Neonatal Methemoglobinemia Due to Transplacental Transfer of Dapsone

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Cyanosis in newborn period is most often caused by pulmonary disease, congenital cyanotic heart disease or decreased cardiac output states. Rarely it is due to hema-tologic problems such as methemoglobinemia^). Herewith we report a case of methemoglobinemia in a neonate caused by maternal Dapsone therapy. To best of our knowledge this is first of such case reported in world literature as per the relevant Medline search (1970 to 1996) performed by us.

Case Report

A 1660 gram male neonate of 34 weeks appropriate for gestational age born by spontaneous vertex vaginal delivery was admitted for routine preterm care. APGAR Scores were 8 and 8 at 1 and 5 minutes, respectively. The neonate was the second child of a 30-year-old woman who was a case of lepromatous leprosy on Dapsone (Diamino diphenyl sulfone) therapy (100 mg once daily) for the last 4 years. For the initial two years of this therapy, she was treated with three drugs; Dapsone, Rifampicin and Clofazimine, and in the later 2 years with dapsone alone, as she was objectively proved to be improving. The elder sibling was a male child of 5 years age and apparently normal.

The neonate was noticed to have central cyanosis without respiratory distress at 30 minutes of life. The general examination and systemic examination did not reveal any other abnormality. The laboratory studies showed the following results: Hemoglobin-17.6 g/dl; hematocrit 56%; WBC count 12,300 with 62% neutrophils, 34% lymphocytes and 4% band forms; platelet count 3,50,000 mm^3; and blood glucose 60 mg/dl. The chest X-ray and ECG were normal. Arterial blood gas estimation in room air revealed pH-7.38, PO_2-70 mm of Hg, PCO^2-21.6 mm of Hg and SaO_2 of *76%.* In 100% inspired oxygen, the arterial blood gas values were pH-7.49, PG\,-222 mm of Hg, $PCO_2$18.9 and SaO_2, 85%. The high PO_2 with 100% inspired oxygen administration clearly ruled out admixture cardiac lesions and observed saturation values were strongly suggestive of abnormal hemoglobin species. The "Red Brown" screening test for methemoglobinemia performed was positive(2). Methemoglobin level estimated by arterial blood gas at this stage was 20%. The G6PD level of the baby was normal. Hb - electrophoresis in the baby as well as both the parents and the elder sibling were normal. Methemoglobin levels of parents and other sibling in blood gases were within normal range. Enzymatic estimation of cytochrome b5 reductase was not done in the neonate as they are not done anywhere in Bombay.

The neonate was treated with single dose of intravenous methylene blue (2 mg/ kg of 1% solution) to which he responded dramatically. On day - 2 of life the methemoglobin level was 2%. At this stage, the mother was revaluated for leprosy by performing clinical examination and skin

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Manuscript Received: February 19,1997; Initial review completed: April 1,1997; Revision Accepted: November 4,1997

biopsy which showed that she had been cured of leprosy. Dapsone therapy was stopped and later breastmilk was started for the neonate. The newborn was discharged on day-12 of life. The child was growing and developing normally at 5 months of age. The cyanosis did not recur subsequently.

Discussion

Methemoglobin is the oxidized derivative of hemoglobin in which the iron of the heme groups is changed from the Ferrous (fe^{++}) to the Ferric (Fe^{+++}) state, and usually accounts for less than 1% of the total hemoglobin^). Congenital methemoglobinemia is caused by either a genetically determined aminoacid substitution in the globin moiety of the hemoglobin molecule or by a deficiency of one of enzyme necessary for reduction of methemoglobin. Acquired methemoglobinemia is caused by exposure to certain oxidizing agents(3). The effect of the methemoglobin formation is two fold. First methemoglobin is unavailable for transport of oxygen. Second, the presence of methemoglobin renders the oxygen dissociation curve more hyperbolic shifting it to left. The total effect is lowered capacity for unloading oxygen to the tissues and hence a tissue susceptibility to anoxia, a state of functional anemia exists(4).

The newborn infant is unusually susceptible to the development of methemoglobinemia on exposure to toxic agents as there is increased sensitivity of fetal erythrocytes to oxidizing agents causing formation of fetal methemoglobin. This has been shown to be function of the gamma chain of HbF(3). Moreover, there is transient physiologic deficiency of cytochrome b5 reductase activity in neonates (approximately 60% of the normal adult value). Even greater reduction in activity is found in premature neonates(3,4).

Methemoglobinemia (when it exceeds 10% of total Fib) presents with generalized cyanosis. Respiratory distress is strikingly absent except when very high levels of methemoglobin are reached. A simple rapid bedside "Red Brown Screening Test" is diagnostic of the condition as in our patient. The presence of methemoglobinemia may be confirmed spectroscopically by demonstrating characteristic absorption peak at 634 mu, which disappears on addition of cyanide(3).

Methylene blue acts as a specific antidote converting methemoglobin to Hb via NADPH flavin reductase. The recommended daily dose is 1-2 mg/kg body weight of 1% solution given intravenously. A favourable response consists of the disappearance of cyanosis and a sharp drop in methemoglobin level to normal within 60 minutes(3). Excessive doses of methylene blue in the newborn may cause acute oxidant type of hemolysis(l,3). Ascorbic acid also reduces methemoglobin but conversion takes place more slowly and is therefore not practical in emergency cases. Exchange transfusion and hemodialysis are other modalities of therapy available as and when methemoglobin concentration is 70% or more(4).

There are several reasons which made us to suspect administration of Dapsone to mother and its transplacental transfer as possible etiologic factor for methemoglobinemia in this case. First, the mother was a case of lepromatous leprosy on dapsone therapy and administration of methemoglobinemia producing agents like dapsone to mother prior to delivery are known to cause cyanosis at birth(3). Second, the neonate was on intravenous fluids, not on any oral feeds and was not exposed to other environmental agents known to produce methemoglobinemia. Thirdly, hemoglobin electrophoresis studies were

normal in the patient as well as in the parents and sibling Fourthly, there was no family history suggestive of methemoglobinemia and methemoglobrn levels of both the parents and elder sibling were normal Fifthly, There is transient physiologic deficiency of cytochrome b5 reductive activity in neonates approximately 60% of the normal adult value, and even greater reduction in premature neonates is known making them more susceptible to oxidant stress leading to methemoglobinemia(3,4) Sixthly, if we consider the possibility of neonate having homozygous cytochrome b5 reductase deficiency and both parents heterozygotes having normal levels of methemoglobrn, the mother, if she was heterozygote could have manifested with methemoglobinemia to strong oxident stress of Dapsone therapy(3) Finally though we were unable to estimate cytochrome b5 reductase enzymatic activity, the prompt response to smgle dose of methylene blue and non recurrence of methemoglobinemia in five months of follow up in the patient subsequently, probably excludes enzymes deficiency as a cause of methemaglobinemia(3)

We recommend that all the neonates born to mothers who receive potential oxidant drugs like Dapsone just before the time of delivery should be carefully monitored for methemoglobinemia

Acknowledgements

We wish to thank Dr PM Pai, Dean, Seth G S Medical College and K E M Hospital for granting permission to publish this case report

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Esophageal Atresia with Right Pulmonary Agenesis

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The association of pulmonary agenesis with esophageal atresia with or without tracheo-esophageal fistula is extremely rare. This combination is often fatal as there is progressive respiratory embarassment which complicates anesthesia. Only seven such cases have been reported so far(l-4).

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Manuscript Received: January 2,1997;
Initial review completed: January 12,1997;
Revision Accepted: October 31,1997