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RESEARCH ARTICLE

Factors Associated to Growth Disorder in Children with Thalassemia Major

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Abstract

Growth disorders in short stature are often found in patients with β -thalassemia major. It is caused by several factors such as hypoxia, hemosiderosis, deficiency of nutritional intake, and micronutrient. Disorder in growth will affect the patient's quality of life. This study aims to determine the prevalence of growth disorders and analyze the factors associated with thalassemia child growth disorders. This study used an observational analytic study with a cross-sectional design on 167 patients with β -thalassemia major at the Palang Merah Indonesia Hospital, Bogor, West Java, in October–December 2018. Data was collected using a transfusion compliance questionnaire and the Morisky Medication Adherence Scale (MMAS-8), while growth was assessed using the CDC 2000 height/age curve. Data analysis used SPSS for Windows version 21.0. Of 167 subjects, 86 subjects (51.5%) were not adherent to transfusion, 97 subjects (58.1%) had low consumption of chelation iron, and 146 subjects (87.4%) had growth problems. The results of bivariate data analysis using the chi-square test for transfusion compliance and parental education on growth obtained p=0.000 and p=0.032. Likewise, for compliance with iron chelation consumption and parents' income to growth, the p value=0.000 was obtained. It was concluded that the prevalence of growth disorders was 87.4%, and there was a relationship between transfusion compliance, parental education level, parents' income, and compliance with iron chelation consumption on growth disorders in thalassemia children.

Keywords: Growth, iron chelation, thalassemia major, transfusion

Faktor-faktor yang Berhubungan dengan Gangguan Pertumbuhan pada Anak Talasemia Mayor

Abstrak

Gangguan pertumbuhan berupa perawakan pendek sering ditemukan pada penderita talasemia β mayor. Hal ini disebabkan oleh beberapa faktor seperti hipoksia, hemosiderosis, kekurangan asupan nutrisi, dan mikonutrien. Gangguan pertumbuhan akan memengaruhi kualitas hidup pasien. Penelitian ini bertujuan mengetahui prevalensi gangguan tumbuh kembang dan menganalisis faktor-faktor yang berhubungan dengan gangguan tumbuh kembang anak talasemia. Penelitian ini menggunakan jenis penelitian observasional analitik dengan desain *cross-sectional* pada 167 pasien talasemia β mayor di RS Palang Merah Indonesia, Bogor, Jawa Barat pada bulan Oktober–Desember 2018. Pengumpulan data dilakukan dengan menggunakan kuesioner kepatuhan transfusi dan *Morisky Medication Adherence Scale* (MMAS-8), sedangkan pertumbuhan dinilai menggunakan kurva tinggi/usia CDC 2000. Analisis data menggunakan SPSS *for Windows* versi 21.0. Dari 167 subjek, 86 subjek (51,5%) tidak patuh pada transfusi, 97 subjek (58,1%) memiliki konsumsi kelasi besi rendah, dan 146 subjek (87,4%) mengalami gangguan pertumbuhan. Hasil analisis data bivariat menggunakan uji *chi-square* untuk kepatuhan transfusi dan pendidikan orangtua tentang pertumbuhan diperoleh p=0,000 dan p=0,032. Begitu pula untuk kepatuhan konsumsi kelasi besi dan pendapatan orangtua terhadap pertumbuhan diperoleh p=0,000. Disimpulkan bahwa prevalensi gangguan tumbuh kembang sebesar 87,4% dan terdapat hubungan kepatuhan transfusi, tingkat pendidikan orangtua, pendapatan orangtua, dan kepatuhan konsumsi kelasi besi dengan gangguan tumbuh kembang

Kata kunci: Kelasi besi, pertumbuhan, talasemia mayor, transfusi

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Introduction

Thalassemia is a blood disorder found in many countries around the world, especially in people that come from the Mediterranean, Middle East, and Asia. Thalassemia is a genetically recessive inherited blood disorder characterized by lack or absence of hemoglobin chain synthesis.1,2 This causes the shape of blood cells to become imperfect and leads to anemia. The World Health Organization (WHO) in 2012 reported that approximately 7% of the world's population has the thalassemia gene, with 40% of cases in Asia.3 The Indonesian Thalassemia Foundation noted an increase in cases of thalassemia major in Indonesia from year to year. In 2018 there were reported 9,028 cases. The prevalence of thalassemia carrier cases in Indonesia was estimated at 3.7%.4 Stunted growth often occurs in pediatric β-thalassemia patients. Adolescents are generally not immediately detected in most patients.

Before the era of transfusion and iron chelation therapy, tissue hypoxia due to anemia and iron toxicity due to repeated blood transfusions were the leading causes of growth disorders. Nutrition is another critical factor for growth.^{1,5} A study conducted in India found that 54% of thalassemia major children had growth problems.⁶ Previous researchers concluded that various factors influenced the relationship between transfusion compliance and iron chelation consumption on growth in children with thalassemia.7,8 Meanwhile, according to the Gomber and Dewan⁹ study, it was concluded that there was no relationship between blood transfusion compliance and iron chelation consumption on growth in children with thalassemia. Another study concluded that the risk factors for growth disorders in thalassemia were age, deferoxamine dose, and family income, serum ferritin levels.^{10,11} This study aims to determine the prevalence of growth disorder and to analyze the risk factors associated with growth in β -thalassemia major children.

Methods

This research was an observational analytic study with a cross-sectional design at Palang Merah Indonesia Hospital, Bogor, West Java, Indonesia, in October–December 2018. The selection of research subjects used consecutive non-random sampling techniques. Data were collected by interview using two questionnaires, namely a transfusion compliance questionnaire recommended by the Minister of Health of the Republic of Indonesia. It consists of 4 questions and a questionnaire on compliance with iron chelation drinking using Morisky Medication Adherence Scales (MMAS-8) consisting of 8 question items. Each item is given a one if the answer is true and o if the answer is wrong. The level of adherence was divided into three categories: high adherence if the score was 8, the score 6-7 was moderate, and the score <6 was low. Growth impairment assessments used the 2000 stature for age percentile CDC curve. If the result is <5 percentile, it is said to have growth problems. Measurement of body height using a microtoise with a measuring capacity of 2 meters and an accuracy of 0.1 cm.

The study inclusion criteria were β -major thalassemia patients aged 7-16 years who received blood transfusions and iron chelation therapy, parents/guardians of patients willing to sign an informed consent. The sample size was determined using the infinite-finite population formula with a 95% significance level of 1.96. The prevalence for counting samples was 54.4%, with a measurement accuracy of 0.05. Based on the calculation, it is required that the research subjects are 167 thalassemia major patients aged 7-16 years. The data processing used SPSS for Windows version 21.0, and data analysis used the chi-square test with a significance level of ≤ 0.05 . This research protocol has passed a research ethics review from the Research Ethics Committee of the Faculty of Medicine, Universitas Trisakti number: 137/KER-FK/VIII/2018.

Results

The results obtained from 167 research subjects were most girls as many as 95 subjects (56.9%). Most of the subjects were \leq 15 years old (70.7%), with an average age of 12 years, 132 cm height, and 34 kg body weight. A total of 86 subjects (51.5%) were included in the non-adherent category for blood transfusion, 97 subjects (58.1%) were in the low category for adherence to iron chelation consumption. The prevalence of growth disorders was found 87.4% of subjects, 70.1% with Hb levels \leq 7 g/dL and 70.1% had ferritin levels \geq 1,000–<2,500 ng/mL. From the parental data, it was found that most parents had a moderate

Variables	x±SD	n=167	%
Gender			
Воу		72	43.1
Girl		95	56.9
Age (year)	12 ± 3.90		
Height (cm)	132 ± 18.50		
Body weight (kg)	34 ± 12.10		
Parent education			
Low		28	16.8
Middle		82	49.1
High		57	34.1
Parent income			
<regional minimum="" td="" wage<=""><td></td><td>88</td><td>52.7</td></regional>		88	52.7
≥regional minimum wage		79	47.3
Siblings (+thalassemia major)			
Yes		15	9.0
No		152	91.0
Transfusion compliance			
Yes		81	48.5
No		86	51.5
Compliance iron chelation			
Low		97	58.1
Middle		48	28.7
High		22	13.2
Growth disturbance			
Yes		146	87.4
No		21	12.6
Pre-transfusion Hb (g/dL)			
≤7		117	70.1
>7		50	29.9
Ferritin level (ng/mL)			
<1,000		7	4.2
≥1,000-<2,500		117	70.1
≥2,500		43	25.7

Table 1 Cl	haracteristic	of Research	Subjects
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level of education (graduated from high school) is 49.1%, and parents' income is below the regional minimum wage of 52.7%. In the family other than the subject, it was found that 9% (15 of 167 subjects) had siblings with thalassemia as well (Table 1).

This study found a statistically significant relationship between transfusion adherence factors, parental education, and growth disorders with p=0.000 and p=0.032. Similarly, there was a statistically significant relationship between parents' income factors and compliance with iron chelation consumption with growth disorders with p=0.000 and p=0.000 (Table 2).

Discussion

This study found that 87.4% of the 167 subjects with β -thalassemia major had growth problems. The prevalence obtained is higher than previous studies conducted in India; 54% of thalassemia major children have growth problems.⁶ Growth disorders in the form of short stature, with a height below the average, are often found in patients who do not routinely perform blood transfusions or consume chelating iron regularly according to doctor's instructions. Many factors cause growth disorders such as chronic anemia and hypoxia with the clinical picture of children

Variables	Growth Diso	n Valua	
Variables	Yes (%)	No (%)	- p value
Transfusion compliance			0.000*
Yes	60 (74.1)	21 (25.9)	
No	86 (100)	0 (0)	
Parent education			0.032^{*}
Low	27 (96.4)	1 (3.6)	
Middle	77 (93.9)	5 (6.1)	
High	42(73.7)	15 (26.3)	
Parent income			0.000^{*}
<regional minimum="" td="" wage<=""><td>88 (100)</td><td>0 (0)</td><td></td></regional>	88 (100)	0 (0)	
≥regional minimum wage	58 (73.4)	21 (26.6)	
Compliance iron chelation			
Low	97 (100)	0 (0)	0.000^{*}
Moderate	45 (93.8)	3 (6.3)	
High	4 (18.2)	18 (81.8)	

Table 2 Bivariate Relationship between Independent Variables and Growth Disorder

Note: *p<0.05 significant

who are pale, weak, and easily tired as well as due to liver dysfunction, deficiency of zinc and folic acid, iron overload, iron chelation toxicity, emotional factors, and endocrine disorders.¹²⁻¹⁴

Adherence to blood transfusion on research subjects showed low-level adherence. Factors that influence this condition were psychosocial factors, economic conditions, worry/fear of other risks from blood transfusions such as hepatitis infection and HIV.13,15 Physical changes in thalassemia children make parents feel embarrassed and cover the child's condition from the community. Economic problems also play a role in the level of transfusion compliance. Even though they have used government health insurance coverage and are not charged for blood transfusions, patients still have to pay for transportation, which prevents patients from going to the hospital for blood transfusions. If blood transfusions are given regularly, and Hb levels are maintained at ≥ 9 g/dL, children with thalassemia will experience average growth and development until 10-12 years.5,16

Repeated blood transfusions will lead to the fulfillment of transferrin capacity in the body, which will cause iron overload. Iron accumulation occurs in various organs such as the liver, pancreas, heart, endocrine glands, and gonads. Free iron/non-transferrin binding protein (NTBI) acts as a free radical and can cause damage to cells and organ tissues. Iron accumulation in the endocrine glands causes endocrine disorders causing hypogonadotropic, adrenal insufficiency, growth hormone (GH) deficiency, hypothyroidism, hypoparathyroidism, hypogonadism, and diabetes mellitus.16-19 Growth disturbances in thalassemia major patients due to hormonal disorders are very complex. This growth disturbance occurs due to iron overload in the endocrine and gonadal glands. which causes hypogonadotropic hypogonadism, hypoparatiorids, hypothyroidism, diabetes mellitus, growth hormone deficiency, adrenal insufficiency.20-22 Iron overload in the anterior pituitary gland causes pituitary damage, resulting in disruption of GH pathways-IGF-I (growth hormone-insulin-like growth hormone factor-I). Damage to the anterior pituitary causes impaired GH secretion, which results in impaired production of IGF-I and IGFBP3 by the liver due to reduced GH stimulation of the liver, resulting in decreased GH and IGF-I. It will affect the speed of bone growth on the bone growth plate so that the child's stature is short.^{17,18,23}

Hypogonadotropic-hypogonadism happens due to damage to the hypothalamus and anterior pituitary caused by hemosiderosis. The gonadotropins produced by the anterior pituitary are very sensitive to oxidative damage caused by iron overload. Several studies have reported hypothyroidism in β -thalassemia major. As is known, thyroid hormone plays an essential role

in bone maturation, influencing GH secretion, directly affecting chondrocytes by increasing IGF-I secretion, and promoting chondrocyte maturation. The hypothyroid condition will play a role in the growth disorders of thalassemia major children.^{19,20} Iron chelation is needed to overcome iron overload and hemosiderosis. Iron chelation therapy requires high commitment and compliance from the patient and family support and community support among thalassemia. The choice of iron chelation for each individual can be different by considering several things: effectiveness, side effects, drug availability, price, patient's quality of life, patient comfort because it must be used continuously. Currently, in Indonesia, there are three types of chelation iron, namely deferoxamine, deferiprone, and deferasirox. Although the administration of iron chelation is provided free of charge by the government, it appears that patient adherence to iron chelation consumption is low. Many things can affect compliance with iron chelation consumption. The low level of adherence to iron chelation consumption is influenced by patient psychological factors (the patient feels bored), side effects of the drug, and also the availability of drugs.

Low adherence to the use of iron chelation was statistically significant to growth disorders. Previous researchers also concluded that irregular consumption of chelation iron would affect the growth of thalassemic children.⁷ In contrast to the results obtained in this study, other researchers concluded that there was no relationship between transfusion adherence and consumption of chelating iron on growth.

In this study, there is a significant relationship between education level and family income with growth disorders. It also correlates with parents' understanding of the disease, management in routine transfusions, the benefits of iron chelation, and the prevention of having the next child with thalassemia major. In addition, nutritional factors are also important things to pay attention to in this case. Multifactor cause growth disturbances in thalassemia patients. Factors that more influence growth and can cause growth disorders are ethnic, genetic, and hormonal factors. Nutritional deficiencies, deficiency of vitamin C, vitamin D, lack of physical activity and psychological disorders also contribute to growth disorders in thalassemia major patients.9-11 Cooperation, communication and good relations between parents and other parents of fellow patients, parents and health workers, both doctors, nurses and pharmacists are needed to overcome problems that arise from this disease.^{24,25} Further research is needed to research other factors that can affect growth disorders in children with thalassemia, such as psychological, nutritional, ethnic, genetic, and hormonal factors.

Conclusions

This study concluded that there was a significant relationship between transfusion compliance with iron chelation consumption and the level of parental education and parents' income on growth in children with β -thalassemia major.

Conflict of Interest

The authors do not have any conflict of interest to declare.

Acknowledgments

We would like to thank the Head of the Education and Training and Research Section of PMI Hospital Bogor, health workers, parents of patients, and thalassemia patients who were willing to be respondents in this study.

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Factors Associated to Growth Disorder in Children with Thalassemia Major

by Meiyanti Meiyanti

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RESEARCH ARTICLE

Factors Associated to Growth Disorder in Children with Thalassemia Major

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Abstract

Growth disorders in short stature are often found in patients with β -thalassemia major. It is caused by several factors sufficiency is hypoxia, hemosiderosis, deficiency of nutritional intake, and micronutrient. Disorder in growth will affect the patient's quality of life. This study aims to determine the prevalence of growth disorders and analyze the factors associated with thalassemia child growth disorders. This study used an observational analytic study with a cross-sectional design on 167 patients with β -thalassemia major at the Palang Merah Indonesia Hospital, Bogor, West Java, in October–December 2018. Data was collected using a transfusion compliance questionnaire and the Morisky Medication Adherence Scale (MMAS-8), while growth was assessed using the CDC 2000 height/age curve. Data analysis used SPSS for Windows version 21.0. Of 167 subjects, 86 subjects (51.5%) were not adherent to transfusion, 97 subjects (58.1%) had low consumption of chelation iron, and 146 subjects (87.4%) had growth problems. The results of bivariate data analysis using the chi-square test for transfusion compliance and parental education on growth obtained p=0.000 and p=0.032. Likewise, for compliance with iron chelation iron, and 146 subjects (87.4%) had growth disorders was 87.4% 2 and there was a relationship between transfusion compliance, parental education level, parents' income, and compliance with iron chelation consumption on growth disorders in thalassemia children.

Keywords: Growth, iron chelation, thalassemia major, transfusion

Faktor-faktor yang Berhubungan dengan Gangguan Pertumbuhan pada Anak Talasemia Mayor

Abstrak

Gangguan pertumbuhan berupa perawakan pendek sering ditemukan pada penderita talasemia β mayor. Hal ini disebabkan oleh beberapa faktor seperti hipoksia, hemosiderosis, kekurangan asupan nutrisi, dan mikonutrien. Gangguan pertumbuhan akan hemengaruhi kualitas hidup pasien. Penelitian ini bertujuan mengetahui prevalensi gangguan tumbuh kembang 23 menganalisis fakt 7 faktor yang berhubungan dengan gangguan tumbuh kembang anak talasemia. Penelitian ini menggunakan jenis penelitian observasional analitik dengan dengan dengan dengan dengan dengan dengan gangguan tumbuh kembang anak talasemia β mayor di RS Palang Merah Indonesia, Bogor, Jawa Barat pada bulan Oktober–Desember 2018. Pengumpulan data dilakukan dengan menggunakan kuesioner kepatuhan transfusi dan *Morisky Me Pation Adherence Scale* (MMAS-8), sedangkan pertumbuhan dinilai menggunakan kurva tinggi/usia CDC 2000. Analisis data menggunakan SPSS for Windows versi 21.0. Dari 167 subjek, 86 subjek (51,5%) tidak patuh pada transfusi, 97 bjek (58,1%) memiliki konsumsi kelasi besi rendah, dan 146 subjek (87,4%) mengalami gangguan pertumbuhan. Hasil analisis data bivariat menggunakan uji *chi-square* untuk kepatuhan konsumsi kelasi besi dan pendapatan orangtua terhadap pertumbuhan diperoleh p=0,000 dan p=0,032. Begitu pula untuk kepatuhan konsumsi kelasi besi dan pendapatan orangtua terhadap pertumbuhan diperoleh p=0,000. Disimpulkan bahwa prevalensi gangguan tumbuh kembang asebesar 87,4% dan terdapat hubungan kepatuhan transfusi, tingkat pendidikan orangtua, pendapatan orangtua, dan kepatuhan konsumsi kelasi besi dengan gangguan tumbuh kembang

Kata kunci: Kelasi besi, pertumbuhan, talasemia mayor, transfusi

Received: 24 February 2021; Revised: 27 July 2021; Accepted: 5 August 2021; Published: 31 August 2021 **Correspondence:** Meiyanti, dr., Sp.F.K. Department of Pharmacology and Medical Pharmacy, Faculty of Medicine, Universitas Trisakti. Jln. Kyai Tapa No. 260, West Jakarta 11440, Special Capital Region of Jakarta, Indonesia. E-mail: meiyanti@trisakti.ac.id Nurbaiti Annisaa Soegiharto and Meiyanti: Factors Associated to Growth Disorder in Children with Thalassemia

Introduction

Thalassemia is a blood disorder found in many countries around the world, especially in people that come from the Mediterranean, Middle East, and Asia. Thalassemia is a genetically recessive inherited blood disorder characterized by lack or absence of hemoglobin chain synthesis.1,2 This causes the shape of blood cells do become imperfect and leads to anemia. The World Health Organization (WHO) in 2012 reported that approximately 7% of the world's population has the thalassemia gene, with 40% of cases in Asia.3 The Indonesian Thalassemia Foundation noted an increase in cases of thalassemia major in Indonesia from year to year. In 2018 there were reported 9,028 cases. The prevalence of thalassemia carrier cases in Indonesia was estimated at 3.7%.4 Stunted growth often occurs in pediatric β-thalassemia patients. Adolescents are generally not immediately detected in most patients.

Before the era of transfusion and iron chelation therapy, tissue hypoxia due to anemia and iron toxicity due to repeated blood transfusions were the leading causes of growth disorders. Nutrition is another critical factor for growth.^{1,5} A study conducted in India found that 54% of thalassemia major children had growth problems.6 Previous researchers concluded that various factors influenced the relationship between transfusion compliance and iron chelation consumption on growth in children with thalassemia.7,8 Meanwhile, according to the Gomber and Dewan⁹ study, it was concluded that there was no relationship between blood transfusion compliance and iron chelation consumption on growth in children with thalassemia. Another study concluded that the risk factors for growth disorders in thalassemia were age, deferoxamine d2se, and family income, serum ferritin levels.^{10,11} This study aims to determine the prevalence of growth disorder and to analyze the risk factors associated with growth in β-thalassemia major children.

Methods

This research was an observational analytic study with a cross-sectional design at Palang Merah Indonesia Hospital, Bogor, West Java, Indonesia, in October–December 2018. The selection of research subjects used consecutive 26

non-random sampling techniques. Data were collected by interview using two questionnaires, namely a transfus 17 compliance questionnaire recommended by the Minister of Health of the Republic of Indonesia. It consists of 4 questions and a questionnaire on compliance with iron chelation drinking using Morisky Medication Adherence Scales (MMAS-8) consisting of 8 question items. Each item is given a one if the answer is true and o if the answer is wrong. The level of adherence was divided into three categories: high adherence if the score was 8, the score 6-7 was moderate, and the score <6 was low. Growth impairment assessments used the 2000 stature for age percentile CDC curve. If the result is <5 percentile, it is said to have growth problems. Measurement of body height using a microtoise with a measuring capacity of 2 meters and an accuracy of 0.1 cm.

The study inclusion criteria were β -m₂₂ r thalassemia patients aged 7-16 years who received blood transfusions and iron chelation therapy, parents/guardians of patients willing to sign an informed consent. The sample size was determined using the infinite-finite population formula with a 95% significance level of 1.96. The prevalence for counting samples was 54.4%, with a measurement accuracy of 0.05. Based on the calculation, it is required that the research subjects are 167 thalassemia majo patients aged 7–16 years. The data proc<mark>5</mark>sing used SPSS for Windows version 21.0, and data analysis used the chi-square test with a significance level 010 0.05. This research protocol has passed a research ethics review from the Research Ethics Committee of the Faculty of Medicine, Universitas Trisakti number: 137/KER-FK/VIII/2018.

Results

The results obtained from 167 research subjects were most girls as many as 95 subjects (56.9%). Most of the subjects were \leq 15 years old (70.7%), with an average age of 12 years, 132 cm height, and 34 kg body weight. A total of 86 subjects (51.5%) were included in the non-adherent category for blood transfusion, 97 subjects (58.1%) were in the low category for adherence to iron chelation consumption. The prevalence of growth disorders was found 87.4% of subjects, 7(24)6 with Hb levels \leq 7 g/dL and 70.1% had ferritin levels \geq 1,000–<2,500 ng/mL. From the parental data, it was found that most parents had a moderate

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Variables	x±SD	n=167	%
Gender			
Boy		72	43.1
Girl		95	56.9
Age (year)	12±3.90		
Height (cm)	132 ± 18.50		
Body weight (kg)	34 ± 12.10		
Parent education			
Low		28	16.8
Middle		82	49.1
High		57	34.1
Parent income			
<regional minimum="" td="" wage<=""><td></td><td>88</td><td>52.7</td></regional>		88	52.7
≥regional minimum wage		79	47.3
Siblings (+thalassemia major)			
Yes		15	9.0
No		152	91.0
Transfusion compliance			
Yes		81	48.5
No		86	51.5
Compliance iron chelation			
Low		97	58.1
Middle		48	28.7
High		22	13.2
Growth disturbance			
Yes		146	87.4
No		21	12.6
Pre-transfusion Hb (g/dL)			
≤7		117	70.1
13>7		50	29.9
Ferritin level (ng/mL)			
<1,000		7	4.2
≥1,000-<2,500		117	70.1
≥ <mark>2</mark> ,500		43	25.7

Table 1	Characteristic	of Research	Subjects
I UDIC I	Chiul accel lotie	or neoscaren	Subject

level of education (graduated from high school) is 49.1%, and parents' income is below the regional minimum wage of 52.7%. In the family other than the subject, it was found that 9% (15 of 167 subjects) had siblings with thalassemia as well (Table 1).

This study found a statistically significant relationship between transfusion adherence facto 6 parental education, and growth disorders with p=0.000 and p=0.032. Similarly, there was a statistically significant relationship between parents' income factors and compliance with iron chela 25 n consumption with growth disorders with p=0.000 and p=0.000 (Table 2).

Discussion

This study found that 87.4% of the 167 subjects with β -thalassemia major had growth problems. The prevalence obtained is higher than previous studies conducted in India; 54% of thalassemia major children have growth problems.⁶ Growth disorders in the form of short stature, with a height below the average, are often found in patients who do not routinely perform blood transfusions or consume chelating iron regularly according to doctor's instructions. Many factors cause growth disorders such as chronic anemia and hypoxia with the clinical picture of children

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Variables	Growth Diso	n Valuo	
variables	Yes (%)	No (%)	- pvalue
Transfusion compliance			0.000*
Yes	60 (74.1)	21 (25.9)	
No	86 (100)	o (o)	
Parent education			0.032^{*}
Low	27 (96.4)	1 (3.6)	
Middle	77 (93.9)	5 (6.1)	
High	42(73.7)	15 (26.3)	
Parent income			0.000^{*}
<regional minimum="" td="" wage<=""><td>88 (100)</td><td>o (o)</td><td></td></regional>	88 (100)	o (o)	
≥regional minimum wage	58 (73.4)	21 (26.6)	
Compliance iron chelation			
Low	97 (100)	o (o)	0.000^{*}
Moderate	45 (93.8)	3 (6.3)	
High	4 (18.2)	18 (81.8)	

Table 2 Bivariate Relationship between Independent Variables and Growth Disorder

Note: *p<0.05 significant

who are pale, weak, and easily tired a well as due to liver dysfunction, deficiency of zinc and folic acid, iron overload, iron chelation toxicity, emotional factors, and endocrine disorders.¹²⁻¹⁴

Adherence to blood transfusion on research subjects showed low-level adherence. Factors that influence this condition were psychosocial factors, economic conditions, worry/fear of other risks from blood transfusions such as hepatitis infection and HIV.13,15 Physical changes in thalassemia children make parents feel embarrassed and cover the child's condition from the community. Economic problems also play a role in the level of transfusion compliance. Even though they have used government health insurance coverage and are not charged for blood transfusions, patients still have to pay for transportation, which prevents patients from going to the hospital for blood transfusions. If blood transfusions are given regularly, and Hb levels are maintained at ≥ 9 g/dL, children with thalassemia will experience average growth and development until 10-12 years.5,16

Repeated blood transfusions will lead to the fulfillment of transferrin capacity in the body, which will causer for overload. Iron accumulation occurs in various organs such as the liver, pancreas, heart, endocrine glands, and gonads. Free iron/non-transferrin binding protein (NTBI) acts as a free radical and can cause damage to cells and organ tissues. Iron accumulation in the endocrine glands causes endocrine disorders causing hypogonadotropic, adrenal insufficiency, growth hormone (GH) deficiency, hypothyroidism, hypoparathyroidism, hypogonadism, and diabetes mellitus.16-19 Growth disturbances in thalassemia major patients due to hormonal disorders are very complex. This growth disturbance occurs due to iron overload in the endocrine and gonadal glands, which causes hypogonadotropic hypogonadism, hypothyroidism, hypoparatiorids, diabetes mellitus, growth hormone deficiency, adrenal insufficiency.20-22 Iron overload in the anterior pituitary gland causes pituitary damage, resulting in disruption of GH pathways-IGF-I (growth hormone-insulin-like growth hormone factor-I). Damage to the anterior pituitary causes impaired GH secretion, which results in impaired production of IGF-I and IGFBP3 by the liver due to reduced GH stimulation of the liver, resulting in decreased GH and IGF-I. It will affect the speed of bone growth on the bone growth plate so that the child's stature is short.17,18,23

Hypogonadotropic-hypogonadism happens due to damage to the hypothalamus and anterior pituitary caused by hemosiderosis. The gonadotropic produced by the anterior pituitary are very sensitive to oxidative damage caused by iron overload. Several studies have reported hypothyroidism in β -thalassemia major. As is known, thyroid hormone plays an essential role

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in bone maturation, influencing GH secretion, directly affecting chondrocytes by increasing IGF-I secretion, and promoting chondrocyte maturation. The hypothyroid condition will play a role in the growth disorders of thalassemia major children.^{19,20} Iron chelation is needed to overcome iron overload and hemosiderosis. Iron chelation therapy requires high commitment and compliance from the patient and family support and community support among thalassemia. The choice of iron chelation for each individual can be different by considering several things: effectiveness, side effects, drug availability, price, patient's quality of life, patient comfort because it must be used continuously. Currently, in Indonesia, there are three types of chelation iron, namely deferoxamine, deferiprone, and deferasirox. Although the administration of iron chelation is provided free of charge by the government, it appears that patient adherence to iron chelation consumption is low. Many things can affect compliance with iron chelation consumption. The low level of adherence to iron chelation consumption is influenced by patient psychological factors (the patient feels bored), side effects of the drug, and also the availability of drugs.

Low adherence to the use of iron chelation was statistically significant to growth disorders. Previous researchers also concluded that irregular consumption of chelation iron would affect the growth of thalassemic children.⁷ In contrast to the results obtained in this study, other researchers concluded that there was no relationship between transfusion adherence and confumption of chelating iron on growth

consumption of chelating iron on growth. 19 this study, there is a significant relationship between education level and family income with growth disorders. It also correlates with parents' understanding of the disease, management in routine transfusions, the benefits of iron chelation, and the prevention of having the next child with thalassemia major. In addition, nutritional factors are also important things to pay attention to in this case. Multifactor cause growth disturbances in thalassemia patients. Factors that more influence growth and can cause growth disorders are ethnic, genetic, and hormonal factors. Nutritional deficiencies, deficiency of vitamin C, vitamin D, lack of physical activity and psychological disorders also contribute to growth disorders in thalassemia major patients.9-11 Cooperation, communication

and good relations between parents and other parents of fellow patients, parents and health workers, both doctors, nurses and pharmacists are needed to over (15) e problems that arise from this disease.^{24,25} Further research is needed to research other factors that can affect growth disorders in children with thalassemia, such as psychological, nutritional, ethnic, genetic, and hormonal factors.

Conclusions

This study concluded that there was a significant relationship between transfusion compliance with iron chelation consumption and the level of parental education and parents' income on growth in children with β -thalassemia major.

Conflict of Interest

The authors do not have any conflict of interest to declare.

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