Brain and Dietary Copper, Cognitive Decline and Alzheimer's Disease Neuropathology: A Community-Based Study

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Background: Copper (Cu) is an essential micronutrient for brain health. Limited studies reported lower brain Cu and high systemic "free Cu" among Alzheimer's disease (AD) patients. We earlier reported that higher dietary Cu in the presence of a high-fat diet associated with faster cognitive decline. However, it is unknown 1) if there is a relation between brain and dietary Cu intake and 2) if these Cu levels are associated with cognitive decline and AD neuropathology in community-based study. Thus, we aim to examine the association of brain and dietary Cu with cognitive decline and AD neuropathology in 625 deceased participants from the Rush Memory and Aging Project. **Methods:** Brain copper levels were measured using ICP-MS in inferior temporal and mid frontal cortices, anterior cingulate, and cerebellum. Over years of follow-up before death, annual cognitive and dietary assessments were done. Mean dietary copper (calorie adjusted) intake was obtained using a validated food frequency questionnaire. Composite global cognition and specific domains were derived from a 19-panel cognitive tests. Diffuse and neuritic plaques and neurofibrillary tangles were assessed in multiple brain regions and summarized as standard measures of AD pathology. We used separate linear mixed-effects models adjusted for age, sex, education, late-life cognitive activity, physical activity, smoking, and APOε4 status for the associations of Cu (grouped in tertiles) with cognitive decline. Further, linear regression and logit models (adjusted for age at death, sex, education and APOε4 status) were used to evaluate the associations of Cu with the AD pathology outcomes. **Results:** The mean age of participants at first cognitive assessment was 82.7(±5.8) years, 71% were women, and 25% carried an APOE-ε4 allele. There was no association between brain Cu levels and mean dietary Cu intake. Participants in the highest and the middle tertile of Brain Cu in the inferior temporal region had a slower annual rate of cognitive decline (T3vs.T1:β= 0.027; T2vs.T1: β= 0.032; p for trend= 0.007). Those with highest and middle tertile of dietary Cu also had slower cognitive decline (T3vs.T1:β= 0.036; T2vs.T1: β= 0.052; p for trend= 0.09) than the lowest tertile. Concentrations of Cu in the other brain regions were not associated with cognitive decline. Overall higher brain Cu levels were also associated with fewer global AD neuropathology (T3 vs. T1:β=-0.10; T2 vs. T1:β =-0.11; p trend=0.007). **Conclusion:** Dietary copper is not related to brain Cu levels but negatively associated with cognitive decline. However, this effect may saturate above a certain level of intake**.** The association of higher brain copper levels in regions vulnerable to Alzheimer's disease, such as the inferior temporal region, with slower cognitive decline supports the role of copper dyshomeostasis in the disease process. Further brain copper inverse association with AD neuropathology, suggests that brain Cu levels either may reflect the severity of the disease or may indicate its potential beneficial effect on the disease process. Further studies are required to understand and further validate copper as a potential therapeutic target for AD.