischemic stroke and intracranial haemorrhage, there are currently no effective disease-modifying therapies to slow or halt the progression of CAA. Additional work is urgently required to develop new therapeutic strategies for CAA. [6]

General guidelines for the treatment of CAA have yet to be developed. In previous studies, most patients received high doses of corticosteroids. Provided evidence for the use of empiric immunosuppressive therapy in patients who meet the criteria for probable CAA and avoid brain biopsy. Clinical and neuroradiological improvement is observed in most cases after immunosuppressive therapy. [7]

Cerebral amyloid angiopathy (CAA) is increasingly recognized as a major factor in the pathogenesis of Alzheimer's disease (AD). To date, vascular deposits, rather than parenchymal plaques, appear to be more sensitive predictors of dementia. Amyloid deposition in and around cerebral vessels plays a central role in a number

of response mechanisms that lead to changes in the integrity of the blood-brain barrier, extravasation of plasma proteins, oedema formation, release of inflammatory mediators and matrix metalloproteases, which in turn cause partial degradation of the basement membrane. with the potential for hemorrhagic complications. The progressive accumulation of amyloid deposits in and around blood vessels chronically restricts blood supply and causes local oxygen deprivation, triggering a secondary cascade of metabolic events, some of which include the formation of nitrogen and oxygen free radicals, followed by oxidative stress and cellular toxicity. [9,17]

The shared role of amyloid-β (Aβ) deposition in cerebral amyloid angiopathy (CAA) and Alzheimer's disease (AD) is perhaps the most striking example of the relationship between neurodegenerative and cerebrovascular processes. Pathogenic pathways of CAA and AD intersect at the levels of Aβ formation, circulation in the interstitial fluid and perivascular drainage pathways, and its clearance in the brain, but differ in the mechanisms of brain damage and disease manifestations. Here, we review the evidence and pathogenetic implications of the interaction between CAA and AD. Both pathologies appear to be due to impaired Aβ clearance, creating conditions for a self-reinforcing cycle of increased vascular Aβ, decreased perivascular clearance, and further progression of CAA and AD. Despite the close relationship between Aβ deposition in vessels and plaques, several factors favour one or the other, such as the carboxy-terminal portion of the peptide and specific co-deposited proteins. The amyloid-related imaging abnormalities that have been observed in anti-Aβ immunotherapy studies are another likely crossover between CAA and AD, reflecting congestion in perivascular clearance pathways and the effects of Aβ removal from CAA-positive vessels. Intersections between CAA and AD point to the critical role of improving vascular function in the treatment of both diseases and point to the next steps needed to determine treatments. [8]

CONCLUSION

CAA has been recognized as one of the morphological features of Alzheimer's disease (AD), but it is also frequently found in the brains of elderly patients who are neurologically healthy. Often, asymptomatic CAA can lead to dementia, intracranial haemorrhage (ICH), or transient neurologic deficits. Intracranial haemorrhage is the most recognized outcome of CAA.

CONFLICT OF INTEREST - The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

REFERENCES:

1. Cerebral amyloidosis, amyloid angiopathy, and their relationship to stroke and dementia. Jorge Ghiso and Blas Frangione Department of Pathology, New York University School of Medicine, New York, NY, USA. J Alzheimers Dis. 2001 Feb;3(1):65-73.

2. The increasing impact of cerebral amyloid angiopathy: essential new insights for clinical practice. Gargi Banerjee, Roxana Carare, Charlotte Cordonnier,Steven M Greenberg,Julie A Schneider,Eric E Smith,Mark van Buchem,Jeroen van der Grond, Marcel M Verbeek, David J Werring. J Neurol Neurosurg Psychiatry. 2017 Nov;88(11):982-994.

3. Prevalence of cerebral amyloid angiopathy: A systematic review and meta-analysisLieke Jäkel, Anna M. De Kort, Catharina J.M. Klijn, Floris H.B.M. Schreuder, Marcel M. Verbeek. J.Alzheimers Dementia Association. 2022 Jan;18(1):10-28.

4. Diagnosis of Cerebral Amyloid Angiopathy, Evolution of the Boston Criteria,Steven M. Greenberg and Andreas Charidimou. J Stroke. 2018 Jan 15.

5. Cerebral Amyloid Angiopathy: Diagnosis, Clinical Implications, and Management Strategies in Atrial Fibrillation. J Am Coll Cardiol. 2017 Aug, 70 (9) 1173–1182.

6. A practical approach to the management of cerebral amyloid angiopathy Mariel G. Kozberg, M.D., Ph.D.,1,2,3 Valentina Perosa, M.D.,1,2,3,4 M. Edip Gurol, M.D., M.Sc.,2,3 and Susanne J. van Veluw, Ph.D.1,2,3 Int J Stroke. 2021 Jun;16(4):356-369.

7. Diagnosis, treatment, and follow-up of patients with cerebral amyloid angiopathy-related inflammation Virginia Cancelloni, Alessandra Rufa, Carla Battisti, Nicola De Stefano, Egidio Mastrocinque, Guido Garosi, Duccio Venezia, Ivano Chiarotti, Alfonso Cerase. J.Italian Neurological Society. 2022 Nov;43(11):6381-6387.

8. Cerebral amyloid angiopathy and Alzheimer disease — one peptide, two pathways. Steven M. Greenberg, Brian J. Bacskai, Mar Hernandez-Guillamon, Jeremy Pruzin, Reisa Sperling & Susanne J. van Veluw. J.Neurology. 2020 Jan;16(1):30-42.

9. Cerebral amyloid angiopathy and Alzheimer's disease Jorge Ghiso, Yasushi Tomidokoro, Tamas Revesz, Blas Frangione, Agueda Rostagno. Hirosaki medical journal. 2010 Jul 8;61(Suppl):S111-S124.

10. A practical approach to the management of cerebral amyloid angiopathy Mariel G Kozberg https://or-

cid.org/0000-0002-9358 262, Valentina Perosa and Susanne J van Veluw. 2021 Jun;16(4):356-369 Int. J of Neurology.

11. Cerebral amyloid angiopathy. Sakai K, Yamada M. J.Brain Nerve. 2014 Jul;66(7):827-35.

12. Pathogenesis of cerebral amyloid angiopathy. Annemieke A M Rensink , Robert M W de Waal, Berry Kremer, Marcel M Verbeek. Brain Research Reviews. 2003 Oct;43(2):207-23.

13. Masuda J, Tanaka K, Ueda K, Omae T. Autopsy study of incidence and distribution of cerebral amyloid angiopathy in Hisayama, Japan. J Stroke. 1988 Feb. 19 (2):205-10. 1988 Feb;19(2):205-10.

14. Boyle PA, Yu L, Wilson RS, Leurgans SE, Schneider JA, Bennett DA. Person-specific contribution of neuropathologies to cognitive loss in old age. Ann Neurol. 2018 Jan. 83 (1):74-83.

15. Ellis RJ, Olichney JM, Thal LJ, Mirra SS, Morris JC, Beekly D, et al. Cerebral amyloid angiopathy in the brains of patients with Alzheimer's disease: the CERAD experience, Part XV. Neurology. 1996 Jun. 46(6):1592-6.

16. Keage HA, Carare RO, Friedland RP, Ince PG, Love S, Nicoll JA, et al. Population studies of sporadic cerebral amyloid angiopathy and dementia: a systematic review. BMC Neurol. 2009 Jan 13;9:3.

17. Talybov D.S, Rakhimbaeva G.S.Principles of early diagnosis and modern treatment of Alzheimer's disease. (monograph) – Tashkent. 2023. – 14p.

AMILOIDOZNING BOSH MIYA KO'RINISHLARI: ERTA DIAGNOSTIKA VA TERAPIYA MASALALARI

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ABSTRAKT

Bosh miya amiloid angiopatiyasi (CAA) — o'rta va kichik diametrli, arteriollar, kamroq tez-tez kapillyar va venalarning leptomeningeal va kortikal arteriyalari devorlarida amiloidning qo'yilishini aniqlashda qo'llaniladigan umumiy termin. Bosh miya amiloid angiopatiyasi bosh miya qon ketishining muhim sababi hisoblanadi, garchi u ishemik infarkt va demensiyaga ham olib kelishi mumkin. CAA bilan og'rigan bemorlar keng klinik spektrga ega bo'lishlari mumkin, shu jumladan kognitiv pasayish, lobar intrakranial qon ketishi va vaqtinchalik fokusli nevrologik epizodlar (paresteziyalarni, holsizlik yoki zaiflikni bosqichma-bosqich tarqatishning takroriy, stereotipli, vaqtinchalik epizodlari, odatda, bir necha soniyadan daqiqagacha davom etadigan, odatda shunga o'xshash davrda hal qilinadi).

Tayanch so'zlar: Bosh miya amiloid angiopatiyasi, Altsgeymer kasalligi, intrakranial qon ketish, MRT.

ЦЕРЕБРАЛЬНЫЕ ПРОЯВЛЕНИЯ АМИЛОИДОЗА: ВОПРОСЫ РАННЕЙ ДИАГНОСТИКИ И ТЕРАПИИ

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АБСТРАКТ

Церебральная амилоидная ангиопатия (ЦАА) является общепринятым термином используют для определения отложения амилоида в стенках лептоменингеальные и кортикальные артерии среднего и малого диаметра, артериолы, реже капилляры и вены. Церебральная амилоидная ангиопатия является важной причиной мозговых кровоизлияний, хотя также может привести к ишемическому инфаркту и деменции. Пациенты с ЦАА могут иметь широкий клинический спектр, включая снижение когнитивных функций, долевой внутричерепное кровоизлияние и транзиторные фокальные неврологические эпизоды (рецидивирующие, стереотипные, транзиторные эпизоды плавно распространяющихся парестезий, онемения или слабости, обычно длящиеся от нескольких секунд до минут, обычно разрешающиеся в течение аналогичного периода).

Ключевые слова: Церебральная амилоидная ангиопатия, болезнь Альцгеймера, внутричерепное кровоизлияние, МРТ.