THE LIVER HEMOSIDEROSIS IN BETA-THALASSEMIA INTERMEDIA AND HEMOGLOBIN H DISEASE

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SUMMARY : To evaluate the degree of secondary hemochromatosis, liver biopsies were taken from 5 patients with ß-thalassemia intermedia and three patients with hemoglobin H disease. The morphological and the clinical findings were compared. The serum ferritin level was correlated with the grade of hemosiderosis (R=0.818). The age of the patients (R=0.340) and the amount of transfusion (R=0.207) however, were not found related. Patients Splenectomized earlier had developed higher degrees of hemosiderosis.

Key Words : Thalassemia, hemoglobin H, ferritin, chelation, hemosiderosis, liver.

INTRODUCTION

Beta thalassemia intermedia (β-thalassemia intermedia) is the milder form of the disease in which the degree of anemia does not necessitate regular blood transfusion. They are also most improved by splenectomy. Hb H disease is a form of α-thalassemia which has similarities clinically to thalassemia intermedia. Although they develop well and reach adulthood, hemosiderosis due to iron accumulation in the tissues like liver and myorcardium is the main cause of fatality in β- and α-thalassemia. In the earlier study of Weatheral *et al.* (1), the iron absorption was found to be higher in β-thalassemia intermedia and thought to be the main cause of iron accumulation. The transfused blood would therefore contribute to the iron load, but to what degree has not yet been clearly elucidated.

In the present study we tried to find a correlation between the clinical findings like the amount of iron stores, transfusion story and previous splenectomy to morphological hemosiderosis of the liver in our thalassemic patients who were mostly diagnosed during their adulthood.

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MATERIALS AND METHODS

The β- and α–thalassemia patients were the follow-up patients of the adult hematology department of Cukurova University Medical School Hospital. Routine hematological parameters were measured by automated counter (Coulter-S plus JR). Hemoglobin F was measured by the alkali de-naturation method of Betke and Hb A2 by micro-column chromatography. Serum ferritin was measured by immunoradiometric assay (OMNIA). Hb H was detected on cellulose acetate electrophoresis at pH 9.2. Diagnosis of α–thalassemia was confirmed each patient with the determination of a/β globin ratio in Dr. Huisman's laboratory, Augusta, Georgia, USA. History of previous blood transfusions (Number of units) and alcohol and drug use were noted in each patient.

For the evaluation of hemosiderosis the liver biopsy was taken during splenectomy in 5 of the patients and percutaneously, using Menghini technique, in the remaining three patients. Informed written consist was given by every patient.

All of the liver biopsies were fixed in 10% dilution of formaldehyde solution and embedded in paraffin. Five micrometer sections were stained with hematoxylin-eosin, and Prussian blue.

The histologic material was reviewed by one of us (N.T.) without knowledge of the clinical and laboratory data.

At the microscopic examination degree of hemosiderosis is evaluated according to deposition of hemosiderin in the Kupffer cells and hepatocytes; such as mild (+), moderate (++), or heavy (+++).

The statistical analysis was performed using Spearman correlation coefficient numbers and the significance were calculated.

RESULTS

The clinical, laboratory and the morphological characteristics of the patients are summarized in Table 1.

There were 8 patients in the study group; 5 with β-thalassemia intermedia and 3 with Hb H disease.The mean age of the patients was found to be 30.63±10.89 (Range 17 to 53).

The mean Hb value was 9.14±1.3 gm/dl and the mean Hct was 28.3±43%. The mean of the mean corpusculer volume (MCV) was found to be 68±7.6 fl, Hb A2 levels were higher than normal (>3.5%) in most of the β-thals and low, being around 1% in α–thals. The Hb F values range from 1.7 to 90% generally being higher in β-thals. The mean ferritin value was 854.4±680.3 μgr/L.

There was only one patient without prior transfusion story: all the other patients had several units of blood transfused during their lifetime. None of them took iron medication.

There were left ventricular hypertrophy in the ECG of the three patients; it was normal in the others.

5 of the 8 patients were splenectomized a few months to 19 years earlier.

The morphological examination of the liver biopsies revealed hemosiderosis in all the eight patients. Grade I hemosiderosis was found in three of the patients who were not splenectomized. The patient who has never had any transfusion was among these three patients. The mean of the units of blood given was the lowest in these patients. They were not on chelation therapy.

There were three patients with grade II hemosiderosis; the mean of units of transfused blood being 9 in this group they were all splenectomized and were on chelating agents.

The other 2 patients were found to have grade III hemosiderosis. The time elapsed since their splenectomy was 19 and 12 years comparing to almost one year in the above mentioned three patients with grade II hemosiderosis. The mean of the transfused blood units in these two patients with grade III hemosiderosis was six units. They also had left ventricular hypertrophy evident in their ECG.

The total number of transfused blood units was not found significantly related to the degree of hemosiderosis (r=0.206) (p=0.312).

There were a positive correlation between the grade of hemosiderosis and the serum ferritin level (R=0.818) (p=0.006) but the time elapsed since the splenectomy appears to be important to increase the iron accumulation in the liver.

The effect of chelation therapy on the liver hemosiderosis can not be deducted with this data since the chelating agents have started to be used only during the recent years.

DISCUSSION

In chronic hemolytic anemia the iron absorption is increased due to expansion of the bone marrow (1). The patient with hemolysis is also given erythrocyte transfusion when needed. The degree of iron accumulation in the tissues considered to be the result of these two effects, whichever is more prominent is difficult to say. On the other hand splenectomy decreases the need for transfusion in transfusion dependent patients as in thalassemia major (2). But the necessity of splenectomy and the age to perform this operation is not well delineated in non-transfusion dependent thalassemia patients who have splenomegaly. So it would be desirable to find a correlation between the clinical status like the amount of iron stores and the grade of hemosiderosis. The grading of hemosiderosis was determined morphologically by investigating the liver biopsy specimens in this study.

In our group of thalassemic patients we did not find a correlation between the grade of hemosiderosis to the amount of transfusion. Event patients who were never transfused had morphological features of liver hemosiderosis. This finding is similar to Flatau et al's observa-

tions (3) who showed iron loading in endocrine organs in β-thalassemia intermedia but not thalassemia combined with sickle cell anemia in non-transfused patients.

Iron overload was also found to be common in adult non-transfused patients with Hb H disease in a study from China (4). In thalassemia the hemosiderosis appears to be developed even only with increased iron absorption without the need of additional iron load of the transfusions. Increased erythropoiesis was considered for the high absorptive rate of iron (1, 5).

The serum ferritin level was strongly correlated with the degree of hemosiderosis as expected. The ferritin level is recommended in follow up of the thalassemic patients while on chelating therapy (6). But how well the ferritin level demonstrates the ameliorating effect of the chelating agents on organ hemosiderosis which was already developed is not very well know. Besides to the ferritin level, the addition of a noninvasive test like tomography (7), skin iron x-ray spectrometry (8) or magnetic resonance imaging (9,10) might be useful in the follow up of thalassemia intermedia patients.

In our group the age of the patient was not found related to the grade of hemosiderosis but the patients splenectomized earlier tended to be loaded more iron in the liver. The reticuloendothelial cells of the liver of our cases might have accumulated more iron after the removal of the spleen.

In their clinical study where they showed significantly higher transferrin saturation and serum ferritin in their splenectomized patients. Fiorelli *et al.* (11) concluded that spleen might have a role in the regulation of iron metabolism. In our group although the 3 un-splenectomized patients had lower degree of hemochromatosis the number is small. The type of genetic mutation causing the thalassemia also might be important in their clinical presentation 1) the time to start on the chelation treatment and to detect the effect of dietary manipulations; 2) the optimal time for the splenectomy operation; and 3) the methods to follow the iron accumulation in the organs there need prospective clinical investigations in larger group of patients in α– and β-thalassemia. We therefore conclude that for further clarification of these observations.

Table 1: The clinical, laboratory and the morphological characteristics of the patients.

No.	Age	Sex	Diag-nosis	Hb gm/dl	Hct (%)	MCV (fl)	Hb A_2 (%)	HbF (%)	Ferritin μgr/L	Total Trans.	ECG	Age of splenec.	Hem (gra.)	Chel. Ther
1	53	F	β-th	8.4	27	67	7.1	7.0	780	5	N	52	II	+
2	30	M	β-th	8.5	27	72	2.7	13.0	1000	5	Left vent. hyp.	11	III	+
3	31	M	β-th	8.4	26	80	3.2	3.7	1760	7	"	19	III	+
4	34	M	β-th	7.9	24	68	7.0	16.0	1950	12	"	34	II	+
5	17	M	β-th	11.4	33	71	1.5	90.0	344	-	N	-	I	-
6	27	F	α-th	8.0	26	56	0.9	1.7	600	10	N	27	II	+
7	20	M	α-th	11.1	33	59	1.0	4.1	280	3	N	-	I	-
8	33	F	α-th	9.4	31	71	1.1	1.7	121	5	N	-	I	-

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