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ORIGINAL ARTICLE

Some Problems of Thalassemia in Jakarta

by

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Abstract

Within 10 years (1964 — 1974) two hundred and twenty one thalassemic children were observed in the Department of Child Health, Medical School, University of Indonesia in Jakarta. They consisted of 119 cases of thalassemia major, 95 thalassemia Hb E disease, 6 Hb H disease and 1 thalassemia Hb S disease.

The main treatment of thalassemia major is still blood transfusion. Splenectomy was performed on 29 children with thalassemia major and 26 cases with thalassemia Hb E disease.

Splenectomy performed on cases before hypersplenism appeared, showed better results then those late cases who have already symptoms of hypersplenism.

Beside the medical points of view thalassemia has also many social aspects to be considered, those of the child itself, the parents and the society or community.

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Introduction

In the last few years the knowledge about the pathogenesis and the molecular basis of thalassemia seems to be rapidly increased, however there has been little progress made in the management of patients with this disorder. The conservative methods for the clinical management of thalassemia syndromes still consist of blood transfusion, prevention or irradication of infections, removal of excess iron deposits, splencetomy in selected cases and supportive treatment. From all the methods mentioned above, blood transfusion is still the main basis of treatment for thalassemia. Speaking of blood transfusion, until this moment, there is still considerable controversy regarding the best type of transfusion regime. The main controversy is whether an attempt should be made to keep the hemoglobin content at a "normal" level or whether the child should be transfused at intervals, sufficient to keep a "safe" level of hemoglobin without showing any symptoms attributable to anemia. Wolman (1964), Wolman and Ortolani (1969), showed a better development of their patients after being maintained at a high hemoglobin level. On the other hand this high transfusion regime may lead to several complications such as iron overload, increase the possibility of serum hepatitis, formation of antibodies and other transfusion reactions.

Splenectomy is one of the treatment which has been performed on patients with thalassemia major for almost as long as the disease has been recognized. The spleen is one of the sites of red cell destruction and causes hypersplenism (Taft and Miller, 1968). Several authors have stated that splenectomy may reduce transfusion requirements (Lichtman et al., 1953; Smith et al., 1960). But on the other hand, especially in younger children, as the spleen plays an important role in the defence mechanism, the removal of it may increase their susceptibility to infections. In countries where infections are still major problems splenectomy should be considered carefully.

The purpose of this paper is to introduce the management of thalassemia in Jakarta as well as some problems and difficulties in facing the patients.

Material and Methods

Our material consisted of 221 thalassemic children derived from 218 families. Most of the children showed severe anemia, hepato-splenomegaly, growth disturbance and facics mongoloides. Their age varied from 3 to 130 months at the time when they were diagnosed. The diagnosis of thalassemia was based on clinical and laboratory examinations. Some of them were supported by radiological examinations. Routine blood examinations including hemoglobin, reticulocytes, white blood cells and differential count were performed by methods described by Dacte and Lewis (1963). Fetal hemoglobin was determined by the Singer's method, improved by Betke et

al. (1959). Hemoglobin analysis was performed by using starch-block electrophoresis (Kunkel et al., 1957), with a Veronal-Na buffer, pH 8.6, and cellulose acetate with a Tris-buffer, pH 9.1.

Results

These 221 thalassemia children consisted of 119 cases thalassemia major, 95 thalassemia -HbE disease, 6 HbH disease and 1 thalassemia -HbS disease. If they are divided in age groups with an interval of 3 years, then we will find that in the group of 0 - 2 years there were 109 children (88 thalassemia major, 19 thalassemia-HbE disease, 1 HbH disease and 1 thalassemia-HbS disease; in the group of 3 - 5 years : 54 children (20 thal. major, 34 thal. -HbE disease); in the group of 6 - 8 years : 32 cases (8 thal. major, 22 thal. -HbE disease and 2 HbH disease); in the group of 9 - 11 years : 22 cases (3 thal. major, 16 thal. -HbE disease and 3 HbH disease) and in the age group of 12 - 14 years there were only 4 children with thalassemia-HbE disease (see Table 1).

Nearly all children showed poor nutritional condition. Radiological pictures of the bones were made on 79 children. Abnormalities of the finger bones were found on 70 cases (70/79), of which 20 cases were below the age of 2 years. Sixty four out of these 79 children showed also abnormalities of the upper extremities, 19 of them were below 2 years of age. Abnormalities of the lower extremities were found in 16 out of 31 children, 3 of them were under the age of 2 years. Widening of the diploeic space of the skull were seen on 39 out of 54 children, 5 of them were under the age of 2 years. Changes of the ribs were encountered on 24 out of 29 cases, 3 of them were below the age of 2 years. Changes of the vertebrae were seen only in 4 older cases (see Table 2).

Family examination

In order to find the carrier in the family, the available sibling of the patients were examined against HbF and HbA_2. There were in total 71 families with thalassemia major comprising 203 children. Eighty four out of this 203 children (41.4%) seem to be carriers (32 cases with high HbF, 34 cases with high HbA_2 and 18 children had high HbF and high HbA_2); 13 children (6.4%) were normal and 106 children (52.2%) were thalassemia major (71 children of the material examined were included to this 106 children) (see Table 3). Normal value of HbF in our laboratory is 1.35% ($\pm$ 0.35) and HbA_2 2.05% ($\pm$ 0.8).

Splenectomy

Splenectomy was performed on 29 children with thalassemia major and on 26 cases with thalassemia-HbE disease. Seventeen cases out of 29 children with thalassemia major were operated on after the symptoms of hypersplenism appeared, while the other 12 children were operated on before the symptoms were present. Eleven out of the "late" cases died after the average period of

follow-up of 39 months. Only 3 died out of 12 children operated on at the "early" stage. They died 4, 9, 17 years post splenectomy due to infections. The other cause of death is usually heart failure.

The interval period of blood transfusion before and after operation in the "early" groups was significantly increased from 2.8 months to 14.4 months, during follow-up of 4 years post splenectomy. In the "late" group the interval period of blood transfusion before and after the operation did not differ significantly (from 1.5 months to 3.1 months) during the same period of follow-up. Only 3 out of 26 children with thalassemia-HbE disease died after splenectomy. Two of them died 5 5/12 years and 1 4/12 years after the operation due to purulent meningitis, while the other one died 7 hours post operation, probably due to surgical complication. Nineteen cases did not require blood transfusion any more during the follow-up of 4 years post operation. During the same period of follow-up, the other 6 cases still need blood transfusion but in longer intervals, from 3 before to 8 months after the operation.

Discussion

There are so many problems that have to be taken into consideration in facing children with thalassemia. Problems concerning the patient itself and problems concerning the family in a small and the nation in a larger scale.

Problems concerning the patients

Most of the children with thalassemia major will die before they reach the adult age. It is very tragic that one of the causes of death in thalassemia is the complication of blood transfusion itself, a main basic treatment which is still used in thalassemia. Excessive blood transfusion may produce hemochromatosis or hemosiderosis of the organs which cause disturbances of its function. Liver and skin biopsies of 19 children showed the presence of excessive iron deposits. One child suffered from diabetes mellitus at the age of 12 years, while another one showed severe iron deposits in the pancreas cut off by accident during splenectomy. Excessive iron deposits in the heart muscle may lead to heart failure. Although iron chelating agents such as Desferal (Ciba) may reduce such condition, not every child can afford the medicine. High regimen of blood transfusion as recommended by Wolman (1964) seems to be of no benefit in our material, due to some situational difficulties such as communication and socio-economic condition of the patients. In our clinic in Jakarta we prefer to maintain the hemoglobin at a "safe" level where the child is still active without any complaint caused by anemia.

Another complication of frequent blood transfusions, is the formation of antibody against the donor's blood itself. This causes difficulties in preparing blood transfusion for them. Two children of the material examined, developed

auto- immune hemolytic anemia. A very interesting problem caused by excessive blood transfusions was the formation of Australia -antibody in 22 out of 53 children examined. One of them showed a very strong Au-antibody in the ascitic fluid which developed during the terminal state. The presence of this Au-antibody is used as resource of antibody for the screening test of Au-antigen in the donor's blood. Fortunately despite so many blood transfusions there was only one child who showed positive Au-antigen.

Splenectomy is one of the treatments, which in selected cases, may reduce the frequency of blood transfusion and therefore relieves some disadvantageous conditions of the child, provided it is performed at the proper moment. On the other hand splenectomy performed on younger children may be followed by severe infections (Horan and Colebatch, 1962; Motulsky et al., 1958).

Our experience revealed that splenectomy performed on children before the signs of hypersplenism or hemosiderosis/hemochromatosis became apparent, gave better results compared to those with hypersplenism or hemosiderosis/hemochromatosis. The interval between 2 series of blood transfusion was significantly prolonged in the former group compared to that of the latter group. The mortality of the former group was 3/12 cases of the latter group was 11/17 cases. Splenectomy on cases with thalassemia-HbE disease gave satisfactory results. Thirteen out of 26 cases with thalassemia-HbE disease did not require blood transfusion anymore during a 4 years follow-up post splenectomy. Six children still required transfusion but in a very rare frequency. The other 6 children did not receive blood transfusion even before the operation. One child died 7 hours post splenectomy (see Table 4). None of the cases with HbH disease and thalassemia-HbS were operated on. They required nearly no blood transfusion.

Although splenectomy may decrease the frequency of blood transfusion, not every case should be the subject for operation, every child must be studied individually before decision for splenectomy is taken (Orsini, 1973).

Due to the high incidence of infections in Indonesia, we prefer to perform splenectomy after 2 years of age.

Mental support will be very helpful for those children who start to go to school. When the hemoglobin content is still high they may join the activity of other healthy children, but heavy physical excercise should be avoided to prevent heart failure and pathologic fracture. Some explanations to their teacher at school concerning the disease are necessary.

Problems concerning the parents

The parents should realize that the disease of their child is incurable and that the child inherits it from them. Any measurement taken by the phycisian for their child is just to lessen the suffering.

It may be advisable to tell the parents not to have another child if they have already healthy children in the family. We can imagine how many hours and material will be lost by the family during the treatment of their child or children. The same problems also happen to the employer where the father or mother works.

The prevalence of thalassemia cases in our clinic in Jakarta is about 10 - 12 new cases a year. Theoretically 2 (50%) new thalassemia carriers will be born from a thalassemia family with 4 children. One thalassemia minor will produce 50% of their children with thalassemia minor when they marry a normal person and 50% thalassemia minor and 25% thalassemia major when they marry another thalassemia minor.

Theoretically from 71 families with thalassemia major there will be 142 children with thalassemia minor (carrier), but fortunately there were only 84 cases of it.

The problem is that most of the children with thalassemia major will die before they reach the adult age. So many hours and material will be lost during this period, especially those families having more than one sick child. In our material there were 2 families, each with 3 children, of whom all were suffering from thalassemia major. One other family with an only child, refused to have another one. Another family has 11 children, 5 of them suffered from thalassemia major. In this material there were 20 families who had more than one sick child.

Problems for the community or nation

We are convinced that if we do not become aware of the increase of thalassemia genes in the population a big social problem will be faced by the community or nation in the future. It is for this reason that some measurements should be taken to prevent the increase of thalassemic genes among the population. Actually the incidence of thalassemia could be reduced if carriers could be persuaded not to marry. It is important to publicise the danger of the disease through counselling clinics in areas with a high incidence of thalassemic gene.

Clearcut heterozygotes must be warned about the dangers of marriage to similar affected individuals. Contraceptic advice or sterilisation for couples who have had a thalassemic child, especially those who have already a healthy child or children in the family is recommended. But there are still many parents especially in the eastern countries who are willing to accept the 75% chance of a healthy child.

Family planning is one of the policies of the government at this time in Indonesia. The family is recommended to have not more then 3 children. The writers are convinced that this policy will have great influence in suppressing the increase of thalassemic genes in the population in a larger scale of time.

So far we have only done retrospective genetic counselling, by giving advices to the parents who have had already a thalassemic child. We try to examine the siblings or close relatives of the sick child for the possibility of the presence of the thalassemic gene. Active finding of the thalassemic gene in the population is not yet feasible at this time.

TABLE 1: *Grouping according to age of 221 Children with Thalassemia*

Age/year	Number of Cases				
	Th. m.	Th. -HbE.	HbH dis.	Th. -HbS.	Total
0 — 2	88	19	1	1	109
3 — 5	20	34	—	—	54
6 — 8	8	22	2	—	32
9 — 11	3	16	3	—	22
12 — 14	—	4	—	—	4
Total	119	95	6	1	221

TABLE 2: *Bone changes*

	Number	%	Remarks
Fingers	70/79	88.6	20 cases < 2 years (7 cases < 1 year)
Upper Extr.	64/79	81.0	19 cases < 2 years (6 cases < 1 year)
Lower Extr.	16/31	51.6	3 cases < 2 years
Skull	39/54	72.2	3 cases < 2 years
Ribs	24/29	82.7	5 cases < 2 years
Vertebrae	4/4	100	All > 2 years

TABLE 3 : *Examinations of HbF and HbA_2 of the Siblings in 71 Families comprising 203 Children*

		Number of cases		
Carrier	HbF	32	15.8	41.4
	HbA_2	34	16.7	
	HbF & HbA_2	18	8.9	
Thal. major		106	52.2	
Normal		13	6.4	
T o t a l		203	100	

TABLE 4 : *Mean Interval Period of Blood Transfusion (in month) during 4 years Follow-Up Post Splenectomy*

Disease	Mean Interval Period of Blood Transfusion (in month)		Remarks
	Before Splenectomy	After Splenectomy	
Thalassemia Major			
Early	2.8	14.4	(12 cases)
Late	1.5	3.1	(17 cases)
Thalassemia HbE	3.0	8.0	(6 cases)
(26 cases)	7.1	Never	(13 cases)
	Never	Never	(6 cases)
	6	(7 hours post op.)	(1 cases)

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