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Glucose-6-phosphate dehydrogenase (G6PD) screening in Pakistani neonates: to be or not to be

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The primary metabolic role of erythrocyte glucose-6-phosphate dehydrogenase (G6PD) is the protection of red cells against oxidative damage. Its deficiency is the commonest inherited red cell enzymopathy as it affects around 400 million people globally with the highest prevalence in tropics and subtropics. Because it is an X-linked disorder, hemizygous males and homozygous females are the ones that are mainly affected. However, approximately 10% of heterozygous females may also be at risk. The presentation is variable depending on the residual enzyme activity and ranges from completely asymptomatic individuals to those who have life long haemolysis. Most significant manifestations are drug-induced haemolysis, favism, neonatal hyper bilirubinaemia and non spherocytic haemolytic anaemia.[1]

There is considerable evidence to believe that G6PD deficiency in Pakistan is not a rarity as various population based studies have shown a prevalence ranging from 2-3.8%[2-5] with highest frequency of 8.6% observed in Pathans.[6] Unfortunately, there is no documentation of characterization of its biochemical variants. Moreover, other than a single contribution from Saha et al[7] which identified presence of 563C-T and silent mutation of 1311 C-T in Pashtoons and Punjabis, nothing is known about the patterns and prevalence of different disease-causing mutations in the various Pakistani ethnic groups.

Infants with severe variants of G6PD deficiency are known to develop hyperbilirubinaemia that may be sufficient to cause kernicterus and even death.[1] Recent research is focusing on decreased bilirubin conjugation rather than haemolysis as the primary aetiology for neonatal jaundice (NNJ) in the enzyme deficient babies with

promoter polymorphism of UDP glucoronyl transferase 1A1 gene (UGT1A1) as the major implicating factor.

To evaluate the magnitude of the problem at the national level, the author explored various local and international search engines. Several single institution based studies conducted at Peshawar and Lahore had shown an incidence of G6PD deficiency varying from 4 to 14% in jaundiced neonates.[8,9] All babies developed hyperbilirubinaemia within 0-5 days of their birth with serum bilirubin reported to be as high as 50 mg /dL in some babies. Phototherapy was required by all the infants with an additional requirement of exchange transfusion in 6-65% of patients. Unfortunately, a significant proportion of G6PD deficient newborns (4-22%) developed kernicterus with mortality ranging from 2-4.3%.

Neonatal G6PD screening programs are enforced in those areas of the world where severe variants of G6PD deficiency are widespread such as Middle East, Eastern Europe and Southeast Asia. These have shown promising results in terms of avoiding acute haemolytic crisis and permanent brain damage in babies. Since the prevalence of severe hyperbilirubinaemia among our neonates was observed to be relatively high with exchange transfusion required in a half of them, early detection of this enzymopathy would be a viable option through mass screening programmes.

Several factors need to be considered in evaluating the feasibility, need and cost effectiveness of any neonatal mass screening programmes: prevalence and severity of the disease in target population, availability of inexpensive user friendly screening tests, access to treatment and follow-ups.

According to world health fact sheet 2007, Pakistan having a population of 165 million and growth rate of 1.8% has the annual birth rate of 27.52 /1000. According to World Health Organization (WHO), 53 neonates out of 1000 live births die of various reasons in our country. The situation is complex in terms of estimation of frequency of neonatal jaundice as over 89 % of our babies are delivered in homes and any organized data on routine health outcomes from rural Pakistan is non existent. Because of these reasons, it is impossible to estimate the burden of overall G6PD deficiency in our country. There is dire need to carry out a large epidemiological study of G6PD deficiency associated neonatal hyperbilirubinemia to elucidate the true dimensions of the problem.

The author inferred from available documentation that during the reporting duration of 22 years (1984 to 2006), 2811 neonates had hospital admissions because of neonatal jaundice. Of these, 256 babies (9.1%) screened positive for G6PD defecieny.[8,9] However, the data is skewed as all studies were done either in Peshawar or at Lahore, which are more likely to be inhabited by Pathans and Punjabis- the ethnic groups that have been identified to be at risk. Needless to say that similar results are expected as G6PD deficiency has been reported in adults from all over the country.

The International Committee for Standardization in Haematology has recommended the fluorescent spot test as a screening test for G-6-PD deficiency. However, some recently published studies of G-6-PD deficiency in neonates have utilized the commercial color reduction kit. The latter test is cheaper, easier to perform, less time consuming, and requires less sophisticated equipment (ultraviolet lamp) than the fluorescent spot test. Later was utilized in the studies reported so far from our country. Thus it may be more appropriate for mass use in developing countries than the more complicated fluorescent spot test. It can be set up and run by unskilled workers in a doctor's office or neighborhood clinic. The cost per test is estimated to be $0.5-0.9 which is negligible when compared to the cost of hospital admissions and exchange transfusions.

The mass screening for G6PD would be invaluable in identifying the deficient babies at the time of their birth. This can easily be achieved by saving cord blood and performing the test on the sample without causing extra discomfort to infant. Serial monitoring of bilirubin for such babies would help in evaluating those infants who can not be discharged from hospitals but appropriately managed with adequate hydration, phototherapy and/or exchange transfusion thus avoiding permanent brain damage. The identification of deficient babies would aid the health workers to counsel parents in avoiding exposure of their babies and themselves (if lactating) to oxidizing agents, to watch for jaundice and to bring jaundiced infant to hospital at their earliest. The mothers can also be advised to check for G6PD levels in other children.

A major fallacy of this program would be failure to diagnose female heterozygote babies as their enzyme levels are enough to give a negative screening result. However, evidence shows that 10% of them can suffer from severe haemolysis, NNJ and kernicterus.[10] The spectrophotometeric quantification of enzyme is advisable in such circumstances if there is strong clinical suspicion of enzyme deficiency in female babies. It is of interest to note that our local data showed 16 G6PD deficient female babies of a total of 252 enzyme deficient infants.[8,9] It can be concluded that these might represent severely affected homozygous females detected on qualitative assays.

For the screening program to be effective, we would not only face the challenge of training doctors, nurses and lady health workers for changing their beliefs and attitudes but also monitoring home deliveries and training dais would be a difficult task.

Our evaluation testifies the importance that initiation of mass neonatal G6PD screening should be considered in our country. It can avoid the incidence of permanent brain damage resulting from hyperbilirubinemia with subsequent kernicterus and death. Such measures can not only guide the pediatricians for successful management of their patients but also provide an opportunity to start comprehensive educational programs for parents thus avoiding lifelong morbidity of enzyme deficient individuals.

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