METHEMOGLOBINEMIA WITH NEUROLOGICAL MANIFESTATIONS: A CASE OF RECESSIVE CONGENITAL METHEMOGLOBINEMIA TYPE II

NÖROLOJİK BULGULARLA BİRLİKTE OLAN METHEMOGLOBİNEMİ: TİP II KONJENİTAL RESESİF METHEMOGLOBİNEMİ OLGUSU

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ABSTRACT

Congenital methemoglobinemia is a rare cause of cyanosis that is characterized by increased methemoglobin levels and caused by mutations in the cytochrome B5 reductase 3 (CYB5R3) gene resulting in deficiencies of the nicotinamide adenine dinucleotide-cytochrome b5 reductase enzyme. The congenital disease has two types: type I, in which the enzyme deficiency occurs only in the erythrocytes, and type II, in which all tissues are affected. Accordingly, cyanosis is the sole clinical manifestation in type I, whereas cyanosis is accompanied by such severe neurological findings as intellectual disability, microcephaly, generalized dystonia, and movement disorders. In this study, a case who presented with respiratory distress was found to have high methemoglobin levels and was diagnosed with type II congenital methemoglobinemia due to the presence of neurological findings was presented. The patient’s treatment was adjusted, the methemoglobin level was reduced, and cyanosis regressed, but no change was observed in neurological findings. This untreatable, rare condition must be included in the differential diagnosis of patients with unexplained cyanosis and high methemoglobin levels, and genetic counseling must be provided to the family, because of its severity and 25% recurrence rate.

Keywords: Methemoglobinemia, congenital, cyanosis, neurological development

ÖZET

Konjenital methemoglobinemi, methemoglobin düzeyinde artış seyreden, nadir siyanoz sebeplerindendir. Hastalıktan sorumlu olan nikotinamid adenin dinükleotit sitokrom b5 reduktaz enzimi eksikliğine sebep olan sitokrom B5 reduktaz 3 (CYB5R3) gen mutasyonlarıdır. Konjenital hastalığın iki tipi vardır; tip I’de sadece eritrositlerde enzim eksikliği görülürken, tip II’de tüm dokular etkilendir. Buna bağlı olarak tip I’de siyanoz görülen tek klinik bulğu iken tip II’de hafif siyanoz yanında bilisel yetersizlik, mikrosefali, jeneralize distoni, hareket bozuklukları gibi ciddi nörolojik bulgular eşlik eder. Bu çalışmada, solunum sıkıntısı yakıncısı ile başvuran, methemoglobin düzeyi yüksek saptanan, nörolojik bulguların eşlik etmesi sebebe ile tip II konjenital methemoglobinemi tanıtılan hasta sunuldu. Hastanın tedavisi düzenlendi, methemoglobin düzeyi düşürüldü, siyanoz geriledi, ancak nörolojik bulgulara değişiklik görülmüsti. Tedavi olmanın bu nadir hastağın, açıklanamayan siyanoz olup methemoglobin düzeyi yüksek saptanan hastaların aynu tanıları arasında yer almaları ve hastalığın şiddetini ve %25 nüks oranı nedeniyle aileye genetik danışmanlık verilmelidir.

Anahtar Kelimeler: Methemoglobinemi, konjenital, siyanoz, nörolojik gelişim

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INTRODUCTION

Methemoglobinemia is a rare condition characterized by elevated methemoglobin (metHb) levels in the blood. Under normal conditions, a small amount of metHb is produced in the erythrocytes upon exposure to various free radicals, and the nicotinamide adenine dinucleotide-cytochrome b5 reductase (NADH-CYB5R) enzyme plays a protective role by reducing 99% of the metHb to hemoglobin A, thus maintaining a metHb level of 1–2%. If this protective mechanism is impaired, the metHb level increases. The reason for metHb level increase can be congenital, resulting from enzyme deficiency; or acquired, such as through exposure to various chemicals (1-3). The congenital form that is inherited in an autosomal recessive fashion has two types: in type I, NADH-CYB5R enzyme deficiencies occur only in the erythrocytes; while in type II, all tissues are affected. The disease can be attributed to mutations on the 22q13 gene chromosome. Clinical manifestations vary depending on the metHb level. Although cyanosis is the only clinical manifestation in recessive congenital methemoglobinemia (RCM) type I, which is the benign form of the condition; RCM type II presents with cyanosis accompanied by neurological findings (1,3,4). Due to the rarity of the disease, it may not be considered in differential diagnoses of patients with cyanosis. The current report presents a patient with RCM type II which presented with respiratory distress.

The patient’s guardian provided informed consent.

CASE PRESENTATION

A 9-year-old female presented to our hospital with respiratory distress and involuntary movements. The patient was born to consanguineous parents (first-degree relatives) with no complications after a normal pregnancy. There was no remarkable family history. The patient had normal development in the first six months of life but then encountered delays in reaching developmental milestones and growth retardation. She developed microcephaly (43 cm, < 3 percentile, -6.5 SDS) in the first year, while other anthropometric measurements remained within normal ranges. Psychomotor retardation had become prominent, and opisthotonus attacks and choreoathetotic movements had increased for the last two years. She had frequent fits of crying and prominent agitation. At age four she was making simple utterances and would smile at familiar faces. It was learned from the mother that she had episodes of cyanosis when she had a fever. During these periods, a slight increase in the methHb level was observed, but it was stated that this was not significant.

A physical examination revealed central cyanosis and neurological findings such as microcephaly, hypertonia in the trunk and extremities, hyperactive deep tendon reflexes, widespread dystonia that became prominent upon physical contact, intense choreoathetotic movements, growth retardation, intellectual disability and delay in speech development. A diagnosis of methemoglobinemia was first considered due to the observation of central cyanosis that was unresponsive to oxygen therapy, chocolate-colored blood (Figure 1), and metHb levels of 17–18.6% measured from an arterial blood gas analysis. No exposure to any toxic substances was detected. Cardiac and respiratory examinations revealed normal findings; chest X-ray and echocardiography showed normal findings; and cranial magnetic resonance imaging study revealed cerebral atrophy and ventricular dilation (Figure 2). Routine laboratory examinations and metabolic screening tests were normal. Electroencephalography was normal. A genetic analysis was conducted with a prediagnosis of RCM based on the clinical and laboratory findings, and revealed a homozygous pathogenic mutation in the CYB5R3 (c.489C>G) gene, as a result of which, the patient was diagnosed with RCM type II. The patient was placed on a treatment of ascorbic acid 500 mg/day and riboflavin 120 mg/day. Despite the improvement in the cyanosis and methHb level (5.3-6.5%), no change was observed in the neurological symptoms at the 3-6 months follow-up. The patient died six months after the diagnosis in a different center, where she applied with respiratory distress and was diagnosed with pneumonia. During this period, the patient continued her medication.

Figure 1: Arterial blood gas samples; A: Chocolate brown colored blood sample of the patient, B: Blood sample from a normal person
DISCUSSION

Methemoglobinemia refers to the abnormal elevation of metHb levels in the blood resulting from a defect in the pathways that maintain metHb within normal ranges. In this form of hemoglobin, ferrous iron is oxidized into a ferric form, leading to a decrease in the oxygen-carrying capacity of erythrocytes, and resulting in cyanosis and hypoxia (1). Clinical manifestations vary depending on the rate of increase in metHb levels and the half-life of the responsible agent in an acquired form. But in the congenital form, compensatory erythrocytosis occurs and a milder presentation is observed in response to chronic increases in metHb levels (5,6). RCM type I is a benign form of the condition in which the enzyme deficiency involves only erythrocytes, and cyanosis is the only clinical manifestation. Whereas in type II, enzyme deficiency occurs in all tissues, and the most distinctive feature is cyanosis accompanied by neurological impairment in those aged 6–9 months, resulting in death in the first years of life (7). Central cyanosis that is unresponsive to oxygen therapy and arterial blood that is darker than normal suggests the possible diagnosis, which can be supported by a measurement of metHb levels. The presence of neurological findings such as progressive intellectual disability, microcephaly, opisthotonus, athetotic movement, and generalized hypertonia accompanying methemoglobinemia suggests the diagnosis of RCM type II. Confirming the diagnosis is easy in the presence of methemoglobinemia with accompanying neurological findings, as was the case in our patient; although it may be more challenging to recognize the condition clinically in the early periods when neurological manifestations have not yet developed. For this reason, acquired factors must first be ruled out in a patient with methemoglobinemia, and the work-up should then proceed with genetic subtyping (3,7,8).

The homozygous mutation identified in our patient, c.489C>G, is one of a few identified mutations causing RCM type II. Up to 80 mutations have been identified in the CYB5R3 gene that are responsible for the condition; with the mutations that cause enzyme instability resulting in type I, and the mutations that cause enzyme inactivation resulting in the type II form (7-9).

There have been a few case reports presenting the cranial imaging findings of patients with RCM type II, brain atrophy was noted in our patient, similar to previously reported cases. The most commonly reported findings include brain atrophy, delayed myelination, and thinning of the corpus callosum, which are non-specific and have limited diagnostic contribution (3,4,9,10).

High-dose ascorbic acid (200–500 mg/day) therapy effectively reduces metHb levels in RCM, and it has been reported that riboflavin (120 mg/day) therapy is also effective in some cases. Methylene blue treatment can be used when the metHb level is very high or when the patient is severely symptomatic. Despite this therapy, patients have a poor prognosis, and the treatment has no effect on any neurological impairments that have already been acquired. Since the pathophysiology of the disease is unknown, the reason for the ineffectiveness of the treatment on neurological findings is also unknown (1,3,4).

CONCLUSION

Recessive congenital methemoglobinemia is a rare disease, with the type II form of the condition being particularly rare and seldom taken into consideration in the differential diagnoses. The condition must be remembered in the differential diagnosis of patients with methemoglobinemia if it is accompanied by neurological manifestations. Families must be provided with genetic counseling for this untreatable condition.

Informed Consent: The patient’s guardian provided informed consent.

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