Copper Deficiency and the Clinical Practice

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Abstract: In 1993, the candidate genes for Menkes disease and Wilson disease were cloned, and remarkable progress has been made in the study of copper metabolism during the past 10 years. The proteins induced by the ATP7A and ATP7B genes are highly homologous. Both are P-type ATP-related copper-transporter membrane proteins, and control cellular copper transport. Recently, three chaperones supplying copper to the intracellular copper-requiring enzymes were discovered, and the physiology of intracellular copper metabolism is becoming more and more clear. Numerous copper-requiring enzymes are present in the body, therefore, copper deficiency may lead to various disorders. Menkes disease is well-known as an inherited disorder of copper transport from the intestine resulting in copper deficiency. In regard to acquired copper deficiency, nutritional deficiency is probably the most common cause, and may be seen in malnourished low-birth-weight infants, newborns, and small infants. Copper deficiency has also been reported to develop after gastrointestinal surgery, intractable diarrhea, and prolonged parenteral or enteral nutrition. In this article, I present a review of copper deficiency and its treatment.

Key words: Copper deficiency; Copper metabolism; Menkes disease

Introduction

Copper is one of the essential trace elements in humans, and disorders associated with its deficiency and excess have been reported. Menkes (kinky-hair) disease is well-known to be associated with copper deficiency due to an inherited disorder of copper transport from the intestine metabolism, and Wilson disease (hepatolenticular degeneration) is a well-known inherited disorder of cellular copper transport resulting in copper accumulation. Acquired copper deficiency is mainly attributable to nutritional deficiency, and may be seen in malnourished low-birth-weight infants, newborns, and small infants. Copper deficiency has also been reported to develop after gastrointestinal surgery, intractable diarrhea, and prolonged parenteral or enteral nutrition. However, since copper supplementation of intravenous and enteral nutritional formulas was made mandatory, the incidence of copper deficiency...
**Table 1** Major Copper-requiring Enzymes and Their Actions

<table>
<thead>
<tr>
<th>Name of major enzymes</th>
<th>Major action</th>
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<tbody>
<tr>
<td>Ceruloplasmin</td>
<td>Oxidase activity, Fe$^3+$→Fe$^6+$</td>
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<tr>
<td>Lysyl oxidase</td>
<td>Elastin cross-linkage, collagen formation (cross linking)</td>
</tr>
<tr>
<td>Superoxide dismutase (SOD)</td>
<td>Superoxide radical metabolism (O$_2$. + O$_2$. + 2H$^+$ ⇌O$_2$ + H$_2$O$_2$)</td>
</tr>
<tr>
<td>Tyrosinase</td>
<td>Melanin synthesis</td>
</tr>
<tr>
<td>Monoamine oxidase</td>
<td>Oxidative deamination</td>
</tr>
<tr>
<td>Dopamine β-hydroxylase</td>
<td>Epinephrine synthesis</td>
</tr>
<tr>
<td>Cytochrome c oxidase</td>
<td>Complex of cytochrome a and a$_6$, respiratory chain terminal enzyme (mitochondria)</td>
</tr>
<tr>
<td>Ascorbate oxidase</td>
<td>Oxidation of vitamin C, etc.</td>
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**Intracellular copper-transport system in hepatic cells (image)**

Intracellular copper-transport proteins (Wilson ATPase: ATP7B) and ceruloplasmin are expressed via an intracellular copper-importing protein (Ctr), intracellular copper-storing protein (Metallothionein: MT), intracellular copper-transporting protein chaperones (Cu or metallo-chaperones: (1) HAH1, (2) Ccs, (3) Cox17) and TGN (trans-Golgi network). ER: endoplasmic reticulum, Golgi: Golgi body, ● Cu, ● Wilson ATP7B.

Copper is taken up from capillary blood across the hepatic cell membrane via Ctr. It is then taken transported to the cellular organelles by three chaperones, consisting of recently discovered intracellular copper-transport proteins, with specific functions. The first is the HAH1-chaperone, which carries copper to the Golgi bodies; the second is the Ccs-chaperone, which carries copper to the Cu/Zn superoxide dismutase (SOD) enzyme; the third is the Cox17-chaperone, which carries copper to cytochrome oxidase (Cco). Metallothionein (MT) works against the stored copper. Holo-ceruloplasmin is secreted from the hepatic cells into the capillary blood. The excess copper in the Golgi body is transported to the intracellular vesicular compartments (lysosomes, endosomes, etc.). After assisting in copper excretion into the biliary canaliculi and executing its role, ATP7B returns to the Golgi body (this is called the trans-Golgi network).

(Quoted with Harris, Z.L., Gitlin, J.D.: Genetic and molecular basis for copper toxicity. Am J Clin Nutr 1996; 63 (5): 836s–841s with modification by the author.)
has decreased dramatically. An acquired copper excess state has been described in cases of Indian childhood cirrhosis, non-Indian childhood cirrhosis, excessive copper intake, and parenteral bolus administration of copper for the treatment of copper deficiency.

Many aspects regarding the physiological roles of copper in the body remain unknown. However, remarkable progress in the understanding of copper metabolism has been made since the cloning of the candidate genes for Menkes disease (ATP7A) and Wilson disease (ATP7B). It has been revealed that the proteins induced by these genes (ATP7A and ATP7B) are highly homologous, and that both are P-type ATP-related copper-transporter membrane proteins that control cellular copper transport. Furthermore, the mechanism by which copper is transported into cells and the chaperones (three kinds) supplying copper to the copper-requiring enzymes have been discovered, and the physiology of cellular copper metabolism is being gradually elucidated.

For lack of space, the physiological roles of copper in humans are not discussed here. Table 1 lists the major copper-requiring enzymes in the body, and Fig. 1 shows a chart of the various steps in copper metabolism in hepatocytes. See cited references for further details.

The discussion in this article is mainly focused on copper deficiency in humans.

**General Symptoms of Copper Deficiency**

The clinical symptoms associated with copper deficiency are extremely diverse. The most common features include anemia, leukopenia, bone lesions (scorbutic-like bone changes and occipital horn), and vesical diverticula. In children, some commonly noted findings are hypotonia, psychomotor retardation, and hypothermia.

1. **Hematological abnormalities**
   1. **Microcytic hypochromic anemia:**
      This is attributable to a decrease in the ferroxidase activity of ceruloplasmin (Cp) and reduced iron oxidation. When anemia is noted in low-birth-weight infants, patients with chronic diarrhea, and patients receiving prolonged enteral or parenteral nutrition, copper deficiency must be suspected in addition to iron deficiency.
   2. **Neutropenia:**
      Granulocyte maturation disorder in the bone marrow and vacuolation in neutrophils are observed.

2. **Bone lesions in copper deficiency states**
   Rachitic-like or scorbutic-like changes (enlargement of the epiphyseal area and changes in the margin) are observed in the bones of extremities. They may be accompanied by osteoporosis and occipital horn formation after adolescence. These are attributable to functional impairment of copper-requiring enzymes, such as ascorbate oxidase and lysyl oxidase, associated with copper deficiency.

3. **Vascular lesions**
   Menkes disease is characterized by tortuosity and winding of arteries and increased capillary fragility. Caution must be exercised to avoid prolonged copper deficiency in humans, since this may lead to abnormal vascular tortuosity and increased capillary fragility.

4. **Central nervous system disorder and convulsion**
   Reports of central nervous system disorder and convulsion associated with secondary copper deficiency are rare, but they are characteristic features of Menkes disease. Progressive Menkes disease can be fatal. Prolonged copper deficiency may cause degeneration of the cerebrum and cerebellum (numerous copper-requiring enzymes are present in the brain, such as dopamine β-hydroxylase and cytochrome c oxidase), associated with slowing of mentation and muscular rigidity, as well as hemorrhagic changes due to increased capillary...
fragility.
In children, hypotonia is often observed.

5. Hair abnormalities\(^{(2,10)}\)
Change of hair texture, namely, kinky-hair, may be observed in children with Menkes disease. Hair changes are, however, considered rare in cases with secondary copper deficiency. On the other hand, the possibility of changes in the hair should be borne in mind in cases of prolonged copper deficiency. The copper content of the hair and nail is decreased in cases of copper deficiency.

6. Others
Attention should be paid to the development of hypothermia, achromoderma, splenomegaly, and susceptibility to infections in copper deficiency states.\(^{(1,2,11)}\)

Diagnosis and Evaluation of Copper Deficiency States and Indicators\(^{(1)}\)
The above-described clinical findings are important pointers for the diagnosis of copper deficiency. In addition, when copper deficiency is suspected, the following tests must be conducted. The most important indicators of the status of copper deficiency are the serum ceruloplasmin (Cp) level and the serum copper level. Caution must be exercised in interpreting their values, because newborns and low-birth-weight infants often have physiological hypoceruloplasminemia and hypocupremia, which make the diagnosis and assessment of copper deficiency difficult in these cases.

1. Serum Cp level
Except in newborns, low-birth-weight infants, and small infants, serum Cp levels may be interpreted as follows: 10 to 20 mg/dl, mild decrease; 5 to 10 mg/dl, moderate decrease; 5 mg/dl or less, marked decrease.

2. Serum copper level
Except in newborns, low-birth-weight infants, and small infants, serum copper levels may be interpreted as follows: 60 to 80 mg/dl, mild decrease; 40 to 60 mg/dl, moderate decrease; 40 mg/dl or less, marked decrease.

In addition, information regarding the copper content of the hair and nails, and a study of the urinary copper excretion and copper balance would be useful.

Treatment of Copper Deficiency\(^{(1)}\)

1. Treatment of copper deficiency in low-birth-weight infants and newborns
When copper is administered intravenously, the amount of copper accumulating is proportional to the amount administered, and a large amount of non-Cp copper in the blood may induce toxicity. Therefore, oral administration is recommended, where possible. Intravenous administration may become necessary if no improvement in the clinical condition is observed after oral administration for about a week. However, this should be avoided as far as possible during the first 3 weeks after

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**Table 2 Copper Treatment for Copper Deficiency (personal proposal)**

<table>
<thead>
<tr>
<th>Segment</th>
<th>Oral dose</th>
<th>Parenteral/intravenous dose</th>
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</thead>
<tbody>
<tr>
<td>Low-birth-weight infants</td>
<td>100–200µg/kg/day</td>
<td>20–30µg/kg/day</td>
</tr>
<tr>
<td>Newborns</td>
<td>2.5–5.0mg/day</td>
<td>20–35µg/kg/day</td>
</tr>
<tr>
<td>Infants/children</td>
<td>2.5–5.0mg/day</td>
<td>20–35µg/kg/day</td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td>5.0–10.0mg/day</td>
<td>15–20µg/kg/day; 900–1,500µg/day</td>
</tr>
</tbody>
</table>
birth, when copper supplementation should be conducted gradually.

2. Treatment of copper deficiency in infants and children

As a general rule, oral administration should be employed. When oral administration is impossible, treatment should be provided by either intravenous or subcutaneous injection.

3. Treatment of copper deficiency in adolescence and adulthood

The doses are shown in Table 2. The route of administration is the same as that for infants and children.

Menkes Disease

Menkes disease is a genetic disorder of copper transport in the body, and disorder of copper absorption and excretion is noted in the intestinal tract and uriniferous tubules. The Menkes disease gene is located on the long arm of the X chromosome (Xq 13.3). The protein induced by this gene is an intracellular copper-transport membrane protein called ATP7A. The Menkes disease gene is predominantly expressed in the duodenum, upper part of the small intestine, and renal proximal tubules, while no expression is noted in hepatocytes (the Wilson disease gene is strongly expressed in the hepatocytes). Therefore, this disease is transmitted by X-linked recessive inheritance and develops in boys, at an estimated incidence of about 1 in 100,000–200,000. In this disease, copper absorption from the intestine is impaired, resulting in a copper deficiency state. Central nervous system disorder, collagen metabolism disorder, bone lesions, vascular lesions, hair abnormalities, abnormality of pigmentation, vesical diverticula, and decreased skin elasticity may be noted. However, hematological abnormalities, which are commonly seen in cases of nutritional copper deficiency are rare. Hypothermia and weak breast-feeding may be noted during the neonatal period in some cases, but many of the infants grow normally until 3 or 4 months of age, when the disease often manifests by features such as convulsion, etc. The central nervous symptoms are progressive, may become serious even during the early stages, and then regress. Typically, kinky hair (nodules, trichorrhexis, and kinky) is noted and the hair is rough, brittle and breaks easily. However, this may not be evident in some cases. Hypoceruloplasminemia and hypocupremia are seen on blood biochemical tests. Copper absorption is noted to be poor in the oral copper sulfate tolerance test, with no increase in the serum Cp level or serum copper level.

The typical form of this disease is called classic Menkes disease, which is a serious condition. In addition, mild Menkes disease and extremely mild Menkes disease (occipital horn syndrome and Ehlers-Danlos syndrome, type IX) may also be seen, and abnormality of the Menkes disease gene has been confirmed in both cases. The mild type develops between 6 and 24 months after birth, and the extremely mild type is often discovered from the age of 5 or 6 years through adolescence.

There is no radical cure for this disease. Parenteral copper administration (intravenous or subcutaneous injection) may be administered, but it is ineffective against advanced cerebral disorder. Parenteral copper administration is believed to resolve the systemic condition, bone and hair changes, and the susceptibility to infection, and to prolong patients’ lives. It is considered effective against mild and extremely mild cases.

Conclusion

The clinical aspects of copper deficiency in humans are discussed in this article, including the characteristic clinical features, methods of diagnosis and evaluation, and treatment. In addition, Menkes disease has been reviewed briefly.
REFERENCES


