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Glucose-6-phosphate Dehydrogenase Deficiency

— Report of 4 Cases —

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common hereditary enzyme disorder and more than 200 million people have a deficiency in this enzyme. It is a globally important cause of neonatal jaundice and causes life-threatening hemolytic crisis in childhood. At later ages, certain drugs such as antimalarials, and fava beans cause hemolysis among G6PD deficiency patients. The frequency and severity is influenced by genetic and cultural factors. It is common in Mediterranean, African, and some East Asian populations but rare in Korea. Four cases of G6PD deficiency which were first noticed in Korea are investigated with their clinical features.

Key Words: *G6PD deficiency*

INTRODUCTION

Hemolytic anemia in certain susceptible individuals after ingestion of antimalarial drugs was first reported in 1926 (Cordes, 1926). In the 1950s, the cause of the hemolysis was considered to be inside the red cells (Dern et al., 1954; Marks et al., 1959). It has been proved that the cause of hemolysis is due to the decreased level of glucose-6-phosphate dehydrogenase (G6PD) in the red cells. Nowadays, G6PD deficiency is the most common hereditary enzyme deficiency, causing hemolysis (WHO working group, 1989). It is transmitted by X-linked recessive trait and about 400 variants have been reported so far (Beutler, 1990). Most of the people with G6PD deficiency are asymptomatic. The clinical manifestations are mainly presented by hemolytic anemia particularly after the administration of certain drugs, exposure to fava beans (favism), during infection and diabetic acidosis, and in the neonatal period (Beutler, 1983). The grade of hemolysis depends on the level of oxidant stress (infection, hypoxia, acidosis, and the amount of drug ingested) and the subtypes of G6PD. The incidence and distribution of G6PD deficiency show racial differences. It is mainly distributed in Mediterranean, African and in some East Asian populations. The highest incidence appears to be among the Kurdish Jews (Szeinbery, 1973) but, it seems to be rare in Koreans (Blackwell et al., 1968; Lee et al., 1990).

The first case was reported in Korea in 1987. We are reporting 3 more cases with their clinical manifestations and the literature is briefly reviewed.

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CASE REPORT

Case 1

A two and a half year old boy was admitted to the Severance Hospital because of fever, cough, sputum for 3 days and gross hematuria for one day. He is the second boy of 2 siblings and the pedigree is as in Figure 1. Prior to this admission, he was admitted due to hemolytic anemia with acute tonsillopharyngitis one and a half years before.

On admission, he looked acutely ill, the conjunctivae were pale, the sclerae were icteric and the throat was injected. The lung sound was coarse with audible rales and the liver and spleen were not palpable. The laborator findings are as follows (Table 1): Hb 7.3 g/dl, Hct 27.4%, reticulocyte count 3.6%, haptoglobin was under 38 mg/dl and there was a picture of hemolytic anemia. The chest X-ray showed pneumonic consolidation on the left lower lobe and the peripheral blood smear showed microcytic hypochromic anemia, nucleated RBCs, polychromasia, spherocytosis, and

anisocytosis. The bone marrow examination showed hypercellularity with M:E ratio of 1:1 and erythroid hyperplasia. On urinalysis, RBC was 2 positive and protein was 3 positive. The cold agglutinin test and Coombs' test were negative. On the G6PD Assay (Dye reduction test) by SIGMA kit, normal control was 30 minutes. However the patient's time was prolonged to 6 hours and the patient's mother was 60 minutes. On the quantitative test for G6PD, normal value was 5.9-12.0 U/gHb but the patient's value was not detectable, the patient's brother was 0.4 U/gHb, while the patient's mother was 5.17 U/gHb.

Case 2

A 4 year and 2 month old boy was admitted to the hospital because of cough, fever and fatigue which had started 2 days previously. He had no specific past history and he is the brother of case 1.

On admission, he looked acutely ill, the conjunctivae were pale, and the sclerae were icteric. The lung sound was coarse with audible rales on the right lung. The liver and spleen were not palpable. The laboratory findings were as follows (Table 1): Hb 8.1 g/dl, Hct 26.3%, reticulocyte count 4.3% haptoglobin was under 38 mg/dl. The chest X-ray showed pneumonic consolidation on the right lung and the peripheral blood smear showed microcytic hypochromic anemia, polychromasia, and spherocytosis and anisocytosis. On bone marrow examination, the marrow was hypercellular and there was erythroid hyperplasia. The urinalysis was normal and cold agglutinin and Coombs' tests were negative. He was previously diagnosed along with his brother in case 1, as mentioned.

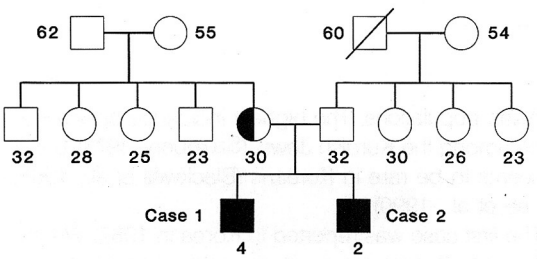

Fig. 1. Pedigree of case 1 and case 2.

Case 3

A 12 year old boy was admitted to the hospital because of dyspnea and icteric sclerae which he had had for 3 days. He had a history of hemolytic anemia of unknown cause 4 times at the age of 9 months, 1, 4, and 6 years respectively. He is the first boy of 2 siblings and there was no specific family history.

On admission, he looked acutely ill, and underdeveloped. The conjunctivae were slightly pale and the sclerae were icteric. The lung sound was coarse with

Table 1. Laboratory findings of G6PD deficiency patients

Case (Sex, Age)	Case 1 (M, 2 6/12)	Case 2 (M, 4)	Case 3 (M, 12)	Case 4 (M, 8)
Hb (g/dl)	7.3	8.1	9.5	5.9
Hct (%)	27.4	26.3	29.2	20.0
MCV (fL)	99.9	89.6	122.6	131.0
MCHC (g/dl)	32.8	33.1	32.6	29.4
RDW (%)	13.3	14.2	13.7	21.3
Reticulocyte count (%)	3.6	4.3	12.8	52.5
T. Bil/D. Bil (mg/dl)	3.4/0.4	2.7/0.3	7.0/0.1	1.7/0.2
Haptoglobin (mg/dl)	<38	<38	<38	<38
SGOT/SGPT (U/dl)	119/22	24/20	17/10	63/23
Coombs test	Negative	Negative	Negative	Negative
G6PD Assay ($U/10^{12}$ RBC, U/gHb)				
Patient	ND/0	ND/0.4	61/2.6	12/0.36
Mother	ND/5.2	ND/5.2	268/8.1	254/8.2
Father	ND/7.9	ND/7.9	261/7.7	250/8.6

* Case 1 and case 2 are brothers.
* ND: Not done

audible rales and the liver and spleen were not palpable. The laboratory findings were as follows (Table 1): Hb 9.5 g/dl, Hct 29.2%, reticulocyte count 12.8%, haptoglobin was under 38 mg/dl. The peripheral blood smear showed macrocytic hypochromic anemia, polychromasia, and anisocytosis. On bone marrow examination, the marrow was hypercellular with reversed M:E ratio of 1:3. On urinalysis, urobilinogen was 2 positive, and the cold agglutinin test, Coombs' test, sugar water test and osmotic fragility test were all negative. On G6PD assay by SIGMA kit, the patient's time was prolonged to 6 hours. On quantitative test for G6PD, the patient's value was 61 $U/10^{12}$ RBC, 2.0 U/gHb, while the patient's mother was 268 $U/10^{12}$ RBC, 81 U/gHb.

Case 4

An 8 year old boy was admitted to the hospital after suffering fever for 7 days and abdominal pain for 4 days. He had a past history of exchange transfusion for neonatal hyperbilirubinemia, and a recurrent attack of pallor during the course of upper respiratory infection. He was admitted to an other hospital with the above chief complaint and gallstones were found upon abdominal ultrasonogram. He was transferred to our hospital for further evaluation and treatment. He is the second boy of 2 siblings and his family history was unremarkable.

On admission, he looked chronically ill. The conjunctivae were pale and the sclerae were icteric. The lung sound was clear and the liver was palpable 2 cm below the right costal margin and the spleen was palpable 3 cm below the left costal margin. The laboratory findings were as follows (Table 1): Hb 5.9 g/dl, Hct 20.0%, and haptoglobin was under 38 mg/dl. The peripheral blood smear showed macrocytic hypochromic anemia, polychromasia, stomatocytosis, anisocytosis, and occasional Heinz bodies (Fig. 2). Reticulocyte count was markedly increased to 52.5% (Fig. 3). On bone marrow examination, the marrow showed hypercellularity and the M:E ratio was reversed to 1:2 with marked erythroid hyperplasia (Fig. 4). In abdominal

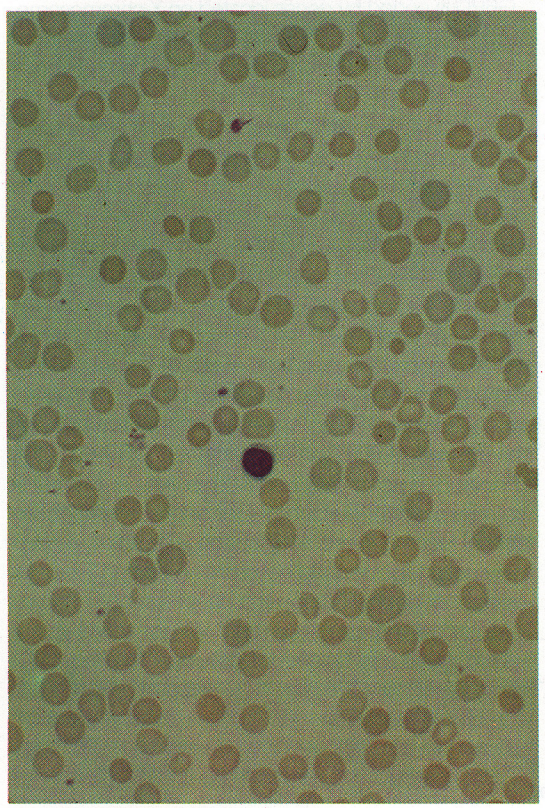

Fig. 2. Peripheral blood smear of case 4 shows polychromasia, anisocytosis, sphercytosis. (Wright stain, ×400)

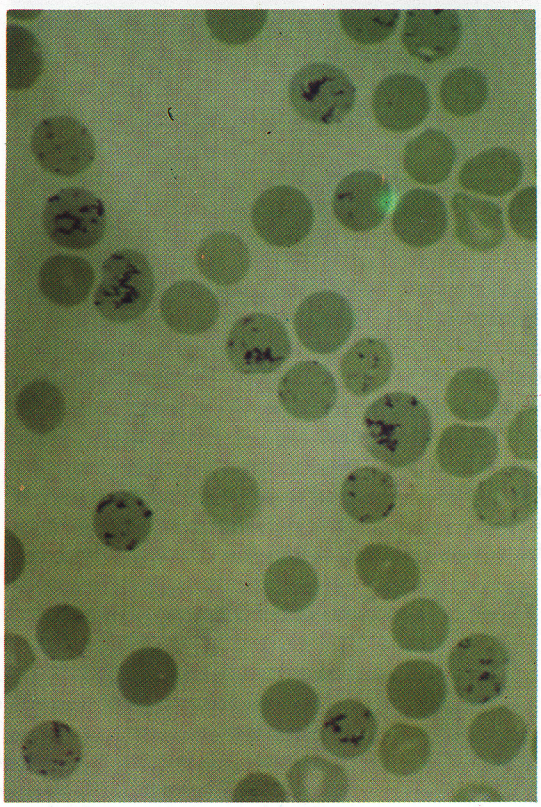

Fig. 3. Supravital stain of case 4 shows marked reticulocytosis of 52.5% (×1000).

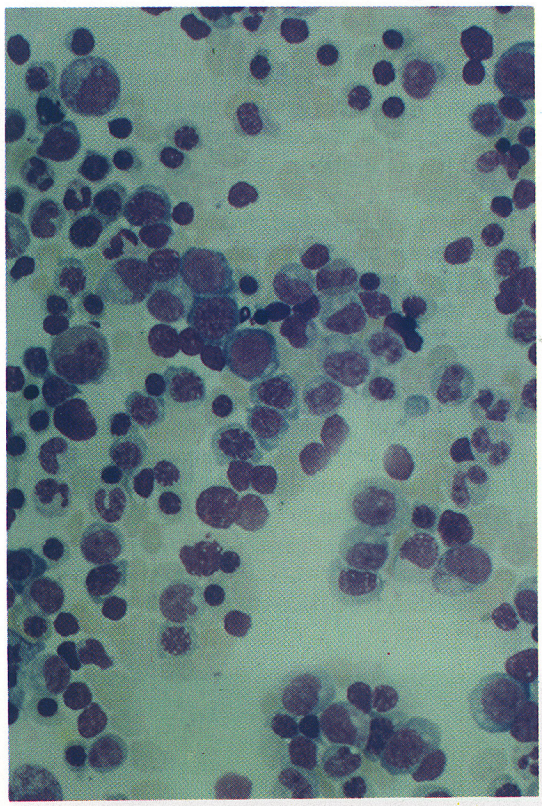

Fig. 4. Bone marrow examination of case 4 shows hypercellularity. The M:E ratio was reversed to 1:2 with marked erythroid hyperplasia (Wright stain, ×400).

ultrasonogram, the liver and spleen were enlarged and gallstones were visible. The urinalysis was normal, and cold agglutinin test and Coombs' test were negative. On G6PD assay by SIGMA kit, the patient's time was prolonged to 6 hours. On quantitative test for G6PD, normal value was 146-376 U/10^{12} RBC, 4.6-13.5 U/gHb, but the patient's value was 12.1 U/10^{12} RBC, 0.31 U/gHb, while the patient's mother was 253.7 U/10^{12} RBC, 8.2 U/gHb, and the patient's father was 250 U/10^{12} RBC, 8.6 U/gHb, respectively.

DISCUSSION

G6PD deficiency is the most common enzyme disorder and is distributed throughout the world affecting more than 200 million people. However, it seems to be rare among Koreans. G6PD is the house-keeping enzyme that is vital for the life of every cells. It converts glucose-6-phosphate to 6-phosphogluconolactone which is the first step in the hexose monophosphate (HMP) pathway and reduces the cofactor nicotinamide-adenine dinucleotide phosphate (NADP) to NADPH. G6PD deficiency affects every cell in the body but its primary effects are hematological (Beutler, 1991). This is because, in red cells, the HMP pathway is the only source of NADPH which is necessary to protect the cell and its hemoglobin from oxidation. Glutathione (GSH) repairs red cells when they are attacked by oxidative stress and is synthesized in red cells. Glutathione reductase and Glutatione peroxidase mediate the redox cycle of GSH and are closely related to G6PD (Srivastava et al., 1970).

G6PD is coded by genes located on X-chromosome. Inactivation of X-chromosome is essentially random during embryonic development and in heterozygous females, and the enzyme activity is intermediate between that of deficient males and normal males (Jandle, 1987). The enzyme activity of homozygous females is as deficient and susceptible to oxidant drugs as to heterozygous males. The normal G6PD enzyme is genetically polymorphic and B form (G6PD B) is the most prevalent in all population groups. The A form (G6PD A) also has normal enzyme activity which has faster electrophoretic mobility and is common in some African populations. A large number of G6PD variants are known and they are identified by the differences in enzyme activity, Michaelis constants (K_m) for Glucose-6-phosphate, electrophoretic mobility, heat stability, and pH optima. About 7.5% of the world population carry one or two genes for G6PD deficiency, with the proportion ranging from a maximum 35% in

Table 2. Classification of G6PD deficiency variants

Class	Enzyme activity	Examples
I	Severely deficient; associated with chronic nonspherocytic hemonlytic anemia	Charleston, Boston
II	Severely deficient; less than 10% residual activity	Mediterranean Corinth, Markam
III	Moderately deficient; 10 to 60% residual activity	A-, Canton
IV	Normal activity; 60 to 150%	A, B
V	Increased activity	Hektoen

parts of Africa, to 0.1% in Japan and parts of Europe (WHO working group, 1989). Oriental populations are supposed to have subtypes of G6PD rather than A or B forms, but the clinical course usually follows that of the B form. Blackwell et al. (1968) reported that the incidence of G6PD deficiency is estimated to be less than 0.9% in Korean males. The subjects were presumably healthy and normal Korean youths in high schools and colleges. The total of 2594 tested subjects included 743 males and 1851 females. All subjects were normal in G6PD level except one male. Saha et al. (1984) investigated the phenotypic distribution of red cell G6PD in 5 East Asian population groups. Chinese from Singapore, Thais, Filipinos and Taiwanese were reported as having a high frequency of the deficient alleles, ranging from 6.7% to 13%, while Koreans had a low frequency (3.5%). The subjects were 140 Koreans who visited the Singapore Anti-Tuberculosis Association for medical examination and 5 of them had deficient alleles (Gd^{B-} and Gd−).

G6PD variants have been classified into 5 groups on the basis of 3 major criteria: clinical manifestation, enzyme activity, and electrophoretic mobility (Table 2). The common pathological variants are all in class II and III (Beutler, 1972). After the first report in 1987 in Korea, we experienced three more cases and all of them had a history of hemolytic anemia. Cases 1 and 2 belong to class II and case 3 belongs to class III. Case 4 possibly belongs to class I because he had hepatosplenomegaly, gallstones and a history of exchange transfusion due to neonatal hyperbilirubinemia. In addition to this, enzyme activity was below 10% of normal.

We suspected the deficiency of G6PD in all four cases because of the history of acute infection, negative Coombs' test, and Heinz bodies in the red cells on special stain by methyl violet and this was confirmed by quantitative test of G6PD. The diagnoses of all 4 cases were not easy to make because of the low incidence and unusual laboratory facilities. The hemolytic attack was self-limited in all cases and they were discharged without complication. Although Koreans seems to have a low incidence of G6PD deficiency, we expect to find more cases in the future.

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