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Case report

A case of Menkes disease with unusual hepatomegaly

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= Abstract =

Menkes disease is an X-linked recessive copper transport disorder characterized by neurological deterioration, connective-tissue damage, and abnormal hair growth. It is caused by the mutation of the ATP7A gene. This report describes a four-month-old boy with neurological symptoms typical of Menkes disease plus unusual liver involvement. He developed seizures at three months of age and exhibited hypotonia, cephalhematoma, a sagging face, redundant and hypopigmented skin, and abnormal hair growth. In addition, he had unexplained hepatomegaly and high hepatic transaminase. We confirmed the diagnosis of Menkes disease by mutation analysis of the ATP7A gene. To exclude other possible causes for the hepatic abnormalities, a liver biopsy was performed, revealing intracytoplasmic cholestasis, focal spotty necrosis, and minimal lobular activity. The patient's liver involvement may be an underestimated complication of Menkes disease. **(Korean J Pediatr 2008;50:538-541)**

Key Words : Menkes disease, ATP7A gene, Heptomegaly, Infantile spasm

Introduction

Menkes disease (OMIM 309400), also known as Kinky hair disease, is an X-linked recessive copper transport disorder characterized by neurological deterioration, connective-tissue damage, and abnormal hair growth[1]. It is caused by the mutation of the ATP7A gene, which encodes for copper-transporting P-type ATPase[2]. ATP7A gene plays an important role in controlling copper efflux from cells. Defects in ATP7A gene cause impairment of copper-trapping in the intestinal mucosa and reducing its availability in the peripheral organs and tissues, resulting in low copper levels in the serum, liver and brain and poor synthesis of cuproenzymes including ceruloplasmin[3]. The most common clinical features of the disease are hypotonia, failure to thrive, seizures, hypothermia, and abnormal hair growth[1, 4-7]. Liver involvement, however, has not previously been reported, in contrast to Wilson disease.

We describe a patient with unusual liver involvement who was diagnosed with Menkes disease by the presence of the ATP7A gene mutation.

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Case report

A four-month-old boy who was having seizures was presented to the authors for evaluation. He was born at 39^{+4} weeks gestation by vaginal delivery. The labor was hard, but he was asymptomatic at birth. His birth weight was 3,800 g, and his length was 51 cm. He showed cephalhematoma, and his head circumference was 36 cm (75-90 percentile). He was admitted to the hospital because of jaundice three days after birth, but the jaundice disappeared after phototherapy. A brain CT scan revealed a skull fracture in the occipital area, and a small epidural hemorrhage. A neurological examination showed no definite abnormality at that time. From the age of two months, he suffered from frequent projectile vomiting, drooling, and lethargy. At three months, he developed seizures, particularly semiologies, atonic seizures characterized by head aversion and eyeball deviation to the left. The condition was accompanied by loss of consciousness, and each seizure lasted for approximately one minute. Severe repetitive seizures persisted despite treatment with phenobarbital and oxcarbazepine. At four months, he was transferred to the Seoul National University Children's Hospital for further evaluation and treatment.

The patient had no family history of metabolic disease.

Physical examination showed cephalhematoma, a sagging face, and redundant and hypopigmented skin. The most striking finding was the appearance of hair on his head that was coarse, sparse, and easily friable (Fig. 1). In addition, his liver and spleen were palpable. The liver was round, not tender, and palpable 4 cm at the anterior axillary line. Neurological examination showed a hypotonic baby who could not control his head or smile. Clinical evaluations included laboratory tests, radiological investigations, and electroencephalogram (EEG) recording.

The serum copper (36.1 ug/dL; normal value: 70-155 ug/dL) and serum ceruloplasmin level (below 7 mg/dL; normal value: 15-40 mg/dL) was lower than normal. There was a noticeable abnormality in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The initial AST (110 IU/L; normal value: 0-40 IU/L) and ALT (107 IU/L; normal value: 0-40 IU/L) were higher than normal. However, bilirubin, protein, and prothrombin time levels were within the normal range.

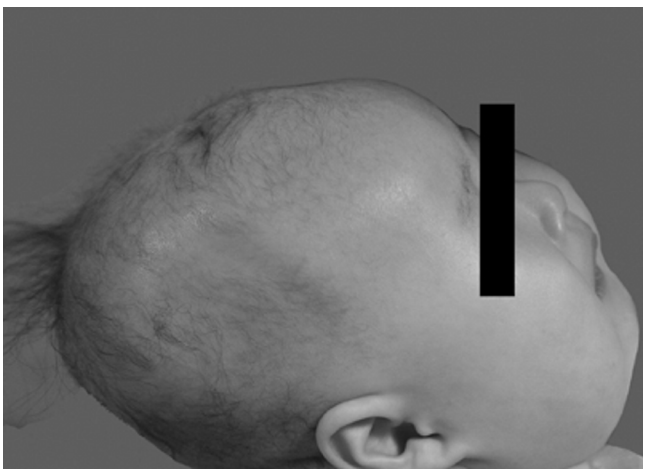

Fig. 1. Characteristic hair abnormality.

To exclude other possible causes, laboratory tests for infection, drug toxicity, autoimmune disease, and metabolic abnormalities were performed. HBsAg was negative and HBsAb was positive. Hepatitis A IgM, hepatitis C IgM, TORCH IgM and EBV VCA IgM were negative. No microorganisms were discovered in either blood or urine cultures. Drug concentrations of antiepileptics were in nontoxic ranges. Antinuclear antibody (FANA) was negative. There was no significant acidosis and ammonia was not increased. Serum lactate, pyruvate, tandem mass screening, serum amino acid, and urine organic acids were all within the normal range. Abdomen sonography showed no anatomical abnormality. Echocardiography revealed an unimpaired cardiac function.

Magnetic resonance imaging (MRI and MRA) showed abnormal signal intensity in both the basal ganglia with delayed myelination at 3.5 months (Fig. 2A). After one month, a new MRI study revealed diffuse brain atrophy, bilateral diffuse prominent sulcus enhancement, and prominent tortuous intracranial vessels (Fig. 2B).

Initial interictal EEG showed a focal spike and wave discharges from the temporooccipital area. The seizures had slightly decreased following treatment with clonazepine.

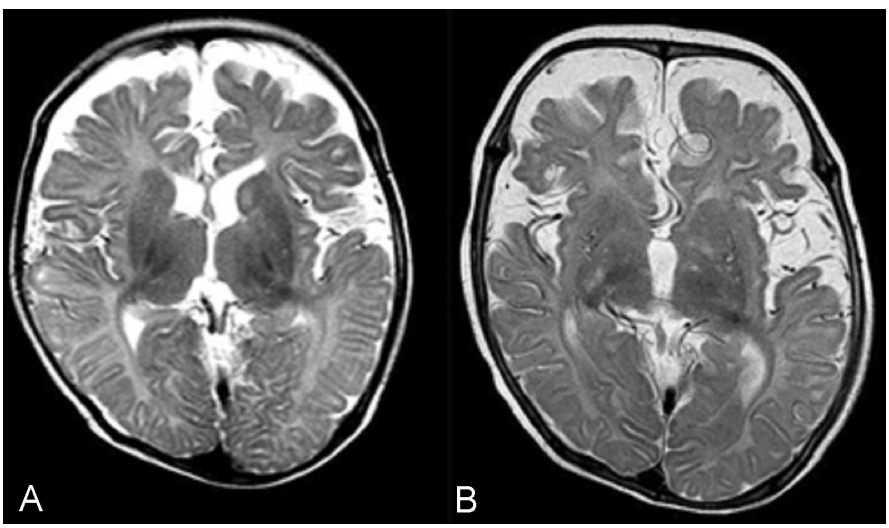

Fig. 2. Magnetic resonance image showing abnormal signal intensity in both the basal ganglia and the delayed myelination at 3.5 months old (A) and brain atrophy with prominent tortuous intracranial vessels at 4.5 months old (B).

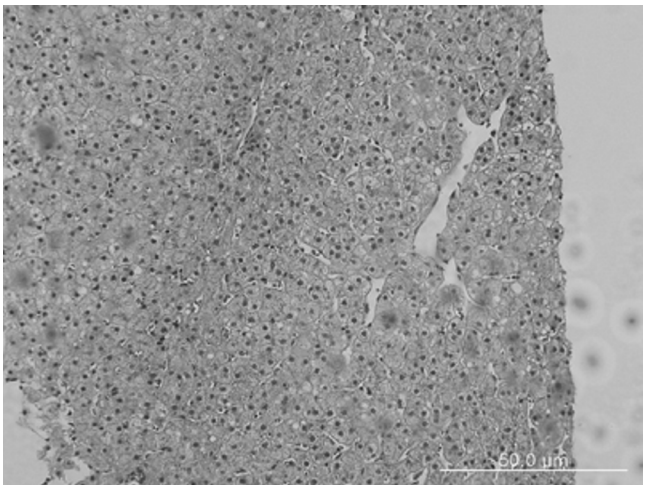

Fig. 3. Liver biopsy specimen focal spotty necrosis and minimal lobular activity (HE stain, ×200).

However a different form of seizure appeared at six months. Video EEG monitoring showed extensor spasms of both arms, and a hypsarrhythmic pattern. After administering vigabatrin, the frequency of the seizures decreased.

The hepatosplenomegaly persisted, however, with a further increase of liver transaminase (AST 237 IU/L; ALT 274 IU/L). A liver biopsy was performed to exclude other metabolic liver diseases. Microscopy showed intracytoplasmic cholestasis, focal spotty necrosis, and minimal lobular activity of the liver tissue (Fig. 3). The results of the gene study demonstrated that the patients ATP7A gene was mutated (Gly727Arg mutation), whereas his parents genes were normal.

Discussion

We describe a patient with Menkes disease exhibiting unusual liver symptoms. Several reviews of the clinical features of Menkes disease have been conducted. Considerable variability has been found in the severity of the diseases clinical expression8). In the classic form of the disease, symptoms appear during the neonatal period. Its most common symptoms are hypothermia, hypoglycemia, poor feeding, and impaired weight gain[1, 6]. Cephalhematoma can be prominent in infants born vaginally. The most common symptoms are seizures, delayed development, and failure to thrive[4, 6, 9]. The face has a characteristic plump appearance, with a depressed nasal bridge, ptosis, and reduced facial movements. The most characteristic finding is abnormal hair, with a coarse, sparse, and friable appearance. Other organs such as the optic disc, kidneys and connective tissue can also be affected[10, 11].

In the present case, the patient had the classic clinical manifestations of the disease, with seizures, hypotonia, developmental delay, redundant skin, and typical hair, but without hypothermia, arthritis or osteoporosis, or hormonal imbalance.

The seizures were the most distinctive of the symptoms. In his original report on the disease, Menkes described the EEG features of Menkes disease as early multifocal spikes, which later become diffuse[12]. Myoclonus is supposed to be the usual seizure type, but electroclinical studies are very rare; epilepsy is a frequent and early feature in this disorder. Recent reports describe the spectrum and course of epilepsy in Menkes disease[9, 13]. Based on these recent studies, the development of the epilepsy can be divided into three phases: (a) an early stage characterized by focal clonic-status epilepticus, usually triggered by fever; (b) an intermediated stage with intractable infantile spasm, in which interictal EEG demonstrated modified hypsarrhythmia, with diffuse irregular slow waves, and spike waves; and (c) a late stage with multifocal seizures, tonic spasms, and myoclonus[9]. Our patient initially presented with atonic seizures at two months. Four months later, his seizures changed to infantile spasms. The patients electroclinical features were similar to those previously reported. Evolution of seizure types may suggest progressive neurological deterioration.

An unusual finding was liver involvement, which has not been previously reported. The cause of hepatomegaly must be proved by exclusion. To exclude other possible causes, laboratory tests for infection, drug toxicity, autoimmune disease and metabolic evaluations and abdominal ultrasound were performed, but no specific abnormalities we found. Liver biopsy revealed nonspecific microscopic cholestasis and focal necrosis. The clinical features of Menkes disease result from a deficiency in copper-dependent enzymes[1]. The pathology in this case cannot be regarded as the result of copper deficiency or copper accumulation. The patient had Gly727Arg misssense mutation, which was already established, but liver involvement was not known. To establish the cause, more reports are needed.

In summary we presented a patient of Menkes disease with unusual association of hepatomegaly, confirmed by ATP7A gene analysis. Liver involvement may represent an underestimated complication of Menkes disease.

한 글 요 약

멘케스병에서 간비대를 보인 1례

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멘케스병은 성염색체 열성으로 유전되는 질환으로 APT7A 유전자의 돌연변이에 의해 발생한다. 기전은 장에서의 구리 흡수와 운반에 결손이 있는 것으로 혈청 구리 및 ceruloplasmin 이 낮다. 특징적인 임상양상은 경련발작, 근육긴장저하, 저체온증을 나타내며 얼굴은 특징적으로 통통하며 저색소 피부색, 꼬이고 윤택이 없고 잘 부스러지는 머리카락을 보인다. 성장장애를 보이는 경우가 흔하며 심한 정신지체와 발달장애를 동반한다. 멘케스병에서 간비대가 간병증을 보이는 경우는 현재까지 보고되지 않았다. 저자들은 유전자 검사를 통해 멘케스병으로 확진된 4개월 소아가 영아연축, 발달장애, 머리카락 이상 외에도 이전에 잘 알려져 있지 않은 간비대를 보인 1례를 보고하는 바이다.

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