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Review Article

Glucose-6 phosphate dehydrogenase deficiency and newborn screening

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ABSTRACT

Glucose-6 phosphate dehydrogenase (G6PD) deficiency is an X-linked recessive disorder causing breakdown of RBCs. It affects over 400 million people, making it the most common enzymopathy in the world. It leads to hereditary predisposition to hemolysis. In India, various study results reveal an incidence ranging from 2 to 27.9% in different communities. It is known globally for its genetic and phenotypic heterogeneity with 13 biochemically characterized variants have been reported from India, G6PD Mediterranean being the most common. It is mostly asymptomatic but certain triggers like infections, some medications, chemicals, stress or food may precipitate hemolysis. It is important to understand the epidemiology and distribution pattern in India because of its higher prevalence in tribal population who are more prone for malaria. Irrational use of drugs for malaria treatment has attributed high mortality especially neonatal mortality, in this community. Newborn screening is one of the best options to diagnose the case at neonatal age. Implementation of newborn screening would aid in identifying the genetic disorders in order to provide comprehensive care along with parental counselling to reduce the complications associated with it.

Keywords: G6PD Deficiency, Mutation, Mediterranean, Newborn screening, Hemolysis

INTRODUCTION

Glucose-6 Phosphate Dehydrogenase (G6PD) deficiency is an X-linked recessive disorder that results in defective G6PD enzyme resulting into breakdown of RBCs.[1] It leads to hereditary predisposition to hemolysis causing about 33,000 deaths in 2015. Certain triggers have been identified which include infections (bacterial and viral), certain medications (aspirin, chloroquine, primaquine, chloramphenicol, sulphanilamide), chemicals (naphthalene and henna), stress, or foods such as fava beans-*Viciafaba*.[1-5] Generally, the affected person does not show any symptoms[2]. However, symptoms such as yellowish discoloration of skin, dark urine, shortness of breath, feeling tired, anaemia and newborn jaundice may appear following a specific trigger.[1,6] Cardiac dysfunction might also be aggravated by a deficiency in G6PD which is a critical antioxidant enzyme essential for maintenance of cytosolic redox status in cardiomyocytes through increased susceptibility to free radical injury and impairment of intracellular calcium transport.[7] This enzyme deficiency, however, confers protection against malaria.[8] G6PD deficiency is an example of balanced polymorphism in which the rate of mortality caused by this disorder is offset by the protection that it offers against *P. falciparum* malaria.[9]

As per world health organization (WHO) the G6PD generic variants are classified into five classes based on biochemical and clinical phenotypes: class I: severe deficiency (<10% activity) with chronic (non-spherocytic) hemolytic anemia, class II: severe deficiency

(<10% activity), with intermittent hemolysis, class III: moderate deficiency (10-60% activity), hemolysis with stressors only, class IV: non-deficient variant, no clinical sequelae, class V: increased enzyme activity, no clinical sequelae,

WHO published a "Guide to G6PD deficiency rapid diagnostic testing to support *P. vivax* radical cure"; since individuals with G6PD deficiency may be at risk of adverse effects from medicines commonly used to cure *P. vivax* malaria, as well as other medicines and substances.[10] This guide contains generic instructions on how to conduct point-of-care testing for G6PD deficiency using currently available rapid diagnostic tests (RDTs) for control and elimination of *P. vivax* malaria.

GENETICS OF G6PD DEFICIENCY

Two variants namely G6PD A- and G6PD Mediterranean are the most common in humans. The occurrence of G6PD A- is about 10% in Africans and African-Americans while the occurrence of G6PD Mediterranean is in the Middle East. The mutated allele is largely limited to people of Mediterranean origin like Spaniards, Italians, Greeks, Armenians, Sephardi Jews and other Semitic people.[11] Both the variants stem from a strongly protective effect against *P. falciparum* and *P. vivax* malaria.[12] It is particularly frequent in the Kurdish Jewish population wherein approximately 1 in 2 males have the condition and the same rate of females are carriers, and the condition is also common in African Americans, Saudi Arabians, Sardinian Males, some African populations and Asian groups.[13]

The mutations responsible for G6PD deficiency are found on the long arm of the X-chromosome, on band Xq 28. The Mediterranean variant arises due to a point mutation (C→T) at nucleotide 563 (Exon 6), leading to a serine to phenylalanine substitution at amino acid 188 in G6PD and this Class II mutation is common in Mediterranean populations.[14] The Mediterranean variant of the G6PD is one of the most common G6PD deficiencies observed in Africa and Southern Europe, several Middle Eastern countries such as Iran and in Egypt.[15-17] This variant is characterized by <10% of normal G6PD activity, making it a severe form of the disease.[18] InG6PD (A-), substitution nucleotide and structure change of Valine to Methionine (VAL68MET) and Asparagine to Aspartic Acid (ASN126ASP) are observed. The point of mutation is at nucleotide 376 (Exon 5) and 202, and structure change to 68 and 126. In this case, there is no enzyme deficiency defect.

The other well-known variants and mutations include: G6PD (A+) where polymorphism nucleotide and structure change of Asparagine to Aspartic Acid (ASN126ASP) are observed; G6PD Canton which is also a nucleotide substitution and where structure change of Arginine to Leucine ((ARG459LEU) are noticed; G6PD Chatham which is a nucleotide substitution with structure change of Alanine to Threonine (ALA335THR) can be seen; G6PD Cosenza which is again a nucleotide substitution with structure change of Arginine to Proline (ARG459PRO); G6PD Mahidol, a nucleotide substitution where structure change of Glycine to Serine (GLY163SER) is seen; G6PD Orissa, another nucleotide substitution involving structure change of Alanine to Glycine (ALA44GLY); and G6PD Asahi which has several substitution of nucleotide and structure change of Asparagine to Aspartic acid (ASN126ASP) and valine to methionine (VAL68MET).

CLINICAL EXPRESSION AND TREATMENT

Clinical symptoms of the deficiency are seen almost exclusively in males (due to X-linked pattern of inheritance) and include rapid heart rate, shortness of breath, hemolytic anemia, dark or yellow-orange urine, fever, fatigue, dizziness, paleness and jaundice. In severe cases, jaundice and splenomegaly with severe hemolysis, right upper quadrant tenderness due to hyperbilirubinemia and cholelithiasis can be seen. Skin ulcers may also occur in extreme cases. G6PD Mediterranean has significantly lower red cell enzyme activity and more severe clinical manifestations.[19] Neonatal jaundice occurs primarily in the Asian and Mediterranean infants with Glucose-6 phosphate dehydrogenase deficiency.[20]

The treatment is mostly symptomatic. In acute hemolysis, blood transfusion or even dialysis in acute kidney failure may be recommended. The emphasis should be given to preventive measures like avoidance of drugs and foods that cause hemolysis and vaccination against some common pathogens like hepatitis A and hepatitis B which may prevent infection-induced attack.[21] Splenectomy may benefit some patients.[22] Folic acid may be of some use since there is high turnover of RBCs. Vitamin E and Selenium, both having antioxidant properties, does not reduce the severity of G6PD deficiency.

EPIDEMIOLOGY

G6PD deficiency is more common in certain parts of Africa, Asia, the Mediterranean, and the Middle East and males are more affected due to X-linked pattern of inheritance.[1] More than 400 million people are affected with this condition which is the most common enzymopathy in the world.[2] [3]This condition has resulted in 3,400 deaths in the year 1990 and 4,100 deaths in the year 2013 and about 33,000 deaths in the year 2015.[24,25] African, Middle Eastern and South Asian people are the most affected including those who have these ancestries.[26]

Different studies in various states of India revealed the range of prevalence of Glucose-6 phosphate dehydrogenase deficiency among adults and newborns as is shown in the Table 1.

Table 1: State-wise distribution of G6PD deficiency.

State	Prevalence (%)	Sample size	Reference
Himachal Pradesh	12.4	5652 Total: M:F= 3000:2652 Affected: M:F= 491:212	Sharma et al [27]
Arunachal Pradesh	4.86	267 Total M:F= Affected M:F=	Bharti et al[28]
Meghalaya	4.78	230 Total M:F=127:140 Affected M:F=10:3	-do-
Tripura	6.57	304 Total M:F=176:128 Affected M:F=17:3	-do-
Mizoram	5.14	214 Total M:F= 137:77 Affected M:F=9:2	-do-
Assam	5.07 (out of neonates presenting with neonatal jaundice)	1224 Total M:F=621:603 Affected M:F=53:24	Islam et al[29]
Chhattisgarh	6.06	1749	Shivwanshi et al30
Madhya Pradesh	In general population: 1.67 In symptomatic children: 3.67	General population:300 Total M:F=168:132 Affected M:F=4:1 Symptomatic children: 300 Total M:F=174:126 Affected M:F=7:4	Singh et al[31]
Gujarat	6.66	150 Total M:F= 84:66 Affected M:F=6:4	Pathak et al[32]
	11.18 in tribal population 1.2 in urban population		Shah et al[33]
West Bengal	14.68	109 Total M:F=63:46 Affected M:F=1:1	Bisoi et al[34]
Andaman and Nicobar Islands	3.44	29	Mukherjee et al [35]
Odisha	1.3 to 17.4		-do-
Karnataka	7.8	5140	Ramadevi et al [36]
Punjab	3.9	1000 Total M:F=499:501 Affected M:F=25:14	Verma et al [37]

In India, results of various studies reveal an incidence ranging from 2 to 27.9% in different communities.[38] Mukherjee and Colah in 2015 reported overall prevalence of G6PD to be 7.7% in a study conducted in 72 tribal groups of 56 districts of 16 States and Union Territories.[39] An epidemiological analysis report by Shah et. al.[40] suggested a similar finding. In one study carried out in India, of the 8800 newborns screened for G6PD deficiency, 4 tested positive with an incidence of 1:2000 (males and females being equal). This is almost same as that reported from the studies among Indians in Singapore.[41] A pilot newborn screening study was undertaken on 1.25 lakh newborn babies wherein G6PD was found to be a common error besides homocysteinemia, hyperglycaemia, phenylketonuria, and hypothyroidism.[42] Another screening study in India involving 18,300 newborns showed about 0.1% prevalence of G6PD deficiency.[43]

In one retrospective hospital-based study on neonatal/community screening for G6PD deficiency in Delhi, 2,479 male and female neonates consecutively born were screened for G6PD levels wherein 28.3% males and 1.05% females were found positive.[44] In another study on 1644 random samples from 404 families

carried out in Surat, 22% incidence of G6PD deficiency was recorded.[45]

While 400 different variants and 90 different mutations of this disease are known globally, 13 biochemically characterized variants have been reported from India. In India the most common mutation is the G6PD Mediterranean (563 C->T) seen in the Vatalia Prajapatis of North India and the Parsis.[44] The other two mutations commonly found in India are the G6PD Kerala-Kalyan mutation (949 G->A) reported from Maharashtra, Kerala, Andhra Pradesh, Tamil Nadu and Punjab; and the G6PD Orissa (131 C->G) found in the tribals of central, eastern and southern India. G6PD Mediterranean is the most severe variety.[46]

NEW-BORN SCREENING

Newborn screening, introduced about 60 years ago by Robert Guthrie for phenylketonuria, serves as one of the best options for diagnosis of a number of diseases in the very first couple of days of life and hence, helps their prevention. In the developed world, newborn screening has been in vogue for diagnosing endocrinopathies and metabolic errors. Owing to the high prevalence of G6PD deficiency in many populations, newborn screening is practised as a diagnostic tool in many developing countries as well viz. Middle East, Eastern Europe and Southeast Asia [47].

Newborn babies with G6PD deficiency are at higher risk of hyperbilirubinemia which may progress to kernicterus, often a fatal condition. WHO recommended that neonatal screening be performed where G6PD deficiency is common i.e. where it affects more than 3-5% of males.[48]

Kapoor and Kabra have opined that since the belt in which these disorders are found in large frequency are different, G6PD screening should also be included in the first phase but in a regionalized manner, and both ELISA and flouroimmunoassay based tests can be used for screening in India.[43]

An individual's G6PD status can be determined in many ways. Genetic tests are suitable for population studies whereas enzyme activity measurement tests are more suitable for case management. Tests for G6PD deficiency can be categorized as either genotyping assays (to ascertain at the DNA level whether someone is G6PD deficient), or phenotyping assays (to measure the G6PD activity in the individual's blood). Genotypic assays (PCR SNP analysis and DNA sequencing) are used for population studies. Phenotypic assays can further be categorised as quantitative or qualitative or cytochemical assays and are mostly used for screening, population studies and case management.

Presently, three reliable screening tests are available for diagnosis of G6PD deficiency. The Beutler Fluorescent spot test has been recommended by the International Committee for Standardization in haematology. Necessity of using an UV light is a major limitation to this test. Color reduction test in which dichlorophenol indophenol is reduced to a colourless state is highly sensitive, specific, cheaper and easy to perform. A similarly acceptable Modified Formazan ring test (based on MTT linked spot test) has been recommended by WHO for screening of babies to diagnose G6PD deficiency.[46]

For the screening program in India, experts suggest that the modified Formazan ring test method would be best suited since the common sample taken through heel prick method within first 48 hours after birth can be used for this purpose. Also, this test is rapid (results available within 24 hours), less expensive, sensitive and specific. An enzyme level less than 100U/ trillion RBCs has been defined as the cut off for classifying the neonate as G6PD deficient.[44] The positive neonates, however, shall have to undergo a definitive quantitative test.[49]

Even though G6PD deficiency is condition that cannot be cured altogether or prevented, it does come with its benefits: Preventive measures immediately after birth could reduce morbidity and mortality, Prophylactic avoidance of triggers and prompt initiation of treatment could save from kernicterus and infections, Once the disease is detected early on, conscious precautions, medications, changes in lifestyle and regular monitoring can give early indicators of any worsening and can prevent complications later in life.

Possible limitations of Newborn Screening in India may include the following: Availability of reliable epidemiological data, Availability of rapid and economical tests which are highly sensitive and specific, High Cost. Even though high cost of NBS program is a major factor but the overall clinical outcome actually reduces morbidity and thus the overall cost, Availability of treatment for the diagnosed condition, above all, social acceptance of the presence of disease at infancy, Lack of awareness among the masses, Facilities for this newborn screening for G6PD deficiency are currently available at some hospitals in the major cities only.

CONCLUSION

Since G6PD does not have any specific treatment, preventive measures immediately after birth can play a major role to reduce morbidity and mortality. Prophylactic measures and early treatment could save from grave complications like kernicterus and infections. For the vast population in India, there still are limitations of newborn screening which may be coped in the future by active measures and interventions. Today, the facilities for this newborn screening for G6PD deficiency are available at some hospitals in the major cities only. But considering the disease burden and its consequences in the future lives of the newborn babies, initiatives should be taken to include G6PD screening test in the Rastriya Bal Swasthya Karyakram (RBSK) under

National health mission (NHM) so as to reach the rural population of the country, may be in partnership with private entities including NGOs.

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