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Original Article

# Depression in children with thalassemia major: prevalence and contributing factors

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## Abstract

***Background*** Thalassemia major is a chronic disease requiring lifetime treatment. A recent study showed that 11-62% of thalassemia patients developed depression, which is associated with high morbidity and mortality. Understanding the extent of the problem related to depression and its contributing factors is important for early management.

***Objective*** To determine the prevalence and contributing factors for depression in children with thalassemia major.

***Methods*** This cross-sectional study included thalassemia major patients aged 7 to <18 years in the Department of Child Health, Dr. Moh. Hoesin General Hospital (RSMH) in Palembang from June to July 2018 and had received blood transfusions at least 3 times. Subjects completed the Children's Depression Inventory (CDI) questionnaire. Depression was defined as a total score > 13. Data were analyzed using *SPSS for Windows ver. 22.0*.

***Results*** There were 64 patients included in this study, with mean age 12 (SD 3) years and 82.8% female. Most subjects came from families with low socio-economic status and low parental education. Deferiprone was the most commonly used type of iron-chelating agent. Depression was detected in 34.4% of respondents. Multivariate analysis revealed that factors affecting depression in children with thalassemia major were low maternal education (OR 4.014; 95%CI 1.066 to 15.112) and use of deferasirox (OR 4.129; 95%CI 1.168 to 14.601).

***Conclusion*** Prevalence of depression in children with thalassemia major is 34.4%. Low maternal education and deferasirox use as an iron-chelating agent are associated with depression in children with thalassemia major. **[Paediatr Indones. 2018;58:263-8; doi: http://dx.doi.org/10.14238/pi58.6.2018.263-8]**.

***Keywords:*** *depression; children; thalassemia major*

Thalassemia is a common hereditary hematologic disorder. In 2001, the *World Health Organization* (WHO) stated that 7% of people worldwide were carriers for thalassemia and predicted 300,000-400,000 thalassemic newborns yearly.[1-5] The prevalence of thalassemia is still high, particularly in the thalassemic belt region, including Indonesia.[4] According to Dr. Moh. Hoesin General Hospital (RSMH) registry data between June 2010 and April 2018, there were 287 patients with thalassemia, and 145 (50.5%) of them were 7 to <18 years old.[6]

Patients with thalassemia major need lifelong, recurrent blood transfusions and iron-chelating agents, necessitating regular hospital admission and check-ups to increase survival rate.[1-5] Psychosocial problems related to the disease or its treatments may appear in these patients.[4,7-10] One study showed that 80% of patients with thalassemia major easily get psychologic disorders, i.e., depression and anxiety.[10]

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Depression is a chronic mental disorder causing changes in mood, cognitive function, behavior, and physical health. It is a serious illness that can alter the ability to enjoy life and cause decreased functioning capacity, even for simple tasks.[11,12] The mechanism of depression in children with thalassemia can be directly caused by thalassemia, its treatment and complications, or chronic stress. Some factors, like early onset in young patients, recurrent admission for blood transfusions, complications from the disease (anemia and iron overload), and type of iron-chelating agent, are related to the thalassemic patients' psychosocial development and quality of life. Activity limitation, overprotective parents, and school absence can influence social interaction among children and their peers. Other factors that can affect depression in children are age, sex, parental education, family socio-economic status, family history of depression, and poor social support.[7,10-12] Depression in children is related to significant morbidity and mortality because of its recurrence and as a cause of suicide, decreased compliance, drug-use, teen pregnancy, as well as educational and psychosocial function disorders. Early diagnosis and appropriate treatment improves symptoms in 70-80% patients with depression.[7,9,11,12]

Several instruments are useful for screening depression in children, such as the Children's Depression Inventory (CDI).[9,10] Screening is very important so that early management can be implemented before complications arise. To our knowledge, there have been no studies on the prevalence of depression and its contributing factors in children with thalassemia major aged 7-<18 years in RSMH. Our objective was to identify the prevalence of depression in children with thalassemia major and its contributing factors. Identifying such factors can help with prevention, administering early management, preventing complications of depression, and increasing patient quality of life.

## Methods

This cross-sectional study was done in the Hemato-Oncology Division, Department of Child Health, RSMH between June and July 2018. Children aged 7 to <18 years with thalassemia major at RSMH and who had been transfused at least three times were consecutively included in this study. Patients with known or ongoing treatment for depression, co-morbid chronic disease like epilepsy, systemic lupus erythematosus (SLE), or leukemia, unable to fill the questionnaire, or not on iron-chelating agent therapy were excluded in this study.

All parents and patients included in this study were given a clear explanation and parents asked to sign an informed consent form before joining the study. Demographic and additional data were recorded from patients' medical records and history-taking from parents. Subjects completed the CDI questionnaire, which comprises 27 questions. Depression was defined as total CDI score of > 13. If positive for depression, subjects were referred to the Department of Psychiatry for further management.

Demographic and clinical data were analyzed descriptively. Factors analyzed for their possible association with depression were gender, age (7-9 years and 10 to <18 years), socio-economic status (low if income per month less than South Sumatra Province minimal wage standard of IDR 2,595,994), parental education (≤ 9 years), family history of depression, frequency of transfusions per month (> 1x per month), type of chelating agent (deferasirox or deferiprone), pretransfusion hemoglobin (< 9 g/dL), ferritin level (≥ 1000 ng/dL), complications of disease (infection, hepatitis, HIV, heart failure, or hormonal disturbances), duration of disease (> 8 years), and duration of iron chelation (> 5 years). Chi-square test and multivariate analysis with binary logistic regression analysis test were performed using *SPSS for Windows version 22.0*. The study protocol was reviewed and approved by the Ethics Committee of RSMH/Sriwijaya University.

## Results

There were 64 patients included in this study and most were female (82.8%). Median CDI score was 8, and 22 subjects were deemed to have depression based on their CDI scores. Baseline characteristics of subjects are summarized in **Table 1**.

Children of mothers with low education (<9 years) had 3.4 times higher risk for depression compared to those with mothers with higher

education (P=0.048). The use of deferasirox for iron chelation conferred 1.7 times higher risk for depression compared to deferiprone use (P=0.033). Bivariate analysis results are shown in **Table 2**.

**Table 1**. Baseline and clinical characteristics of subjects (N=64)

| Characteristics | (N=64) |
|---|---|
| Sex, n (%) | |
| Male | 11 (17.2) |
| Female | 53 (82.8) |
| Mean age (SD), years | 12 (3) |
| Age by group, n (%) | |
| 7-9 years | 16 (25) |
| 10 to < 18 years | 48 (75) |
| Median age at diagnosis (range), years | 3 (2-17) |
| Family socio-economic status, n (%) | |
| Low | 48 (75) |
| High | 16 (25) |
| Paternal education status, n (%) | |
| <9 years | 37 (57.8) |
| >9 years | 27 (42.2) |
| Maternal education status, n (%) | |
| <9 years | 42 (65.6) |
| >9 years | 22 (34.4) |
| Family history of depression, n (%) | |
| None | 62 (96.9) |
| Positive | 2 (3.1) |
| Frequency of blood transfusions, n (%) | |
| <1x/month | 52 (81.3) |
| >1x/month | 12 (18.7) |
| Type of iron-chelating agent, n (%) | |
| Deferiprone | 48 (75) |
| Deferasirox | 16 (25) |
| Mean duration of illness (SD), years | 8 (4) |
| Mean duration of iron-chelating agent use (SD), years | 5 (3) |
| Mean pre-transfusion Hgb level (SD), g/dL | 7.18 (0.96) |
| Hgb level by group, n (%) | |
| <9 g/dL | 63 (98.4) |
| >9 g/dL | 1 (1.6) |
| Median ferritin level (range), n/dL | 3.992 (288-14.000) |
| Ferritin level by group, n (%) | |
| <1000 ng/dL | 8 (12.5) |
| >1000 ng/dL | 56 (87.5) |
| Complication of thalassemia, n (%) | |
| Yes | 16 (25) |
| No | 48 (75) |
| Median CDI score (range) | 8 (0-29) |
| Result of CDI, n (%) | |
| No depression | 42 (65.6) |
| Depression | 22 (34.4) |

Multivariate analysis revealed that maternal education <9 years (OR 4.014; 95%CI 1.066 to 15.112) and use of deferasirox as an iron-chelating agent (OR 4.129; 95%CI 1.168 to 14.601) were independent factors positively associated with depression in children with thalassemia major (**Table 3**).

## Discussion

Sixty-four subjects in this study had mean age of 12 (SD 3) years and median age at diagnosis of 3 years. These results were similar to those of Sri Rejeki *et al.*, who noted that patients' mean age was 12.28 years and age at diagnosis was 3.78 years.[13] According to CDI scores, 22 subjects (34.4%) had depression. Our result was higher than a Korean study by Shin *et al.*[14] (14%) and a study by Mednick *et al.* (11%).[15]

Various studies have shown that patients with thalassemia major were susceptible for depression.[7,10,15] Depression in patients may be due to the chronicity of thalassemia. Chronic illness may lead reduced confidence, feeling different from their peers, and dependency on others, all of which can leave them feeling isolated and depressed.[10] The differences in proportion of depression in our study may also have been due to genetic and socio-demographic factors, psychological factors, social support, and different type of questionnaires.

Low maternal education status (<9 years) was significantly associated with depression, but paternal education was not. Risk of depression was four times higher in children from mothers with low education status. This result was consistent with a Chinese study, which found that risk of depression in children from mothers with low education was 2.88 times higher compared to children from mothers with higher education. Parents with low educational status may be less sensitive to psychological alterations in their children, thus providing less emotional support to their children. This behavior may dramatically increase risk of depression in children.[16]

In our study, subjects who used deferasirox as an iron-chelating agent had four times higher risk for depression compared to those who used deferiprone. Kontoghiorhers showed adverse neurologic effects in patients using deferasirox. These neurological

**Table 2**. Factors potentially associated with depression in thalassemia major patients

| Factors | Depression, n(%) | No depression, n(%) | OR (95% CI) | P value |
|---|---|---|---|---|
| Sex | | | | |
| Male | 6 (54.5) | 5 (45.5) | 2.775 (0.738 to 10.428) | 0.117* |
| Female | 16 (30.2) | 37 (69.8) | | |
| Age | | | | |
| 7-9 years | 7 (43.8) | 9 (56.3) | 1.711 (0.536 to 5.464) | 0.362 |
| 10- <18 years | 15 (31.3) | 33 (68.8) | | |
| Family socio-economic status | | | | |
| Low | 17 (35.4) | 31 (64.6) | 1.206 (0.359 to 4.501) | 0.761 |
| High | 5 (31.3) | 11 (68.6) | | |
| Paternal education status | | | | |
| ≤9 years | 16 (43.2) | 21 (56.8) | 2.667 (0.873 to 8.413) | 0.08 |
| >9 years | 6 (22.2) | 21 (77.8) | | |
| Maternal education status | | | | |
| ≤9 years | 18 (42.9) | 24 (57.1) | 3.375 (0.973 to 11.708) | 0.048 |
| >9 years | 4 (18.2) | 18 (81.8) | | |
| Family history of depression | | | | |
| Yes | 0 (0) | 2 (100) | - | 0.247* |
| No | 22 (35.4) | 40 (64.6) | | |
| Frequency of blood transfusions | | | | |
| ≤1 x/ month | 18 (34.6) | 34 (65.4) | 1.059 (0.280 to 4.001) | 0.608* |
| >1 x/ month | 4 (33.1) | 8 (66.7) | | |
| Type of iron-chelating agent | | | | |
| Deferasirox | 9 (56.3) | 7 (43.8) | 1.667 (0.932 to 2.982) | 0.033 |
| Deferiprone | 13 (27.1) | 35 (72.9) | | |
| Pre-transfusion Hgb level | | | | |
| <9 g/dL | 21 (33.3) | 42 (66.7) | - | 0.344* |
| ≥9 g/dL | 1 (100) | 0 (0) | | |
| Ferritin level | | | | |
| <1000 ng/dL | 3 (37.5) | 5 (62.5) | 1.168 (0.252 to 5.420) | 0.565* |
| ≥1000 ng/dL | 19 (33.9) | 37 (66.1) | | |
| Complications of thalassemia | | | | |
| Yes | 16 (33.3) | 32 (66.7) | 0.833 (0.257 to 2.703) | 0.761 |
| No | 6 (37.5) | 10 (62.5) | | |
| Duration of illness | | | | |
| >8 years | 10 (31.3) | 22 (68.6) | 0.758 (0.269 to 2.132) | 0.599 |
| ≤ 8 years | 12 (37.5) | 20 (62.5) | | |
| Duration of iron- chelating agent use | | | | |
| >5 years | 10 (27.8) | 26 (72.2) | 0.513 (0.18 to 1.458) | 0.208 |
| ≤ 5 years | 12 (42.9) | 16 (57.1) | | |

*Fisher's exact test

complications included sleep disturbances, depression, Parkinson's, and anxiety.[17] In contrast, Mednick *et al.* in their longitudinal study on 276 subjects (including 41 children) with thallasemia found no correlation between type of iron-chelating agent and depression.[15]

**Table 3**. Multivariate analysis of factors affecting depression

| Factors | OR (95%CI) | P value |
|---|---|---|
| Maternal education < 9 years | 4.014 (1.066 to 15.112) | 0.040 |
| Deferasirox use | 4.129 (1.168 to 14.601) | 0.028 |

We found no correlation between frequency of blood transfusions per month, pre-transfusion hemoglobin level, ferritin level, complications of thalassemia, duration of illness, or duration of iron-chelating agent treatment with depression. More frequent blood transfusion per month was not also correlated with depression. Mednick et al. had similar findings.[15] However, other studies demonstrated

correlations between frequency of blood transfusions and depression. More frequent blood transfusions increased school absences and affected the patients' social interaction with their peers. Hence, they felt isolated and were susceptible to depression.[7,10,18]

Mean pre-transfusion hemoglobin level in our study was 7.18 (SD 0.96) g/dL. Saini *et al.* also showed a similar result, with mean hemoglobin level of 8.5 (SD 1.41) g/dL. There was no correlation between hemoglobin level and depression in either study.[19] Other studies demonstrated that poorly controlled anemia in thalassemia resulted in brain hypoxia that may affect the limbic system and depression.[7,10,19-21]

High ferritin level leads to higher risk for depression because iron gets deposited in many organs including the brain. Hemosiderosis in the hypothalamic and pituitary area alters endocrine function, resulting in decreased serotonin level and depression.[22] Increased iron level also induces production of reactive oxygen species (ROS) which, if affecting the limbic system, causes depression.[22,23] In our study, median ferritin level was 3,992 ng/dL (288-14,000 ng/dL), and there was no significant association with depression. This result may have been because a high majority of children had iron overload, thus the influence of ferritin on depression could not be demonstrated. Saini et al. noted ferritin level of 3,832 (SD 1,796) ng/dL in subjects, but found no association between ferritin and depression.[19] However, Aydinok et al. demonstrated an association between ferritin level > 2,500 ng/dL and depression.[21]

Mean duration of illness was 8 (SD 4) years in our study, but we found no association with depression. However, Saini et al. reported a mean duration of illness of 6.91 (SD 3.08) years, with a statistically significant association between duration of illness and depression and behavior disorders.[19] Other studies stated that the longer the duration of illness, the more frequently patients are regularly hospitalized for blood transfusions, leading to higher risk for complications and depression.[7,10,18]

The cross-sectional study design limited our ability to explore causal relationships between depression and other factors. Another limitation of this study was that we did not include all other psychosocial stressors and we did not investigate potential biological factors (e.g., hormone levels, etc.) in this study.

We recommend routine examinations for children with thalassemia major using the CDI questionnaire for early detection and treatment of depression. Further studies are needed to compare CDI results between patients with thalassemia major and normal subjects and to evaluate the effect of defarasirox on depression. A prospective study for risk factors of depression is also needed. In conclusion, low maternal education and deferasirox use have significant associations with depression in children with thalassemia major.

## Conflict of interest

None declared.

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