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CASE REPORT
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Coexistence of molybdenum cofactor deficiency type A and hypertrophic pyloric stenosis, a new case

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What is already known on this topic?

Molybdenum cofactor deficiency is a very rare neurometabolic disease, its association with hypertrophic pyloric stenosis has so far been described in two cases.

What this study adds on this topic?

It was concluded that the relationship between molybdenum cofactor deficiency and pyloric stenosis may be related to sulfur oxidase metabolism.

ABSTRACT

Molybdenum cofactor deficiency is a rare neurometabolic disease that is usually characterized by seizures, abnormal muscle tonus, developmental delay and poor nutrition, and is seen soon after birth. Pyloric stenosis causes serious vomiting in the first months of life. The presence of neurologic damage in molybdenum cofactor deficiency and possible abnormal innervations may cause pyloric stenosis; however, the pathogenesis is unclear. Pyloric stenosis with molybdenum cofactor deficiency has been described in two cases. Herein, we report the third case and suggest that hypertrophic pyloric stenosis should be kept in mind as a clinical manifestation of molybdenum cofactor deficiency.

Keywords: Molybdenum cofactor deficiency type A, newborn, pyloric stenosis

Introduction

Molybdenum cofactor deficiency (MoCD) is a rare autosomal recessive metabolic disease. Molybdenum cofactor is essential for sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase (1). Since the first definition of Duran et al. (2), more than 100 patients from various ethnicities have been diagnosed as having the disease. Among the most common clinical symptoms are persistent newborn seizures, nutritional deficiency, and developmental delay. Additionally, hypouricemia and hematuria can be seen because of the increased renal metabolism of xanthine and hypoxanthine (3). The gold standard diagnostic method is to show the absence of sulfite oxidase in skin or fibroblast cultures. Most infants die in the first days or weeks of their lives even if they are diagnosed during the newborn period (2).

Hypertrophic pyloric stenosis causes projectile vomiting in the first few months of life. Usually, it becomes evident in the 3rd or 4th weeks of life with projectile nonbilious vomiting and assumed to be caused by the inadequate development of inhibitory neurons in the mesenteric plexus of the pyloric region where vasoactive intestinal peptide and nitric oxide (NO) are used as neurotransmitters for the relaxation of the sphincter (4, 5).

It is generally accepted that damage to nerve tissue in the absence of molybdenum cofactor is probably due to the toxic effect of sulfite deposition. In patients with MoCD and sulfite oxidase deficiency (SOD), alternative nitric oxide (NO) production pathways may also be affected, leading to low levels of NO. As low NO levels cause a failure of pyloric relaxation, pyloric stenosis in MoCD may be due to decreased NO production. Also, toxic accumulation of sulfite in cerebral white matter and long tracts in the spinal cord may affect other neuronal channels, such as those of the myenteric plexus of the enteric system. This neuronal toxicity can also result in abnormal innervations of the muscle layer of the pylorus and subsequently pyloric hypertrophy, hyperplasia, and obstruction (5, 6).

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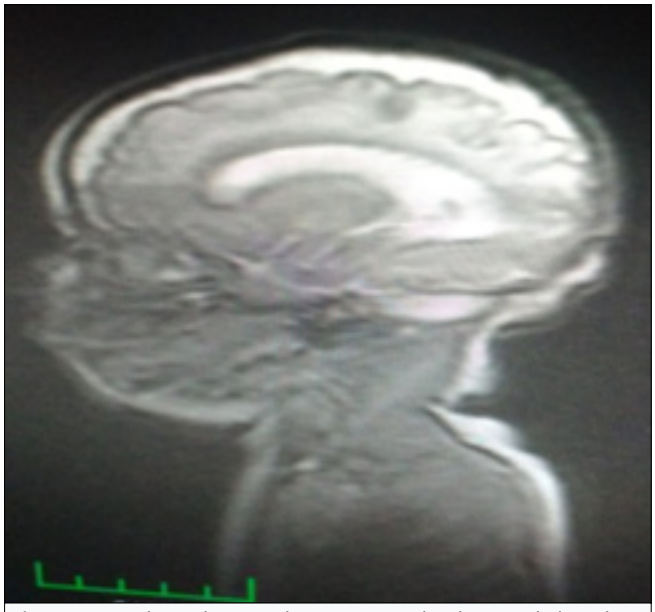

Figure 1. Cranial MRI shows pachygyria, incomplete lissencephaly and cerebellar hypoplasia

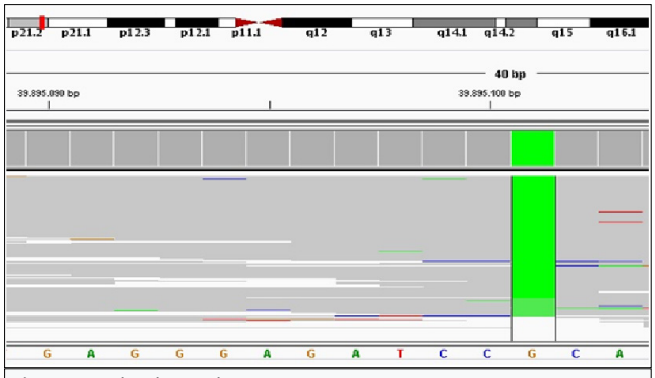

Figure 2. Molecular analysis presenting MOCS1 mutation, p.R73W in Integrative Genomics Viewer - IGV™ software result

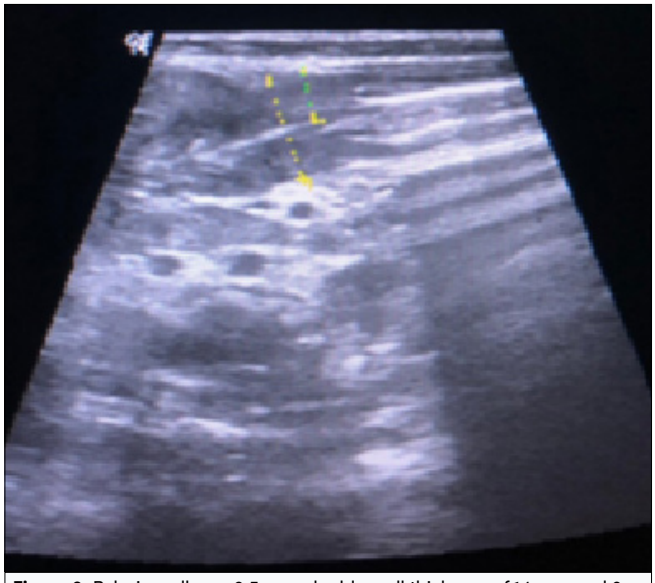

Figure 3. Pyloric wall was 6.5 mm, double wall thickness of 14 mm and 3 cm in vertical axis

Pyloric stenosis has been described in one patient with isolated sulfide oxidase deficiency, and there have only been two cases of MoCD (5-7). Here, we present the third case of pyloric stenosis and MoCD coexistence.

Case Presentations

A baby boy was born by cesarean section from a 28-year-old mother as her 3rd living baby among four pregnancies. His birth weight was 3600 g and APGAR scores were 8 and 10 at the 1st and 5th minutes, respectively. In 24-48th hours of life, the baby was hospitalized due to inadequate breastfeeding, apnea, and desaturation. He had coarse facial features. He had vertical nystagmus and hypotonia. A cardiologic examination was normal. He was intubated and ampicillin and gentamicin were started. The parents were consanguineous and they had two other healthy children; however, one boy other than these two had neuromotor deficiency and hypertrophic pyloric stenosis and died at the age of 18 months.

During hospitalization, the patient had clonic convulsions and received phenobarbital plus phenytoin. Clonazepam and midazolam infusions were added for refractory seizures. An amplitude-integrated electroencephalogram (aEEG) showed low-grade irregularity in the base rhythm and epileptic abnormalities, which were thought to originate from cortical tissues. He was receiving ventilator support.

Existence of consanguinity, history of the death of a child, and refractory seizures led us to examine for neurometabolic disorders. Tandem mass spectrometry, organic acid in urine, and long-chained fatty acids were found to be normal. Serum total carnitine was 15 µmol/L (normal range: 17-41), serum free carnitine was 12 µmol/L (normal range: 10-21), lactic acid was 38 mg/dL, pyruvic acid was 1.4 mg/dL, thyroid-stimulating hormone (TSH) was 2.9 mIU/mL, free thyroxine (fT4) was 1.2 ng/dL, and TORCH screening was found to be negative. The uric acid level was 0.9 mg /dL and the follow-up level was found as 0.1 mg/dL. As urine sulphite test was positive, MoCD was diagnosed. Cranial MRI revealed pachygyria, incomplete lissencephaly and cerebellar hypoplasia (Figure 1). Tests for MOCS1, MOCS2, sulphite oxidase gene mutations, and chromosomal analysis were performed. Molecular analysis revealed a *MOCS1* mutation, p.R73W in the Integrative Genomics Viewer - IGV™ software (Figure 2).

The baby had projectile vomiting when he was aged 45 days and further examinations revealed the thickness of the pyloric wall was 6.5 mm and double-wall thickness (14 mm) and 3 cm in the vertical axis (Figure 3). He underwent surgery on the 55th day of life. However, he deteriorated on the 3rd postoperative day when he was age 58-days and died of septic shock. Written informed consent was obtained from patient parent.

Discussion

Molybdenum cofactor deficiency is a rare autosomal recessively inherited disorder that leads to loss of activity of molybdenum cofactor-dependent enzymes including sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase. Clinical findings cannot be distinguished from isolated sulfide oxidase deficiency (1). In affected individuals, typically persistent sei-

zures, metabolic acidosis, intracranial hemorrhage, feeding difficulties, irregular autonomic function, exaggerated startle reactions, dysmorphic facial features, severe developmental delay, changes in muscle tone, progressive cerebral palsy, microcephaly, lens dislocation, and kidney stones are present in neonatal or early infancy period (2, 8). Seizures are difficult to control with anticonvulsive drugs.

Approximately 75% of infants show facial dysmorphism with puffy cheeks, small nose, long philtrum, and coarse facial features. The survivors develop a clinical condition including increased spasticity, severe mental retardation, and microcephaly. Dislocated lenses and seborrheic rash occur after infancy. Sometimes dislocated lenses can be observed even at 2 months of age (3). The present case had dysmorphic facial features, there were persistent seizures, feeding difficulty, low blood uric acid levels, and increased urine sulphide levels. With these clinical findings, he was diagnosed as having MoCD.

Symptoms of encephalopathy in MoCD are due to sulfite metabolites. Sulfite can directly damage mitochondrial function by disrupting membrane integrity or indirectly interfere with the tricarboxylic acid cycle (TCA). Uric acid is a powerful antioxidant and is a normal product of TCA cycle. When serum uric acid levels decrease, free oxygen radicals accumulate and lead to neurologic damage, which is the main feature of MoCD (9, 10).

Hypertrophic pyloric stenosis has been reported in one patient with previously reported sulphide oxidase deficiency and two Turkish patients with MoCD (5-7). Abnormal innervation of the pyloric muscle due to decreased nerve terminals and a decreased amount of nitric oxide as a means of relaxation in the gastrointestinal tract are pathophysiologic mechanisms considered in the formation of pyloric stenosis (5). Another explanation could be the close positioning of MoCD genes and pyloric stenosis genes or a different gene that has not yet been defined could cause both disorders in one patient.

In conclusion, three reported cases indicate a relationship between hypertrophic pyloric stenosis and MoCD. Physicians should keep in mind the coexistence of these two disorders and perform abdominal USG because patients with MoCD have feeding problems. Moreover, detailed immunohistochemical evaluation of pyloric neuronal tissue in patients with MoCD may provide clues to the pathogenesis of this disease.

Informed Consent: Written informed consent was obtained from patients' parents who participated in this study.

Peer-review: Externally peer-reviewed.

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

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