The Role of Copper in Cerebral Amyloid Angiopathy

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The Role of Copper in Cerebral Amyloid Angiopathy

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Alzheimer's disease & other dementias

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Cerebral Amyloid Angiopathy, Copper, Vascular Cognitive Impairment, Amyloid, Familial Cerebral Amyloid Angiopathy

Research Abstract

Vascular cognitive impairment & dementia (VCID) is defined as a form of dementia that is triggered by damage to cerebral blood vessels or cerebrovascular disease. Cerebral amyloid

angiopathy (CAA), which is accumulation of amyloid ß-protein (Aß) within and along primarily small and medium-sized arteries and arterioles of the brain and in the cerebral microvasculature, is a common cerebral vascular condition that can cause VCID in the elderly. Not surprisingly, with the involvement of Aß, CAA is the most common vascular comorbidity found in the brains of Alzheimer's disease (AD) patients. Although there is evidence that both parenchymal plaque amyloid and cerebral microvascular amyloid can contribute to dementia in patients with AD and related disorders, there is growing recognition that the latter is a potent driver of cognitive impairment. Yet, the reasons as to why cerebral vascular amyloid forms and its contribution to downstream pathologies and early cognitive impairment remain unclear. Altered copper homeostasis has been considered an important factor in the neurodegenerative diseases. Earlier findings suggest that copper may play an important role in the formation of amyloid deposits and in subsequent neuronal dysfunction and cognitive impairment. However, relatively little is known about the accumulation of copper in cerebral vascular amyloid deposits, which are associated with early-onset VCID. Thus, the overall hypothesis of our proposal is that copper plays a role in driving fibrillar amyloid assembly in CAA and that the subsequent accumulation of copper in the cerebrovascular amyloid deposits promotes downstream pathologies and early- onset cognitive impairment. In order to test this hypothesis we propose to three specific aims. First, we will determine if vascular amyloid deposits exhibit high levels of copper compared to parenchymal amyloid plaques in post mortem human brain tissue samples of AD, sporadic CAA and familial CAA patients and in transgenic mouse models. Second, we will investigate the effects of copper on Aß fibril assembly. Third, we will determine the effects of increasing or reducing copper levels on the development of CAA, downstream pathologies and cognitive impairment in Tg-SwDI mice. Currently, there are no effective therapies or reliable biomarkers specifically for CAA. These deficiencies are complicated by our lack of understanding of the assembly and unique structural attributes of cerebral vascular amyloid and their distinctive features that lead to CAA formation and subsequent pathologies. The present proposal, focused on the role of copper in these events, will seek to fill this critical void in our knowledge and will advance our understanding of the pathogenesis of CAA and provide insight into the development of novel diagnostic markers and potential therapeutic interventions for CAA and VCID.

Lay Summary
Amyloid ß-protein assembly and deposition in brain blood vessels is the key pathological feature of cerebral amyloid angiopathy (CAA) and associated vascular cognitive impairment & dementia (VCID). Amyloid deposits accumulate copper and can promote cognitive impairment. The purpose of this proposal is to determine how copper impacts amyloid ß-protein assembly and to use transgenic mouse models to investigate the accumulation of copper in brain blood vessel amyloid deposits. Experiments will also determine if copper- altering strategies can influence brain blood vessel amyloid and its associated pathologies linked to cognitive impairment.

Further information available at:

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