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Review article

Pathology, clinical features and treatments of congenital copper metabolic disorders – Focus on neurologic aspects

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Abstract

Genetic disorders of copper metabolism, including Menkes kinky hair disease (MD), occipital horn syndrome (OHS) and Wilson's disease (WD) are reviewed with a focus on the neurological aspects. MD and OHS are X-linked recessive disorders characterized by a copper deficiency. Typical features of MD, such as neurologic disturbances, connective tissue disorders and hair abnormalities, can be explained by the abnormally low activity of copper-dependent enzymes. The current standard-of-care for treatment of MD is parenteral administration of copper–histidine. When the treatment is initiated in newborn babies, neurologic degeneration can be prevented, but delayed treatment is considerably less effective. Moreover, copper–histidine treatment does not improve connective tissue disorders. Novel treatments targeting neurologic and connective tissue disorders need to be developed. OHS is the mildest form of MD and is characterized by connective tissue abnormalities. Although formal trials have not been conducted for OHS, OHS patients are typically treated in a similar manner to MD. WD is an autosomal recessive disorder characterized by the toxic effects of chronic exposure to high levels of copper. Although the hepatic and nervous systems are typically most severely affected, initial symptoms are variable, making an early diagnosis difficult. Because early treatments are often critical, especially in patients with neurologic disorders, medical education efforts for an early diagnosis should target primary care physicians. Chelating agents and zinc are effective for the treatment of WD, but neurologic symptoms become temporarily worse just after treatment with chelating agents. Neurologic worsening in patients treated with tetrathiomolybdate has been reported to be lower than rates of neurologic worsening when treating with other chelating agents.

Keywords: Copper; Menkes disease; Wilson's disease; Occipital horn syndrome; ATP7A; ATP7B; Neurologic diseases

1. Introduction

Copper is an essential trace element for all living organisms and functions as an integral component of cuproenzymes, which include cytochrome C oxidase, lysyl oxidase, dopamine-β-hydroxylase, superoxide dismutase, tyrosinase, ascorbic acid oxidase and ceruloplasmin. When present in excess amounts, however, its oxidative potential induces reactive free radical production that results in cellular damage. Thus, the tight regulation of copper homeostasis, which is maintained by mechanisms including uptake, transport, storage and excretion of copper, is required. Disruptions to normal copper homeostasis are evident in three human genetic disorders: Menkes disease (MD), occipital horn syndrome (OHS) and Wilson's disease (WD) [1]. Each disease is caused by the absence or dysfunction of homologous copper-transporting ATPases. The responsible gene for MD and OHS is the *ATP7A* gene, and the *ATP7B* gene is responsible for WD [1]. These three diseases exhibit neurologic disorders. However, the pathology of MD and OHS is completely different from that of WD; that is, MD and OHS are characterized by a copper deficiency while WD is characterized by toxicity due

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to an excess of copper. The reason for this difference is related to the particular cell types in which the ATP7A and ATP7B proteins are expressed. ATP7A is expressed in almost all cells with the exception of hepatocytes, whereas ATP7B is primarily expressed in hepatocytes. Here we review MD, OHS and WD with a focus on neurologic aspects.

2. Copper homeostasis

The average daily intake of copper in healthy adults is about 2 mg. Ingested copper is absorbed from the intestine into the blood, and the majority is then transported into the liver. The majority of copper in the liver is excreted via the bile, but a small amount is excreted in the urine. Fig. 1 shows the molecular mechanism of copper metabolism in cells. Ctr1 is a high-affinity copper transporter located on the plasma membrane of the cells and mediates copper uptake. Copper in the cytosol is delivered to Cu/Zn superoxide dismutase in the cytosol, to the Golgi apparatus, and to mitochondria by Ccs2, HAH1 (ATOX1) and Cox 17, respectively, and are generically named copper chaperones [1]. ATP7A and ATP7B are localized to the trans-Golgi membrane and transport copper from the cytosol into the Golgi apparatus within cells. Copper transported into the Golgi apparatus is excreted from cells as a part of copper enzymes. ATP7A is expressed in almost all cells other than hepatocytes, including those of the intestine, kidney and components of the blood brain barrier; ATP7B is mainly expressed in hepatocytes and acts to excrete copper into the bile and blood [2,3].

Genetic disorders of copper metabolism in humans manifest in the form of MD, OHS and WD (Table 1).

3. Menkes disease (MD) and occipital horn syndrome (OHS)

3.1. Genetics

The phenotypic features of ATP7A mutations can be divided in at least three categories; Classical MD with death in the early childhood (generally called as MD), mild MD with long survival, and OHS (the mildest features) [4]. Inheritance of MD and OHS is X-linked recessive; patients are typically male, and their mothers are heterozygous carriers of the disease. The incidence of MD in Japan is estimated to be 1/140,000 live male births [5]. A small number of females with X-linked chromosomal abnormalities have also been reported to be affected by MD [1]. Patients with MD exhibit a large variety of mutations in the *ATP7A* gene [1,6,7]. Moller described that they had identified about 357 different mutations [4].

OHS and mild MD are extremely rare. Major mutations in the *ATP7A* gene in OHS and mild MD are splice-site or missense mutations [4], and residual activity of ATP7A still exists [6,7].

3.2. Pathology

In MD-affected cells, copper accumulates in the cytosol and cannot be excreted. Copper accumulation in the intestine results in a failure of copper absorption, which leads to copper deficiency in the body and reduces the activity of copper-dependent enzymes. Copper also accumulates in the components of the blood–brain barrier and cannot be transported from the blood vessels to neurons. The characteristic features of MD can be explained by a decrease in the activity of copper-dependent enzymes (Table 2).

Neurologic degeneration in MD is mainly caused by decreased activity of cytochrome C oxidase in neurons. In addition, subdural hemorrhage often occurs secondary to disorders of brain arteries due to decreased activity of lysyl oxidase, resulting in neurologic damage. Hypotonia may be caused by reduced activity of cytochrome C oxidase in the muscle [8].

Characteristics of OHS include connective tissue disorders caused by a decrease in lysyl oxidase activity.

3.3. Clinical features

3.3.1. Neurologic manifestations

Characteristic clinical features including seizures, delayed development, marked muscular hypotonia and abnormal hair, become prominent between the ages of 2 and 4 months when copper deficiency becomes advanced. Because clinical abnormalities are absent or subtle in affected newborns, the diagnosis is difficult prior to 2 months of age. As the disease progresses, patients are bedridden and never smile. Most patients with MD die by the age of 3 years, although some patients survive into their teenage years [1,7].

Epilepsy is observed in most patients with MD. Bahi-Buisson et al. reported the characteristics of epilepsy as divided into three periods [9]. Focal clonic status epilepticus and intractable infantile spasms are observed in the early stage (median age: 3 months) and intermediate stage (median age: 10 months), respectively. Multifocal seizures, tonic spasms and myoclonus are observed in the late stage (median age: 25 months). Ozawa et al. also reported that infantile spasms with EEGs containing hypsarrhythmic patterns are observed in 50% of epileptic patients with MD [10]. Brain MRIs of the patient shows brain atrophy and delayed myelination or demyelination. Subdural hemorrhage/effusion is often observed (Fig. 2). Magnetic resonance angiography shows a tortuosity of intracranial and cervical blood vessels [1,7]. Additionally, ^{1}H-magnetic resonance spectroscopy (^{1}H-MRS) shows a lactate peak and a decrease in