

SEATO MEDICAL RESEARCH STUDY ON HEMATOLOGY

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Period of Report: 1 April 1966 — 31 March 1967

STUDY REPORTS

1. Title: Pathology of Abnormal Hemoglobin Diseases Seen in Thailand

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Objective:

The objective of this study is to evaluate the morphological changes in the various organs of Thai patients who carry genes for abnormal hemoglobins. These genes may occur in combinations and produce various forms of diseases. The common forms with severe clinical pictures are beta thalassemia hemoglobin E disease, hemoglobin H disease, and hydrops fetalis due to Bart hemoglobinopathy. Other individuals may harbor these genes in heterozygous form with mild or inapparent clinical manifestations. Of interest would be the evaluation of host responses of these subjects to some of the undesirable environmental factors e.g. infectious diseases or malnutritional factors. Base line information is needed, however, before further study can be made. Studies have been planned in stages as follows:

1. The pathology seen in fatal cases of beta thalassemia hemoglobin E disease. This part of the study is completed, and the final paper will be published in June 1967.

2. The pathology of hemoglobin H disease. This form of abnormal hemoglobinopathy is fairly common in Thailand (Minnich et al 1956, Na-Nakorn et al 1965). Hemoglobin H disease is generally considered to occur as a result of defective alpha-chain synthesis from two alpha-thalassemia genes, leading to more production of beta-chains. The clinical manifestations of hemoglobin H disease are generally considered to be milder than thalassemia hemoglobin E or thalassemia major (Na-Nakorn et al 1965). Seven autopsy cases of hemoglobin H diseases have been collected and reviewed (See Table I). At autopsy, jaundice was noted in 5 cases. Some degree of retardation of physical growth was present in three cases. Mongoloid facies, i.e. flat and broad face with prominent cheek bone and sunken nose, was seen in the 10-year-old male but not in others. Three cases had splenectomy for a period of 3 months to 2 years, while in one case the patient died because of bronchopneumonia in the post operative period. Six cases showed definite cardiac hypertrophy based on weight and measurement of cardiac walls. Iron containing pigment is not present in the myocardial fibers, but in two cases hemosiderin pigment is noted in the endocardial and pericardial tissue. Perinuclear lipochrome pigment is increased in myocardial fibers in 4 cases.

In the pancreas, only 2 cases show a mild deposit of hemosiderin granules in the acinar cells. None of the adrenal glands show iron deposit. In one case the skin reveals heavy deposit of hemosiderin in the connective tissue cells of the corium and in the subcutaneous fat. The livers of these patients were considered to be enlarged, considering the normal weights of each age group. A moderate amount of hemosiderin (3+) is present in the liver cells, whereas in the Kupffer cells a relatively small amount of iron containing pigment is present. Some enlargement of the portal areas is seen, mainly due to an increase in

connective tissue and proliferation of perilobular ductules but there is no definite formation of connective tissue septa, and regenerating pseudolobules are not seen. The Kupffer cells were markedly hypertrophic and showed excessive erythrocytic phagocytosis, especially in cases where splenectomy had been done for some time. Extramedullary hemopoiesis was noted in two cases and in one of these a large erythroblast was seen. Cholestasis was not observed in any case. In one case, submassive hepatic necrosis was seen which was considered to be fulminating viral hepatitis. The spleens were enlarged in all the cases. In two cases siderotic nodules consisting of iron containing crystals surrounded by collagenised fibrous tissue are seen in the trabeculae of the spleen. Trapping of erythrocytes in the Bilroth cords was prominent in all cases. The amount of lymphoid tissue in the white pulps was slightly reduced in one while in others it was within normal limits. Germinal center reaction is not noted. Focal extramedullary hemopoiesis was seen in the sinusoids in one case. Fibrosis of either red pulps or white pulps was not present. The kidneys of these patients showed a mild to moderate degree of glomerular enlargement. In two cases focal endothelial cell proliferation was observed. Hemosiderin pigment was present in the straight tubules in five of six cases. A small number of bile casts and hemoglobin droplets was also observed. The bone marrow revealed marked depletion of both erythroid and myeloid elements in one case with proliferation of macrophages showing active phagocytosis of cellular debris. Other cases showed hypercellularity of bone marrow of both erythroid and myeloid elements. In one case, plasma cells were markedly increased in number.

Comparing the findings observed in this series of hemoglobin H disease with those seen in beta-thalassemia hemoglobin E disease, a few observations can be made. Subjects who harboured hemoglobin H (hemoglobin A and H) do show pictures of chronic hemolytic anemia, but the morphological changes appear to be less severe than in the other condition. Most of the cases of hemoglobin H diseases survive to adulthood or show manifestation of the disease later in life. In our autopsy experience, during 1960-1966, only two autopsy cases of hemoglobin H disease in children were encountered out of a total of seven cases of this type, while fourteen out of twenty autopsy cases of beta thalassemia hemoglobin E disease were in pediatric age group. The extent of hemosiderosis is much less in the spleen and other visceral organs in hemoglobin H disease but hemosiderosis of the liver is somewhat comparable to what was observed in thalassemia hemoglobin E disease. The degree of extramedullary hemopoiesis was relatively mild. The spleens of thalassemia hemoglobin H disease appear to be effectively trapping the erythrocytes since the Bilroth cords are bulging and degenerating erythrocytes are present. The liver changes in hemoglobin H disease are also relatively milder. No formation of pseudolobules nor extensive connective tissue septum formation is noted.

3. The pathology of hydrops fetalis associated with hemoglobin Bart's. Hydrops fetalis associated with high production of hemoglobin Bart's was first recognized by Lie In Jo in Malaysia in 1962. Subsequently, it was shown that in this condition there is an inherited homozygosity of alpha-thalassemia genes resulting in a suppression of alpha chain synthesis and over production of gamma chain to form hemoglobin Bart's (hemoglobin gamma 4). The pathology of this interesting condition has only been briefly described. A series of 20 autopsy cases of hydrops fetalis by the Department of Pathology of Chiangmai Medical School has just been made available for a cooperative study on the pathology of this condition to be conducted jointly between Dr. Anong Nontasut and the principal investigators: The result of this study is not available.

Summary:

Pathological studies in fatal cases of hemoglobin H disease have been made. In general the findings resemble those in Beta thalassemia hemoglobin E disease but the morphological damages are relatively milder. The spleen in Beta thalassemia hemoglobin H patients appear to trap more effectively the abnormal erythrocytes. Liver disease does not progress as much as in Beta thalassemia hemoglobin E disease. Less hemosiderosis and extramedullary hemopoiesis are also observed.

Publications:

"Pathology of abnormal hemoglobin diseases in Thailand." American Journal of Clinical Pathology, June 1967.

TABLE I

CASE	AGE	SEX	DURATION OF SYMPTOMS	HEMOG* LOBIN LEVEL (a)	NO. OF BLOOD TRANS-FUSIONS (b)	DURATION AFTER SPLENEC-TOMY	CONDITIONS AT DEATH	DEVELOPMENT
1	2	F	1 mos.	3.3 gm%	Several	—	Acute non-specific ulcerative colitis	Retarded
2	10	M	3 yrs.	6.4 gm%	2	3 mos.	Acute hepatic failure	Retarded
3	21	F	10 yrs.	—	3	—	Hemolytic crisis	Normal
4	25	F	6 yrs. +	6.9 gm%	Several	2 yrs.	Heart failure-post op. manual extraction of placental adhesions	Normal
5	29	M	29 yrs.	4.9 gm%	5	—	Congestive heart failure Pregnancy 28 weeks	Retarded
6	32	M	5 yrs.	4.2 gm%	5	4 yrs.	Tetanus-chronic ulcer of left leg	Normal
7	33	F	19 yrs.	3.9 gm%	11	3 days	Bronchopneumonia	Normal