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A review of G6PD deficiency in Pakistani perspective

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A review of G6PD deficiency in Pakistani perspective
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Introduction
Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the commonest genetic disorder and is one of the most frequent red cell enzymopathies worldwide. It was discovered in 1956 by Alving and his colleagues while investigating the unusual primaquin sensitivity of erythrocytes in Blacks. Later, it was discovered that G6PD deficiency was not unique to Africans but was prevalent in other ethnic groups as well. Nearly a decade after its discovery, various associated clinical syndromes were defined.

Epidemiology
It is estimated that 400 million people carry the defective gene globally. Historically, geographical distribution of G6PD deficiency parallels the endemicity of malaria. Hence, high prevalence is seen typically in Africa, Asia, Mediterranean countries and Latin America. Transmigration of population led to its worldwide emergence. A recent meta-analysis showed a global prevalence of 4.5% G6PD deficiency and indicated an incidence of 1.8% in Pakistan. However, it ignored several of our locally published non indexed papers that reported an incidence of 2% to 4% in Pakistani males (Figure-1) with a high incidence of 8% in Pathans. Two large national studies reported that 26% and 30% of all hospital admissions respectively in 1624 and 6454 babies were required for evaluation of neonatal jaundice. Low birth weight, ABO or Rh incompatibility and sepsis were recognized as important contributors for jaundice while G6PD deficiency was observed in 8% of jaundiced babies.

Structure and function of G6PD
G6PD is a dimer with each monomer having a molecular weight of 59kDa and consisting of 515 amino acids. At normal pH, G6PD molecule exists as a tetramer and each subunit carries NADP[nicotinamide adenine dinucleotide phosphate] has its own active site. Therefore, NADP can be considered both as a structural and a functional domain of G6PD molecule. G6PD is the enzyme catalyzing the first and the rate limiting step in pentose phosphate pathway. The latter is the dominant form of glycolysis in red cells. The enzyme assists conversion of glucose 6 phosphate into 6-phosphogluconolactone and is a significant source of NADPH [reduced form of NADP]. NADPH is crucial for red cell survival and promotes glutathione reduction, catalase stabilization thereby neutralizing their antioxidant properties (Figure-2). In contrast to other cells,

Figure-1: Prevalence of G6PD deficiency in Pakistan

Figure-2: Biochemical role of G6PD enzyme in the cells [GSH: reduced glutathione; GSSG: oxidized glutathione; G6P: Glucose 6 phosphate; F6P: Fructose 6 phosphate; NADP: nicotinamide adenine dinucleotide phosphate; NADPH: nicotinamide adenine dinucleotide phosphate reduced].

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erythrocytes lack mitochondria and therefore are exclusively dependent on PPP as the only source of NADPH in the body. Thus in the absence of G6PD and therefore NADPH, erythrocytes cannot resist oxidative stress and the accumulated free radicals precipitate their untimely lysis.

Genetics and Inheritance
G6PD is present on the long arm of the X-chromosome [Xq2.8] and therefore mode of inheritance is sex linked for G6PD deficiency. Women who are heterozygous are the carriers of defective genes and may have normal, intermediate or severely low G6PD enzyme activity depending on randomization of X-chromosome. There are 400 G6PD variants reported so far. The most common variant in Africans is regarded as G6PD A-(202A>G) whereas G6PD 563C>T is the most frequent genotype in southern Europe, Middle East countries and Indian sub-continent. Recently, G6PD Mediterranean was reported in 78% of Pakistanis with G6PD Chatham and Orissa being less common confirming an earlier report. Associated 1311 C/T polymorphism was also observed in substantial subjects with G6PD 563C>T.

Patho-physiology of G6PD deficiency
Small quantities of enzyme produced by G6PD deficient red cells are enough for their survival in normal circumstances. However on challenging with oxidative stress, these red cells lyse because of low NADPH production. The haemolysis and therefore icterus is self-limiting despite the continued stress as the older erythrocytes with lowest enzyme activity are haemolysed first. Young red cells or reticulocytes are rich in enzymes and therefore are able to sustain the oxidative stress. This is however not the explanation for icterus seen in neonates. Evidence has indicated that it is poor hepatic handling of unconjugated bilirubin rather than increased haemolysis which significantly contributes towards neonatal hyperbilirubinaemia. Additionally, focus has been placed on UGT1A1 mutation of gene promoter or coding region in G6PD gene producing a Gilbert like condition in G6PD deficient infants.

Clinical Features
G6PD deficient subjects are asymptomatic unless subjected to oxidative stresses induced by drug administration, infections and ingestion of fava beans. 2. Favism: Fava beans contain oxidants like glycosides, divicine and isouramil and other unknown factors. Ingestion of fava beans lead to acute haemolysis in some but not all G6PD deficient subjects.

3. Neonatal hyperbilirubinaemia: This is the most devastating effect of G6PD deficiency with potential threat to acute encephalopathy culminating in permanent brain damage.

4. Chronic non spherocytic haemolytic anaemia (CNSHA): this is a rare and a severe form of G6PD deficiency. Unlike the usual variant with episodic haemolysis on oxidative challenges, subjects with CNSHA demonstrate chronic haemolysis and splenomegaly.

Other clinical considerations
G6PD deficiency has been linked to susceptibility to sepsis although not definitely proven. Complete absence of G6PD deficiency is incompatible with life resulting in early foetal loss.

Management
Lab Diagnosis
CBC shows normochromic normocytic anaemia. White cell count and platelets are typically normal but might by minimally elevated secondary to haemolysis. Reticulocytosis is marked and peripheral film typically shows spherocytes, polychromasia, bite and blister cells. Indirect bilirubin and LDH are elevated as in any acute haemolysis. The diagnostic test is G6PD enzyme assay. This should be done when reticulocytosis has subsided as newly formed red cells are well replenished with enzyme and may give a false normal value during haemolysis. Several screening tests are available such as dye decolourization test, monospot fluorescent test, methaemoglobin reduction test and formazan test. More recently a novel cytofluorometric test based on methaemoglobin has been devised. All these tests evaluate the production of NADPH. G6PD quantitative assay is also available in Pakistan. The reference ranges of G6PD assay are 6.7-14.3, 5.8-13.5 and 7.0-19 U/gHb for Pakistani adults, children and neonates respectively. Carriers are difficult to diagnose through screening tests as a heterozygote can have normal or near normal G6PD activity.

Prevention: There are several drugs that can precipitate haemolysis and need to be avoided. G6PD deficient subjects should be given a list of these drugs which must be avoided while prescribing medications to such subjects. Recently, an evidence based literature addresses
this issue\textsuperscript{21} and listed medications that do and donot cause haemolysis (Table-1).

Table: Medications that are safe and harmful in G6PD deficiency.\textsuperscript{21}

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
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<tbody>
<tr>
<td>Methyl blue</td>
<td>Paracetamol</td>
<td>Colchicine</td>
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<tr>
<td>Nitrofurantoin</td>
<td>Aspirin</td>
<td>Doxorubicin</td>
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<tr>
<td>Phenazopyridine</td>
<td>Ascorbic acid</td>
<td>Levodopa</td>
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<tr>
<td>Primaquin</td>
<td>Chloroquin</td>
<td>Doxorubicin</td>
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<tr>
<td>Dapsone</td>
<td>Chloramphenicol</td>
<td>Phenacetin</td>
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<tr>
<td>Rasburicase</td>
<td>Ciprofloxacin</td>
<td>Phenylbutazone</td>
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<tr>
<td>Toluidine blue</td>
<td>Nalidixic acid</td>
<td>Streptomyacin</td>
</tr>
<tr>
<td></td>
<td>Quinine</td>
<td>Vitamin K derivatives</td>
</tr>
</tbody>
</table>

Group 1: Medications that should be avoided.
Group 2: Medications that are safe in therapeutic doses.
Group 3: Medications having no evidence to contravene their usage.

Treatment: Haemolysis seen in a G6PD deficient subject is a limiting condition and does not require any treatment. Severe rapid anaemia may warrant red cell transfusions. Splenectomy is not required as haemolysis is mainly intravascular.\textsuperscript{1,12}

Future Directions

It is the nature of science to raise new questions as the old ones are answered. We now have a comprehensive picture of G6PD biochemical and molecular properties as well as clinical and laboratory features of this enzymopathy. For us, few questions are still unanswered: What are the unknown variants of G6PD in our country besides G6PD Mediterranean variant? What is the carrier rate in our country? Should we screen all our neonates for G6PD enzyme? Or should we just monitor icterus?\textsuperscript{22} A large prospective study is needed for probing into these queries.

References