

# May There Be A Link Between Molybdenum Cofactor Deficiency And Pyloric Stenosis?

MOLİBDEN KOFAKTÖR EKSİKLİĞİ İLE PİLOR STENOZU ARASINDA BİR BAĞLANTI OLABİLİR Mİ?

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### SUMMARY

Molybdenum cofactor deficiency is a neurometabolic disorder that typically presents shortly after birth with seizures, abnormal muscle tone, developmental delay and poor feeding. Pyloric stenosis is a condition that causes severe vomiting in the first few months of life. The pathogenesis of both diseases remains unknown. We report a female infant with molybdenum cofactor deficiency and pyloric stenosis. Whether this is a coincidence or molybdenum cofactor deficiency may predispose to pyloric stenosis is not known, but neuronal toxicity suggests a common etiology.

**Key words:** Molybdenum cofactor deficiency, vomiting, pyloric stenosis

### ÖZET

Molibden kofaktör eksikliği tipik olarak doğumdan hemen sonra nöbetler, anormal kas tonusu, gelişme geriliği ve beslenme güçlüğü ile kendini gösteren bir nörometabolik hastalıktır. Pilor stenozu ise hayatın ilk birkaç ayında ciddi kusmalara neden olan bir durumdur. Her iki hastalığında patogenezi bilinmemektedir. Bu yazıda molibden kofaktör eksikliği ve pilor stenozu olan bir kız süt çocuğu sunulmaktadır. Her ne kadar bu durumun bir koinsidans mı yoksa molibden kofaktör eksikliğinin bir sonucumu olduğu bilinmese de, nöronal toksisite ortak bir etiyoloji düşündürmektedir.

**Anahtar sözcükler:** Molibden kofaktör eksikliği, kusma, pilor stenozu

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Molybdenum cofactor deficiency is an autosomal recessive metabolic disorder. Molybdenum cofactor is necessary for the function of sulfite oxidase, xanthine dehydrogenase and aldehyde oxidase enzymes (1,2). The most common clinical symptoms are intractable neonatal seizures, feeding difficulties and developmental delay. Patients may also present with hematuria due to increased renal excretion of xanthine and hypoxanthine combined with hypouricemia and low urinary uric acid (3). The

definite diagnosis of the molybdenum cofactor deficiency depends on demonstration of the absent sulfite oxidase activity either skin or fibroblast culture (4). Pyloric stenosis is a condition that causes severe vomiting in the first few months of life. There is narrowing of the opening from the stomach to the intestines, due to enlargement of the muscle surrounding the pylorus. It is uncertain whether there is a real congenital narrowing or there is a functional hypertrophy of the muscle which develops in

the first weeks of life. Abnormal muscle innervation leading to failure of relaxation of the pylorus is another suggested pathogenetic mechanism (5). Pyloric stenosis was previously described in only two cases with isolated sulfite oxidase deficiency and molybdenum cofactor deficiency (5,6).

#### CASE

A female infant was born as the product of first pregnancy of a 21-year-old mother. The parents were first cousins. Birth history was unremarkable. The patient was transferred to neonatal intensive care unit on the third day of life with hypotonia, seizures and feeding difficulties. On physical examination, she was hypotonic and newborn reflexes were absent. Initial metabolic work-up and septic screening were negative except very low levels of uric acid (0.5 and 0.3 mg/dL). The multifocal clonic seizures were controlled with phenobarbital and phenytoin treatments

and she was commenced on nasogastric feeds. Brain magnetic resonance imaging revealed generalized cerebral atrophy with multicystic encephalomalacia (Figure). The urine dipstick test was positive for sulfite reaction. An extremely low plasma uric acid levels and a positive urinary dipstick test suggested the diagnosis of molybdenum cofactor deficiency.

On the 20th day of life, the patient was discharged from the hospital with nasogastric feeding. Ten days later, she was again admitted to the hospital with intractable vomiting after feeding. Blood gas analysis revealed hypokalemic hypochloremic metabolic alkalosis and abdominal ultrasound confirmed the diagnosis of hypertrophic pyloric stenosis. The patient underwent pyloromyotomy and was discharged home one week post-operatively. The patient still suffers severe mental motor retardation, seizures and feeding difficulties.



**Figure.** Sagittal magnetic resonance imaging delineated cerebral atrophy and multicystic encephalomalacia

## DISCUSSION

Molybdenum cofactor deficiency is characterized by lack of activity of the enzymes sulfite oxidase, aldehyde dehydrogenase and xanthine oxidase and clinical findings are indistinguishable from isolated sulfite oxidase deficiency (1,2). Laboratory findings in our case suggested molybdenum cofactor deficiency because in isolated sulfite oxidase deficiency, there are increased levels of sulfite in the urine, whereas blood uric acid levels remain normal. In the present case, repeated serum uric acid levels revealed very low levels.

Two previously reported cases together with our case suggest that sulfite oxidase deficiency and molybdenum cofactor deficiency may predispose pyloric stenosis (6,7). Abnormal innervation of the pyloric muscle due to deficient number of nerve terminals and decreased amount of nitric oxide which is a mediator of relaxation in the gastrointestinal tract are postulated pathophysiologic mechanisms for pyloric stenosis (8,9). The encephalopathy symptoms in molybdenum cofactor deficiency are related to sulfite metabolites. Sulfite might damage mitochondrial function by causing disruption of membrane integrity or indirectly by interfering with the tricarboxylic acid cycle. Uric acid is a potent antioxidant and a normal product of this cycle. When uric acid levels decrease in the blood, reactive oxyradicals can accumulate and contribute to neurologic injury which is a characteristic of molybdenum cofactor deficiency (10). The neuronal toxicity in molybdenum cofactor deficiency may also result in abnormal innervation of the muscular layer, failure of relaxation of the pyloric muscle and subsequent hypertrophy, hyperplasia and obstruction. On the other hand, xanthine oxidase is an important alternative enzyme in nitric oxide synthesis. When molybdenum cofactor is deficient, this pathway may be disrupted and reduced levels of nitric oxide may predispose to the development of pyloric stenosis (11-13).

In conclusion, three reported cases suggest an association between pyloric stenosis and molybdenum cofactor and sulfite oxidase deficiency. Pyloric stenosis should be kept in mind in patients with molybdenum cofactor deficiency and intractable vomiting. Detailed immunohisto-

chemical evaluation of the neuronal tissue of pylorus in patients with molybdenum cofactor deficiency may provide possible finding for the pathogenesis of this disorder.

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