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Epidemiological Clinical and LaboratoryStudy of G6PDDeficiencyin children

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ABSTRACT:
Objective: Glucose-6-Phosphate Dehydrogenase deficiency is the most common inherited hematological disorder among Iraqis. The aims of this study is to determine the epidemiological, clinical and laboratory profile of glucose-6-phosphate dehydrogenase (G6PD) deficiency and compared it with previous data from other parts of Iraq.
Methods:A total of 437 children were admission to the Hospital in period from January, 2019 to December, 2020. Epidemiological, clinical and laboratory studies were done. By using clinical examination and different laboratory methods includedcomplete blood picture, general urine examination, general stool examination, blood group, hepatitis study, bacterial and viral profile and G6PD enzyme assay.
Results: Twenty child were found to had G6PD deficient. In prevalence rate was 4.57% (20/437). The results of study revealed that most months of detection are months of Spring, the deficient was more in male 65% (13) than female 35% (7), also it more among aged group 1 year – 3 year and 3 year – 6 year, in percentage 35% and 30% respectively. Children in rural area composed of 70% than urban child 30%.Family history was positive in 15%. There were 20% of children had other diseases. In this study obtained different S/S in different proportions. Also there were results in association between blood groups, blood transfusion and numbers of blood transfusion with G6PD deficient. Among different laboratory tests were done, there were different results in different percentage.
Conclusion: The G6PD deficiency is one of common hemolytic diseases. Our study was concluded that most of G6PD deficient children admitted to hospital for blood transfusion.There are many factors effected diagnosis, management, prognosis and outcome of G6PD deficiency.
Key Words:*G6PD deficiency, hemolytic, Favism, neonatal jaundice, anemia,*

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INTRODUCTION:

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most commonenzyme-pathological disease in humans. This disease is described as a widespread, heritable,X-chromosome linked abnormality (Reclos, *et al.*, 2000). It is estimated that it affectsapproximately 400 million people worldwide (Noori-Daloii, *et al.*, 2004). This disease is seenmost frequently in approximately all of Africa, Asia, and the countries near theMediterranean Sea (Frank, 2005). G6PD enzyme was demonstrated to play an active role insurvival of erythrocytes. It is known that in the pentose phosphate pathway of erythrocytes,glucose-6 phosphate dehydrogenase (G6PD) enzyme provides the production of NADPHand GSH. GSH, produced by pentose phosphate pathway can react with H2O2 and reduce itto H2O. This prevents the generation of oxidative stress within red blood cells; oxidativestress can be induced in erythrocytes whose G6PD enzymes are deficient. In this situation,GSH is not produced and H2O2 is not reduced to H2O, leading to oxidative stress andhemolysis. This is the only mechanism available for the erythrocyte in order to generatereducing equivalence, therefore making it essential for the survival of erythrocytes. Inindividuals whose G6PD enzyme is deficient, different kinds of hemolysis from mild tosevere are seen bound to differences in variants of the disease (Beutler, 1983, Luzzatto,1989).G6PD deficiency was identified in 1956 by Carson *et al.* (Alving, *et al.*, 1956), and its X-chromosomalinheritance was discerned in the 1950s by Childs *et al.* (Childs, *et al.*, 1958).G6PD was cloned and sequenced by Persico *et al.*(Persico, *et al.*, 1986) in1986 and independently by Takizawa and Yoshida (Takizawa, *et al.*, 1986) G6PD (Misumi, *etal.*, 1982) is in the hexose monophosphate pathway, the only NADPH-generation process inmature erythrocytes, which lack the citric acid cycle. Deficiency of this enzyme inerythrocytes causes various forms of illnesses such as favism, anemia, chronicnonspherocytic hemolytic anemia, drug-sensitive hemolytic anemia, primaquine sensitivityand jaundice in newborns (Beutler, *et al.*, 1968).

A child with G6PD deficiency who is exposed to certainmedication, food or infection that triggers the destructionof red blood cells may have no symptoms at all. In moreserious cases, a child may exhibit symptoms of anemiaand hemolysis: Paleness (in darker-skinned children paleness issometimes best seen in the mouth, especially on thelips or tongue), extreme tiredness, rapid heartbeat, rapid breathing or shortness ofbreath,jaundice or yellowing of the skin and eyes,especially in newborns,an enlarged spleen,dark, tea-colored urine. Once the trigger is removed or resolved, the symptomsof G6PD deficiency usually disappear fairly quickly,typically within a few weeks.If symptoms are mild, usually no medical treatment isneeded as the body naturally makes new red blood cells.If symptoms are more severe, a child may need to behospitalized for supportive medical care such asproviding oxygen, fluids, and, if needed, bloodtransfusion.In some people, for example, the Mediterranean-type, G6PD deficiency from drug intake occurs, although not a permanent hemolytic condition. In erythrocytes, NADPH cannot form with G6PD deficiency and unformed NADPH creates a deficiency in conversion of the oxidized form of glutathione (GSSG), to its reduced form (GSH) (Lachant, *et al.*, 1984, Beutler, 1994).The hemolytic anemia is self-limited when G6PD deficiency is relatively mild because only the older RBCs are destroyed and the young RBCs have normal or nearly-normal enzyme activity (Beutler, 1994).Infections are probably the most common cause ofhemolysis in people with G6PD deficiency. A large number of bacterial, viral andrickettsial infections have been reported as predisposing factors. Infectious hepatitis(hepatitis A), pneumonia and typhoid fever are known to trigger hemolysis. Involving

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theupper respiratory tract and gastrointestinal system, viral infections have been reported tocause a more severe hemolysis (Luzzatto, 2001). The mechanism of infection-inducedhemolysis is not clear, but it is thought to be that during the infection, superoxide anion andH_2O_2 production by macrophages causes the hemolysis (Glader, 1999, Luzzatto, 2001).

Favism is an illness that occurs in G6PD deficiency individuals with acute hemolysis byeating raw beans (Vicia fabu). Wet, dry or frozen fava bean ingestion of grains, even if themother eats fava beans can cause hemolysis in newborn infants through breast milk mayoccur (Luzzatto, 2001). Individuals with G6PD deficiency hemolytic effect caused by thebeans contained many glycosides that are toxic due to the visin and konvisin (Beutler, 1994,Akhter, *et al.*, 2011). In addition, β-glucosides in bean seeds, maturity stage of fava beansattain very high amounts causing a severe course of hemolytic crisis (Katz & Schall, 1979,Greene, 1993, Beutler, 1994). Often, in the G6PD Mediterranean variant, acute and a verysevere hemolytic crisis are seen due to fava bean ingestion, even capable of causing death(Fairbanks, 1999, Luzzatto, 2001).24-48 hours after ingesting foods like fava beans, characteristic symptoms occur in theform of pallor, jaundice and hemoglobinuria (Ninfali, *et al.*, 2000). In addition, jaundice,headache, backache, nausea, fever, and chills are all signs of acute hemolysis (Tyulina, *et al.*,2000). Favism is most common seen in children between the ages of 2-5, and is also 2-3 timesmore common in boys than in girls (Luzzatto, 2001). Clinical signs of favism begin earlierand are more severe than drug-induced hemolytic crises. Rarely, as a result of pollen of favainhalation, hemolysis may occur within hours (Beutler, 1994).One of the most threatening consequences of G6PD deficiency is neonatal jaundice (Beutler,1994). Jaundice in babies with G6PD enzyme deficiency could be mild or severe enough tocause kernicterus, a spastic type of cerebral palsy, and may even cause death (Luzzatto,1993).

Various tests can be used for the detection ofG6PD deficiency, which are based on the assessment of the NADPH production capacity ofG6PD. The most frequently used tests that measure NADPH production are the fluorescentspot test, cytochemical assay and spectrophotometric assay. However, fluorescent spot testand the spectrophotometric assay are not reliable for the detection of heterozygous females.In addition, DNA analysis can be done to detect G6PD deficiency for the homozygous,hemizygous, and heterozygous-deficient patients. However, we have to design primers forall mutations (Peters & Van Noorden, 2009).

Substances which should be avoided by people with G6PD deficiency*	
ANALGESICS/ ANTI-PYRETICS	Acetanilide, Acetylsalicylic acid, Acetophenetidin (Phenacetin), Antipyrine, Dipyrone, Phenazopyridine
SULFA DRUGS	Sulfanilamide, Sulfapyridine, Sulfacetamide, Sulfamethoxazole, Sulfisoxazole
ANTI-MALARIALS	Aminoquinolones – primaquine, pemaquine, Pentaquine, Quinacrine, Quinine, Quinidine
ANTIBIOTICS	Chloramphenicol, Dapsone, Furazolidone, Nalidixic acid, Nitrofurantoin, Niridazole, Para-aminosalicylic acid
MISCELLANEOUS	Aminopyrine (Used in liver tests), Dimercaprol (Antidote), Mestranol (Contraceptive), Methylene Blue (Antidote), Probenecid (Gout), Prochlorperazine (antipsychotic, antiemetic, anxiety), Synthetic Vitamin K, Toluidine blue, Uricase, Rasburicase
FOOD & DOMESTICS	Fava (Broad) Beans, Naphthalene (mothballs, henna)
***http://www.g6pd.org/en/G6PDDeficiency/SafeUnsafe.aspx**	

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The main treatment for G6PD deficiency isavoidance of oxidative stressors. Rarely, anemiamay be severe enough to warrant a bloodtransfusion. Splenectomy generally is notrecommended. Folic acid and iron potentiallyare useful in hemolysis, although G6PDdeficiency usually is asymptomatic and theassociated hemolysis usually is short-lived (Beutler, 1994).

MATERIALS AND METHODS:

An epidemiological study done in our Hospital. The study include all children were admitted to the pediatric wards through period from January, 2019 to December, 2020. A questionnaire sheet done and ask about sex, age, residency, family history, associated diseases, causes of admission, symptoms and signs, history of blood transfusion, numbers of blood transfusion, drugs history, history of jaundice, past history of neonatal jaundice, month of presentation, socioeconomic status of family and types of food. Clinical examination done for every child through that period and included general, regional and physical examination. The laboratory tests done for each admitted child which involved complete blood picture, general urine examination, general stool examination, blood group, hepatitis study, viral profile and G6PD enzyme assay.

RESULTS

All the study population are 437 children, aged from 1 hr to 18 years old. Twenty child only were diagnosed clinically and laboratory had G6PD deficiency.

Tab 1. Prevalence of G6PD

Diagnosis	No of	%
G6PD positive	20	4.57
G6PD negative	417	95.43
Total	437	100

Tab 2. Prevalence among month of year

Month of year	No of children admission	G6PD	%
January 2018	49	2	10
February 2018	33	3	15
March2018	35	3	15
April 2018	45	5	25
May 2018	44	1	5
June 2018	33	0	0
July 2018	37	1	5
August 2018	27	0	0
September 2018	42	1	5
October 2018	33	1	5
November 2018	30	2	10
December 2018	29	1	5
Total	437	20	100

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Tab 3. Relation between G6PD and sex group

Sex	No	%
M	13	65
F	7	35
Total	20	100

Tab 4. Prevalence among age groups

Age	No	%
1 hr – 1 year	1	5
1 year – 3 year	7	35
3 year – 6 year	6	30
6 year – 9 year	2	10
9 year – 12 year	2	10
12 year – 15 year	1	5
15 year – 18 year	1	5
Total	20	100

Tab 5. Relation between G6PD and residence of children

Residency	No	%
Urban	6	30
Rural	14	70
Total	20	100

Tab 6. Relation of family history and G6PD

Family history	No	%
Positive	3	15
Negative	17	85
Total	20	100

Tab 7. Association between other Dz and G6PD

Associated Dz (hepatitis, UTI, CVD, GIT, Hemolytic,……	No	%
Positive	4	20
Negative	16	80
Total	20	100

Tab 8. Prevalence among s/s

S/S	No (20)	%
Pallor	20	100
Dark urine	13	65
Jaundice	15	75

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Abdominal pain	3	15
Bony pain	1	5
Joint pain	2	10
Fever	11	55
Anorexia	4	20
SOB	8	40
Other (vomiting, abd distension, ……	3	15

Tab 9. Association between blood groups and G6PD

Rh / Blood group	+	%	_	%	Total	%
A	6	30	2	10	8	40
B	5	25	1	5	6	30
AB	1	5	0	0	1	5
O	4	20	1	2	5	25
Total	16	80	4	20	20	100

Tab 10. Frequency of blood transfusion (BT) of G6PD children

BT	No	%
1-2	5	25
2-3	7	35
3-4	5	25
>4	3	15
Total	20	100

Tab 11. Neonatal j and G6PD

Neonatal j / G6PD	Positive	%	Negative	%
20	7	35	13	65

Tab 12. Neonatal j management

Neonatal j management	No	%
Exchange transfusion	7	100
Phototherapy	7	100
No Rx	0	0

Tab 13. Laboratory parameters data

Test		No	%
CBP	Normal	0	0
	Abnormal	20	100
Hb g%	<4	0	0
	4 – 8	18	90
	8 – 12	2	10
	>12	0	0

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Blood film	Normal	0	0
	Abnormal	20	100
G6PD enzyme assay	Positive	20	100
	Negative	0	0
GUE	Normal	7	35
	Dark tea urine	13	65
GSE	Normal	12	60
	Clay color stool	8	40
HBV & HCV	Positive	1	5
	Negative	19	95
Typhoid	Positive	0	0
	Negative	20	100

DISSCUSION:

G6PD deficiency has been recognized as acommon inherited hematological disorderin Iraqis since the 1970 (Halmaek and Stevenson, 2002), and a frequencyof 6.0% as documented in this study is notunexpected and is comparable with afrequency of 6.3% found in a recent studyfrom the capital Baghdad at the center ofthe country (6.1%) (Verma et al, 1999) and to prevalencerates reported from neighbouring Kurdishpopulation of western Iran (5.3%).15However, it is lower than the prevalence of10.9% from Kurdish population of Duhokand 15.3% reported from Basrah inSouthern Iraq (Verma et al, 1999; Yaish et al, 1998; Joseph et al, 1999). G6PD deficiency iscommon throughout the EasternMediterranean region, though itsfrequencies are variable and range between2-65% (Flym and Hesia, 2000; Verma et al, 1999; Yaish et al, 1998;AL-Namaand AL-Ssadoon, 1963).

Iraq is situated within a region of ahigh frequency of G6PD deficiencygenotype, with a carrier frequency in thepopulation of 6.3% (Omar, 1998; Taj El-Din et al, 1963;). Studying thepattern of G6PD deficiency in thepopulation is essential for a number ofreasons: the increasing costs of healthcare associated with frequent hospitalizations (Merenstien et al, 2005); the substantial morbidity interms of psychosocial burden and disturbedfamily environment for parentscoping with children with chronic illness (Rao et al, 2004); and for planning preventive strategies (Atwood et al, 1997).

A past history of neonatal jaundicewas found in similar proportions of childrenin this study in Baghdad (11.5%)and the previous study in Mosul(14.8%) (Atwood et al, 1997). Severe neonatal jaundice,particularly when it requires exchangetransfusion, should alert paediatriciansto the possibility of G6PD deficiency.Currently, most hospitals routinely testfor G6PD when screening neonatesbefore they are discharged from hospital (Iwai et al, 2003).A positive family history of G6PDdeficiency was reported at a higher ratein the Baghdad (19.2%) than in Mosul(13.6%). This may be due to the observationthat many patients are asymptomaticand unaware they are G6PDdeficient unless they are investigated orexposed to an oxidizing agent.Dark colour urine, pallor, jaundiceand hepatosplenomegaly were the leadingclinical presentations in both areas ofIraq. This observation is consistent withprevious studies (Verleetal, 2000; Grunfeld, 2001; Laosombat et al, 2006). When liverfunction is normal, jaundice typicallydoes not occur until more than 50% oferythrocytes have been haemolysed (Edwards, 2002). The size of the spleen and liver inboth studies varied from just palpable to3–4 cm below the costal margin.Fever was documented in

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37.8% ofthe patients in the Baghdad study comparedwith 44.3% in the Mosul study.Many individuals develop fever afterthe onset of infections such as urinarytract infection, enteric fever and chestinfections.

CONCLUSION:

The G6PD deficiency is one of common hemolytic diseases. Our study was concluded that most of G6PD deficient children admitted to hospital for blood transfusion.There are many factors effected diagnosis, management, prognosis and outcome of G6PD deficiency.

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