멘케스병 환자의 경과와 발작에 대한 치료

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Clinical Findings of Menkes Disease and the Treatment of Epilepsy

Menkes disease (also known as kinky hair disease) is an X-linked recessive neurodegenerative disorder caused by diverse mutations in a copper-transport gene, *ATP7A*. Affected patients are characterized by kinky hair, hypotonia, and generalized myoclonic seizures. Here, we report a case of Menkes disease in which the patient presented with progressive hypotonia and intractable seizures. A 4-month-old male infant visited our pediatric clinic for focal seizures with blinking eyes. He was generally hypotonic and suffered from malnutrition. The focal seizures became more frequent, and the patient became intractable to anti-seizure medications. An electroencephalogram (EEG) indicated diffuse cerebral dysfunction with focal seizure, and a brain magnetic resonance imaging (MRI) showed tortuous and ectatic intracranial arteries, as well as several ischemic lesions. A genetic analysis was performed, and a c.2473_2474del (p.Leu825fsX1) of the *ATP7A* gene was detected.

Key Words: Menkes kinky hair syndrome, ATP7A protein, Epilepsy

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Introduction

Menkes disease is a lethal, multisystemic disorder of copper metabolism with X-linked recessive inheritance. Progressive neurodegeneration and connective tissue disturbances, together with the peculiar 'kinky' hair, are the main manifestations. Menkes disease occurs due to mutations in the *ATP7A* gene, and the majority of *ATP7A* mutations are intragenic mutations or partial gene deletions¹⁾. Epilepsy is one of the main clinical features of this disease but it has been described in detail by only a few authors. Most patients develop seizures from 2 to 3 months of age, accompanied by a neurodevelopmental regression. We report a case of a 4-month-old boy with Menkes disease who presented with progressive hypotonia and intractable seizure and was diagnosed by genetic analysis, detecting c.2473_2474del (p.Leu825fsX1) in exon 11 of the *ATP7A* gene. The focal clonic seizures were controlled with anticonvulsant therapy at the early stage, whereas with the progression of disease, he showed multifocal, myoclonic, and tonic seizures that were resistant to antiepileptic drugs.

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Case Report

On November 27, 2007, a 4-month-old male infant visited the Konkuk University Hospital pediatric clinic for lethargy, floppy muscle tone, poor oral intake and developmental delay. The infant could not support his head well and did not show eye contact. After 2 weeks, he started demonstrating focal seizures, with his right eye blinking repeatedly. His hair was kinky, brown colored and fragile (Fig. 1). The child was born at a gestational age of 34 weeks and 5 days by cesarean section due to maternal placenta abruption and fetal distress. His birth weight was 2,420 g. He was hospitalized for one week for close observation and discharged without any clinical problems.

Fig. 1. A photograph of the patient's head shows kinky, brown-colored and fragile hair.

The initial electroencephalogram (EEG) showed depressed background activities from the right side, as well as two episodes of 2 Hz rhythmic delta activities starting from the right temporo-occipital area and lasting approximately 15 to 20 seconds. There was no significant acidosis, and the ammonia level was not increased. Tandem mass screening, serum amino acid, and urine organic acids were all within normal ranges. A tortuous and ectatic intracranial and vertebral artery was observed on the magnetic resonance imaging (MRI), and there were suspicious ischemic lesions at the right caudate nucleus and basal ganglia (Fig. 2). In addition to this magnetic resonance (MR) image finding, the patient's clinical symptoms showing floppy muscle tone, focal seizure, and his characteristic appearance of kinky hair made us to check for the defect in copper metabolism. Biochemical markers showed low serum copper (9.0 $\mu\text{g/dL}$, reference range: 70–130 $\mu\text{g/dL}$) and ceruloplasmin (5.5 mg/dL , reference range: 16–31.5 mg/dL) levels.

The focal seizures were initially treated with phenobarbital, with a dose of 5 mg/kg/d , and carbamazepine 20 mg/kg/d were added as seizure became more frequent. As the disease progressed, the patient showed clusters of tonic seizures, and vigabatrin, with a dose of 35 mg/kg/d was added. A follow-up EEG showed an irregular delta wave, slowing with right and left frontal or occipital spikes, followed by brief suppression of the background activities, which indicated diffuse cerebral dysfunction, with focal seizures.

In the genetic analysis by polymerase chain reaction (PCR) sequencing, c.2473_2474del (p.Leu825fsX1) in exon 11 of the *ATP7A* gene was detected, and the infant was diagnosed with Menkes disease (Fig. 3). The patient's mother also underwent gene study

Fig. 2. Brain MRI of the patient. T2 coronal view shows vascular tortuosity and diffuse brain atrophy. Patchy lesion in basal ganglia shown in T1 axial view.

and was normal. We have gone through the gene analysis under the full explanation and consent of the patient's mother taken in advance, and this research was approved by the Institutional Review Board of the Konkuk University Medical Center (Protocol No; KUH1090059).

The patient started taking copper histidine (800 mcg/day), and he reached the normal ranges of copper (117 µg/dL) and ceruloplasmin (29.1 mg/dL) at 2 years of age. However, his seizure became extremely resistant to antiepileptic drugs despite the high dosage of the drug. Moreover, he repeatedly suffered from recurrent upper respiratory infection, and dehydration due to poor oral intake; to treat the condition, he underwent percutaneous endoscopic gastrostomy to supply nutrition, but he pulled it out himself, rendering it useless and leading to cachexia. The patient died at age 2 year 4 month.

Discussion

Menkes disease is a copper transport disorder caused by pathogenic variants in *ATP7A*, encoding a copper-transporting ATPase, characterized by low concentrations of copper in some tissues as the result of impaired intestinal copper absorption, accumulation of copper in other tissues, and reduced activity of copper-dependent enzymes²⁾. The specific clinical features of Menkes disease are hypotonia, failure to thrive, and seizures between the ages of six and ten weeks. Hair changes occur as the scalp and eyebrow hair being short, sparse, coarse, twisted, and often lightly pigmented. The radiological findings of this disease include bone changes, tortuous cerebral vessels and cerebral atrophy.

The natural history of untreated Menkes disease typically leads

to death within 2–3 years after birth, although some individuals live beyond this age. In the latter cases, however, profound neurodevelopmental delays complicate the quality of life in these patients³⁾. In the case, at the late phase of the disease, the patient suffered from recurrent upper respiratory infection and poor oral intake getting him into cachexia status.

In the classic variant of Menkes disease, 3 stages are usually identified during the longitudinal course of epilepsy: an early stage characterized by focal clonic seizures, an intermediate stage with epileptic spasms, and a late stage with multifocal seizures, tonic spasms, and myoclonus^{4,5)}. The patient in this case shows the stage of Menkes disease representing focal seizures in the early stage, and multifocal seizure and clusters of brief tonic spasm in the late stage.

In many cases that have been reported, initial focal seizures are treated with phenobarbital, with a dose of 4 to 5 mg/kg/d, in monotherapy, often associated with benzodiazepines as rescue therapy^{4,6-9)}. We also started the treatment by phenobarbital, at the same dose, but added other anticonvulsant shortly, carbamazepine, as the seizure was uncontrollable. Later, when the patient showed clusters of tonic spasm, vigabatrin was added. However, with the progression of the disease, the seizures became uncontrollable with any anticonvulsant therapy.

In summary, Menkes disease is characterized by kinky hair, hypotonia, and seizures. The epilepsy is an important feature of Menkes disease and is almost always present in the natural history of the disease. Generally, the long-term prognosis of epilepsy is poor and the large majority of patients are resistant to all AED. In the case, we used three AEDs including phenobarbital, carbamazepine, vigabatrin in high dose, but the patient showed resistance to it.

Fig. 3. Gene analysis by PCR reveals c.2473_2474del mutation in exon 11 of *ATP7A* gene. It is a frameshift mutation, p.Leu825fsX1.

요약

멘케스 병은 구불구불한 머리, 근긴장도 저하, 그리고 발작 증상을 특징적으로 나타낸다. 그 중 발작은 멘케스 병에서 가장 보편적이고 중요한 증상으로, 병의 경과에 항상 동반된다. 일반적으로 발작의 장기적 예후는 좋지 않으며, 병이 진행됨에 따라 많은 경우에 항경련제로도 조절되지 않는다. 본 증례에서는 phenobarbital, carbamazepine, vigabatrin을 포함하는 항경련제를 통해 발작을 조절하였으나, 병의 진행됨에 따라 이로도 조절이 되지 않았다.

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