Case Report

A New Family with Beta-Thalassemia Intermedia

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In a Japanese family several members in three generations had, on hemoglobin analysis, typical findings of heterozygous β-thalassemia. However, hemoglobin concentrations, red cell morphology, splenic size and clinical histories indicated that the disorder was more severe than in the usual β-thalassemia trait. From the previous and the present studies folic acid supplements appeared to be beneficial in ameliorating the anemia. The findings may provide an apparent pathophysiologic and genetic explanations for the more severe anemia and red-cell abnormalities present in a small proportion of families with β-thalassemia trait.

Key Words: Thalassemia, Hemoglobin, Hemolytic anemia, Ultrasonography

Heterozygous β-thalassemia has been characterized as a form of mild anemia, occurring in early life and rarely associated with splenomegaly.1 This results from an inherited abnormality of β-globin production. The discovery of patients apparently heterozygous for β-thalassemia who have a relatively severe degree of anemia and splenomegaly illustrated the importance of considering this form of hemoglobinopathy as a possible cause of severe hemolytic diseases, even where the occurrence of the thalassemia syndromes are not very frequent.2,3 In this communication, we report the results of studies on a new family with β-thalassemia intermedia. Of importance, in this instance, is the fact that cholelithiasis which appeared to be interacting with the anemia occurred in 6 of the 15 carriers as a complication of sustained hemolysis. Beneficial effects of folic acid supplements are discussed.

CASE REPORT

The proband, a 59-year-old Japanese man, was admitted to the Saiseikai Karatsu Hospital in July, 1981, for evaluation of anemia that had been detected since childhood. Two years before the admission, the patient had undergone gastrectomy and cholecystectomy because of peptic ulcer and cholelithiasis. In one year after the surgical treatment the patient had the mechanical intestinal obstruction produced by adhesions which was then treated operatively. At the time, he was noted to be anemic and was given a regimen of iron therapy without effects. On admission the patient appeared to be pale and slightly icteric. The liver with increased consistency was palpable 2 cm below the right costal margin. An enlarged spleen, although not palpable, was demonstrated ultrasonographically, as expressed by the spleen index of 94 (cm²) that exceeded the normal 10 to 40 (cm²) range. Atrial fibrillation was shown on ECG. Urine was +++ positive for urobilinogen. Hematological parameters are shown in the table. Laboratory testing revealed the followings: total bilirubin, 2.5 mg/100 ml, with 0.7 mg/100 ml of
the direct form; SGOT, 39 unit/l; SGPT, 36 unit/l; LDH, 264 unit/l; ALP, 5.5 K.A. unit/l; serum iron, 168 µg/100 ml; folic acid, 6 ng/ml; vitamin B₁₂, 1060 pg/ml; and haptoglobin, trace. Peripheral blood smear showed markedly deformed and poorly hemoglobinized red cells with numerous target cells (Fig. 1). Bone marrow aspiration disclosed normoblastic hyperplasia, with 58.6% of erythroid series. Hemoglobin electrophoresis was normal except for an increase in the intensity of hemoglobin A₂ band. Isopropanol test was negative for unstable hemoglobins. From these results a diagnosis of β-thalassemia intermedia was made. In an attempt to ameliorate the anemia, folic acid in a dose of 10 to 25 mg/day was administered either intramuscularly or orally. Two months after initiation of the therapy, hemoglobin level rose to 10.5 g/100 ml. Both nutritional care and rests were thought to contribute additively to the clinical improvements during hospitalization. The patient was kept on this folic acid supplements for up to 12 months after discharge. Regular follow-ups in an outpatient clinic saw the hemoglobin level maintained at 8 to 10 g/100 ml.

Family Studies. An identical clinical and hematological picture was seen in 6 relatives of the propositus, all of whom had undergone cholecystectomy. Nine other members were similarly affected (Fig. 2). These members had raised peripheral blood smears with numerous target cells (Fig. 1). Bone marrow aspiration disclosed normoblastic hyperplasia, with 58.6% of erythroid series. Hemoglobin electrophoresis was normal except for an increase in the intensity of hemoglobin A₂ band. Isopropanol test was negative for unstable hemoglobins. From these results a diagnosis of β-thalassemia intermedia was made. In an attempt to ameliorate the anemia, folic acid in a dose of 10 to 25 mg/day was administered either intramuscularly or orally. Two months after initiation of the therapy, hemoglobin level rose to 10.5 g/100 ml. Both nutritional care and rests were thought to contribute additively to the clinical improvements during hospitalization. The patient was kept on this folic acid supplements for up to 12 months after discharge. Regular follow-ups in an outpatient clinic saw the hemoglobin level maintained at 8 to 10 g/100 ml.

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hemoglobin A2 level in the 4 to 5% range (mean 4.51% ± 0.3 s.d.), and slightly raised hemoglobin F in the 2 to 9% range (mean 3.99% ± 2.34 s.d.). Their mean corpuscular hemoglobin (M.C.H.) values were between 15.9 pg and 23.6 pg (mean 20.7 pg ± 2.33 s.d.), being invariably lower than those of the normal subjects. An enlarged spleen was shown on abdominal ultrasonography in all of the 7 affected members examined so far (Fig. 3). It is remarkable that there is a significant correlation between the spleen indices and the hemoglobin levels which reflect severity of the chronic hemolysis and that of the anemia, respectively (r = -0.798; P < 0.01).

DISCUSSION

A disorder with the clinical features of β-thalassemia intermedia was traced through 3 generations of a Japanese family. The patients apparently heterozygous for β-thalassemia have a relatively severe degree of anemia and splenomegaly. Thus, the recognition of thalassemia states is important both for clinical managements of this disorder and for genetic counseling. This report confirms the previous suggestions that phenotypic expression of β-thalassemia gene might be modified by some environmental factors.1,3) The reasons for such a clinical variation in heterozygous β-thalassemia have not been extensively investigated. The folic acid deficiency secondary to the pronounced erythroid hyperplasia has been suggested to be a contributory cause for producing relatively severe form of the hemolytic disease.4) The requirement for folic acid rises sharply in hemolytic anemia associated with chronic overactivity of the bone marrow.5,6) Our tentative conclusion that folic acid requirements are abnormally high in this case rests not only on the decrease in the reticulocyte percentage relative to the hyperactivity of the erythropoiesis in the bone marrow, but also on the fact that therapy with folic acid is effective only if unusually large doses (up to 25 mg per day) are given. With folic acid supplements, erythropoiesis becomes more effective, leading to a temporary increase in the absolute reticulocyte count and thereafter in hemoglobin concentration. Although megaloblastic changes are not always apparent in these cases, it is likely that substantial increase in the requirements of folic acid occurs at the site of hemopoiesis since the total erythron in β-thalassemia may be hypertrophied as much as fortyfold.1) Therefore, it is important to see that patients receive adequate folic acid supplements in periods of stress such as pregnancy or infections. Furthermore, regular folic acid supplements might be a feasible adjunct to the managements of thalassemia. The efficacy of the long term supplements of folic acid is currently under investigation.

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REFERENCES