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Cleft palate association described for the first time in a rare molybdenum cofactor deficiency Type B newborn case

Yarık damakla birliktelik gösteren molibden kofaktör eksikliği Tip B tanısı alan yenidoğan vakası

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ABSTRACT

Molybdenum Cofactor Deficiency (MoCD) is an extremely rare and severe autosomal recessive metabolic disorder with serious clinical manifestations. Symptoms, such as lethargy, hypotonia, and seizures, are commonly observed in affected individuals and may appear immediately or within days of birth. It is crucial to differentiate MoCD from hypoxic-ischemic encephalopathy (HIE), which can present with similar neurological symptoms and require urgent medical intervention. In this case report, we describe a newborn who presented with HIE-like symptoms but was eventually diagnosed with MoCD by laboratory testing and brain magnetic resonance imaging (MRI). Further genetic analysis confirmed the diagnosis with the identification of a MOCS2 Type B (c.226G>A, (p.G76R) (p.Gly76Arg) mutation, which has only been observed in a small number of cases. Additionally, this case is unique in that the patient also had a cleft palate, a rare occurrence of MoCD. We aimed to emphasize the importance of accurate diagnosis in newborns presenting with neonatal encephalopathy, as inappropriate treatment with therapeutic hypothermia may have serious consequences.

Keywords: Molybdenum cofactor deficiency, cleft palate, newborn

ÖZ

Molibdenum Kofaktör Eksikliği (MoCD), nadir ve ciddi klinik bulgularla seyreden, otozomal resesif kalıtılan doğumsal bir metabolik hastalıktır. Klinik olarak letarji, hipotoni ve nöbetler gibi nörolojik bulgular gözlenir. Klinik bulgular doğumdan hemen sonra veya günler içinde ortaya çıkabilir. Nörolojik bulguların doğumdan hemen sonra görülebildiği ve acil tedavi gerektiren hipoksik-iskemik ensefalopatiden (HİE) hızla ayırt edilmesi gereklidir. Bu çalışmada, doğumdan hemen sonra HİE benzeri klinik bulgular gösteren ve laboratuvar ile beyin manyetik rezonans görüntüleme (MRI) yardımıyla hızla MoCD tanısı konulan hastamızı sunuyoruz. Takip sürecinde, hastamızda tanı, genetik olarak az sayıda vakada tanımlanan Molybdenum kofaktör sentezi 2 (MOCS2) Tip B (c.226G>A, (p.G76R) (p.Gly76Arg) mutasyonu) ile doğrulandı. Ek olarak, vakamız, MoCD'ye yarık damak eşlik eden ilk vaka olmasıyla dikkat çekmektedir. Bu vakayı sunmaktaki amacımız, doğumdan hemen sonra neonatal ensefalopatiye neden olan durumların ayırt edilmesinin önemini vurgulamak ve hipoksik-iskemik ensefalopati tanısının hatalı konulması nedeniyle uygunsuz şekilde terapötik hipotermi tedavisi verilmemesi gerektiğini belirtmektir.

Anahtar Kelimeler: Molibden kofaktör eksikliği, yarık damak, yenidoğan

INTRODUCTION

Although the incidence of Molybdenum Cofactor Deficiency (MoCD) is 1 in 100,000–500,000 live births, approximately 200 cases have been reported to date. MoCD occurs as a result of a congenital genetic metabolic error caused by deficiency of sulfite oxidase, xanthine dehydrogenase, and aldehyde oxidase, which are enzymes dependent on molybdenum cofactor. Mutations in the autosomal recessive MoCD, Molybdenum Cofactor Synthesis 1 (MOCS1, Type A), molybdenum cofactor synthesis 2 (MOCS2, Type B), gephyrin (GPHN, Type C), and molybdenum cofactor synthesis 3 (MOCS3) genes have been previously described. Approximately 75% of the cases are MOCS1, and the rest are genetic mutations (1,2).

Sulfite, xanthine, and hypoxanthine accumulate in the body of MoCDs. This causes neuronal damage, particularly in the brain. Therefore, it may clinically present with neonatal encephalopathy such as hypo- or hypertonia, malnutrition, lethargy, seizures, and neurological deficits after birth. It may be accompanied by microcephaly or macrocephaly, lens dislocation, spherophakia, and nystagmus. Neurodegeneration with severe consequences can develop rapidly within a few days or months of clinical follow-up, ultimately leading to fatal outcomes (2,3). Brain magnetic resonance images (MRI) of patients show typical diffuse cerebral edema, cortical necrosis and atrophy, gliosis, cessation of myelination development, inactive areas affecting the white matter, basal ganglia, and cortex, and multicystic encephalomalacia (2-4).

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Our patient was born with neonatal encephalopathy including decreased neonatal reflexes, hypotonia, and lethargy. In our patient, who did not have an antenatal diagnosis, hypoxic-ischemic encephalopathy (HIE) was considered as the most likely preliminary diagnosis. Postnatal dysmorphic findings supported the diagnosis of MoCD after a low serum uric acid level in the first laboratory test. Our patient was diagnosed with MoCD on the basis of other laboratory and cranial MRI findings. Subsequently, the genetic diagnosis of MoCD Type B was confirmed. Thus, appropriate treatment for MoCD was initiated early without applying therapeutic hypothermia, which is not appropriate for MoCD.

We emphasize the urgent need to distinguish between the neonatal case we present here and patients with similar neonatal encephalopathy, such as HIE and MoCD. We also aimed to present the first case from our country with the c.226G>A mutation in exon 4 and the association between MoCD and cleft palate.

CASE

Our patient was born vaginally at 37 weeks as a 3170 g (50-75 percentile) male baby, the third of her 27-year-old mother's 5th pregnancy. The 1st minute Apgar score was 4 and the 5th minute Apgar score was 7. His birth head circumference was 35 cm (75-90 percentile) and height was 50 cm (50-75 percentile). Positive-pressure ventilation was applied once for 30 seconds to the patient with apnea in the delivery room. In our patient's family history, it was learned that the mother and father were 1st degree cousins, and that the mother had no pregnancy follow-up. The family asserted that no genetic, neurological, or metabolic disorders were present within the family.

In the physical examination of the patient, inadequate respiration, decrease in muscle tone and neonatal reflexes (sucking, searching, catching and Moro), plump cheeks, broad nasal bridge, long philtrum, dysmorphic facial appearance, and cleft palate were detected as pathological examination findings. The other systemic examination findings were normal. The patient was started on respiratory support with nasal continuous positive airway pressure (nCPAP) and free-flow oxygen due to respiratory distress. Our patient was admitted to the neonatal intensive care unit with a preliminary diagnosis of syndromic infant, neonatal encephalopathy, and HIE.

Because he was hypotonic at birth and his Apgar score was low, HIE, which is the most common cause of neonatal encephalopathy, was considered as a preliminary diagnosis. However, in the patient's umbilical cord blood gas, pH: 7.30, partial carbon dioxide pressure (pCO2): 51 mmHg, bicarbonate (HCO3): 21 mmol/L, bass deficit (Bd): -4.4 mmol/L and lactate: 3.9 mmol/L. Based on the

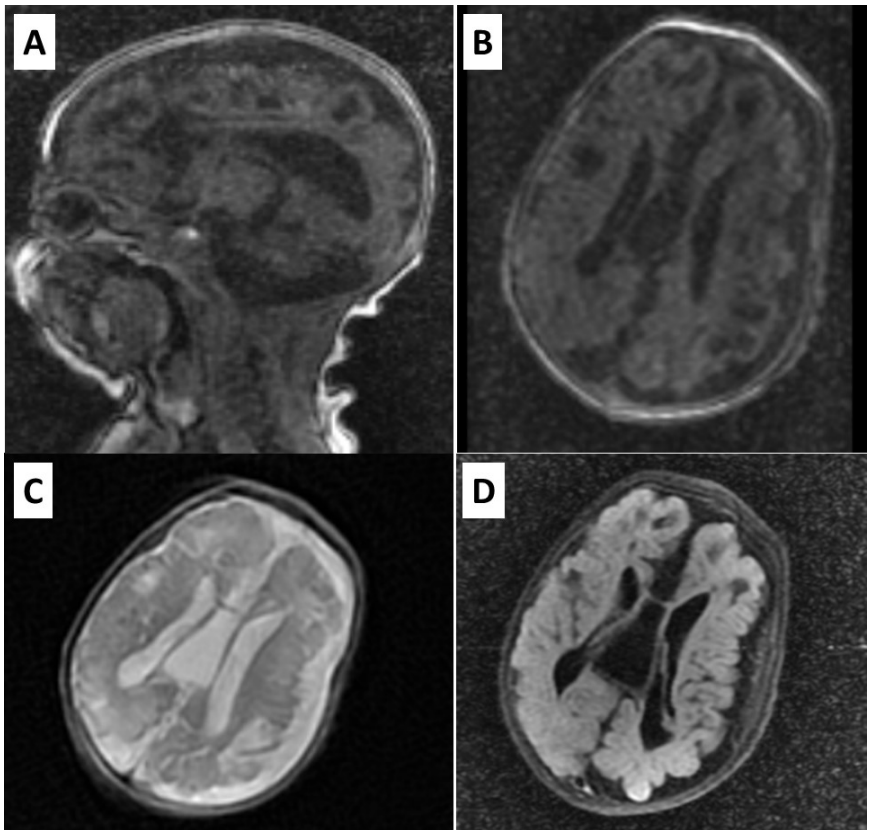

Figure 1. A and B: millimetric cystic encephalomalacia and cortical atrophy on non-contrast magnetic resonance, C and D: widespread cortical diffusion restriction on diffusion magnetic resonance

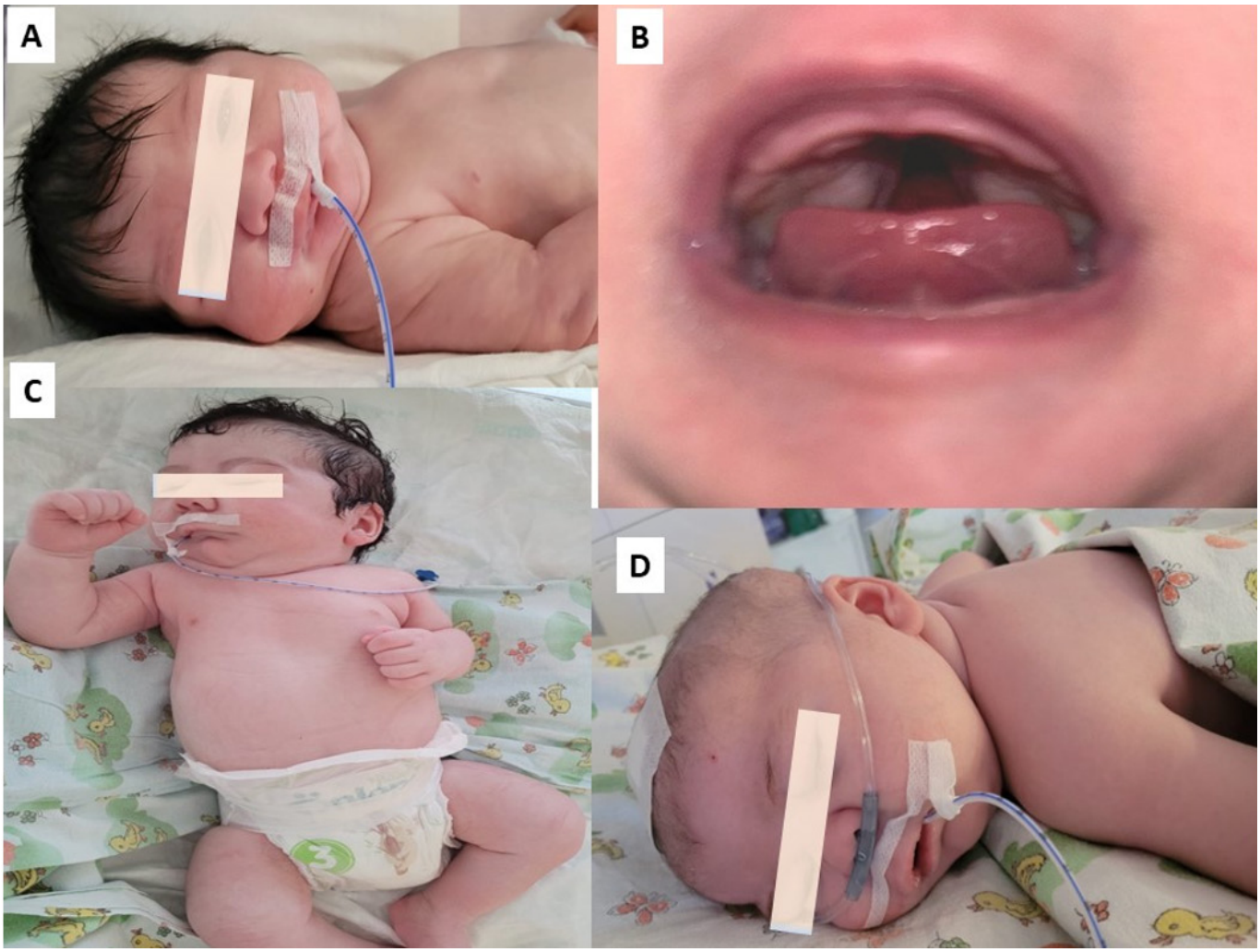

Figure 2. A: postnatal photo of the patient, B: cleft palate photo, C: photo at the 6th postnatal month, D: photo at the 10th postnatal month

blood gas results, a diagnosis of HIE was considered suspicious. Considering other laboratory findings, the complete blood count, blood sugar, and kidney and liver function tests were within the normal limits for a newborn baby. In addition, MoCD was suspected because the uric acid value was determined to be 0.1 mg/dL (2.2-11), thus was well below the normal reference values, as well as its dysmorphic appearance and accompanying neurological findings. The homocysteine level was 0.4 µmol/L (5-15) and was found to be low. A positive sulfite test, high urine S-sulfocysteine and xanthine levels, low cystine levels in the blood and urine, and low urine uric acid and taurine levels confirmed a diagnosis of MoCD.

Brain MRI of patient was revealed corpus callosum agenesis, dilated lateral ventricles, increased frontotemporoparietal subarachnoid cerebrospinal (CSF) distances, widespread cortical diffusion restriction, diffuse millimetric cystic encephalomalacia at the interventricular level and in both cerebral hemispheres, cortical atrophy, and hyperintense signal changes. Hemorrhagic deposits and laminar necrosis were also observed. Levels in the basal ganglia, internal capsule, thalamus, cerebellum, mesencephalon, and pons were normal, and these findings were compatible with MoCD (Figure 1). On electroencephalography (EEG), the background activity was evaluated as a focal paroxysmal disorder with 4-5 Hz theta waves, 3-4 Hz delta waves, and sharp wave discharges. The patient's preliminary diagnosis of MoCD was confirmed using cranial MRI and EEG.

Our patient's Apgar scores and laboratory findings were not compatible with HIE (5). Within the first 6 h after birth, the diagnosis of HIE was excluded using clinical, laboratory, and imaging methods, and our patient was diagnosed with MoCD. Since the patient's results were compatible with MoCD, therapeutic hypothermia treatment was not initiated. The genetic test performed for the diagnosis of MoCD detected a homozygous single nucleotide change NM_004531.5: c.226G>A, (p.G76R) (p.Gly76Arg) in exon4 of the MOCS2 gene. The diagnosis of MoCD Type B was confirmed and pyridoxine therapy was initiated.

Our patient, who was examined for other systemic findings of MoCD, showed normal echocardiographic, abdominal ultrasonography, and eye examination findings. During clinical follow-up, antiepileptic treatment was initiated for resistant myoclonic seizures on the first postnatal day. During follow-up, the patient required triple antiepileptic treatment for refractory seizures. The patient's respiratory support was provided in the form of free-flow oxygen and nCPAP according to her needs until the 11th postnatal month. The patient was fed via an orogastric tube due to sucking dysfunction. During postnatal follow-up, while weight and height development were appropriate for age, head circumference remained constant at 35 cm and no growth was achieved. During the follow-up period, serious neurodevelopmental delay was detected according to age. As our patient had no seizures during follow-up, seizure control was achieved with a single antiepileptic treatment. Images of our patient at birth, at 6th month, and 10th month were shown in Figure 2. Our patient died in the 11th postnatal month because of clinical deterioration characterized by severe bradycardia and desaturation unresponsive to treatment while he was receiving respiratory support treatment with a mechanical ventilator due to lower respiratory tract infection.

DISCUSSION

There are four main molybdoenzymes: sulfite oxidase, xanthine oxidase, aldehyde oxidase, and a mitochondrial amidoxime-reducing component. As a result of deficiency in these enzymes, MoCD develops, and sulfite accumulation occurs in the body (2,3,6). Sulfites cause cellular damage by reacting with lipids and proteins to form radicals that damage nucleic acids and attack disulfide bonds. Sulfites disrupt the tricarboxylic acid cycle in the mitochondria, causing adenosine triphosphate (ATP) loss and magnesium release. It causes excitotoxic neuronal damage by increasing intracellular calcium and magnesium levels due to the excessive production of sulfur-containing amino acids (e.g., S-sulfocysteine) and excessive activation of the N-methyl-D-aspartate (NMDA) receptor. As a result of neuronal damage, seizures and neurodevelopmental delay occur clinically (2,6,7).

The vast majority of patients with MoCD (75%) harbor MOCS1 mutations, while the remaining portion (25%) harbor mutations in MOCS2, GEPH, or MOCS3, with the latter being the least likely (3,7). Mutations in MoCD2 are autosomal recessive, and extremely rare. Patients with MOCS2 mutations may exhibit two different forms: the early type, which presents with symptoms in the neonatal period, and the late type, which has a later onset. The number of early-onset cases reported is very low (2,6,8). In the early onset form of MoCD, there are severe encephalopathy symptoms, such as refractory seizures, hyper/hypotonia, apnea, and feeding difficulties, that begin in the first days of life. The patients had narrow bifrontal diameters, micro/macro cephalad, long faces, elongated palpebral fissures, lens dislocation, widely spaced eyes, small nose, asymmetric skull, prominent forehead, deep-set eyes, broad nasal bridge, long philtrum, and thick plump cheeks. Facial dysmorphism, such as lip dysmorphism, can be detected (1,6). It can be confused with HIE, especially postnatal neonatal encephalopathy, as observed in our patient. Having dysmorphic findings is a warning for clinician (6,8). Some dysmorphic findings previously described for MoCD were observed in our patient. However, cleft palate association in our patient has not been previously described in MoCD. Patients with late-onset MoCD generally exhibit mild symptoms (6). Antenatal diagnoses are not commonly performed and the follow-up process is often devastating, ultimately leading to patient death. However, enzyme activity in chorionic villus samples and sulfocysteine levels in amniotic fluid are sometimes used to diagnose conditions during pregnancy. DNA analysis is also used to confirm the diagnosis (1,6,8).

To ensure an accurate diagnosis of MoCD, it is crucial for the clinic to collaborate with the laboratory. The first diagnostic test is typically a biochemical test to detect low uric acid levels. Additionally, low serum homocysteine levels, a positive sulfite test, elevated S-sulfocysteine and xanthine levels in the urine, and low cystine levels in both the blood and urine can support the diagnosis of MoCD. Furthermore, low uric acid and taurine levels in the urine may also indicate the presence of the disorder. Serum uric acid levels should be evaluated for the differential diagnosis of HIE and MoCD in patients with neonatal encephalopathy, as in our patient. In the presence of low uric acid, the diagnosis of MoCD should be suspected (1,4,8).

Cranial MRI is the preferred imaging method for the diagnosis of MoCD and typically shows MRI findings. Early brain MRI revealed cerebral hemispheres, basal ganglia, thalamus, globus pallidus, cerebral peduncles in the midbrain, corpus callosum thinness or absence, cortical atrophy, thalamic and subthalamic diffuse brain edema, diffuse diffusion restriction, hyperintense signal changes, cystic encephalomalacia, and atrophy in the cortex and white matter. These images, similar to HIE, include curvilinear areas with reduced signal intensity at the gray/white matter junction, hemorrhagic deposits and laminar necrosis, which are more specific findings for MoCD (2,6,7,9). In HIE, diffusion restriction occurs in the deep cortical regions, whereas in MoCD, it is more common in the cerebral cortex and is a supportive finding for the diagnosis of MoCD. While MRI images can be detected even in the early stages in MoCD, MRI findings in HIE can be seen in the later days (2,4,10). In our patient, the diagnosis of HIE was excluded and the diagnosis of MoCD was supported by the corpus callosum,

cortical atrophy, cystic encephalomalacia, and diffuse diffusion restriction in the cortex on cranial MRI. In addition to the typical MRI findings, the diagnosis of MoCD was confirmed in our patient using clinical and biochemical tests and genetic analysis. As in our case, the distinction between HIE and other congenital metabolic diseases should be made immediately after birth to differentiate neonatal encephalopathy. Especially in cases of accompanying dysmorphic findings in patients with neonatal encephalopathy, MoCD is considered and uric acid levels provide diagnostic guidance. Although patients with MoCD seem rare, as in our case, HIE overlap may occur. Therefore, rapid differentiation of neonatal encephalopathy can prevent incorrect diagnosis of HIE (6,7). The treatment and prognosis of HIE and MoCD are completely different from each other. In addition, a diagnostic distinction between HIE and MoCD should be made, and therapeutic hypothermia treatment for HIE should be initiated within the first six hours after birth.

In recent years, minimal improvements in clinical and laboratory findings have been observed with dietary sulfur-containing amino acid restriction, cyclic pyranopiterine monophosphate (cPMP), an NMDA receptor antagonist MK801, treatment in only a small number of patients with MOCS1 mutations, and molybdate treatment in patients with GPHN mutations (2,4). However, its positive effects on cranial injuries have not been determined (2,9). Therefore, there is currently no definitive treatment for patients (4,9). In patients with MOCS2 mutations, pyridoxine treatment may help to reduce some symptoms (2,9). It may have been possible with pyridoxine treatment to reduce antiepileptic treatment for seizure control in our patient and to avoid the need for mechanical ventilation and respiratory support in most of his life. Neurodevelopmental retardation in our patient demonstrates that the effect of pyridoxine on the central nervous system and neurological findings is limited (2,9). The primary objective of MoCD is to manage complications effectively through early comprehensive supportive care. The severity of cerebral lesions established prior to initiating treatment significantly influenced patient outcomes. Although therapy improves life expectancy, sadly, many patients still pass away in their infancy (2,6,7).

Approximately 30 patients with MOCS mutations and MoCD type B have been previously described (8). To date, mutations in exon 4 (c.226G>A) have been identified in 4 patients of Asian origin. However, no MoCD patient with a mutation in Type B exon 4 (c.226G>A) has been previously described in our country. This is the 5th case in the world and the first case from our country with a mutation in exon 4 (c.226G>A). In addition, cleft palate in our patient has not been previously reported among the dysmorphic findings of MoCD. The association between cleft palate and MoCD may be a new component of the MoCD clinical complex.

CONCLUSION

Newborns with neonatal encephalopathy may exhibit symptoms, such as neonatal seizures and feeding difficulties, which may serve as the first signs of MoCD. Serum uric acid levels should be measured to differentiate MoCD and HIE in newborns. Moreover, dysmorphic findings, laboratory tests supporting the diagnosis of MoCD, and typical cranial MRI findings should be considered within six postnatal hours to avoid inappropriate treatment. Therefore, it is crucial to genetically support MoCD diagnosis. In our patient, we identified a rarely identified MOCS2 type B homozygous mutation and presented an association between MoCD and cleft palate for the first time. Although there is no effective treatment for MOCS2 patients, early diagnosis and genetic analysis can facilitate adequate genetic counseling.

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