European Journal of Therapeutics

DOI: 10.5152/EurJTher.2018.808

Case Report

Two Cases of Menkes Disease Diagnosed with Hair Findings and Novel Mutation

Sedat Işıkay, Serkan Kırık

Division of Pediatric Neurology, Kahramanmaraş Sütçü İmam University School of Medicine, Kahramanmaraş, Turkey

ABSTRACT

Menkes disease is a rare neurodegenerative disorder. Its clinical signs and symptoms appear due to a defect in copper metabolism. Its clinical manifestation is marked by pili torti and trichorrhexis nodosa, which are the disease-specific hair findings. Additionally, neurological signs may occur, such as hypotonia and convulsions. Detection of a mutation affecting the P-type ATPase gene is highly specific. The lack of an effective treatment modality has increased the importance of prenatal diagnosis and genetic counseling. Here, we report two patients who were diagnosed with Menkes disease by virtue of hair findings and genetic studies while being tested for hypotonia. One of the patients was detected to have a novel mutation.

Keywords: Genetic, hair, hypotonia, Menkes disease

INTRODUCTION

Menkes disease (Menkes kinky hair syndrome) is an X-linked recessive neurodegenerative disorder that starts to manifest clinical findings in early infancy (1). In 1967, Menkes (2) first defined the disease in five male children from the same family who presented with neuromotor delay, growth retardation, white hair, and cerebral-cerebellar degeneration. The gene responsible for the disorder is found in Xq13.3 and causes deficiency of P-type ATPase (ATP7A) that is responsible for copper absorption and transport. The classical form of the disorder is characterized by severe neurological signs and has a fatal course. On the other hand, the more rarely encountered milder Menkes disease and the occipital horn syndrome are the milder forms. Serum copper and ceruloplasmin levels are low (3, 4). The disorder is typically seen in males, but it also rarely affects females. It has an estimated incidence of 1:35,000-1:250,000 (5). In this case report, the two classical cases of Menkes disease presented were reported to emphasize the disorder's genetic-based diagnosis and the importance of hair findings for its recognition.

CASE PRESENTATIONS

Case 1

A 12-month-old male infant was admitted to the pediatric neurology outpatient clinic for hypotonia and reduced attention to his environment. He had no notable feature regarding his prenatal history. He had been born on term spontaneously via normal vaginal route. His birth weight was 3250 g. His parents were first-degree cousins. On physical examination, he was conscious, restless, and hypoactive. He had a body temperature (armpit) of 36.6°C, a cardiac apex beat rate of 108/min, a respiratory rate of 24/min, blood pressure of 78/42 mmHg, body weight of 10 kg (50%), height of 76 cm (50%), head circumference of 43 cm (10%-25%), an anterior fontanel of 1×1 cm with normal curvature, a dry skin, a fair complexion, a dysmorphic face, brown eyes, and a wide auricula. No organomegaly or cardiac, respiratory, or gastrointestinal abnormality was noted. On neurological examination, hypotonia was revealed. He could not establish eye contact. His fundoscopic examination was normal. His deep tendon reflexes were hyperactive. On laboratory tests, complete blood count, routine biochemistry, including kidney and liver function tests, ammonia, lactate, coagulation tests, urinary organic acid, congenital metabolic screening, serum quantitative amino acid levels, vitamin B12 level, and biotinidase level were all normal. There was no abnormality regarding intrauterine infectious antibody (TORCH) titers. His cranial magnetic resonance (MR) and diffusion cranial MR imaging (MRI) tests showed cerebral atrophy (Figure 1). His cardiac examination, echocardiography, and abdominal ultrasonography (USG) were all normal. As he had light hair, his hair was examined microscopically, which showed pili torti and trichorrhexis nodosa (Figure 2). Serum copper level was <10 µg/dL (normal level: 85-190 µg/dL), and ceruloplasmin level was 0.06 g/L (normal level: 0.15-0.48 g/L). His whole gene analysis (Miseq-Illumina, Illumina Way, San Diego, CA/USA) revealed deletions in ATP7A gene's 15th, 16th, and 17th exons. The patient's family was offered genetic counseling. He was consulted by the

How to cite: Işıkay S, Kırık S. Two Cases of Menkes Disease Diagnosed with Hair Findings and Novel Mutation. Eur J Ther 2019; 25(4): 315–7.

ORCID IDs of the authors: S.I. 0000–0003–0103–9612; S.K. 0000–0002–8658–2448

Corresponding Author: Serkan Kırık **E–mail:** srknkrk@hotmail.com

Received: 05.06.2018 • **Accepted:** 24.07.2018

Figure 1. Marked atrophy of the brain parenchyma in the frontotemporal region in Case 1

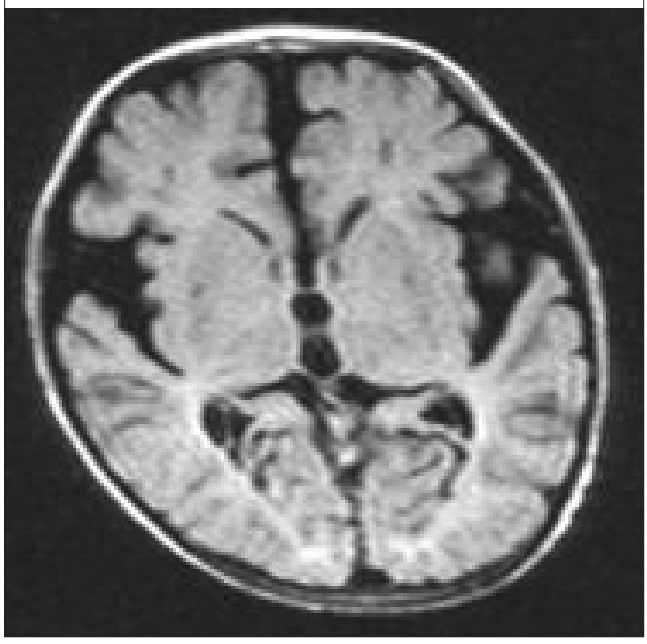
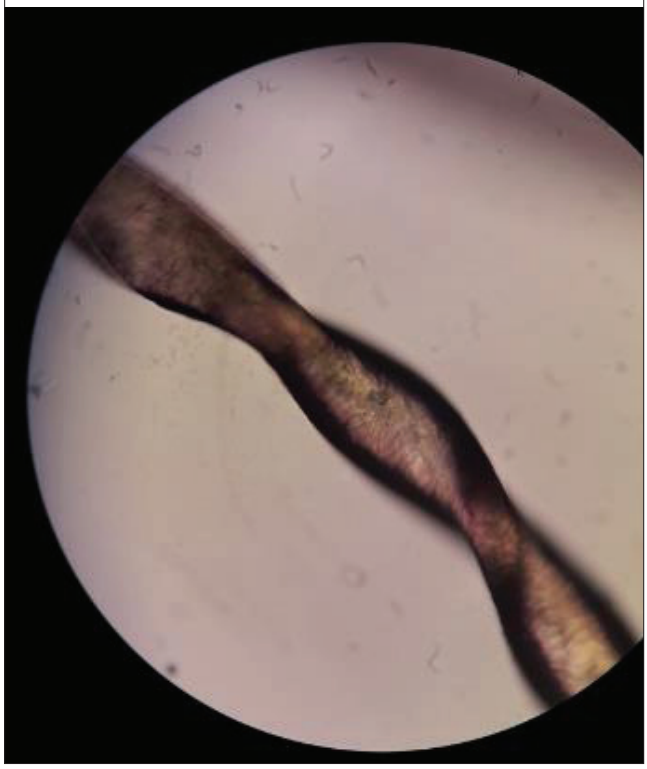
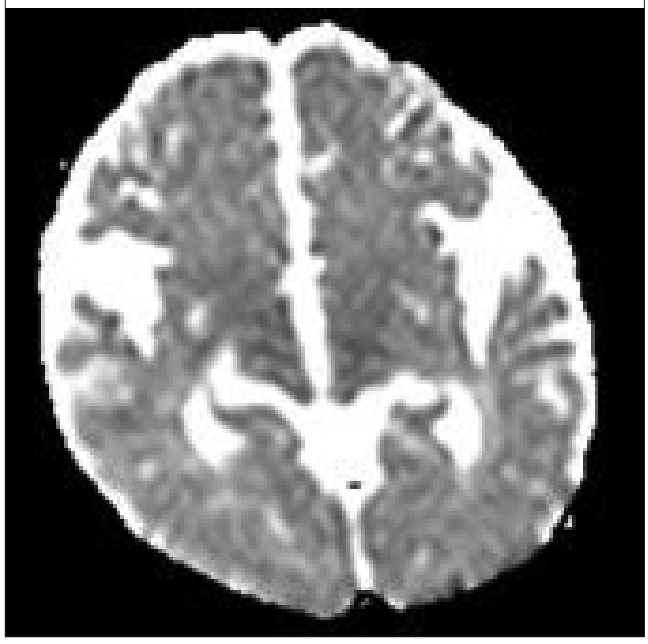


Figure 2. The pili torti sign in the microscopic examination of the hair in Case 1



physical therapy and rehabilitation clinic and started an exercise program. Written informed consent was obtained from the patient's parents.

Figure 3. Brain magnetic resonance imaging shows frontotemporal cortical atrophy in Case 2



Case 2

A 7-month-old male infant was admitted with weak head control and inability to sit unassisted. His prenatal history was unremarkable. He had been born on term via normal spontaneous vaginal route. His birth weight was 3080 g. His parents were second-degree relatives. On physical examination, he was conscious, restless, and hypoactive. He had a body temperature (armpit) of 37.2°C, a cardiac apex beat rate of 118/min, a respiratory rate of 27/min, blood pressure of 80/50 mmHg, body weight of 7.5 kg (25%-50%), height of 68 cm (25%-50%), an anterior fontanel of 3×2 cm with normal curvature, a dry skin, and a light complexion. He did not have organomegaly and cardiac, respiratory, or gastrointestinal abnormality. On neurological examination, he was hypotonic and made weak eye contact. His fundoscopic examination was normal. His deep tendon reflexes were active. On laboratory tests, complete blood count, routine biochemistry, including renal and hepatic function tests, ammonia, lactate, coagulation tests, urinary organic acid, congenital metabolic screening, blood amino acid levels, vitamin B12 level, and biotinidase level were all normal. There was no abnormality regarding intrauterine infectious serology (e.g., TORCH IgM and IgG). Cranial MR and diffusion cranial MR imaging showed cerebral parenchymal atrophy (Figure 3). On cardiac examination, a 2/6 murmur was revealed. On echocardiography, he had patent foramen oval and pulmonary stenosis. His abdominal USG was normal. As he had fair hair, a microscopic hair examination was performed, which revealed pili torti and trichorrhexis nodosa. His serum copper level was 36 µg/dL (normal level: 85-190 µg/dL), and ceruloplasmin level was 0.11 g/L (normal level: 0.15-0.48 g/L). A whole gene sequence analysis by in silico examination (Miseq-Illumina, Illumina Way, San Diego, CA/USA) showed a novel, previously unreported IV58

homozygous mutation in the ATP7A gene. Written informed consent was obtained from the patient's parents.

DISCUSSION

Copper is a trace element that is essential as a cofactor of many enzymes. ATP7A is the protein that is responsible for copper release from the intracellular to extracellular space, as well as copper transport in the intracellular space. The deficiency of this protein causes copper to accumulate inside the cell, making copper-dependent enzymes dysfunctional (1). In Menkes disease, the clinical signs appear due to dysfunctional copper-dependent enzymes, such as tyrosinase, cytochrome c oxidase, dopamine beta-hydroxylase, and lysyl oxidase (3). Its signs and symptoms include hypotonia, difficulty nourishing, convulsions, dysmorphic face, and cognitive and motor retardation that typically start in the first months of life (6). These signs may be confused with many chronic neurometabolic disorders. The available findings suggested neurometabolic disorders in both of our patients. As cerebral parenchymal atrophy was detected by cranial MRI, metabolic causes were sought. Our tests revealed no finding suggestive of congenital metabolic, infectious, or cardiac disorder. His neurological signs progressed during follow-up. His history was remarkable for consanguineous marriage, dysmorphic signs, and a progressive neurological course, which altogether suggested a neurodegenerative disorder. However, no specific finding was found in this regard. Our patient had no hair in the early infancy stage, and he was suspected to have Menkes disease only after he grew hair.

Hair signs are the major sign that supports the diagnosis of Menkes disease (4). Although rare, patients may have normal hair at birth, which later evolve into light-colored, short, brittle, wooly hair. The microscopic examination of the hair may reveal pili torti and trichorrhexis nodosa (1-5). Both of our patients were detected to have pili torti and trichorrhexis nodosa by the pathology examination of their light-colored, brittle, wooly hair. Light hair and pili torti may also be present in some other metabolic, hereditary disorders, such as phenylketonuria, trichorrhexis nodosa, or biotin deficiency (4, 5). The above differential diagnoses were excluded by family history of our patients, as well as their clinical, imaging, and laboratory findings.

Menkes disease is diagnosed based on reduced serum copper and ceruloplasmin levels (1, 3, 4). Our patients' low serum copper and ceruloplasmin levels supported the diagnosis. The definitive diagnosis of the disorder is made by genetic analysis (1-3). Prenatal diagnosis is now possible (1-5). The blood samples of our patients were studied for genetic etiology, and the mutations were revealed in both patients. The families were recommended genetic counseling, but they could not be reached thereafter.

Currently, there is no effective treatment for Menkes disease. The mean life expectancy for Menkes disease is 3 years. Starting treatment with subcutaneous copper histidine when the diagnosis is made in the early postnatal days has been reported to improve prognosis (6). The first patient was diagnosed at age approximately 12 months, and the second patient was diagnosed at age 7 months. Physical treatment and symptomatic treatment are applied to the patients for severe neurological complications.

CONCLUSION

In addition to progressive neurological signs, it should be kept in mind that typical hair signs may cause Menkes disease in the infancy period, and they have a prominent role for the differential diagnosis of chronic neurological disorders. The presence of a possible genetic diagnosis and genetic counseling opportunities increases the importance of the disorder.

Informed Consent: Written informed consent was obtained from patient's parents.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - S.I., S.K.; Design - S.I., S.K.; Supervision - S.K.; Resources - S.K.; Materials - S.I.; Data Collection and/or Processing - S.I., S.K.; Analysis and/or Interpretation - S.I.; Literature Search - S.I., S.K.; Writing Manuscript - S.K.; Critical Review - S.I.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Culotta VC, Gitlin JD. Disorders of copper transport. In: Scriver CR, Beaudet AL, Sly WS, Walle D (eds). The Metabolic and Molecular Bases of Inherited Disease (8th ed). New York: McGraw Hill Inc 2001: 3105-26.
2. Menkes JH. Kinky hair disease. Pediatrics 1972; 50: 181-3.
3. Ahmed MI, Hussain N. Neuroimaging in Menkes disease. J Pediatr Neurosci 2017; 12: 378-82. [CrossRef]
4. Kodama H, Fujisawa C, Bhadhprasit W. Pathology, clinical features and treatments of congenital copper metabolic disorders-Focus on neurologic aspects. Brain Dev 2011; 33: 243-51. [CrossRef]
5. Kaler SG, Holmes CS, Goldstein DS, Tang J, Godwin SC, Donsante A, et al. Neonatal diagnosis and treatment of Menkes disease. N Engl J Med 2008; 358: 605-14. [CrossRef]
6. Barnes N, Tsivkovskii R, Tsivkovskaia N, Lutsenko S. The copper-transporting ATPases, menkes and wilson disease proteins, have distinct roles in adult and developing cerebellum. J Biol Chem 2005; 280: 9640-5. [CrossRef]