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Case report

Almost misdiagnosed Menkes disease: A case report

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ABSTRACT

Background: Menkes disease is a disorder of copper metabolism and which follows a progressive degeneration of brain. It is a rare X-linked recessive disorder that results from mutations in ATP7A gene. The early diagnosis of Menkes disease is critical to patients' prognosis.

Case presentation: We report a case of Menkes disease. A 4-month-old boy presented with intermittent convulsions for a week. The brain MRI showed excessive tortuosities of intracranial vessels, and radiologists prompted for further examinations to confirm that it was Menkes disease. Patient was advised for biochemical investigations and genetic tests. Reduced level of ceruloplasmin (0.04 g/L; normal range, 0.2–0.6 g/L) was revealed. Genetic testing revealed a missense mutation within exon 18, c.3548 G > A, p.G1183D. This patient was almost misdiagnosed as epilepsy. Fortunately, based on the clues from radiologist, further physical examination and experimental tests were carried out.

Conclusion: We reported the imaging features of a case of Menkes disease, which can provide clinicians with more clues to consider the possibility of this rare disease.

1. Introduction

Menkes disease (MD), also known as kinky hair syndrome, is a rare X-linked recessive disorder [1]. The incidence of the disease is 1 per 300, 000 live births [1]. It occurs due to loss-of-function mutations in ATP7A gene located on chromosome X [2]. Currently available treatment for MD is subcutaneous copper histidine injection, and it might only modify disease progression in an early age [2]. Hence, the early diagnosis is important for MD patients to receive proper treatment so as to improve survival. Due to the rarity of the disease, inexperienced pediatric clinicians might misdiagnose it.

2. Case report

A 4-month-old boy was admitted to the hospital with intermittent epileptic seizures for 3 days. None special physical examination signs were noticed initially. Patient was referred for neuroimaging because of convulsions. MRI findings revealed massive leukoencephalopathy with hyperintensity of white matter in bilateral parietal-temporal, and occipital lobe on T2-weighted imaging (T2WI) (Figure 1 A). The bilateral basal ganglia were hyperintense on T2WI and fluid-attenuated inversion recovery (FLAIR) MR imaging (Figure 1 A, B). Diffusion weighted imaging (DWI) showed restricted diffusion in the head of the caudate nucleus, anterior putamen and globus pallidus (Figure 1 C). It is noteworthy that the significant tortuous line-like hyperintensity on fluid-attenuated inversion recovery (FLAIR) sequence was found along cortical surface in the subarachnoid space (Figure 1 D) and the tortuosity of intracranial vessels were observed on T2WI obviously as well (Figure 1 E). In order to show the tortuosity of blood vessels more intuitively, we did MRI angiography examination. MRI angiography (MRA) revealed excessive tortuosity of intracranial vessels (Figure 1 F). After MRI, patient was advised for biochemical investigations and genetic tests. The level of ceruloplasmin was decreased (0.04 g/L; normal range, 0.2–0.6 g/L).

We performed the whole-exome sequencing. Genome-wide copy number analysis was performed using Illumina Human Cyto-SNP12 BeadChip (Illumina, San Diego, CA). The data were analyzed using Karyo Studio v1.4. WES and subsequent data analysis were conducted with central laboratory of Wuhan Children's hospital. Genetic testing revealed a missense mutation within exon 18, c.3548 G > A, p.G1183D (Figure 2 A). The mutation was confirmed to be a novel pathogenic mutation after comparison with the gene pools [Human Gene Mutation Database (www.hgmd.org), *ATP7A* database in Leiden Open variation Database 3.0 (www.LOVD.nl/ATP7A)]. We performed a detailed physical examination. The patient has pale skin, light color hair. And the hair

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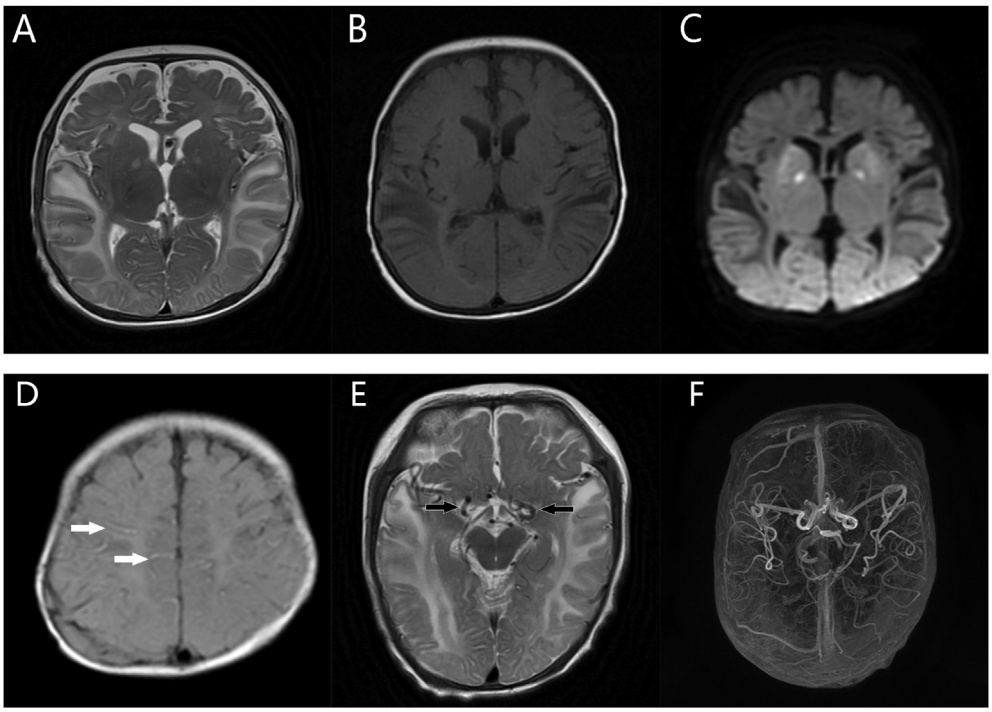

Figure 1. Magnetic resonance imaging of brain of Menkes syndrome. Axial T2 (A) and FLAIR-weighted image (B) showing white matter hyperintensities, suggesting leukoencephalopathy. Diffusion weighted image (C) showed restricted diffusion in basal ganglia. FLAIR (D) showed FVH (white arrows), T2WI (E) showed flow-voids (black arrows) and MRA (F) showed excessive tortuosity of cervical arteries.

was easy to twist broken which can be easily overlooked. Then, the patient's parents were advised for genetic test. ATP7A gene sequencing of the patient's mother was heterozygous (Figure 2 C). On the basis of the characteristic laboratory testing results, genetic testing results and imaging findings, our patient was diagnosed as Menkes disease (MD) finally.

3. Discussion

MD is an inherited X-linked disorder that results from mutations in ATP7A gene [3]. As a consequence, that would cause the disorders of Cu homeostasis [4]. The mutations of ATP7A gene result in low levels of Cu in serum and brain, and failure of enzymes that need the micronutrient as a cofactor. Ceruloplasmin, the main copper-binding protein in blood, has copper dependent ferroxidase activity, which facilitates iron binding to transferrin, and which is affected by low copper bioavailability [5]. The reduced blood levels of Cu and ceruloplasmin can be used as a basis for diagnosis. Affected infants might present with failure to thrive, kinky hair (pili torti), impaired cognitive and sensorimotor development and reduction in life expectancy [6]. Even though the typical physical examination signs of MD patients were distinctive, MD is rare that inexperienced clinicians may ignore it. Meanwhile radiologists can provide clinicians with more diagnostic ideas based on some typical imaging findings. The application of MRI helps us to find more clues for diagnosis. A typical diagnostic feature of MD is increased artery tortuosity on MRI. Tortuosity of intracranial arteries present severe stenosis, leading slow anterograde or retrograde leptomeningeal collaterals, showing an absence of flow-void phenomenon (FVH) as a result of sluggish blood flows. In our case, a remarkable FVH was found in parietal and occipital regions (Figure 1 D). T2WI and MRA revealed excessive tortuosity of intracranial vessels (Figure 1 E, F). These findings are related with collateral circulation distal to large-vessel stenosis.

Increased artery tortuosity is the typical feature in MD [7], while other cerebrovascular diseases such as moyamoya may present similar feature. Moyamoya disease is a chronic cerebrovasculopathy [8]. It is characterized by stenosis or occlusion at proximal anterior cerebral arteries, proximal middle cerebral arteries and distal internal carotid arteries [8, 9]. And another feature of moyamoya disease is the development of collateral vessels, located at the base of the brain [9]. It looks like “a puff of smoke” in the angiographic images. The abnormal manifestation on MRA should be differentiated with MD. It's important that the main identification of MD is large vessels tortuosity with corkscrew patterning. In MD, MRA showed marked tortuosity of intracranial vessels that are attributed to abnormalities in the internal elastic laminae [7], without the sign of “smoke”. Tortuosity of the arteries on MRI combined with clinical manifestations like abnormal hair hypopigmentation should be helpful in the differentiation.

Whole exon sequencing revealed a novel mutation (c.3548 G > A) in the ATP7A gene of the patient in our case, which led to the mutation of the 1183 amino acid residue Gly to Asp. When compared with the gene pools [Human Gene Mutation Database, ATP7A database in Leiden Open variation Database 3.0], it was confirmed that the missense mutation in this patient was a novel mutation. However, the onset of MD occurred 5 months after birth. Thus, the patient's MD differed from that of classic MD which occurs in the neonatal period. The severity of MD depends on the function of ATP7A. Severe truncation of the gene product and significant loss of function cause severe classic MD that can lead to the early death of children [1, 6, 10]. Missense mutations with retention of protein function are associated with milder phenotypes [11]. In this case, the onset of MD was late, might be a milder phenotype. However, Whether the function of ATP7A is altered by this missense mutation is unknown. Functional analyses need to be conducted to further explain the effects of mutations on the clinical phenotype.

This patient was almost misdiagnosed as suffering from epileptic seizures of unknown origin. Fortunately, based on the clues from radiologist, further physical examination and experimental tests were carried out. Radiologist play an important role in the diagnosis. The treatment for MD is subcutaneous copper histidine injection, and it might only modify disease progression at an early age. Consequently, early diagnosis is particularly important for MD patients.

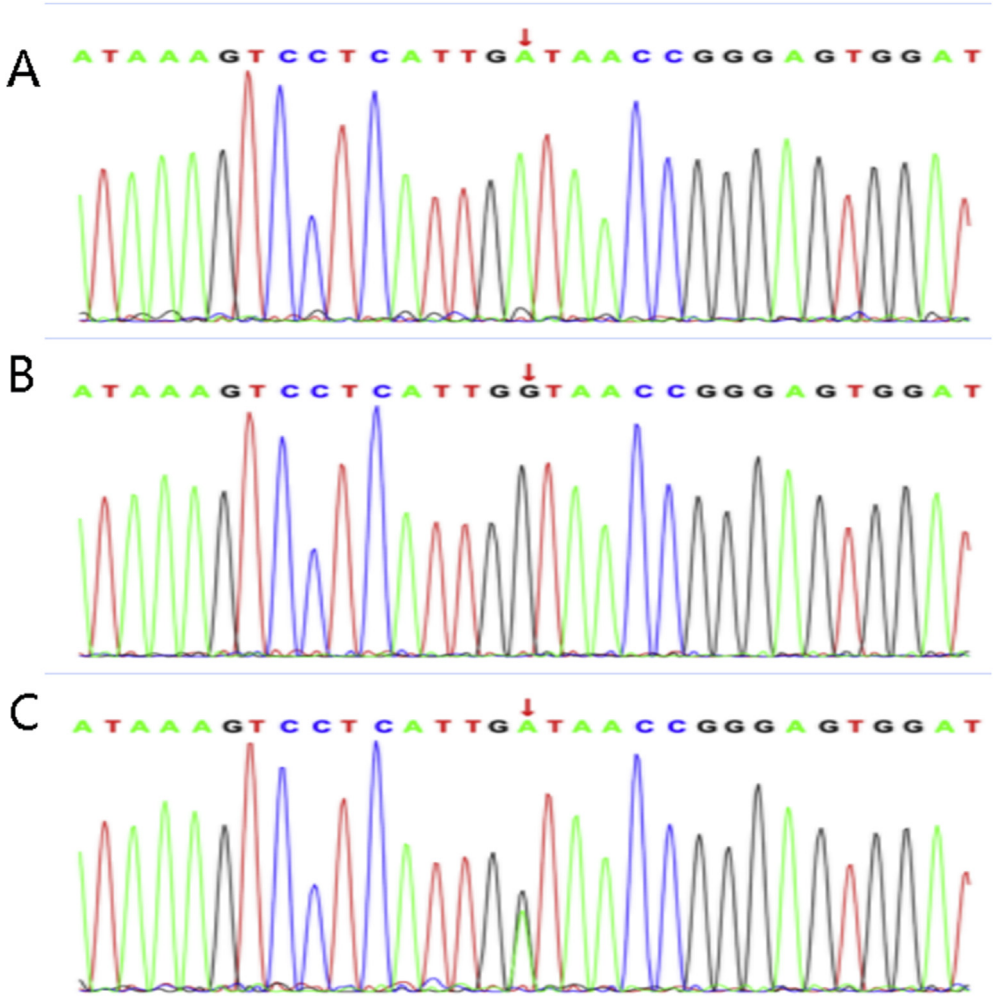

Figure 2. Sanger sequencing of *ATP7A* mutations. (A) A gene analysis revealed a c.3548 G > A at exon 18 of the patient (p.G1183D). (B) *ATP7A* gene sequencing of the patient's father was normal. (C) *ATP7A* gene sequencing of the patient's mother was heterozygous.

In conclusion, the clinical manifestations such as abnormal hair hypopigmentation and seizures in combination with FVH and tortuous vessels on MRI are important diagnostic clues for Menkes disease.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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