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De Novo Mutation in ATP7A Gene with Severe Menkes Disease

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CASE REPORT

ABSTRACT

Menkes disease (MD) is an X-linked neurodegenerative disorder, which occurs in early infancy, and is caused by the impairment of P-type ATPase.

An 8-month-old boy presented with seizure and difficulty of feeding. His hair was blond, thin, and weak. He had poor head control and could not sit. The microscopic appearance of the patient's hair was pili torti. Brain magnetic resonance imaging revealed diffuse cerebral and cerebellar atrophy, and vascular tortuosity was observed in both middle cerebral and vertebrobasilar arteries in magnetic resonance angiography. Molecular genetic analysis was performed for suspected MD and a hemizygous mutation (p. G1118S [c.3352G>A]) was detected in ATP7A gene.

Although it is not specific for the disorder, microscopy of the hair allows early diagnosis when the differential diagnosis is broad or other tests are not conclusive. Since it is a fatal neurodegenerative disorder, genetic counseling must be provided to the family.

Keywords: ATP7A, De Novo Mutation, Menkes Disease

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INTRODUCTION

Menkes disease (MD) is an X-linked neurodegenerative disorder, which occurs in early infancy, and is caused by the impairment of P-type ATPase (ATP7A), which is essential for copper homeostasis. The responsible gene was mapped on Xq21.1. The disorder is characterized by hypotonia, feeding difficulties, seizures, dysmorphic facial features, psychomotor retardation, and connective tissue anomalies (1).

Gastrostomy tube replacement for the management of feeding, antiepileptic drugs for seizures, and surgery for bladder diverticula and/or subdural hematomas are some treatment options for supportive care. It has been reported that copper histidine reduces seizure frequency when the treatment is started in the early period (2).

CASE REPORT

An 8-month-old male infant presented with seizure and difficulty of feeding. His body weight was 8.2 kg (25%-50% percentile), height was 73 cm (50%-75% percentile), and the head circumference was 45 cm (25%-50% percentile). His hair was blond, thin, and weak (Figure 1a). He had poor head control and he could not sit.

The patient was the second child of a nonconsanguineous Turkish couple. Prenatal, obstetric, and family history were unremarkable. The parents also had a 2-year-old healthy daughter.

In laboratory investigations, complete blood count, blood glucose, liver enzymes, and creatine kinase levels were within normal limits.

He fixed his vision on one point; his activities reduced for a few minutes in his first days of hospitalization. Electroencephalography (EEG) revealed a sharp wave activity in the temporo-occipital and parieto-occipital regions of the left hemisphere also slowing of the ground rhythm in the posterior half of both hemispheres and temporal region of the left hemisphere. Due to the presence of hypomotor seizures, phenobarbital was started and seizures were controlled.

Brain magnetic resonance imaging (MRI) revealed diffuse cerebral and cerebellar atrophy; magnetic resonance angiography (MRA) showed vascular tortuosity in both the middle cerebral and vertebrobasilar arteries (Figure 2).

Metabolic studies were performed due to psychomotor retardation and seizures. Blood lactate, pyruvate, biotinidase activity, plasma and urine amino acid analysis, tandem mass spectroscopy, and urine organic acid analysis were normal.

The microscopic appearance of the patient's hair was pili torti (Figure 1b). Therefore, the patient was evaluated for MD. Serum ceruloplasmin level was 0.08 g/L (normal range [NR]: 0.31–0.91), and serum copper level was 22 g/dL (NR: 50–155).

Molecular genetic analysis was performed for suspected MD and a hemizygous mutation (p. G1118S [c.3352G>A]) was detected in the ATP7A gene (Figure 3a). The information about the risk of transmitting the ATP7A mutation was provided to the family. Mutation-targeted molecular testing was performed to proband and the females at risk by the Sanger sequencing method (ABI 3500). They have no mutation in the suspected gene region (Figure 3b). These results suggested that the mutation of the proband is a de novo mutation. Pedigree of the family is shown in Figure 3c.

The patient is 21 months old now. He is bedridden and has a significant feeding difficulty. He was hospitalized due to pulmonary infection several times.

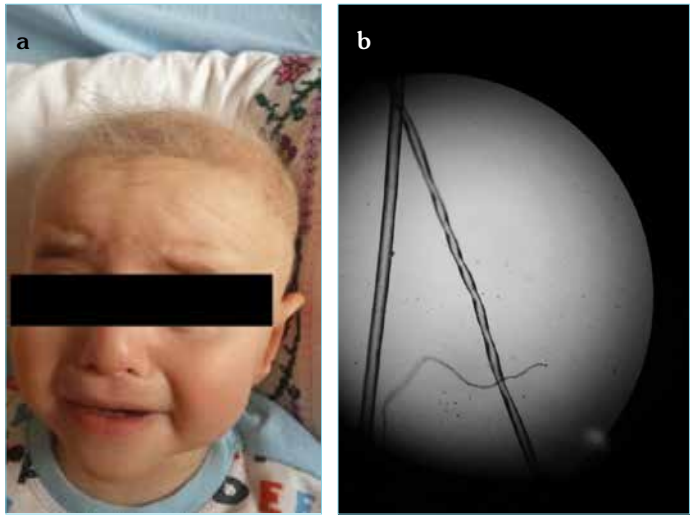

Figure 1. a, b. General view (a) of the patient's hair and pili torti (b)

DISCUSSION

Although hypotonia, hypothermia, feeding difficulties, seizures, dysmorphic facial features, and cognitive and motor retardation are major clinical findings of MD, they are not specific. It can be misdiagnosed as many chronic neurological diseases.

Seizures are common in MD. Early onset seizures typically start with focal seizures and show a progression to epileptic spasms. The late forms of chronic seizures can appear as tonic seizures, myoclonic jerks, infantile spasms, multifocal epileptiform activity, or hypsarrhythmia on EEG. Rizk et al. (3) reported a patient with epilepsia partialis continua, and MRA of this patient showed relatively tortuous but patent intracranial vessels, with an appearance of a "hair pin" sign. Middle cerebral, vertebral, and basilar arteries

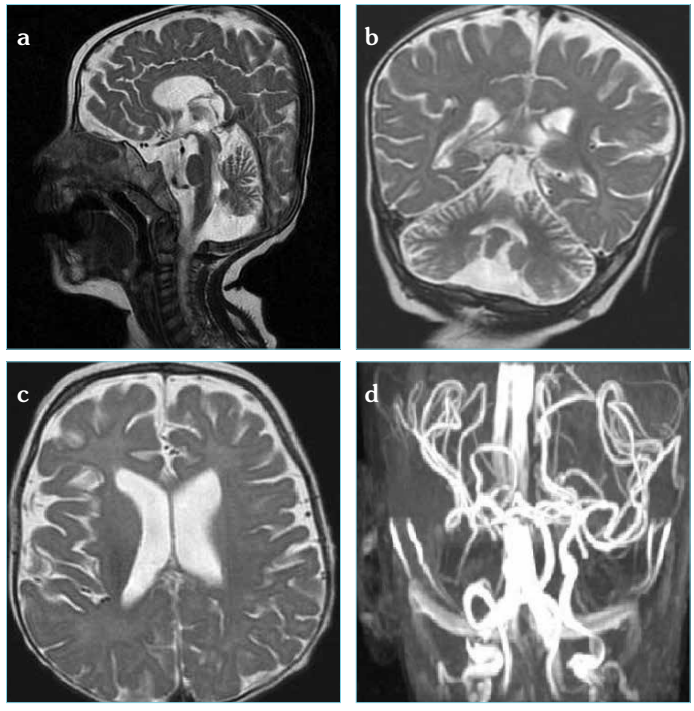

Figure 2. a-d. Sagittal (a) and coronal (b) and axial (c) T2W images of MRI show diffuse cerebral and cerebellar atrophy and MRA (d) image shows severe intracranial and extracranial vascular tortuosity in both middle cerebral and vertebrobasilar arteries

Table 1 Clinical features, molecular genetic analyses, and disease severity of the patients with Menkes Disease

Author	Country	Age onset	Mutation	Clinical features	Disease severity
Procopis et al., (6)	Australia	21 months	c.4085C>T	Hypotonia, ataxia, dysmorphic facial features	Mild form
Choi et al., (8)	Korea	5 months	c.3352G>A	Seizures	Severe
Rizk et al., (3)	Saudi Arabia	17 months	c.1138G>A	Epilepsia partialis continua, regression of milestones, repetitive episodes of hypothermia	Severe
Lin et al., (7)	Taiwan	4 months	c.3502 C>T	Hypotonia, epilepsy, dysmorphic facial features	Severe
Current report	Turkey	8 months	c.3352G>A	Hypotonia, epilepsy, poor feeding	Severe

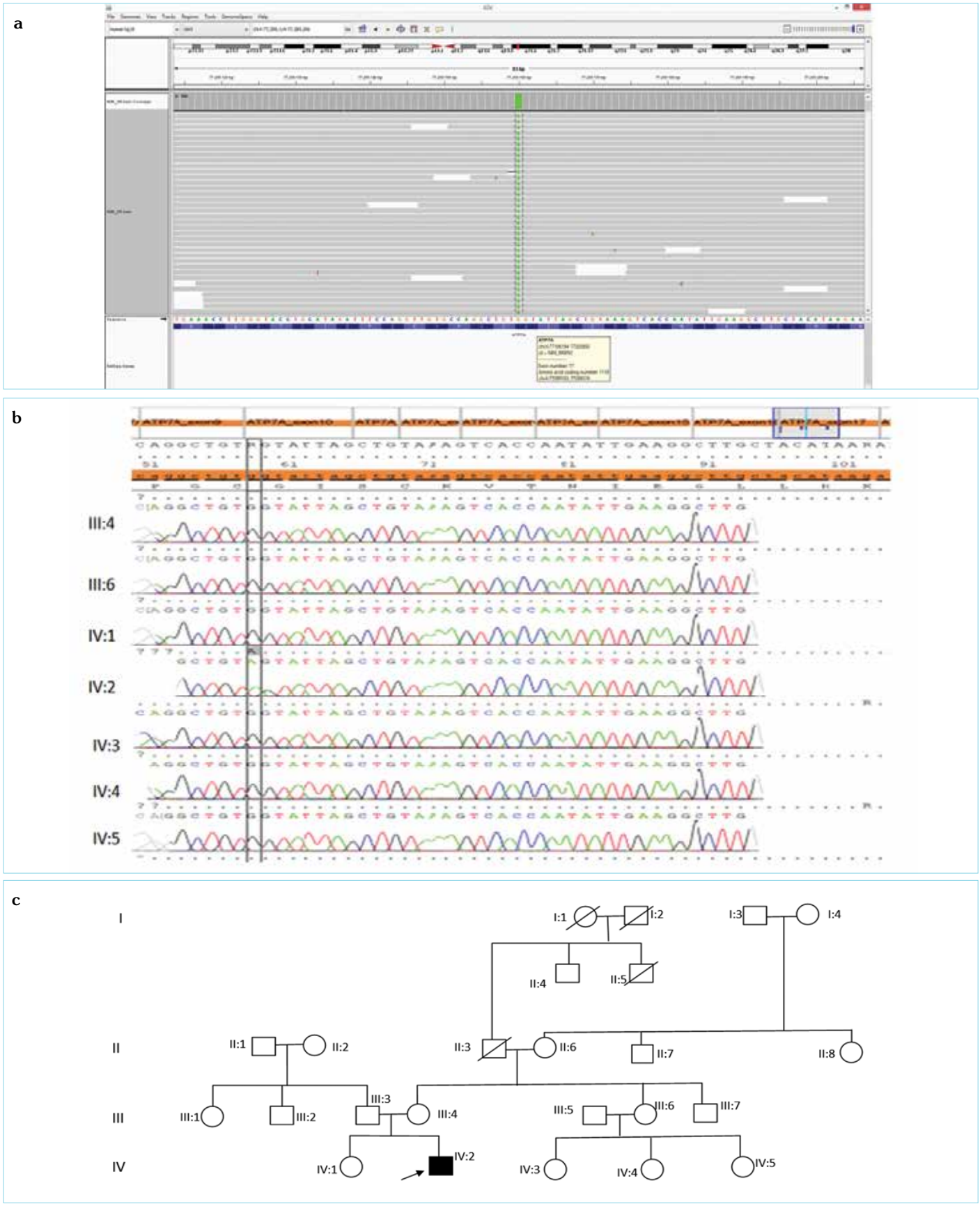

Figure 3. a-c. Next generation sequencing image (a) shows hemizygous [p. G1118S (c.3352G>A)] mutation in ATP7A gene and the sanger sequencing image (b) shows the confirmation of the patient and the females at risk and the pedigree (c) of the family

are elongated and tortuous in MRA, as in the present case. Our patient presented with hypomotor seizures and, which were controlled with phenobarbital.

Light-colored hair can be seen in phenylketonuria and trichorhexis nodosa; pili torti can be seen in ectodermal dysplasia, argininosuccinic aciduria, or biotinidase deficiency. Metabolic tests of our case were normal. Therefore, these inborn errors of metabolic diseases have been excluded.

Although microscopy of the hair allows early diagnosis when the differential diagnosis is broad and/or other tests are not conclusive, it is not specific for MD (4). Serum copper and ceruloplasmin levels are supportive diagnostic tests, but they are also not specific for MD.

To date, 274 different disease-causing variations of ATP7A have been reported, but some of them are not disease related. Splice site nonsense mutations and exon deletions are most common (5). Procopis et al. (6) reported a mild form of the disorder. This patient had a mutation (c.4085C>T) in the ATP7A gene. Hypotonia, ataxia, and dysmorphic facial features were major clinical findings of this patient.

Lin et al. (7) reported a truncating de novo point mutation in a patient with severe MD who presented with hypotonia, epilepsy, and dysmorphic facial features.

Choi et al. (8) reported the same mutation (p. G1118S [c.3352G>A]) in a 5-month-old male infant who had seizures at the time of diagnosis and was bedridden when he was 3 years old, similar to the present case.

Clinical features, molecular genetic analyses, and disease severity of the patients with MD are shown in Table 1.

The diagnosis was possible at around 9 months in our case and only symptomatic treatment was applied; seizures were controlled after antiepileptic treatment. There have been few reports about the long-term survival in MD. Tchan et al. (9) reported a patient (previously reported by Procopis et al.) who received copper supplementation for >30 years with mild intellectual impairment.

Disease variants have been reported in some females and are associated with translocations on X-chromosome. Heterozygous females are thought to be asymptomatic and one-half of the carrier females were shown regions of pili torti. Mutation-targeted molecular testing was performed on the females of the family at risk, and no mutation has been identified in our study. Gu et al. (10) reported that 25% of mothers of the patients with MD were not carriers similar to the present family.

CONCLUSION

Although it is not specific for the disorder, microscopy of the hair allows early diagnosis when the differential diagnosis is broad and/or other tests are not conclusive. Also, serum copper and ceruloplasmin levels are not specific for MD. Therefore, molecular confirmation has to be made for the correct diagnosis. Since it is a fatal disorder, the genetic counseling must be provided to the family in the presence of an index case.

Informed Consent: Written informed consent was obtained from the parents of the patient who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Conceived and designed the experiments or case: PSÜ, ASG. Performed the experiments or case: AK, AY. Analyzed the data: ŞEB, SG. Wrote the paper: PSÜ.

All authors have read and approved the final manuscript.

Conflict of Interest: Authors have no conflicts of interest to declare.

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