

Compound Heterozygous Hemoglobin SD Disease Presenting as Sickle Cell Crisis in Pregnancy

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Introduction

Hemoglobinopathies are the diverse group of inherited disorders of hemoglobin production and function. They represent the most common single gene disorder which are found in humans and are distributed in various frequencies throughout the world. Hemoglobinopathies are broadly classified as disorders that result from structurally altered hemoglobin molecules (e.g. Sickle cell anemia) or disorders that arise from numerical imbalance of otherwise normal globin chain synthesis (β Thalassemia)¹. Sickle cell disease (SCD) is the most common inherited condition globally. Around 300000 children are born each year with SCD, two third being in Africa². The prevalence of sickle cell gene ranges from 2-34% in India³. SCD includes homozygous (HbSS) as well as heterozygous forms of HbS in combination with other hemoglobins like hemoglobin C (HbSC), hemoglobin beta thalassemia (HbSB), hemoglobin D (HbSD), and E (HbSE). SCD occurs due to the polymerisation of abnormal hemoglobin under low oxygen tension leading to formation of fragile sickle shaped cells resulting in hemolytic anemia and vasoocclusion of small blood vessels² (RCOG 2011). Hemoglobin D also known as Hb D Punjab is very rare in homozygous disease and results from substitution of glutamate by glutamine at codon 121 of β chain. Heterozygous state of hemolobin D may combine with sickle cell gene HbS and may manifest as hemoglobinopathy (moderate to severe HbSD) especially in north Indian states like Punjab^{4, 5}. Pregnancy in women with sickle cell disease is associated with an increased risk of morbidity and mortality because of the combination of underlying haemolytic anemia and multiorgan dysfunction associated with this disorder. Awareness of this type of haemolytic anemia and associated obstetric complications are of paramount importance for managing this rare SCD. Multidisciplinary team approach involving obstetricians, hematologists, paediatricians and anaesthetists is required for optimum perinatal outcome. HbSD (sickle cell hemoglobin in combination with Hb D) has not been reported so far in pregnancy. We hereby report a case of heterozygous HbSD with sickle cell crisis in pregnancy secondary to infection.

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Case Report

A twenty four years old primigravida, resident of Punjab (India), with primary level of education supervised at a tertiary institute, date of her last menstrual period was 7th April 2013, making expected date of delivery as 14th January 2014. She was diagnosed as HbSD disease during routine antenatal investigation of hemoglobin electrophoresis for hemoglobinopathies done at at 13 weeks POG (Period of gestation) and was under regular follow up in antenatal and hematology clinic. Subsequently report of hemoglobin electrophoresis of husband was normal .She developed urinary tract infection at 14 weeks POG which was treated with antibiotics. Her antenatal period was uncomplicated till 28 weeks POG when she presented to Gynae emergency room with complaints of fever, non productive cough and pain lower limbs of 2 days duration. Her glucose tolerance test was deranged for which she was started on diabetic diet and subsequently sugars were well controlled. There was no history of menorrhagia, epistaxis, gum bleeding, easy bruisability, previous blood transfusion in the past.

On examination, she was febrile with temperature of 38 degree Celsius, icteric & pale with a pulse rate of 102 beats /minutes and blood pressure of 120/70 mm Hg. Fine crepitations were present on right side of chest in the middle zone. On abdominal examination, symphysis fundal height corresponded to 30 weeks POG with normal fetal heart sounds and there were no hepatosplenomegaly. On investigations, her hemoglobin was 5.8gm/dl, total leucocyte count of 48300/cumm, platelet count 1.24lakh and total serum bilirubin concentration of 12.1mg/dl with conjugated fraction of 5.7 mg/dl. Her SGOT/SGPT were normal but alkaline phosphatase was markedly raised to 1505U/L. Sickle cells were present on peripheral smear. Chest X-ray showed opacity in right middle zone suggestive of pneumonia. Ultrasonography confirmed a singleton live fetus in breech presentation corresponding to 28 weeks POG with amniotic fluid index of 6.4. A clinical impression of sickle cell crisis with pneumonia was made.

She responded to supportive management in the form of oxygen supplementation, antibiotics, oral hydration, analgesics and three units of packed red blood cells and was discharged in a satisfactory

condition after 1 week. She had regular maternal & fetal surveillance by means of weekly biophysical profile and fortnightly fetal biometry. A discrepancy of four weeks of POG between fetal biparietal diameter and abdominal circumference on ultrasonography, thus confirming the diagnosis of intrauterine growth restriction (IUGR), was made at 34 weeks POG.

She was planned for elective caesarean section in view of breech with IUGR at 37 weeks POG however she presented to labour room in active phase of spontaneous labour at 36 weeks POG, and had assisted breech vaginal delivery of a live female baby weighing 1.75 kg with Apgar scores of 7, 9 at first and fifth minutes respectively. Breast feeding was initiated with adequate oral hydration & thromboprophylaxis in the postpartum period. Both mother and baby were discharged in a satisfactory condition at day 5 postpartum.

Discussion

Hemoglobin D Punjab itself does not cause polymerisation but enhances the polymerisation of HbS by β^{121} glutamine residue thereby increasing the severity of disease⁵. Heterozygous Hb SD may produce a significant sickling^{6, 7} during pregnancy and serious complications as seen in HbSS genotype can also occur in women with HbSD⁸. Detection of Hb SD early in the pregnancy is important to realize in order to take preventive measures to avoid maternal and fetal complications. Serum electrophoresis by HPCL (High performance liquid chromatography by BioRad Variant 2) is an, appropriate screening investigation for determining the presence of various normal and common abnormal variant of hemoglobin, especially in the area of maximum concentration of HbD genotype. This is a fairly accurate method for the diagnosis, yet the confirmation was done after genomic DNA extraction from peripheral blood. Specific Polymerase chain reaction (PCR) amplification was done of beta globin gene followed by restriction enzyme digestion for HbS using R.E. DdeI and for HbD Punjab EcoR1 was used. Once detected such patients should be treated as high risk pregnancy due to increased incidence of abortions, preterm labour, increased chances of hospitalisation, infections, preeclampsia, antepartum haemorrhage,

thromboembolic episodes, acute painful crisis, caesarean rate, intrauterine growth retardation and intrauterine fetal death.^{2, 9-11} Although the entire pregnancy is a high risk state in presence of SCD but the maximum risk occurs in late pregnancy, during delivery and in the postpartum period⁹. The present case needed hospitalization due to development of pneumonia, painful crisis and anemia at 28 weeks POG. In a study by Patricia et al, vasoocclusive crisis was the most common cause of hospitalisation, urinary tract infection (UTI) occurred in 44.2% of cases and frequency of blood transfusion was 83.3%⁸. The usual precipitating factors for such crisis include dehydration, hypoxia, infection, cold temperature, weather changes, overexertion and tobacco smoking¹². Particular attention should be paid to prompt treatment of infection like UTI, respiratory tract infection etc and dehydration due to hyperemesis gravidarum and due to lactation and labour. During pregnancy, the main focus of management is prevention of acute painful crisis, organ damage, achieving optimum fetal health and decreasing maternal mortality¹³. Sickling often leads to tissue hypoxia and thus IUGR, hence making serial fetal growth monitoring mandatory. Treatment of painful crisis includes fluid rehydration, oxygen supplementation and pain control with opioids. Blood transfusions if required should be given after extended cross matching of the blood. Antibiotics should be considered as infection is usually associated with vasoocclusive crisis. Labour is a stress inducing hence may precipitate sickle cell crisis. Proper analgesia, prevention and treatment of dehydration, regional anaesthesia without hypotension are preventive in nature. Epidural analgesia is an effective method for pain control during labour whereas for the patients not in labour, opioids should be the choice. General anaesthesia can lead to postpartum sickling complication; hence should be avoided¹². Continuous intrapartum fetal monitoring is also required due to increased chances of stillbirth. Present case was monitored by CTG (Cardiotocography) during labour and adequate hydration as well as fetal oxygenation, maintained during intra as well as postpartum period. Compression devices and prophylactic anticoagulation are advisable due to increased risk of thromboembolic disease in the postpartum period¹¹.

According to a recent prospective study, the better quality of obstetric and neonatal care has resulted

in a significant reduction in the maternal mortality rate (from 4.1% to 1.7%) with improved fetal survival (from 60 to 80%) . As seen in present case pulmonary causes were the major causes of near miss morbidity (66.7%) among the factors predicting maternal death⁸.

Conclusion

Although this is a first case report of HbSD in pregnancy, increased awareness and high index of suspicion would lead to detection of such cases in future. Since this type of hemoglobin is not uncommon in this region of world, this heterogeneous state of HbD as HbSD may have been under reported due to lack of awareness. An obstetrician must know that heterogeneous state may also present clinically indistinguishable from homozygous state and hence be prepared to manage in the similar way. Screening for hemoglobinopathy in early pregnancy, husband's electrophoresis and prenatal genetic testing should be offered to rule out 25% chance of vertical transmission of sickle cell disease. Preconceptional counselling regarding avoidance of precipitating factors of sickle cell crisis and possible obstetric complications has a major role in achieving the best maternal and neonatal outcome.

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