Severe Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency Associated with Chronic Hemolytic Anemia, Granulocyte Dysfunction, and Increased Susceptibility to Infections: Description of a New Molecular Variant (G6PD Barcelona)


Molecular, kinetic, and functional studies were carried out on erythrocytes and leukocytes in a Spanish male with G6PD deficiency, congenital nonspherocytic hemolytic anemia (CNSHA), and increased susceptibility to infections. G6PD activity was absent in patient’s red cells and was about 2% of normal in leukocytes. Molecular studies using standard methods (WHO, 1967) showed G6PD in the patient to have a slightly fast electrophoretic mobility at pH 8.0 with otherwise normal properties (heat stability at 48°C, apparent affinity for substrates, optimum pH, and utilization of substrate analogues). Other tests showed the patient’s granulocytes to engulf latex particles normally, but to have impaired reduction of nitroblue tetrazolium and ferricytochrome-c as well as reduced iodination. Chemotaxis and random migration of the patient’s granulocytes were normal as were myeloperoxidase, leukocyte alkaline phosphatase (LAP), and ultrastructural features. The molecular characteristics of G6PD in the patient differed from those of all previously reported variants associated with CNSHA, so the present variant was provisionally called G6PD Barcelona to distinguish it from other G6PD variants previously described. Possible mechanisms for the severe deficiency of G6PD in erythrocytes and granulocytes were investigated by studies on the immunologic specific activity of the mutant enzyme.

Glucose-6-phosphate dehydrogenase (G6PD, E.C. 1.1.49) deficiency is the most common genetically determined enzymatic abnormality in humans.1-3 It has probably affected more than 100 million males and the variability of the clinical expression of G6PD deficiency is paralleled by the different biochemical characteristics of the variant enzymes. While the majority of individuals with G6PD deficiency are either hematologically normal or show hemolysis only when exposed to exogenous agents,1,2 other G6PD variants are associated with chronic hemolytic anemia.4,5 Chronic hemolytic anemia in patients with severely reduced activity of G6PD in leukocytes is rarely associated with increased susceptibility to recurrent bacterial or fungal infections or with a clinical picture similar to that of chronic granulomatous disease (CGD).6,8 Although chronic hemolytic anemia is usually observed in association with rare structural G6PD mutations,1-5 the molecular characteristics of severely deficient G6PD variants associated with increased susceptibility to infections due to functional granulocyte defects are unknown. To date, only six patients with a deficiency of leukocyte G6PD severe enough to enhance susceptibility to infection have been reported,6,8 and in no case have the molecular properties of the variant enzyme been characterized. It might be noted, however, that in the patient studied by Gray et al.9 molecular and immunologic studies were performed that revealed the complete absence of G6PD, making kinetic and other measurements impossible.

This article describes the clinical, biochemical, and functional studies performed in a patient with severe G6PD deficiency, chronic nonspherocytic hemolytic anemia (CNSHA), and increased susceptibility to bacterial infections. The virtual absence of red cell G6PD activity was accompanied by a severely reduced granulocyte enzyme activity and phagocytic dysfunction.

We found the molecular properties of the enzyme to differ from all other previously described G6PD-deficient variants associated with CNSHA. We describe the enzyme in the present report under the provisional name “G6PD Barcelona.”

Materials and Methods

Case Report

The patient was a white male of Spanish origin (Badajoz, Extremadura Province). He was 34 yr old at the time of this study in 1980. He was examined initially at our clinic in 1972 because of a history of fever, jaundice, and hepatosplenomegaly. At the age of 4 yr, the patient had jaundice accompanied by low-grade fever, chills, dark urines, scleral icterus, and sometimes bilateral lumbar pain. These conditions persisted in variable intensity throughout childhood. The patient frequently had severe hemolytic crisis in the course of recurrent infections of upper respiratory tract during childhood, and repeated blood transfusions were required to main-
tain his hemoglobin level in the acceptable range. Family study demonstrated a slight hemolytic anemia with G6PD deficiency in the patient's mother (40% of normal activity), while his brother and sister were clinically and hematologically normal. The patient was diagnosed at the age of 25 yr as having hemolytic anemia on the basis of studies carried out on peripheral blood (hemoglobin 7.2 g/dl, corrected reticulocyte count 29%, direct serum bilirubin 19.66 μmole/liter, total bilirubin 25.65 μmole/liter, normal serum bilirubin values in our laboratory: 5.2–17.2 μmole/liter).

The patient had three episodes of bacterial pneumonia with protracted course between the ages of 25 and 34, with pleural effusion and bilateral multifocal pneumonia infiltrates during two of the episodes. The patient was anemic at the time of the study, and laboratory tests gave the following values: hemoglobin 8.2 g/dl, packed cell volume 0.21, corrected reticulocyte count 20%, total and indirect serum bilirubin 36.76 μmole/liter and 32.49 μmole/liter, respectively, leukocyte count of 14 x 10^9/liter with 90% neutrophils, 4% monocytes, and 6% lymphocytes. Total serum proteins was 56 g/liter with normal electrophoretic pattern. No abnormal hemoglobin could be demonstrated by electrophoresis and hemoglobin stability was normal. Immunoglobulin assays, expressed respectively, leukocyte count of 14 x 10^9/liter with 90% neutrophils (S/V) and 10-12 WBC and 4-5 RBC per high power field. Blood urea nitrogen (BUN) level was 15.7 nmole/liter and serum creatinine level was 141.1 nmole/liter.

General Hematologic Studies

Routine hematologic tests were done by standard methods. Hemoglobin electrophoresis was performed on cellulose acetate strips, and thermolabile hemoglobin study, erythrocyte enzyme assays, red cell glutathion concentration, and glutathione stability test were performed by the methods cited.

Molecular and Immunologic Studies of G6PD

Blood from the patient and from normal control subjects was collected in heparin (10 U/ml) and stored at +4°C. Granulocytes were isolated from whole blood using the dextran T500 method, and G6PD assays of frozen-thawed lysates were performed by the standard method. Molecular study of G6PD was performed on partially purified enzyme preparation according to the recommendations of the WHO Scientific Group and Motulsky et al. G6PD was partially purified from a leukocyte-enriched red cell suspension according to the method of Rattazzi.

This purification procedure is identical to the second method recommended by the WHO Scientific Group except that DEAE-Sephadex A-50 is used instead of DEAE-cellulose to obtain a better yield. The partially purified enzyme, devoid of hemoglobin and 6-phosphogluconic dehydrogenase (6PGD) activity, was stored as a 70% ammonium sulphate slurry at 4°C prior to analysis. Normal values for molecular parameters were established by studies carried out on blood obtained from 50 normal donors.

Electrophoresis of leukocyte and partially purified preparations of normal and G6PD-deficient samples were performed at pH 8.0 and 7.0 on horizontal starch gels using Tris-EDTA-borate and phosphate-EDTA buffer systems, respectively, with a running time of 16 hr at 4°C and 6 V/cm.

Michaelsen constant (K_m) for G6P and NADP was taken from the plots of (S/V) versus (S). The reaction velocity was measured at four to seven different concentrations of NADP in order to determine the K_m for G6P (K_m-G6P), while G6P was held constant at 0.6 mM and the concentration of NADP, confirmed spectrophotometrically, was varied between 5 and 100 μM for determination of K_m-NADP. Optimum pH, heat stability, and utilization of substrate analogues 2-deoxy glucose-6-phosphate (2dG6P) and deaminoadenosine-5'-pentaphosphate (deamino-NADP (d-NADP) were determined in a Tris-Glyciphosphate buffer system, as proposed by WHO. Immunologic study of the mutant enzyme was performed by electroimmunodiffusion of freshly prepared leukocyte extracts with specific staining of immunoprecipitate peaks for G6PD activity according to the technique described by Kahn et al. The immunologic specific activity represented by the ratio of enzyme activity to immunologic reactivity was given by the slope of the straight line: enzymatic activity = f (surface of the immunoprecipitate peak). The results were expressed in percentage of those found for leukocytes freshly extracted from a normal control.

Granulocyte Function Studies

Granulocytes were isolated practically free of platelets and red cells from fresh 50-ml samples of heparinized whole blood as previously described. One volume of 2% dextran T500 (Pharmacia, Uppsala, Sweden) in 0.15 M sodium chloride was mixed with an equal volume of blood and was allowed to settle for 45 min at room temperature (25°C). After sedimentation of the majority of red blood cells, the granulocyte-rich supernatant was mixed gently with an equal volume of 0.86% ammonium chloride to hemolyze remaining red blood cells. After three centrifugations (8 min at 150 g) and washings with Krebs-Ringer phosphate (KRP) buffer without calcium (pH 7.4), a differential count was made (95% of neutrophils and 5% of mononuclear cells). The final cell suspension was adjusted to 10^9 granulocytes/liter by adding KRP buffer. Viability of isolated leukocytes was determined by 1% trypan blue test.

Granulocyte function studies were performed according to methods described elsewhere. Latex-stimulated cytochemical nitroblue tetrazolium (NBT) reduction test, performed according to Windhorst et al., was expressed as the percentage of mature granulocytes that engulfed latex particles, and among these, the percentage of those that reduced NBT. Zymosan-stimulated (zymosan A from Saccharomices cerevisiae) quantitative NBT reduction was performed according to Baehner and Nathan. Incubation time was 15 min at 37°C and results were expressed in ΔOD x 2.5 of reduced NBT per minute and per 10^9 mature granulocytes. Zymosan-stimulated O2 production was measured according to Curnutte and Babior as modified by Weening et al. Incubation times were 5 and 15 min, and the results, expressed in nanomoles of O2-dependent ferricytochrome-c reduced per minute and per 10^9 mature granulocytes, were the mean of three incubation times. The activated iodonation test was done in the presence of 20 nmole/liter iodide at 37°C according to Pincus and Klebanoff as modified by Hakim et al. Results were expressed per 10^9 mature granulocytes as nanomoles of iodide converted into trichloroacetic (TCA) precipitable form at 10 and 20 min.

Chemotaxis was measured according to Cutler and Nelson et al. Chemotaxis of control granulocytes in 20% serum taken from the patient or from control subjects was measured in parallel. The attractants used were: (A) autologous serum (AS), (B) zymosan-activated AS, (C) the supernatant of a Klebsiella culture, (D) Klebsiella-activated AS. The results of patient's granulocyte chemotaxis were expressed as percentage of the control chemotaxis run in parallel.

Myeloperoxidase (MPO) and leukocyte alkaline phosphatase (LAP) scores were evaluated cytochemically on peripheral blood smears by methods previously described.

Ultrastructural and Morphometric Analysis of Blood Polymorphonuclear Neutrophils (PMN)

Blood for these studies was obtained from the patient and from 10 healthy donors. Granulocytes were isolated by means of Boyum's
method and were processed and studied with the conventional ultrastructural technique. Micrographs were randomly obtained with a JEOL 100-B electron microscope at 80 kV and magnification of 8000. The magnification of the instrument was controlled by means of a carbon grating replica (Ladd Res, Int, Burlington, Vt., Catalogue number, 5000), and prints were obtained at final magnification of 16,000.

Twenty-five granulocytes from each individual were studied. Cytoplasmic and nuclear area of 250 granulocytes was determined by a planimetric method, and granules of each granulocyte section were counted.

Mean and standard deviation (SD) for the following parameters were computed: cellular area, cytoplasmic (C) and nuclear (n) areas, n/c index, and number of granules per cell.

RESULTS

General Hematologic Studies

The patient had severe hemolytic anemia characterized by persistently elevated reticulocyte counts (20%–30%). Occasional spherocytes and basophilic stippling, moderate poikilocytosis, and anisocytosis were seen in the stained smear of the patient’s peripheral blood. No hemosiderin was present in his urine. The half-life of whole blood, which is just below the normal range (62–79 mg/dl), and GSH showed marked instability (–49%) after 2-hr incubation with acetylsalicylic acid (ASA).

Molecular and Immunologic Studies of G6PD

Molecular characteristics of the partially purified G6PD from the patient were summarized in Table 2. The results, representing the average of two separate studies, are compared to those of 50 normal subjects evaluated by identical methods in our laboratory and those of 30 subjects with the so-called G6PD Betica deficient variant, which has been found in about 60% of Spanish patients with acute hemolytic anemia due to G6PD deficiency.

The activity of G6PD was absent in the patient’s erythrocytes and only about 2% of normal in leucocytes. Molecular studies of deficient G6PD showed normal heat stability, apparent affinity of G6PD for substrates (Km-G6P, KmA-NADP), utilization of substrate analogues (2 dG6P and d-amino NADP), and optimum pH. The only molecular abnormality observed in G6PD from the patient was a slightly fast electrophoretic mobility (105% of normal B+ enzyme) in both leucocytes and semipurified enzyme preparation when a Tris-EDTA buffer system (pH 8.0) was used (Fig. 1). Immunologic determination of G6PD and enzymatic assays showed the newly synthesized enzyme in the patient’s leucocytes to have an “immunologic specific activity” of 82%, which was only slightly below normal (Fig. 2).

Functional and Ultrastructural Studies on Granulocytes

Results of studies on granulocyte function are summarized in Table 3. Envelopment of latex particles

Table 1. Erythrocyte Enzyme Activities Other Than G6PD in the Patient and in Normal Controls

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Activity (U/g Hb)</th>
<th>Patient</th>
<th>Normal Mean ± 50%</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hexokinase</td>
<td>1.8</td>
<td>1 ± 0.2</td>
<td>0.8–1.2</td>
<td></td>
</tr>
<tr>
<td>Phosphoglucone isomerase</td>
<td>49.6</td>
<td>47.5 ± 4.5</td>
<td>43–52</td>
<td></td>
</tr>
<tr>
<td>Phosphofructokinase</td>
<td>8.6</td>
<td>8.6 ± 1.6</td>
<td>7–10.2</td>
<td></td>
</tr>
<tr>
<td>Fructose diphosphate aldolase</td>
<td>5.6</td>
<td>3.3 ± 0.9</td>
<td>2.4–4.2</td>
<td></td>
</tr>
<tr>
<td>Glycerol diphosphate dehydrogenase</td>
<td>173.2</td>
<td>185 ± 27.6</td>
<td>157.4–212.6</td>
<td></td>
</tr>
<tr>
<td>Phosphoglycerate kinase</td>
<td>254.3</td>
<td>269 ± 35</td>
<td>234–304</td>
<td></td>
</tr>
<tr>
<td>Phosphoenol pyruvate hydratase (enolase)</td>
<td>5.23</td>
<td>4.8 ± 0.6</td>
<td>4.2–5.4</td>
<td></td>
</tr>
<tr>
<td>Pyruvate kinase</td>
<td>18.4</td>
<td>10.5 ± 2.3</td>
<td>8.2–12.8</td>
<td></td>
</tr>
<tr>
<td>Triosephosphate isomerase</td>
<td>2,319.0</td>
<td>1.945 ± 374</td>
<td>1.571–2.319</td>
<td></td>
</tr>
<tr>
<td>Bisphosphoglycerate synthase</td>
<td>4.5</td>
<td>4.7 ± 1.06</td>
<td>3.72–5.84</td>
<td></td>
</tr>
<tr>
<td>Phosphoglycerate mutase</td>
<td>9.9</td>
<td>10.9 ± 1.78</td>
<td>9.12–12.68</td>
<td></td>
</tr>
<tr>
<td>6-Phosphogluconate dehydrogenase</td>
<td>11.6</td>
<td>7.34 ± 1.03</td>
<td>6.31–8.37</td>
<td></td>
</tr>
<tr>
<td>Glutathione reductase</td>
<td>11.3</td>
<td>6.1 ± 1.19</td>
<td>4.91–7.29</td>
<td></td>
</tr>
<tr>
<td>Glutathione peroxidase</td>
<td>23.0</td>
<td>17.6 ± 2.6</td>
<td>15–20.2</td>
<td></td>
</tr>
<tr>
<td>Adenylate kinase</td>
<td>142.8</td>
<td>141.8 ± 23.1</td>
<td>118.7–164.9</td>
<td></td>
</tr>
</tbody>
</table>

*Obtained with 50 hematologically normal blood donors.
Table 2. Molecular Characteristics of G6PD in the Patient, Normal White Controls and Subjects With the Common Spanish Variant G6PD Betica

<table>
<thead>
<tr>
<th></th>
<th>Patient (Mean ± SD)</th>
<th>Normal B* Enzyme (Mean ± SD)</th>
<th>G6PD Betica (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte activity (U/g Hb)</td>
<td>0</td>
<td>7.97 ± 1.5</td>
<td>1.25 ± 1.25</td>
</tr>
<tr>
<td>Leukocyte activity (U/mg protein)</td>
<td>0.004</td>
<td>0.29 ± 0.03</td>
<td>0.23 ± 0.06</td>
</tr>
<tr>
<td>Electrophoretic mobility (% of normal B* enzyme)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tris-EDTA-borate, pH 8.0</td>
<td>105</td>
<td>100</td>
<td>111 ± 2</td>
</tr>
<tr>
<td>Phosphate EDTA, pH 7.0</td>
<td>100</td>
<td>100</td>
<td>114 ± 2</td>
</tr>
<tr>
<td>K_m-G6P (µM)</td>
<td>40</td>
<td>53.5 ± 6.5</td>
<td>55.5 ± 7.5</td>
</tr>
<tr>
<td>K_m-NADP (µM)</td>
<td>6</td>
<td>7.69 ± 1.61</td>
<td>8 ± 1</td>
</tr>
<tr>
<td>Substrate analogues utilization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2dG6P (% of G6P rate)</td>
<td>5</td>
<td>2.32 ± 0.51</td>
<td>2.61 ± 0.7</td>
</tr>
<tr>
<td>Deamino NAD- (% of NADP rate)</td>
<td>60</td>
<td>51.5 ± 6.5</td>
<td>50 ± 8</td>
</tr>
<tr>
<td>Optimum pH</td>
<td>Normal</td>
<td>Inflexion</td>
<td>Normal</td>
</tr>
<tr>
<td>Heat stability at 46 °C (residual activity after 60 min of incubation) (%)</td>
<td>68</td>
<td>70.5 ± 7.8</td>
<td>62 ± 9.3</td>
</tr>
<tr>
<td>Clinical manifestations</td>
<td>CNSHA</td>
<td>None</td>
<td>Favism</td>
</tr>
</tbody>
</table>

by the patient's granulocytes was normal, whereas the cytochemical NBT reduction test was severely decreased. The spectrophotometric assay of zymosan-stimulated NBT reduction confirmed the results obtained with the cytochemical test. Accordingly, superoxide radical (O_2^-) production measured through the ferricytochrome-c reduction and iodination test were strongly decreased in the patient's granulocytes. On the other hand, MPO index, LAP score, chemotaxis, and random migration of patient's PMN were within normal limits and ultrastructural studies provided no evidence for abnormalities either in size or in number of granules in the patient's granulocytes (Table 4).

**DISCUSSION**

G6PD deficiency can be divided into four classes on the basis of erythrocyte enzyme activity and associated clinical manifestations.\(^3\) Class 1 deficiency is characterized by severely reduced activity of G6PD and chronic nonspherocytic hemolytic anemia (CNSHA); class 2 consists in a severe deficiency of G6PD usually not associated with hemolytic anemia; class 3 corresponds to moderate to mild G6PD deficiency; and class 4 refers to very mild or unapparent enzyme deficiency.

The enzyme variants within each class can be divided further on the basis of their electrophoretic mobility, kinetic characteristics, pH optima, and utilization of substrate analogues. In general, G6PD-deficient patients who suffer from CNSHA (class 1) have inherited an uncommon variant characterized by decreased G6PD activity in leukocytes and platelets\(^4\)\(^5\)\(^6\)\(^7\)\(^8\)\(^9\)\(^10\)\(^11\) together with severe erythrocyte G6PD

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**Fig. 1.** Starch-gel electrophoresis at pH 8.0 of partially purified G6PD from the patient and two controls. Electrophoretic mobility of G6PD Barcelona is intermediate between normal B' enzyme and the fast Gd+1A black variant. Arrow indicates sample origin (0).

**Fig. 2.** Electroimmunodiffusion of normal B' enzyme and deficient G6PD Barcelona obtained from freshly prepared leukocytes. In normal B' enzyme, the activity of the first leukocyte dilution applied to the gel is indicated. The other dilutions were in the ratio 1:2, 1:4, and 1:8. In deficient G6PD Barcelona, the activity of the first immunoprecipitate peak was obtained with an undiluted leukocyte extract containing 220 x 10⁶ µl white blood cells.
deficiency and CNSHA. The present patient has class 1 G6PD deficiency. As a rule, the variant enzyme in patients with class 1 G6PD deficiency shows grossly abnormal kinetic characteristics and/or decreased heat stability in vitro than can account for their defective function in vivo.1,2,15

It is noteworthy, therefore, that the present variant was characterized by normal in vitro heat stability and kinetic properties, unlike previously reported cases of class 1 G6PD deficiency.1,4,5 In addition, electrophoretic studies on the present variant showed the only G6PD abnormality to have slightly fast mobility at pH 8. Because the characteristics of the enzyme in the present patient appear to be unique, we propose that the enzyme be called G6PD Barcelona in order to distinguish it from other enzymes associated with class 1 G6PD deficiency.

The most interesting aspect of the present variant is its strongly decreased residual activity in leukocytes in absence of in vitro heat stability or strongly diminished immunologic specific activity. Therefore, it seems reasonable to assume that the main molecular mechanism of the enzymopathy is probably a decrease in the number of kinetically normal G6PD molecules rather than an accelerated breakdown of the enzyme shortly after its synthesis. The fast electrophoretic mobility of G6PD Barcelona can be explained either by the structural gene mutation itself or by posttranslational modifications of muted enzyme in vivo or during the purification process.

When sufficiently severe, leukocyte G6PD deficiency gives rise to metabolic and bactericidal defects of granulocytes and in some instances to clinical manifestations that resemble those of patients with chronic granulomatous disease (CGD).1,8 These two conditions usually differ, however, with respect to the time of appearance of infection and the presence of hemolytic anemia.6-8,14-17 Thus, none of the 50 different variants of G6PD deficiency associated with CNSHA gave rise to increased susceptibility to bacterial infections,1,2,4,5,13,32,33 and only 6 patients with G6PD deficiency, including the present case, are known in which CNSHA was associated with infections in the upper respiratory tract or urinary tract.7,8 The condition of these 6 patients was characterized by a complete absence of erythrocyte G6PD activity and a severely decreased (<5% of normal) enzyme activity in granulocytes which, like CGD granulocytes, lack respiratory burst, fail to stimulate hexosmonophosphate (HMP) shunt activity, do not reduce NBT to purple formazan, and do not generate bactericidal hydrogen peroxide during phagocytosis.7,8

Leukocytes in the present patient showed G6PD activity of about 2% of normal and as expected in accordance with the views of Baehner et al.,7 NBT reduction, ferricytochrome-c reduction, and iodination were markedly decreased in the patient's granulocytes, suggesting abnormally low HMPS activation during phagocytosis. What is more, the patient had clinical signs of enhanced susceptibility to infection. It is not clear, however, whether the molecular abnormalities or the kinetic properties of G6PD Barcelona contributed to the severity of impairment in granulocyte function. To date, only one G6PD deficiency variant is known in which the advantageous kinetic properties of the mutant enzyme (G6PD Benavento-like) have been considered to provide an explanation for the absence of granulocyte bactericidal defect despite the presence of leukocyte G6PD activity below 5% of normal.38 The present variant has the same degree of leukocyte enzyme deficiency as seen in G6PD Benavento-like, but it shows a normal kinetic pattern. Perhaps the present variant is less efficient than G6PD Benavento-like for maintaining HMP shunt activation during...
phagocytosis, thus leading to clinical manifestations of enhanced susceptibility to infections. Further studies are needed to investigate this possibility. Nevertheless, the present report provides further evidence for the role of G6PD in PMN function.

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Severe-glucose-6-phosphate dehydrogenase (G6PD) deficiency associated with chronic hemolytic anemia, granulocyte dysfunction, and increased susceptibility to infections: description of a new molecular variant (G6PD Barcelona)

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