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Alzheimer's disease as copper deficiency

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Summary Four classes of etiologic agents can produce toxic, hereditary, infectious and deficiency diseases. Recent research on Alzheimer's disease generally addresses pathogenesis related to the first three classes of agents with little emphasis on cause. Low copper and cytochrome oxidase in Alzheimer brain can be attributed to low copper intakes or higher than average nutritional requirements. Experiments with animals deficient in copper involving amyloid, ceruloplasmin, copper transport, cytochrome oxidase, myelination, organ analysis and oxidative defense are consonant. Decreased cognition and increased tau in cerebrospinal fluid in Alzheimer's disease also are associated with low copper status. A high requirement for copper may explain early onset of Alzheimer's disease in Down's syndrome. Copper deficiency is a plausible cause of Alzheimer's disease. This hypothesis should be tested with a lengthy trial of copper supplementation.

Background

In 1977 I divided all diseases into two classes [1] depending upon whether or not their etiologies were comprehensible or incomprehensible. The comprehensible class of diseases was divided further into toxic, hereditary, infectious and deficiency diseases, i.e., into diseases caused by four classes of etiologic agents.

Diversity within these subclasses is immense. Tens of thousands of chemicals, thousands of genes, hundreds of infectious agents can be involved in human illness and approximately fifty essential nutrients can preserve health [1–4]. Based on these concepts, it was suggested [2] that there are only four ways of becoming ill.

The etiology of Alzheimer's[1] disease has been mysterious for more than a century [5,6]; clearly Alzheimer's disease falls into the incomprehensible class. Recent research generally addresses pathogenesis with little emphasis on cause. Intoxication seems to have fallen from favor; the genetics of apolipoprotein E and presenilin [7], for example, are being emphasized. Subtle, viral infection with a long incubation period has been mentioned [8].

Nutritional deficiency does not seem to be under consideration. It will be argued here that sufficient

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[1] Citation in several texts and articles of Alois Alzheimer's first article on the disease named for him by Kraepelin is quite variable. The article cited here seems to be the original based on the description of the middle-aged woman and comparison of the article with a recent translation. The full title of the journal is ''Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin'' which may be translated as The Journal of General Psychiatric and Forensic Medicine.

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evidence has accumulated to support an hypothesis that Alzheimer's disease is the result of dietary deficiency of copper.

Facts about Alzheimer's disease

Epidemiology

Alzheimer's disease is the leading cause of dementia in the elderly with a prevalence, near Rochester Minnesota, of 123 cases/10,000 [9]. Cost of annual care in the United States approaches $100 billion [10]. Familial aggregation occurs [10]. Alzheimer's disease is more common in people with Down's syndrome and it occurs earlier in these people than in most others [7]. Alzheimer's disease can be considered a chronic inflammatory disease of brain [8]; acute phase reactants are implicated [10].

Pathology

Brains of people with Alzheimer's disease show cortical atrophy with shrinking gyri and widening sulci [11]. Myelin loss occurs [12].

Synapses are lost in Alzheimer's disease. Loss can be detected by morphometry [13—23] and by measurement of proteins specific to synapses [24—28]. This loss reflects mental performance and disability [23—25,29,30].

People with Alzheimer's disease are thinner than normal [31—37]. Weight loss precedes dementia [34,38] and greater weight loss is associated with greater dementia [35,37]. Low weight and weight loss are associated with greater neurobehavioral symptoms [39]. Nutritional compromise contributes to morbidity [10].

Facts about copper biochemistry and physiology

According to Golden [40], copper deficiency can be diagnosed by measuring its concentration in suitable tissue, testing an appropriate metabolic pathway or demonstrating the effect of replacing copper on a functional system. Numerous experiments with deficient animals reveal low copper in various organs and decreased activities of enzymes dependent on copper. Some of these experiments have been summarized [41].

The Western diet often is low in copper [42,43] according to pooled data on more than 900 adult diets chemically analyzed and summarized from several articles. Recently, 62% and 36% of diets of 80 randomly selected adults in Baltimore [44] were below the recommended dietary allowance and the estimated average requirement for adults, 0.9 and 0.7 mg daily, respectively [45].

Biochemistry

Ceruloplasmin depends on copper for its activity [45]. It is as acute phase reactant that increases in inflammation [46].

Cytochrome oxidase or cytochrome *c* oxidase is the terminal link in the electron transport chain [47]. Its activity is depressed in various organs, including brain, of several species of animals deficient in copper [41].

Copper is at the active site of superoxide dismutase in erythrocytes [41]; copper deficiency decreases this enzyme activity [48]. The gene [49] for superoxide dismutase is located on chromosome 21. The enzyme is elevated in Down's syndrome (trisomy 21) [49] and is decreased in people with monosomy [49].

Although a low concentration of copper in plasma or serum can be used to diagnose copper deficiency, high values found in a variety of medical conditions and physiological states do not necessarily reflect nutritional status [45]. Numerous animal experiments show that normal or high blood values can accompany low values in important organs (some are reviewed in [50]).

May et al. [51,52] evaluated chemical equilibria between cupric ions and many low-molecular-weight ligands in plasma and calculated that copper ion is practically nonexistent (10^{-18} M) in mammalian fluids. There may be only one copper ion per cell as copper ions bind tightly to many ligands.

Copper and the central nervous system

Copper deficiency early in life impairs the development of the central nervous system in several species of animals [48]. Myelination is impaired in animals deficient in copper [53].

The adult nervous system also can be damaged by copper deficiency. A syndrome of myelopathy, spastic gait and sensory ataxia from copper deficiency has been described recently [54]. Copper therapy halts disease progression and sometimes improves neurological deficits [54].

Effects of excess zinc

Numerous reports in the last half century reveal that a high zinc intake can induce copper deficiency in animals and people. ''High dietary zinc can increase copper requirements and lessen copper toxicity'' [55,56]. At present, induction of copper deficiency is the only identified mechanism by which zinc intox-