Congenital Methemoglobinemia in Newborn: Case report

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Abstract
Congenital methemoglobinemia is a rare cause of cyanosis in a newborn. Methemoglobin (MetHb) is a form of haemoglobin (Hb) in which heme iron is oxidized and unable to bind oxygen. The causes of methemoglobinemia are classified as congenital or acquired. We herein report a case of a preterm neonate with cardiopulmonary compromise and cyanosis, eventually diagnosed to have congenital methemoglobinemia. The baby developed cyanosis, which did not improve on oxygen supplementation. Blood gas analysis showed raised Methb levels which was further confirmed by co-oximetry. The baby was started on Oral Vitamin C and improved subsequently and was discharged in a stable condition.

Keywords: Methemoglobinemia, Cyanosis, Newborn

Introduction

A preterm (27 weeks) female baby was delivered operatively by elective LSCS in view of PROM at a tertiary care centre. Mother was third gravida with no known adverse antenatal influences. There was no family or past history of any major medical ailment in family. Mother was not on any other medication apart from routine medications given during pregnancy. The baby was vigorous at birth but needed resuscitation in view of extreme prematurity, respiratory distress and unable to maintain SpO2. Surfactant was given in delivery room and baby to shifted to NICU on a T-piece resuscitator for further management.

In NICU, baby was started on CPAP at PEEP of 6 cm H_2O, flow of 8 litre/min and FiO_2 of 50%, which was gradually tapered to 21% by 24 hours with target Saturation (SpO_2) of >90%. Other supportive treatment like TPN, antibiotics (Inj. Ampicillin, Inj. Gentamicin) and Inj. Caffeine was started. Baby maintained normal vitals except for tachypnea. Head to toe examination was normal with no dysmorphic features. Chest X-Ray done showed Respiratory Distress Syndrome (RDS) like picture with normal cardiac morphology. Baby had repeated episodes of apnea requiring repeated loading with Inj. Caffeine. On 10^{th} day of life, baby had falling SpO_2 of 80-85% on CPAP, not associated with bradycardia or cyanosis. SpO_2 did not increase with increase in PEEP or FiO_2 to 100%. ABG done showed no acidosis or alkalosis with PaO_2 of 86 mmHg. Sugars were normal. In view of persistence of poor saturation in a baby who did not have respiratory distress or bradycardia, the differential diagnosis of cyanotic congenital heart disease, persistent pulmonary hypertension and polycythemia were thought of. Septic screen was repeated which was negative. Liver function test, kidney function test and serum electrolytes were all within normal range. USG Cranium was normal. 2D Echo done showed PFO with left to right shunt with mild peripheral PS. Antibiotics (Inj. Cefotaxime and Inj. Amikacin) were started in view of suspected sepsis. Baby was continued on OG feed. However, baby persisted to have SpO_2 ranging 80-85% despite above treatment.

Due to persistence of low SpO_2 despite normal PaO_2 levels, which showed no improvement on oxygen supplementation, differential diagnosis of abnormal haemoglobin was thought of. Blood gas analysis revealed Methb level of 4.8%, which was later confirmed by blood sample, where the level was 34%. G6PD screening excluded the deficiency. Methemoglobin levels in mother was normal. This clinched the diagnosis of congenital methemoglobinemia, an exceedingly rare disorder.

Baby was continued on CPAP in view of prematurity and recurrent apnea episodes. Baby was started on Oral Ascorbic Acid on 21st day of life at 7.5 mg/kg 8 hourly. Baby was eventually shifted to HHHFNC and then weaned off respiratory support by 35th day of life. No other treatment was given for methemoglobinemia as levels were low and baby was improving clinically with SpO2>90% intermittently on room air. Hemoglobin electrophoresis was unremarkable. Cytochrome B5 reductase (CYB5R) activity level, sequence analysis of the Beta and Gamma Globin genes were not obtained, due to limited availability in the region.

Baby was discharged on 62nd day of life at SpO2 level of 92-95% on room air.

Discussion

Neonatal cyanosis may be peripheral or central in nature. Peripheral cyanosis involves the distal extremities and often occurs due to sluggish blood flow in peripheral capillaries, leading to increased oxygen extraction. By contrast, central cyanosis involves the entire body and can occur due to various mechanisms, including hypoventilation, ventilation-perfusion mismatch, right to left cardiac shunt, alveolar diffusion impairment, or inadequate oxygen transport by an abnormal haemoglobin such as Methb, Sulphmethemoglobin etc [1]. Methemoglobinemia should be suspected in newborns, in the absence of any obvious cardiac and pulmonary dysfunction that are persistent cyanotic and hypoxic and did not improve in the administration of oxygen supplementation [2].

Red blood cells contain approximately 1% Methb levels (range: 0-3 %). This is maintained by two mechanisms; the hexose-monophosphate shunt pathway and nicotine adenine dinucleotide (NADH) diaphorase I and nicotine adenine dinucleotide phosphate (NADPH) diaphorase II system. The NADPH system can be pharmacologically activated. This is the basis of treatment with methylene blue [3].

Methemoglobinemia has two forms; inherited and acquired. Inherited disorder causing methemoglobinemia resulted from an enzymatic deficiency of Nicotinamide adenine dinucleotide cytochrome b5 reductase, which is classified into two distinct phenotypes. In type I, the most common form, the deficiency of NADH cytochrome b5 activity is found only in erythrocytes, with other cells unaffected. In type II, the enzyme deficiency is present in all cells of the body [2].

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. At levels of 12-15%, patients have central cyanosis non responsive to administration of oxygen. Neurologic and cardiovascular symptoms are commonly present when levels are 20-30%. As levels of MetHb increase, the patient suffers with reductions in the level of consciousness, respiratory depression, shock and death. Levels of MetHb above 70% are usually fatal [5]. However, in the index case MetHb levels were 34% and the baby had desaturation which was non responsive to oxygen supplementation.

In a case of methemoglobinemia, when an arterial blood gas is drawn, the colour of blood is commonly brown or chocolate colour. A simple bedside test is to place one or two drops of the patient's blood on white filter paper. If the infant has methemoglobinemia the blood will not turn red when exposed to air, it will have chocolate hue [2]. Blood gas analysis measures arterial oxygen partial pressure and estimates oxygen saturation by comparison with a standard curve. Arterial blood gas analysis is deceptive because the partial pressure of oxygen is normal in subjects with excessive levels of methemoglobin. The index case had SpO2 of 80-85 % and PaO2 of 86 mmHg. Co-oximetry is the gold standard for the diagnosis of MetHb which has peak absorbance at 631nm [5].

Once the diagnosis of methemoglobinemia has been made, there are various assays available to quantify NADH-cytochrome b5 reductase activity. Adult levels of enzyme function are attained by 2-3 months of age, and in the neonate, methemoglobin reductase levels are normally 60% of the normal adult value [6]. When congenital methemoglobinemia is suspected, enzyme activity in all immediate family members should be evaluated. In our index case, only the mother was tested for methemoglobin levels which was 2%.

In the treatment of hereditary enzymopenic methemoglobin, many variables have to be taken into consideration. In the neonate period, it is recommended to keep MetHb levels below 10% as persistence of fetal haemoglobin already compromises oxygen delivery to the tissues [7]. Methylene blue is the treatment of choice for severe methemoglobinemia. In the presence of NADPH, methylene blue is converted to leucomethylene blue, which results in nonenzymatic reduction of metHb. (8) Ascorbic acid directly reduces methemoglobin, but the rate of the reaction is too slow for it to be effective to be used alone. 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 [7].

Conclusion

Methemoglobinemia is a rare disease, with its incidence largely unknown. The diagnosis requires high index of clinical suspicion and ruling out other common comorbidities causing cyanosis in a neonate. So, early recognition is necessary to prevent unnecessary investigations and delay management.

Follow UP

Baby was followed up until 6 months of age, during which the baby was thriving, with normal growth and development.

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References

1. Dom Bourian, M, Ezhuthachan A, Kohn A, Berman B, Sykes E. A 5-Hour-Old Male Neonate with Cyanosis. Laboratory Medicine. 2015; 46(1):60-63.
2. Shakya S, Shrestha N, Subedi K. Methemoglobinemia in a Newborn. Medical Journal of Shree Birendra Hospital. 2020; 19(1):45-47.
3. Van de Vijver M, Parish E, Aladangady N. Thinking outside of the blue box: a case presentation of neonatal methemoglobinemia. Journal of Perinatology. 2013; 33(11):903-904.
4. Larokar S, Manoli P, Halkar M, Pejaver R. Congenital Methemoglobinemia. Perinatology, 2016, 17(3).
5. Khade H, Raju U, Deshmukh T, Srivastav G, Kadiri V. Neonatal Congenital Methemoglobinemia- A Case Report. Indian Journal of Medical Case Reports. 2016; 5(4):12-17.
6. Wright R, Lewander W, Woolf A. Methemoglobinemia: Etiology, Pharmacology, and Clinical Management.

Annals of Emergency Medicine. 1999; 34(5):646-656.
7. Da-Silva S, Sajan I, Underwood J. Congenital Methemoglobinemia: A Rare Cause of Cyanosis in the Newborn--A Case Report. Pediatrics. 2003; 112(2):e158-e161.
8. Grauer S, Giraud G. Toxic methemoglobinemia after topical anesthesia for transesophageal echocardiography. Journal of the American Society of Echocardiography. 1996; 9(6):874-876.