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Commentary

Thiamine Metabolites and Dementia?

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The determinants of amyloid deposition in the brain, increased intracerebral phosphorylated tau, hippocampal atrophy, and loss of synapses in areas of brain (the pathogenic determinants of most dementia) remain undetermined except for Mendelian genetic disorders and higher risk of both amyloid deposition and dementia among individuals who carry the apolipoprotein ε4 (*APOE* ε4) genotype, especially homozygous ε4 (Kuller et al., in press; Vardarajan et al., 2014; Leduc et al., 2010).

The incidence of dementia doubles every 5 years after the age of 65 and probably 2/3 or more of incident dementia cases occur over the age of 80 (Prince et al., 2013). The increasing longevity of the population is a major determinant of the 'epidemic of dementia' in many countries. There is little evidence that Alzheimer's disease (AD) pathology or incidence of dementia varies substantially among countries or within countries. Better-educated individuals and those with higher IQ have lower age-specific incidence of dementia attributed to 'brain reserve.' An excess or restriction of an exposure in the environment, lifestyle, such as consumption of a nutrient like thiamine, could be a determinant of increased or decreased risk of an age-associated disease like dementia, specifically AD. The brain requirement of a specific nutrient, e.g. thiamine, could increase with aging, either due to loss of a cellular receptor or changes in intracellular metabolism, greater degradation of the metabolite or increase in interfering agents, e.g. drugs.

A vitamin deficiency in the past, e.g. pellagra, was a 'cause of dementia' that was successfully treated by diet change well before the specific vitamin was identified (nicotinic acid) (Terris, 1964). There is no evidence at present that deficiency of thiamine or any other B vitamin decreases risk of dementia. However, it could be necessary to consume a specific metabolite of the vitamin to have a beneficial effect in the brain.

An alternative hypothesis is that lower thiamine metabolites in patients with AD identified in the paper by Xiaoli Pan and colleagues in *EBioMedicine* (Pan et al., 2015) is due to changes in patients' diet after diagnosis of dementia or secondary to comorbidity after diagnosis of dementia, e.g. reverse causality.

The next steps would be to compare blood levels of thiamine metabolites in longitudinal studies with available stored blood samples prior to diagnosis of dementia. If the relative risk of AD or dementia is increased in relation to thiamine metabolites independent of age and education, then small feeding experiments in humans could evaluate whether thiamine metabolites have any effect on cognition in cognitively normal, mild cognitive impairment (MCI), and dementia patients and finally test the hypothesis by feeding metabolites in larger clinical trials of both risk of dementia among those who are cognitively normal and effects on changes in cognition in MCI and possibly dementia patients.

The search for a nutrient that could prevent or delay onset or even reverse pathology of AD or other pathologies associated with dementia should have high priority given the worldwide magnitude of dementia, growing incidence and prevalence, and lack of effective therapies for prevention and treatment. It is very possible that a deficiency of a nutrient could be a cause of dementia among older individuals, possibly the nutrient is important only in susceptible individuals based on unique genotype, older ages, or comorbidities.

Conflict of Interest Disclosure

None.

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