Incidence of Erythrocyte Glucose - 6 - Phosphate Dehydrogenase Deficiency in Male Neonatal Hyper - bilirubinemia in Kerbala Region : Iraq

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الخلاصـــة

إن أحد أهم أهداف هذه الدراسة هو تحديد نسبة انتشار عوز نازعة هيدروجين الكلوكوز- ٦-فوسفات الحاد لدى الأطفال الذكور ذو النمو الجنيني المتكامل والمصابين بمرض اليرقان الولادي في مدينة كربلاء. تمت الدراسة باستعمال ٣١٨ عينة عشوائية من الأطفال الذكور حديثي الولادة ومن الفترة من ١- تشرين الأول – ٢٠٠٧ ولغاية ١٢-تموز-٢٠٠٨ ولأعمار تراوحت ما بين ١ – ٢٨ يوما. ولقد تمت تحديد مجاميع الدراسة إلى ثلاثة مجاميع اعتمادا على تركيز البيليروبين الكلي وكما يلي :-

- المجموعـة الأولـى وهـي مجموعـة السـيطرة والتـي شـملت ٥٦ (17.61%) طفـلا حـديث الولادة وكان تركيز البيليروبين الكلي طبيعيا ولا يتجاوز الـــ TSB < 1 mg/dl .

- المجموعة الثانية واتي شملت ٦٥ (20.44%) طفلا حديث الولادة وكان تركيز البيليروبين الكلي مرتفعا ولا يتجاوز الـــ TSB < 15 mg / dl . وقد انخفض نشاط إنزيم بشكل متوسط في٧ حـالات مـن مـرض اليرقـان الـولادي وكانـت نسبة الانتشـار هـي (10.77%) وان معـدل البيليروبين الكلي قد ارتفع وكان متوسط تركيزه هو 9.58 ± 1.48 mg/dl .

- المجموعـة الثالثـة والتـي شـملت ١٩٧ (61.94%) طفـلا حديث الولادة وكـان تركيز البيليروبين الكلي قد ارتفع و تجاوز الـــ TSB ≥15 mg / dl .

ولقد تمت هذه الدراسة على الإنزيم بمتابعة تـأثير العـوز الحـاد للإنـزيم علـى بعـض المتغيرات الكيموحيوية وخاصة على تركيز كل من البيليروبين الكلي والبيليروبين المقترن في بلازما الدم . لقد تم الكشف النوعي أولا عن نشاط الإنزيم ومن ثم قياسه كميا في الحـالات الغير طبيعيـة ومقارنتها مع مجموعة السيطرة. ولقد وجد أن نشـــــــاط إنزيم نازعة هيدروجين الكلوكوز – ٦ – فوسفات قد انخفض معنويا ووصل إلى 0.56 ±0.32 U/g Hb مقارنة مع المعدل الطبيعـي لـه 10.4 ± 1.78 U/g Hb وكـان عدد الأطفال المصابين بالنقص الحاد لنشاط الإنزيم هو ١٨ طفلا وان معدل تركيز البيليروبين الكلي TSB قد ارتفع إلى 20.51 ± 4.34 mg/dl . وان نسبة انتشار النقص الحاد للإنزيم في أطفال المجموعـة الثالثـة هـي ٩.١٤% . بينما انخفض البيليروبين المقترن معنويا في مرض اليرقان الولادي الحاد والمتوسط.

Abstract

   Newborn G6PD deficiency screening has been recognized as an essential component of public health care in most developed and some Mediterranean countries. However, such screening is yet to be widely embraced in Kerbala region of Iraq. The aim of the present study was to determine the normal values of G6PD and the percentage of incidence of this enzyme in male neonatal jaundice of Kerbala region. A total of 318 male neonates with normal and hyperbilirubinemic patients with abnormal TSB levels were included in the study. G6PD activity was firstly detected by fluorescent spot test , then its activity levels was quantitatively measured for those patients with G6PD-deficient. Normal mean values of G6PD activity in normal healthy male neonates were 10.4 ± 1.78 IU/g Hb and for moderate G6PD-deficient neonates with total serum bilirubin , TSB < 15 mg/dl were 3.39 ± 1.43 IU/g Hb, whereas the mean activity levels in severe G6PD-deficient neonates with TSB ≥ 15 mg/dl were decreased to 0.56 ± 0.32 IU/g Hb.   The frequencies identified in severe and moderate G6PD-deficient male neonatal hyperbilirubinemic patients in this region of Iraq were 9.14% and 10.77% respectively. The percentage of incidence in moderate neonatal hyperbilirubinemia (TSB < 15 mg/dl) was observed in 20.44% and that found in severe hyperbilirubinemia (TSB ≥ 15 mg/dl) was 61.95% of the total full-term neonatal cases studied. The conjugated serum bilirubin, CSB levels was decreased in both moderate and severe neonatal hyperbilirubinemic patients as compared with normal neonates.

Introduction

   G6PD deficiency is one of the well-known human genetic abnormalities and has been identified in more than 400 million subjects worldwide. Distribution of the deficiency varies among different population reflecting geographic and ethnic variations. For example, G6PD deficiency has been reported among certain parts of Europe such as 0.44% of Croatian Adriatic coast population ; 3.14% in Greece ; 0.2–15% in Italy ; 21% in West Africa ; and in Middle East with 18–42% in Saudi Arabia [1-5]. Kurdish Jews have the highest known frequency of the G6PD deficiency with an estimated gene frequency of 65% [6]. The distribution of G6PD deficiency among the different ethnic groups varied widely, ranging from 1% for Egyptians to 11.55% for Iranians( ). In Kuwait Alfadhli, et. al., characterized G6PD-Med, and A− genotypes as the most common variants among the G6PD-deficient population, representing 0.742 and 0.124 allele frequencies, respectively, and the other mutations, G6PD Chatham and Aures, were found at lower frequencies (0.101 and 0.034, respectively [7] .

   McCurdy, et. al. indicate the heterogeneity of red cell G6PD deficiency in Egypt and described several variants including G6PD El-Fayoum, G6PD El-Kharga, G6PD Siwa and G6PD Tahta, whereas, Karadsheh, et. al. identified the incidence of G6PD deficiency in Jordan Valley 8.5% which was higher than that in Amman area 3.2% due to higher rate of malaria, and the common G6PD variant found was the Med mutation (53.3%) and the frequency of G6PD A- mutation was higher in Jordan Valley which could be attributed to the African ancestry of its population[8-9]. In other Arab country the incidence of G6PD deficiency ranged between 1.84% to 3.3% in Tunisia and Sudan respectively, while in UAE the incidence ranged between 0.9% to 9.1% and the common G6PD variant found in these countries was G6PD Med followed by G6PD A-, whereas other reports indicate the frequency of G6PD deficiency in males ranged between 11-15% and in females is 5%. The least frequency of G6PD deficiency in Arab World was found in Yemen which is 0.6%[10,11].

   The frequency of erythrocyte G6PD deficiency also shows considerable regional variation in Iraq. **G**enes for G6PD deficiency and sickle-cell disease were first reported

in Iraq, whereas other report of G6PD deficiency described an Iraqi Jewish family with the red cell G6PD variant (G6PD-Baghdad) and kernicterus[12]. Others investigate G6PD in the blood of 305 males and 394 females. The percentage of deficiency was estimated at 12.4% for males and 8.8% for females of all ages; it was, however, highest among children and lowest among those over 50 years. Other reports carried out in Baghdad and Najef shows that the prevalence of severe G6PD deficiency identified in neonatal jaundice were 15% and 13.3% respectively[13-15]. The Jews of Kurdistan are a small inbred population with a high incidence of β-thalassemia and G6PD deficiency. Recently, it was reported that the β-thalassemia in this population shows an unusual mutational diversity; 13 different mutations were identified, of which 4 had not previously been observed in any other population. In contrast, others report that the G6PD deficiency, which has the highest known incidence in the world, and which affects about 70% of males, is almost entirely attributable to a single widespread mutation, G6PD Med [16].

   Published studies have revealed frequencies of 12.5% in Basrah which was observed in 1064 couples aged 14-60 years and the deficiency was detected in 133 individuals, whereas others attempted to characterize biochemically the G6PD variants in Iraqi individuals. Their studies include a randomly 758 healthy Iraqi males aged 18–60 years and 46 (6.1%) were G6PD deficient [17, 18].

   In this paper we try to document the commonly known incidence of G6PD deficiency in neonatal patients with hyperbilirubinemia found in Kerbala region of Iraq.

Materials and Methods

   A total of 318 blood samples were collected from full-term deliveries male neonates with age ranged between 1-28 days which were admitted in Kerbala pediatrics teaching hospital / Kerbala-Iraq during 1st , Oct., 2007 and 12th , July , 2008. Fifty six of them were control with normal TSB levels, whereas the remaining 262 neonates were hyperbilirubinemic patients and their TSB levels exceed 1 mg/dl, Any G6PD-deficient neonates with other possible etiologies causing hyper-bilirubinemia, such as infants of diabetic mothers, polycythemia, perinatal infection, gastrointestinal obstruction, permaturity, ABO incompatibility, sepsis or those that had received intensive phototherapy; those in which the TSB level rose by more than 5 mg/dl per day or was higher than 20 mg/dl within the first 24 hours after birth; and those with signs and symptoms suggestive of serious illness were excluded.

   Blood samples in a quantity of (3-5 ml) were taken from a peripheral vein in EDTA anticoagulant collecting tube (in 300 µL EDTA , 0.5 M) from both control and patient neonates. Samples were stored at 4°C until assayed within 24 h after collection. Activity of G6PD in erythrocyte lysate was quantitatively measured at 30°C by spectrophotometric methods using Sigma diagnostics kits which based on the procedure recommended by WHO in 1967 and was modified by Kornberg and Horecker, (1955) and of Lohr and Waller in (1974) which involving the following reaction as described below [19, 20]:

$$\text{G-6-P} + \text{NADP}^+ \xrightarrow{\text{G6PD}} \text{6-PG} + \text{NADPH} + \text{H}^+$$

$$\text{6-PG} + \text{NADP}^+ \xrightarrow{\text{6PGD}} \text{Ribulose-5-Phosphate} + \text{NADPH} + \text{H}^+ + \text{CO}_2$$

According to this method, the rate of the reduction of $NADP^+$ to NADPH when the sample was incubated with G6PD and the rate of formation of NADPH was monitored as an increase in absorbance at 340 nm which proportional to the G6PD activity. Production of a second molar equivalent of NADPH by erythrocyte 6-phosphogluconolactonate dehydrogenase (6-PGD) was prevented by use of maleimide, a specified inhibitor of 6-PGD as shown in the following reaction: The activity was expressed in micromole of NADPH formed per minute per gram hemoglobin in hemolysates. Hemoglobin concentration was determined in erythrocyte hemolysate and the G6PD activity was expressed as international units per gram hemoglobin (U/g Hb) in hemolysate.

Total serum bilirubin in control and neonatal jaundice patients was measured by adding caffeine reagent as accelerator followed by the addition of diazotized sulfanilic acid. During the incubation period, both conjugated and unconjugated bilirubin react with the diazo reagent to produce azobilirubin. After the addition of diazotized sulfanilic acid, solutions of ascorbic acid, alkaline tartrate, and dilute HCl to the reaction mixture, the absorbance of blue-green azobilirubin produced was measured at 600 nm[21]. Blood hemoglobin concentration was determined by Drabkin's method.

Results and Discussion

The results of the present study involved a total of 318 full-term deliveries neonatal male samples which were admitted in Kerbala pediatrics teaching hospital with age ranged between 1-28 days.

Neonatal hyperbilirubinemia may be physiologist jaundice or may be due to other causes which include ABO incompatibility, unstable Hb, urinary tract infections, sepsis, septicemia, Crigler-Najjar syndrome, hepatitis, pyruvate kinase deficiency, G6PD deficiency, hypothyroidism, galatosemia, breast milk jaundice. Some G6PD-deficient neonates were excluded because of their concurrent neonatal diseases. A total serum bilirubin levels TSB $\geq$ 15 mg/dl was chosen to indicate the presence of severe hyperbilirubinemia since an infant with this degree of jaundice is thought to be at high risk of kernicterus [22].

The overall incidence of moderate neonatal hyperbilirubinemia with abnormal TSB ranged between 1-15 mg/dl which was identified in 65 neonate patients and its percentage of incidence determined was 20.44%. The TSB levels in these neonates was significantly elevated (P<0.05) and the mean ± SD values identified was 9.58 ± 2.55 mg/dl as compared with that found in normal group 0.57 ± 0.25 mg/dl., whereas in severe neonatal hyperbilirubinemia the TSB was also significantly elevated (P<0.05) and its mean ± SD values was 20.51 ± 4.34 mg/dl as compared with control group and the percentage of incidence identified was 61.95%. , (Tables -1-) .

These data are in agreement with similar studies that performed in Italy ; Iran ; and in Canada [23-25] in which they concerned with the frequency of neonatal hyperbilirubinemia with TSB≥15 mg/dl due to different causes, see Fig.-1-.

Serum conjugated bilirubin (SCB) was also determined as shown in the same table, the mean ± SD values of SCB in severe hyperbilirubinemic patients were significantly lower than that found in moderate hyperbilirubinemic patients (P<0.05) , and also that the SCB level in both groups were significantly lower than that found in control group (P < 0.05). Conjugated bilirubin was undetectable in 7 patients (38.89%) of the 18 severe G6PD deficient neonatal hyperbilirubinemic patients detected which imply a partial defect of bilirubin conjugation.

Table-1- Serum TSB and SCB levels in normal and abnormal neonates with hyper-bilirubinemic patients with their percentage of incidence in Kerbala region of Iraq.

Group of Subject	Number of Samples	SCB levels Mean ± SD mg/dl	TSB levels	
			Mean ± SD mg/dl	Incidence %
Normal	56	0.15 ± 0.08	0.57 ± 2.55	17.61%
Moderate Hyper-bilirubinemia	65	0.11 ± 0.04	9.58 ± 1.48	20.44%
Severe Hyper-bilirubinemia	197	0.053 ± 0.046	20.51 ± 4.34	61.95%

These results confirmed other studies performed in Isreal, Italy, and Taiwan which suggest that the G6PD–deficient neonates are at increased risk for hyper-bilirubinemia.[26,27]. Therefore, our data may probably suggest that severe neonatal hyperbilirubinemia may be continuously to be cause a problem in this region of Iraq, which show that those neonates with severe G6PD-deficiency who developed higher maximal TSB values had significantly lower SCB fractions than those who remained only moderately jaundiced. Conversely, those with lower SCB values at the time of sampling were at higher risk for the subsequent development of hyperbilirubinemia. Serum bilirubin profile demonstrated in the subsequently hyperbilirubinemic with severe G6PD-deficient neonates (high TSB, with low SCB) is reminiscent of that seen in conditions of partial deficiency of the bilirubin conjugating enzyme UDP-glucuronosyl transferase1 A1 (UGT1A1), such as Gilbert's Syndrome [28] .

The data observed in this study support functionally the concept of the gene interaction demonstrated between G6PD deficiency and the variant promoter for the gene encoding the bilirubin conjugated enzyme UGT1A1 as suggested by Huang, et. al. and then diminished bilirubin conjugated ability [29]. Gene variants is reported to be in association with an increased risk for neonatal hyperbilirubinemia include those of [30,31]:

(1) The red blood cell enzyme (*G6PD*) ;

(2) The hepatic bilirubin-conjugating enzyme UGT1A1 ;

(3) The hepatic organic anion transporter polypeptide1 B1 (OATP1B1) .
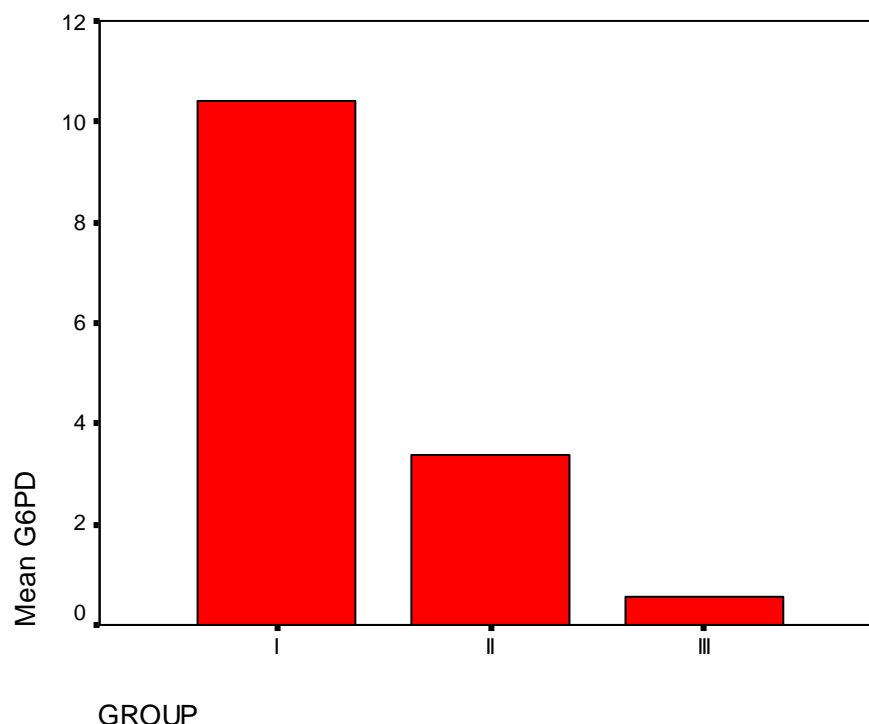
Fig. – 1 – Mean G6PD activity levels in Normal (Group I) and neonatal hyperbilirubinemia with each of Moderate G6PD-deficient (Group II) and Severe G6PD-deficient (Group III) in Kerbala Governorate.

G6PD gene variants may be a predispose to neonatal hyperbilirubinemia via either an acute hemolytic event with or without an identifiable environmental trigger or a low-grade hemolysis coupled with UGT1A1 gene polymorphisms [29]. More recent findings suggested that gene polymorphisms of OATP1B1 a putative bilirubin transporter localized to the sinusoidal membrane of hepatocytes (i.e, the blood hepatocyte interface), may be a predispose to neonatal hyperbilirubinemia by possibly limiting hepatic bilirubin uptake[31]. The primary site of the pathogenesis of the hyperbilirubinemia therefore appears to be localized to a deficiency in bilirubin conjugation. As a result, G6PD-deficient neonates who become hyperbilirubinemic have bilirubin conjugation ability which is even more inefficient than that of the physiological immaturity of conjugation normally found in neonates. Those with an excessively immature bilirubin eliminating capacity are more likely to develop hyperbilirubinemia than those with a more mature ability. This mechanism may exist to a certain extent in all neonates but may be exacerbated in the G6PD deficiency state because of increased hemolysis and the resultant additional bilirubin load[24]. Measuring of the TSB level and further testing (blood group, coombs and G6PD tests) at the time / or before infants are discharged from hospital is helpful in predicting which infants will be experience severe hyperbilirubinemia and to evaluate the risk and to prevent it.

Our results also show that deficient bilirubin conjugation which reflected by low SCB values measured, is a cardinal factor in the pathogenesis of G6PD deficiency associated with neonatal hyperbilirubinemia. In G6PD-deficient neonates who conjugate bilirubin less efficiently, hyperbilirubinemia is more likely to result. In contrast, those neonates with higher neonatal bilirubin conjugation ability are less likely to develop

clinically significant hyper-bilirubinemia as shown in moderate G6PD deficient and in control group.

G6PD deficiency is the most common red cell enzymopathy that cause neonatal hemolysis and jaundice. Good population data are available from West Africa, the Miditerranean and the Far East and it is clear that perhaps as many as one-third of all males with neonatal hyperbilirubinemia have G6PD deficiency[4]. A higher incidence of enzyme deficiency in males than females was reported in many studies because G6PD deficiency in homozygous males is a sex-linked dominant disorders[32]. The etiological relationship between G6PD deficiency and neonatal hyperbilirubinemia has been confirmed by several studies. The incidence of hyperbilirubinemia for G6PD-deficient neonates was higher than that for G6PD-normal neonates in both sexes under an environment where exogenous hemolytic agent was absent[33]. The association between G6PD deficiency with severe neonatal hyperbilirubinemia and kernicterus was first described in 1960[34]. Many researchers had documented that G6PD deficiency was at higher risk to develop neonatal hyperbilirubinemia which is in agreement with our results performed in Italy and Thailand, while it is less than that seen in Kurdish Jews, China and Saudi Arabia [35]. Similar results had reported by Lo, et. al., in (1994) in which G6PD enzyme activity in G6PD-deficient male infants with TSB > 20 mg/dl was significantly lower than those with TSB < 20 mg/dl. Whereas others reported the development of neonatal jaundice with G6PD deficiency and correlated with the amount of NADPH [36].

A total of 318 neonatal samples were randomly screened for G6PD activity deficiency by hemi-quantitative fluorescent spot test, and then quantitative measurements for erythrocyte G6PD was performed to confirm the diagnosis of G6PD deficiency in those who had positive results from screening to determine whether or not this deficiency could play a role in the development of neonatal hyperbilirubinemia. Of these subjects, 56 (18.57%) individuals showed a normal enzyme activity levels, whereas the remaining neonates were found to have moderate and severe G6PD-deficient.

Among them only 7 cases of moderate G6PD-deficient patients were diagnosed and found to have a hyperbilirubinemia with TSB < 15 mg/dl and their mean ± SD of G6PD activity identified were significantly ($p<0.05$) decreased to 3.39 ± 1.43 U/g Hb as compared with the control group (Tables -2-), and its percentage of incidence was 10.77%. All the neonatal hyperbilirubinemic patients with moderate G6PD deficiency received phototherapy for less than a week, and no neonatal patients of this group required exchange blood transfusion.

On the other hand, only 18 patients of hyperbilirubinemic neonate patients with TSB ≥ 15 mg/dl was diagnosed and found to have severe G6PD deficiency resulting in the percentage of incidence which is 9.14%. Their mean ± SD of G6PD activity levels were significantly decreased ($p<0.05$) to 0.56 ± 0.32 U/g Hb as compared with that found in control G6PD activity 10.4 ± 1.78 U/g Hb. The mean ± SD of erythrocyte G6PD activity levels in each of healthy control, moderate and severe G6PD-deficienct neonates group with their incidence were indicated in (Tables -2-).

All neonatal hyperbilirubinemic patients with severe G6PD deficiency included in this group received phototherapy as shown below:

- 7 (38.89%) patients received phototherapy for less than a week in which their TSB levels ranged between 15 – 20 mg/dl..

- 9 (50%) patients received phototherapy for more than one week because their TSB levels were greater than 20 mg/dl.

- 2 (11.1%) patients required exchange blood transfusion and had kernicterus sign.

Table-2- Serum G6PD activity levels in normal and abnormal neonates with moderate and severe hyperbilirubinemic patients with their percentage of incidence in Kerbala region of Iraq.

Group of Subjects	Number of Samples	No. of G6PD-deficient neonates	G6PD activity Mean ± SD U/g Hb	Incidence %
Normal	56	----------	10.4 ± 1.78	-----
Moderate Hyper-bilirubinemia	65	7	3.39 ± 1.43	10.77%
Severe Hyper-bilirubinemia	197	18	0.56 ± 0.32	9.14%

The first and most important studies in Iraq was published by Amin-Zaki, et. al., which was conducted in Baghdad and involved 563 adult males including students, healthy blood donors and patients from Republic Hospital in Baghdad [37]. Their results showed that the overall frequency of G6PD deficiency was 8.9%. In another work conducted by in which 305 male children and adults were enrolled, and the results revealed a frequency of G6PD deficiency was 12.4% by using the fluorescent spot test which may give false positive results in the presence of hemolytic anemia [13]. A frequency of 6.1% of G6PD deficiency was also reported in Iraq by Hilmi, who applied the methemoglobin reduction test to diagnose the affected individuals [18]. Al-Naamah, et. al., found that 51% of 186 Iraqi neonates with TSB ≥ 15 mg/dl were G6PD deficient and of these neonates, 53% were female subject with intermediate G6PD activity. The data obtained in this study was in agreement with that found in Najef in which the prevalence of G6PD deficiency was 13.3% in neonatal patient, and with others who found its prevalence was 15% in Baghdad neonatal patients [38, 14-15].

The frequency of G6PD deficiency differs markedly among different populations. The overall percentage of severe G6PD deficiency incidence in the current study which related with neonatal hyperbilirubinemia is 9.14%. This frequency is lower than that reported in other neighboring countries such as Bahrain 21%, Oman 27% , UAE 15% [11,39]. Furthermore, the results of the present study are dissimilar to those of Al-Ali in Saudi Arabia who reported a frequency of 49.5% [40]. Karadsheh, et. al. identified that the incidence of G6PD deficiency in Jordan Valley was 8.5% which is higher than that in Amman area 3.2% due to higher rate of malaria, and the common mutation found was the Mediterranean mutation (53.3%) [8].

The similarity of results may be attributed to the phyllogenetic relationship between populations within regional countries which might be explained in turn by the migration among neighboring countries throughout the history, whereas the differences in frequencies of G6PD deficiency might be attributed to the differences in the races, sociological and cultural characteristics of various communities as for example, the traditional consanguineous marriages, which increases the frequency of autosomal recessive disorders [41].

It has been suggested that variation of G6PD activity in different regions may be associated with adaptation by factors such as starvation, climate, nutrition, carbohydrate metabolism, sex hormones and use of different laboratory methods. Determination of the enzyme activity using reliable and sensitive test techniques is very important. G6PD deficiency may induce manifestations such as chronic non-spherocytic anemia, drug-induced hemolysis, serious neonatal jaundice, cataract, malaria [4]; hence, its screening should be conducted in the area that is found to have a higher prevalence of the enzyme deficiency.

These results indicated that there is a significant negative correlation ($r = -0.551$; p < 0.05)) between G6PD activity levels decreased and TSB concentrations elevated in severe G6PD-deficient hyperbilirubinemic patients with the TSB $\geq$ 15 mg/dl but not in control individuals as shown in (Figures -2-).
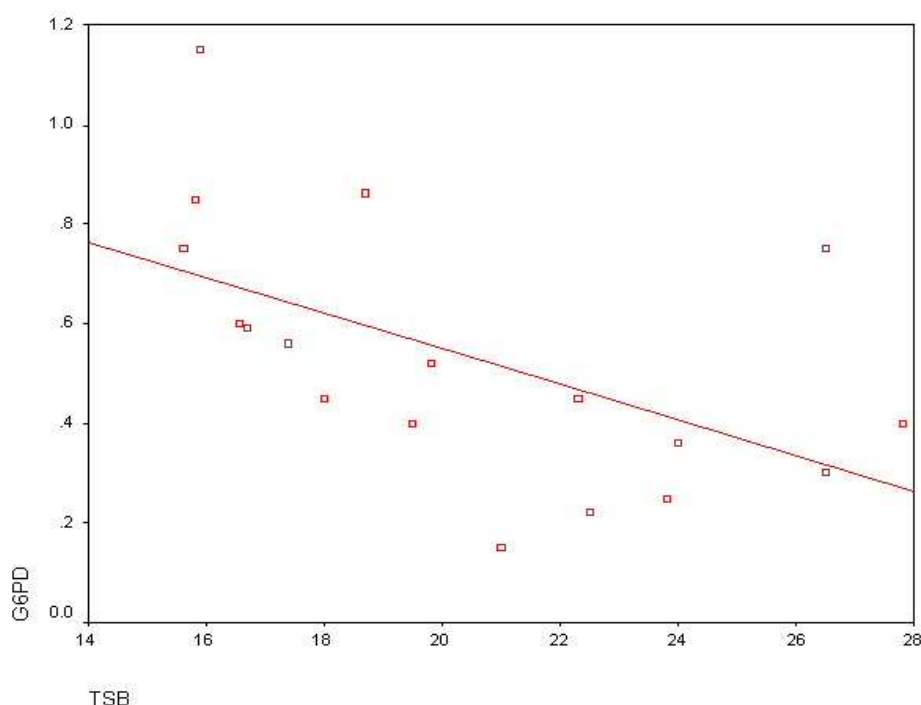

Fig. -2 – The correlation between G6PD activity level and TSB conc. in severe G6PD-deficient male neonatal hyperbilirubinemia in Kerbala region (*P* < 0.05 ; *r* = - 0.551)

The mechanism of the relationship between G6PD activity and neonatal hyperbilirubinemia is not clear. The presence of another genetic factors has been postulated in the pathogenesis of neonatal hyperbilirubinemia in G6PD deficiency. Kaplan, et. al., reported that UGT1A1 gene mutation, diminishing activity of the conjugated enzyme UGT1A1 , was associated with neonatal hyperbilirubinemia in G6PD deficiency, whereas others reported that the expression of heme oxygenase-1 , a rate-limiting enzyme in the production of bilirubin and inducible under the exposure to oxidative stress, was increased in G6PD deficiency. Recent studies suggest that bilirubin was a strong endogenous antioxidant [24,26]. Therefore, it is reasonable to suggest that the neonatal hyperbilirubinemia caused by increased heme oxygenase-1 in G6PD deficiency is the consequence of genetic interaction to compensate the decreased antioxidant activity. Therefore, the low levels of G6PD activity in male infants may play a role in the interaction of different genes, such as UGT1A1 and heme oxygenase-1

, and subsequently aggregative the high TSB levels. Phototherapy has been documented as an effective treatment to reduce neonatal hyperbilirubinemia in G6PD deficient infant. Therefore, the difference in the incidence of hyperbilirubinemia between G6PD deficient and G6PD normal neonates may be masked by early phototherapy. It seems that, in severe hyperbilirubinemia (TSB ≥ 15 mg/dl) the prevalence of G6PD deficiency is more than moderate hyperbilirubinemia (TSB < 15 mg/dl) that may be a risk factor for some complication and kernicterus.

Conclusions

   1. G6PD deficiency is a major public health problem. Geographically, it is heterogenous among Iraqi population.

   2. High percentage of incidence of severe G6PD deficiency with TSB ≥ 15mg/dl was observed in Kerbala region of Iraq (9.14%).

   3. The results obtained concluded that severe neonatal hyperbilirubinemia continues to be a problem in this region.

   4. The data obtained indicate that severe G6PD deficiency play an important role
     as a common etiologic factors in neonatal hyperbilirubinemia in this region of Iraq.

   5. Severe G6PD deficiency was associated with hyperbilirubinemic kernicterus and even death.

   6. Moderate G6PD deficiency was also observed in neonatal hyperbilirubinemic patients with TSB level < 15 mg/dl and its percentage of incidence was 20.77%.

   7. Phototherapy and exchange blood transfusion were very effective in lowering the TSB levels.

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