Clinical Significance of G6PD Variants among Palestinians

N. Scott Reading, PhD1,2,3, Mahmoud M Sirdah, PhD3,4, Mohammad E Shubair, MD5, Benjamin E Nelson, BS1, Mustafa S Al-Kahlout, MD6, Jamal M Al-Tayeb, MD6, Lina N Aboud6, MSc, Maysaa Abu Shaban7, MD, Lucio Luzzatto, MD8, and Josef T Prchal, MD1,2,3

1Institute for Clinical and Experimental Pathology, ARUP Laboratories, Salt Lake City, UT; 2Department of Pathology, University of Utah, Salt Lake City, UT; 3Division of Hematology, University of Utah, Salt Lake City, UT; 4Biology Department, Al Azhar University-Gaza, Palestine; 5Department of Laboratory Medical Sciences, Islamic University-Gaza, Palestine; 6Al Nasser Pediatric Hospital, Palestinian Ministry of Health, Palestine; 7Maternity Hospital, Al Shifa Medical Compound, Palestinian Ministry of Health, Palestine; 8Department of Hematology, Muhimbili University of Health and Allied Sciences, Dar-es-Salaam, Tanzania

Abstract

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 in-population (466 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 anaemia 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 mitral anemia and icterus os sakay 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-.

Results

• G6PD deficiency is a manageable genetic disorder with the proper awareness, intervention and education programs

Discussion

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) result 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 or females 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 these expression varies depending on the variant involved and cannot be assessed from the literature because reports from different countries reflect not only different gene 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 deficiency variants present at polymorphic frequencies: G6PD Mediterranean, G6PD A- and G6PD Cairo (A644C). 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 these 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).

References

1) NS Reading, et al. (2016) Favism, the commonest form of severe hemolytic anemia in Palestinian children, varies in severity with three different variants of G6PD deficiency within the same community. BCMD, 9(1):44-48.