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Management Thalassemia in Indonesia : A Literature Review

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Abstract: *Thalassemia is a disease classified in the group of hereditary hemolytic anemia caused by the failure of the formation of one of the four amino acid chains forming Hb, causing incomplete Hb formation. Thalassemia carriers account for 7% of the world's population. At present, the cornerstone of treatment for β-TM in Indonesia remains supportive, including blood transfusions and iron chelation therapy. With a comprehensive discussion about thalassemia in Indonesia, it is hoped that the diagnosis and treatment of thalassemia will be more optimal and effective in future research.*

Keywords: *Thalassemia, Management, Treatment, Indonesia*

1. INTRODUCTION

The countries with the highest prevalence in the world include the Mediterranean, some North and West African countries, the Middle East, the southern Far East, and Southeast Asia (De Sanctis, et al. 2017). There are 300-500 thousand babies born with severe Hb abnormalities every year. About 1.5% of the world's population are beta thalassemia carriers, about 60,000 of whom are babies born with symptoms. There are approximately 40,618 children born with thalassemia beta major, 25,511 of whom are transfusion dependent throughout their lives. Indonesia is included in the world thalassemia belt with a high frequency of carrier genes, around 3-10%. Until 2020, there are more than 10,000 thalassemia patients in Indonesia, with an estimated newborn with thalassemia major of more than 2,000 patients each year MHRI (2021).

The therapy given is in accordance with the condition of thalassemia. In Indonesia, the management of patients with thalassemia centers on supportive therapy. The most common therapy is routine blood transfusion and iron chelation therapy. Chronic anemia in thalassemia patients means that they need blood transfusions for the rest of their lives to keep their hemoglobin (Hb) levels within normal limits. Continuous blood transfusions can cause iron accumulation in organs such as the kidneys, liver, spleen, and others MHRI (2021).

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2. DEFINITION

Thalassemia is a disease classified as hereditary hemolytic anemia. This disorder is caused by the failure of the formation of one of the four amino acid chains that form hemoglobin, so that the formation of hemoglobin in erythrocytes becomes incomplete, which will be easily damaged and the cells will be short-lived (less than 120 days). Based on the type of symptoms, clinical signs, onset, and blood transfusion requirements, thalassemia is divided into three groups, namely thalassemia minor, major, and intermedia (Rahayu, et al. 2016).

3. EPIDEMIOLOGY

Approximately 50-100 thousand children die from beta thalassemia, with most of these cases coming from developing countries, including Indonesia. Indonesia is also included in the list of countries with a high risk of thalassemia. Thalassemia is a non-communicable disease that is in the 5th position, with a total of 281,577 cases, which is then followed by kidney failure, stroke, cancer, and heart disease. Thalassemia cases in Indonesia are increasing. From 2012 to 2021, data on thalassemia patients in Indonesia has increased by 6,077 cases from 4,896 cases. The distribution of beta thalassemia trait carriers in Indonesia, the first rank was occupied by Nangroe Aceh Darussalam Province with a percentage of 13.4%, DKI Jakarta at 12.3%, followed by South Sumatra, Gorontalo, Riau Islands, West Nusa Tenggara, Maluku, and West Papua. The number of thalassemia major patients in Indonesia increases every year, in 2018 there were around 8,616 cases, in 2019 there were 9,028 cases, and in 2020 there were 10,515 people MHRI (2021).

4. CLASSIFICATION

Based on the type of symptoms, clinical signs, onset, and blood transfusion requirements, thalassemia is divided into three groups, namely thalassemia minor, major, and intermedia MHRI (2018).

Thalassemia minor

Thalassemia minor or commonly referred to as carrier thalassemia, where the patient does not show any clinical symptoms. Gene abnormalities in thalassemia minor are only carried by one of the two chromosomes it contains, which can come from the father or mother. If there is only one gene that is still normal, it is enough to help the process of forming good blood cells MHRI (2018).

Thalassemia intermedia

Thalassemia intermedia occurs due to abnormalities in the two chromosomes inherited by the father and mother. The inherited genes are a combination of severe and mild mutants or between mild mutants. Symptoms and clinical signs are usually milder than those of thalassemia major. The clinical manifestations may appear in adolescence or adulthood. Thalassemia intermedia patients do not have regular blood transfusions, sometimes only every three months, six months, or one year. Thalassemia intermedia can develop into thalassemia major if the anemia is not treated properly or even if it has manifested to cause damage to other organs such as the liver, kidneys, spleen, or pancreas MHRI (2018).

Thalassemia major

Thalassemia major or commonly referred to as Cooley's anemia or Mediterranean anemia, is the most severe condition in thalassemia cases. In this condition there is an abnormality when the gene encoding Hb on two chromosomal alleles. Clinical signs and symptoms in thalassemia major patients appear earlier, generally at the age of 7 months or under 3 years. Early symptoms seen on physical examination are pale skin, weakness, enlarged abdomen due to enlarged liver and/or spleen. Patients need blood transfusions starting from the first year of growth, which is age 6-24 months until their lifetime. Thalassemia major blood transfusions are repeated about every two weeks to four weeks. Thalassemia major patients who do not undergo blood transfusions often experience growth and nutrition disorders due to endocrine function disorders MHRI (2018). In addition, growth and nutritional disorders are the result of iron chelation drugs that are not taken regularly (Khan I, et al. 2024).

Genetically, the classification of thalassemia is based on globin chain subunit abnormalities, namely thalassemia α (alpha), thalassemia β (beta), and thalassemia αβ (alpha-beta) MHRI (2018).

Alpha thalassemia

Occurs due to the reduction or absence of the alpha globin chain in the Hb structure, at least one of the four globin alleles. Normally, the encoding of the alpha globin chain is done by a total of four alpha gene alleles. The main abnormality in the alpha gene is the deletion type of mutation, while the point mutation type is only a minority. The number of defective alpha globin alleles will depend on the type and severity of the disease MHRI (2018).

Table 1. General Classification Of A Gene Disorders

Variant	Deletion of α gene	Genotype	Description
Normal	No deletion	(αα/αα)	-
Silent carrier	Deletion 1 of 4 α genes	(α-/αα)	Asymptomatic
Thalassemia trait	Deletion 2 of 4 α genes	(--/αα)	Minor Thalassemia; Asymptomatic, Mild microcytic anemia
HbH Disease	Deletion 3 of 4 α genes	(α-/--)	Intermedia/ major thalassemia
Hb Bart Syndrome	Deletion of 4 α genes	(--/--)	Hydrops fetalis (letal)

Beta thalassemia

Beta thalassemia can occur due to the absence or loss of beta globin chains (β0) or also due to the reduction of beta globin chains (β+). The impact of beta thalassemia leads to an imbalance in the production of alpha and beta globin chains that form HbA, resulting in increased levels of HbF and HbA2 MHRI (2018) & De Sanctis, et al. (2017).

Table 2. General Classification Of A Gene Disorders

Variant	Genotype	Description
Normal	(β/β)	-
Beta thalassemia trait	(β/β0) (β/β+)	Minor thalassemia: Asymptomatic, mild microcytic hypochromic anemia
Beta thalassemia intermedia	(β+/β+) (β+/β0) (βE/β+) (β+/β0)	Mild to moderate anemia, iron overload
Beta Thalassemia major	(β0/β0)	Severe nemia, transfusion dependent, iron overload

5. ETIOLOGY

The ineffective erythropoiesis process can inhibit hepatic production of hepcidin, which functions to inhibit the uptake and release of iron from macrophages and hepatocytes. In beta thalassemia, there is an increased uptake and release of iron by macrophages. As a result, there is an accumulation of iron stored in the form of ferritin in the organs.

Furthermore, it will degrade into hemosiderin. Therefore, in thalassemia patients, there is an increase in serum ferritin and hemosiderin levels (De Sanctis, et al. 2017).

6. CLINICAL MANIFESTATION

Signs and symptoms in patients appear from the first two years of birth, which is around 6-24 months of age. Things can be seen in the physical body of beta major thalassemia patients, namely a weak body, yellowish skin (jaundice), fast fatigue, stunted growth, eating problems, recurrent fever, diarrhea, and there is enlargement in the abdomen due to enlarged liver, lien, or kidney due to the process of extramedullary hematopoiesis. The diagnosis of thalassemia is based on anamnesis, physical examination, laboratory examination, and DNA (Deoxyribonucleic acid) analysis MHRI (2018).

7. DIAGNOSIS

Anamnesis

Anamnesis is needed to obtain information about the patient's health condition. Questions that need to be asked in thalassemia beta major patients include early onset of chronic pallor, history of regular blood transfusions, family history of thalassemia and repeated blood transfusions, enlarged abdomen due to hepatosplenomegaly, ethnic or tribal origin, such as Mediterranean, Middle Eastern, Indian, or Southeast Asian race. In addition, a history of delayed growth and/or puberty should be noted MHRI (2018).

Physical Examination

In making a diagnosis of thalassemia beta major, a physical examination is required. The patient may be found with pale and hyperpigmented skin, icterus, cooley facies (squinted eyes, prominent forehead, widened eye distance, protrusion of maxillary bone, dental malocclusion, and short stature due to growth disturbance and malnutrition MHRI (2018).

Laboratory Examination

Supporting laboratory examinations that can be done are Complete Peripheral Blood Count (CBC) examinations, with Hb levels < 7 g/dL, Mean Corpuscular Volume (MCV) < 80 fL which indicates microcytic, Mean Corpuscular Hemoglobin (MCH) < 27 pg which interprets hypochromic. Electrophoretic Hb examination, the HbA content in the blood of thalassemia beta major patients decreased, which should be in normal people which is 96-98% to around 0-3% and HbF levels around 95%, while in normal people <1%. Meanwhile, HbA2 is >5%. Peripheral blood picture examination is performed to strengthen the

diagnosis, namely by finding a picture of hypochromic microcytic, anisopoikilocytosis, including tear-drop formation, target cells, basophilic stippling, and nucleated erythrocytes. RDW (Red Cell Width) examination is a routine examination to determine the size variation of red blood cells. In thalassemia beta major patients, RDW levels increased by 16.9 ± 1.4% MHRI (2018).

8. TREATMENT & MANAGEMENT

Blood Transfusion

Blood transfusions are done to control hematopoiesis and optimize the child's growth and development. The treatment of blood transfusion in each patient varies depending on the condition of each patient. Blood transfusion is mandatory in patients diagnosed with thalassemia beta major or when the Hb level is <7 g/dL after two examinations with an interval of more than two weeks in the absence of infectious causes or if Hb level >7 g/dL is obtained in the presence of growth failure, and / or bone deformities due to thalassemia. If the Hb level before transfusion is >6 g/dL, then the volume of blood transfused is around 10-15 mL/kg / time with a speed of 5 mL / kg / hour, while if the Hb level before transfusion is <6 g/dL and / or the patient's condition with any Hb level, but in the patient there is heart failure, then the volume of blood transfused is 2-5 ml / kg / time with a transfusion speed of 2 mL / kg / hour so that the body fluid does not excess. In addition, in the clinical condition of chronic anemia with heart failure, non-routine transfusions should be given. The target Hb after transfusion is no more than 14-15 g/dL, while the Hb level after the next transfusion is expected to be no less than 9.5 g/dL. The blood used for transfusion should be from the same blood group of both ABO and Rh (Rhesus) types to minimize the occurrence of alloimmunization MHRI (2018).

Iron Chelation Drug

The role of chelators needs to be used to help the body excrete iron that cannot be excreted naturally. Iron chelators can bind iron that is not bound to transferrin in the blood plasma, so as to remove iron in the body. Iron chelation is given when the blood serum ferritin level reaches 1000 ng/mL, or transferrin saturation ≥70%, or if it has been transfused 10-20 times or about 3-5 L. The type of iron chelation used is in accordance with the patient's condition continuously, while considering effectiveness, side effects, drug availability, economy, and patient quality of life. Iron chelation currently used are deferoxamine, deferiprone, and deferasirox MHRI (2018).

Deferoxamine

Deferoxamine is the first line of iron chelation in children, given at a dose of 30-60 mg/kg/time subcutaneously, intravenously, or intramuscularly. This drug has a short half-life, so it is given about 8-12 hours a day. The risk of toxicity is higher in pediatric patients under 2 years old. Possible side effects include hearing loss, visual impairment, growth disturbance, allergic reactions, or local reactions MHRI (2018).

Deferiprone

Deferiprone at a dose of 75-100 mg/kg/day orally after meals, divided into three doses. Side effects that can arise are mild neutropenia, arthralgia, and gastrointestinal disorders, such as nausea, vomiting, abdominal pain and diarrhea MHRI (2018).

Deferasirox

The dosage of Deferasirox is 20-40 mg/kg/day. Good oral bioavailability and a long half-life make this drug sufficient to be consumed once per day on an empty stomach 30 minutes before or after meals. The side effect of using this drug is decreased kidney function MHRI (2018).

Splenectomy

Indications for splenectomy are patients with hypersplenism, leukopenia, and thrombocytopenia. Splenectomy is performed by incising the spleen. However, this procedure should not be performed on patients under 5 years of age because they are at high risk of sepsis due to viruses, bacteria, fungi, and protozoa. However, post-splenectomy patients rarely experience thrombosis MHRI (2018).

9. PREVENTION

Optimizing preventive programs may be the most suitable option for the current thalassemia condition in Indonesia. Education is the main step that needs to be conveyed to the community, regarding early symptoms, disease progression, and how to prevent it. The involvement of thalassemia education to the community requires participation from various sectors, such as doctors, nurses, competent organizations, mass media, various health facilities, the Office of Religious Affairs, and the role of community awareness itself. Then, genetic counseling efforts are also needed by making a definite diagnosis from a doctor to parents or couples at risk and further reviewing the desire for a pregnancy program. Prenatal evaluation is also needed to find out the condition of the fetus as early as possible. In order to identify carriers of thalassemia, carrier screening is needed in a population. Screening can be done at any time and age. The examinations carried out are routine hematology,

peripheral blood examination, serum ferritin level examination, Hb analysis, and DNA analysis MHRI (2018) & Cousens, N. E., et al (2010).

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