Case Report

Menkes Syndrome: A Case Report

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Menkes syndrome is caused by mutation of ATP_7A 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*

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Menkes syndrome is a rare X-linked fatal neurodegenerative disorder of copper transport. The incidence of disease has been estimated to be between 1/250,000 and 1/2,980,000 live births. It is caused by mutation of ATP_7A gene[1] that encode 165 kDa copper-binding membrane protein localized to the trans-Golgi membrane[2-4]. 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. Metabolic involvement includes neurotransmitter biosynthesis (dopamine β-monooxygenase), connective tissue cross-linking (lysyl oxidase), cellular respiration (cytochrome-C oxidase), neuropeptide maturation (peptidyl α-amidating enzyme) antioxidant defense (Cu-Zn superoxide dismutase) and pigmentation (tyrosinase). Most of them are of severe lethal form and the others represent mildly affected with different degrees of nervous system and connective tissue involvement.

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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). Microscropic examination of hair showed

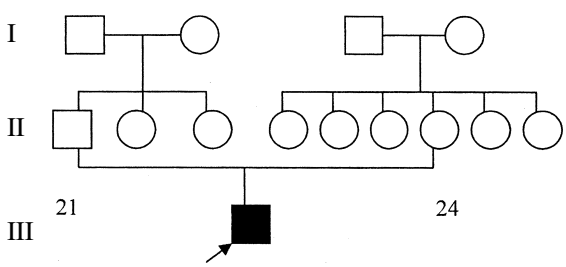


Fig. 1 Pedigree of Menkes syndrome family

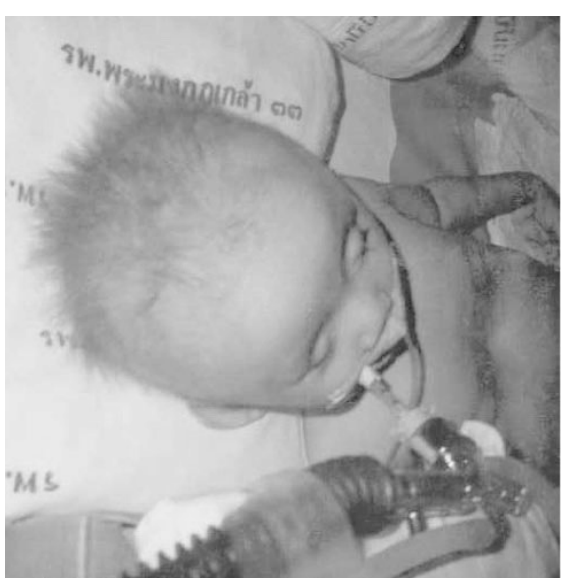
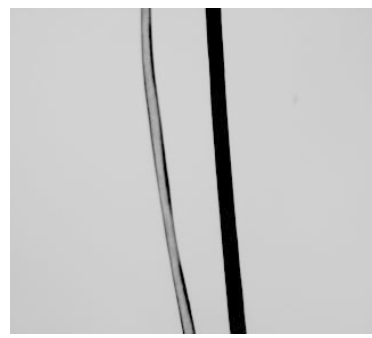


Fig. 2 The patient was intubated due to uncontrollable seizure. He was lethagic, depigmented with kinky hair



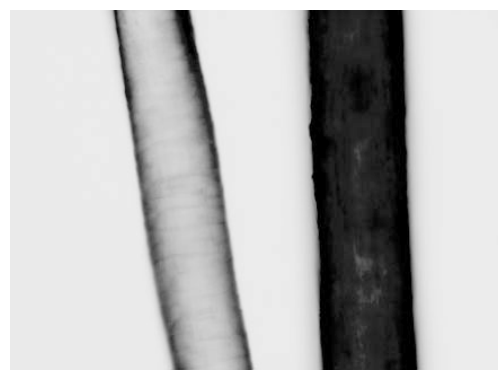
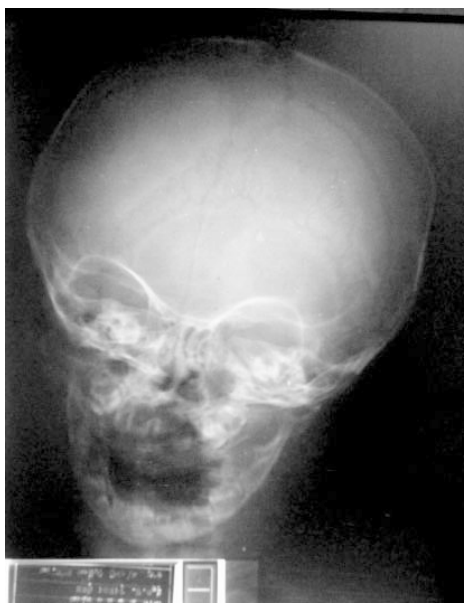


Fig. 3 Microscopic examination of the hair shows pili torti and depigmentation when compared to normal hair (A). Maximized microscropic examination of the abnormal hair (B)

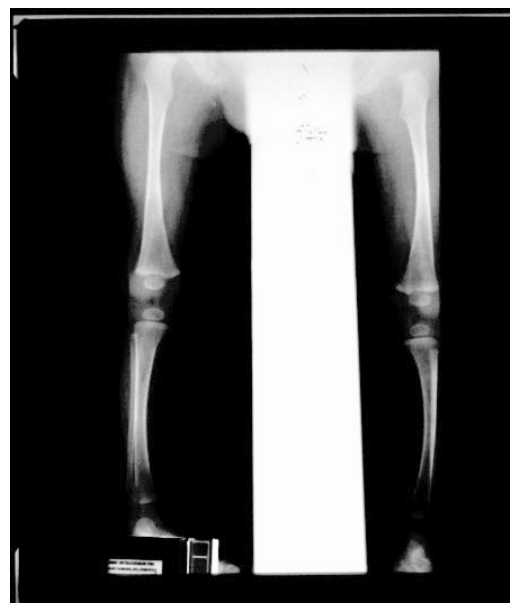
pili torti (Fig. 3). Bony X-ray of skull and long bones show Wormian bone, osteopenia and flared metaphysis (Fig. 4). Computerized tomography of the brain showed generalized cerebral and cerebellar atrophy (Fig. 5). He had been treated by intravenous copper (copper chloride) and anticonvulsant for 1 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



(A)



(B)

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

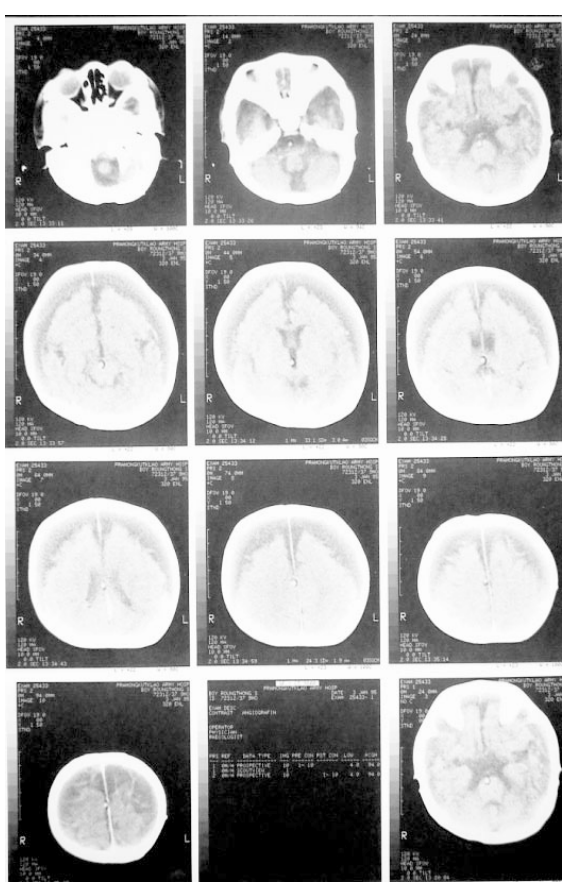


Fig. 5 Computerized tomography of the brain shows generalized cerebral and cerebellar atrophy

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}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_7A 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_7A 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

Table 1. Comparative clinical presentations to the former reports

Menkes syndrome	Phramongkutklao Hospital	Prince of Songkla University[5]	Siriraj Hospital[6]
Birth weight	2560 gm	2850 gm	3500 gm
Head size	25-50 % ile	25 % ile	10-25 % ile
Onset of delayed development	3 month	4 month	3 month
Onset of seizure	5 month	-	3 month
Skin	loose	smooth	loose
Serum copper	3.9 umol/l	5.5 umol/l	0 umol/l
Serum ceruloplasmin	5.33 mg/dl	2.3 mg/dl	0 mg/dl
Bony X-ray	Wormian bone	Wormian bone	Wormian bone
CT-brain	Cerebral/cerebellar atrophy	Cerebral/cerebellar atrophy	Cerebral/cerebellar atrophy
Family history	negative	negative	negative
Complication	Pneumonia/sepsis	Urinary tract infection	Pneumonia

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)[5] and Siriraj Hospital (2002)[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_7A 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.

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รายงานผู้ป่วย โรค Menkes Syndrome

มหัทธนา กมลศิลป์

โรค Menkes syndrome เป็นโรคที่เกิดจากความผิดปกติของจีน ATP_7A ที่อยู่บนโครโมโซม X ซึ่งเป็นผลให้โปรตีนที่ทำหน้าที่ขนส่งสารทองแดงที่อยู่ที่ผนังของ Golgi apparatus ในเซลล์เสียการทำงานไป สารทองแดงจะสะสมที่เซลล์ผนังลำไส้ ขณะที่ร่างกายผู้ป่วยจะขาดสารทองแดงและเกิดอาการจากความบกพร่องของเอนไซม์ที่เกี่ยวข้องกับสารทองแดง รายงานนี้ผู้ป่วยเด็กอายุ 8 เดือน มีอาการเส้นผมสีจางและหยิกมาตั้งแต่แรกเกิด เมื่ออายุ 3 เดือน มีอาการชักแบบ myoclonus เมื่อตรวจร่างกายพบผมสีจาง พัฒนาการช้า กล้ามเนื้ออ่อนแรง หน้าอกบุ๋ม ผิวหนังและข้อหย่อน มีภาวะเลือดจาง ระดับสารทองแดงและ ceruloplasmin ในเลือดต่ำ เอกซเรย์กะโหลกศีรษะพบกระดูก Wormian กระดูกท่อนยาวมีลักษณะบาง เอกซเรย์สมองมีสมองฝ่อทั่วไป ได้เปรียบเทียบลักษณะอาการและผลทางห้องปฏิบัติการผู้ป่วยรายนี้กับผู้ป่วยที่เคยมีการรายงานมาก่อน 2 ราย จากมหาวิทยาลัยสงขลานครินทร์และโรงพยาบาลศิริราช พบว่ามีลักษณะใกล้เคียงกัน การรักษาในรายนี้ไม่ได้ผล เนื่องจากไม่มี copper-histidinate และผู้ป่วยมีการทำลายของสมองอย่างรุนแรงมาก่อนหน้านี้แล้ว การให้คำปรึกษาแนะนำทางพันธุศาสตร์มีความสำคัญในการป้องกันการเกิดโรคซ้ำในครอบครัว การตรวจวินิจฉัยทางชีวเคมีหรือทางอณูพันธุศาสตร์สามารถยืนยันการวินิจฉัยและช่วยในการวินิจฉัยก่อนคลอดได้ แต่ยังมีขีดจำกัด