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HAEMOGLOBINOPATHIES IN PREGNANCY

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Abstract : INTRODUCTION Haemoglobinopathies in pregnancy are rare inherited disorders of haemoglobin . The haemoglobinopathies has predilection for certain regions and ethinicity. There were two interesting haemoglobinopathies in our hospital which are illustrated in this presentation. CASE First case was a mother who is a known case of sickle cell anaemia , who was admitted for blood transfusion at 39 weeks of gestation. Her both brothers had sickle cell anaemia and one of the brothers died of sickle cell crisis. Her first two sons were found to be sickle cell trait. She was induced with cerviprime at 40 weeks and delivered an alive female baby and the baby was also tested and found to have sickle cell trait. As we were unable to do sterlisation for her, her husband underwent vasectomy. Second case was a primi who was admitted at 39 weeks with anaemia and persistent indirect hyperbilirubinemia. Her viral markers in liver were found to be normal. The physicians opinion was asked for persistent hyperbilirubinemia and as per physicians advice the patient was referred to haematologist. Haematologist asked for haemoglobin chromatogram and she was found to be beta thalassemia minor. The patient was transfused with two units of packed cells to improve her anaemia status. She was induced with cerviprime at 40 weeks and delivered an alive female baby of 2.8 kgs. Her baby was tested to be normal with high performance liquid chromatography. CONCLUSION These two cases were presented for its rarity in this med ejournal to emphasize the importance of haemoglobinopathies. In addition to nutritional anemia haemoglobinopathies should also be suspected in pregnancy, as the management of haemoglobinopathies is different from nutritional anemia.

Keyword : Haemoglobinopathies, sickle cell anaemia, beta thalassemia minor, chronic anaemia

HAEMOGLOBINOPATHIES IN PREGNANCY:

Haemoglobinopathies are inherited disorders of haemoglobin. The haemoglobinopathies are more common in certain families and certain ethinic groups from Africa, Caribean, south-east Asia, middle east and far east. Approximately 1000 haemoglobin gene variants were identified worldwide.

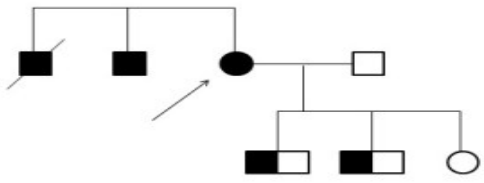
There are two types of haemoglobinopathies:

1. Sickle cell anaemia-Structural abnormality in haemoglobin.
2. Thalassemia-Impaired globin chain production.

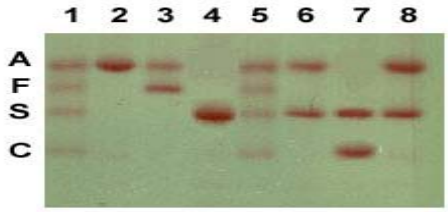
These two haemoglobinopathies are illustrated with two cases:

CASE 1:

26 Years old Mrs. k G3P2L2 of gestational age 39 weeks who was booked and immunised with regular antenatal visits with LMP-20/1/2013,EDD-27/10/2013 who was a known case of sickle cell anaemia attended opd with h/o increased fatiguabilty (since 10days) and admitted with anaemia for blood transfusion. She was married since 10 years, nonconsanguinous. Present pregnancy was the third pregnancy with a spontaneous conception. She was a known case of sickle cell anaemia since childhood and had repeated blood transfusions. She was not a known case of hypertension, diabetes mellitus,thyroid disease, asthma or epilepsy. Her both brothers had sickle cell anaemia and one of the brothers died of sickle cell crisis. Her previous 2 children had sickle cell trait. The prevalence of sickle cell anaemia in family is shown in the following pedigree chart:

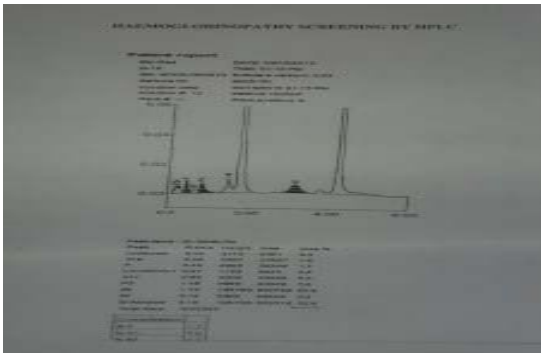


On admission, the patient was found to be anaemic and her BMI was 28.On local examination uterus corresponds to term pregnancy, head mobile and FHS was good. Following investigations were done: Haemoglobin-8.3gm/dl, serum iron:205.6microgram/dl, MCV: 87.2fl,MCH: 26.5pg, MCHC: 30.4%, Serum ferritin: 72.7mg/dl, Vitamin B12: 145pg/ml, Blood group: A positive, Screening: negative , Peripheral smear:normocytic normochromic anaemia showing sickled cells and Osmotic fragility test was reduced.



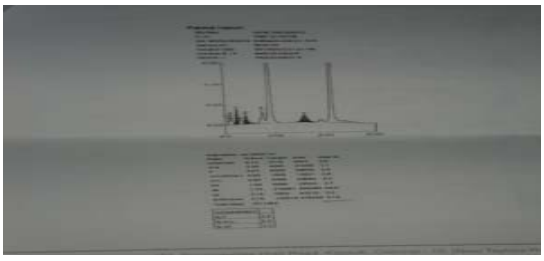
The above Haemoglobin electrophoresis showed fetal haemoglobin:12.5%,HbA2:9.5%,Abnormal Hb:Hb variant 95.9% seen in HbS window (grossly increased)., HbH preparation :negative,HbA:0.5% very much decreased, Sickle cell test: positive. Electrophoretic pattern suggestive of HbS (Sickle cell anaemia). High performance liquid chromatography was performed for her children. Her both the children were found to be sickle cell trait.

REPORT OF FIRST SON:



In this report HbF was 1.7%, HbA was 55.4% (moderately reduced),HbA2 was 3.2% and Hbs was 32.6%(moderate elevation) suggestive of HbAS , Heterozygous sickle cell disease (sickle cell trait).

REPORT OF THE SECOND SON:



In the above report,the fetal haemoglobin was 2.6%, haemoglobin A was 54.3%(moderately reduced), haemoglobin A2 was 3.3% and haemoglobin S was 31.9%(moderate elevation). The chromatogram pattern suggestive of heterozygous sickle cell disease (HbAS); Sickle cell trait.

Management:

Antenatally the patient was jointly managed by obstetrician, hematologist and physician, Oral iron was withheld and the patient received blood transfusion at 16 weeks and 30 weeks as she was anaemic with haemoglobin 8.3gm/dl. After transfusion, patient developed hemolytic crisis with symptoms of fever, icterus and elevated LFT with total bilirubin of 3.79mg/dl, direct bilirubin of 2.31 mg/dl and indirect bilirubin of 3mg/dl. Patient was induced at 40 weeks with prostaglandin E2 gel after 4 hours of application of 1st dose she delivered an alive girl baby weighing 3.7 kgs on 9th October 2013 at 1.17am. In the Postnatal period patient was anaemic,1 unit of packed cell contemplated to prepare her for sterlisation. Cross matched blood sample was found to be incompatible with 20 units of blood. Haematologist opinion obtained regarding this repeated crossmatch incompatibility. It was opined that the patient had developed red cell autoantibodies with direct coomb's test:1+ positive, Indirect coomb's test:2+ positive and hence advised adequate hydration, prophylactic antibiotic and to postpone sterlisation. As the patient was unfit for sterlisation due to severe anaemia, her husband was counselled for vasectomy. Vasectomy was done on December 2013 in the surgery department of Rajiv Gandhi Government General Hospital. The newborn baby was also found to be sickle cell trait.

DISCUSSION:

Sickle cell anaemia is a hereditary haemoglobinopathy caused by point mutation at sixth codon in beta globin gene that changes glutamic acid to valine .The sickle cell anaemia is divided into three types:

1.Homozygous sickle cell disease with Hb S/A:100/0, HbF 2-25% Mcv:80-100.In which HbS increased and HbA is nil or very minimal.

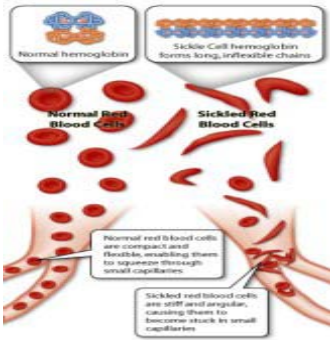
2.Heterozygous sickle cell trait withHbS/A:40/60 and Mcv:normal.In which HbA is moderately reduced around 60%.

3.Mixed variants:Three common mixed varients were A). S/°Thalessemia – Hbs/A:100/0, HbF:1-10% and Mcv:70-80,

B).S/+Thalessemia-HbS/A:60/40 and Mcv:70-80 C). HemoglobinSC – HbS/A:50/0,MCV 80-100.

PATHOPHYSIOLOGY:

HbS polymerises reversibly, when it is deoxygenated. It polymerises to form gelatinous network of fibrous polymers which stiffen the RBC membrane, increase the viscosity and cause dehydration due to potassium leakage and calcium influx, these changes produce sickled shape.



INHERITANCE AND INCIDENCE: It is inherited as a autosomal co-dominant condition. World wide 4000 to 6000 pregnancies are at risk of sickle cell disease. The computed incidence of sickle cell anaemia among African Americans and Hispanics is 1 in 576. In India, in the north incidence is 2 times higher than south .The incidence among the south indian population is 5.38 per 1,00,000 population. In India it is more in middle eastern and north eastern states. In south India it is more common in nilgiri tribes(irulars, kurubas, panyas) .

EFFECTS OF SICKLE CELL ANAEMIA ON PREGNANCY: Abortion, prematurity, IUGR, fetal loss and increased incidence of pre eclampsia, postpartum hemorrhage and infection. There are two types of crisis: 1.

Hemolytic crisis characterized by rapidly developing anaemia, fever and leucocytosis usually after blood transfusion as in this patient. 2.painful sickle cell crisis: which is more common in the last trimester and lasts for few hours to two weeks. This is characterised by lung infarction, heart failure etc. If this painful crisis occurs >3episodes/year,it requires hospitalization.

DIAGNOSIS:

The diagnostic tests includes complete haemogram , red cell indices, osmotic fragility test, genotyping in family members, high performance liquid chromatogram haemoglobin electrophoresis and doppler carotid flow in the fetus.

MANAGEMENT:

Management in pregnancy includes

1. Preconceptional
2. Antepartum management
3. Intrapartum management
4. Postpartum management
5. Contraception

PRECONCEPTIONAL: Chronic diseases and inflammatory conditions should be assessed. Women with hypertension, proteinuria and proliferative retinopathy should be identified. Those who have multiple blood transfusions should be screened for red cell antibodies. Partner should be screened for hemoglobinopathy and other serious genetic diseases. Genetic counselling is considered preconceptionally. If the patient is treated with Hydroxyurea, it should be stopped atleast 3 months before conception and an echocardiography should be done to assess pulmonary hypertension and cardiac dysfunction.

ANTENATAL MANAGEMENT:

Antenatal care should be given jointly by obstetrician, hematologist and physician. Women advised to avoid the precipitating factors of sickle cell crisis such as extremes of temperature, dehydration, high altitude, overexertion and any infection must be promptly treated. Oral iron should be with held. Urine analysis monthly for screening of asymptomatic bacteriuria. Daily low dose aspirin 75mg to decrease the incidence of preeclampsia and IUGR.

INTRAPARTUM MANAGEMENT:

Elective delivery is preferred after 38 weeks. If IUGR ,earlier delivery is preferred. The women should be kept warm, adequate hydration and oxygenation should be maintained.

POSTPARTUM MANAGEMENT:

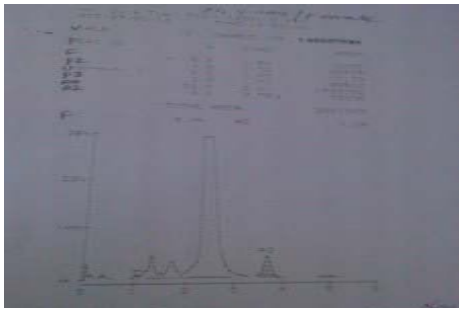
Infection should be watched for and treated vigorously and the Baby should be tested for sickle cell disease.

CONTRACEPTION:

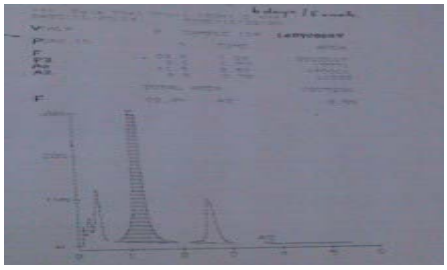
Tubal sterlisation is the ideal method. Progesterone only pill may be used if sterlisation is not possible. If the patient is unfit for surgery, levonorgestrol intrauterine system can be used.

CASE 2:

23 Years old primi Mrs.S with gestational age 39 weeks 2 days who was booked and immunised in Salem GH was referred to ESIC KK Nagar with jaundice. Her LMP was 3/12/2013 and EDD was 10/9/2014.She presented to OPD with h/o easy fatiguability for blood transfusion. Her menstrual history was regular and she was married since 1 year, nonconsanguinous. In the antenatal period, the patient was evaluated for unconjugated hyperbilirubinemia. . The viral markers in liver were found to be negative. Patient was started on tab udiliv(ursodeoxycholic acid) by the physician and hematologist opinion was advised by the physician. High performance liquid chromatography was advised by the haematologist to rule out haemoglobinopathies. bThalessemia minor was diagnosed by high performance liquid chromatography. No h/o blood tranfusion,chronic anaemia and malignancy in the family.



In the high performance chromatogram report, fetal hemoglobin was 0.4%, hemoglobin A was 95% and hemoglobin A2 was 4.6%.In the chromatogram picture the fourth peak indicates increased HbA2.Elevated HbA2 was suggestive of heterozygous bthalassemia. The patient was anaemic and moderately built. The other investigations were Haemoglobin:7.8gm/dl, Liver function test: Total bilirubin:2.9 mg/dl, Direct bilirubin:0.5mg/dl, Indirect bilirubin:2.3 mg/dl,SGOT:33, SGPT:34,Alkaline phosphatase:109,Gamma glutamyl transpeptidase:11. Urine bilesalts & bilepigments: positive. Thyroid function test:TSH: 1.67 and free T4:1.19. The patient was transfused with 2 units of packed cell. She was induced with PGE2 gel on the due date. she delivered an alive female baby of birth weight 2.8kgs.Her postnatal period was uneventful. The baby was tested for haemoglobinopathies. The high performance liquid chromatography was found to be normal.



The newborn baby's report showed fetal hemoglobin of 82.4%, Hemoglobin A of 17.1% and Haemoglobin A2 of 0.5%.In this chromatogram the fourth peak is absent in the A2 region. Thus the chromatogram was normal. The patient was counseled and inserted intrauterine uterine contraceptive device to postpone the next pregnancy.

DISCUSSION:

The highest proportion of thalassemia is in mediteranean region. The word thalassemia is derived from a greek word which means “thalassa” meaning sea as thalassemia is prevalent near sea coast. Incidence: carriers in Mediterranean region was 1:7,In UK the incidence is 1:10000.The beta thalassemia trait in India is around 3.3%.The higher frequency of thalassemia is in north India compared to south. It is more common in Punjab, Gujarat and northeast India.

PATHOPHYSIOLOGY:

The genetically determined haemoglobinopathy is characterized by impaired production of globin peptide genes, abnormal synthesis may result in ineffective erythropoiesis. There are two types of thalassemia:

1. Alpha thalassemia: Impaired synthesis of alpha chain and
2. Beta thalassemia :was due to abnormality in synthesis

of beta chain.

Alpha thalassemia:

The alpha globin gene is located in chromosome 16. a0 thalassemia is due to deletion of both loci of chromosome and a+thalassemia is due to deletion of single loci of chromosome. The deletion of all loci of alpha genes can result in haemoglobin bart (g4) and haemoglobin H(b4) formed as a tetramer. The fetus with thalassemia major dies inutero.

b THALESSEMIA:

This is due to Impaired production of beta globin gene. More than 150 mutations are responsible for b Thalessemia. Single nucleotide substitutions produce translocation and transcription abnormalities. The decrease in beta chain results in available alpha chain to bind with gamma chain resulting in the increased fetal hemoglobin and alpha chain bind with delta chain resulting in increased haemoglobin A2.The increase in alpha chain stabilizing enzyme may also result in beta thalassemia major.

DIAGNOSIS: Complete haemogram, peripheral smear, liver function test, high performance liquid chromatogram, osmotic fragility and haemoglobin electrophoresis.

TREATEMENT:

1. There is no specific treatment for beta thalassemia minor, As in the sickle cell anaemia iron should be given orally only if necessary, the indiscriminate use of iron causes hemosiderosis and hemochromatosis.
2. Although iron is not necessary, folic acid supplementation is important. Daily administration increases haemoglobin concentration
3. Recurrent ultrasound is necessary for fetal growth and NST (Non Stress Test) for fetal well being

CONCLUSION:

These two cases were presented for its rarity in this med Ejournal to emphasize the importance of diagnosing haemoglobinopathies in a pregnant women with chronic anaemia, as the management of haemoglobinopathies is entirely different compared to nutritional anaemia illustrated in this presentation.

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