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Original Article

Profile of alanine aminotransferase and hepatic iron accumulation in thalassemic patients with or without anti-hepatitis C virus

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ABSTRACT

Background Repeated blood transfusions in thalassemic patients cause iron accumulation in tissues and might impair organ function. Other peril of blood transfusion is hepatitis C virus infection.

Objectives This study aimed to find out the proportion of increased alanine aminotransferase (ALT), increased transferrin saturation (TS), and positive anti hepatitis C virus (anti-HCV) among thalassemic patients and to get the profile of ALT among thalassemic patients who have increased TS and positive anti-HCV.

Methods This cross-sectional descriptive study was conducted on β- and β-HbE-thalassemic patients at the Thalassemia Outpatient Clinic, Department of Child Health, Medical School, University of Indonesia–Cipto Mangunkusumo Hospital in May 2002.

Results Subjects were 57 homozygous β-thalassemic and 33 β-HbE-thalassemic patients. No one had regular desferoxamine or history of splenectomy. Proportions of increased ALT, TS, and positive anti-HCV were 76%, 78%, and 6%, respectively. Duration of illness, total volume of packed red cell (PRC) transfusions, TS level, and positive anti-HCV seemed to have role in the increased proportion of subjects with increased ALT, whereas duration of illness and total volume of PRC seemed to have role in the increased TS.

Conclusion Factors that seem to have a role in the increased proportion of subjects who had increased ALT and TS were (1) duration of illness, total volume of PRC transfusion, TS, and positive anti-HCV; 2) duration of illness and total volume of PRC transfusion, respectively **[Paediatr Indones 2004;44:85-89].**

Keywords: *alanine aminotransferase, hepatic iron accumulation, transferrin saturation, anti hepatitis C virus, thalassemia*

Thalassemia is a group of congenital anomaly with anemia as its major symptom. Children who suffer from this disease need a life-long repeated blood transfusion to maintain their hemoglobin level around 12 g/dL, but unfortunately those will cause an accumulation of iron in various tissues accompanied by an increased serum iron level. The accumulation of iron, which might cause damage to the parenchyma of the tissues and organ function impairment, is known as hemochromatosis.[1-4] One of the organs that is impaired by the iron accumulation is the liver.[5] Fibrosis and cirrhosis are the major manifestation of chronic iron accumulation in the liver. The development of fibrosis and cirrhosis is assumed to be caused by peroxidation of hepatocellu-lary lipid that causes cellular damage and or death.[6-8] At advanced stage, the liver iron accumulation might cause hepatocellular carcinoma.[6]

Another peril of blood transfusions to thalassemic patients is hepatitis C virus (HCV) infection. Hepatitis C virus is the major cause of post-transfusion hepatitis.[9] Liver cells that contain the virus tend to accumulate iron.[10,11] In the condition of iron accumulation and chronic viral hepatitis, there is an

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increase of serum iron level, transferrin saturation, and ferritin level.[4,10-14] Transferrin saturation examination is considered effective to prove early hemochromatosis.[4,12-14] To judge the extend of liver cells damage caused by iron accumulation, we need to assess the serum transaminase enzymes [aspartate aminotransferase (AST) and alanine aminotransferase (ALT)]. Iron accumulation and hepatitis C virus infection cause an increase of transaminase enzymes level.[6,11,15-20]

This study aimed to find out the proportion of increased ALT, transferrin saturation, and positive anti-HCV among thalassemic patients, and to get the profile of ALT among thalassemic patients who have increased transferrin saturation and positive anti-HCV.

Methods

This cross sectional descriptive study was conducted on β- and β-HbE-thalassemic patients at the Thalassemia Outpatient Clinic, Department of Child Health, Medical School, University of Indonesia, Cipto Mangunkusumo Hospital in May 2002.

Inclusion criteria were patients who had homozygous-β- or β-HbE-thalassemia, had gotten total volume of packed red cells (PRC) transfusions of 5 liter or more since 1996, were not obese, did not drink alcohol, were not on certain medication (penicillin, ciprofloxacin, nitrofurantoin, ketoconazole, fluconazole, isoniazide, phenytoin, carbamazepine, non steroid anti inflamation, Chinese herbal medication, anabolic steroid, cocaine, amphetamine), did not suffer from myositis or DMP, and had permission from the parents.

We took data about the subjects' identity, sex, age of diagnosis, kind of thalassemia, history of transfusion, desferoxamine consumption, and history of splenectomy. The subjects were assessed for serum iron level (SI) and total iron binding capacity (TIBC), level of ALT, and anti-HCV using Entebe dipstick. Transferrin saturation (%) was calculated from percentage of SI divided by TIBC. It was considered increased (= iron accumulation) if the result was 55% or more.[12,13] Level of ALT was considered increased if it was more than 40 U/L.[19]

Results

The study was conducted on 90 β-thalassemic patients consisting of 57 homozygous-β-thalassemic and 33 β-HbE-thalassemic patients. No study subject got regular desferoxamine and no one had undergone splenectomy. The subjects consisted of 41 boys and 49 girls, aged 3-13 years (median 7 year-old). Duration of illness ranged between 1.5 and 6.5 years (median 4.5 years) and total volume of transfused PRC were 5,080-33,900 mL (median 11,397.5 mL).

Increased ALT was found in 68 subjects (76%). **Table 1** shows that the proportion of increased ALT increased in relevance with duration of illness (0-5 years, 44/65; >5 years, 24/25) and total volume of PRC transfusions (5,000-11,397.5 mL, 33/45; >11,397.5 mL, 35/45).

Increased TS was found in 70 subjects (78%). **Table 2** shows that the proportion of subjects who had increased TS was increased in relevance with duration of illness (0-5 years, 45/65; >5 years, 25/25), total volume of PRC transfusions (5,000-11,397.5 mL, 33/45; >11,397.5 mL, 37/45), but not with positive anti-HCV (negative anti-HCV, 66/84; positive anti-HCV, 4/6).

Positive anti-HCV was found in 6 subjects (6%). **Table 3** shows that the proportion of subjects with positive anti-HCV did not increase in relevance with duration of illness (0-5 years, 4/65; >5 years, 2/25) and total volume of PRC transfusions (5,000-11,397.5 mL, 5/45; >11,397.5 mL, 1/25).

The proportion of subjects who had increased ALT increased among subjects who had increased TS (normal TS, 1/20; increased TS, 67/70) and among subjects who were positive for anti-HCV (negative anti-HCV, 63/84; positive anti-HCV, 5/6). This is presented in **Table 4.**

Table 1. Profile of ALT in relevance with duration of illness and total volume of PRC transfusions

	ALT		Total
	Normal	Increased	
Duration of illness (years)			
0-5	21	44	65
>5	1	24	25
Total PRC (mL)			
5,000-11,397.5	12	33	45
>11,397.5	10	35	45

TABLE 2. PROFILE OF TRANSFERRIN SATURATION IN RELEVANCE WITH DURATION OF ILLNESS, TOTAL PRC, AND ANTI-HCV

	Transferrin saturation		Total
	Normal	Increased	
Duration of illness (years)			
0-5	20	45	65
>5	-	25	25
Total PRC (mL)			
5,000-11,397.5	12	33	45
>11,397.5	8	37	45
Anti HCV			
Negative	18	66	84
Positive	2	4	6

TABLE 3. PROFILE OF ANTI-HCV IN RELEVANCE WITH DURATION OF ILLNESS AND TOTAL PRC

	Anti-HCV		Total
	Negative	Positive	
Duration of illness (years)			
0-5	61	4	65
>5	23	2	25
Total PRC (mL)			
5,000-11,397.5	40	5	45
>11,397.5	44	1	45

TABLE 4. PROFILE OF ALT IN RELEVANCE WITH TRANSFERRIN SATURATION AND ANTI-HCV

	ALT		Total
	Normal	Increased	
Transferrin saturation			
Normal	19	1	20
Increased	3	67	70
Anti-HCV			
Negative	21	63	84
Positive	1	5	6

Discussion

This study found almost equal numbers of boys and girls (ratio 1:1.2). Jaiswal *et al*[19] in India found more boys than girls with a ratio of 1.8:1. A relatively wide range of age (3-13 years old) in this study was the consequence of the inclusion of β-HbE-thalassemics. Beta-HbE-thalassemics are usually diagnosed and get the first transfusion at older age than major β-thalassemics. The age range among major β-thalassemic subjects was 3-10.5 year-old, whereas in β-HbE-thalassemic subjects was 5-13 year-old.

This study found a higher proportion of increased ALT (76%) compared to Jaiswal *et al*[19] who found that 38% of major β-thalassemic patients with repeated transfusions had impaired liver function. The proportion of subjects with increased ALT increased in relation to duration of illness, which was similar to what was suggested by Modell.[5] Both the 0-5 year and the >5 year groups of duration of illness showed that increased ALT seemed to be related to long duration of illness, total volume of PRC transfusions, and the iron accumulation that occurred.

The proportion of subjects who had increased ALT increased with the more total volume of PRC transfusions they had gotten. This was in accordance with the study by Jaiswal *et al.*[19] The higher proportion of subjects who had increased ALT among subjects who got total volume of PRC of >11,397.5 mL was caused by higher total volume of PRC transfusions and longer duration of illness. All subjects in this group who had increased ALT also had increased TS, suggesting that iron accumulation was the cause of their impaired organ function.

The proportion of increased TS (78%) was similar to the result of the study by Roesli[21] who found that 73.44% of his subjects suffered from iron accumulation. The proportion of subjects who had increased TS was increased in relation to duration of illness. This was in accordance with Modell's statement.[5] The increased proportion of subjects who had increased TS among those who had duration of illness of >5 years seemed to be influenced by the longer duration of illness and higher total volume of PRC transfusions. All subjects in both duration of illness groups of 0-5 years and >5 years who had increased TS also had increased ALT, suggesting an iron accumulation accompanied with impaired liver organ function.

The increased proportion of subjects who had increased TS in relation with increased total volume of PRC transfusion was in accordance with the result of the Modell's study.[5] Longer duration of illness and higher total volume of PRC transfusions seemed to increase the number of subjects who had increased TS among the subjects with total PRC volume of >11,397.5 mL.

The proportion of subjects who had increased TS did not increase among subjects with positive anti-HCV. This result differed from the result of Wonke *et al*[22]and Lau[23] studies who found increased ferritin level among thalassemic patients infected by hepatitis C. Normal level of TS was found in 2 patients, one sub-

ject aged 3 years with duration of illness of 2 years and total volume of PRC transfusions of 5,100 mL, and the other aged 8 years with duration of illness of 3 years and total volume of PRC transfusions of 6,445 mL. This normal level of TS was probably caused by a relatively short duration of illness and a relatively small amount of total volume of PRC transfusions they had received.

The finding of only a small number of positive anti-HCV (6%) in this study was different to other similar studies abroad. Jaiswal *et al*[19] in India found that prevalence of hepatitis among thalassemic patients was 21%, whereas Okada *et al*[20] in Japan found a higher number, 39%. This different result was probably caused by the different method of anti-HCV assessment used in these studies. Other probable cause is that the subjects in these studies were those who started to get their PRC transfusions after the year of 1996, the time when the blood bank started to screen donated blood for HCV. The Jaiswal study in India was conducted on subjects aged 14 months to 15 years, so that there were subjects who started to get their PRC transfusions before the year of 1996. The Okada study in Japan did not state the time of sampling and when the subjects started to get their PRC transfusions. Our finding also differed from the result of the studies of Saberi-Firoozi *et al*[24] and Al-Fawaz *et al*[25] who found that the prevalence of positive anti-HCV was related to duration of illness, and the study of Jaiswal[19] who found that it was related to total volume of PRC transfusions. This finding was probably because our subjects were patients who started to get their PRC transfusions after the year of 1996, which meant that the donated blood was already screened for HCV so that the prevalence of hepatitis infection did not increase despite the longer duration of illness and the higher total volume of PRC transfusions. The subjects of Saberi-Faroozi and Al-Fawaz studies were not limited to those who had PRC transfusion after 1996 so that the prevalence of hepatitis C was higher.

Our study still found subjects with positive anti-HCV in spite of the blood screening. This was probably because the subjects were already infected by HCV before the transfusions, suggesting a source of infection in the surrounding; this warrants examination of other family members, especially the mother. Some studies reported a prevalence of intrafamilial transmission positive anti-HCV of 8.1-14.9%, whereas the figure was 9% among infants born to mothers with positive HCV-RNA.[9] Another probable cause was that the blood donors were in the "window period" at the time of blood screening so that no anti-HCV was found at that time.

The increased proportion of subjects who had increased ALT among subjects with increased TS suggests the role of iron accumulation in the occurrence of impaired liver function. Vullo *et al*[26] stated that iron accumulation in organs could cause some damages to the organs. This was in accordance with the studies by Lau[23]and Li *et al*[27] who found that ferritin level had a role in the increment of ALT level.

The increased proportion of subjects with increased ALT among subjects with positive anti-HCV in this study was in accordance with the studies of Jaiswal *et al*[19] and Bhatti *et al.*[28] They found increased ALT among 63% and 90% thalassemic patients, respectively, who were infected by HCV.

To sum up, the proportion of increased ALT, TS, and positive anti-HCV among thalassemic patients were 76%, 78%, and 6%, respectively. Factors that seems to have a role in the increased proportion of subjects who had increased ALT and TS were 1) duration of illness, total volume of PRC transfusion, TS and anti-HCV; 2) duration of illness and total volume of PRC transfusion, respectively. Duration of illness and total volume of PRC transfusion were probably have no role in the increased proportion of subjects with positive anti-HCV.

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