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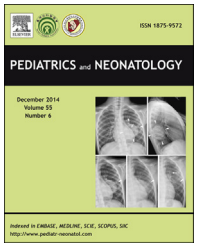

CASE REPORT

A Truncating De Novo Point Mutation in a Young Infant with Severe Menkes Disease

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Menkes disease is a rare neurodegenerative disorder caused by mutations in *ATP7A* gene. Deficiency in copper-dependent enzymes results in the unique kinky hair appearance, neurodegeneration, developmental delay, seizures, failure to thrive and other connective tissue or organ abnormalities. Other than biochemical tests, DNA-based diagnosis is now playing an important role. More than two hundred mutations in *ATP7A* gene were identified. Early copper supplementation can help improve neurological symptoms, but not non-neurological problems. Further molecular studies are needed to identify additional mutation types and to understand the mechanism of pathogenesis. This may help in discovering the possible treatment measures to cure the disease. We present a case with the clinical features and biochemical findings, abnormal brain magnetic resonance imaging as well as the effects of treatment with copper-histidine. Direct sequencing of ATP7A gene revealed a de novo point mutation which resulted in an early stop codon with truncated protein.

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1. Introduction

Menkes disease (MD; MIM# 309400) is a disorder of copper metabolism caused by mutations in *ATP7A* gene. The clinical manifestations are progressive neurologic deterioration, seizures, hair and connective tissue abnormalities. Early diagnosis is difficult. Up-to-date, effective cure has not been reported; however, early copper supplementation can improve neurological outcomes.[1] We demonstrate a case whose gene sequencing revealed a de novo truncating mutation.

2. Case report

A four-month-old male infant was brought to our Pediatric outpatient clinic because of seizure. The pattern of seizure was head shaking with upward gaze, lasting for one minute in each episode, and five to six episodes a day for two days. The infant was delivered via cesarean section at 36 3/7 weeks' gestation with birth weight of 2,620 gm at a local obstetric clinic. The Apgar score was 9 and 10 at 1 and 5 minutes, respectively. The prenatal examination of the 37-year-old G2P2 mother was normal. No other family members had seizure history or hereditary disease. The results of newborn screening tests were normal.

This was his fourth time of admission. Histories of hyperbilirubinemia, bilateral inguinal hernias, pectus excavatum, left side grade III vesicoureteral reflux, diffuse multiple urinary bladder diverticula, and normocytic anemia were documented in the previous three courses of hospitalization.

On admission, physical examination revealed flat occiput, flat face and depressed nasal bridge with bilateral large floppy ears. The scalp hair was hypopigmented, sparse, curly and brittle (Figure 1). The color of the iris was normal. He had prominent funnel chest, cutis laxa and loose joints. Deep tendon reflexes were increased with hypotonia of four limbs. He failed in reaching the normal developmental milestones, including social smile, head control and rolling over.

Phenobarbital and valproic acid were prescribed and seizure subsided after the 3rd day of hospitalization. Initial cranial sonography revealed moderate brain edema with decreased resistance index. The electroencephalography (EEG) showed epileptiform discharges over left temporal and posterior area, with contralateral propagations. Brain magnetic resonance imaging (MRI) disclosed encephalomalacia in bilateral temporal and left frontal lobes (Figure 2A,B). T2WI and T2 FLAIR sequence revealed symmetric faint hyperintense areas in bilateral head of caudate nucleus and putamen (Figure 2C). T1WI sequence showed faint hypointensity in the same areas. Dysgenesis of the genu and anterior body of corpus callosum was also observed (Figure 2D).

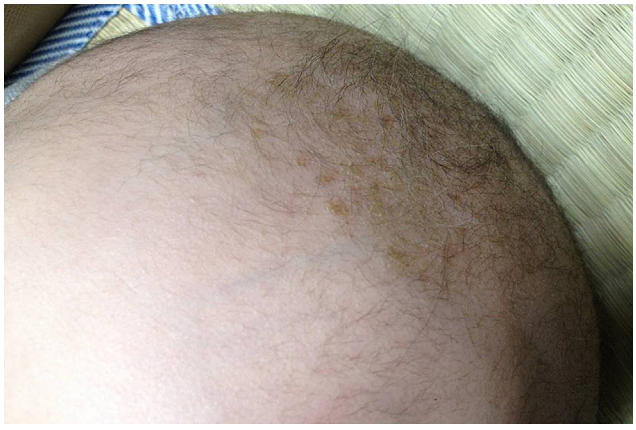

Figure 1 The scalp hair is hypopigmented, sparse, curly and brittle.

The lesions over basal ganglia provided a clue of potential metabolic disorder. Another clue was the elevated lactate-to-pyruvate ratio. The ratios checked initially and 2 days later were 21 and 24.6, respectively. A Geneticist was then consulted for his physical anomalies and possible metabolic disorder. Tests of plasma amino acids profile, urine organic acids analysis, plasma carnitine levels, and mitochondrial DNA sequencing showed normal results, except for elevated lactic acid level in organic acids analysis. The serum concentrations of copper and ceruloplasmin were 116 ppb (ref: 700—1500 ppb) and 5 mg/dL (ref: 20—60 mg/dL), both lower than the normal range. The laboratory findings above, together with his clinical manifestations, made the diagnosis of Menkes kinky hair disease highly suspicious. Molecular study then confirmed a point mutation in *ATP7A* gene (c.3502 C>T) leading to an early stop codon with truncated protein (p.Gln1168X). The mother is not a carrier of the mutation. Treatment with daily subcutaneous injections of copper-histidine was started from the age of eight-months. On follow-up at twelve months of age, MRI and magnetic resonance angiography showed brain atrophy (Figure 3A), and tortuosity of bilateral internal carotid arteries and M1 segment of right middle cerebral artery (Figure 3B). He received surgery for left distal femur fracture and laparotomy for intestinal obstruction at the ages of twelve and fourteen months, respectively. Under the treatment, the patient showed improved alertness, better response to external stimulation, and darker and less brittle scalp hair. Social smile was observed at the age of ten months. He is now sixteen months old and still has hypotonia and head lag. Speech delay was also noted. The seizure pattern has changed to infantile spasms from the age of seven months. The anticonvulsants used currently are levetiracetam, topiramate and vigabatrin.

3. Discussion

MD is a rare neurodegenerative disorder caused by mutations in *ATP7A* gene (MIM# 300011), leading to malfunction of copper-dependent enzymes. The incidence estimated ranges from 1 in 50,000 to 1 in 300,000 live births.[1,2] In Asia, one survey in Japan calculated the incidence as 1 in 354,507 live births.[3] Most patients are males for the X-linked recessive inheritance, though some female patients have been reported.[4]

The location of *ATP7A* gene is on the long arm of the X chromosome between positions q13.2 and q13.3. It encodes a copper-transporting P-type ATPase. The 8.5 kb

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