Role of copper in human neurological disorders\textsuperscript{1–3}

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ABSTRACT
Copper is a trace element present in all tissues and is required for cellular respiration, peptide amidation, neurotransmitter biosynthesis, pigment formation, and connective tissue strength. Copper is a cofactor for numerous enzymes and plays an important role in central nervous system development; low concentrations of copper may result in incomplete development, whereas excess copper maybe injurious. Copper may be involved in free radical production, via the Haber-Weiss reaction, that results in mitochondrial damage, DNA breakage, and neuronal injury. Evidence of abnormal copper transport and aberrant copper-protein interactions in numerous human neurological disorders supports the critical importance of this trace metal for proper neurodevelopment and neurological function. The biochemical phenotypes of human disorders that involve copper homeostasis suggest possible biomarkers of copper status that may be applicable to general populations. *Am J Clin Nutr* 2008; 88(suppl):855S–8S.

INTRODUCTION
Copper is one of many metal ions that are required for essential body functions but are toxic in excess (1, 2). Copper is present 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 (2). Enzymes in the central nervous system that depend on copper for their function include tyrosinase, peptidylglycine α-amidating mono-oxygenase, copper/zinc superoxide dismutase, ceruloplasmin, hephaestin, dopamine-β-hydroxylase, and cytochrome c oxidase (3–5). Copper is implicated directly or indirectly in the pathogenesis of numerous neurological diseases, including aceruloplasminemia, Alzheimer disease, amyotrophic lateral sclerosis, Huntington disease, Menkes disease, occipital horn syndrome, Parkinson disease, prion disease, and Wilson disease (Table 1). In this review, we provide an overview of current knowledge about the effect of copper deficiency and excess on the brain and neural tissues through the context of these disorders and suggest possible biomarkers of copper status that may be applicable to population screening.

ACERULOPLASMINEMIA
Ceruloplasmin contains 95\% of the copper in plasma and it functions as a ferroxidase. Deficiency is associated with progressive iron accumulation involving the retina and basal ganglia. Aceruloplasminemia is an autosomal recessive condition (6, 7). Copper does not directly affect the rate of synthesis or the secretion of ceruloplasmin; however, failure to incorporate copper into apoceruloplasmin results in an unstable apoprotein that is rapidly degraded (8). The clinical consequences of aceruloplasminemia include dystonia, abnormal gait, dysarthria, and dementia.

ALZHEIMER DISEASE
Progressive cognitive impairments are characteristic in the dementia of Alzheimer disease. An increased concentration of copper in cerebrospinal fluid with normal plasma copper concentrations has been noted in some patients with Alzheimer disease (9). Copper interacts with amyloid precursor protein and β-amyloid peptide in the self-aggregating plaques and neurofibrillary tangles characteristic of Alzheimer disease and may contribute to the pathogenesis of this disorder via cellular oxidative stress (2, 3, 10–13).

AMYOTROPHIC LATERAL SCLEROSIS
Gain-of-function mutations in the cytosolic copper enzyme Cu/Zn-superoxide dismutase result in motor neuron degeneration characteristic of amyotrophic lateral sclerosis. This selective neuronal damage leads to loss of muscle strength and respiratory problems, with an eventual fatal outcome (9). Some evidence suggests a direct pathogenic role for copper in this process; enhanced free radical generation is suspected (2, 6, 9, 14). Amyotrophic lateral sclerosis is considered a model disorder for neurodegeneration involving deterioration of the anterior horn cells in the spinal cord.

HUNTINGTON DISEASE
Huntington disease is caused by a triplet repeat expansion of a protein (huntingtin) that leads to oxidative stress, energetic insufficiency, and striatal degeneration. Elevated concentrations of copper are found in human Huntington disease brain (15). It is hypothesized that increased amounts of copper bound to low affinity binding sites in huntingtin promote excitotoxic stress and neurodegeneration.

MENKES DISEASE

Menkes disease is an infantile neurogenetic disorder caused by mutations in an X-linked gene, ATP7A (1, 2, 4, 5, 16–21). This gene encodes a copper-transporting P-type ATPase, so named because it forms a covalently phosphorylated intermediate from transfer of the gamma-phosphate of ATP to a specific aspartate residue at the catalytic site of the protein. Deficiency of the ATP7A gene product results in abnormal cellular copper transport and decreased activities of numerous copper-dependent enzymes. Persons with Menkes disease have a defect in copper transport across the placenta, gastrointestinal tract, and blood–brain barrier. Circulating concentrations of copper and ceruloplasmin are low, and neurochemical concentrations affected by the copper enzyme dopamine-H2O2/H2O3-oxidase, are distinctively abnormal (17, 18, 21). Decreased activity of the copper-dependent enzyme cytochrome c oxidase is likely a major factor in the brain damage associated with Menkes disease. Because copper is a noncompetitive antagonist of the N-methyl-D-aspartate receptor, it may also have a role in regulation of neuronal excitability. Synaptic N-methyl-D-aspartate receptor activation results in rapid and reversible trafficking of ATP7A, which suggests a link between copper homeostasis and neuronal activation within the brain (2). Despite the known association of anemia and severe copper deficiency (22), Menkes disease patients rarely have hematologic manifestations.

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 Menkes disease 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. Patients with Menkes disease 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.

The neurological phenotype of Menkes disease involves 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.

OCCIPITAL HORN SYNDROME

Occipital horn syndrome is a neurologically less severe allelic variant of Menkes disease with connective tissue problems including cutis laxa, hyper-mobile joints, and bony protuberances of the occiput (5, 23, 24). These findings are related to decreased lysyl oxidase activity, which leads to disruption of collagen and

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TABLE 1

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
<th>Neuronal effects</th>
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<tbody>
<tr>
<td>Aceruloplasminemia</td>
<td>Autosomal recessive trait</td>
<td>Progressive neurodegeneration (retina, basal ganglia)</td>
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<td>Absence of ceruloplasmin</td>
<td>Dystonia/abnormal gait, dysarthria, dementia</td>
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<td>Accumulation of iron (liver, pancreas, basal ganglia)</td>
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<td>Alzheimer disease (AD)</td>
<td>Mutations in amyloid precursor protein cause familial AD</td>
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<td>Adult-onset dementia and behavioral changes</td>
<td>Self-aggregating plaques and neurofibrillary tangles</td>
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<td>Amyotrophic lateral sclerosis</td>
<td>Gain-of-function mutations in Cu/Zn superoxide dismutase cause small percentage of cases</td>
<td>Associated with cellular oxidative stress</td>
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<td>Huntington disease</td>
<td>Autosomal dominant trait</td>
<td>Death ultimately due to respiratory failure</td>
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<tr>
<td></td>
<td>Teenage- or adult-onset</td>
<td>Progressive cerebral atrophy</td>
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<tr>
<td>Menkes disease</td>
<td>X-linked recessive gene</td>
<td>Dysmyelination</td>
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<td></td>
<td>Poor copper absorption and distribution</td>
<td>Abnormalities of intracranial vessels</td>
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<td></td>
<td>Connective tissue problems</td>
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<tr>
<td>Occipital horn syndrome</td>
<td>Mild allelic variant of Menkes</td>
<td>Mild cerebral atrophy</td>
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<td>Symptoms of dysautonomia</td>
<td>Slightly delayed myelination</td>
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<td>Connective tissue problems</td>
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<td>Parkinson disease</td>
<td>Primary movement disorder</td>
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<td>Bradykinesia/akinesia</td>
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<td>Prion diseases</td>
<td>Transmissible neurodegenerative disease</td>
<td>Result of modified PrPs:PrPSc and PrP85</td>
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<td>Spongiform encephalopathy</td>
<td>Possible inappropriate metallation of PrP with Mn instead of Cu</td>
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<td>Wilson disease</td>
<td>Autosomal recessive</td>
<td>Predilection for copper accumulation in basal ganglia</td>
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<td>Carrier frequency: 1 in 90</td>
<td>Neuronal loss, gliosis, and cavity degeneration</td>
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<td>Clinical presentation</td>
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<td>Hepatic versus neurologic</td>
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PrP, prion protein; PrPSc, prion protein scrapie variant; PrP85, prion protein mutant form.
elastin cross-linking. As in Menkes disease, dopamine-β-hydroxylase activity is decreased in occipital horn syndrome, producing symptoms of dysautonomia (25, 26). The autonomic nervous system is involuntary and plays a crucial role in the maintenance of homeostasis through innervation of cardiac muscle, smooth muscle, and endocrine and exocrine glands (26). The autonomic nervous system has 2 divisions: the sympathetic and the parasympathetic systems. Both are tonically active, and the frequency of discharge of neurons in both systems can increase or decrease. With diminished production of norepinephrine, there is impaired innervation of postganglionic sympathetic targets. This may produce bradycardia, orthostatic hypotension, and chronic diarrhea in persons with occipital horn syndrome (23–25). The overall biochemical phenotype (low serum copper and ceruloplasmin and abnormal plasma and cerebrospinal fluid catecholamine concentrations) is similar to that seen in Menkes disease, although often less severe.

**PARKINSON DISEASE**

Parkinson disease is a common neurodegenerative movement disorder characterized by impaired motor function, including resting tremors, rigidity, bradykinesia, and postural instability (27). The pathophysiology of Parkinson disease includes dopaminergic neuron death and accumulation of Lewy bodies associated with mutations in α-synuclein, a 14-kDa protein predominantly expressed in the central nervous system (27, 28). Oxidative injury appears to be one effect of α-synuclein aggregates and could ultimately produce neuronal cell death (27). The kinetics of α-synuclein aggregation are modulated by several factors in vitro, including the presence of certain metal cations. Copper is the most effective in accelerating aggregation, suggesting a possible link between abnormal copper homeostasis and this condition (28).

**PRION DISEASES**

The prion diseases are a group of neurodegenerative diseases that affect the gray matter of the central nervous system and produce neuronal loss, gliosis, and spongiform degeneration (29, 30). Prion diseases are caused by prion proteins (PrPs) that have been modified such that they fold improperly. PrPs are highly expressed in the central nervous system and contain high-affinity copper-binding sites in their amino-terminal regions. In vitro, copper enhances renaturation and stabilization of PrPs, enhancing protease resistance and infectivity, and leading to speculation about copper’s role in the pathogenesis of prion diseases (6, 30).

**WILSON DISEASE**

Wilson disease is an autosomal recessive disorder caused by the loss-of-function mutations in the copper transport gene ATP7B (1). This results in hepatic cirrhosis and progressive basal ganglia degeneration in the brain (31). There is impairment in the ability of copper to be incorporated into ceruloplasmin, which, as previously discussed, contains 95% of blood copper. The loss of ATP7B results in production of apoceruloplasmin, which is rapidly degraded in the plasma, resulting in reduced copper-carrying capacity. There is concomitant impairment in excretion of copper into bile. This leads to hepatic copper accumulation and damage, elevated levels of non-ceruloplasmin-bound copper in the plasma and, ultimately, copper overload in extrahepatic tissues (31, 32). Copper accumulation in the basal ganglia leads to Parkinonian symptoms, including tremors and dystonia. Indeed, Wilson disease may properly be classified as a movement disorder. In addition to liver and brain, the eye is also a primary site of copper deposition in Wilson disease. A pathognomonic sign, the Kayser-Fleischer (KF) ring, is an annular deposition of copper in the periphery of the cornea. Copper can also accumulate in the lens and cause “sunflower” cataracts. About ~65% of patients with a neurological presentation manifest the Kayser-Fleischer ring compared with ~95% of those with a hepatic presentation (32). Oral copper chelating agents are effective in restoring copper homeostasis in many patients with Wilson disease (31, 32).

**COPPER BIOMARKERS**

If reliable biomarkers of total-body copper status were available, potentially undesirable health effects due to excess or deficiency of this trace metal could be prevented. Several biomarkers can be considered to screen for copper deficiency. As previously discussed, dopamine-β-hydroxylase (DBH), a copper enzyme, functions in the synthesis of norepinephrine. In copper deficiency, DBH activity may decrease and result in elevated ratios of dopamine to norepinephrine, as seen in Menkes disease (21). Impaired activity of DBH also leads to increased urinary ratios of homovanillic acid to vanillylmandelic acid (33). Other cuproenzymes may also be measurable as potential biomarkers of copper deficiency. Ceruloplasmin contains 95% of the copper found in plasma, and levels decrease during severe copper deficit (22). Copper/zinc superoxide dismutase, cytochrome c oxidase, peptidylglycine α-amidating monooxygenase, and lysyl oxidase are all cuproenzymes whose activity or gene expression may be influenced by copper deficiency (34–38).

We also note several potential biomarkers of copper excess. Excess copper is deposited in the liver where high levels can cause injury. Although nonspecific, the hepatic aminotransferases, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, and γ-glutamyl-transferase, are biomarkers for liver damage due to elevated copper. Interleukin-2 may also be useful as a biomarker of copper excess; concentrations of interleukin-2 increase in response to copper supplementation (39). Urinary β2-microglobulin may also be a useful marker of copper excess (21). Binding of copper ions destabilizes native β2-microglobulin (40), and changes in renal tubular dysfunction may parallel the serum concentrations of copper (41).

**CONCLUSIONS**

Recent evidence highlights the important role of copper in the development and maintenance of the mammalian nervous system. Further advances in understanding these functions will affect our understanding of the human neurological disorders reviewed here and hopefully will suggest useful therapeutic approaches. The biochemical phenotypes associated with some of these disorders suggest potential for detection of copper excess and deficiency in the general population. Evaluation of the utility of such biomarkers awaits formal population surveys.
The contributions of the authors were as follows—VD prepared serial drafts of the manuscript and SGK edited the drafts and delivered the symposium presentation. The authors had no conflicts of interest to report.

REFERENCES