Clinical Significance of G6PD Variants among Palestinians

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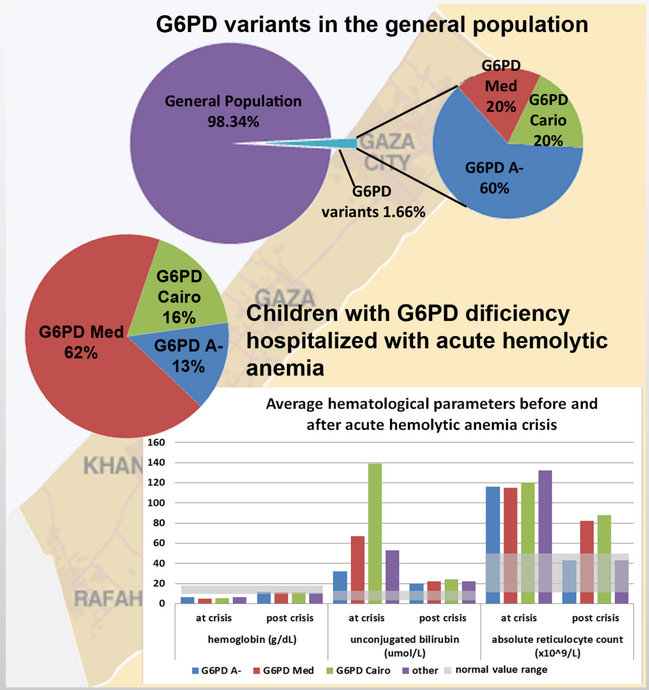
For more information

Abstract



Introduction: Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a common enzymatic abnormality known to predispose to acute hemolytic anemia (AHA), which can be triggered by certain drugs or by infection. However, the commonest trigger is the ingestion of fava beans (Vicia faba), causing AHA (favism), which may be life-threatening especially in children. G6PD deficiency is genetically highly heterogeneous, as nearly 200 different mutations have been observed in the *G6PD* gene.

Methods: We have investigated the hematological and genetic features of acute favism in the Palestinian Gaza community utilizing 131 children hospitalized for G6PD deficiency induced AHA and comparing the findings with indices from the general Gaza population.

Results: We discovered the polymorphic coexistence of three different G6PD deficiency genes (G6PD A-, G6PD Cairo, G6PD Mediterranean) in the Gaza society. We have found by comparison to the general population (485 adults and 466 newborns) that children with favism, in terms of relative frequency, G6PD A- was under-represented, whereas G6PD Mediterranean was over-represented. We also found that the severity of anemia was significantly greater with G6PD Mediterranean and G6PD Cairo than with G6PD A-; and with G6PD Cairo, compared to the other two variants, there was greater hyperbilirubinemia, as well as persistence of mild anemia and reticulocytosis for as long as 4 months after recovery from favism.

Conclusion: We conclude that children with G6PD A- deficiency are also susceptible to AHA, but demonstrate in direct comparison within this same population that G6PD Mediterranean and G6PD Cairo are more severe forms of deficiency than G6PD A-. Further, we show that the heretofore poorly studied G6PD Cairo may be associated with low-level, chronic hemolysis. This study illustrates favism is a significant public health problem in Gaza due to fava beans as a staple in the diet and the coexistence of polymorphic G6PD deficiency variants in the society. Favism is an easily preventable and manageable genetic disorder with the proper awareness, intervention and education programs.

References

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Background

Favism (OMIM 134700) was recognized for over a century as a form of acute hemolytic anemia (**AHA**) that is life-threatening, especially in children. Glucose-6-phosphate dehydrogenase (**G6PD**; EC 1.1.1.49) is an essential inherited predisposition to develop favism. Favism was characterized initially in Greece, Italy, Middle East, North Africa, and in some 30 other countries. Full recovery from favism without sequelae is possible, but without appropriate management it is still a life-threatening condition.

Located on the **X chromosome** (band Xq28) mutations in the *G6PD* gene (OMIM 305900) results in enzyme deficiency. G6PD deficiency, which is therefore **X-linked**, is highly heterogeneous at the genetic level, since different mutations underlie different variants, many of which have polymorphic frequencies in areas where malaria is or has been endemic. G6PD deficiency is never complete: nearly all G6PD mutations are missense mutations or in-frame deletions**,** and all have some residual G6PD enzyme activity. Most large clinical studies of favism have been carried out in countries where **G6PD Mediterranean** (**S188F**) is by far the commonest G6PD deficiency variant.

Since **G6PD A-** (**G202A, A376G**; the G6PD deficiency variant most common in people from Africa or African ancestry) has a residual enzyme activity higher than G6PD Mediterranean, it was thought for some time that it would not be associated with the risk of favism; but subsequently favism was also documented with G6PD A-. Favism can occur in males hemizygous and in females homozygous for G6PD deficiency; it can also occur in heterozygous females, but its severity will depend on the pattern of X-chromosome inactivation in the individual heterozygote. Favism can occur with any type of G6PD deficiency: the severity of its expression varies depending on the variant involved and cannot be assessed from the literature because reports from different countries reflect not only different genetic variants but also different contexts in terms of environment and health facilities.

Favism is the single commonest cause of transfusion-requiring AHA in Palestinian children in Gaza (1). The high prevalence of G6PD deficiency in Gaza emphasizes the need to identify children at risk and establish appropriate interventions (2,3). In Gaza there are 3 different G6PD variants are present at polymorphic frequencies: G6PD Mediterranean, G6PD A-, and **G6PD Cairo** (**A404C**). As the majority of children with favism in Gaza are admitted and treated in the same hospital (Al Nasser Pediatric Hospital), we were able to compare the clinical presentation, hematological features and the clinical course of favism, including follow-up, in children with three different genetic variants of G6PD deficiency. We report that favism is more common with G6PD Mediterranean and G6PD Cairo; although some children with G6PD A- had favism as severe as that seen with the other two variants. We also found that post-hemolytic recovery may be delayed with G6PD Cairo (1).

Methods

All studies were approved by the Palestinian Review Board adhering to the Declaration of Helsinki (approval number PHRC/HC/48/13). Informed consent was obtained from all adults and from the parents or guardians of the children enrolled in the study.

Study Subjects: 131 children from Gaza, Palestine admitted to Al Nasser Pediatric Hospital for AHA due to G6PD deficiency. 120 male, 11 female; Ages: 2 – 8 years old. Diagnosis of favism were based on findings of anemia, jaundice, and a history of fava bean ingestion. Blood transfusion was administered according to hospital protocol when hemoglobin levels were 8 g/dL or less at admission.

Population Studies: 951 unrelated, healthy adults (466) and neonates (485) from Gaza, Palestine.

Sample Collection: Whole blood was obtained from all subjects and either processed directly or applied as blood spots on filter paper for later DNA extraction. Initial Blood samples were taken at time of hospitalization for AHA. Follow-up blood samples were taken a minimum of 4 months following AHA crisis.

Laboratory Studies: Hematological and biochemical analysis was performed at Al Nasser Pediatric Hospital as described (2,4).

G6PD Genotyping: Genetic analysis was conducted at ARUP Laboratories**.** *G6PD* sequencing was conducted as described (2,4). Rapid G6PD enzymatic and SNE screening for *G6PD* variants were conducted as described (1). Enzymatic analysis screened for 4 variants common to the Gaza population. SNE fragment analysis screened for 14 variants commonly reported in European-Arab-African populations.

G6PD variants commonly reported in European-Arab-African populations						
Orissa c.131G	Aures c.143C	A- c.202A	Namoru c.208C	A+ c.376G	Cairo c.404C	Seattle c.844C
Mediterranean c.563T	Mexico City c.680A	Santa Maria c.542T	Kerala c.949A	Betica c.968C	Chatham c.1003A	Iowa c.1156G

G6PD variants common in Gaza Strip, Palestine			
A- c.202A	A+ c.376G	Cairo c.404C	Mediterranean c.563T

Results

-empty ovals represent heterozygous females
-shaded areas are normal range values: Hemoglobin (10.5-12.7 g/dL);Unconjugated bilirubin (3.4-12.0 µmol/L); Absolute reticulocytes (8.8-56.1 X 10^9/L)

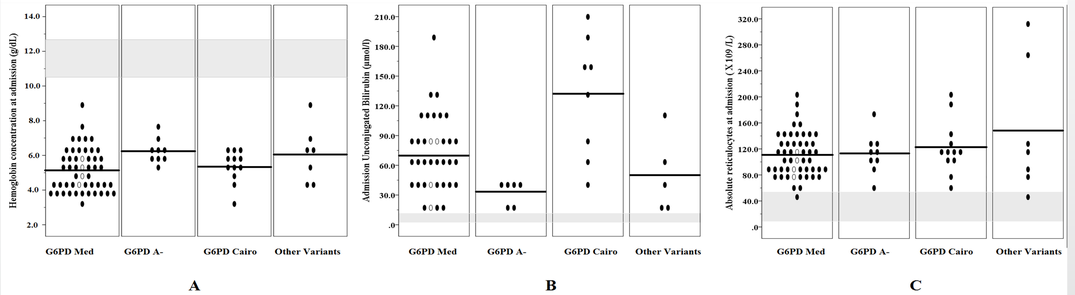

Figure 1: Individual laboratory data in all children (71 boys and 8 girls) with acute favism on admission (A) Hemoglobin; (B) unconjugated bilirubin; (C) absolute reticulocyte count.
** Unconjugated bilirubin is not available from every patient on admission.*

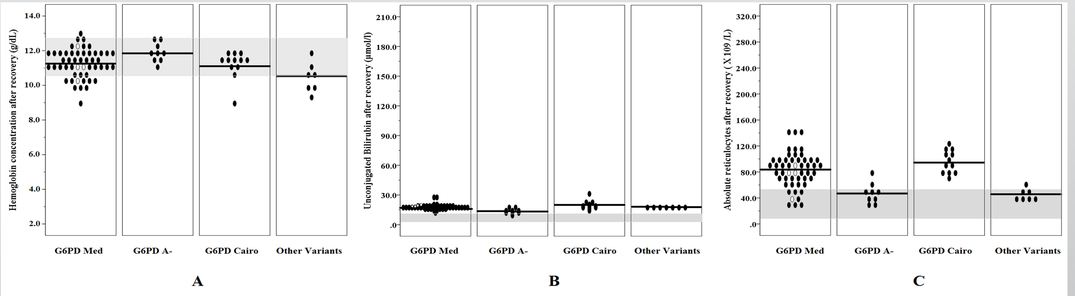

Figure 2: Individual laboratory data after recovery in all children (71 boys and 8 girls) with acute favism. (A) Hemoglobin; (B) unconjugated bilirubin; (C) absolute reticulocyte count. Samples were obtained at a time of at least 4 months after the original admission for acute favism.

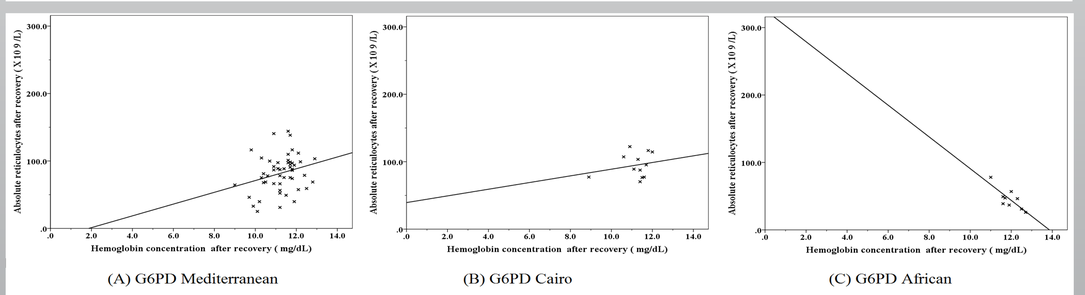

Figure 3. Correlation between absolute reticulocytes and hemoglobin level at steady state in the three G6PD variants: (A) G6PD Mediterranean, (B) G6PD Cairo, and (C) G6PD A-.

Conclusion

- Favism is a significant public health problem in Gaza
  - fava beans are a dietary staple
  - coexistence of polymorphic *G6PD* deficiency variants in the society
- Children with G6PD A-, G6PD Mediterranean and G6PD Cairo deficiency are susceptible to AHA
- G6PD Mediterranean and G6PD Cairo are more severe forms of G6PD deficiency
- G6PD Cairo may be associated with low-level, chronic hemolysis
- G6PD deficiency is a manageable genetic disorder with the proper awareness, intervention and education programs

Acknowledgement: The research activities in Gaza were financially supported by a Qatar Charity IBHATH Project grant funded by the Gulf Cooperation Council through the Islamic Development Bank for the Reconstruction of Gaza.