심한 방광요관역류가 첫 증상으로 나타난 *ATP7A* 유전자의 새로운 돌연변이에 의한 멘케스병 1예

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A Case of Menkes Disease First Manifested as Severe Vesicoureteral Reflux Caused by a Novel Mutation in *ATP7A* Gene

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Menkes disease is a rare, neurodegenerative, copper metabolism disorder characterized by mutations in *ATP7A* gene. Clinical symptoms include epilepsy, growth delay, reduced muscle strength, skin hyperextension, hair deformation and urologic abnormalities. However, since these clinical symptoms occur 2-3 months after birth, early diagnosis of Menkes disease is very difficult for clinicians. We report here the case of a patient who initially presented urinary tract infection followed by neurologic symptoms of Menkes disease; he was accurately diagnosed via *ATP7A* genetic analysis and found to harbor a novel mutation. Although neurological symptoms are the primary diagnostic feature of Menkes disease, clinicians should take into account urinary abnormalities as well, which may be an important clue to the early diagnosis of these patients.

Key Words: Menkes disease, Vesicourethral reflux, *ATP7A*, mutation

Introduction

Menkes disease (OMIM #309400) is a rare, neurodegenerative, copper metabolism disorder with an incidence of 1 in every 150,000–250,000 births¹⁾. It is an X-linked recessive disease characterized by mutations in *ATP7A* gene, which encodes a P-type copper-transporting ATPase and is located at Xq13.3²⁾. A defect in this gene reduces the activity of *ATP7A* protein, which is involved in copper transport in the cells and intestinal mucosa, and the genetic defect is found in 60–70% of all patients with Menkes disease³⁾. Clinical symptoms manifest owing to deficiency of various enzymes that contain copper, and include growth delay, reduced muscle strength, skin hyperextension, hair discoloration and deformation, skeletal impairment, ophthalmological impairment and repetitive urinary tract infection (UTI) with vesicourethral reflux⁴⁾. The most serious symptoms are neurologic manifestations and are characterized by hypotonia, seizures, and loss of developmental milestones beginning at the age of 6–8 weeks, and death in early childhood. Urological abnormalities are frequent in Menkes disease. In particular, urological findings

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vary from the most frequent bladder diverticula to vesicourethral reflux⁵⁾. We report the case of a patient who initially presented UTI with vesicourethral reflux followed by neurologic symptoms of Menkes disease; he was diagnosed via *ATP7A* genetic analysis and found to harbor a novel mutation.

Case report

A 13-day-old male neonate was brought to our clinic for fever with 38.7°C lasting two days. He had no specific symptoms other than fever and decreased oral intake. He was the first baby of non-consanguineous parents. He was born at 37+5 weeks of gestational age by cesarean section with birth weight of 2,600 g (5th–10th percentile). The patient's vital signs included a pulse of

150 beats/min, respiratory rate of 32 breaths/min, and body temperature of 38.7°C. On physical examination pale skin and decreased activity were noted. Urine culture analysis performed at the time of admission showed 50,000 cfu (colony forming unit)/mL of methicillin-resistant *Staphylococcus aureus* (MRSA). Kidney ultrasonography showed bilateral hydronephrosis and voiding cystourethrography (VCUG) showed severe (grade V) right vesicourethral reflux (Fig. 1). He was treated with antibiotics and discharged after 16 days in healthy condition.

At three months of age, he was readmitted because of recurrent seizure and lethargy lasting one week. No family history of seizures, developmental disorders or hereditary disorders was noted. The following measurements were recorded; height: 54 cm (5th–10th percentile), body weight: 5.3 kg (25th–50th percentile), and head circumference: 34 cm (3th–5th percentile). Physical examination revealed pale skin with sparse

Fig. 1. Voiding cystourethrogram demonstrates right vesicoureteral reflux, grade V in voiding view.

Fig. 2. Patient's appearance: kinky, fragile hair, and pale skin.

Fig. 3. Electroencephalography showed asynchronous high amplitude slow waves with disorganized background activity.

depigmented hair (Fig. 2) and generalized hypotonia. Seizures were characterized by upward gaze and tonic movement of both upper extremities lasting up to five minutes. The electroencephalography showed asynchronous high amplitude slow waves with disorganized background activity, suggesting diffuse cerebral dysfunction (Fig. 3). Brain MRI (magnetic resonance imaging) showed no parenchymal abnormalities, however MR angiography revealed significant vascular tortuosity (Fig. 4A and 4B). Biochemical studies showed low serum copper level (13 µg/dL, normal range: 75–145 µg/dL) and low ceruloplasmin level (10 mg/dL, normal range: 16.2–35.6 mg/dL). Molecular study identified a 10-bp deletion in *ATP7A* gene (c.3015_3024 del) leading to frameshift in exon 15 (p.Gly1005fs*5) (Fig. 5), a novel mutation that has not been previously reported. He has been treated with copper–histidine since the age of three months and is currently receiving antiepileptic drug therapy, but his seizures

are not under control. At 11 months of age, gastrostomy and fundoplication were performed for severe gastroesophageal reflux (GER), and the patient is currently receiving intermittent oxygen owing to respiratory difficulty. The patient is currently 26 months old and is alive.

Discussion

Menkes disease is an inherited disorder caused by *ATP7A* mutations. In patients with Menkes disease, copper levels decrease in the plasma, liver and brain tissues⁶⁾. In addition, activities of copper-requiring enzymes are impaired that lead to progressive neurodegeneration with connective tissue disturbances⁷⁾. In this case, the patient was first diagnosed having severe vesicoureteral reflux (VUR) with UTI, before

Fig. 4. (A) T2-weighted image shows normal brain parenchyma (B) Brain MR angiography shows vascular tortuosity.

Fig. 5. The c.3015_3024 deletion in exon 15 of *ATP7A* gene (p.Gly1005fs*5) revealed by genetic analysis.

neurological symptoms were prominent. Urologic abnormalities are found in about 40% of Menkes disease cases⁸⁾. Urological findings vary from the most frequent bladder diverticula and VUR towards calculus of the bladder and very marked enlargement of the bladder and ureters^{5,9)}. These complications may be attributed to the decrease in lysyl oxidase activity that is necessary for collagen formation¹⁰⁾. Although neurological symptoms are the most serious manifestations of Menkes disease, clinicians should be aware of the possibility of urinary abnormalities as well, which may provide an important clue to the early diagnosis of these patients.

To date, more than 300 different disease-causing mutations have been reported (www.hgmd.org, www.LOVD.nl/ATP7A). Missense, splice-site, nonsense, and exon deletion or duplication mutations are commonly detected in Menkes disease cases¹¹⁾. Our patient was found to have a c.3015_3024 deletion in exon 15 of *ATP7A* gene that, which leads to a frameshift resulting in premature stop codon at the amino acid position 1005 and the addition of five novel amino acid residues (p.Gly1005fs*5). This mutation is located in the transmembrane domain 6 of *ATP7A*, which is near CPC motif (Cys-Pro-Cys) that has been shown to be important for copper translocation through the cell membrane⁷⁾. Thus, the mutation of our patient is presumed to disrupt normal translocation of copper, resulting in the phenotypes of classic Menkes disease.

The early diagnosis of Menkes disease is very difficult for clinicians. Most patients seem to be normal after the neonatal period until 2–3 months of age. Moreover, in the neonatal period, levels of biochemical markers such as serum copper and ceruloplasmin are physiologically low, which make early diagnosis more difficult¹²⁾. Although characteristic appearance such as sparse, kinky hair and pale skin is notable in neonates, it is not sufficient for suspecting Menkes disease. Because of these factors, diagnosis is often delayed until 3–4 months of age when hypotonia and seizures become prominent. After this period, various symptoms appear, such as developmental delay, loss of early development skills, hypothermia, hair abnormality, hypotonia and convulsion. Ultimate diagnosis of Menkes disease is the identification of a molecular defect in the *ATP7A* gene. Our patient was diagnosed with Menkes disease after having a seizure at the age of 3 months; even though he had been previously admitted to our hospital, he was not correctly diagnosed at that time because of the rarity of this condition and lack of suspicion. There are several reports that suggest early diagnosis and copper-histidine therapy in the neonatal period are beneficial¹³⁾. Thus, a high index of suspicion is required for clinicians to improve the prognosis of patients with Menkes

disease.

요약

멘케스병은 *ATP7A* 유전자의 돌연변이에 의한 드문 신경변성 구리 대사질환이다. 임상증상으로는 경련, 성장지연, 근력저하, 피부 과진전, 모발변형 및 비뇨기계 이상 등을 나타낸다. 하지만 이런 임상증상은 생후 2-3개월 이후에 나타나기 시작하므로 초기에 진단되기 어렵다. 저자들은 처음 요로감염으로 입원한 환자에서 추후 보인 신경학적 증상으로 멘케스 병을 진단하였으며 *ATP7A* 유전자 분석을 통해 새로운 변이를 발견하였다. 비록 신경학적 증상이 멘케스병에서 가장 중요한 증상이지만, 멘케스병에 비뇨기계 이상이 흔히 동반되는 것을 인식하는 것 또한 조기진단에 단서가 될 수 있으므로 중요하다고 하겠다.

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