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PREVALENCE OF G6PD DEFICIENCY IN NEWBORNS OF LOCAL COMMUNITY OF QUETTA, PAKISTAN

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ABSTRACT

Glucose 6-phosphate dehydrogenase (G6PD) plays an important functional role in the pentose phosphate pathway specifically in red blood cells (RBCs). G6PD deficiency is an X-linked single genetic disorder which is very common in human neonates especially in males. Infants with G6PD deficiency show a high level of hyperbilirubinemia that may lead to permanent neurological defects. Affected babies require intensive medical care and their mortality rate is 4%. Prevalence of G6PD deficiency in the local community of Quetta, Pakistan has been analyzed. Neonates born in or admitted in Bolan Medical Complex, Quetta, Pakistan from January-2018 to December-2018 has been screened for G6PD deficiency by the help of Met-hemoglobin reduction test (MRT). An overall prevalence of 10.1% has been documented with the highest percentage in male babies (14.5%) than females (5.0%). Among five different local ethnic groups, a higher percentage of affected babies have been noted for Baloch, Pashtun and Afghan Refugees with 10.3, 11.1 and 10.1% respectively. High prevalence among these populations indicates the need for urgent attention about the screening of newborns so that complex medical conditions can be managed in time. Along with this, it is need of the time to design a large scale molecular studies so that underlying mutations can be identified and a genetic map can be constructed for the local community.

KEYWORDS: G6PD deficiency, male babies, Baloch, Pashtun, new-born screening.

Abbreviations: G6PD: Glucose 6-phosphate dehydrogenase, RBCs: red blood cells, MRT: Met-hemoglobin reduction test, X-linked: X chromosome-linked genes.

INTRODUCTION

Glucose 6-phosphate dehydrogenase (G6PD) deficiency is one of the most common single-gene genetic diseases in human neonates, identified in nearly 400-million people around the globe, especially in Asia, Africa, the Middle East and the Mediterranean.[1,2] Although, G6PD deficiency influence all cell-types in the body, yet its principal impacts are complex hematological due to its solitary role in energy generation via the pentose phosphate pathway.[3] Deficiency of G6PD in red blood cells results in the development of oxidative stress which ultimately results in anemia and hemolysis, the latter is often triggered by fava beans that's why another term "Fauvism" (derived from fava bean) is employed as an alternative to G6PD deficiency. Some other factors like antimalarial drugs, antibiotics, acute illness, and infections also encourage induction of hemolysis in an affected individual.[4] In general, it is an asymptomatic disease, however, a serious kind of hemolytic anemia occurs in some cases which ultimately result in hyperbilirubinemia. In a few cases, high level of hyperbilirubinemia can avert a threat of permanent neurological defects. It is often said that the catabolism of unconjugated bilirubin plays the main role in the development of neonatal hyperbilirubinemia.[5] Some critical cases in neonates can advance in severity and progress into cerebral jaundice and ultimately lead to cerebral palsy accompanied by mental retardation.[2,6]

The *G6PD* gene is located on the long arm of X-chromosome and it encodes 515 amino acids long peptide chain with the help of its 13-exons while the 2-introns are removed out by splicing. More than 200 *G6PD* mutations have been reported in the literature from all around the world and it is accepted that regional

and racial factors have a strong correlation with rate and type of mutations.[7,8] Mutations in coding or promoter regions like UGT1A1 or other point mutations have been identified for approximately 400 G6PD variants.[9] With the advancement of modern biotechnology and sequencing techniques, different types of studies have been carried out either to identify or to characterize new mutations.

G6PD deficiency is an X-linked recessive congenital fault in metabolism which is most common in males due to homozygosity, however, females with one faulty copy of G6PD gene (heterozygous) may be unaffected, intermediate or significantly deficient in G6PD function as all these conditions are possible due to random X-chromosome inactivation.[1,10] To describe the actual phenotype, many types of biochemical and molecular tests have been reported in the literature and most of these tests can easily differentiate between a normal and affected individual. However, it is rather difficult to define one universal value for normal (100%) G6PD activity, and due to this, test values that are considered normal for a region or ethnic group can be used as a standard to check the status of G6PD activity of a particular individual.[11] Due to the difference in expressivity, a significant number of heterozygous females which are possibly suffering from partial G6PD deficiency are difficult to detect by some tests. Therefore, it is important that the cut-off values for the screening of G6PD must be evaluated and optimized by considering gender factor, geographical region and ethnic group.

Previous studies, conducted at the national level in Pakistan, have reported that around 30% of all hospital admissions were admitted for the screening of neonatal jaundice. Significant contributor for jaundice includes blood group incompatibility, low birth-weight, sepsis as well as G6PD deficiency which alone is responsible for 8% jaundice cases.[5] With two-thirds of babies that are born outside the hospitals in Pakistan, the real figures of G6PD deficiency and hyperbilirubinemia are supposed to be much-higher than observed. In this regard, the objective of the present study was to determine the prevalence of G6PD in the babies of the local community of Quetta, Pakistan and to advise the physicians that newborn screening for G6PD should be considered as it is a significant reason for neonatal jaundice.

Study design

A total of 716 neonates, borne in or admitted (Age 1 to 40 days) in the Pediatric unit of Bolan Medical Complex Hospital, Quetta, from January 2018 to December 2018 were selected for this study. Neonates were selected randomly however, those who are undergoing hemolysis were excluded. This study was conducted after approval from the Medical Ethics Committee, Quetta, and Bolan Medical Complex, Quetta.

Blood samples were taken after informed consent from the parents of neonates. Blood samples were drawn by following a standard protocol and preserved with 3.2% sodium citrate anticoagulant for G6PD estimation.[12] Samples were immediately transferred to the screening lab and stored at room temperature until further processing. Met-hemoglobin reduction test (MRT) was employed for the detection of G6PD deficiency and the test was performed within an hour of sampling.[12] MRT test is based upon the formation of met-hemoglobin when nitrites are added in the blood followed by the reduction of met-hemoglobin to oxyhemoglobin, caused by methylene blue. MRT test was always performed with positive and negative control.

RESULTS

Out of total 716 newborns (379 males and 337 females), analyzed for G6PD enzyme activity by the help of MRT, 644 were normal and 72 (10.06%) were deficient. Out of 379 male and 337 female babies, 55 (14.51%) and 17 (5.04%) babies were G6PD deficient respectively (Table 1). It clearly indicates a 3:1 male to female ratio which is frequently reported from Pakistan.

Our study group comprised of at least 5 different ethnicities: Baloch or Brohi, Pashton, Afghan refugees, Punjabi and Hazarvi. We have noted the nearly the same percentage of G6PD deficiency in Balochi (10.3%), Pashton (11.1%) and Afghan Refugee (10.1%) populations. Prevalence of G6PD deficiency was slightly low in Hazarvi (9.6%) population, however, Punjabi population has only 4.65% which is less than half as compared with Baloch or Pashton population (Fig. 1). Out of 16 babies whose ethnic record was missing, one baby was G6PD deficient and it is not included in the percentage of ethnic groups.

Table Headings

Table 1: Statistics of sample size, healthy and G6PD deficient babies.

Table 1

No.	Gender	Total	Healthy	Diseased	Percentage
1	Male babies	379	324	55	14.51%
2	Female babies	337	320	17	5.04%
3	Over all total	716	644	72	10.06%

Figure heading
Figure 1

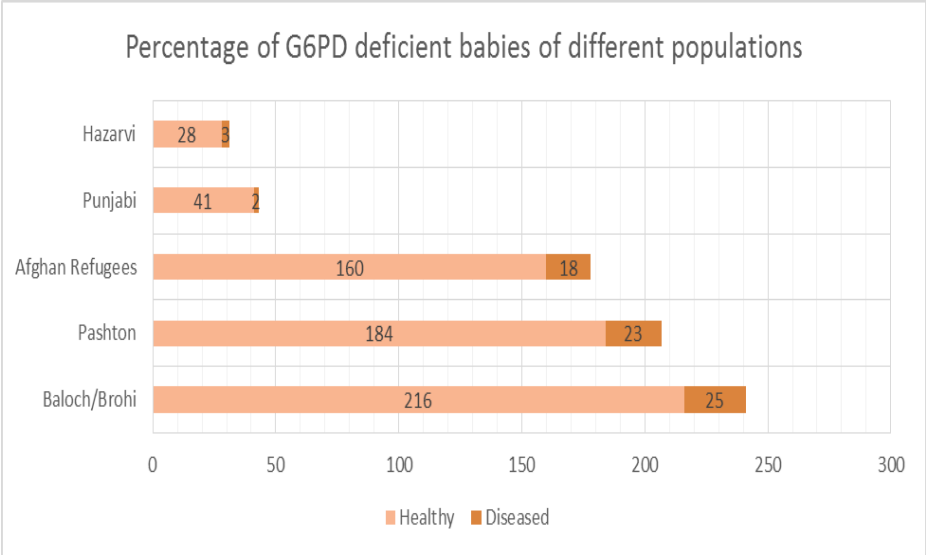

Figure 1: Total number of healthy and diseased babies of different ethnic groups.

DISCUSSION

G6PD is translated in all type of cells in the body and it plays an indispensable role to start pentose- phosphate shunt as it generates 6-phosphogluconolactone from glucose-6-phosphate. Reduction of hydrogen peroxide during this redox reaction further increases the significance of this enzyme. Because of this, in G6PD deficient RBCs, oxidative stress is developed which ultimately lead to the hemolysis.[13] Individuals deficient of G6PD may have less than normal quantity of this enzyme in many other cells i.e. kidney, liver, platelets, and leukocytes. Usually, no cell is completely dependent on G6PD, and there are some alternates to generate products of pentose phosphate shunt. However, when the deficiency is too severe, the efficiency of neutrophils for bactericidal activity is reduced and the infected person is susceptible to recurrent infections.[14] In some cases, like hepatitis, pneumonia and enteric fever, the affected individual show severe response and sometimes, conditions become even more complex due to severe RBCs breakdown.[15] Though the relation of G6PD deficiency with hemolysis is most significant, yet many research studies have highlighted that it also has a connection with certain other medical conditions like hypertension, cardiac disease, preeclampsia, diabetes mellitus, infertility and aging process.[15-17] All these conditions are also frequently found in local community of Quetta, Pakistan.

The activity of enzyme depends on the types of mutations. The frequency and range of respective mutations vary among geographical regions and within the ethnic groups of a region. It is relatively more common in sub-tropical and tropical regions. For example, Greece population has a frequency between 20-30%, Thai population has 5-16%, Saudi Arabian has 6%, South Chinese has 5.5% and it is around 2.5% in the Indian population.[4,18,19] Many research studies have been performed on the Pakistani population, mainly on healthy asymptomatic adults during the past 40 years.[20,21] A study performed by Bouma *et al.*, on Pakistani Pathan and Afghan Refugees, has found 7% G6PD prevalence in the tested populations.[21] In addition to this, the highest percentage (4 to 14%) of G6PD deficiency has also been reported for jaundiced neonates. It is also indicated in these reports that babies developed jaundice within five days after their birth.[5,22,23] G6PD deficient babies were treated by blood exchange and phototherapy, however, 22% of them were suffered from acute bilirubin-encephalopathy with a mortality rate of 4%.[23] In our present study, we screened 716 neonates and found 10.06% of cases of G6PD deficiency. Prevalence of G6PD was significantly higher in Bloch, Pashtun, and Afghan Refugee ethnic groups with 10.3, 11.1 and 10.1% respectively. The higher percentage seems to be due to consanguineous marriages and common ancestry of these populations with Greeks. A similar percentage has also been reported by Moiz *et al.*,[5] In addition to this, 9.6% of G6PD deficiency has been found in Hazarvi ethnic group which is a very close ethnic group to Pashtun and Baloch. However, Punjabi ethnic group has only 4.65% of G6PD deficiency which is significantly lower from others.

G6PD deficiency has a positive influence on an individual in terms of providing a level of protection against malaria caused by *Plasmodium falciparum*. It is reported that *P. falciparum* and *P. vivax* are the common malarial endemic in Pakistan.[15] G6PD deficiency provides effective protection to females who carry one or two copies of the deficiency against *P. falciparum* and *P. vivax* infections, however, defense against *P. vivax*, which is a major cause of malaria outside Africa, is less effective as it normally attacks neocytes which usually have an ample amount of G6PD. The rate of *P. vivax* caused malarial infection has correlation with the

prevalence of G6PD deficiency which may exceed 10% in areas where malaria is common.[15,24] It is, therefore, apparent that the protection provided by G6PD abnormality against *P. falciparum* may confer a selective effect on G6PD deficient population. Commonly prescribed antimalarial drugs can cause slight to a serious level of hemolysis in G6PD deficient patient. Reports have shown that resistance has been developed against chloroquine in Pakistan and because of this, quinine is now commonly recommended by physicians. On the other hand, to deal with the relapse rate of *P. vivax*, primaquine has been extensively prescribed.[25] But primaquine likely has some serious side-effects and to avoid such complications, it is strongly recommended that individuals must be screened for G6PD deficiency before starting a treatment.[4,15] The relationship between and level of protection provided by G6PD deficiency to the Pakistani population have not been extensively reported so far. Such studies may be difficult to plan in the past because of the very low frequency of G6PD deficient individuals but as the number of affected people are rising, this area of research will also get attention.

Although, it is reported that approximately 7.5% of individuals in this world carry G6PD defective gene yet deficiency in females is rare. However, this may be only true for homozygous females as heterozygous females commonly have apparent indications for G6PD deficiency. In fact, the medical condition of a heterozygous female individual depends on G6PD deficient RBCs population which is always very difficult to predict.[26] Cousin-marriages and gene frequency are solely responsible for the high prevalence of G6PD deficiency in any geographical region and frequency of deficient female individuals may rise to 10% in such areas. Several reports have shown that the percentage of moderately deficient female individuals is relatively high as compared with the percentage of severe cases. For example, Jalloh *et al.* have found 12 deficient females individuals from 57 severe cases and 29 female individuals from 34 mild cases.[27] Male to female ratio for G6PD deficiency has also been predicted for the Pakistani population and it ranges from 3:1 to 5:1. It is necessary that cases of acute hemolysis G6PD deficient females must be kept in view.[12,19] In our study, we have a nearly equal number of male and female babies and we have documented an overall percentage of 14.51 and 5 for G6PD deficient male and female babies respectively.

In addition to this, the type of test used to detect G6PD has a strong influence on results as different tests have different threshold values and variable detection rate. With the advancement in biotechnology and medical research, G6PD enzymatic deficiency has been characterized at both quantitative and qualitative level and it is concluded that conditions of acute hemolysis cannot be predicted by only analyzing enzymatic activity and it has poor correlation with clinical features.[28] It is stated that four variants responsible for G6PD inefficiency are relatively more important at epidemiological and clinical level: G6PD-B does not affect enzymatic activity and it is considered as normal throughout the world. G6PD-A is another normal variant that is most common in Africa. G6PD-A- is also common in Africa and this variant shows 8-20% normal activity. G6PD-Med is the most severe variant as it decreases the enzymatic activity to <5% and it is relatively more common in Pakistan, India, Iran and Iraq.[15] This disease shows a range of clinical features in Pakistani population; starting from complete asymptomatic conditions to chronic non-spherocytic hemolytic-anemia and severe acute hemolysis.[15] It is, therefore, evident that several genetic variants/mutations exist in the Pakistani population and a wide-spread study is required to develop the population genetic map.

Different kinds of biochemical and molecular tests are available for G6PD deficiency detection. Almost all the test normally used for regular screening is based on the common principle of estimation of enzymatic deficiency. Hemolysis is often followed by the marked increase in a number of reticulocytes which have a relatively high level of G6PD enzyme and if screening tests are performed at this stage, it will definitely end in false positive results. All the test that analyze enzymatic activity suffer from this limitation, however, molecular analysis for detection of mutations remain un-affected. Dye-decoloration test, met-hemoglobin reduction test (MRT), new formazan method and fluorescent spot test (FST) are few examples of tests that are used for screening at large scale.[19,27,29] MRT has certain superiority over other tests in terms of test performance and cost-effectiveness.[12,14] MRT can also differentiate between homozygous and heterozygous female individuals. In the present study, MRT has given acceptable sensitivity and specificity.[15] Condition to perform the MRT test within one hour of sampling is the most serious limitation of MRT as compared with other available tests like FST which can be performed on three-week-old frozen samples.

Estimation of the status of G6PD in an individual is always helpful to avoid hemolysis linked diseases progress and death rate. Sometimes, G6PD deficiency becomes apparent as neonatal jaundice or acute-intravascular hemolysis and both these medical conditions are relatively more common indicators of the presence of G6PD deficiency. It is reported in the literature that infants with 29 to 32 weeks of gestation period have relatively higher G6PD activity as compared with the infants that born with complete gestation period and this factor may misrepresent the frequency of G6PD deficiency in a population.[15] In addition to this, most of the test designed for G6PD deficiency screening failed to estimate the actual status of G6PD mainly under the conditions of heterozygosity or higher count of reticulocytes. However, an underlying mutation in the gene remain unchanged during the whole life and it can be detected by DNA sequencing analysis. Understanding

about the range of mutations present at a particular region or in a certain population is much helpful for genetic-mapping for mutations, selection of restriction sites and for primer designing. A range of mutations has been reported from different regions so far and these mutations decide the type of G6PD variant. For example, G6PD-Med, G6PD-Orissa, and G6PD-Kerala Kalyan are the most common variants in India.[30] A unique range of clinical heterogeneity exists in Pakistani population. It includes CNSHA, acute life-threatening hemolysis, adults mild-symptoms, silent carriers and heterozygous females with severe deficiency symptoms. It is probable that many other clinical manifestations may exist in the Pakistani population that need to be explored at a large scale.

In conclusion, though G6PD deficiency can be measured at any life stage and by many chemical and molecular methods, yet screening at the neonatal stage and use of biochemical test are much more helpful to not only define requirement of medical treatment but also to plan more detailed molecular tests. Our sample size is relatively small and an overall conclusion about the prevalence of G6PD deficiency for the whole local population cannot be derived from this, yet it is clear from this study that percentage G6PD deficiency is higher in Baloch, Pashtun and Afghan Refugee population that may be due to consanguineous-marriages and common origin of ethnic groups. A large-scale study is still required to analyze G6PD deficiency, may be at other medical hospitals or testing center to drive an overall prevalence rate. Along with this, screening of G6PD deficiency at the molecular level is need of the time to identify the respective mutations, so that a genetic map for the local community of Quetta, Pakistan can be constructed.

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