Commentary

Low copper-2 intake in Switzerland does not result in lower incidence of Alzheimer's disease and contradicts the Copper-2 Hypothesis

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Impact statement

The Western world is faced with an Alzheimer's epidemic. Identifying the life style and anthropogenic factors involved has become a priority. This is a formidable challenge due to the complexity and the slow progression of the disease. A hypothesis put forth by George Brewer postulates divalent copper (copper-2), chiefly present in drinking water from copper pipes, to be a major risk factor for Alzheimer's disease. In Switzerland, copper pipes are not used for drinking water, but the frequency of Alzheimer's disease is similar to that of other Western countries. This contradicts Brewer's hypothesis and suggests that other factors are responsible for today's Alzheimer's epidemic.

Abstract

In recent years, the "Copper-2 Hypothesis" has been put forth in an attempt to explain the epidemic of Alzheimer's disease (AD) in the Western world. According to this hypothesis, "free" copper (copper-2) in drinking water, dietary supplements, and meat is the chief cause of the increased incidence of AD in recent decades. In contrast to the US, copper plumbing for drinking water is not used in Switzerland and tap water is very low in copper. Other "risk" factors including dietary supplements and meat consumption are also lower in Switzerland than in the US. Yet, the incidence of AD is closely similar in the two countries. This contradicts the Copper-2 Hypothesis.

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder of the elderly, associated with behavioral symptoms and dementia. The rise in the occurrence of AD in the Western world in recent decades has raised the notion that an anthropogenic factor promotes the disease. The progression of the neuroanatomical changes takes place over decades, but the cognitive decline becomes evident only at an advanced state of the disease. The aggregation of amyloid-beta protein (Aß) into plaques and fibrils in the brain is considered a marker for AD, and copper has been shown to contribute to Aß aggregation.[1,2] Although this copper could originate from the normal copper chemistry in the brain, such as the release of copper ions by neurons during signaling, the Aß aggregation-copper connection has sparked much research into possible connections between nutritional copper and AD.

George Brewer has advanced the hypothesis that the anthropogenic factor causing the current AD epidemic is "free" copper in drinking water, dietary supplements, and meat; he calls this "copper-2," chemically Cu^{2+} or Cu(II).[3–5] In contrast, he calls copper in other food, such as vegetables, as "bound" copper or "copper-1," chemically Cu^{+} or Cu(I), which is supposedly benign. Why would copper-2 be more toxic than copper-1? Brewer argues that that this is due to the ability of copper-2 to bypass the liver and to appear in the blood already 1–2 h after consumption,

while copper-1 takes 1–2 days to pass to the blood stream.[6] It is doubtful whether such a sharp distinction between copper-1 and copper-2 can be made. Once copper ions have been taken up by the body, it is the local environment (oxidizing in blood, reducing in cells) and the binding to proteins and small molecules that dictates the +1 or the +2 oxidation state, irrespective of how the copper entered the body. Also, there is only one very limited study available on the oxidation state of copper in food.[7] Conceivably, the oxidation state of copper is only secondary to other effects it might have.

Brewer's "Copper-2 Hypothesis" is necessarily based on indirect evidence and there is a large body of literature on copper and AD. For a review, see Sensi et al. and references therein.[8] Animal studies in support of the Copper-2 Hypothesis face the usual criticism that they cannot readily be translated to humans. A prospective study by Morris et al. is usually taken as prominent human evidence for the Copper-2 Hypothesis, but needs commenting.[9] An accelerated rate of cognitive decline was observed in persons aged 65 years or older, if they consumed a diet high in *trans* fats combined with an elevated copper intake. Points of concern with this study are the inaccurate measurement of the dietary copper intake and the omission of measuring the copper consumed with drinking water. Also, the complicated evaluation of the study limits causal interpretation. In fact, the authors warn that "this finding of accelerated cognitive decline among persons whose diets were high in copper and saturated *trans* fats must be viewed with caution. The supporting evidence on this topic is limited." So, the weight of this study remains unclear and decisive evidence for the Copper-2 Hypothesis remains outstanding.

Unfortunately, there has been no systematic review of the connection of copper intake to AD frequency in different Western countries. So, the unique case of Switzerland should be considered, as it bears on the Copper-2 Hypothesis. In Switzerland, copper plumbing for drinking water has never been used (although some websites wrongly state so). Instead, zinc-plated steel or stainless steel pipes are employed. Being a highly industrialized country, tap water is supplied by municipal water supplies to over 90% of households and its copper content is very low (<0.02 ppm).[10] So, the large majority of the Swiss population consumes drinking water with a very low copper content.

Also, the consumption of mineral supplements, which according to Brewer is another AD risk factor because some of them contain copper-2, is significantly lower in Switzerland compared to the US. According to a recent study, 51% of the US population regularly consume multivitamin/mineral supplements,[11] while in Switzerland, only 17% of the population regularly consume such supplements, based on a study of 6188 individuals aged 35–75 years.[12] How much copper is actually consumed with mineral supplements is not possible to assess because the definitions and categorizations of dietary supplements are not standardized. However, it appears safe to conclude that copper supplementation of the diet is much less frequent in Switzerland than in the US.

Meat consumption, which according to Brewer is another risk factor for AD, is also lower in Switzerland than in the US. The average meat consumption in Switzerland amounts to 50 kg/y[13] versus 99 kg/y in the US.[14] So, all three risk factors for AD proposed by Brewer, namely, copper in drinking water, meat consumption, and mineral supplement use, are substantially lower in Switzerland than in the US. Yet, the incidence of AD in these two countries is very similar, with 1.68% in Switzerland and 1.77% in the US.[15] These observations argue against the Copper-2 Hypothesis, i.e. copper-2 as the primary cause of the AD epidemic.

In terms of the Copper-2 Hypothesis, it is also interesting to compare Switzerland to Germany. These two countries have genetically very similar populations, closely similar cultures, and comparable eating habits. Meat consumption in Germany amounts to 60 kg/y (https://www.statista.com/statistics/525199/meat-per-capita-consumption-germany), compared to 50 kg/y in Switzerland. The use of mineral supplements is higher in Germany than in Switzerland. Of 4261 adults aged 19–80 years, 27.6% regularly consumed dietary supplements in Germany versus 17% in Switzerland.[12,16] However, approximately 60% of German households consume water from copper pipes.[17] In a field study involving 1674 German households, the mean copper content of drinking water from copper-pipe house installations was in range of 0.106 to 0.183 ppm.[18] So, two out of three risk factors, namely, meat consumption and mineral supplement use, are very similar in Switzerland and Germany, while copper-2 consumption with tap water is much higher in Germany. But the incidence of AD is comparable in Germany and Switzerland, with 1.66% and 1.68%, respectively.[15] Taken together, these observations also do not support the promotion of AD by copper-2.

Clinical diagnoses of dementia usually fail to reflect the pathologic complexity. Based on 443 brain autopsies in the Honolulu Asia Aging Study, five lesion types could be linked to cognitive impairment.[19] It appeared that these lesions develop independently of one another and that the co-prevalence of two or more lesion types increases dramatically with age. So, cognitive decline and dementia should not be regarded as a discrete, present-or-absent condition and strategies for reducing the risk of dementia in late life will require interventions that target different disease processes. Also, an increasing number of genetic risk factors appear to be associated with AD.[20] As a corollary to this, it appears unlikely that a single environmental factor, e.g. copper-2, is responsible for the recent rise in AD; rather, several anthropogenic factors are probably involved. Given the tight homeostatic control of copper in the body, it does not seem plausible that comparatively small changes of copper in the diet could have such far-reaching effects as causing AD. In the light of the complexity of the problem, the association of environmental risk factors with dementia remains extremely challenging.

In summary, the case of Switzerland with an incidence of AD similar to that of the US, but with half the meat consumption, a third of the mineral supplement use, and the absence of copper pipes in drinking water supplies contradicts the Copper-2 Hypothesis. The direct link between

copper exposure and AD could cause undue concern and potentially adverse "adjustments" in behavior by the public, such as minimizing copper intake. The public needs to remain aware of copper's essentiality for good health.

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