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Cerebral amyloid angiopathy: a cross-sectional study in a single center in Northeastern Brazil

Angiopatia amiloide cerebral: um estudo transversal em um único centro no Nordeste brasileiro

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ABSTRACT

Background: Cerebral amyloid angiopathy (CAA) is a cerebrovascular disorder caused by progressive deposition of β-amyloid peptides in the walls of small and medium-sized cortical and leptomeningeal vessels. Until today, the prevalence of CAA is unknown in our region. **Objective:** This study aims to analyze the prevalence of this entity in a specific elderly population in a tertiary hospital in Northeastern Brazil. **Methods:** A cross-sectional, retrospective study with the enrollment of patients aged 65 or older followed in the neurological outpatient service of the Universidade Federal do Piauí, Brazil, who underwent brain magnetic resonance imaging (MRI) from July 2016 to June 2018. **Results:** One hundred and seventy-four patients were enrolled, of whom 100 were women (57.4%) and 74, men (42.6%), aged from 65 to 91 years old (median age 73.27). Nine patients were excluded from the study due to unavailability of MRI sequences needed for an appropriate analysis. Out of the 165 remaining patients, 12 (7.2%) had established the diagnosis of CAA, according to the modified Boston criteria. **Conclusion:** The prevalence of CAA in our study was like those of medical literature, with a progressive age-related increase.

Keywords: Cerebral Amyloid Angiopathy; Cerebral Hemorrhage.

RESUMO

Introdução: A angiopatia amiloide cerebral (AAC) é uma desordem vascular causada pela deposição progressiva de peptídeos β-amiloides nas paredes de pequenos e médios vasos corticais e leptomeníngeos. Até a presente data, a epidemiologia da AAC é desconhecida em nossa região. **Objetivos:** Avaliar a prevalência da AAC em uma população específica de pacientes idosos de um hospital terciário no nordeste brasileiro. **Métodos:** Estudo transversal, retrospectivo, com seleção de pacientes com idade igual ou superior a 65 anos, acompanhados no serviço de Neurologia do Hospital Universitário da Universidade Federal do Piauí, Brasil, e que foram submetidos a exame de ressonância nuclear magnética entre julho de 2016 e junho de 2018. **Resultados:** Foram recrutados 174 pacientes, dos quais 100 eram mulheres (57,4%) e 74 homens (42,6%), com idades entre 65 e 91 anos (média de 73,27). Nove pacientes foram excluídos devido à indisponibilidade de sequências de ressonância magnética necessárias para uma análise apropriada. Dos 165 pacientes restantes, 12 (7,2%) foram diagnosticados com AAC de acordo com os critérios de Boston modificados. **Conclusão:** A prevalência da AAC em nosso estudo foi semelhante ao resultado encontrado na literatura médica, com um aumento progressivo relacionado à idade.

Palavras-chave: Angiopatia Amiloide Cerebral; Hemorragia Cerebral.

Cerebral amyloid angiopathy (CAA) is a heterogeneous set of disorders that share the neuropathological characteristic of the progressive deposition of β-amyloid peptides in the walls of small to medium-sized blood vessels of the brain and leptomeninges, configuring an important cause of lobar intracerebral hemorrhage (ICH) in the elderly population[1,2,3,4,5].

CAA mainly occur as a sporadic disorder in older people, but it can occur as a familial syndrome in young patients. In addition, it shares pathological features with Alzheimer's disease (AD), and it is an important contributor to the cognitive impairment in these patients[1,2,3].

It is difficult to assess the exact prevalence of CAA in the general population, given that the definite diagnosis still requires the histopathological analysis of the brain. However, presumptive diagnosis *in vivo* has become possible with specific criteria due to the emerging interest in this

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disease and to the improve in neuroimaging techniques over the last decades[4], especially in magnetic resonance imaging (MRI) sequences that allow the detection of blood-breakdown products before the occurrence of a symptomatic ICH[4,5].

Epidemiology of CAA is unknown in our region according to the literature review. This study aims to evaluate the prevalence of this condition in a specific population of elderly patients followed at the Neurology service of a tertiary hospital in Northeastern Brazil, with the diagnosis established based on the modified Boston criteria[6].

METHODS

Population

This is a cross-sectional, retrospective study, with enrollment of elderly patients (65 years old and older) followed at the neurological general outpatient service of Hospital Universitário of Universidade Federal do Piauí (HU/UFPI), who underwent brain magnetic resonance imaging (MRI) in the corresponding period, between July 2016 and June 2018. MRI scan had been performed, according to medical records, due to different indications, such as cognitive impairment, headache investigation, parkinsonism, previous history of stroke or transient ischemic attack and seizures.

Exclusion criteria

Patients who did not have T2* gradient-echo (GRE) imaging sequence available in the brain MRI examination or poor quality of imaging acquisition to compromise the appropriate analysis were excluded from the study.

Clinical data

Detailed medical history was collected with phone calls and medical records, and included complete demographic and clinical information, medication use, previous history of stroke, brain tumor, head injury or coagulopathy.

Neuroimaging analysis

Neuroimages were obtained in a 1.5T General Electric (Boston, MA, USA) MRI station. Imaging protocol acquisition: axial pre and post gadolinium administration T1, T2 fluid-attenuated inversion recovery (FLAIR), diffusion-weighted imaging (DWI), T2* gradient-echo (GRE), sagittal T1 and coronal T1. Slices thickening=1 mm. Imaging examinations were analyzed by two accredited Neuroradiologists with a particular interest in searching for lobar, cortical or cortico-subcortical intraparenchymal hemorrhages/micro-hemorrhages, and focal or disseminated cortical superficial siderosis (CSS). The diagnosis was established according to the modified Boston criteria (Table 1).

Ethics

According to Resolution 466/12 of the National Health Council, this study was approved by the Research Ethics Committee of Hospital Universitário of Universidade Federal do Piauí — HU/UFPI (No. 106/18). All participants signed the Informed Consent Form.

Statistical analysis

The data obtained were first organized in Excel (Microsoft, Redmond, WA, USA) spreadsheets and then imported to the Statistical Package for the Social Sciences (SPSS) for Windows, version 18 (SPSS Inc., Chicago, IL, USA) software for statistical analysis of the results. The sample analysis was performed using the Shapiro-Wilk test.

RESULTS

A total of 174 patients were enrolled, of whom 100 were women (57.4%) and 74, men (42.6%), aged from 65 to 91 (median age 73.27). Mean age of patients diagnosed with CAA was similar to the average of the sample (76.8±1.82 versus 73.2±0.51 years), with no significant difference ($p>0.05$) found after statistical analysis using the Mann-Whitney test.

Table 1. Modified Boston Criteria for cerebral amyloid angiopathy.

Classification	Modified Boston Criteria
Definite CAA	Full *post-mortem* examination demonstrating: Lobar, cortical, or cortical-subcortical hemorrhage Severe CAA with vasculopathy Absence of other diagnostic lesion
Probable CAA with supporting pathology	Clinical data and pathological tissue (evacuated hematoma or cortical biopsy) demonstrating: Lobar, cortical, or cortical-subcortical hemorrhage (including ICH, CMB, or CSS) Some degree of CAA in specimen Absence of another diagnostic lesion
Probable CAA	Clinical data and MRI or CT demonstrating: Multiple hemorrhages (ICH, CMB) restricted to lobar, cortical, or cortical-subcortical regions OR Single lobar, cortical, or cortical-subcortical hemorrhage and CSS (focal or disseminated) AND Age>55 years old AND Absence of other causes of hemorrhage*
Possible CAA	Clinical data and MRI or CT demonstrating: Single lobar, cortical, or cortical-subcortical hemorrhage (ICH, CMB) OR CSS (focal or disseminated) AND Age>55 years old AND Absence of other causes of hemorrhage*

CAA: cerebral amyloid angiopathy; ICH: intracerebral hemorrhage; CMB: cerebral microbleed; CSS: cortical superficial siderosis; MRI: magnetic resonance imaging; CT: computed tomography. *Other causes of hemorrhage: previous head trauma, ischemic stroke with hemorrhagic transformation, arteriovenous malformation, hemorrhagic brain tumor, warfarin therapy with INR>3, vasculitis.

After applying the exclusion criteria, 9 patients were excluded from the study; 8 because they did not have T2* gradient-echo (GRE) sequence available in MRI, and one due to poor quality in the images acquisition (movement artifacts).

Out of the 165 remaining patients, 12 (7.2%) had established the diagnosis of CAA, according to the modified Boston criteria. Of these, 9 (5.4%) were diagnosed with probable CAA and 3 patients (1.8%) with possible CAA (Figure 1).

In our sample, patients with multiple cerebral microbleeds (CMB) of a strictly lobar location were found, associated or not to CSS and lobar ICH, and patients with isolated CSS were also observed (Figures 2 and 3). The presence of deep location CMB (thalamus, basal ganglia or brainstem), evidenced in some patients, excluded the diagnosis of CAA (Figure 4) based on the modified Boston criteria.

Analysis by age group of patients included in the study showed that 71 of them were between 65 and 70 years old at the time of enrollment. Among this group, 2 (2.8%) patients were diagnosed with AAC. On the other hand, 32 patients were in the age group between 71 and 75 years old, and 2 (6.2%) of them received the diagnosis of CAA. Lastly, 62 patients were over 75 years old, and 8 (12.9%) of them were diagnosed with CAA, which shows a disease prevalence increase with age progression (Table 2).

By investigating radiological findings, the hemorrhagic alterations evidenced in MRI were focal or multiple cerebral microbleeds (CMBs), lobar hemorrhages and focal or disseminated CSS (Table 3).

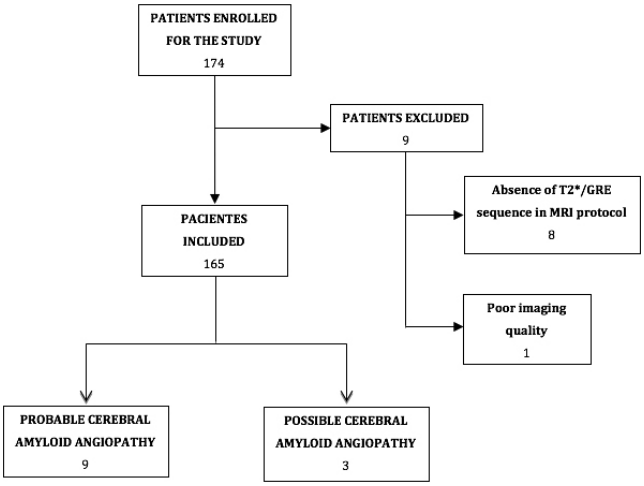

Figure 1. Study profile.

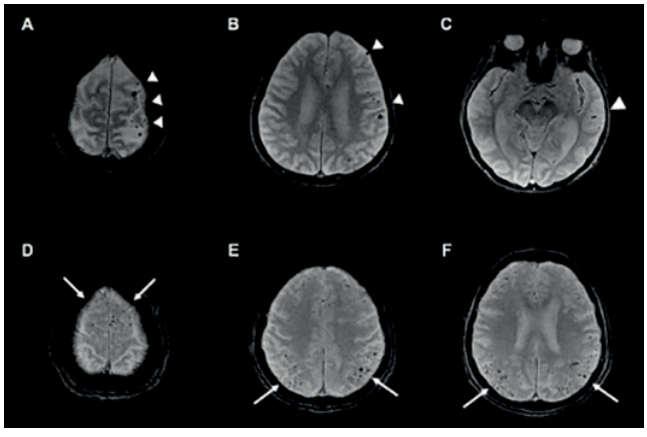

Figure 2. 1.5T axial brain MRI, T2* GRE sequences showing multiple strictly lobar cerebral microbleeds (CMB) supporting the diagnosis of probable cerebral amyloid angiopathy. A-C: A 77-year-old patient (CMB=arrowheads); D-F: A 83-year-old patient (CMB=white arrows).

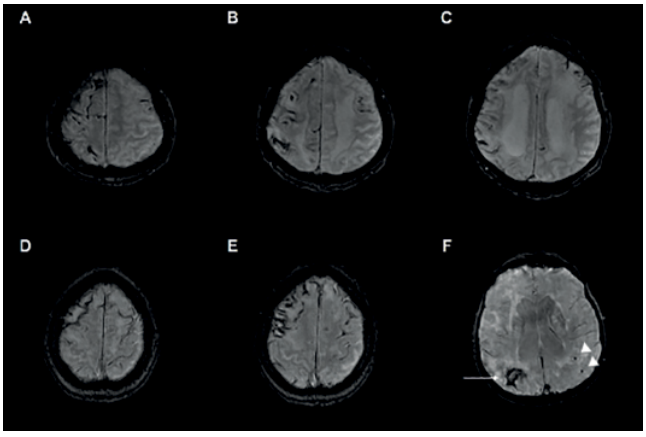

Figure 3. 1.5T axial brain MRI, T2* GRE sequences. Disseminated cortical superficial siderosis (CSS) in a 66-year-old female patient (A-C) and 74-year-old male patient (D-E); F: A right lobar intracerebral hemorrhage (white arrow) in a 77-year-old male patient, with two lobar (cortical and cortical-subcortical location) microbleeds (arrowheads).

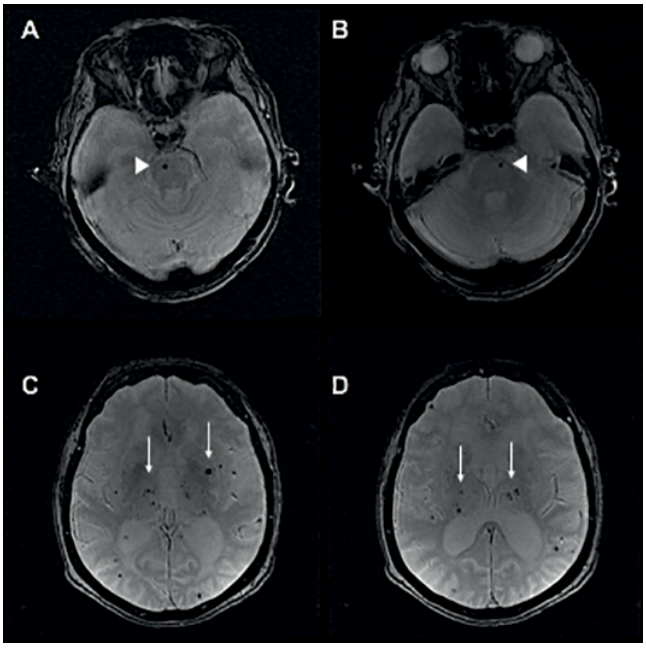

Figure 4. 1.5T axial brain MRI, T2* GRE sequences. Distribution of cerebral microbleeds (CMB). A-B: CMB located in the brainstem/pons (arrowhead); C-D: Mixed distribution (lobar and deep location), with CMB in internal capsule, basal ganglia and thalamus (white arrows). In these situations, diagnosis of cerebral amyloid angiopathy is excluded.

Regarding medication use in CAA diagnosed group, 5 (41.6%) were on antiplatelet (acetylsalicylic acid) and 4 (33.3%) were on statin therapy. None of the diagnosed patients were on anticoagulant use.

Among patients diagnosed with CAA, there was no report of brain tumor, previous traumatic brain injury or coagulation disorder.

DISCUSSION

Incidence of CAA, like in Alzheimer's disease, progressively increases with age. Based on a series of 784 autopsies, the prevalence of moderate to severe CAA was estimated at 2.3% for patients between 65 and 74, 8% between 75 and 84, and 12.1% for patients over 85. Symptoms related to sporadic CAA are uncommon in patients younger than 60 years old, being evident in the genetic forms for younger age groups[7,8].

Since the original description of neurovascular amyloid deposits reported in 1909 by Oppenheim[9], there has been a marked advance in the understanding of CAA, particularly in recent decades. Until the initial publication of the Boston criteria in the mid-1990s, the diagnosis of this condition could only be established by a histopathological analysis of the brain tissue, either with brain hematoma evacuation, biopsy or autopsy analysis. Since then, using a combination of clinical, neuroimaging and histopathological criteria, the Boston criteria established three levels of certainty for the diagnosis of CAA: definite, probable and possible. The diagnosis, therefore, could be reached *in vivo*, sometimes preceding the occurrence of a symptomatic ICH[10,11,12]. In 2010, since the publication of the modified Boston criteria, there was the inclusion of CSS as a hemorrhagic lesion, increasing sensitivity without reducing specificity of the diagnosis (original criteria had a sensitivity range from 57.9 to 76.9% and a specificity range from 87.5 to 100%)[13].

To date, there is no specific treatment or prevention strategy for CAA[10]. It is known that antithrombotic therapy with anticoagulant or antiplatelet medications increases mortality after an ICH and can be harmful if the hemorrhage is associated to the amyloid pathology[10,14,15,16]. With an average risk of recurrence of ICH in patients with CAA around 9% per year[17], antithrombotic strategies that increase the relative risk of ICH should be weighed against benefits, even in patients with atrial fibrillation. Therefore, the use of these therapies must be individualized.

Regarding the use of statins, scientific data is still insufficient to recommend restrictions on the use of this class of medication until now[18]. The use of statins in patients with ICH has been controversial since the publication of the SPARCL (Stroke Prevention by Aggressive Reduction on Cholesterol Levels). This study evaluated 4,731 patients with a recent stroke (ischemic or hemorrhagic), or TIA, and found an increased risk of recurrent ICH in those using high-dose atorvastatin (55 ICH vs 33 in the placebo group; HR 1.68, 95%CI 1.09–2.58)[19,20].

Our study has limitations due to its retrospective model and the type of sample analyzed, composed only of elderly patients followed in a specialized service of Neurology in a tertiary hospital, and therefore, the results cannot be expanded to the general population. However, it serves as a basis for a better understanding on CAA in the local reality, encouraging interest in this pathology, drawing the attention of health professionals for its occurrence and assisting the decision-making process in the diagnosed cases.

Another limitation found was the lack of susceptibility-weighted imaging (SWI) sequence in the MRI protocol, which has a greater sensibility and specificity to detect CMB and CSS.

Table 2. Patients diagnosed with cerebral amyloid angiopathy according to Modified Boston Criteria, by age group.

Age group (years old)	Patients (total sample=165)	Patients diagnosed with CAA
65–70	71 (43%)	2 (2.8%)
71–75	32 (19.4%)	2 (6.2%)
>75	62 (37.6%)	8 (12.9%)

CAA: cerebral amyloid angiopathy.

Table 3. Radiological findings in patients diagnosed with cerebral amyloid angiopathy.

Patients diagnosed with CAA	Cerebral microbleeds	CSS/LOBAR ICH	Classification
Patient 1	2	0	Probable CAA
Patient 2	0	Focal CSS	Possible CAA
Patient 3	Multiple	Focal CSS	Probable CAA
Patient 4	2	0	Probable CAA
Patient 5	0	Disseminated CSS	Possible CAA
Patient 6	Multiple	0	Probable CAA
Patient 7	2	Focal CSS	Probable CAA
Patient 8	Multiple	0	Probable CAA
Patient 9	Multiple	0	Probable CAA
Patient 10	0	Disseminated CSS	Possible CAA
Patient 11	Multiple	Lobar ICH	Probable CAA
Patient 12	Multiple	0	Probable CAA

CAA: cerebral amyloid angiopathy; CSS: cortical superficial siderosis; ICH: intracerebral hemorrhage.

CONCLUSION

CAA is a vascular disorder that plays an important role as a cause of lobar ICH, particularly in the elderly population. This disease is caused by the progressive deposition of β-amyloid peptides in the walls of small and medium-sized cortical and leptomeningeal vessels. Although it is not a rare

condition, as the studies show, it is still an underdiagnosed disease. The prevalence increases with age and the inadvertent use of medications (such as antiplatelet agents and anticoagulants) may be harmful and could contribute to a worse clinical outcome in these cases.

The diagnosis of this condition can be defined in a simple and non-invasive way with clinical and neuroimaging data, particularly with the use of MRI sequences that allow the early detection of hemoglobin-breakdown products and with the application of well-established criteria in the literature.

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