Título: SPORADIC CEREBRAL AMYLOID ANGIOPATHY, BEYOND INTRACEREBRAL HEMORRHAGE: MULTIMODAL BIOMARKER STUDIES OF ATYPICAL PRESENTATIONS

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Resumen: Cerebral Amyloid Angiopathy (CAA) is defined by β-amyloid protein deposition in the media and adventitia of leptomeningeal and cortical small arteries and capillaries. CAA is a major cause of lobar intracerebral hemorrhage (ICH), transient focal neurological episodes, and an important contributor to age-related cognitive decline and dementia in the elderly. The main radiological correlates in the magnetic resonance imaging are cortico-subcortical microbleeds and cortical superficial siderosis. However, CAA is associated with a wide spectrum of clinico-radiological phenotypes. Sporadic CAA is commonly found in the elderly and in patients with Alzheimer's disease (AD), albeit typically mild and clinically silent.

Over the last few years, our understanding of CAA has greatly improved as a result of substanttial progress in neuroimaging techniques, which has allowed the characterization of the spectrum of hemorrhagic and non-hemorrhagic brain injuries associated with CAA as well as different clinical entities. CAA now is considered not only a specific cerebrovascular pathologic disorder, but also a clinical syndrome (or syndromes) with brain parenchymal lesions that can be detected by neuroimaging. It is becoming increasingly evident that CAA is not a uniform entity, but a complex and heterogenous disease that involves several pathophysiological pathways.

In this thesis, we took advantage of several cerebrospinal fluid (CSF), neuroimaging, and genetic biomarkers to study CAA from a translational point of view. We tried to go beyond the CAA-related ICH perspective and

provide a wider framework for CAA characterization starting from other less frequent presentations. The main body of this thesis consists of a compilation of three articles:

First, we studied a cohort of patients with CAA-related atraumatic convexal subarachnoid hemorrhage, a rare cerebrovascular disease that occurs in people over age 60 and usually presents with transient focal neurological symptoms and signs. Twenty-two patients were included and we found that despite its initial, seemingly benign course, a high prevalence of cognitive impairment and lobar ICH occurred during the follow-up. We also found lower levels of Aβ40 and Aβ42 in the CSF and an overrepresentation of the APOE-ε2 allele in these patients when compared to healthy controls.

CAA can also present with acute or subacute focal neurological symptoms in the setting of CAA-related inflammation (CAA-ri), a form of CAA caused by an inflammatory response against the vascular amyloid deposition. In the second article, we studied four patients with CAA-ri and we found high titers of autoantibodies anti-Aβ in CSF. After immunosuppressive therapy, autoantibodies titers return to normal values and focal neurological symptoms improved significantly. CAA-ri was associated to APOE- ε4 allele and amyloid biomarkers in the CSF and Florbetapir-PET.

Finally, because CAA contributes to the clinical presentation of sporadic Alzheimer disease (AD), we studied CAA associated neuroimaging and CSF features in sporadic and genetically determined forms of AD in a cohort of 256 subjects, including autosomal dominant AD, Down syndrome, and sporadic early onset AD patients, and healthy controls. We found that CAA is more frequent in genetically determined AD than in sporadic AD and that CSF-Aβ40 levels are not a useful biomarker of CAA in the context of an AD process.

A thorough study of the entire clinical spectrum associated with CAA, including infrequent presentations, is basic for the understanding of this heterogeneous entity. A multimodal approach such as this is essential to provide new insights to disease processes, to establish new accurate diagnostic tools, and, potentially, to discover new therapeutic targets.