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Cerebrospinal fluid biomarkers and apolipoprotein E genotype in cerebral amyloid angiopathy. A narrative review

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ABSTRACT

Sporadic cerebral amyloid angiopathy (CAA) is a cerebral small vessel disease, characterized by the deposition of β-amyloid within the cortical and leptomeningeal blood vessel walls. It has attracted interest concerning new therapeutic perspectives. However, there are scarce data regarding the cerebrospinal fluid biomarkers (CSF) and genetic factors in sporadic CAA.

In this narrative review, we investigated the literature regarding the cerebrospinal fluid core biomarkers profile of patients with probable or possible CAA and its subtype, the CAA- related inflammation (CAA-ri), taking into account the clinical and radiological characteristics of the patients. We also analyzed the Apolipoprotein E (APOE) genotype differentiations among the different subtypes of cerebral amyloid angiopathy.

Our results demonstrate specific CSF patterns of β-amyloid ($A\beta_{42}$ and $A\beta_{40}$) and tau-proteins (t-tau and p-tau) which may serve as molecular biomarkers for CAA/ CAA-ri and could prove helpful for novel therapeutic procedures. Specifically, decreased levels of $A\beta_{40}$ and $A\beta_{42}$ in both CAA and CAA-ri, mildly increased concentrations of tau protein in patients with CAA-ri and a strong association between APOE $\varepsilon 4/\varepsilon 4$ genotype and CAA-ri are the main findings.

Introduction

Sporadic cerebral amyloid angiopathy (CAA) [1] is a common degenerative small vessel disease of the brain. The main pathological feature of the disease is the cerebrovascular deposition of the β-amyloid ($A\beta_{40}$ as the major isoform in CAA and $A\beta_{42}$ as well), affecting mainly the cortical and leptomeningeal vessels. This is in contrast with Alzheimer's Disease (AD), where the $A\beta_{42}$ mainly accumulates in the brain parenchyma as extracellular senile plaques. However, the main risk factors for CAA are the advancing age and the co-occurrence of AD.

Major lobar intracerebral hemorrhages, transient focal neurological episodes and rapidly progressive or chronic cognitive impairment represent the clinical spectrum of cerebral amyloid angiopathy. The key MRI-features of CAA includes multiple strictly lobar cerebral microbleeds (the hallmark of the Boston criteria for CAA diagnosis), white matter hyperintensities, enlarged perivascular spaces in the centrum semiovale, cortical microinfarcts, cortical superficial siderosis (cSS) and convexity subarachnoid hemorrhage [2].

In the last years there was a great interest on CAA. The first effort to introduce a CAA-anti-amyloid immunotherapy with Ponezumab was unsuccessful because of triggering inflammatory and hemorrhagic manifestations in the treatment-group [3,4].

Additionally, major interest is focused on the cerebrospinal fluid (CSF) molecular biomarkers, which could provide a useful tool in studying the underlying CAA features, even in the early stages of the disease and contribute to the recruitment of patients suitable for future clinical trials. A limited number of studies demonstrate that both $A\beta_{40}$ and $A\beta_{42}$ concentrations are decreased in CAA relative to healthy controls and patients with AD, without associated increased tau levels [5].

Therefore, we conducted a narrative review of the literature and sought to present the data regarding the CSF biomarkers profile in patients with possible or probable sporadic cerebral amyloid angiopathy, according to the modified Boston criteria and more especially in patients with isolated cSS, lobar microbleeds and the inflammation related subtype of CAA. Additionally, we investigated the literature, regarding the association between APOE genotype and CAA phenotypes.

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Methods

A search was performed to select studies in PUBMED database from study inception to November 10, 2020. There were no restrictions performed during the literature search. Keywords used to query the database included: “sporadic cerebral amyloid angiopathy”, “cerebrospinal fluid”, “biomarkers”, “cortical superficial siderosis”, “cerebral microbleeds” and “APOE”. References or retrieved articles were also screened. Case reports, case series, editorials, reviews, case-control and cohort studies were also evaluated and relevant information was abstracted. Duplicate publications and publications associated with familial types of cerebral amyloid angiopathy were excluded from further evaluation. Reference lists of all articles that met the criteria and references of relevant review articles were examined to identify studies that may have been missed by the database search. Literature search protocol was conducted by two independent authors (AT and GP).

Results

β-amyloid and t-tau/p-tau in CAA

Since the CSF amyloid and tau levels was already used as diagnostic biomarkers in AD, the idea to explore their profile in CAA was born.

The first published effort to analyze $A\beta_{40}$ and $A\beta_{42}$ proteins in the CSF was conducted by Verbeek M., et al in 2009, showing decreased $A\beta_{40}$ and $A\beta_{42}$ concentrations in CSF of CAA patients relative to controls and AD-patients. In this cohort CSF t-tau and p-tau levels were increased in CAA-patients, but not as high as in the AD-patients. A possible explanation for this observation could be that neurofibrillary tangles (characteristic for AD) are not among the pathological hallmarks of CAA, but on the other hand, the co-occurrence of AD is often observed, even in the non-demented CAA patients.

Based on the modified Boston criteria Renard et al in 2012 analyzed for CSF biomarkers 13 possible or probable CAA patients and compared them with health controls and AD-patients [6]. In this cohort t-tau concentrations were higher than controls and lower than AD-patients, and p-tau levels were similar to the levels of controls, and thus lower than in AD. $A\beta_{40}$ and $A\beta_{42}$ concentrations in CAA were found lower than in healthy controls, with $A\beta_{42}$ levels to be closer to the levels of AD patients.

In 2015 Martinez-Lizana et al. published another observational study, which showed that the CSF profile was similar in patients with cortical Subarachnoid Hemorrhage (cSAH) and in patients with CAA without acute cSAH, suggesting that the underlying mechanism in these patients was the amyloid angiopathy. Additional they found that the CSF $A\beta_{40}$ and $A\beta_{42}$ levels in these two groups were significantly lower and the t-tau levels were higher as compared to healthy controls. However the t-tau and p-tau concentrations were significantly higher in AD group than in cSAH and CAA groups and there was no difference in $A\beta_{42}$ & $A\beta_{40}$ levels.

Charidimou et al. in 2018 conducted and published a comprehensive meta-analysis, confirming that in patients with symptomatic CAA both CSF $A\beta_{42}$ and $A\beta_{40}$ concentrations are lower as compared to controls and, when comparing with AD patients $A\beta_{42}$ levels are similar but $A\beta_{40}$ concentrations are lower [7]. Concentrations of t-tau in CAA intermediate between controls and AD have been observed and p-tau levels in CAA were shown to be higher than in controls and significantly lower than in patients with AD.

The most recent cohort study from Banerjee et al. in 2020 showed results similar to the previous studies, with significantly lower CSF $A\beta_{40}$ and $A\beta_{42}$ in CAA patients than both AD and control groups [8]. For the t-tau and p-tau markers there were no statistically significant difference between CAA and control group. However, AD patients showed higher levels of tau-markers than both CAA and control groups.

CSF β-amyloid and cortical superficial siderosis (cSS)

cSS, as a magnetic resonance imaging marker of cerebral amyloid angiopathy has been included in the modified Boston criteria for the diagnosis of CAA [9]. Despite that, cSS could be the first and sole imaging sign of CAA. Additionally, it has been shown to be associated with worst cognitive impairment, with a higher co-occurrence of lobar microbleeds and with a higher risk of future lobar hemorrhages [10]

However, there are scarce data regarding the CSF biomarkers profile of both patients with isolated cSS in MRI and patients with cSS in probable/possible CAA. Renard et al. published in 2016 the first study, comparing the biomarker profile in patients with isolated cSS to CAA-, AD- and non-degenerative-control groups [11]. The results demonstrated lower concentrations of t-tau, p-tau and $A\beta_{40}$ in cSS comparing to AD patients and higher t-tau but lower $A\beta_{42}$ in cSS comparing to controls. The cSS biomarker profile was similar to the CAA patients, indicating that this MRI feature may be CAA- specific.

In 2016 as well Shams et al. offered a cohort of memory clinic patients, analyzing the CSF biomarkers regarding the presence of cSS. The results from this study showed lower $A\beta_{42}$ concentrations in patients with cSS, with no significant difference between focal and disseminated cSS. This finding may suggest that cSS is a sign of cerebrovascular amyloid accumulation and probable a marker of advanced CAA in this specific memory clinic population [12].

A recent cohort study with 101 patients with probable and possible CAA conducted by Catak et al, and published in 2019, confirmed the lower $A\beta_{42}$ levels in patients with cSS and observed that $A\beta_{42}$ levels are lower in patients with disseminated comparing to those with focal cSS [13].

According to the above data, isolated presence of cSS could be a hallmark of future CAA diagnosis and its presence in association with the extent of cSS and the presence of lower $A\beta_{42}$ levels may act as a sign of CAA severity.

CSF β-amyloid and lobar microbleeds

Cerebral amyloid angiopathy-related microbleeds have a lobar and less commonly cerebellar distribution. The lobar distribution seems to favor posterior cortical regions and especially the occipital lobe [14]. Decreased levels of $A\beta_{40}$ and $A\beta_{42}$ in patients with CAA and radiological findings of lobar microbleeds were described in different cohorts. Interestingly enough, Noguchi-Shinohara et al, observed significantly decreased levels of $A\beta_{40}$ and $A\beta_{42}$ in patients with cortical microbleeds as compared to those without microbleeds [15]. Additionally, lower CSF p-tau concentrations were observed in AD patients with cortical microbleeds that in those without. Since the levels of $A\beta_{40}$ in AD are not decreased, the above results reflect a coexistence of CAA pathology i.e. deposition of $A\beta_{40}$ and $A\beta_{42}$ in the cerebrovasculature in AD patients with co-occurrence of cerebral microbleeds. Similar findings were reported by Shams et al., which showed lower $A\beta_{42}$ levels in AD patients with lobar microbleeds, supporting the coexistence of CAA in these patients, whereas deep and infratentorial microbleeds were associated with high $A\beta_{42}$ levels, consistent with a different underlying pathology for these lesions [16].

APOE genotype and CAA phenotypes

In the pathophysiology of CAA, genetic factors, such as APOE genotype, may play an important role as well. Already in 2011, a meta-analysis from Maxwell et al. found that carriers of the $\varepsilon 4$ allele have an increased risk of presenting with cerebral microbleeds, particularly in strictly lobar brain locations [17]. One year later, in 2012, an interesting review and meta-analysis from Rannikmäe and colleagues summarized the highly significant and dose-dependent association between APOE $\varepsilon 4$ and vascular β-amyloid deposition in pathologically proven CAA [18].

However, Charidimou et al. in 2015 published the results of a systematic review and meta-analysis, suggesting that the $\varepsilon 4$ allele is more frequent in non-hemorrhagic CAA patients, whereas the $\varepsilon 2$ allele is associated both with the symptomatic ICH clinical phenotype and with a higher prevalence of disseminated cSS in patients with CAA and hemorrhage [19].

These results were confirmed in the meta-analysis of Charidimou et al. in 2019, which showed a stronger association for disseminated cSS in symptomatic CAA patients with the $\varepsilon 2$ allele, and especially with the $\varepsilon 2/\varepsilon 2$ and APOE $\varepsilon 2/\varepsilon 4$ genotype [20].

Summarizing the above data, two associations were observed in patients with CAA: (a) first, the $\varepsilon 4$ allele is more frequently associated with the non-hemorrhagic CAA and (b) the $\varepsilon 2$ allele may be a risk factor for severe cSS. The underlying mechanisms are still not well recognized and should be further investigated, contributing probably in future precise therapeutic interventions in CAA.

CSF and APOE genotype in CAA – related inflammation

The CSF core biomarker profile in patients with CAA-ri is shown to be similar with that of CAA. Decreased levels of $A\beta_{42}$ and $A\beta_{40}$ with increased CSF concentrations of t-tau and p-tau are the main findings of different cohorts. Renard et al. in 2016 reported that $A\beta_{42}$ levels were more specific for CAA-ri, since they observed even significantly lower levels compared to CAA and control groups [21]. However, another cohort from Renard et al. in 2017 reported that lower $A\beta_{40}$ levels in CAA-ri and CAA groups were able to discriminate these from AD patients [22].

Statistically significantly increased anti-$A\beta$ autoantibodies were also reported in CAA-ri patients compared to AD patients, possibly offering a useful tool, not only for the diagnosis, but also for monitoring the response to steroid treatment in CAA-ri, while a post-treatment titer reduction and normalization is documented in another case series [23,24].

Genetically, an important association between APOE $\varepsilon 4/\varepsilon 4$ and CAA-ri has been documented in a case series from Kinneton et al, in 2007, supporting an underlying biologic association [25].

Discussion

In this narrative review we studied the available evidence regarding the pattern of β-amyloid and tau protein concentrations in CSF of patients with symptomatic sporadic CAA and its subtype, CAA-ri. We also investigated the associations between different APOE genotypes and radiological phenotypes of CAA/CAA-ri. Significant to report is the limited number of studies dealing with these topics.

The main results, derived from this review are consistent with significantly lower CSF concentrations of $A\beta_{40}$ and secondarily of $A\beta_{42}$ in patients with CAA compared with AD and healthy controls. t-tau and p-tau CSF levels were comparable to healthy controls and lower than in patients with AD [8]. Patients with cSS either as the first and sole radiological sign of CAA or as one of the modified Boston criteria for the diagnosis share a similar CSF biomarker profile with the sporadic CAA patients. Importantly, the extent of cSS in association with lower levels of $A\beta_{42}$ could function as a prognostic factor for the future severity of CAA [13]. The existence of lobar microbleeds is associated with lower levels of $A\beta_{42}$, even in patients with coexistent AD, who present lower levels of p-tau protein compared to those with AD but without microbleeds [15,16]. APOE genotype may play a significant role in the pathophysiology of CAA, since an association between non-hemorrhagic CAA and the APOE $\varepsilon 4$ allele and another between the APOE $\varepsilon 2$ allele and severe cSS in patients with CAA are well described [19,20].

We discussed the CSF biomarker profile with mainly decreased levels of $A\beta_{40}$ and secondarily $A\beta_{42}$ and mildly increased concentrations of tau protein in patients with CAA-ri. Additional core characteristics of this CAA subtype are the high CSF titer of $A\beta$-autoantibodies and the strong association with the APOE $\varepsilon 4/\varepsilon 4$ genotype [23,24,25].

Strongly associated with AD are the decreased CSF levels of $A\beta_{42}$, due to parenchymal amyloid deposition and the increased levels of t-tau and p-tau proteins. Increased t-tau CSF concentration reflects neuronal/axonal degeneration and the high p-tau levels reflect tangle formation. The overlap between AD and CAA has been already described and attributed to the co-existence of some degree of cerebrovascular amyloid deposition and amyloid plaque pathology in some patients [5].

From our experience, we can refer to a case series of six patients, who presented to our cognitive disorder department. All the patients had radiological findings compatible with CAA but core CSF biomarker profile was suggestive of AD. Half of them had cognitive decline as the presenting symptom and the remaining fifty percent developed cognitive symptoms during the disease progress. This series consists an example of co-occurrence of these two disorders due to common underlying pathobiochemical mechanisms [26].

Another neurodegenerative disease, the dementia with Lewy bodies (DLB) consists the second neurodegenerative dementia coexistent with CAA. In a recent case report, a patient presented with mixed features, compatible with the coexistence of cerebral amyloid angiopathy with DLB [27].

Conclusions

Despite the scarce literature regarding the CSF biomarker profile in CAA the available data support well defined core biomarker patterns in Cerebral amyloid angiopathy and CAA-ri. Further research is needed to clarify the underlying mechanisms, to improve the diagnostic and, probably, the prognostic value of biomarkers and to contribute, through these molecular biomarkers, to future clinical trials, aiming to novel disease-modifying treatments.

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Author contributions

Dr. Theodorou: Study concept and design, Acquisition of Data, Analysis and interpretation, critical revision of the manuscript for important intellectual content

Dr. Tsantzali: Acquistion of Data, Critical revision of the manuscript for important intellectual content

Dr. Kapaki: Acquisition of Data, Critical revision of the manuscript for important intellectual content

Dr. Constantinides: Analysis, critical revision of the manuscript for important intellectual content

Dr. Tsivgoulis: Critical revision of the manuscript for important intellectual content

Dr. Paraskevas: Study concept, Critical revision of the manuscript for important intellectual content

Conflict of interest disclosure statement

Dr. Theodorou reports no disclosures
Dr. Tsantzali reports no disclosures.
Dr. Kapaki reports no disclosures.
Dr. Constantinides reports no disclosures.
Dr. Voumvourakis reports no disclosures.
Dr. Tsivgoulis reports no disclosures.
Dr. Paraskevas reports no disclosures

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Declaration of Competing Interest

None.

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