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Glucose Phosphate Isomerase Deficiency

Unusual acute hemolytic crisis in a middle-aged woman

Koichi Maeda, MD,* Sheikh M. Saeed, MD,* Raymond W. Monto, MD,** and Ernest Beutler, MD***

Hereditary hemolytic anemia associated with glucose phosphate isomerase (GPI) deficiency was first reported in 1967. Since then, about 30 cases have been reported in the literature; their ages ranged between 1 and 26 years. We present a case of glucose phosphate isomerase deficiency in a 56-year-old woman. Steroid therapy seemed to resolve our patient's acute stage. Since it has not been mentioned previously, further evaluation is necessary. Consideration of this deficiency may be helpful in investigating hemolytic anemia, regardless of the patient's age.

Case Report

Our patient, a 55-year-old white woman, had been anemic since she was 10 years old. Her hemoglobin had ranged between 8 and 12 g/dl, and she had required more than 20 blood transfusions. With every episode of acute hemolysis, she experienced weakness, lethargy, pallor, and mild jaundice. Some episodes were related to infections, such as those in the urinary tract. Most of her therapy had been symptomatic, i.e., multivitamins and various hematins. Physical examination was unremarkable, except for pallor. The family history was negative for hemolytic disease; her parents were not related by blood ties.

The patient's most recent laboratory hematologic parameters, prior to admission, were as follows: erythrocyte count 2.61 million/cu mm, hemoglobin (Hgb) 10.5 g/dl, hematocrit (Hct) 32.6%, mean cell volume (MCV) 124 fl, mean cell hemoglobin (MCH) 40.1 pg, mean cell hemoglobin concentration (MCHC) 0.321. The leucocyte count was 4,500/cu mm and differential was unremarkable. The blood film showed moderate macrocytosis, polychromasia, and mild anisopoikilocytosis. The platelet count was 350,000/cu mm. The reticulocyte count was 15.2%. The 91Cr red cell survival showed half-life of 3.5 days. The bone marrow aspirate showed marked erythroid hyperplasia. The erythrocytogenesis was normoblastic and macronormoblastic. Granulocytes and megakaryocytes were unremarkable. The total protein was 7.3 g/dl, albumin 4.5 g/dl, SGOT 76 U/L, LDH 469 U/L, total bilirubin 2.4 mg/dl. Autohemolysis test showed 8.7% hemolysis at 48 hrs with no additions. Incubation with ATP and glucose revealed 5.2% and 3.3% hemolysis, respectively.

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The patient was admitted to the hospital on July 12, 1978, with headache and myalgia, and fever of three days' duration. Her temperature was 102° F and she was jaundiced. Her liver was not palpable, but the tip of the spleen was felt. The hemoglobin concentration of the blood was 5.9 g/dl, the white cell count was 13,000/cu mm, reticulocyte count 25%, and LDH 1,062. A second determination of hemoglobin on the same day was 4.5 g/dl. The patient received three units of washed, packed red cells. In addition, she was given 100 mg of hydrocortisone by IV and was started on prednisone, 20 mg q.i.d. Her symptoms rapidly abated, and the hemoglobin level was stable at 10 g/dl after transfusion. She was discharged on the seventh day.
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Materials and Methods

Red blood cell enzyme assays were carried out by standard methods (20). In determining GP activity, fructose-6-P serves as a substrate and the glucose-6-P formed is measured by linking it to the reduction of NADP through glucose-6-P dehydrogenase. The 6-phosphogluconate formed is oxidized further through the action of 6-phosphogluconic dehydrogenase, reducing additional NADP. The reduction of NADP is measured. Electrophoresis of GPI was performed by the method of Detter, et al (2). Starch-gel electrophoresis at 4°C was done for 18 hrs at 6V/cm, and pH 8.0 (bridge buffer contained 0.25 M tris and 0.057 M citric acid and gel buffer 0.017 M tris and 0.0032 M citric acid). The gel was incubated at 37°C for 20-40 min with overlay consisting of 9.2 x 10^{-11} M F-6-P, 1.1 mg NADP, 1.2 mg MTT, 0.6 mg PMS, and one unit G-6PD in 12 ml of buffer-starch solution. The buffer contained 0.06 M tris, pH 8.1. A 6.75% starch was used instead of agar.

| TABLE I |
| Red Blood Cell Enzyme Activities in a Patient with GPI Deficiency |
| Patient | Normal Values |
| Hexokinase | 3.53 EU/gm Hgb (1.27 ± 0.18) |
| Glucose-Phosphate Isomerase | 8.37 (60.8 ± 11.0) |
| Aldolase | 1.11 (3.19 ± 0.86) |
| Triosephosphate Isomerase | 1573 (2111 ± 397) |
| Glyceraldehyde Phosphate Dehydrogenase | 236.3 (226 ± 41.9) |
| Phosphoglycerate Kinase | 326.8 (320 ± 36.1) |
| Diphosphoglycerate Mutase | 7.87 (4.78 ± 0.65) |
| Monophosphoglycerate Mutase | 17.66 (19.3 ± 3.84) |
| Enolase | 8.27 (5.39 ± 0.83) |
| Pyruvate Kinase | 19.03 (15.0 ± 1.99) |
| Lactate Dehydrogenase | 234.5 (200 ± 26.5) |
| Glucose-6-Phosphate Dehydrogenase | 21.93 (12.1 ± 2.09) |
| 6-Phosphogluconic Dehydrogenase | 15.14 (8.78 ± 0.78) |
| Glutathione Reductase | 7.65 (7.18 ± 1.09) |
| FAD | 8.42 (10.4 ± 1.50) |
| FAD | 31.97 (31.71 ± 2.97) |
| Glutathione Peroxidase | 223.05 (258 ± 29.3) |
| Adenylate Kinase | 223.05 (258 ± 29.3) |
| Glutamic Oxaloacetic Acid Transaminase | 15.29 (3.02 ± 0.67) |
| PLP | 15.63 (3.02 ± 0.67) |

Results

The results of red blood cell enzyme assays are summarized in Table I. The values were determined before the recent hemolytic crisis. The patient's blood cells showed a marked decrease in GPI activity, while the activities of other enzymes were normal or increased commensurate with the degree of reticulocytosis. Electrophoresis of the red blood cell GPI was abnormal, with only the more rapid of the isozymes present (Fig. 1). Hematologic data obtained on the parents and three brothers of the patient were normal (Table II). When the red blood cells of the family members were assayed for GPI levels, the parents and one of the brothers showed levels consistent with heterozygosity (Table II).

Discussion

GPI deficiency appears to be the third most common red cell enzyme deficiency (3), after glucose-6-phosphate dehydrogenase deficiency and pyruvate kinase deficiency (4), respectively. Only about ten families with these defects have been reported in the United States (1,2,5,6). GPI is indeed a rarely recognized deficiency. Most of the patients are of European ancestry (1,2,5,7-15), although cases have been described in Mexicans and Japanese (16). No sex predilection appears to be present. Chronic hemolytic anemia is usually found in childhood. All reported patients have been under 30 years old (1,2,3,5,7-15,23,24). Our patient, age 56, may be unique. Nevertheless, consideration of GPI deficiency may be helpful in investigating hemolytic anemia, regardless of the patient's age.
Clinical findings often indicate jaundice, splenomegaly, and exacerbation of hemolysis associated with infection (10). The hemoglobin value generally ranges between 6 to 12 g/dl. The peripheral blood smear and the bone marrow findings are nonspecific and suggest nonspherocytic hemolytic anemia. The smear usually shows macrocytosis, polychromasia, and mild anisopokilocytosis. These findings are accentuated during acute crises. The bone marrow shows erythroid hyperplasia, and mild megaloblastoid change may be present. Red cell survival studies show shortened life span, as expected. An abnormal autohemolysis test partially corrected by glucose has been described (1).

Our patient has most of the characteristics described above. Interestingly, the autohemolysis test was corrected to normal level by glucose. The variability of this test suggests that it does not provide useful information in the differential diagnosis of nonspherocytic hemolytic anemia.

The enzyme assay of GPI in these patients displays markedly decreased activity, while in the heterozygous family members it shows about 50% of normal activity. The electrophoretic pattern is abnormal in most cases (2,6,8), as it was in our patient.

In 1972, Blume and Beutler described a screening procedure for GPI deficiency (17) that is simple and easy to perform. The hemolysate is incubated with a substrate and spotted on chromatography paper at timed intervals. Dry spots are examined under ultraviolet light. If enzyme is present, NADPH fluorescence begins to appear after about 5-10 minutes.

Variants of GPI based on molecular heterogeneity and biologic characteristics have been described. Paglia and Valentine published an excellent review in 1974 (6). When the thermostability was tested in the reported cases, it was markedly decreased (5). Recently Kahn, et al have shown that the defective enzymes in a study of four families were antigenetically normal (8).

Schroter and Tillman suggested that decreased deformability of GPI-deficient erythrocytes predisposes to splenic sequestration (18), while Van Biervliet has described excessive hepatic glycogen storage with hepatomegaly (19).

Since acute hemolytic episodes are often related to infection, prompt control of infection is important in these patients. The transfusion requirement varies from case to case. Splenectomy has improved nearly all cases, including two children, two and three years of age (5). For clinically severe cases, it is the treatment of choice. In our patient, steroid therapy given during her acute crisis seemed to stabilize her condition, but since steroid therapy has not been mentioned previously, further evaluation is required.
References


