ORIGINAL ARTICLE

Prevalence of Glucose-6-phosphate dehydrogenase deficiency in Northern Border Region of Saudi Arabia

RASHAD QASIM ALI OTHMAN[1], NAJLA JOMAH[2], AMAL MISBAH AGGOUR[3]
[1]*Department of Pathology, Faculty of Medicine, Northern Border University, Saudi Arabia*
[2]*Department of Chemistry, Faculty of Science, Northern Border University, Saudi Arabia*
[3]*Arar maternity and pediatric hospital, Directorate of Health Affairs in the Northern Border Principality, Ministry of Health, Saudi Arabia*
Correspondence to Dr. Rashad Qasim Ali Othman, Email: raqaa76@gmail.com, Mobile: 00966537838731

ABSTRACT

Aim: Glucose-6-phosphate dehydrogenase deficiency (G6PDD) is a worldwide problem with about 400 million cases recorded globally. The current work was conducted to investigate the prevalence of G6PDD as a cause of hemolysis among children attended to Arar maternity and pediatric hospital during five years (from first of January, 2014 to the end of December, 2018).
Methods: Data file for children attended to Arar maternity and pediatric hospital during five years (from first of January, 2014 to the end of December, 2018) were collected with reference to their demographic data, manifestations, severity, genetic types, and triggering factors.
Results: During the period of study, hemolysis was found in 194 cases. Only 59 cases (30.4%) were diagnosed as G6PD deficiency in Arar city. The majority of the recorded cases were males (93.2%) aged blow 6 years (about 55%). Positive family history of G6PD was reported in [21/59 cases (35.6%)] of cases while infections were reported to be the commonest (in about 50% of the cases) predisposing factor for hemolysis in the studied population. Regarding the variants of G6PD among the diagnosed cases, Med Variant was the commonest [40/59 cases (67.8%)], followed by B+Variant in about 14% of the diagnosed G6PDD cases. Among G6PD cases, pallor, tiredness and dark urine were the most common suggestive symptoms among the diagnosed cases.
Conclusion: G6PDD remains a main cause of hemolysis among children which necessitate more awareness among the health staff and the general population about the disease for early proper management.
Key words: Blood hemolysis, hemolytic anemia, Glucose 6—phosphate dehydrogenase enzyme, Glucose 6—phosphate dehydrogenase deficiency, favism**,**

INTRODUCTION

Hemolytic anemia is a group of disorders in which the red blood cells are destroyed faster than the bone marrow can make them [1]. Hemolytic anemia can be caused by intrinsic and extrinsic causes. The intrinsic causes include sickle cell anemia, thalassemia, or spherocytosis. While the extrinsic causes of hemolysis include infections, medicines, autoimmune disorders or hypersplenism[2].

Glucose-6-phosphate dehydrogenase deficiency (G6PDD) is a worldwide problem with about 400 million cases recorded globally with higher prevalence in certain parts of Africa, Asia, the Mediterranean, and the Middle East. It was reported to cause 33000 deaths in 2015[3-5] . Its highest prevalence was reported among the Kurdish Jewish population, where in approximately 1 in 2 males have the condition and the same rate of females are carriers[3].

G6PDD is an X-linked recessive inborn error of metabolism that predisposes to red blood cell breakdown [1]. The mutations are mainly located on the short arm of the X-chromosomes. The most common genetic variants of the diseases are G6PD A− and G6PD Mediterranean. G6PD A− has an occurrence of 10% of Africans and African-Americans while G6PD Mediterranean is prevalent in the Middle East [6].

Hemolysis mainly occur following a specific trigger as infections, certain medication, stress, or foods such as fava beans [7,8]. Hemolysis due to G6PDD is more reported among males. The severity of hemolysis is based on the underlying type of mutation [9]. Diagnosis is mainly based on the history, clinical data and some supporting blood tests and genetic studies[10] Avoiding of the triggering agents is the corner stone of the proper management of cases of G6PDD[11]. Furthermore, some researchers recommended testing for G6PDD before prescription of certain medications as primaquine[2].

G6PD deficiency was firstly reported in Saudi in 1965 in villages of the Eastern Province of Saudi Arabia [13] with subsequent frequent publication about G6PDD from the different Saudi region with notices differences in its prevalence in the different studied area [14-16]. Data regarding G6PDD in the northern Border region is still deficient. Hence this study aimed to investigate the prevalence of G6PDD as a cause of hemolysis among children attended to Arar maternity and pediatric hospital during five years (from first of January, 2014 to the end of December, 2018) with reference to their demographic data, manifestations, severity, genetic types, and triggering factors.

MATERIAL AND METHODS

The current study was conducted as a retrospective study for all cases diagnosed as G6PD during the study years from first of January, 2014 to the end of December, 2018. For all cases with suggestive history, all details of history were collected for further analysis. G6PD deficiency routine standard investigations data were revised and collected for all diagnosed cases.

Routinely, all cases with suspected G6PD deficiency were diagnosed by complete blood count followed by enzyme assay activities and electrophoresis to estimate the variant of the diseases among the diagnosed cases. Blood

samples were collected in EDTA tube (2 ml.). Firstly, complete blood cell count (CBC) was conducted using automated blood cell analyzer (Sysmex KX 21N). Then, the activity of G6PD enzyme was measured by oxidation of glucose-6 phosphate (G6P) to 6-phosphogluconate (6-PG) with concomitant reduction of NADP+ to NADPH. using a commercial kit (Cat. No. 97089, BIOLABO, France & RANDOX Laboratories Ltd, United Kingdom. Cat. No. PD 410) and the rate of absorbance was read at 340 nm under the ultraviolet light after one-hour incubation by the spectrophotometer. G6PD activity was represented in relation to the hemoglobin concentration. The enzyme activities were estimated within 48 hours after collection. Samples were kept at 4-6ºC till the enzyme activity assay. Results were interpreted as the percentage of normal controls G6PD activity. Severe deficiencies were considered in cases with enzyme activity less than 10% of the controls. Moderate enzyme deficiencies were considered in cases with G6PD activity about 10-60% of the controls, while mild deficiencies were considered in cases with activity higher than 60% of the activity measured in the controls samples.

From all diagnosed cases, a fresh hemolysate sample was subjected to cellulose acetate electrophoresis using Titan III Plates and Supra Heme buffer at pH 8.6 for 20 min. at 350V. G6PD bands were visualized by using G6PD staining reagent (Helena Cat. No. 5620) at 20°C and scanned using a Quick Scan Densitometer. Then, the plates were fixed in 7.5% trichloroacetic acid, for 2-3 minutes and washed with 5% acetic acid, then naturally dried stored.

Statistical Analysis: All data were collected and analyzed by Microsoft office Excel 2007 and SPSS programs. P-value of less than 0.05 was considered significant.

RESULTS

During the period of study, hemolysis was found in 194 cases [120 males (61.8%) and 74 females (38.2%)]. ABO incompatibility among newborns was the commonest cause of hemolysis among the studied cases [87 cases (44.8%)]. Only 59 cases (30.4%) were diagnosed as G6PD deficiency in Arar city. Among these cases 44 were diagnosed as G6PD for the first time, while the remaining cases had been diagnosed before in previous attacks. The frequency of cases in the studied years in relation to their ages, genders, and nationalities are shown in table (1). The majority of the recorded cases were males (93.2%) aged blow 6 years (about 55%) (Table 2)

Positive family history of G6PD was reported in [21/59 cases (35.6%)] of cases while infections were reported to be the commonest (in about 50% of the cases) predisposing factor for hemolysis in the studied population (Table 3).

Regarding the variants of G6PD among the diagnosed cases, Med Variant was the commonest [40/59 cases (67.8%)], followed by B+ in about 14% of the diagnosed G6PDD cases (Table 4)

Among G6PD cases, pallor, tiredness and dark urine were the most common suggestive symptoms among the diagnosed cases (table 5).

Table 1: Causes of hemolysis among Saudi children in Arar from 2014 to 2018

Years	Cases with hemolysis	G6PD		ABO incomp.		Rh incomp.		Others	
2014	29	7	24.1	14	48.3	5	17.2	3	10.3
2015	41	11	26.8	19	46.3	8	19.5	3	7.3
2016	36	12	33.3	15	41.7	7	19.4	2	5.6
2017	45	14	31.1	18	40.0	9	20.0	5	11.1
2018	43	15	34.9	21	48.8	5	11.6	2	4.7
Totals	194	59	30.4	87	44.8	34	17.5	15	7.7

Table 2: Gender and ages data of glucose 6 phosphate dehydrogenase deficiency diagnosed in Arar from 2014 to 2018.

Years	Total n(%)	Gender				Ages (years)			
		Male		Females		<6		≥6	
		n	%	n	%	n	%	n	%
2014	7(100)	5	71.4	2	28.6	4	57.1	3	42.9
2015	11(100)	10	90.9	1	9.1	5	45.5	6	54.5
2016	12(100)	12	100.0	0	0.0	6	50.0	6	50.0
2017	14(100)	14	100.0	0	0.0	9	64.3	5	35.7
2018	15(100)	14	93.3	1	6.7	8	53.3	7	46.7
Totals	59(100)	55	93.2	4	6.8	32	54.2	27	45.8

Table3: Family history and precipitating factor for hemolysis among cases of glucose 6 phosphate dehydrogenase deficiency diagnosed in Arar from 2014 to 2018.

Years	Total	Family History				PPF					
		Pos.		Neg.		F.B		Drugs		Inf.	
		n	%	n	%	n	%	n	%	n	%
2014	7(100%)	3	42.9	4	57.1	2	28.6	2	28.6	3	42.9
2015	11(100%)	5	45.5	6	54.5	1	9.1	3	27.3	7	63.6
2016	12(100%)	3	25.0	9	75.0	6	50.0	0	0.0	6	50.0
2017	14(100%)	5	35.7	9	64.3	4	28.6	2	14.3	8	57.1
2018	15(100%)	5	33.3	10	66.7	6	40.0	3	20.0	5	33.3
Totals	59(100%)	21	35.6	38	64.4	19	32.2	10	16.9	29	49.2

Table (4). Mutation genetic varianats among cases of glucose 6 phosphate dehydrogenase deficiency diagnosed in Arar from 2014 to 2018.

Years	Total	A+		B+		A-		Med		Hetero	
		n	%	n	%	n	%	5	71.4	N	%
2014	7(100)	0	0.0	2	28.6	0	0.0	8	72.7	0	0.0
2015	11(100)	1	9.1	1	9.1	1	9.1	9	75.0	0	0.0
2016	12(100)	2	16.7	0	0.0	0	0.0	9	64.3	2	16.7
2017	14(100)	1	7.1	3	21.4	0	0.0	9	60.0	2	14.3
2018	15(100)	1	6.7	2	13.3	1	6.7	40	67.8	1	6.7
Totals	59(100)	5	8.5	8	13.6	2	3.4	5	71.4	5	8.5

Table 5: The main complaints among cases of glucose 6 phosphate dehydrogenase deficiency diagnosed in Arar from 2014 to 2018.

Complaints	n	%
Pallor	59	100.0
Headache	46	78.3
Drowsiness	15	26.1
back pain	14	23.9
Tiredness	45	76.1
Abdominal pain	22	37.0
Discoloration of urine	53	89.1
Foot pain	18	30.4
Low grade fever	10	17.4
Jaundice	14	23.9

DISCUSSION

The current work was conducted to investigate the prevalence of G6PDD as a cause of hemolysis among children attended to Arar maternity and pediatric hospital during five years (from first of January, 2014 to the end of December, 2018) with reference to their demographic data, manifestations, severity, genetic types, and triggering factors. During the period of study, hemolysis was found in 194 cases. Only 59 cases (30.4%) were diagnosed as G6PD deficiency in Arar city. The majority of the recorded cases were males (93.2%) aged blow 6 years (about 55%). Positive family history of G6PD was reported in [21/59 cases (35.6%)] of cases while infections were reported to be the commonest (in about 50% of the cases) predisposing factor for hemolysis in the studied population. Regarding the variants of G6PD among the diagnosed cases, Med Variant was the commonest [40/59 cases (67.8%)], followed by B+Variant in about 14% of the diagnosed G6PDD cases. Among G6PD cases, pallor, tiredness and dark urine were the most common suggestive symptoms among the diagnosed cases.

In the current study G6PDD was shown to cause 30% of cases of hemolysis among children. G6PDD was reported in all provinces in Saudi Arabia with different prevalence rate among the general population in the different regions with the highest in the eastern province followed by the southwestern with lower rates in the north (0.06 in males only and zero % among the studied females) [17]. In nearby Jordon The prevalence of G6PD deficiency in the north of Jordan was around 5.5%, while then prevalence of G6PDD was estimated to be 4.9 among the Egyptian neonates in 2017[18]. These Egyptian and Jordan numbers are lower than our study as we have only estimated the prevalence of G6PDD as a cause of hemolysis among the cases attended to the hospital in acute attacks of blood hemolysis while the other studies were focused to estimate the prevalence of G6PDD among the general population.

The current data showed that Med Variant was the commonest [40/59 cases (67.8%)], genetic mutation variant in the diagnosed G6PDD cases followed by B+ genetic variant in about 14%. This is in not accordance with the previous studies published data as Warsy et al. (2011)[17], who reported B+ as the commonest genetic variant in Saudi Arabia. This is because that our study targeted the symptomatizing cases and it is known that G6PD-Mediterranean is the most frequently Symptomatizing variant which is also called as favism with high incidence of hemolytic anemia under oxidative stress[4,9].

G6PDD was more frequently reported among males as the it is an X-linked recessive pattern with its The gene associated with this condition located on the X chromosome. So one altered copy of the gene in males, X-chromosome will be sufficient to cause the symptom. While in females 2 altered copy of the gene of both X-chromosomes are mandatory for the condition to be manifested by the characteristic hemolytic attacks[19]. In addition, this inheritance back ground highlights the importance of family history for development of the diseases [20]. G6PDD is mainly inherited to males from their carrier or diseased mothers with altered one of both copies of the gene on their X-chromosomes.

In the reported cases infections were reported to be the commonest (in about 50% of the cases) predisposing factor for hemolysis in the studied population, followed by fava beans and drugs. Other studies were reported fava beans as the commonest trigger factors for hemolysis among cases of G6PDD [21], However fava beans are not commonly used in Arar Hence infection seem to have the upper hand in our studied cases. Infection were also reported as major trigger for hemolysis as enteroviruses, hepatitis A, typhoid fever, and pneumonia [22, 23]. Also, some drugs were reported to have a role as antibiotics, anti-malarial agents, aspirin, and sulfonamides[7].

CONCLUSION

Inspit of the expected low prevalence of G6PDD in the Northern regions of Saudi Arabia, G6PDD remains a common cause of hemolysis (about one third of the diagnosed cases) among children in the Northern Border

province of Saudi Arabia. Infections play a major role to trigger hemolysis among these cases. Hence physician should be minded about G6PDD as a cause of hemolysis. In addition, outreach campaign should be arranged to improve the public awareness about G6PDD.

Conflict of interest: No conflict of interest.

Acknowledgement: The authors are grateful to the scientific research deanship of the Northern Border University, Saudi Arabia for funding this project

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