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Copper Deficiency and Central Nervous System

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Abstract: Copper, a microelement essential for all living organisms, is involved in normal physiological functioning of numerous enzymes. In central nervous system, it is involved in various metabolic pathways besides its involvement in mitochondrial activity, defense against oxidative stress, myelination, neurotransmitter synthesis and storage as well as modulation of synaptic activity. Homeostasis of copper is achieved by copper transporters, metallo-chaperones as well as exporters which prevents both deficiency and accumulation of this element. Acquired copper deficiency is rare but alterations in lifestyle and eating habits have made this rare deficiency more prevalent. Studies have linked copper deficiency to various neurodegenerative diseases including Alzheimer's and Parkinson's. Copper deficiency in central nervous system is also associated with myeloneuropathy. This review assesses the impact of copper deficiency on the central nervous system.

Keywords: Copper, Copper deficiency, Myeloneuropathy, Central nervous system

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Introduction

Dietary micronutrient deficiencies are of significant health problem in developing as well as developed countries (Tulchinsky, 2010). Due to its redox potential copper has the ability to interact with more than 30 enzymes (Arredondo and Núñez, 2005). Burkhead and Collins (2021) reported that shellfish, organ meats, wheat-bran cereals, whole-grain products, seeds, nuts as well as chocolate are rich source of copper. The recommended dietary allowance (RDA) intake of

copper for adults is 900 µg/day (IOM, 2001). Variable copper concentration was reported in human brain in the range of 2.9 - 10.7 mg Cu/g wet weight while rat brain appears to have a low copper content 1-2.3 mg Cu/g wet weight (Lutsenko *et al.*, 2010). Kardos *et al.* (2018) reported heterozygous distribution within the brain as concentrations observed were high in the cerebellum, hippocampus, substantia nigra, hypothalamus, olfactory bulb and locus coeruleus.

Glial cells had more copper concentration compared to neurons (Scheiber *et al.*, 2014). This review assesses the impact of copper deficiency on the central nervous system.

Copper transporters in brain:

In brain it is the free copper and not the protein bound copper (Cu-Ceruloplasmin / Cu-albumin) which is transported through the blood brain barrier (BBB) and the blood-cerebrospinal fluid barrier (BCB). Both BBB and BCB maintain copper homeostasis in the brain. Copper transporters like Ctr1, DMT-1, ATP7A and ATP7B are more common in brain barrier compartments than in brain parenchyma and may be involved in the copper uptake in the brain (Choi and Zheng, 2009; Monnot *et al.*, 2011).

Copper deficiency in brain:

Experimental evidence indicated that copper deprivation during gestation and lactation in rats and mice reduces copper accumulation in the neonatal brain leading to significant drop in brain copper concentration (Prohaska and Hoffman, 1996). Studies on perinatal copper deficiency on 22 days old Sprague Dawley rats revealed that copper concentration is reduced by 80% in brain (Johnson and Prohaska, 2000). Dietary copper deficiency for 6–8 weeks resulted in decreased brain copper levels with residual copper levels being 21.6% that of control (Zucconi *et al.*, 2007). Studies have revealed that neurodegenerative diseases are associated with low levels of copper in brain where Alzheimer's-brain regions revealed significant decrease in copper levels up to 52.8-70.2% and Parkinson's affected brain regions showed 35%-50% reduction of copper content in substantia nigra and locus coeruleus (Xu *et al.* 2017; Bisaglia and Bubacco, 2020).

Copper deficiency and development:

Studies involving laboratory and domestic animals revealed that maternal copper deficiency causes intrauterine growth impairment, teratogenesis and fetal mortality (Keen *et al.*, 1998). The offspring of the sheep and farmed deer fed on copper-deficient grass were born with enzootic

ataxia - swayback (Bennetts and Chapman, 1937; Vengust *et al.*, 2015) characterized by muscular paralysis, seizures and abnormality in coordination and vision. In embryos from copper deficient mothers incubated in copper deficient serum, short crown-rump lengths, short head and low protein concentrations have been observed (Mieden *et al.*, 1986). Wistar rats fed with the low copper diet exhibited foci of whitish opaque areas of evident necrosis and complete olfactory lobes degeneration in approximately one-half of the deficient animals and revealed typical neurological symptoms of copper deficiency including tremors, inactivity, locomotor dysfunction, malaise, torpor and occasional aggressive behavior (Morgan and O'Dell, 1977). The progeny born to copper-deficient dams showed significant reduction in responses to auditory startle although tactile startles were not affected (Prohaska and Hoffman, 1996). Zucconi *et al.* (2007) demonstrated that copper deficiency in SV129 mice resulted in various neurological symptoms including ataxia, hind limb paresis with milder abnormalities such as reduction of mobility, hunched posture to wobbling along with splaying of hind toes. Copper deficiency in central nervous system is often associated with myeloneuropathy while some of the symptoms exhibited by humans include impaired coordination, parasthesias, progressive weakness as well as numbness (Grossman and Ruiz, 2021; Mutti *et al.*, 2021).

Copper deficiency and mitochondrial function:

Experiments revealed that copper deficiency can decrease CCO activity by up to 80% (Prohaska and Wells, 1975). Brain mitochondria from Cu-deficient rats had 13% low level of COX IV as detected in choroid plexus and 1.7-fold lower in cerebellum with reduced CCO activity with glycolytic inhibition following perinatal copper deficiency (Gybina and Prohaska, 2006). Rossi *et al.* (2001) discovered that brain tissue from brindled mice has increased cytochrome c release into the cytosol and a sharp decline in mitochondrial Bcl-2 suggesting apoptosis in this copper limitation scenario. Electron microscope

studies showed abnormal mitochondria in the brains of copper deficient rats indicating that brain energy metabolism was adversely affected (Gybina *et al.* 2009). Brain of mouse pups appears to be the first organ to exhibit high lactate during copper deficiency which indicates that brain mitochondria is quite sensitive to copper deficiency (Rusinko and Prohaska, 1985) as also seen in Menkes disease patients (Munakata *et al.*, 2005). Significant reduction in brain copper levels in AD brain showed a marked effect on cellular energy metabolism (Xu *et al.*, 2017). Cendrowska-Pinkosz *et al.* (2022) demonstrated that removal of copper from the diet or replacing inorganic copper with metallic one resulted in impaired energy metabolism and the changes in gene expression revealed the mobilization of energy metabolism pathways for increased NADH demand in the brain prefrontal cortex. Mass spectrometry studies in post-mortem brain regions of AD revealed marked reduction in copper levels and significant increase in glucose, sorbitol and fructose in all brain regions and this may potentially contribute to the pathogenesis of neurodegeneration in AD (Xu *et al.*, 2016).

Copper deficiency and Myelination:

Hypomyelination in the brain is linked to increased brain lactate levels and decreased N-acetylaspartate concentrations which are required by oligodendrocytes for myelin synthesis (Gybina *et al.*, 2009) as well as reduced activity of cerebellar 2',3'-cyclic nucleotide 3'-phosphohydrolase (myelin rich protein) and low norepinephrine levels (Prohaska and Smith, 1982). Three generations of rats fed with copper deficient diet revealed marked decline in myelination although the chemical composition of myelin was not altered except the molecular weight of major myelin glycoprotein of copper deficient animals increased and dietary copper replacement before conception resulted in normal myelination suggesting that copper is essential for myelination during embryonic development (Matthieu *et al.*, 1974). Immunohistochemical staining showed that dietary copper deficiency

caused hypoplastic myelination in the cerebrum of macular mouse with elevated number of cleaved caspase-3 positive cells indicating oligodendrocyte dysfunction (Takikita *et al.*, 2015). It is well established that adequate copper in diet is essential for normal myelination thus Kleavy, (2013) suggested that individuals suffering from traumatic brain injury should be monitored for serum copper levels as altered myelination is distinct in these cases. Prolonged treatment of Wilson disease with zinc supplements without frequent monitoring of serum copper and ceruloplasmin levels of patients may result in hypocupremia with low serum coppers leading to demyelination of CNS (Narayan and Kaveer, 2006). Herring and Konradi (2011) demonstrated that administration of copper chelator - cuprizone caused demyelination in specific brain areas which may be one of the reason for accounting the possible role of copper deficiency in demyelination and resulting cognitive deficits in schizophrenic patients.

Copper deficiency and oxidative stress:

Copper has a crucial role in antioxidant defense system through its structural and functional activities in superoxide dismutase (SOD1 and SOD3) (Fukai and Ushio-Fukai, 2011). Embryo culture study revealed decreased SOD enzyme activity and increased superoxide anion levels in copper deficient embryos and concentrated in the forebrain (Hawk *et al.*, 2003). Gomi and Matsuo (1995) reported that dietary copper deficiency resulted in 16% reduction in the Cu-Zn SOD activity in cerebrum of 6 month old rats. Brain mitochondria from copper deficient rats revealed marked increase in CCS and significant decrease in Cu-Zn SOD (Gybina and Prohaska, 2006). Studies have identified copper-deficient state of SOD1 as main culprit for the toxicity generated by mutant SOD1 in amyotrophic lateral sclerosis suggesting therapeutic potential of copper in restoring the copper-deficient state of SOD1 (Gil-Bea *et al.*, 2017).

Copper deficiency and ceruloplasmin:

Ceruloplasmin is a serum ferroxidase, responsible

for 90% of copper transport which requires copper for its normal structural and functional stability. Copper deficiency resulted in significant decrease by 95% in serum ceruloplasmin activity of young and old rats and 16% Cu-Zn SOD activity of cerebrum (Gomi and Matsuo, 1995). Copper deficiency in the central nervous system is likely to cause clinical signs identical to aceruloplasminemia such as neuronal degeneration, apoptosis and altered iron metabolism which worsens with age (Lutsenko *et al.*, 2010). Adequate copper concentration in diet of dams is required for deposition of iron in brains of pups during embryonic development (Prohaska and Gybina, 2005). Moreover, in PD patients the serum level of copper, ceruloplasmin and its oxidase activity as well as copper atoms per ceruloplasmin molecule were low in comparison to age-matched healthy individuals and may be implicated in neurodegeneration associated with PD (Bisaglia and Bubacco, 2020; Scholefield *et al.*, 2021).

Copper deficiency and neurotransmission and neuromodulatory function:

Copper plays a role in neurotransmitter synthesis through peptidyl- α -amidating monooxygenase (PAM) and dopamine- β -hydroxylase (DBH) which are involved in the amidation of neuropeptides and production of norepinephrine (Lutsenko *et al.*, 2010). In copper deficient brain, activities of these cupro-enzymes are altered with low concentration of the neurotransmitter and norepinephrine synthesized by the copper dependent enzyme dopamine- β -monooxygenase activity (DBM) and high concentration of dopamine-substrate for DBM (Prohaska and Bailey, 1994). Copper deficiency may decrease norepinephrine levels which can alter morphology and function of the copper-deficient brain (Prohaska and Smith, 1982). The biochemical effects of copper deficiency on several central neurotransmitter indicated a preferential reduction of muscarinic and dopaminergic receptors in forebrain regions suggesting an involvement of copper in interactions between receptors/between a

receptor and some other membrane protein (Feller *et al.*, 1982; Farrar *et al.*, 1985). Copper is a non-competitive antagonist of NMDA (N-methyl-D-aspartate) receptors and their expression and copper supply is regulated by ATP7A in hippocampal neurons and absence of ATP7A significantly increases NMDA receptor excitability in the neurons resulting in seizures (Schlief *et al.*, 2006).

Conclusion

Copper deficiency is becoming more prevalent being implicated in various neurodegenerative diseases. Previously copper deficiency was considered rare as it was unrecognized or misdiagnosed. Copper deficiency has shown adverse affects on the central nervous system resulting in various neurological manifestations. Copper deficiency adversely affects brain development, mitochondrial function, myelination, ceruloplasmin activity as well as neurotransmission and neuromodulation. However, further research is required so as to detect deficiency at an early stage besides considering clinical history before treatment.

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