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COPPER AND PAEDIATRIC NEUROLOGICAL DISORDERS: A MINI-REVIEW

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ABSTRACT

Copper is one of the essential elements for maintaining normal physiological activity of multiple essential enzymes as cytochrome c-oxidase, superoxide-dismutase and dopamine-β-hydroxylase. Enzymes deficiencies result in severe neurological symptoms and serious neurological diseases, some of them has been present for more than a century now. In this mini-review, I aim to provide a synopsis of current knowledge regarding copper related disorders and available lines of management which may improve the overall outcome in case of early recognition and prompt intervention.

KEYWORDS: Copper, Wilson, Menkes, occipital horn, MEDNIK.

INTRODUCTION

Copper is an essential element in multiple critical enzymatic reactions, presents throughout the brain and is most prominent in the basal ganglia, hippocampus, cerebellum, numerous synaptic membranes, and in the cell bodies of cortical pyramidal and cerebellar granular neurons.[1]

Copper plays an important role in antioxidant reactions, cellular respiration and catecholamine synthesis.[2] Multiple enzymes in the central nervous system depend on copper including tyrosinase, peptidylglycine alpha amidating mono-oxygenase, copper/zinc superoxide dismutase, ceruloplasmin, hephaestin, dopamine beta hydoxylase and cytochrome *c* oxidase.[3,4,5]

Neuronal copper levels depend on proper homeostatic control.[6]; this involves mechanisms that govern its gastrointestinal uptake, its transport to the developing brain, especially targeted intracellular delivery to copper dependent enzymes, and finally: hepatic excretion of

copper into the biliary tract.[7] This cycle is mostly dependent on the function of a pair of evolutionarily related copper-transporting ATPases, ATP7A and ATP7B. Defects in ATP7B cause a single known phenotype, Wilson disease (WD).[8] whereas mutations in ATP7A are associated with three distinct conditions: Menkes disease (MD).[9] Occipital Horn Syndrome (OHS), a less severe neurologic phenotype of Menkes disease.[9]; and an isolated distal motor neuropathy, often with adult onset and without overt signs of copper metabolic derangements.[10,11]

Copper is also implicated in the pathogenesis of other numerous neurological diseases, including aceruloplasminemia, Alzheimer disease, Amyotrophic lateral sclerosis, Huntington disease, Parkinson disease, Prion disease.[12] and recently re-discovered: mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratodermia (MEDNIK) disease.[13,14]

Copper transport system in the human brain includes: Copper transporter 1, Atox1, ATP7A, and ATP7B copper transport proteins. Interestingly, the substantia nigra contained twice as much copper than that in other brain regions, suggesting an important role for copper in this brain region. Furthermore, ATP7A levels are significantly greater in the cerebellum, supporting an important role for ATP7A in cerebellar neuronal health.[15]

Wilson Disease (WD)

WD was first defined in 1912 by Sir K. Wilson in Brain, The Lancet and La Revue Neurologique. Though the role of copper in Wilson disease was not described until 1929 as a result of copper overload with subsequent toxicity, presents with hepatic and neurological deficits, including dystonia and Parkinsonism. Other extrahepatic features include renal, osteo-articular, myocardial and endocrine disturbances.

WD can present as early as in infancy and late-onset manifestations in adults older than 70 years of age. Clinical diagnosis can be easily confirmed through detection of ATP7B mutations; located on chromosome 13 with more than 500 mutations and 100 polymorphisms identified to date.

Early diagnosis of WD is crucial to ensure that patients can be started on adequate treatment, but uncertainty remains about the best possible choice of medication. Furthermore, WD needs to be differentiated from other conditions that also present clinically with hepato-lenticular

degeneration or share biochemical abnormalities with WD, such as reduced serum ceruloplasmin concentrations.[16]

Treatment of WD is based on the use of copper chelators (D-penicillamine & Triethylenetetramine) to promote copper excretion, supplementation of zinc salts to reduce copper absorption. In addition; Tetratiomolybdate appears to be a promising treatment.[17]

Copper ions or complexes in excess concentrations can damage DNA as well as chromosome structure; promoting epigenetic changes leading various diseases, including cancer, Alzheimer's disease, Lewy body dementias, and spongiform encephalopathies.

Overall, and except in unusual genetic states that lead to copper overload in specific cells (particularly in liver), it appears that excessive intake of copper is not a significant factor in the development of disease states.[18]

Menkes Disease (MD)

MD is an infantile neurodegenerative copper deficiency disorder caused by mutations in an X-linked gene; *ATP7A*. This gene encodes a copper-transporting P-type ATPase. Deficiency of the *ATP7A* gene product results in abnormal cellular copper transport and decreased activities of numerous copper-dependent enzymes. Patients with MD have a defect in copper transport across the placenta, gastrointestinal tract, and blood brain barrier. Circulating concentrations of copper and ceruloplasmin are usually low and neurochemical concentrations affected by the copper enzyme dopamine hydroxylase, are distinctively abnormal.[8] Despite the known association of anemia and severe copper deficiency.[19], MD patients rarely have hematologic manifestations.

Decreased activity of copper dependent enzyme; cytochrome *c* oxidase; is likely a major factor in the brain damage associated with MD. As copper is a noncompetitive antagonist of the *N*-methyl-D asparate (NMDA) receptor, it may also have a role in regulation of neuronal excitability. Furthermore, Synaptic *NMDA* receptor activation results in rapid and reversible trafficking of ATP7A, which suggests a link between copper homeostasis and neuronal activation within the brain.[1]

ATP7A plays a significant role in the development and maintenance of the central nervous system, which can be seen by the marked behavioral, neurological, and developmental

abnormalities observed in MD patients. ATP7A serves as a copper transporter in vascular endothelial cells and retinal pigment epithelium forming the blood-brain barrier and is thus important for delivery of copper to the brain.

The neurological phenotype of MD involves refractory epilepsy.[20], profound truncal hypotonia with poor head control. Deep tendon reflexes are hyperactive, and visual fixation and tracking are often impaired. The natural history of the disease often involves death by 3 y of age.

Patients with MD show progressive cerebral atrophy and delayed myelination on magnetic resonance imaging of the brain. At autopsy, diffuse atrophy, focal gray matter degeneration, prominent cell loss in the cerebellum, abnormal dendritic arborization, and focal axonal swelling are noted.

MEDNIK syndrome

MEDNIK (mental retardation, enteropathy, deafness, neuropathy, ichthyosis, and keratodermia) syndrome has been recently described as a new disorder of copper metabolism. This multisystem disease combines clinical and biochemical signs of both Menkes and Wilson's diseases, in which liver copper overload is treatable using zinc acetate therapy.

A growing number of diseases have been associated with mutations in genes coding for adaptor protein complexes subunits and were proposed the term adaptinopathies, as disorders of intracellular trafficking, which offers the opportunity to dissect the mechanisms involved in the crosstalk between the Golgi apparatus and the other organelles.[13]

MEDNIK syndrome (OMIM 609313) —acronym for mental retardation, enteropathy, deafness, neuropathy, ichthyosis, keratodermia—is caused by AP1S1 gene mutations, encoding 1A, the small subunit of the adaptor protein 1 complex, which plays a crucial role in clathrin coat assembly and mediates trafficking between trans-Golgi network, endosomes and the plasma membrane. MEDNIK syndrome was first reported in a few French-Canadian families sharing common ancestors, presenting a complex neurocutaneous phenotype, its pathogenesis is not completely understood.

A Sephardic-Jewish patient, carrying a new AP1S1 homozygous mutation, showed severe perturbations of copper metabolism with hypocupremia, hypoceruloplasminemia and liver

copper accumulation, along with intrahepatic cholestasis. Zinc acetate treatment strikingly improved clinical conditions, as well as liver copper and bile-acid overload.

Copper-related metabolites and liver function were evaluated retrospectively in the original French-Canadian patient series. Intracellular copper metabolism and subcellular localization and function of copper pump ATP7A were investigated in patient fibroblasts. Copper metabolism perturbation and hepatopathy were confirmed in all patients. Studies in mutant fibroblasts showed abnormal copper incorporation and retention, reduced expression of copper-dependent enzymes cytochrome-c-oxidase and Cu/Zn superoxide dismutase, and aberrant intracellular trafficking of Menkes protein ATP7A, which normalized after rescue experiments expressing wild-type AP1S1 gene.

The patho-genetic mechanism of MEDNIK syndrome, demonstrating that AP1S1 regulates intracellular copper machinery mediated by copper-pump proteins. This multisystem disease is characterized by a unique picture, combining clinical and biochemical signs of both Menkes and Wilson's diseases, in which liver copper overload is treatable by zinc acetate therapy, can be listed as a copper metabolism defect in humans and may also contribute to understanding the mechanism of intracellular trafficking of copper pumps.[14,21]

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