The relationship between neonatal factors and involving with glucose-6-phosphate dehydrogenase deficiency (G6PD) and patients' outcome in Fars Province

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Abstract

Introduction: Glucose-6-phosphate dehydrogenase deficiency (G6PD) or fauvism is the most common enzyme deficiency in human, so that 400 million people are living with this disease worldwide. This study aimed to investigate the role of some neonatal factors among newborns suffering from G6PD deficiency and neonatal outcomes associated with this disease.

Materials and methods: In this study, two methods including case-control and retrospective cohort regarding some neonatal factors associated with G6PD deficiency were used. These methods were performed on 142 children with this kind of deficiency and 142 healthy infants in the city of Marvdasht during 2013- 2014. The analysis of data was based on chi-square tests, t-test, logistic regression, descriptive statistics and estimation of odds ratios or relative risks via SPSS16 software.

Results: Totally 284 newborns including 132 (46.6%)/ 152 (53.4%) boys/girls and mean weight on birth of 3163 ± 471 (gr) were analyzed. Comparison of case and control samples did not show any significant differences between sex and involving with G6PD deficiency but the chance of having a baby with this defect in pregnancy intervals between 6 to 8 years was increased (95% CI: 1- 4.4, OR: 2). Relative risk of jaundice in infected and healthy infants was estimated as 3.73, which demonstrated a statistically significant association (95% CI: 1.33- 10.4).

Conclusion: The results of this study showed that the number of hospitalization is increased due to jaundice in infants with G6PD. There is also an insignificant relation between low birth weight, rank of birth and type of delivery.

Keywords: Iran, Fars, Favism, Neonate, Newborn, G6PD

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Introduction

Glucose-6-phosphate dehydrogenase deficiency (G6PD) is one of the most common genetic defects and about 400 million people are living with this disease worldwide (1). G6PD enzyme-linked recessive gene has an inheritance pattern which is located on the X chromosome and therefore, often males are ill and females are carriers of the defect (2). This defect increases the susceptibility of red blood cells to oxidant agents such as oxidants present in raw beans, some medications and oxidative stress caused by infections (3) and in the case of facing with oxidative agents, clinical realizations of G6PD including acute hemolytic anemia, chronic hemolytic anemia and hyperbilirubinemia in newborns will appear and in severe cases it can lead to kernicterus. This severe complication resulting from the accumulation of unconjugated bilirubin in the brain cells at the first month of birth may lead to infant death, and those who survive are mostly involved with mental retardation, disability and vestibule-auditory disorders, seizures, hearing loss, speech disorders and so on (4,5).

The frequency of G6PD deficiency in the Middle East is 1-2 percent in total population (6). In Iran, according to World Health Organization estimations, the frequency of G6PD deficiency has been estimated from 10 to 14.9 percent in general population (1), and according to different studies, from Iran, these percentages have been reported: in Iranshahr 24.5% (7), Yasouj 12.7% (8), Zahedan 5.9% (9) and Zanjan 2.1% which shows that the prevalence of the disease in different parts of the country was affected by ethnic, racial, and environmental factors. Due to the high proportion of these defects in our region, the World Health Organization suggested that in case of total serum bilirubin more than 7 mg/dl among Asian infants, or existence of coombs negative hemolytic anemia, the deficiency of the enzyme should be examined (1, 10).

Some factors associated with G6PD deficiency, such as gender, familial marriage, hyperbilirubinemia, anemia, place of residence and prematurity have been already reported by various studies (9,11,13).

Considering the high prevalence of G6PD deficiency in Fars province and the imposition of its direct and indirect costs on health systems and also existence of unfavorable clinical outcomes among involved babies particularly bearing some limitations regarding oxidizing substances and drugs throughout their life, identification of associated neonatal factors as well as clinical outcomes of babies with this defect is beneficial. This study aimed to investigate some neonatal factors associated with G6PD deficiency and neonatal outcomes among involved individuals.

Materials and methods

Patients: This study was performed in two stages and via two methods including a case-control and a retrospective cohort among 840 neonates, suspected for G6PD deficiency, after screening test in the city of Marvdasht during 2013 and 2014. For the current study, 142 children with confirmed diagnosis (through relevant tests) of G6PD were chosen by random sampling either as cases for case-control study or as exposed group for cohort study and 142 healthy newborns either as controls for case-control study or as non-exposed group for cohort study.

The frequencies of neonatal factors were collected by a standard questionnaire to identify the odds ratio and any associated factor for G6PD deficiency via case-control method. The frequencies of some outcomes among either exposed or non-exposed groups, with G6PD deficiency, during neonatal period and their relevant relative risks were evaluated via cohort method.

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In order to control some confounding variables, such as socioeconomic status and lifestyle, the cases and controls were chosen from the same health centers. Babies who had chronic underlying diseases or birth anomalies were excluded from the study. The analyzed variables in these patients included gender, birth order, type and intervals of pregnancy low birth weight, jaundice and frequency or duration of hospitalization during neonatal period.

The sample size needed in this study was estimated based on 95% CI, 90% power and 5% error rate, respectively. Chi-square and Mann-Whitney tests were used for any relationship between different variables. Odds ratio was estimated for relevant variables investigated via case-control method and relative risk was estimated for relevant variables evaluated via cohort method. Variables associated with case-control method were gender, type of delivery, birth order, birth interval, and those associated with cohort study were low birth weight, prematurity, jaundice, and frequency of hospitalization during neonatal period.

The analysis of data was performed via SPSS16 software and p value less than 0.05 was considered as significant for investigated variables. This study was approved by the Ethics Committee at the Ilam University of Medical Sciences.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution\'s human research committee.

Results

In this study 284 children including 132 boys (46.6%) and 152 girls (53.4%) were evaluated. Average birth weight and average pregnancy interval were estimated as 3163 ± 471 gr and 6.52±3.2 years, respectively. Birth characteristics of neonates are shown in Table 1.

Table 1. Demographic characteristics of newborns, selected for G6PD deficiency study in Fars Province.

Variables		N	%
Gender	Boy	132	46.6
	Girl	152	54.4
Birth order	≤2	231	81.6
	>2	52	18.4
Type of delivery	Caesarean section	150	57.5
	Vaginal	111	42.5
Birth weight (gr)	2500-3500	210	75
	<2500	16	5.7
	>3500	54	19.3
Gestational age (weeks)	≤37	6	2.1
	>37	276	97.9
Hospitalizations because of jaundice	Yes	22	7.9
	No	258	92.1
Birth Interval (years)	First child	108	38
	≤2	14	4.9
	2.1-4	36	12.7
	4.1-6	51	18
	6.1-8	35	12.3
	>8	40	14.1

The results showed that the annual incidence of disease among girls was more than boys, but gender difference was not statistically significant (P=0.6, OR: 0.88). 16.8 percent of infants in the case group and 8.5 percent of infants in the control group showed a pregnancy distance of 6-8 years with significant differences, so that chances of having a baby with G6PD in pregnancy with distance of 6 to 8 years was 2 times more than healthy babies (P=0.08, OR: 2). Mann-Whitney test

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revealed a significant relation between the average of distance pregnancy and the risk of G6PD deficiency (P= 0.048). In comparison with healthy infants, the number of G6PD-deficient infants born by cesarean section was more (60.2% versus 54.9%), but using the chi-square test and estimating the odds ratio, there was no relationship between mode of delivery and incidence of this defect (Table 2).

Table 2. Factors associated with G6PD deficiency among participants for G6PD deficiency study in Fars Province.

Variable		Case number (%)	Control number (%)	OR (95% CI)	X^2	P #
Gender	Girl	78 (54.9)	73 (51.8)	1		
	Boy	64 (45.1)	68 (48.2)	0.88 (0.55 – 1.4)	0.28	0.6
Birth order	2<	23 (16.2)	29 (20.6)	1		
	≥2	119 (83.8)	112 (79.4)	1.34 (0.73 -2.46)	0.9	0.34
Delivery type	Vaginal	51 (39.8)	60 (45.1)	1		
	Caesarean section	77 (60.2)	73 (54.9)	1.24 (0.76 – 2.03)	0.74	0.39
Birth interval	First child	53 (37.3)	55 (38.7)	1	0.048*	
(year)	≤2	5 (3.5)	9 (3.6)	0.58 (0.18 -1.83)	0.89	0.35
	2.1-4	13 (9.2)	23 (16.2)	0.59 (0.27 -1.28)	1.82	0.18
	4.1-6	28 (19.7)	23 (16.2)	1.26 (0.65 -2.64)	0.47	0.49
	6.1-8	23 (16.2)	12 (8.5)	2(1 -4.4)	2.93	0.08
	>8	20 (14.1)	20 (14.1	1.04 (0.5 -2.14)	0.01	0.99

OR,odds ratio.
Significance level
* Mann-Whitney Test
$ Chi square

The hospitalization rates due to jaundice in the exposed group (G6PD deficiency) was estimated for 12.1% compared to only 3.6% in the unexposed group. The relative risk of hospitalization due to jaundice caused by G6PD deficiency was calculated 3.73 which was statistically significant (P= 0.008). Only 6.3% of infants among exposed group and 5.1% of the non-exposed group were underweight and their difference was not statistically significant. Moreover, there was no significant difference in the incidence rate of prematurity between groups (Table 3).

Table 3. The relative risk of G6PD deficiency among participants for G6PD deficiency study in Fars Province.

Variable		Case number (%)	Control number (%)	RR (95% CI)	X^2	P #
Birth weight (gr)	2500-3500	108 (76.1)	103 (73.9)	1	0.82*	
	<2500	9 (6.3)	7 (5.1)	1.24(0.44-3.4)	0.14	0.8
	>3500	25 (17.6)	29 (21)	0.8(0.45-1.5)	0.45	0.5
Gestational age (weeks)	≥37	139 (97.9)	137 (97.9)	0.99(0.2-4.97)		
	<37	3 (2.1)	3 (2.1)		0.001	0.99
Hospitalizations because of jaundice	Yes	123 (87.9)	135 (96.4)	3.73(1.33-10.4)		
	No	17 (12.1)	5 (3.6)		7.1	0.008

RR, relative risk.
Significance level
* Mann-Whitney Test
$ Chi square

Regression analysis showed that birth order with less than two infants (P= 0.02), average distance pregnancy (P= 0.02) and hospitalization due to jaundice (P= 0.01) were significantly associated with the occurrence of G6PD deficiency. But, there was no significant relation between low birth weight and prematurity associated with this defect (Table 4). Logistic regression model revealed a relationship between birth rank and G6PD deficiency and confirmed that increasing the distance between pregnancies was associated with increasing rate of newborns involved with G6PD deficiency. This analysis also revealed an association between neonatal hospitalization due to jaundice and G6PD deficiency; however, did not show any relation between low birth weight or prematurity and G6PD deficiency.

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Table 4. Estimated regression coefficients of neonatal factors associated with G6PD deficiency based on logistic regression model.

Variable	β coefficient	SE	Retrograde Wald	Df	P*
Birth order	-0.882	0.387	5.2	1	0.023
Birth interval	-0.132	0.057	5.36	1	0.021
Birth weight	-0.17	0.8	0.04	1	0.83
Gestational age	0.69	0.94	0.54	1	0.46
Hospitalized because of jaundice	-1.36	0.55	6.15	1	0.013

* Significant level. SE, standard error. Df, degree of freedom.

Discussion

The current study revealed that the incidence rate of G6PD deficiency was higher among males than females but non-significantly. Our finding was in consistent with the results reported by Noorbakhsh and colleagues from Shahrekord (9), and a study performed in Rafsanjan by Alidalaki et al (12) and both of these studies reported non-significant relationship between gender and G6PD deficiency. However, two other studies from Amol (13) and Isfahan (14) reported a male /female ratio of 10/1 and 3/1 respectively. Based on the Lyon's hypothesis, the high risk of G6PD deficiency in females in some studies, including the present study, could be due to random inactivation of the X chromosome which is manifested in those heterozygous females, who have a large proportion of cells with the enzyme deficiency, through symptoms which are similar to those of homozygous males (15).

In regards to pregnancy interval, this study revealed that along with increasing the distance between pregnancies (more than 4 years), the risk of G6PD deficiency was increased too and based on both the Mann-Whitney test and logistic regression model their relationship was significant. This relationship may be due to the age increasing of mothers due to longer pregnancy intervals, which can enhance genetic- related adverse effects. In this study, the birth order was less than 2 and the frequency of cesarean delivery was higher in infants with G6PD deficiency, but their relationships with the disease were not significant.

In the present study, there was a significant relationship between G6PD deficiency and hospitalization due to jaundice; so that the risk of hospitalization in involved infants was 4 times more than healthy infants. Noorbakhsh and colleagues also reported an increased significant relation between this deficiency and hospitalization due to jaundice and all babies with jaundice had experiences of hospitalization too (9). Haji Ebrahim and colleagues also reported that in all patients with increased enzyme deficiency, the serum bilirubin and the peak incidence of jaundice were occurred at the first three days of birth (16). In our study, the incidence rate of G6PD was 12.1 per 100 live births. These figures were 7.7% and 8.8% in Amini et al. and Bahmani et al. studies, respectively which were lower than our result.

The risk of low birth weight in newborns with G6PD deficiency was 1.2 times more than healthy babies, but their relationship was not significant based on chi-square and Mann-Whitney tests' results. There was no significant difference, in the incidence rate of prematurity, between groups. In a study from Tehran, conducted by Amini et al, no significant difference was observed between the risk of G6PD deficiency and prematurity (17), which was consistent with the results of our study.

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Limitations

One of the limitations of this study was lack of some information in the newborns' files and also lack of data to show the homozygousness or heterozygousness of getting G6PD deficiency.

Conclusion

G6PD deficiency increases the risk of hospitalizations due to jaundice in newborns. There is also a relation between pregnancy interval of more than 4 years and G6PD deficiency. Though non-significant, this enzyme deficiency leads to an increase in the rate of low birth weight babies and more need to cesarean delivery. Additionally, further researches with more samples are needed to reveal any possible relationship between those variables with higher rates among involved babies compared to healthy individuals, which were insignificant in our study.

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Conflict of interest

We declare that there was no conflict of interest between authors for this work.

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