Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.47750/jptcp.2023.30.15.021

G6pd Deficiency And Hyperbilirubinemia In Newborn Baby(Prospective Study)

Myasar Hafedh Ibrahim[1*], Ibrahim Mahmood Saeed[2], Sundus Mohammed Hussein[3]
[1]Al.Battol Teaching Hospital
[2,3]Khanaqin General Hospital
***Corresponding author:** Myasar Hafedh Ibrahim, Al.Battol Teaching Hospital,
Email: meaasarhafuz@yahoo.com

Submitted: 28 April 2023; Accepted: 16 May 2023; Published: 05 June 2023

ABSTRACT

Background: The most prevalent enzyme deficit in humans is glucose-6-phosphate dehydrogenase insufficiency. Objectives**To investigate the significance of G6PD deficiency in hyperbilirubinemic newborns.

Aims: To assess additional parameters associated with newborn hyperbilirubinemia.

From December 2017 to April 2018, two hundred newborn babies were enrolled in a prospective study at the Neonatal Care Unit of Child's Hospital ; one hundred were diagnosed with clinical and biochemical neonatal jaundice, while the other hundred served as a control group. The activity of G6PD was measured by a met haemoglobin reduction test, with both groups further classified into G6PD deficient and normal subsets.Results G6PD deficiency was found in 25% of infants with jaundice but only 8% of those without jaundice (the control group). Twenty of the G6PD-deficient individuals were men (80%) and five were women (20%).Recommendations and findingsThere is an elevated risk of newborn hyperbilirubinemia associated with G6PD deficiency, and a considerable percentage of affected infants (10-40%) would need an exchange blood transfusion as a result.

In high-risk communities like ours, screening for G6PD in cord blood is one option to consider. Early diagnosis of the enzyme deficit by newborn screening is recommended in a community with a high prevalence rate so that necessary treatments may be taken to prevent the consequences of hemolysis and future issues of neonatal jaundice owing to G6PD deficiency.

Goals of Research

1. To investigate the significance of G6PD deficiency in hyperbilirubinemic newborns.
2. to investigate additional potential causes of newborn hyperbilirubinemia.

Keywords: *G6PD deficiency, hyperbilirubinemia, newborn, gene*

INTRODUCTION

Etiology

Encoding the enzyme glucose-6-phosphate dehydrogenase (G6PD) around 18 kilobytes in length, 13 exons, and 12 intro introns. The location of this gene on the X chromosome is Band Xq28 that contains the gene for the G6PD enzyme. Deficiency in G6PD is triggered by defects in the G6PD gene It has a pattern of inheritance similar to X-linked recessive disorders. These enzyme activity is often reduced in polymorphism forms. as well as decreased enzyme stability, which is typically noted disturbances in the folding of proteins (1–3). X-linked inheritance explains afflicted by mutations in the G6PD gene tend to be men rather than women. to ladies. Half of males are wild-type (WT), whereas the other half are mutations in the G6PD gene lead to an enzyme called G6PD. deficiency. The G6PD gene is duplicated in females; carrying two copies of a mutant allele (homozygous) causes Negative G6PD status. Females with a wild-type and a mutant allele you have two copies of the G6PD gene (heterozygotes). People like that have a moderate G6PD deficiency and are therefore classified. Yet because of when it comes to X-inactivation at random, Heterozygous females have lower than average amounts of G6PD, and some heterozygotes be functionally defective in G6PD, whilst others may not affected. Such variety complicates our efforts to babies with partial G6PD deficiency should be screened for the condition. Traditional screening procedures fail to discover (4, 5).Global and Regional Perspectives on Epidemiology According to one study, G6PD deficiency affects an estimated roughly 400 million people, or 4.9% of the world's population impacted, making it the most common enzyme in human beings. deficiency. G6PD occurs in many different parts of the world. deficit, with sub-Saharan Africa having the greatest recorded frequency Deserts of the Sahara in Africa. After there comes the middle Arabian Peninsula. Southeast Asia, the Mediterranean, and Latin America U.S.A. (6&7). High population concentration means that most of G6PD deficiency sufferers are expected to be of Asian descentnations (7).Carson et al. first identified it in 1956, and since then its prevalence has and health problems caused by G6PD deficiency determined in a number of regions, enabled by the ease and low cost of being screened. While in others, newborn screening programmes in developing countries the plan of action for avoiding severe cases of newborn jaundice. G6PD deficiencies as a primary contributor to the development of severe hyperbilirubinemia of infancy, which can have serious consequences Kernicterus complication. Initiated by the World Health Organisation being a major worldwide health concern, G6PD deficiency must be addressed with the release of a detailed illness categorization, assessment, care, and safeguards (8). The incidence of There is still a widespread problem with kernicterus due to severe jaundice population growth, especially in low-income regions of the world. It is More than 400,000 infants are predicted to have jaundice annual basis, with around 75% resident in South- China, East Asia, and sub-Saharan Africa (9, 10). This occurrence the incidence of severe hyperbilirubinemia (over 340 mmol/L) is around In Indonesia, bilirubintoxicity affects 2% of patients. repercussions (11). High- and moderate-prevalence populations may.The United States has implemented a newborn screening programme to detect this disease and recommendations for closely observing any infants. Phototherapy for early detection and treatment Easy and inexpensive methods for spotting infants at danger, keeping tabs on them, and intervening and quickly address hyperbilirubinemia to forestall kernicterus. Despite the fact that diagnosis and prevention could be fairly simple, a lot is still unknown about the pathophysiology. Given the variation within this genetic disorder causes the severe effects of hyperbilirubinemia in newborns. Economic efficiency in nations with universal healthcare systems constrained resources and a rapidly expanding disease load .The rate of hospital bed turnover should be given serious thought. G6PD deficiency is frequent in nations like Malaysia. since it contributes significantly to severe cases of newborn jaundice (12, 13).The government has instituted mandatory newborn screening. by the Malaysian Department of Health since 1986. Although Despite the positive results of the screening programme,

Recommended Fluorescent Spot Test Sensitivity remains problematic since it fails to correctly diagnose some patients. female homozygotes who are deficient and those who lack the G6PD enzyme hemolysis occurring at a rapid rate. Moreover, not all people who lack the enzyme G6PD

Neonatal jaundice is a serious problem that affects newborns and whether or if some varieties are more susceptible than others, whether or whether concomitant risk variables play a intense jaundice. In this regard, newborns with a deficiency in G6PD children who spend their first week of life being closely produce less than 6.76 U of enzyme per gramme of haemoglobin or G6PD

Significant health risks are linked to the Kaiping (c.1388G > A) variation. hyperbilirubinemia that needs to be treated with light (14).A panel of enzymes is used in a quantitative enzyme activity assay. Targeting individuals with high-risk genetic variations for severe jaundice baby risk assessment and care coordination. Yet It's also puzzling since newborns with G6PD deficiency frequently show signs of There may be no outward symptoms of severe hyperbilirubinemia. blood film hemolysis or severe reticulocytosis (15), which is typical of most diseases that result in haemolytic illness, including anaemia and jaundice. These results suggest that potentially a number of cases of hyperbilirubinemia in infants caused by Mechanistically, G6PD deficiency differs from other rather than a sudden crisis of hemolysis brought on by exposure to oxidants, the favism example shows.

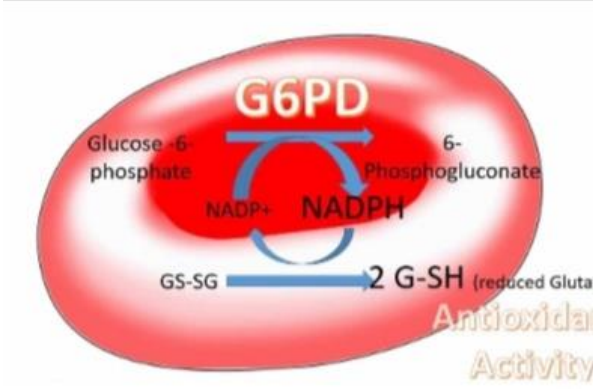
The Role of Antioxidants in Pathophysiology Mutations in Genes Cells consistently produce the G6PD enzyme and contributes greatly to the pentose phosphate pathway's function. Glucose-6-phosphate is oxidised by this enzyme to 6-phosphogluconolactone. G6PD, critically, restores the Niacinamide adenine dinucleotide phosphate in its reduced form [NADPH; (16)]. Cofactor and reducing agent NADPH to Thioredoxin and Glutathione Reductase catalyses the reduction of glutathione (GSH) and acts as a reductase. respectively, thioredoxin (Trx) (Figure 1). As a result, Trx levels engages in the scavenging of peroxiredoxins, which Together with glutathione (GSH), they are the primary antioxidants in erythrocytes. [RBC; (17, 18)]. Hydrogen peroxide is lowered thanks to these antioxidants. and thereby prevent oxidative stress on the RBC. Two of the most prominent clinical symptoms in Symptoms of a G6PD deficiency include blackwater fever and favism. as a result of severe and sudden blood loss. Just like that hemolysis in G6PD-deficient individuals, by Luzzatto and Arese (19) Favism causes RBCs to form because the cells are unable to produce enough NADPH to neutralise an overabundance of hydrogen peroxide and in addition to other reactive oxidants. The conventional wisdom, however,

Glutathione peroxidase, an enzyme that breaks down glutathione, requires NADPH. New information about catalase systems necessitates a rethink. shape of a different key participant in red blood cell antioxidant defence,Prdx2 is a peroxiredoxin. Glutathione peroxidase is less common than prdx2. plus catalase. Because of its extreme reactivity, it requires careful handling. primary RBC hydrogen peroxide consumer in low concentrations reduce free radical activity. Due to its antioxidant properties, NADPH is also required for Prdx2. Prdx2 oxidation results in an interchain disulfide, a byproduct of thioredoxin recycling thioredoxin reductase, which needs reducing equivalents in order to function. by using NADPH. Prdx system antioxidant action should be jeopardised in the absence of NADPH using the phosphoenolpyruvate route. There was proof of this by RBC Prdx2 in newborns with G6PD deficiency, leading to increased .Those that have been proven to sustain an oxidised condition and low reactivation rate following peroxide stress (20). Further,The modelling of Prdx2 recycling following a,The bolus of hydrogen peroxide suggested that several genes played a

Prdx2 activation and G6PD variations. The many forms resulted in variations in kinetic reaction rates, which mightThe reuse of Prdx2. Previous kinetic data are shown in Table 1.G6PD mutations' effects on activity parameters(21, 22).Therefore, decreased Prdx2 antioxidant activity may have a role in G6PD-related illnesses, and thisrely on the G6PD version of the gene as well. In-Depth Studies is required to investigate the function of Prdx2 in G6PDdeficientAcute hemolysis in babies and healthy infants. The O2 Transporting the RBC's function leads to the production of radical oxygen produced during cellular metabolism, which causes ongoing oxidative stress from both internal and external factors stress. Therefore, keeping your GSH and Prdx2 antioxidant levels up is essential. are necessary to shield red blood cells from oxygen radicals, oxygen-free species (ROS). It's also worth noting that RBCs don't have any enzymes that generate NADPH, and any depletion of NADPH is catastrophic. other routes of compensation. As a result, G6PD has an

impact Particularly problematic is a lack of NADPH due to an enzyme shortage. red blood cell marked. Because of this drop in NADPH production, when there is not enough glutathione disulfide (GSSG) reduction.

and Prdx2, reducing the efficiency of the body's antioxidant defences (20). In contrast, glutathione may have an important protective role. in inhibiting the oxidation of cytoplasmic sulfhydryl membrane proteins, especially those that let the cell survive high levels of oxidative glutathione reductase has been linked to favism, thus it's not an easy and a lack of glutathione synthetase, despite normal Since G6PD was regular, NADPH was as well (23). Deficiency in red blood cells oxidative stress can cause damage to the G6PD enzyme. causing blood loss due to hemolysis, especially when exposed to oxidative agents. On the other hand, acute favism can be distinguished in the clinic and severe hyperbilirubinemia in newborns might be due to differences in potential roles and contributions from different Red blood cell antioxidants. Possible ground for further study would be to investigate this factor in premature babies. antioxidant capacity is typically reduced in the G6PD deficiency history.



Baby Sickness: Jaundice and Hyperbilirubinemia

Neonatal hyperbilirubinemia is strongly associated with G6PD. deficiency. Having a deficiency in G6PD has been linked to newborns are more likely to have neonatal jaundice, and if they do, it will be a more severe kind. kernicterus. sums up some of the variations that have been seen to be connected to high bilirubin levels in newborns. Interestingly, These factors have a weak relationship in babies with a G6PD deficiency. in the presence of hemolysis and Heinz bodies. Potentially, this could be because acute jaundice does not produce newborn hyperbilirubinemia. hemolytic anaemia, but rather by a combination of internal variables that increase a baby's risk of developing jaundice. The supravital blood stain, often known as crystal violet, is one such case. child suffering with severe hyperbilirubinemia due to a lack of G6PD did not reveal any Heinz dead corpses. babies born without the G6PD gene were more likely to develop Hemolytic anaemia caused by naphthalene or fava bean poisoning Consistent with the foregoing, there were indeed Heinz corpses present. Khefacha et al. . reported the creation of Heinz bodies in a laboratory dish a G6PD-deficient individual's red blood cells (RBC) when henna was applied specimen of neonatal blood. Having access to genotyping and This infant's peripheral blood film would be helpful because they may offer explanations for the lack of or the presence of in vivo clearance of those packaged in Heinz. Additionally, red blood cells (RBCs) in newborns are bigger. have a lower average lifetime than adults (120 days). The average RBC from a newborn will die between 60 and 90 days later. while preterm babies' lives span just 35-50 days. Overall, glutathione-enzyme levels are lower in neonatal RBCs. critical enzymes like peroxidase and carbonic anhydrase control cell balance and membrane stability; these parameters potentially raises oxidative damage risk. Someone who lacks the enzyme G6PD state may exacerbate the shortening of the lives of RBC. All of these factors contribute to a higher bilirubin burden in the circulation in the baby's blood and in the liver cells. In addition, the The liver of a newborn is still developing, making it less efficient. a reduction in the body's ability to remove bilirubin. As an example of This is the ligandin concentration found in the liver of a newborn. cells. The binding of bilirubin to this protein is essential for its function. liver, and its levels are only elevated for the first the first few weeks of life. The other factor is reduced liver cell glucuronosyltransferase activity for uridine diphosphate causing a drop in liver bilirubin conjugation. It co-inheritance of a uridine diphosphate was also discovered. gene variation of glucuronosyltransferase 1A1 (UGT1A1) contributes role in G6PD-deficient neonates' increased risk of hyperbilirubinemia Newborn boys. Overall, a high bilirubin concentration in the blood, and the liver's inability to properly eliminate them leads to newborn jaundice by increasing blood bilirubin levels. hyperbilirubinemia, a more serious and common

condition in newborns with a lack of G6PD. The neonatal RBC also stands apart because of something else: mostly composed of HbF (foetal haemoglobin). In general, HbF tends to under oxidative stress, to denature and precipitate, hence RBC membrane, which helps explain why RBCs don't live as long as other cells. Heinz bodies are composed of denatured HbFs that have precipitated. most newborns with hyperbilirubinemia have a condition called Heinz body features should be present in people with a G6PD deficiency.

This, however, is not the situation. One probable reason is that The removal of Heinz bodies is substantially more effective. when Hb is changing from foetal to adult levels. Additionally,

The susceptibility can be lowered by taking a different route. Hb's susceptibility to oxidative denaturation. The vast majority different metabolites from the heme moiety the bile, such as mesobilifuscins and bilidoxins, are expelled in much lower concentrations bile, stool, and urine. There's a need for more study to the correlation between G6PD variants and this different catabolic route in Heinz's body that Clarify this haematological oddity for me.

Women who are heterozygous are typically viewed as little more than carriers. leading to a failure to properly identify G6PD deficiency as the cause. reason for the hyperbilirubinemia's severity. This is a noteworthy example is a healthy, full-term, Malay female infant. liver damage and jaundice on day three of life. Common haematological measurements included normal, with the exception of an elevated reticulocyte count at 6.28%. No abnormalities were seen in the peripheral blood smear. causes hemolytic anaemia. Admitting patients' G6PD enzyme levels over 6.76 U/g Hb (considered normal). What we found without the evidence of G6PD deficiency, the that the enzyme activity spike was unwarranted because of the elevated reticulocyte percentage. More research is needed.

Molecular testing for changes in the G6PD gene indicated that The patient carried two copies of the G6PD Mahidol mutation (c.487G > A).

Table (1): *shows (WHO) classification of G6PD variants on the Basis of magnitude of the enzyme deficiency and the severity of hemolysis.* [19]

WHO Class	Variant	Magnitude of enzyme deficiency	Severity of Hemolysis
I	Harilaou, Tokyo,Guadala Jaram,Stony Brook	2% of normal activity	CNSHA
II	Mediterranean	3% of normal activity	Intermediate hemolysis
III	A⁻	10-60% of normal activity	Intermediate hemolysis usually associated with infection or drugs
IV	B (Normal)	100% of Normal activity	No hemolysis

Table (2): *Comparison of the two most common variants of G6PD deficiency.* [1]

	G6PD Mediterranean	G6PD A⁻
World Health Organization class	Class II	Class III
Populations affected	Italian, Grecian, Spanish, Arabic, Jewish (Kurdish) descent	African descent
Neonatal hyperbilirubinemia	Yes, may be more severe	Yes
Favism	More common	Less common
Hemolysis with oxidative Drugs	Yes	Yes

Box (1): *Drugs and chemicals that should be avoided by persons with G6PD deficiency.* [12]

Acetanilide	Phenazopyridin
Doxorubicin	Primaquine
Furazolidone	Sulfacetamide
Methylen blue	Sulfamethoxazole
Nalidixic acid	Sulfanilamide
Naphthalene	Sulfapyridine
Niridazole	Thiazolesulfone
Nitrofurantoin	Toluidine blue
Phenyl hydrazine	Trinitrotoluene (TNT)

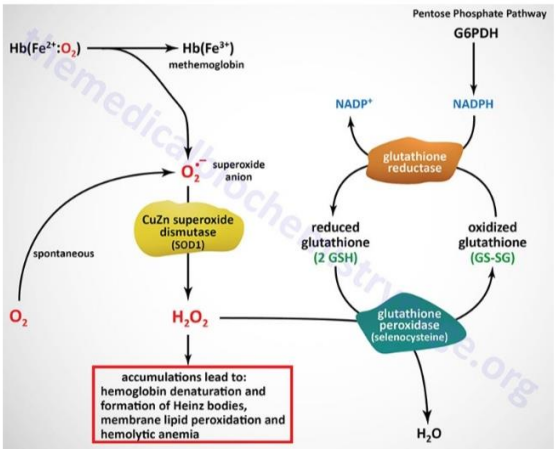
Box (2): *Drugs that can possibly safely be given in normal therapeutic doses to G6PD deficient subjects without nonspherocytic hemolytic anemia.* [12]

Acetaminophen (paracetamol)	p-Aminobenzoic acid
Acetophenitidin	Phenylbutazone
Acetylsalicylic acid (Aspirin)	Phenytoin
Aminopyrine	Probencid
Antazoline	Procainamide hydrochloride
Antipyrine	Pyrimethamine
Ascorbic acid (Vit.C)	Quinidine
Benzhexol (Artane)	Quinine
Chloramphenicol	Streptomycin
Chlorguanidin	Sulfacytin
Chloroquine	Sulfadiazine
Colchicine	Sulfaguanidine
Diphenhydramine	Sulfamerazine
Isoniazide (INH)	Sulfamethoxypyridazine
L-Dopa	Sulfisoxazole
Menadione sodium bisulfite	Trimethoprim
Menapthone	Vit. K

Diagnosis and testing in the laboratory ,

METHODS

With the advent of point-of-care testing, chance to check for this frequent genetic condition worldwide. An easy-to-use, quick, and reliable point-of-care test (POCT) high quality resources that can be easily accessed by regions with scarce G6PD deficiency has a high enough frequency that it might aid in the detection and severe hyperbilirubinemia by providing guidance and support on doing what needs to be done to intervene quickly. Molecular It's possible that a genetic test wouldn't be feasible or cost-effective. historically, because to preexisting facilities and technical requires specialised knowledge, yet developing rapidly Gene chips make this more generally available. Test with Fluorescent Spots Measuring enzyme activity is the standard method for establishing G6PD state. from a whole reticulocyte. Newborn cord blood screening treatment for G6PD deficiency is widely used, particularly in low- and middle-income countries having a high wealth and a high frequency. Those people who who reside in malaria hotspots also get G6PD testing. prior to the use of 8-aminoquinolone drugs. The most used approach for detecting G6PD deficiency A semi-quantitative assay known as the fluorescent spot test (FST). Although Despite being cheap and simple to implement, this technique can only discover instances with normal G6PD activity of 20% or less and largely ignores, in females at least, the little G6PD activity .The heterozygotes are four in number.



PATIENTS AND METHODS

One hundred infants diagnosed with jaundice on admission to the neonatal care unit at Baghdad's Child's Central Teaching Hospital between December 2017 and April 2018 were included in the research.One hundred infants from the maternity ward who visited the outpatient clinic but showed no signs of jaundice served as a comparison group. Members of the immediate family were interviewed to collect information such as the infant's age, gender, birth weight, mode of delivery, and when jaundice first appeared, whether the baby was full-term or premature. It was recorded if there was a history of newborn jaundice, phototherapy, exchange blood transfusion, anaemia, or kernicterus in the family. It was also noted what kind of food was consumed.Rh-incompatible newborns were not included in the analysis. Using sterile tubes, two millilitres of blood were collected from the patient's forearm's superficial vein and sent off to be tested for G6PD activity by met haemoglobin decrease (any sample less than two millilitres was either disregarded or recollected if feasible). The colour of normal blood is the same clear red as that of the standard reference tube. The brown hue of the defective reference tube is reflected in the blood of deficient people. (1. Important investigations for neonates admitted to the hospital with jaundice included PCV, blood group typing and Rh antigen testing for both mother and newborn, reticulocyte count, and assessment of total serum bilirubin concentration at admission. Both the jaundiced and the non-jaundiced (control) groups undergo G6PD testing by the met haemoglobin decrease test.We didn't include two subsets of infants in our analysis: One infant infected quite severely. There are two infants that are Rh-negative.

Statistical analysis

The information was cleaned and analysed by SPSS (SPSS Inc., Chicago, IL, USA) version 21. Percentages and frequency counts were used to illustrate the outcomes. The 95% confidence interval was based on a p-value of less than 0.05, the threshold for statistical significance

RESULTS

Out of 100 jaundiced newborn babies, 25 (25%) were G6PD deficient while onlyS(8%) newborn babies were G6PD deficient in the control group (table 3)

TABLE 3: The association between hyperbilirubinemia and G6PD deficiency in neonate

	G6PD deficency		G6PD normal	
	NO.	%	NO.	%
Neonates with Jaundice n = 100	25	25%	75	75%
Neonates without Jaundice n = 100	8	8%	92	92%
P value = 0.001	RR = 3.13 TIME	95% CI = 1.48-6.59		

Twenty (80%) of the G6PD deficient were male and five(20%) wer female, with male: female ratio 4:1. While In the control group there were 750 (%male and 2(25%) female were G6PD deficient with male: female rati 3:1. Sex difference was not significant between case and control grou (P=1.00).(table 4)

TABLE 4: Sex distribution of G6PD deficiency in Jaundice newborns and control groups.

	Male		Female		P value
	NO.	%	NO.	%	
Neonates with Jaundice					
G6PD deficency n = 25	20	80	5	20	0.071
G6PD normal n = 70	42	60	28	40	
Neonates without Jaundice					0.429
G6PD deficency= 8	6	75	2	25	
normal= 92	56	61	36	39	
P value	0.002	0.002	0.163	0.163	

TABLE 5: The relationship of G6PD deficiency and control groups to some variables.

	G6PD deficency n = 25		G6PD normal n = 75		P value
	NO.	%	NO.	%	
Family history of NNJ	11	44%	29	41%	0.637
TSB 20mg dl	9	36%	11	16%	0.021
PCV 45%	18	72%	50	71%	0.621
Phototherapy	25	100%	75	100%	
Exchange transfusion	1	40%	14	20	0.031

In G6PD deficient neonates had a mean bilirubin level of 19.2-+5.2 while In G6PD normalneonates17.1+4.1 (P=0.03). The age at onset of jaundice in normal neonates was the same as In deficient group. All the neonates required phototherapy in both groups, 10(40%) of G6PD deficient and14 (20%) of normal G6PD neonates required exchange blood transfusion (P=0.04) .In 43% of G6PD deficiency neonates, there was a positive family history of neonatal jaundice, compared with G6PD normal was 41%(P=1.000). Eighteen percent(18%) had a sibling admitted for neonatal jaundice and treated with phototherapy. In 7% there was previous family history of exchange transfusion; one had positive family history of kernicterus. Eighty percent of G6PD deficient and 88.5%of G6PD normal neonates were delivered by vaginal.

Delivery (P=0.32) . 60% of G6PD deficient and 68.5% of G6PD normal were exclusively breast fed (P=0.46). Table 6.

TABLE 6: Demographic details of neonates studies.

	G6PD deficency n = 25		G6PD normal n = 75		P value
	NO.	%	NO.	%	
Birth weight mean ±SD grams	3152±366		3295± 419		0.131

J Popul Ther Clin Pharmacol Vol 30(15):e189–e198; 05 June 2023.

Vaginal delivery	20	80	66	88	0.318
Exclusively breast fed	15	60	51	68	0.465

DISCUSSION

G6PD deficiency was found in 25% of neonates hospitalised to the newborn care unit with jaundice. These results were lower than those reported by ALSowad (Baghdad), who found 34% were G6PD deficient (25), and AL-Omran (Saudi Arabia), who found 30.3% were G6PD deficient (29), but higher than those reported by Alnaama (0) (Basra), who found 51%; the latter's high result may be attributable to the use of a more sensitive test for the G6PD enzyme assay, and to the factMales outnumbered females by a factor of 4:1 (20/25 cases), consistent with the disease's sex-linked recessive inheritance pattern. Similarly to the numbers reported by Kaplan and Abramov (14% (51)) and Al-Omran (19%), 20% of G6PD defective individuals were female.(29) The high frequency of inactivation of the normal xchromosomes in female heterozygotes, as well as the high number of female homozygotes, may contribute to the overall high incidence of G6PD deficiency in females, as proposed by the Lyon hypothesis.(23,24)Al-Sowad reported that the proportion of G6PD-deficient neonates with a PCV level above 45% was 61%, while 88% had a PCV level above 40%, and the mean reticulocyte count was 4.3%. These results rule out severe hemolysis as a potential source of jaundice. This is typical of infants with a G6PD deficiency, as seen here. (25). When comparing normal G6PD newborns to those with the deficiency, the researchers found that 37% of G6PD-deficient neonates had a serum bilirubin level of more than 20mg/dl (340umol/L) upon admission. One-sixth of them had a TSB level above 20mg/dl. T.S.B levels were shown to be considerably elevated in G6PD defective newborns.G6PD defective neonates were more likely to get an exchange blood transfusion (40%) than normal G6PD neonates (20%). AlSowad also reported 41%, which is comparable but higher than the 20% reported by Al-Omran. Several factors, including early neonatal discharge, similarity to physiologic jaundice, and a lack of parental knowledge, lead to delayed presentation and delayed treatment of these G6PD-defficient neonates, which may explain the high rate of exchange transfusion reported in this study among G6PD deficient neonates. (39,40) Controlling hereditary blood illnesses like G6PD deficiency has been observed in Bahrain thanks to ongoing efforts in education, awareness, campaigns, screening of carriers, and prenuptial counselling.(41) Jaundice, similar to physiological jaundice, began on day two or later in the vast majority of G6PD deficient neonates. However, only 6.7% of these infants were born with the condition. This is consistent with what has been observed in investigations conducted on newborns by Al-Swoad and Al- Omran.(28, 29) There were two peaks in the average age of patients admitted on the third and fifth days. Serum bilirubin tends to rise more noticeably the sooner hemolytic events occur. Similar to the findings of Al -Sowad and Niazi's study, this one revealed that the mode of delivery (vaginal vs caesarean section) and the mode of feeding had no substantial influence on daily bilirubin level. (28,43)

CONCLUSIONS

1. A sizable proportion of women are G6PD impaired.
2. Many infants born to mothers with G6PD impairment need to undergo exchange blood transfusions because they develop hyperbilirubinemia at birth.
3. In G6PD deficient newborns, indirect hyperbilirubinemia is a valid haematological indication, while haemoglobin, blood morphology, and reticulocyte count are not.
4. There is currently no routine neonatal screening for G6PD in Iraq.

RECOMMENDATIONS

1. To identify G6PD-deficient newborns who may need a longer postnatal hospital stay and closer monitoring of their serum bilirubin before and after discharge, we propose G6PD screening of cord blood. Conversely, newborns who have normal G6PD activity may allow for earlier discharge and more frequent monitoring.
2. G6PD deficiency should be ruled for in all newborns with jaundice, especially males.
3. The identification and subsequent care of these newborns requires a high level of clinician knowledge.

REFERENCES

1. Jennifere.Frank, American Academy MALMC. Of Family Diagnosis Physicians, and 2005: Management 72:1277-82of G6PD deficiency
2. Lazzatto L . Metha A. G6PD deficiency .In Metabolic and Molecular bases of Inherited disease. Editors: Scriver, Charles R. , Arthur I Beaude, and Williams S. , 7th ed, New York, MeGraw Hill, 1995:3367-98
3. Segel G B. Enzymatic defects In: Behrman R.B ., Kliegman R.M ., JensonHB, Stanton BF.(Editors), Nelson Textbook of Pediatrics, 18? ed. Philadelphia, WB Saunders, 2007; 468: 2039-42..
4. LuzzattoL. Glucose-6-phosphate dehydrogenase deficiency and hemolytle anemia. In: Nathan D.G ., Orkin S.H ., Ginsburg D. , Look A. T ., (Editors)Nathan and Oski's Hematology of Infancy and Childhood, Sixth ed ., New York, Saunders, 2003; 17:721-38
5. Beutler E. The molecular biology of G6PD variants and other red cell enzyme defects. Ann Rev Med 1992; 43: 47-59.
6. Hassan M K, Taha J Y, Al-Naama L M, Widad N M, and Jasim S N.6.Frequency of hemoglobinopathies and glucose -6- phosphate dehydrogenase deficiency in Basra. Eastern Mediterranean health journal, 2003; 9:49-53.
7. Margaret JA, Adams MJ, Naylor CE. Glucose-6-phsphate dehydrogenase mutationcausingenzymedeficiency,Blood 1996; 87; 2974-2982 .
8. Mehta deficiency. A,Mason Baillieres PJ,Best Vulliamy Pract Res TJ. Clin Glucose-6-phosphate Haematol 2000; 13: 21-38.dehydrogenase.
9. Chen E Y, "Sequence of human glucose-6-phosphate dehydrogenase cloned in plasmids and a yeast artificial chromosome"Genomics1991; 10:792
10. Glucose-6-Phosphate Dehydrogenase Deficiency and Neonatal Hyperbilirubinemia: Insights on Pathophysiology, Diagnosis, and Gene Variants in Disease Heterogeneity Heng Yang Lee1, Azlin Ithnin2, Raja Zahratul Azma2, Ainoon Othman3, Armindo Salvador4,5,6 and Fook Choe Cheah1*
11. Greco C, Arnolda G, Boo NY, Iskander IF, Okolo AA, Rohsiswatmo R, et al. Neonatal jaundice in low- and middle-income countries: lessons and future directions from the 2015 Don Ostrow Trieste Yellow Retreat. Neonatology. (2016) 110:172–80. doi: 10.1159/000445708
12. Lie-Injo LE, Virik HK, Lim PW, Lie AK, Ganesan J. Red cell metabolism and severe neonatal jaundice in WestMalaysia. Acta Haematol. (1977) 58:152–60. doi: 10.1159/000207822
13. Singh H. Glucose-6-phosphate dehydrogenase deficiency: a preventable cause of mental retardation. Br Med J (Clin Res Ed). (1986) 292:397–8. doi: 10.1136/bmj.292.6517.397
14. Wong FL, Ithnin A, Othman A, Cheah FC. Glucose-6-phosphate dehydrogenase (G6PD)-deficient infants: enzyme activity and gene variants as risk factors for phototherapy in the first week of life. J Paediatr Child
15. Health. (2017) 53:705–10. doi: 10.1111/jpc.13509
16. Kaplan M, Wong RJ, Stevenson DK. Hemolysis and glucose-6-phosphate dehydrogenase deficiency-related neonatal hyperbilirubinemia. Neonatology. (2018) 114:223–5. doi: 10.1159/000489820
17. Pandolfi PP, Sonati F, Rivi R, Mason P, Grosveld F, Luzzatto L. Targeted disruption of the housekeeping gene encoding glucose 6-phosphate dehydrogenase (G6PD): G6PD is dispensable for pentose synthesis but essential for defense against oxidative stress. EMBO J. (1995) 14:5209–15. doi: 10.1002/j.1460 2075.1995.tb00205.x
18. Low FM, Hampton MB, Winterbourn CC. Peroxiredoxin 2 and peroxide metabolism in the erythrocyte. Antioxid Redox Signal. (2008) 10:1621–30. doi: 10.1089/ars.2008.2081
19. Forman HJ, Zhang H, Rinna A. Glutathione: overview of its protective roles, measurement, and biosynthesis. Mol Aspects Med. (2009) 30:1–12. doi: 10. 1016/j.mam.2008.08.006
20. Luzzatto L, Arese P. Favism and glucose-6-phosphate dehydrogenase deficiency. N Engl J Med. (2018) 378:60–71. doi: 10.1056/nejmra1708111
21. Cheah FC, Peskin AV, Wong FL, Ithnin A, Othman A, Winterbourn CC. Increased basal oxidation of peroxiredoxin 2 and limited peroxiredoxin recycling in glucose-6-phosphate dehydrogenase-deficient erythrocytes from newborn infants. FASEB J. (2014) 28:3205–10. doi: 10.1096/fj.14-250050
22. Beutler E. The genetics of glucose-6-phosphate dehydrogenase deficiency. Semin Hematol. (1990) 27:137–64.
23. Coelho PMBM, Salvador A, Savageau MA. Relating mutant genotype to phenotype via quantitative behavior of the NADPH redox cycle in human erythrocytes. PLoS One. (2010) 5:e13031. doi: 10.1371/journal.pone.0013031
24. Corrons JL, Alvarez R, Pujades A, Zarza R, Oliva E, Lasheras G, et al. Hereditary non-spherocytic haemolytic anaemia due to red blood cell glutathione synthetase deficiency in four unrelated patients from Spain: clinical and molecular studies. Br J Haematol. (2001) 112:475–82. doi: 10. 1046/j.1365-2141.2001.02526.x
25. Minucci A, Moradkhani K, Hwang MJ, Zuppi C, Giardina B, Capoluongo E. Glucose-6-phosphate dehydrogenase (G6PD) mutations database:

review of the “old” and update of the new mutations. Blood Cells Mol Dis. (2012) 48:154–65. doi: 10.1016/j.bcmd.2012.01.001
26. Gómez-Manzo S, Marcial-Quino J, Vanoye-Carlo A, Serrano-Posada H, Ortega-Cuellar D, González-Valdez A, et al. Glucose-6-phosphate dehydrogenase: update and analysis of new mutations around the world. Int J Mol Sci. (2016) 17:2069. doi: 10.3390/ijms17122069
27. Bahr TM, Lozano-Chinga M, Agarwal AM, Meznarich JA, Yost CC, Li P, et al. A novel variant in G6PD (c.1375C>G) identified from a Hispanic neonate with extreme hyperbilirubinemia and low G6PD enzymatic activity. Neonatology. (2020) 117:532–5. doi: 10.1159/000510300
28. Tong Y, Liu B, Zheng H, Bao A, Wu Z, Gu J, et al. A novel G6PD deleterious variant identified in three families with severe glucose-6- phosphate dehydrogenase deficiency. BMC Med Genet. (2020) 21:150. doi:10.1186/s12881-020-01090-2
29. Alina MF, Azma RZ, Norunaluwar J, Azlin I, Darnina AJ, Cheah FC, et al. Genotyping of Malaysian G6PD-deficient neonates by reverse dot blot flowthrough hybridisation. J Hum Genet. 65(3), 263-270. Erratum in J Hum Genet. (2020) 65:635. doi: 10.1038/s10038-019-0700-7
30. Malik S, Zaied R, Syed N, Jithesh P, Al-Shafai M. Seven novel glucose- 6-phosphate dehydrogenase (G6PD) deficiency variants identified in the Qatari population. Hum Genomics. (2021) 15:61. doi: 10.1186/s40246-021-0 0358-9
31. Xu W, Westwood B, Bartsocas CS, Malcorra-Azpiazu JJ, Indrák K, Beutler E. Glucose-6 phosphate dehydrogenase mutations and haplotypes in various ethnic groups. Blood (1995) 85:257–63. doi: 10.1182/blood.V85. 1.257.bloodjournal851257
32. Chen TL, Yang HC, Hung CY, Ou MH, Pan YY, Cheng ML, et al. Impaired embryonic development in glucose-6-phosphate dehydrogenasedeficient Caenorhabditis elegans due to abnormal redox homeostasis induced activation of calcium-independent phospholipase and alteration of glycerophospholipid metabolism. Cell Death Dis. (2017) 8:e2545. doi: 10. 1038/cddis.2016.463
33. Yoshida A, Beutler E, Motulsky AG. Human glucose-6-phosphate dehydrogenase variants. Bull World Health Organ. (1971) 45:243–53.
34. He Y, Zhang Y, Chen X, Wang Q, Ling L, Xu Y. Glucose-6-phosphate dehydrogenase deficiency in the Han Chinese population: molecular characterization and genotype-phenotype association throughout an activity distribution. Sci Rep. (2017) 10:17106. doi: 10.1038/s41598-020-74200-y
35. Boonyuen U, Chamchoy K, Swangsri T, Saralamba N, Day NP, Imwong M. Detailed functional analysis of two clinical glucose-6-phosphate dehydrogenase (G6PD) variants, G6PDViangchan and G6PDViangchan+Mahidol: decreased stability and catalytic efficiency contribute to the clinical phenotype. Mol Genet Metab. (2016) 118:84–91. doi: 10.1016/j.ymgme.2016.03.008
36. Pietrapertosa A, Palma A, Campanale D, Delios G, Vitucci A, Tannoia N. Genotype and phenotype correlation in glucose-6-phosphate dehydrogenase deficiency. Haematologica. (2001) 86:30–5.
37. Scopes DA, Bautista JM, Naylor CE, Adams MJ, Mason PJ. Amino acid substitutions at the dimer interface of human glucose-6-phosphate dehydrogenase that increase thermostability and reduce the stabilising effect of NADP. Eur J Biochem. (1998) 251:382–8. doi: 10.1046/j.1432-1327.1998. 2510382.x
38. Mason PJ, Bautista JM, Gilsanz F. G6PD deficiency: the genotype-phenotype association. Blood Rev. (2007) 21:267–83. doi: 10.1016/j.blre.2007.05.002
39. Gómez-Manzo S, Terrón-Hernández J, De la Mora-De la Mora I, González-Valdez A, Marcial-Quino J, García-Torres I, et al. The stability of G6PD is affected by mutations with different clinical phenotypes. Int J Mol Sci. (2014) 15:21179–201. doi: 10.3390/ijms151121179
40. Ainoon O, Alawiyah A, Yu YH, Cheong SK, Hamidah NH, Boo NY, et al. Semiquantitative screening test for G6PD deficiency detects severe deficiency but misses a substantial proportion of partiallydeficient females. Southeast Asian J Trop Med Public Health. (2003)34:405–14.