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Pregnancy with Thalassemia B /Hemoglobin E Disease: A Case Report

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Abstract: ***Thalassemias are group of inherited autosomal recessive hematologic disorders that cause hemolytic anemia. Worldwide, patients with thalassemia beta/hemoglobin E (β-thal/HbE) represent 50 % of severe beta thalassemia. The highest frequencies are observed in India and throughout Southeast Asia including Indonesia. In one study by Suchaya et al.(2008), 0.2% of all pregnant women were affected by β-thal/HbE disease. In this case report, we would discuss management of patient 28 years old with diagnose first pregnancy 27-28 weeks + moderate anemia (Hb : 6.2 g/dL) + Thalassemia (β-thal/HbE). She got three times blood transfusions during pregnancy. Finally, at 37-38 weeks she delivered 2500 g male baby in vigorous condition with no major congenital anomaly. From DNA examination, known her husband has normal DNA, her father carrier of HbE disease whereas her mother carrier of minor β-thalassemia.***

Keywords: Globin, Hemoglobin E, Thalassemia β

1. Introduction

Thalassemia β/ hemoglobin E (β-thal/HbE) disease is a genotype which may be found in half of β mayor thalassemia. Patient who suffered (β-thal/HbE) disease often experience anemia either mild or severe, which needed blood transfusion. According to blood morphology, anemia type of (β-thal/HbE) disease is classified into hypochromic microcytic anemia.

According to World Health Organization (WHO), hemoglobin disorder carrier reach number 269 million people worldwide.[1] In Indonesia thalassemia carrier is estimated 3-5% of total population.[2] It may caused by migration, whereas for (β-thal/HbE) disease alone mostly found in India, Bangladesh, South East Asia, including Indonesia.

In Indonesia, based on RISKESDAS data 2007, province with the most rate of thalassemia is Aceh (1.34%), whereas in our province i.e Bali Province rate of thalassemia is 0.04%.[3]

Genetic defect in thalassemia is based on absence of mRNA of one or more globin chain or may occur resulting from deletion or substitution of globin gen.[3]It may produce damage of red blood cell, which may cause increasing of erythropoietin, bone marrow expansion, bone deformity, splenomegaly, and growth restriction.[4]

This case is a rare case of pregnancy with (β-thal/HbE) disease , which in our hospital , we don't have any practical guidelines to establish diagnose and to manage therapy. Therefore we formed multidisciplinary team which consist of :Obsgyn, pediatrics, and internist (hematology division) to treat this patient comprehensively. By knowing screening and managing of patient with (β-thal/HbE) disease will improve maternal outcome and reduce inherited major thalassemia in neonatal.

2. Case Report

A 28 years oldprimi gravid pregnant woman came to Midwifery Emergency Unit of Sanglah General Hospital at November 17th, 2014 with complained of labor pain and watery vaginal discharge. She then diagnosed with G1P0 37-38 weeks 1st stage of labor (rupture of membrane) + mild anemia (9.12) (Hypochromic-Microcytic) + β minor thalassemia/HbE disease. From progress of labor, at 08.57 am she delivered vaginally baby boy, with birth weight 2500 g in vigorous condition. Two weeks before she already done fetal scanning at Polyclinic by fetomaternal division and they found no major congenital anomaly in the baby with normal Doppler velocimetry of MCA (Middle Cerebral Artery) and Umbilical Artery.

From past medical history knowing that the first time she visited Midwifery Polyclinic Sanglah General Hospital at September 6th, 2014. At that time she felt fatigue and dizzy for 1 week. Neither history of vaginal bleeding nor labor pain was she complained at that time. Fetal movement was felt good. From laboratory result, hemoglobin was 6.2 g/dL with MCV (Mean Corpuscular Volume) value was 75.5 fl and MCH (Mean Corpuscular Hemoglobin) value was 24.7 pg. Whereas Serum Iron, TIBC and Ferritin value still within normal limit. Then she was diagnosed with G1P0 27-28 weeks single/life + moderate anemia (6.2) (Hypochromic-Microcytic) + β minor thalassemia/ HbE disease. She planned to get PRC transfusion until hemoglobin reach 10 g/dL. In the next occasion she admitted to hospital for two times again to get PRC transfusion i.e at October 12th, 2014 and October 27th, 2014.

She already diagnosed with β minor thalassemia since year 2009. In which the laboratory result at 2009 : her blood type was B, rhesus (+), with high levels of HbA2 + HbEi.e 45% (normal : 2.0-5.6%), and high level of HbFi.e 51.1 % (normal < 1%). From her family history, knowing that her first sister was diagnosed with thalassemia at age 32 years old and died 6 months after the diagnosis was established.

Whereas her young sister also known suffered thalassemia at age 6 years old and died at age 18 years old.

From Thalassemia DNA Analyze result, she known to had mutation of β minor thalassemia iemutation at codon 26,GAG$^{(Glutamic)}$became AAG($^{lysine)}$. In which from the resulting DNA Analyze we may concluded that she inherited this (β-thal/HbE) disease because her father is carrier of HbE disease and her mother is carrier of minor β-thalassemia.

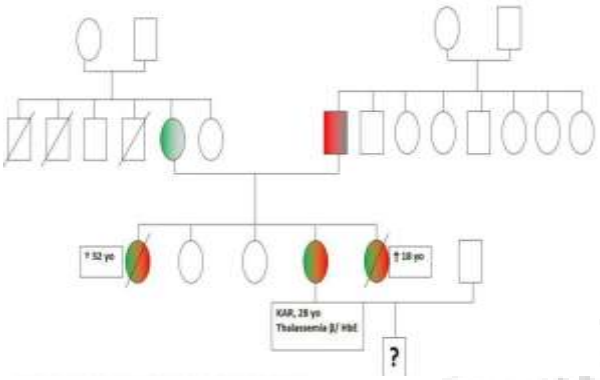

Figure 1: Thalassemia DNA Analyze

	PATIENT	HUSBAND	FATHER	MOTHER	UNIT	NORMAL VALUE
HGB	7,3	15,6			g/dL	12.0-16.0
MCV	79,3	80,5			fL	80.0-100.0
MCH	24,8	25,8			Pg	26.0-34.0
Feritin	282,6	245			ng/mL	20-200
HbA	45,6	86,6	59,5	78,7	%	Undetected - <1
HbA2	(+HbE) 24,1	2,9	(+HbE)26,1	6,6	%	2.0-5.6
HbF	21,5	0,2	0,5	6,4	%	<2 (age-dependent)
DNA ANALYSIS	mutation HbE (codon26,GAG^{Glut}	normal	-	-	-	

Figure 2: Patient's Family Pedigree

From her family pedigree we can find also that her parents have thalassemia trait, which manifest into thalassemia phenotype in her and two of her sister.

3. Discussion

Thalassemia is a genetic defect which caused by decrease of synthesis rate or capability to produce one or more globin chain α, β or other globin type, therefore occur total or partial globin gen deletion and substitution, deletion or insertion of any nucleotide.[5] Globin gen α located at chromosome 16 while globin gen β located at chromosome 11. Thalassemia disease is inherited to offspring by autosomal recessive genotype.

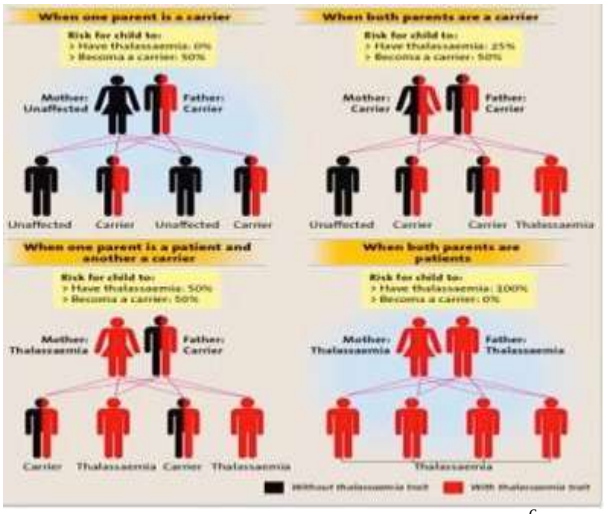

Figure 3: Inheritance of Thalassemia Trait[6]

Hemoglobin E (HbE) is one variant of hemoglobin structure with mutation occur at globin β gen which cause substitution of glutamic acid into lysine in globin chain β 26. This disorder may appear as a heterozygote (carrier HbE), homozygote (HbE), and mixed heterozygote (genotype β thalassemia / Hemoglobin E or sickle cell/hemoglobin E).[1]

This β thalassemia/hemoglobin E disease often found in South East Asia countries like Thailand and Indonesia with prevalence 30-40%.[1]

According to severity of clinical condition, (β-thal/HbE) disease may classified into :[5,7]

1) Mild (β-thal/HbE) disease
   Occur at 15% of total (β-thal/HbE) cases inSouth East Asia region. This disease accompanied by mild microcytic anemia with no need of blood transfusion.
2) Moderate (β-thal/HbE) disease
   This group is the most often found in population, with level of hemoglobin 6-7 g/dL. It may no need blood transfusion, unless present of infection which may worsen the anemia state.
3) Severe (β-thal/HbE) disease
   May occur severe anemia with hemoglobin level 4-5 g/dL. Symptoms and management of this group resemble to major β thalassemia.

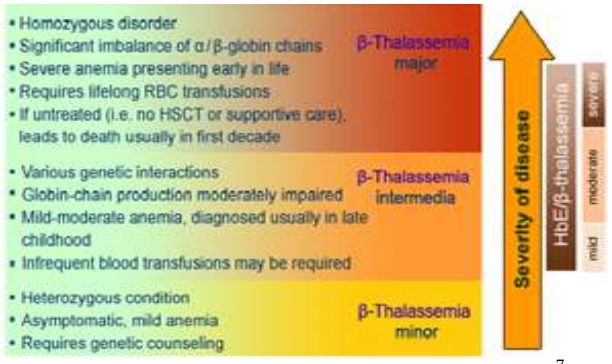

Figure 4: Classification of (β-thal/HbE)Disease[7]

Diagnosis of(β-thal/HbE) disease is established based on anamnesis, physical examination and others supporting examination. Pregnant woman with (β-thal/HbE) disease may complain anemia symptoms like dizzy, fatigue, and

syncope. From medical history we may found history of admission to hospital due to the need of blood transfusion. From physical examination pregnant woman with (β-thal/HbE) disease may be found with pale of eyes, jaundice and hepatosplenomegaly.[4]

Whereas from laboratory examination, pregnant patients with (β-thal/HbE) disease may reveal :[3,8,9]

a) Complete Blood Count
   Microcytic anemia with MCV < 80 fl and MCH < 27 pg.
b) Increase reticulocyte count : 2-8%
c) Blood Smear :
   On blood smear we may found reticulocyte, poikilocytosis, basophilic stippling, tear drops cell and target cell.
d) Ferritin, Serum Iron (SI) and Total Iron Binding Capacity (TIBC): Ferritin in α and βthalassemia often normal or increase, whereas ferritin level in iron deficiency anemia usually low.
e) Bone Marrow Test
   Active erythropoiesis process in thalassemia disease with ratio of myeloid and erythroidis 8:10, compare with normal bone marrow with ratio 10:3.
f) Gel Electrophoresis
   It is a definitive diagnostic which performed by doing separating hemoglobin contain of patient's blood. In non patologic hemoglobin will consist of : 97% HbA, 2,5% HbA2 and <1% HbF. In thalassemia β^0/ hemoglobin E disease will be find HbE, HbA2 dan HbF (50-70%), whereas in thalassemia β^+/ hemoglobin E disease will be find contain of hemoglobin such as HbE, HbA (10%), HbA2 and HbF.

Management of thalassemia in pregnancy is particularly fulfill the need of blood transfusion during pregnancy until after delivery. Hemoglobin value must keep in the level $\geq$ 10 g/dL. Serial fetal ultrasound should be done regularly to know fetal well being intrauterine. Supplementation of folic acid is important especially in first trimester due to increasing of erythropoiesis process. Therapy of chelating agent like Desferrioxamine during pregnancy is prohibited which can cause fetal bone abnormality.[10]

Prenatal diagnosis is not less important than management of thalassemia during pregnancy. In obstetric practical this prevention is done by doing screening in marriage couple who having risk to inheriting thalassemia trait to their offspring. First screening performed on pregnant woman, if the result screening is positive then the screening is continued to her husband. If both of couple has a positive result, they may performed hemoglobin typing or DNA analyze to confirm the thalassemia diagnosis.[6]

In these couple, to know if their fetus exposed to thalassemia, they may do prenatal examination such as :[6]

a) Chorionic Villous Sampling (CVS)
   This technique can be performed at 10-14 weeks of gestational age. It performed by taking any biopsy specimen from fetal chorionfrondosum which guided by fetal ultrasound.
b) Amniocentesis
   This technique can be performed at 16-20 weeks of gestational age. It performed by doing aspiration of amniotic fluid using sterile spinal needle.
c) Fetal Blood Sampling / Cordocentesis / Percutaneous Umbilical Cord Sampling
   It can be performed at 18-22 weeks. By using ultrasound guidance, performed identify of umbilical cord, then doing aspiration 1-2 ml of fetal blood from it to do hemoglobin typing and DNA analyze.

This optional fetal examination can be performed based on fetal gestational age, parent's willingness and availability of resources.

In this patient, from anamnesis we got complain of fatigue with history of thalassemia diagnosis was established 5 years ago, but without any requirements of blood transfusion. From physical examination conjunctiva of eyes were pale. One of symptoms of (β-thal/HbE) disease is anemia which can be worsen during pregnancy, like happened to this patient. In which before pregnancy this patient never get any blood transfusion, whereas during pregnancy until puerperal period she had already got 18 bag of PRC transfusion.
From laboratory examination we got anemia hypochromic microcytic from MCV and MCH result. Then we performed SI, TIBC and ferritin examination. These results were appropriate to thalassemia diagnosis where TIBC value was normal, while SI and ferritin value were higher than normal.[11]

To confirm the result, we performed hemoglobin electrophoresis. From this examination we found increasing level of HbF and HbA2, therefore it directed us to the diagnosis of β thalassemia. By looking from her history which never get blood transfusion, her disease classified into minor β thalassemia. From electrophoresis, we also found any presence of hemoglobin E in her blood, which is one of group of hemoglobin variance that happened because of mutation of β globin chain at codon 26. Level of HbF in thalassemia is one predictor of morbidity degree. In this patient level of HbF was high enough 51.5%. Therefore it may worsen the morbidity of illness in this patient.

Table 1: Hematological Indices of Iron Deficiency and Alpha and Beta Thalassemia [12]

Test	*Iron deficiency*	*Beta thalassemia*	*Alpha thalassemia*
MCV (abnormal if < 80 fl in adults; < 70 fl in children six months to six years of age; and < 76 fl in children seven to 12 years of age)	Low	Low	Low
Red blood cell distribution width	High	Normal; occasionally high	Normal
Ferritin	Low	Normal	Normal
Mentzer index for children (MCV/red blood cell count)	> 13	< 13	< 13
Hb electrophoresis	Normal (may have reduced HbA2)	Increased HbA2, reduced HbA, and probably increased HbF	Adults: normal Newborns: may have HbH or Hb Bart's

Hb = hemoglobin; HbF = fetal hemoglobin; MCV = mean corpuscular volume.

In pregnant women with thalassemia may occur severe anemia which increases risk of IUGR (Intrauterine Growth Restriction), Low birth weight, abortion and preterm birth.

Mode of delivery in pregnant women with (β-thal/HbE) disease is based on obstetric indication accompanied with attention to heart condition. After born, babies from mother with (β-thal/HbE) disease may then be checked of their umbilical cordfor further examination. There is no specific evidence regarding the timing or mode of delivery for women with thalassemia. The timing of delivery should be based on national guidelines dependent on any issues identified in the pregnancy (e.g. diabetes or fetal growth restriction).[13]

Women who are not on chelating agent, may have risk of toxic iron in her blood, which may causes cardiac dysrhythmia when the women is under condition of stress labor. Therefore any chelating agent is recommended on peripartum in this case. Desferrioxamine is secreted in breast milk but not orally absorbed, therefore not harmful to the newborn.[13]

Optional contraception that can be offered to women with (β-thal/HbE) disease is hormonal contraception like oral pill or injection. In this case, the patient prefer to use 3 monthly injection contraception. In other hand breastfeeding is safe in thalassemia and should be encouraged to all patient.[13]

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Disclosure

None

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