**Case Report**

**Menkes Syndrome: A Case Report**

Mahattana Kamolsilp MD*

*Department of Pediatrics, Phramongkutklao Hospital, Bangkok 10400, Thailand

Menkes syndrome is caused by mutation of ATP7A gene that encode copper-binding membrane protein localized to the trans-Golgi membrane. Mutation of this gene causes defective exportation of copper from the cell. Intracellular accumulation of copper does not reach the toxic state, as copper entering the body is trapped in the intestinal epithelium. Copper requiring enzymes are dysfunction and cause multisystemic manifestations. The authors report a Thai boy 8 months of age who had depigmentation and kinky hair at birth. He developed myoclonic jerk at 3 months of age. He had hypopigmentation of the skin, delayed development, hypotonia, pectus excurvatum, loose skin and joints. He had anemia, very low serum copper and ceruloplasmin. X-ray showed Wormian bone of skull, osteopenia of long bones and generalized brain atrophy. The presented case has similar clinical and laboratory findings to 2 previous reports by Songkla University and Siriraj Hospital. Treatment is not effective due to unavailability of copper-histidinate and the patient already had severe brain damage. Genetic counseling is important to prevent the next offspring. Biochemical and molecular diagnosis are available for confirmation and prenatal diagnosis, but these techniques have limitations in Thailand.

**Keywords:** Menkes syndrome, Kinky hair, Ceruloplasmin


Full text. e-Journal: [http://www.medassocthai.org/journal](http://www.medassocthai.org/journal)
Case Report

An 8-month-old boy was referred to Phramongkutklao Hospital with the presentation of myoclonic jerk. He had depigmentation and kinky hair at birth. At 3 months of age, he had delayed development, hypotonia and seizure. He was the first child in this family (Fig. 1). Physical examination revealed lethargy, hypotonia, no staring eyes, depigmented and kinky hair, pectus excavatum, loose skin and joints (Fig. 2). Laboratory findings showed anemia, very low serum copper = 3.9 umol/l (normal = 12.6-23.6 umol/l) and ceruloplasmin level = 5.33 mg/dl (normal = 25-43 mg/dl). Microscopic examination of hair showed pili torti (Fig. 3). Bony X-ray of skull and long bones show Wormian bone, osteopenia and flared metaphysis (Fig. 4). Computerized tomography of the brain showed generalized cerebral and cerebellar atrophy (Fig. 5). He had been treated by intravenous copper (copper chloride) and anticonvulsant for 1 month. His serum copper and serum ceruloplasmin had been changed to 3.5 umol/l and 46.9 mg/dl respectively after treatment with no improvement of seizure. Genetic counseling for this family was done. He developed aspiration pneumonia, sepsis and died at 2.5 years of age. His father died 2 years later and his mother was lost to follow up.

Discussion

Menkes syndrome is easily diagnosed by looking at the patient’s hair and can be confirmed
by serum copper and ceruloplasmin\(^{(1)}\). However, interpretation of these signs may be difficult in the first months of life, as serum copper and ceruloplasmin levels may also be low in normal infants in this period. Biochemical diagnosis is evaluated in culture fibroblasts by measuring radioactive copper \((^{64}\text{Cu})\) retention after a 20-h pulse, and impaired efflux is directly determined after a 24 h pulse-chase. However, these techniques require expertise and are carried out only in a few specialized centers in the world. Demonstration of a defect in the ATP\(_7\)A gene is the ultimate diagnostic proof. It was isolated in 1993 and encodes a protein with homology to the family of bacterial P-type ATPase. These are integral membrane proteins that use an aspartyl phosphate to transport cations across the membranes. Deletions, mutations and reduced mRNA synthesis are all evidence that ATP\(_7\)A is responsible for Menkes disease. However, it should be kept in mind that mutation detection is challenging; the gene is very large and genetic defect shows great variety\(^{(7)}\). More recently, the MNK protein has been localized to the trans-Golgi

---

Fig. 4  Bony X-ray shows Wormian bone of skull, osteopenia and flared metaphysis of long bones

Fig. 5  Computerized tomography of the brain shows generalized cerebral and cerebellar atrophy
network (TGN). The MNK protein cycles between the TGN and the plasma membrane, depending on the concentration of copper within the cell\(^{2-4}\).

In the past 12 years in Thailand (1993-2005), there were 2 previous cases reported from Prince of Songkla University (1993\(^{\text{5}}\)) and Siriraj Hospital (2002\(^{\text{6}}\)) that had comparative clinical presentation with the presented case in Table 1. All cases were similar in clinical onset of delayed development and seizure. Serum copper and ceruloplasmin of them were very low. They had severe cerebral and cerebellar atrophy.

The objective of treatment for Menkes disease is to provide extracopper to the tissue and the enzyme requiring copper for their normal function. Copper uptake is normal, but a defect ATP \(_{7}\) transporter disturbs the intracellular copper balance. Copper cannot be extruded from the cell, and the copper pool shifts to metallothionein, meanwhile, copper enzymes are deficient in copper. Oral administration of copper is ineffective, as copper is trapped in the intestines, the first step defective in the overall copper-transport pathway. In blood, the main copper-carrying molecules are ceruloplasmin, albumin and copper amino acid complex, including histidine. The copper-histidine complex has, therefore been preferred in the treatment of Menkes disease patients\(^{8}\) but it is only palliative treatment. In Thailand copper-histidinate is not available. The authors had to treat by copper chloride, while Menkes disease at Siriraj Hospital was treated by copper sulfate for 1 month\(^{6}\). Both of them did not respond to treatment (no improvement of seizure, no improvement of serum copper and ceruloplasmin).

Another reason of unresponsiveness is due to the fact that the patients already had severe cerebral and cerebellar atrophy. Genetic counseling is important for the affected family to prevent the next affected offspring.

**Acknowledgements**

The authors wish to thank Prof. Pornswan Wasant and Prof. Somchit Jaruratanasirikul who provided their clinical data from the Faculty of Medicine Siriraj Hospital, Mahidol University and Prince of Songkla University.

**References**

Menkes Syndrome

Menkes syndrome is a genetic disorder characterized by disturbances in copper metabolism, leading to various neurological and developmental issues. The defect is caused by mutations in the ATP7A gene, which encodes the Menkes protein, involved in copper transport. Patients with Menkes syndrome often present with myoclonus and intellectual disability, and copper therapy is essential for managing the debilitating symptoms.