

A rare cause of mental motor retardation: recessive congenital methemoglobinemia type II

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Recessive congenital methemoglobinemia (RCM) is a very rare disorder caused by NADH- cytochrome b5 reductase (cytb5r) deficiency. It has been classified into four types. Type I presents with mild cyanosis due to a significant deficiency of cytb5r in erythrocytes only. In type II, the deficiency occurs in all tissues and causes growth and mental retardation and other neurological impairments. RCM types I and II are caused by a defect in a single gene, which is located on chromosome 22 (locus DIA 1: q 13.31-qter). Prenatal diagnosis is possible. Cyanosis can be well treated by 200-500 mg of ascorbic acid daily; there is no effective therapy for the progressive neurological impairments. This report presents two siblings with central cyanosis, growth retardation, mental retardation, microcephaly, dystonia and hypertonia diagnosed as RCM type II.

Key words: recessive congenital methemoglobinemia, mental motor retardation, cyanosis.

Methemoglobin, which is the oxidized form of hemoglobin (Fe^{3+}) and measures <1% in the blood of healthy individuals, is normally reduced to active hemoglobin by NADH-cytochrome b5 reductase and cytochrome b5¹. NADH-cytochrome b5 reductase (cytb5r) -variously named methemoglobin reductase or diaphorase- has been proven to be a component of the system. A deficiency in or structural abnormalities of this enzyme result in recessive congenital methemoglobinemia (RCM)². Two forms of this enzyme are known - a membrane-bound form found in microsomes of all investigated tissues and a soluble form that is present in red blood cells. In red blood cells, the soluble enzyme is involved in the reduction of methemoglobin, while in other cells the membrane-bound microsomal enzyme participates in the desaturation and elongation of fatty acids. Both isoforms are generated from the same gene³⁻⁵. RCM has been known since 1845 and Jaffe⁶ classified it into four types in 1986. Type I, due to a lack of erythrocyte cytb5r, leads to cyanosis and can be easily controlled with medical treatment. Type II, which shows reduced activity of both the soluble cytb5r in erythrocytes and the microsomal

cytb5r in various tissue such as leukocytes, muscle cells, fibroblasts, and brain cells, results in severe illness with severe progressive neurological involvement^{7,8}. Type III is due to hematopoietic cytb5r deficiency without neurological symptoms. Type IV, deficiency of cytochrome b5, is another rare cause of methemoglobinemia⁶. Types I and II methemoglobinemia are encoded by a single gene that is located on chromosome 22. Prenatal diagnosis is possible⁷. This report presents two siblings with central cyanosis, growth and mental retardation, microcephaly, dystonia, and generalized hypertonia, who were diagnosed as RCM type II.

Case Reports

Case 1

The boy was born at term as the first child of healthy consanguineous Turkish parents, who were first cousins. They lived in the Middle Black Sea zone. Central cyanosis was noted shortly after birth. In spite of persisting cyanosis and investigations, the diagnosis of RCM was not considered. At the age of two years, the patient was referred to our hospital

for diagnosis of severe mental motor retardation. The parents reported frequent vomiting and inability to lag head, sit, and crawl, grasp objects or talk. Physical examination revealed central cyanosis, marked growth and mental retardation, microcephaly (head circumference of 42 cm, below the 2nd percentile), micrognathia, retrognathia, high palate, short philtrum, generalized hypertonia, and dystonia triggered with touching.

Methemoglobin concentration was measured in arterial blood gas by oximetric method (OSM3 hemoximeter) (normal range: 0 to 0.028 g/dl). The patient's methemoglobin concentration was increased, at 1.3 g/dl (28%). The complete blood cell count findings were as follows: hemoglobin: 12 g/dl, white blood cell: 6600/mm³ and platelet count: 288000/mm³. Echocardiography revealed normal cardiac functions. There was no evidence of any abnormal hemoglobin by high-resolution electrophoresis, and glucose-6-phosphate dehydrogenase (G6PDH) deficiency was not found. Methemoglobin gene and enzyme analyses could not be performed due to parental refusal. Cranial magnetic resonance imaging (MRI) revealed cerebral atrophy, retarded myelinization, and thinning of diffuse corpus callosum. Treatment with ascorbic acid (500 mg daily) was started.

Case 2

The boy was born at term as the second child of the same parents. Central cyanosis was noted shortly after birth. In spite of persisting cyanosis and extensive investigations, the diagnosis of RCM was not considered. At the age of one year, the patient was referred to our hospital for diagnosis of severe mental motor retardation. The parents reported frequent vomiting and inability to lag head, sit, and crawl, grasp objects or talk. Physical examination revealed central cyanosis, marked growth and mental retardation, microcephaly (head circumference of 39 cm, below the 2nd percentile), strabismus, micrognathia, retrognathia, high palate, short philtrum, and generalized hypertonia.

Methemoglobin concentration was found highly elevated to 26% (1.1 g/dl). The complete blood cell count findings were as follows: hemoglobin: 13.3 g/dl, white blood cell: 7200/mm³ and platelet count: 331000/mm³. Echocardiography revealed normal cardiac functions. There was no evidence for the

presence of any abnormal hemoglobin by high-resolution electrophoresis, and G6PDH deficiency was not found. Methemoglobin gene and enzyme analyses could not be performed due to parental refusal. Cranial magnetic resonance imaging revealed cerebral atrophy, retarded myelinization, and thinning of diffuse corpus callosum. Treatment with ascorbic acid (500 mg daily) was started.

Discussion

In an infant with persisting cyanosis after birth but without cardiac or pulmonary disease, the diagnosis of methemoglobinemia can be made easily by measuring the concentration of methemoglobin in blood^{9,10}. Acquired forms of methemoglobinemia, G6PDH deficiency, and hemoglobinopathies should be ruled out.

The clinical history of our patients illustrates the signs and symptoms generally seen in RCM type II. Both our patients presented with cyanosis within hours after birth. Lack of normal increase in head circumference was one of the earliest signs for the distinction between RCM types I and II. Developmental delay became obvious at the early age of 3-4 months. The symptoms of the patients with methemoglobinemia type II are, in addition to cyanosis, severe mental retardation, microcephaly, growth retardation, opisthotonus, attacks of bilateral athetoid movements, strabismus, and generalized hypertonia-dystonic posture⁷⁻¹⁰. The progressive neurological signs, which become apparent before the age of one year, may be related to the major role of the membrane-bound form of NADH-cytb5r in desaturation and elongation of fatty acids and in cholesterol biosynthesis¹¹. Cytb5r takes part in the saturation of fatty acids such as oleic acid. This acid is one of the components of the myelin phospholipids. It is suggested that deficiency of cytb5r in brain microsomes may cause poor myelinization of the central nervous system and thus mental retardation⁶. The early microcephaly is due to the reduced amount of white matter. Both patients with prominent microcephaly had cortical atrophy and retarded myelinization on cranial MRI. Cyanosis can be well treated with 200-500 mg of ascorbic acid daily but there is no effective therapy for the progressive neurological problems. Consequently, patients with type II methemoglobinemia usually die at a young age.

Clinically, the visible cyanosis is well tolerated in type I and the only complaints may be headache, fatigue and dyspnea at exercise. Life expectancy in type I is normal. The molecular differences might very well lead to variations in stability or structure of the protein or other enzymatic characteristics, which explain the clinical differences between methemoglobinemia types I and II⁹.

With a recurrence risk of 25%, prenatal diagnosis of methemoglobinemia type II may be important to parents, especially after the birth of a previous child with methemoglobinemia type II. Analysis of NADH-cytb5r activity in cultured amniotic fluid cells has been described previously by Kaftory et al. in 1986⁷. Unfortunately, the family did not give permission for enzyme and genetic analysis although both siblings suffered from the same disease. Consequently, this report presents two siblings with central cyanosis, growth and mental retardation, microcephaly, dystonia and generalized hypertonia. Both clinical symptoms and the high methemoglobin level led us to the diagnosis of RCM type II.

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