Indian Journal of Medical Case Reports ISSN: 2319–3832(Online)
An Open Access, Online International Journal Available at http://www.cibtech.org/jcr.htm
2016 Vol.5 (4) October-December, pp. 12-17/Khade et al.

Case Report

NEONATAL CONGENITAL METHEMOGLOBINEMIA– A CASE REPORT

***Harshal Khade, Uma Raju, Tejas Deshmukh, Geethanjali Srivastav and Varun Kadiri**
NICE Hospital, 11-2-247/248, Shantinagar Colony, Masab Tank, Hyderabad, Telangana 500057
**Author for Correspondence*

ABSTRACT

A term, male neonate, product of a non-consanguineous marriage, was born to a 2nd gravida mother operatively. There were no known adverse antenatal influences. The baby was vigorous at birth but was visibly cyanosed and oxygen saturation was 70% in room air. There was no respiratory distress. The baby was provided with oxygen (FiO2-100%) which brought up SpO_2 to 80-85%. On examination in NICU, the baby was term gestation with anthropometric parameters within 50th-90th centile for age. The neonate had central and peripheral cyanosis with oxygen saturation of 70% in room air, which improved to 80-85% on high-flow oxygen with FiO2 100%. He was normotensive. Systemic examination was normal. Complete blood picture and routine biochemistry were unremarkable. Chest radiograph showed well expanded lungs and normal cardiac shadow. 2D-Echocardiography revealed a structurally normal heart with no evidence of pulmonary hypertension. In view of persistent cyanosis in the absence of significant pulmonary or cardiac disease, the rare possibility of an abnormality in haemoglobin structure was entertained. Laboratory assessment revealed serum methemoglobin levels were 5.8 gm/dl (Normal-1-3 gm/dl) and sulphmethemoglobin levels 0.8 gm/dl, suggestive of mild methemoglobinemia. G6PD screening revealed no deficiency. Detailed family history was non-contributory. Parental screening for methemoglobinemia was negative. Baby was treated with oral Vitamin C (5mg/kg 6th hourly) and could be weaned off to room air on 7th day of life. Baby is on oral daily ascorbic acid therapy with the advice to seek medical attention in case of occurrence of cyanosis. He is growing normally with no clinical cyanosis and SaO_2 in normal range. Congenital methemoglobinemia presenting in newborn period is rare, and associated with severe disease. The confounding features in this case is that though the methemoglobin levels were mildly deranged, the baby was significantly cyanosed and required treatment right from birth. This presentation of congenital methemoglobinemia is contrary to those cases reported so far and highlights the need to entertain a high degree of suspicion in cases of cyanosis at birth without significant cardiac or pulmonary issues.

Keywords: *Central Cyanosis, Congenital Methemoglobinemia, Co-oxymetry*

INTRODUCTION

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 usual causes of central cyanosis at birth are respiratory in origin, related to non-establishment of effective respiration. Less commonly, it is due to structural anomalies of the heart and lungs. Other causes of central cyanosis at birth are exceedingly rare. Cyanosis at birth can be related to 2 major groups of disorders viz. those involving deoxygenated hemoglobin and those of abnormal hemoglobin. The former is a common occurrence in the NICUs and is managed based on the system involved. The latter, which is abnormal forms of hemoglobin, is a rare occurrence and more often than not a diagnosis of exclusion.

We report an exceedingly uncommon cause of cyanosis in the early newborn period viz. Methemoglobinemia (MetHba). 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. The index case was likely to be due to an inherited disorder. The interesting feature was that the neonate had symptomatology which were out of preopertion to the levels of methemoglobin and needed medication to remain acyanotic which is an observation contrary to reported cases so far.

Case Report

CASES

A term male baby was delivered operatively by elective cesarean section at a city birthing center. He was vigorous at birth and required no resuscitation. Mother was a 2nd gravida with no known adverse antenatal influences. There was no family or past history of any major medical ailment in family. Mother was not provided with any drugs other than routine supplements during pregnancy. At birth, baby was vigorous with normal respiratory and heart rates. He was normotensive. Central and peripheral cyanosis was marked and the oxygen saturation in room air was 70%. The baby was comfortable with no respiratory distress and was provided oxygen by head box. However, he remained cyanotic and oxygen saturation was low. Hence, he was transferred to our centre for further care.

On admission at 4 hours of life, the baby was active and vigorous with quite respiration. His vital parameters were within normal limits. However, the baby had profound central cyanosis. Oxygen saturation in room air was 65-70%. Head to toe examination was normal and there were no dysmorphic features. Cardiac examination revealed no murmurs and was essentially normal. The chest radiography showed normal lung and cardiac shadows. Arterial blood gas analysis showed- pH-7.35, pCO2-34 mmHg, pO2-92 mmHg, HCO3-20 mEq/L on 100% oxygen. In view of the presence of central cyanosis and poor saturation in a baby who did not have respiratory distress, the differential diagnosis of cyanotic congenital heart disease, persistent pulmonary hypertension and polycythemia were entertained. 2D-Echocardiography was carried out which was normal and complete blood picture showed normal blood counts. The possibility of a rare form of hematological disorder was therefore entertained. Rapid bedside screening test of placing a drop of blood on filter paper showed a red colour with no change on exposure to oxygen.

Studies for methemoglobinemia revealed 5.8 gm/dl suggesting mild derangement and normal sulfmethemoglobin levels (0.8 gm/dl). G6PD screening excluded the deficiency. Parental methemoglobin screening was normal. This clinched the diagnosis of congenital methemoglobinemia, an exceedingly rare disorder.

Baby was provided oxygen therapy which marginally brought up the oxygen saturation to 85%. As the methemoglobin levels revealed mild disease, we did not provide methylene blue therapy. However, in view of onset of disease in early newborn period and to enable normal growth and development, we provided ascorbic acid therapy at 5mg/kg/dose four times per day. Over next week, baby showed gradual improvement in oxygen saturation, and oxygen could be weaned off. He was discharged on 9th day of life. On follow-up he was thriving well and maintaining oxygen saturation of 90% and is showing the normal growth and development.

Unusual feature about this index case was that although laboratory evaluation suggested mild methemoglobinemia, he was cyanotic and needed medication to maintain normal oxygen saturations and to enable normal growth and development.

DISCUSSION

Methemoglobinemia (MetHba) is a clinical syndrome caused by an increase in the blood levels of methemoglobin (MetHb). Being an exceedingly rare condition, incidence of this disorder in neonates has been rarely reported. It is mainly of two types, viz congenital and acquired. Congenital methb is a result of changes in hemoglobin (Hb) synthesis or metabolism; and acquired disease is due to exposure to several chemical agents which cause acute imbalances in reduction and oxidation reactions.

The molecule of Hb is a tetramer. The most common form of Hb in adults (HbA) consists of two α and β chains. Each Hb molecule has four atoms of iron ferrous iron (Fe^{+2}). Each ferrous iron can reversibly link one O_2 molecule, for a total of four molecules of O_2 transported by each Hb molecule. Methemoglobin, along with carboxyhemoglobin (COHb) and sulfhemoglobin (SHb), represents a dyshemoglobin (dysHb), i.e., a type of hemoglobin that does not bind O_2. Methemoglobin is the oxidized form of Hb, whose heme Fe^{+2} is oxidized to ferric iron (Fe^{+3}) and thus, cannot bind oxygen. Ferric iron also increases its O_2 affinity, thus causing shift of the dissociation curve of partially oxidized Hb to the left, hindering the release of O_2 in the tissues. Tissue hypoxia caused by MetHb is secondary to a reduction in free Hb to transport O_2

(relative anemia) and the difficulty to release O_2 in the tissues (Nascimento *et al.,* 2008).
There are two pathways for reduction of methemoglobin back to hemoglobin:
a) The physiologically important pathway is the NADH-dependent reaction catalyzed by cytochrome b5 reductase (b5R).
b) An alternative pathway that is not physiologically active utilizes NADPH generated by glucose-6-phosphate dehydrogenase (G6PD) in the hexose monophosphate shunt. However, there is normally no electron carrier present in red blood cells to interact with NADPH methemoglobin reductase. Extrinsically administered electron acceptors, such as methylene blue (MB) and riboflavin, are required for this pathway to be activated. This non-physiologic pathway becomes clinically important for the treatment of methemoglobinemia (Prchal *et al.,* 2016).
Causes of Methemoglobinemia are either congenital or acquired. Congenital methb is of two types viz:
a) ***Cytochrome b5 Reductase Deficiency–*** Most cases of hereditary methemoglobinemias are autosomal recessive and are due to homozygous or compound heterozygous deficiency of cytochrome b5 reductase. Cytochrome b5 reductase participates in the transfer of electrons to cytochrome b5 from the NADH generated by glyceraldehyde-3-phosphate dehydrogenase. The gene for NADH-CB5R is located on chromosome 22 (de Alarcón *et al.,* 2013).
b)***Hemoglobin M Disease–*** Autosomal dominant hemoglobin M disease due to mutations in either the alpha or beta or, rarely, gamma globin gene. Administration of methylene blue (MB) does not correct this type of congenital methemoglobinemia. There is no effective treatment for the methemoglobinemia seen in this condition, should it be required (Agarwal *et al.,* 2009).
c) ***Cytochrome b5 Deficiency–*** Rarest form of congenital methemoglobinemia.
Methemoglobinemia associated with enzyme deficiency are of three types viz:-
Type I Deficiency- is limited to RBCs and is manifested by methemoglobinemia only.
Type II Deficiency- is widespread enzyme deficiency and is characterized by mental retardation in addition to methemoglobinemia.
Type III Deficiency- Affects leukocytes and platelets, but is not associated with mental retardation (de Alarcón *et al.,* 2013).
Hemoglobin M (HbM) disease is autosomal dominant defect caused by point mutations that alter a single amino acid in the structure of normal globin. Ten known hemoglobin M mutations are known out of which three affect the alpha globin chain, five alter the beta globin chain, and two involve the gamma chain. Only the alpha and gamma globin chain mutations are associated with neonatal methemoglobinemia, because these are the globin chains in hemoglobin F, the predominant hemoglobin found in neonatal RBCs. Neonatal methemoglobinemia is transient when produced by one of the two gamma chain mutations because the normal developmental switch from fetal to adult hemoglobin eliminates all but a trace of the mutant hemoglobin. Hemoglobin M heterozygotes inheriting alpha or beta globin mutations appear cyanotic their entire life because of the increased met-hemoglobin levels present in their RBCs, but they are otherwise asymptomatic. No therapy is needed (and none is possible). The homozygous state is incompatible with life. Diagnosis of hemoglobin M disorders is made by hemoglobin spectroscopy (Agarwal *et al.,* 2009). Acquired methemoglobinemia is a result of increased methemoglobin formation by various exogenous agents.
Clinical manifestations of MetHb reflect the reduction in carrying capacity, leading to tissue hypoxia. In general, MetHb under 15% causes only a grayish pigmentation of the skin, but the condition is frequently overlooked. However, in the index case though Methb levels were 5.8%, the baby presented with significant central cyanosis at birth which did not regress with oxygen therapy. At levels of 12-15%, patients have central cyanosis non-responsive to the administration of oxygen. Neurologic and cardiovascular symptoms (dizziness, headache, anxiety, dyspnea, symptoms of low cardiac output, somnolence, and seizures) are commonly present with fMetHb above 20-30%. As levels of MetHb increase, the patient suffers with reduction in the level of consciousness, respiratory depression, shock, and death. Levels of MetHb above 70% are usually fatal (Chui *et al.,* 2005).
The presence of methemoglobin can be suspected when the oxygen saturation as measured by pulse

oximetry is more than 5 percent lower than the oxygen saturation calculated from arterial blood gas analysis ("saturation gap"). In practice, this saturation gap may be as great as 45 percent. When pulse oximetry shows an oxygen saturation ≤90 percent and the arterial oxygen partial pressure is ≥70 mmHg is also indicative of methemoglobinemia. In the present case, oxygen saturation was 70-75%, and PaO2-92 mm of Hg.

In a case of methemoglobinemia, when an arterial blood gas is drawn, the colour of blood is commonly a brown or chocolate colour. Upon exposure to air, the colour of the blood does not change in a case of methemoglobinemia. Rapid screening test can be done bedside by placing a drop of blood on filter paper and then waving the filter paper in the air to allow the blood to dry. Deoxygenated normal hemoglobin turns red, whereas methemoglobin remains brown. Using this technique, methemoglobin levels of 10% or more can be detected. In the index case, both case and control samples turned red, suggesting ours is a case of mild methemoglobinemia (Figure 1).

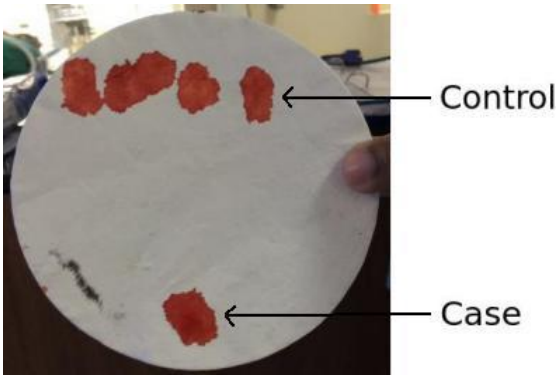

Figure 1: Rapid Screening Filter Paper Test

Filter Paper test shows no change in colour of both case and control samples on exposure to oxygen.

Blood gas analysis measures arterial oxygen partial pressure and estimates oxygen saturation by comparison with a standard curve. Since arterial oxygen partial pressure is normal in subjects with methemoglobinemia, blood gas analysis will give falsely high levels of oxygen saturation in the presence of methemoglobin. Methemoglobinemia is strongly suggested when there is clinical cyanosis in the presence of a calculated normal arterial pO_2 (PaO_2) as obtained by arterial blood gases. Arterial blood gas analysis is deceptive because the partial pressure of oxygen is normal in subjects with excessive levels of methemoglobin (Prchal *et al.*, 2016).

Co-oximetry is the gold standard for the diagnosis of MetHba which has peak absorbance at 631 nm. The co-oximeter is capable of measuring the concentration of different types of Hb in the blood through spectrophotometry, using different wavelengths. When dyshemoglobins are present, only multiple-wavelength co-oximetry can give accurate measurements of the true oxygen-carrying status because it assesses all hemoglobin species (Haymond *et al.*, 2005). A fresh specimen should always be obtained as methemoglobin levels tend to increase with storage. False positives may occur in the presence of other pigments, including sulfhemoglobin and methylene blue (MB). Methemoglobin detected by the co-oximeter should be confirmed by the specific Evelyn-Malloy method.

Evelyn-Malloy method is used for confirmation of methemoglobinemia. Addition of cyanide binds to the positively charged methemoglobin, eliminating the peak at 630 to 635 nm in direct proportion to the methemoglobin concentration. The subsequent addition of ferricyanide converts the entire specimen to cyanomethemoglobin for measurement of the total hemoglobin concentration. Methemoglobin is then expressed as a percentage of the total concentration of hemoglobin. Use of the Evelyn-Malloy method for determining the concentration of methemoglobin is especially important after the therapeutic use of MB, since the co-oximeter "reads" MB as if it were methemoglobin.

Incubation of blood with MB distinguishes cytochrome b5R deficiency from HbM disease; this treatment

will result in the rapid reduction of methemoglobin through the NADPH-flavin reductase pathway in cytochrome b5R deficiency but not in HbM disease. Measurement of the level of cytochrome b5R activity or cytochrome b5 is required to distinguish cytochrome b5R deficiency from cytochrome b5 deficiency; however, these assays are not available easily (Prchal *et al.,* 2016). Hemoglobin electrophoresis is done for diagnosis and confirmation of HbM disease. A poor response to methylene blue is seen in G6PD-deficient individuals, hence G6PD levels should be determined before starting methylene blue therapy.

The treatment options most often employed are methylene blue (MB) and ascorbic acid (vitamin C) (Prchal *et al.,* 2016). Methylene blue is a thiazine dye with dose-dependent antiseptic and oxidizing properties. It activates NADPH methemoglobin reductase, which reduces methylene blue to methylene leucoblue, which transforms MetHb in reduced hemoglobin by a non-enzymatic mechanism via the NADPH-dependent pathway (Nascimento *et al.,* 2008). MB (1% solution) is given intravenously in a dose of 1 to 2 mg/kg diluted in normal saline as an infusion over 5-10 minutes (Venkateswari *et al.,* 2007). Milder cases and follow-up severe cases can be treated orally with methylene blue 60 mg three to four times a day. Methylene blue is not indicated in cases of HbM (Ramanamurthy, 2013). The response to methylene blue is both therapeutic and diagnostic. MB should not be administered to patients with known G6PD deficiency, since the reduction of methemoglobin by MB is dependent upon NADPH generated by G6PD. As a result, MB may not only be ineffective, but it is also potentially dangerous since MB has an oxidant potential that may induce hemolysis in G6PD-deficient subjects precipitating acute hemolysis, thus, further decreasing oxygen delivery (Rosen *et al.,* 1971). N-acetyl-cysteine (another electron donor) has been used on those cases (Maddali and Fahr *et al.,* 2005).

Ascorbic acid (vitamin C) has direct reducing action on methemoglobin rather than to restoration of the normal enzymatic reduction mechanism. Acquired (acute) MetHba does not respond to ascorbic acid because its capacity to reduce MetHb is much inferior to that of endogenous enzymatic systems (Gibson, 1943). Dose of ascorbic acid used is 5mg/kg/dose (Shonola and Da-Silva, 2003). Riboflavin is also being used in some cases. NADPH undertakes around 5% of this activity in RBCs under normal conditions, requiring NADPH and an electron acceptor cofactor. Riboflavin act as electron acceptors to reduce MetHb (McDonagh *et al.,* 2013). Use of riboflavin in high dose i.e. 120 mg/d has been reported (Hirano *et al.,* 1981). In vitro, NO-induced methemoglobin formation is significantly decreased partially by high riboflavin concentrations (120 microM) (Dötsch *et al.,* 2000).

For treatment of acute acquired methemoglobinemia a thorough search for an offending agent should be made and, if found, the agent should be removed and/or discontinued. Methylene blue 2 mg/Kg diluted in normal saline as an infusion over 5-10 minutes, followed by a repeat dose of 1 mg/Kg an hour later is usually effective (Venkateswari *et al.,* 2007). In patients unresponsive to Methylene blue, hyperbaric oxygen therapy and Exchange-transfusion is advised. Hyperbaric oxygen therapy increases the level of O_2 dissolved in the plasma and brings CO_2 close to the minimum necessary to maintain the metabolism, even in the of severe anemia. With hyperbaric treatment it is possible to maintain the O_2 temporarily, until the oxygen carrying capacity is restored with Exchange transfusion. Therefore, both hyperbaric oxygen therapy and Exchange-transfusion are reserved for severe cases that do not respond to methylene blue (Jansen *et al.,* 2003).

Conclusion

Congenital methemoglobinemia is a rare syndrome with multiple etiologies. Because of its rare occurrence in the neonatal period, its incidence is largely unknown. The diagnosis should be considered in cases of severe cyanosis non-responsive to oxygen administration, after ruling out cardiopulmonary dysfunction. Such cases are detected usually accidently or in perioperative period due to anaesthetic complications. Our index case is an example of congenital methemoglobinemia which presented with cyanosis at birth, and was diagnosed early because of exclusion of cardiopulmonary disease and estimation of methemoglobin levels. The interesting feature was that the neonate had symptomatology which were out of proportion to the levels of methemoglobin and needed medication to remain acyanotic as well as to ensure normal growth and development.

Funding*:* Nil

Conflict of Interest: Non Identified
Author Contribution: HK, UR, GS, VK and TD were responsible for management of the case, collection of data and drafting the report. HK and UR were responsible for conceptualizing the report as well as managing the case.

REFERENCES

Agarwal N, Nagel RL and Prchal JT (2009). Dyshemoglobinemias. In: *Disorders of Hemoglobin: Genetics, Pathophysiology, and Clinical Management*, 2nd edition, Steinberg M (Edition), (Cambridge University Press, Cambridge, UK) 607.

Chui JSW, Poon WT, Chan KC *et al.*, (2005). Nitrite-induced methaemoglobinaemia— aetiology, diagnosis and treatment. *Anaesthesia* **60** 496-500.

de Alarcón PA, Werner EJ and Christensen RD (2013). *Neonatal Hematology-Pathogenesis, Diagnosis, and Management of Hematologic Problems* 2nd edition (Cambridge University Press, New York, USA) 110.

Dötsch J, Demirakça S, Kratz M, Repp R, Knerr I and Rascher W (2000). Comparison of methylene blue, riboflavin, and N-acetylcysteine for the reduction of nitric oxide-induced methemoglobinemia. *Critical Care Medicine* **28**(4) 958-61.

Gibson QH (1943). The reduction of methaemoglobin by ascorbic acid. *Biochemical Journal* **37** 615.

Haymond S, Cariappa R, Eby CS *et al.*, (2005). Laboratory assessment of oxygenation in methemoglobinemia. *Clinical Chemistry* **51** 434-444.

Hirano M, Matsuki T, Tanishima K, Takeshita M, Shimizu S, Nagamura Y and Yoneyama Y (1981). Congenital methaemoglobinaemia due to NADH methaemoglobin reductase deficiency: successful treatment with oral riboflavin. *British Journal of Haematology* **47**(3) 353-9.

Jansen T, Barnung S, Mortensen CR *et al.*, (2003). Isobutyl-nitrite-induced methemoglobinemia; treatment with an exchange blood transfusion during hyperbaric oxygenation. *Acta Anaesthesiologica Scandinavica* **47** 1300-1301.

Maddali MM and Fahr J (2005). Postoperative methemoglobinemia with associated G6PD deficiency in infant cardiac surgery-enigmas in diagnosis and management. *Pediatric Anesthesia* **15** 334-337.

McDonagh EM, Bautista JM, Youngster I, Altman RB and Klein TE (2013). PharmGKB summary: methylene blue pathway. *Pharmacogenetics and Genomics*. Available: https://www.pharmgkb.org/pathway/PA165980834, https://www.pharmgkb.org/pmid/698125.

Nascimento TS, Pereira ROL and Mello HLD (2008). Methemoglobinemia: from Diagnosis to Treatment. *Revista Brasileira de Anestesiologia* **58**(6) 651-664.

Prchal JT, Schrier SL, Mahoney DH, Burns MM, Tirnauer JS and Armsby C (2016). Clinical features, diagnosis, and treatment of methemoglobinemia. *Uptodate, Literature Review*. *Available at:* http://cursoenarm.net/UPTODATE/contents/mobipreview.htm?25/40/26240?source=HISTORY; Visited: Dec 2016.

Ramanamurthy SV (2013). Methemoglobinemia: a reappraisal with an Indian perspective. *Hematology* **23** Chapter 77 344-349.

Rosen PJ, Johnson C, McGehee WG and Beutler E (1971). Failure of methylene blue treatment in toxic methemoglobinemia. Association with glucose-6-phosphate dehydrogenase deficiency. *Annals of Internal Medicine* **75** 83.

Shonola S and Da-Silva MD (2003). Congenital Methemoglobinemia: A Rare Cause of Cyanosis in the Newborn—A Case Report. *Pediatrics* **112** e158.

Venkateswari R, Ganesh R, Deenadayalan M, Mahender E, Ramachandran B and Janakiraman L (2007). Transient Methemoglobinemia in an Infant. *Indian Journal of Pediatrics* **74** 69-70.