



A Rare Cause of Hypoxemia: Hereditary Methemoglobinemia

Nadir bir Hipoksemi Sebebi; Herediter Methemoglobinemi

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Abstract

Hereditary methemoglobinemia is one of the rare causes of hypoxemia. Mutations in the CYB5R3 gene cause autosomal recessive hereditary methemoglobinemia. Mostly, symptoms such as shortness of breath, bruise and and fatigue occur. It may not display any symptoms until adult ages. Our case was at the age of 18 and had sometimes recurring bruise in hands and lips, shortness of breath, palpitations and oxygen saturation (SaO₂) was 85%. Methemoglobin (Methb) level was %20 (N;0-1.5) No cardiac or pulmonary cause could be detected, which could account for dyspnea and cyanosis, and due to low saturation and high Methb. levels, methemoglobinemia was considered and high dose IV ascorbic acid was administered. In follow up period, saturation increased and Methb. level gradually decreased and with genetic tests, homozygous missense c.136C>T (p.R46W) mutation was detected with CYB5R3 gene sequence analysis. Patient was diagnosed with autosomal recessive hereditary methemoglobinemia type 1. This case is presented in order to emphasize that hereditary methemoglobinemia should be kept in mind when shortness of breath, hypoxia and cyanosis, occur together and can not be attributed to pulmonary and cardiovascular causes.

Keywords: Hereditary methemoglobinemia, CYB5R3 gene mutation, hypoxemia, dyspnea, cyanosis

INTRODUCTION

Hereditary Methemoglobinemia, is one of the rare causes of hypoxemia. Methemoglobin (MetHb), is the non functional form of hemoglobin produced by transformation of ferrous (Fe⁺²) hemoglobin iron to ferric form (Fe⁺³) by oxidation. Methemoglobin can not transport oxygen and hence tissue hypoxia and cyanosis arises. In normal metabolism, due to erythrocyte enzyme systems (NADH-cytochrome b5 reductase and NADPH Methb reductase), MetHb level is kept

Öz

Herediter Methemoglobinemi hipokseminin nadir sebeplerinden biridir. CYB5R3 geninde oluşan mutasyonlar otozomal resesif herediter methemoglobinemiye neden olur. Çoğunlukla nefes darlığı, morarma, halsizlik gibi semptomlar görülebilir. Bazen erişkin yaşa kadar semptom vermeyebilir. Onsekiz yaşında ellerinde ve dudaklarında zaman zaman tekrarlayan morluk, nefes darlığı, çarpıntısı olan olgumuzun, pulseoksimetre ile ölçülen oksijen saturasyonu (SpO₂) %85 saptandı. Methemoglobin (Methb) düzeyi %20 (N;0-1,5) idi. Dispne ve siyanozu açıklayacak kardiyak ve pulmoner neden saptanmayan olguda saturasyonu düşüklüğü ve methb yüksekliği nedeniyle methemoglobinemi düşünülerek, yüksek doz intravenöz askorbik asit verildi. Saturasyonu yükselen ve methb düzeyi tedricen düşen hastanın takiplerinde genetik testler sonucunda CYB5R3 geni sekans analizi ile homozigot missense c.136C>T (p.R46W) mutasyonu saptandı. Hasta otozomal resesif herediter methemoglobinemi tip 1 olarak kabul edildi. Pulmoner ve kardiyovasküler nedenlerle açıklanamayan nefes darlığı, hipoksi, siyanoz birlikteliğinde nadir görülen herediter methemoglobineminin akla gelmesi gerektiğini vurgulamak için bu vakamızı sunuyoruz.

Anahtar kelimeler: Herediter methemoglobinemi, CYB5R3 gen mutasyonu, hipoksemi, dispne, siyanoz

under 1%. Congenital deficiency or acquired impairment of these systems lead to Methemoglobinemia, which may be innate or acquired.^[1]

Hereditary methemoglobinemia is a rarely occurring disease all over the world and its prevalence and incidence is unknown. Hereditary methemoglobinemias may not exhibit any symptoms until adult ages.^[2] The CYB5R3 gene, located in the chromosome 22q13.2 region, is involved in



the synthesis of the enzyme named Nicotinamide-adenine dinucleotide (NADH) -cytochrome b5 reductase.^[3,4] The CYB5R3 gene, which consists of nine exons, is 32 kb in size.^[5] There are two known isoforms of (NADH) -cytochrome b5 reductase enzyme, the membrane-bound form found in all somatic cells, and the soluble form found only in erythrocytes. Its membrane-bound form functions in the elongation and desaturation of fatty acids, cholesterol biosynthesis, and the metabolism of various molecules and drugs. The soluble form found in erythrocytes takes place in the electron transport system to reduce methemoglobin to functional hemoglobin.^[6] Mutations in the CYB5R3 gene cause autosomal recessive congenital methemoglobinemia.^[7] There are two different phenotypes of the disease, type 1 and type 2, depending on the functional change caused by the mutation in gene function. CYB5R3 gene mutations that cause autosomal recessive congenital methemoglobinemia type 1 typically decrease enzyme activity or stability, and the only finding observed in the sick individual is cyanosis.^[7] Ferric iron (Fe³⁺) cannot be converted effectively to ferrous iron (Fe²⁺), which causes an increase in the erythrocyte's methemoglobin. Autosomal recessive congenital methemoglobinemia type 2 occurs if the mutation in the CYB5R3 gene leads to a complete loss of function in the enzyme, resulting in a more severe clinical picture.^[8-11]

This case is presented to emphasize that hereditary methemoglobinemia, which is one of the rare causes of hypoxemia, should be borne in mind in cases presenting with dyspnea, cyanosis and hypoxemia.

CASE

An 18 year old female patient presented with the symptoms of bruise in lips and hands and dyspnea. In history, it was learned that she had recurrent bruise in the past and underwent investigation a few times for this reason since childhood, but the cause could not be found. Patient did not receive any drug or anesthetic before admission for any reason. In physical examination, cyanosis was detected in finger tips and lips and respiratory system examination were normal. In cardiovascular system examination, tachycardia was observed (120/min). In ambient air, with pulse oximeter, oxygen saturation was found to be (SpO₂)%85. Hematological and biochemical parameters were unremarkable. Lung graphy and respiratory function tests were normal.

In arterial blood gas, partial oxygen pressure (PaO₂) was 99 mmHg, SaO₂ % 96 and Methemoglobin (Methb) level %20 (N;0-1.5). Saturation gap was % 11 (N<%5) In investigations carried out for pulmonary embolism, no pathology was found. Echocardiography results were also normal. No pulmonary or cardiological pathology was detected and peripheral blood smear and hemoglobin electrophoresis yielded normal results as well. Since there was no cause which could explain hypoxia and cyanosis and methHb level was high, methemoglobinemia was considered. Patient was administered high dose IV Vitamin

C (3×500mg). This dose was repeated a few times. Subsequent to treatment, cyanosis improved and level of methemoglobin gradually decreased. Pulse oxygen saturation increased to 93%. As a result of the genetic examinations of the patient, homozygous missense c.136C> T (p.R46W) mutation was detected with CYB5R3 gene sequence analysis. The mutation was in the exon 2 region of the gene, resulting in the placement of the positively charged arginine amino acid at codon 46 with the non-polar neutral amino acid tryptophan. The detected variant was evaluated as pathogenic in analysis using public in silico prediction tools such as Mutation Taster and Varsome.

Patient was considered as autosomal recessive hereditary methemoglobinemia type 1 in view of recurrent cyanosis, absence of drug or anesthetic substance use, high Methb level and the presence of mutation in cytochrome b5 reductase (CYB5R3) gene (c.136C>p.R46W) and mild to moderate clinical picture. There is consanguinity in our patient's parents. In the segregation analysis, heterozygous mutations were detected in the same region in both parents of the patient. The absence of any findings related to the disease in the mother and father was found to be compatible with the heterozygous situation. There is no known individual with a history of similar disease in the patient's pedigree. According to the autosomal recessive inheritance pattern, the patient and her family were given genetic counseling, and the patient was informed about the 25% risk of affecting each sibling, 50% risk of being an asymptomatic carrier, and 25% healthy.

DISCUSSION

Hereditary methemoglobinemia diagnosis is made with deficiency of cytochrome b5 reductase enzyme or presence of M hemoglobins. Cytochrome b5 reductase gene is located on chromosome 22. To date, 43 different cytochrome B5 reductase gene mutations have been described. Cytochrome b5 reductase enzyme deficiency Type 1 is the most common one.^[12] In this patient group, solely enzyme deficiency is present in erythrocytes. Depending upon methemoglobin level, at times, fatigue and dyspnea and cyanosis occur. Blood MethHb level is under 1% in normal conditions. When MethHb level increases over 1.5 g/dl, cyanosis starts to appear and becomes marked when MethHb level reaches 10%. Unless MethHb level rises over %25-40 or cardiopulmonary dysfunction is present, normal life can be expected in this group. However, in Type 2, enzyme deficiency is present in many tissues such as liver, fibroblast and brain in addition to erythrocytes. Neurological syndrome encompassing severe mental retardation, growth delay, opisthotonus and generalized symptoms is encountered. Clinical picture is quite severe.^[13,14]

It has been demonstrated that many agents cause acquired methemoglobinemia. The most common causes are sulphonamides, local anesthetic drugs and nitrate containing vegetables. Acquired methemoglobinemia may have a more severe clinical course than hereditary one.^[12] While

It has been demonstrated that many agents cause acquired methemoglobinemia. The most common causes are sulphonamides, local anesthetic drugs and nitrate containing vegetables. Acquired methemoglobinemia may have a more severe clinical course than hereditary one.^[12] While

no symptoms and signs may be observed in mild cases, in severe cases, cyanosis, tachypnea, tachycardia, hypotension, confusion and even death may occur.^[13]

In hereditary methemoglobinemia, diagnosis is made based on the appearance of cyanosis, which does not have a respiratory or cardiovascular background and does not respond to oxygen treatment. Recurrent cyanosis and presence of family history suggests hereditary methemoglobinemia, whilst methemoglobinemia produced by drug and chemical substances suggests acquired form. In spite of cyanosis, arterial blood oxygen pressure is within normal range. Oxygen saturation may be low. Definitive diagnosis is made with the measurement of blood level and demonstration of deficiency in cytochrome B5 reductase enzyme. Type 1 enzyme deficiency is in merely erythrocytes, while in type 2, it is in both erythrocytes and leukocytes.^[15] At present, there is no cure for hereditary methemoglobinemia. These patients should avoid oxidizing drugs. For cosmetic defects, (blue skin), treatment with ascorbic acid (300-500mg/day), methylene blue (100-30 mg/day and riboflavin (60-120 mg/day) is recommended.^[15]

In our patient, dyspnea, cyanosis and hypoxemia, which did not improve despite oxygen treatment, were present. In view of low saturation, high methemoglobin levels and the presence of mutation in cytochrome b5 reductase (CYB5R3) gene and the response to Vitamin C, hereditary methemoglobinemia type 1 enzyme deficiency was considered. Patient was recommended to avoid oxidizing drugs.

CONCLUSION

In the combination of dyspnea, hypoxia and cyanosis, which can not be explained by respiratory and cardiovascular causes, autosomal recessive hereditary methemoglobinemia type 1, which is a rare entity, should be kept in mind.

ETHICAL CONSIDERATIONS

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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