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Congenital Methemoglobinemia : A rare cause of cyanosis in a newborn – A Case Report

KEYWORDS

E-resources, first MBBS students, learning process, Internet.

Dr.Lathiesh kumar

Post graduate in DM Neonatology, Institute of child health, Egmore, Chennai.

Dr.Mangalabharathi

Associate professor, Department of Neonatology, Institute of child health, Egmore, Chennai.

Dr.C.N.Kamalarathnam

Head of the department, Department of Neonatology, Institute of child health, Egmore, Chennai.

ABSTRACT Congenital methemoglobinemia is a rare genetic disorder and can be one of the important causes of cyanosis in the newborn. **Case characterisitics** - We herein present a newborn with central cyanosis in the first month of life in whom congenital methemoglobinemia was found to be the cause; and timely diagnosis and treatment with ascorbic acid helped to avoid life threatening situation. **Conclusion** – Even a rare cause such as congenital methemoglobinemia needs to be kept in mind while evaluating newborns for cyanosis, in order to provide timely diagnosis for early and effective management thereby avoiding complications.

Introduction:

Cyanosis is a physical finding that can occur at any age but presents the greatest challenge when it occurs in the newborn. The cause is multiple, and it usually represents an ominous sign, especially when it occurs in association with neonatal sepsis, cyanotic congenital heart disease, and airway abnormalities. Cyanosis caused by abnormal forms of hemoglobin can also be life-threatening, and early recognition is mandatory to prevent unnecessary investigations and delay in management.

Case report:

A 22days old term male neonate with birth weight 2550gm, product of spontaneous normal vaginal delivery with normal APGAR score at birth, presented with complaints of bluish gray discoloration of body since 13th day of life. There were no antenatal or perinatal complications. There was no history of usage of any medications and parental consanguinity was denied.

Central cyanosis was noted on physical examination. Pulse oximetry was 70% in room air and with fraction of inspired oxygen 1.0, it continued to remain 70%. All the other vital parameters were within the normal range and his Head to toe examination, Systemic examination and anthropometric measurements revealed no abnormalities.

Chest radiograph and Echocardiography were normal. Obtained arterial blood had a dark chocolate brown colored appearance, and blood gas analysis revealed normal levels, Serum methemoglobin level was 19.7%. There was no clinical or laboratory evidence suggestive of sepsis. Hemoglobin electrophoresis , Pyruvate kinase level and G6PD levels were normal.

Hemoglobin and hematocrit values were within the normal limits.

At this point, a deficiency of reduced nicotinamide adenine dinucleotide(NADH) – cytochrome b5 reductase was suspected, and whole blood samples of the infant and his parents were collected. The samples were analysed for cytochrome b5 reductase (methemoglobin reductase b) enzyme activity.The infant's enzyme activity level was 14.01 while the maternal and paternal enzyme activity levels were 26.5 and 28.15 respectively, as opposed to a normal range of 30 – 40 IU/g haemoglobin.

Hence a diagnosis of Congenital Methemoglobinemia (Type -1 cytochrome b5 reductase) was made and the infant was started on daily dose of 5mg/kg ascorbic acid orally and was asked to follow up after a month. A repeat Methemoglobin level on follow up showed a drop to 16.3%. No additional clinical manifestations of methemoglobinemia were noted.

Discussion:

Cyanosis is a physical finding of multiple causes that can occur at any age but poses the greatest diagnostic and management challenges when it involves the newborn infant. The clinical manifestation of cyanosis depends on the amount of reduced hemoglobin in the circulation. Approximately 5 g/dL reduced hemoglobin is required to produce the clinical manifestation of cyanosis in disorders involving deoxygenated hemoglobin. However, only 1.5 g/dL is required for disorders involving nonfunctional hemoglobin.[1]

The differential diagnosis of cyanosis therefore can be divided into 2 major groups: disorders involving deoxygenated hemoglobin and disorders of abnormal hemoglobin. The former and more common group can be further categorized on the basis of anatomic location of the disorder: the central nervous system and muscle, the upper airway, the lungs, the heart, and the circulatory system.[2]

Abnormal forms of hemoglobin such as methemoglobin can also cause cyanosis when present in significant amounts. Methemoglobinemia is an uncommon clinical problem in the newborn infant and when present is usually caused by environmental toxicity from strong oxidizing agents and only very rarely from an inherited disorder of hemoglobin metabolism.[3-6] Although an autosomal recessive form of methemoglobinemia was described in 1845, it is so rare that no known incidence and prevalence has been established.

Methemoglobin is produced from oxidation of ferrous iron (Fe2_) to ferric iron (Fe3_) within the hememoiety of hemoglobin.[7] Methemoglobin, which normally constitutes _1% of the total hemoglobin, cannot carry oxygen. Furthermore, as a consequence of allosteric interactions within the molecule, there is an increased affinity for oxygen at the remaining binding sites, causing a left shift in the oxygen dissociation curve.3 Both of these phenomena contribute to a reduction in the delivery of oxygen to tissues and, if severe enough, hypoxemia and lactic acidosis

In cases of congenital methemoglobinemia, cytochrome b5 reductase activity is diminished and there is a resultant decrease in the rate of methemoglobin reduction. The oxidant load under these circumstances is derived from endogenous sources.[8]

In 1845, Francois, a French physician, described a patient with enduring congenital cyanosis in the absence of any obvious cardiac

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or pulmonary dysfunction.[6] Although this was the first documented case of congenital methemoglobinemia in the professional literature, it was not until 1932 that Hitzenberger recognized idiopathic cyanosis to be a familial ailment.[9]

In the 1940s, Gibson [10,11] argued and subsequently showed that there was a diminution in the ability of the erythrocytes to reduce methemoglobin in such individuals.

Now generally referred to as NADH-cytochrome b5 reductase, a functional deficiency in this enzyme is universally recognized as the underlying cause of congenital methemoglobinemia.

Congenital methemoglobinemia is classified into two types. Type I shows Cytochrome b5 reductase deficiency, demonstrable only in the erythrocytes, presents as uncomplicated,benign methemoglobinemia, clinically seen as cyanosis. Whereas Type II shows generalized cytochrome b5 reductase deficiency, demonstrable in all tissues, is accompanied by severe, lethal and progressive neurological disability, in addition to methemoglobinemia.

Methylene blue is the treatment of choice for severe methemoglobinemia.[2,12] In the presence of nicotinamide adenine dinucleotide phosphate(NADPH), methylene blue is converted to leucomethyleneblue, which results in nonenzymatic reduction of methemoglobin.[2,13] Ascorbic acid directly reduces methemoglobin, but the rate of the reaction is too slow for it to be effective when used alone.[10] Finally, if the combination of ascorbic acid and methylene blue fails to reduce the methemoglobin level, then hyperbaric oxygen and exchange transfusions are alternative therapies.

Conclusion:

Congenital Methemoglobinemia, although rare, is still a very important cause of neonatal cyanosis and should always be considered and investigated early in order to avoid life threatening situations and delay in management.

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