Minireview

Avoiding Alzheimer's disease: The important causative role of divalent copper ingestion

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Impact statement

The work described in this review is very important to scientists working on Alzheimer's disease (AD) because it reveals a cause for the explosive epidemic of this disease. It is also important to the public because it provides a method to avoid this newly revealed cause, and thereby avoid AD. The field is advanced because this review reveals new information about the mechanism of AD pathogenesis, namely copper, and specifically divalent copper, toxicity is important. New information about divalent copper toxicity in the brain affecting cognition is revealed. The field is impacted strongly because, in view of the frustrations that have occurred in treatment developed, now most AD can be prevented. This means the suffering of the patient, the prolonged and difficult care required by caregivers, and the enormous expenditures for this one disease, can now be avoided.

Abstract

In this review, we point out that developed countries are undergoing an epidemic of Alzheimer's disease, not shared by undeveloped countries. We also point out that this epidemic is new, developing during the 20th century. This suggests that an environmental change occurring in the 20th century in developed countries is causing the epidemic. The author hypothesizes that the environmental change causing the epidemic of Alzheimer's disease is ingestion of divalent copper. The hypothesis is based on data indicating that food copper is primarily monovalent copper, and humans evolved safe ways of channeling monovalent copper, but not divalent copper. Humans were not exposed to divalent copper until the 20th century, due to the use of copper plumbing and supplement pills containing copper, and that exposure, which occurs in developed countries, does not occur in undeveloped countries. Data in support of the hypothesis show that tiny amounts of divalent copper added to drinking water of Alzheimer's disease animal models greatly enhance Alzheimer's disease, and ingestion of copper (which is always divalent copper)-containing supplement pills by humans is quite toxic to cognition.

Keywords: Alzheimer's disease, divalent copper, copper 2, Alzheimer's disease epidemic, cause of Alzheimer's disease epidemic, copper 2 hypothesis, copper levels in drinking water

Experimental Biology and Medicine **2019; 244: 114–119. DOI: 10.1177/1535370219827907**

Introduction

It is easy to show that Alzheimer's disease (AD) is a very bad disease. It robs people in their retirement years of memory and other cognitive functions. They cannot remember their loved ones, or the events they experienced together during their lives. As the disease progresses, patients require care 24/7. They become completely dependent on their caregivers. And AD is becoming very common as will be shown below. Currently, there are no treatments to prevent the inevitable progression. So if there is a way to prevent AD, it is obvious it should be pursued with the utmost vigor. And there is a way for about 95% of cases to be prevented, and without very much difficulty, as will be shown in the following sections.

Two important facts about the history and epidemiology of AD

Fact 1

Currently, there is an epidemic of AD in developed countries, not shared by undeveloped countries. For example, in the US, 20% of those age 70 and over and 30% of those age 80 and over have AD.[1] In contrast, in rural India, the AD prevalence is 1.07% in those 65 and over,[2] and in

Nigeria the prevalence in those 65–74 is 0.52% and in those 75–84 is 1.69%.[3]

Fact 2

The epidemic is relatively new, developing in the 20th century. That is, there is relatively good evidence that an AD-like dementia was very rare prior to 1900. Waldman and Lamb,[4] the authors of the book Dying for a Hamburger, deserve the credit for being the first to point this out, and developing very good evidence to support it. This evidence includes the writings of Osler,[5] an internist, who consolidated all medical knowledge into a series of books written in the 19th century, including a book devoted to diseases of the brain, and did not describe an AD-like dementia. Gowers[6] wrote a textbook of neurology, published in 1888, and also did not describe an AD-like dementia. Freud and his co-workers,[7] who wrote extensively on behavioral disorders of the brain in this period, also did not mention an AD-like disease. Perhaps most important, Boyd,[8] who wrote a textbook of pathology with the first edition published in the 1800s, last edition in 1938, did not describe the amyloid plaques and neurofibrillary tangles, hallmarks of AD brain pathology, in the brains of people autopsied in this period.

There are two arguments often used by those who do not believe the epidemic is recent, and both of these can be shown to be invalid. The first is that since AD is a disease of aging, and the population is aging, of course we have many cases now, but there were not enough old people in the 19th century to reveal the disease. This is wrong, in that there were plenty of people in the 1900s in an age range to show the disease. For example, half the population of France in 1911 were living to age 60 and over.[4] The 1900 US census showed 3.2 million people age 60 and over, enough to generate over 300,000 AD patients at today's rate. This would have supplied many patients for the clinics of Osler,[5] Gowers,[6] and Freud,[7] and to have shown AD pathology by Boyd[8] in brains at autopsy.

The second argument is that AD was not noted as a specific disease in the 19th century, but just thought to be a part of normal aging. Conceivably, this could have occurred with the clinicians Osler, Gowers, and Freud, although it is hard to believe given their thoroughness, but it would not explain the absence of amyloid plaques and tangles in brains at autopsy, in pathological work, such as those of Boyd.

Reviewing, there is a major epidemic of AD in developed countries, but not in undeveloped countries. Second, it is clear that this epidemic began in the 20th century. What are the causes of epidemics? By far the most common one is infection. But, AD is not an infectious disease. After infection, environmental change is the most common cause of epidemics. Examples are lung cancer and heart disease from cigarette smoking, and obesity from a number of environmental changes leading to an altered lifestyle of less exercise and more food. So, an environmental change, in developed countries in the 20th century is a major suspect as the cause of the epidemic of AD.

Ingestion of divalent copper as the environmental cause of the AD epidemic: The "Copper-2 Hypothesis"

In a book on this topic recently published by the author,[9] various environmental agents that have previously been put forward as possible causes of AD were carefully examined, and all but divalent copper, were ruled out. The ruled out agents included other metals such as aluminum, lead, mercury, zinc, and iron. Also ruled out were general diet, specific nutrients and foods, and physical activity. It is beyond the scope of this paper to examine all the negative findings, and we will focus on the positive result, involving divalent copper ingestion.

Some copper background

For background, copper is an essential element, vital to life and involved in many important reactions in the body. It is present in two valence forms, monovalent copper $^{(Cu+)}$, also called copper-1, and divalent copper $^{(Cu++)}$, also called copper-2. An important study has shown that most food copper is copper-1.[10] This is a bit surprising, because in life, in both plant and animal tissue, copper is a combination of copper-1 and copper-2, where they form a redox doublet, important for catalyzing many reactions. But apparently at death or harvest, in the absence of oxygen transport, most copper-2 is reduced to copper-1 in the tissue.

Thus, mammals, including humans, evolved ingesting copper-1 and not copper-2. As a result, we have an intestinal receptor, Ctr1[11] for copper, which will bind copper-1 but not copper-2. Binding to this receptor causes the copper-1 ingested with food to be transported to the liver, where it is put in safe channels. Copper is a potentially toxic molecule, being very reactive, and it must be kept carefully bound. Ingested copper-2 is absorbed partially by direct diffusion into the blood without passing through the liver first. This explains why, when the author's group did ^{64}Cu studies, where ^{64}Cu is ingested orally to examine efficacy of zinc therapy, in the absence of zinc a large part of the ^{64}Cu dose appears in the blood in 1–2 h.[12] However, if food copper is radioactively labeled, the radioactive copper does not appear in the blood until two days or so. The difference is that the ^{64}Cu is given as copper-2, and it does not get processed by the liver with much of it appearing in the blood immediately, while the food copper is copper-1, and it is processed by the liver, put into safe channels, and takes days to appear in the blood. In summary, the two valence forms are absorbed differently, with one being processed by the liver and a large part of the other being absorbed without processing.

Two relevant studies involving copper-2 ingestion and AD

In the early 2000s, Larry Sparks was using a rabbit model for AD studies, involving administration of cholesterol to cause AD to develop. The model was working well in his W. Virginia laboratory, but then he was recruited to Arizona, and the model stopped working. He finally

realized that in Arizona they were using distilled water for the rabbits' drinking water, whereas in W. Virginia it was tap water. A careful study to find out what it was in tap water that caused the difference revealed it was tiny amounts of copper. It was found that addition of 0.12 parts per million (ppm) of copper to the distilled drinking water greatly enhanced the amyloid plaques of AD in the brain, and caused memory loss in the animals. Copper in drinking water is copper-2. Sparks and Schreurs[13] published this work. For reference, the Environmental Protection Agency (EPA) allows 1.3 ppm of copper in human drinking water,[14] 10 times the amount found toxic in the animal studies. Later Sparks et al.[15] saw these same results in other animal models of AD, and the findings were also confirmed in another laboratory.[16]

The second relevant study was a nutritional study in a large Chicago population, in which the intake of nutrients was studied while cognition was measured over time. It was found that those in the highest quintile of copper intake, if they also ate a high fat diet as many Americans do, lost cognition at several times the rate of other groups.[17] These people were in the highest quintile of copper intake because they were ingesting copper containing supplement pills.

What do the AD animal model[13] and the human cognition[17] studies have in common? In both cases, the copper ingested was copper-2. Copper in drinking water and copper in supplement pills are both copper-2. It is clear that copper-2 is very toxic to cognition and can cause AD in animals. It appears that the direct absorption of copper-2 into the blood without liver processing gives it a clear channel to the brain where it is toxic to cognition.

To be clear about the "Copper 2 Hypothesis," it is not being proposed that copper 2 is the "cause" of AD. Rather it is being proposed that copper 2 ingestion is the cause of the AD epidemic. The cause of AD is aggregation of beta amyloid (Aβ) into amyloid plaques that become neurotoxic and release damaging oxidant radicals. The role of copper 2 is to enhance the aggregation of Aβ into amyloid plaques and then bind to the plaques and cause release of oxidant radicals, all of which will be discussed in more detail later. Copper 2 enhances the formation of plaques and their toxicity so much that it triggers the disease in a very large number of people, causing the epidemic.

More data to support "The Hypothesis"

It is proposed here that copper-2 in human drinking water is a major cause of the AD epidemic, and that leaching of copper from copper plumbing is causing the copper to be in the drinking water. There are two pieces of data needed to evaluate this assertion. One is, how does the use of copper plumbing concur timewise with the development of the AD epidemic? The second is, does copper actually leach from copper plumbing in high enough amounts to cause AD?

Addressing the first, the use of copper plumbing began in the early 20th century, but was curtailed by two world wars, and then took off about 1945, such that now, about 90% of US homes have copper plumbing.[18] This use of copper plumbing history concurs timewise, very closely with the history of the AD epidemic. The AD prevalence increased only slowly during the first half of the 20th century, and then exploded after 1950.[4]

Regarding the second question, by coincidence the author collected household drinking water samples from all over N. America as a part of his work with Wilson's disease patients. Since Wilson's disease is a disease of copper toxicity, the drinking water collections were done to make sure the patients were not ingesting high levels of copper in their drinking water. As a result, 280 drinking water samples were collected from all over N. America, and the copper levels measured.[19] It was found that one-third of the samples had copper levels higher than 0.1 ppm, the level that caused AD in the animal models. Another one-third of the samples had copper levels below 0.01 ppm, low enough to probably be safe. The last one-third had copper levels between 0.1 and 0.01 ppm, and is of unknown safety. Thus, one-third to two-thirds of drinking water samples in N. America are potentially causative of AD, according to the animal models.

The question might be asked, is it appropriate to use the levels of copper that were toxic in animal models to extrapolate that these same levels would be toxic in humans? The answer is when humans cannot be the experimental subjects to test toxicity for ethical and other reasons, animal studies are next best to estimate the levels which are likely to cause toxicity in humans. There is a long tradition of this in the FDA, who requires that new drugs be tested against animals, often more than one species, and then they set the level of human exposure well below the level that was toxic in animals. Here we are more conservative, suggesting that toxic levels in animals would also be toxic in humans. Several animal models for AD have shown the same toxic response to the same low levels of copper, so it seems safe to use the animal models as a guide to the potentially toxic levels of copper in human drinking water.

Summarizing, copper plumbing use fits closely with the epidemic of AD in developed countries, and enough copper is leached from copper plumbing to cause the AD epidemic, according to the animal models. Copper leached into drinking water quickly becomes copper-2.

The situation with AD in the Japanese adds interesting and strong support for the hypothesis. Japan is a developed nation but has a low prevalence of AD,[20] and the Japanese have shunned copper plumbing for fear of toxicity. But when Japanese migrate to Hawaii, where copper plumbing is used, their prevalence of AD increases to match that of other developed countries.[21]

Another piece of data probably in support of the hypothesis comes from China. The soil content of copper in the various provinces of China correlates positively with the prevalence of AD.[22] For example, AD prevalence is 2.6 times as high if the copper soil concentration is 60–80 ppm vs. 20–40 ppm. If the soil concentration of copper in China correlates with the drinking water concentration of copper, as it probably does, it supports the hypothesis. It should be mentioned that numerous other metals and potentially toxic agents, besides copper were studied in Shen *et al.*,[22] and only copper levels correlated with AD prevalence.

In previous publications,[9,23] we have presented some of the aspects of the hypothesis that copper 2 toxicity is the cause of the current epidemic of AD.

Mechanism of copper-2 toxicity in the brain

It is known that an underlying feature of the injury in the AD brain is oxidant damage, and of course, copper causes damage through oxidant toxicity. But is there more specific information on how copper-2 causes brain damage? It turns out there is.

Amyloid plaques are a consistent feature of the AD brain. These plaques consist of aggregates of amyloid beta (Aβ). Aβ is a piece of the amyloid precursor protein, and is clipped off the protein in normal brains, but does not accumulate and aggregate in normal brains as it does in the AD brain. It was shown two decades ago that copper-2 induced Aβ aggregation.[24] This was elaborated on in further work where it was shown that copper-2 potentiates Aβ neurotoxicity.[25] Aβ reduces copper-2 to copper-1 and in the process generates hydrogen peroxide (H_2O_2), which is a potent source of damaging oxidant radicals.[25]

A more recent line of investigation indicates glycation of Aβ may be involved.[25] Glycation is the non-enzymatic addition of a sugar to an amino acid. It is an appealing mechanism because superoxide anion, a reactive oxygen species (ROS), is generated during the glycation process. In the presence of copper-2, superoxide is converted to hydroxyl radical, an ROS, which according to this group, is the source of oxidative damage in AD. Extensive glycation in AD is supported by the finding that large amounts of Aβ in the plaques of AD patients are found in the form of advanced glycation end-products (AGEs). According to this group, all three components of AD plaques, Aβ, sugars, and copper-2, are necessary for the resulting neuronal DNA damage.[26] (Sugars provide the glycation substrate).

In all these proposed mechanisms of oxidant damage, copper-2 plays a necessary role. So, the direct absorption of copper-2 into the blood, as shown in the ^{64}Cu studies cited,[12] without liver processing to put the copper-2 in safe channels, with presumed more or less direct access of copper-2 to the brain, would be expected to be quite neurotoxic.

Prevention measures to avoid copper-2 ingestion and to avoid AD

Since the two main sources of copper-2 ingestion are supplement pills containing copper and drinking water containing too much copper, prevention is simply avoiding the ingestion of these two sources of copper-2.

All multimineral and multivitamin-multimineral pills that the author is aware of contain copper, and it is copper-2. So this type of pill should be avoided. Multivitamin pills (without minerals) are safe. If a mineral such as iron or calcium needs to be taken, it can be taken as an individual pill. There is now a company (Mito-Synergy) that makes copper-1 pills for the occasional patient, such as those with malabsorption problems, that must take a copper supplement.

With regard to drinking water, the first thing is to have the water from the tap used for drinking and cooking tested for copper levels. This is a good thing to do even if copper plumbing is not present, because in some parts of the country, source water is high in copper. It is a good idea to let the water run for a few minutes before collecting the sample. There are many companies now that offer water testing service, including copper assay.

If the water copper level is 0.01 ppm or lower, it is safe. If it is over that, the copper plumbing need not be removed, and copper is a good plumbing material. The "fix" is to install a copper removal device on the tap used for drinking and cooking, such as an inexpensive reverse osmosis device.

The "Copper-2 Hypothesis" is still a hypothesis, but it is very well supported by the data. It will take a long time and considerable effort to finally prove the hypothesis. In the meantime, those who take these preventive measures, which are not very expensive or arduous, will have greatly benefitted already when the hypothesis is finally accepted.

It is suggested here that these preventive measures will prevent 95% of the AD cases – in other words the cases comprising the AD epidemic. That number comes from using the baseline number of AD cases caused by risk factors other than copper, which appears to be about 1%, as seen in undeveloped countries. If we use an average current prevalence of 20% in the developed countries experiencing the AD epidemic, this means that 19 of the 20% are due to the epidemic. So roughly 95% of overall cases are due to the epidemic, and preventable by avoiding copper-2 exposure if "The Hypothesis" is correct.

An addendum to "The Hypothesis"

There are additional data which suggest there is an additional cause besides copper-2 of the AD epidemic, and it also involves copper, but copper in general, not a specific valency of copper. This stems from the work of Dr Rosanna Squitti and her group, in Italy. First, she and her group have shown that the fraction of copper in blood, known as "free copper," is intimately involved with the pathogenesis of AD. By way of background, the blood copper can be thought of as in two pools. One pool, comprising about 90% of the total blood copper, is tightly (covalently) bound to the ceruloplasmin (Cp) molecule. The other 10% of copper is loosely bound to albumin and other molecules in the blood. This smaller fraction, known as non-Cp copper, and also known as free copper, is what the body uses for its day to day needs for copper. It is also this pool that is greatly expanded in a disease of copper accumulation and copper toxicity, Wilson's disease (WD). The free copper is toxic when the pool is enlarged too much. Dr Squitti's group has shown that the free copper pool is enlarged in AD,[27] that the levels of the free copper correlate with measures of cognition in AD,[28] that the levels of free copper predict rates of cognition loss over time in AD,[29] and that free copper levels predict the risk of conversion of mild cognitively impaired (MCI) patients to full AD

patients.[30] These data indicate strongly that AD is, at least in most patients, a disease of copper toxicity. These data are neutral to the copper-2 hypothesis, because the free copper measured by Dr Squitti could be both copper-1 and copper-2. But the Squitti data are compatible with the direct absorption of copper-2 into the blood, as has been discussed, increasing the level of free copper in the blood, and causing toxicity to cognition.

Dr Squitti and her group have also shown something else that is relevant. They have shown that patients with a mutated ATP7B gene are at an increased prevalence among AD patients.[31,32] ATP7B is the gene that when both copies are mutated so that they lose their function, cause Wilson's disease, a disease of copper accumulation and copper toxicity. The ATP7B gene regulates the body's copper levels, by causing excretion of copper in the stool, and its function is required to prevent copper toxicity.

Wilson's disease is inherited as an autosomal recessive disease, and full siblings of an affected patient have a 25% chance of also having the disease in a pre-symptomatic form, 50% of the siblings are heterozygous carriers, and 25% are completely clear of the mutated gene. After diagnosing a new patient, it is important to work up the family to detect the affected pre-symptomatic siblings, and treat them prophylactically. In those family workups, we observed that heterozygous carriers always have an increased load of copper, manifested by elevated urine and liver copper, but never to the level seen in affected siblings, and never requiring treatment.

If we assume that the AD patients studied by Dr Squitti who carried an ATP7B variant and were at increased prevalence in the AD population, also carried a mild increase in body load of copper as did the heterozygous carriers in Wilson's disease families, it means that carrying a mild increase in body copper load is a risk factor for AD. Then the question becomes are there any factors occurring in developed countries in the 20th century to increase body loading of copper, and thus be another explanation for the AD epidemic? The answer is yes – and the factor is increased meat eating.

By way of background, copper is much better absorbed from meat than from vegetable foods.[33] Some estimates are that in a diet rich in meats, 50% more copper is absorbed than from a vegetarian diet. During the 20th century, meat eating greatly increased in developed countries as a result of a greatly expanded poultry industry, and the development of food lot technology for hogs and cattle. This dietary change did not occur very much in undeveloped countries because of the expense.

So, to be thorough in our preventive measures, we would also advise a reduction in meat eating. How much to reduce meat eating is a bit of a guesstimate, but a 50% reduction should be adequate. Such a reduction in meat eating should also be healthful. A 50% reduction in meat eating is estimated to reduce all-cause mortality by 50%.[34]

Of the two proposed AD-epidemic causing factors, increased copper-2 ingestion and increased meat eating, which is the more important in AD causation and therefore the most important to abate to avoid AD? It is the opinion of the author that copper-2 ingestion is the more important. This opinion is based on the observations in Japanese, where they go from a low prevalence of AD in Japan, but to higher, developed country type, prevalence in Hawaii. The major difference after the migrations to Hawaii is in copper-2 ingestion from copper plumbing. The ingestion of meat would not be expected to change very much. But this opinion is a "guesstimate." The relative importance of the two factors might vary considerably depending on many factors. So to be on the safe side, it would be best to both eliminate copper-2 ingestion and reduce meat intake.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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