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REFERENCE VALUES FOR QUANTITATIVE TESTING OF G6PD DEFICIENCY IN NEWBORNS FROM THE REPUBLIC OF NORTH MACEDONIA

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Glucose-6-phosphate dehydrogenase is a key regulatory enzyme in the pentose-phosphate cycle that participates in the formation of reduced equivalents to maintain the cellular redox status. The G6PD enzyme activity is crucial in protecting cells from oxidative stress. Deficit of the glucose-6-phosphate dehydrogenase (G6PD) has been recognized as the most common inherited enzymopathy worldwide. In the Republic of North Macedonia (RNM), the deficit of glucose-6-phosphate dehydrogenase has been infrequently investigated. Moreover, no reports exist on quantitative testing of G6PD in newborns from the RNM.

Scope: The aim of our study was to determine the reference values for the level of G6PD in erythrocytes of newborns from the Republic of North Macedonia. For this purpose, eighty-two healthy newborns were selected and tested for G6PD by the quantitative spectrophotometric method.

Results: The mean ± SD of the G6PD quantitative value in the examined group was 229.12 ± 24.2 mU/10^{9}Er ranging from a minimum of 191.7 to a maximum of 288, and a median of 228.0 mU/10^{9}Er, values that were lower than the preset reference values of the diagnostic test in use.

Conclusion: We speculated that by establishing a specific reference value (range) for the target population and for the appropriate diagnostic test, we would gain increased sensitivity of the test. This would help optimize detection of G6PD deficient newborns, mild-variant hemizygotes and female heterozygotes for the deficiency.

Keywords: GLUCOSE-6-PHOSPHATE DEHYDROGENASE DEFICIENCY, QUANTITATIVE TESTING, REFERENCE VALUES, REPUBLIC OF NORTH MACEDONIA

INTRODUCTION

The basic function of erythrocytes is to transport oxygen from the lungs to the tissues through the transport of hemoglobin. In the erythrocytes, even in the absence of nucleus and mitochondria, dynamic metabolic processes occur. About 90% of the glucose is used by anaerobic glycolysis, and the remaining 10% is broken down oxidatively by the pentose-phosphate cycle (hexose monophosphate shunt) (1). The Glucose-6-phosphate dehydrogenase (G6PD) is a key regulatory enzyme in the pentose-phosphate cycle that catalyzes the first oxidation reaction of the glucose-6-phosphate (G6P) into the 6-phosphogluconolucto-ne, thus participating in the formation of reducing equivalents such as nicotinamide-adenine-dinucleotide-phosphate (NADPH) to meet the cellular antioxidative needs (2). The pentose-phosphate cycle is the only source of NADPH in erythrocytes, pointing out the key role of the G6PD enzyme in protecting cell's hemoglobin from oxidative stress (1, 3).

Deficit of the glucose-6-phosphate dehydrogenase (G6PD) has been recognized worldwide as the most common inherited enzymopathy affecting more than 400 million people. At the molecular level, 191 mutations or combination of mutations have been identified for this X chromosome-linked gene (4). At the level of phenotype, the most common presentations comprise acquired hemolytic anemia, favism, and neonatal hyperbilirubinemia (2).

The association of severe G6PD-associated neonatal hyperbilirubinemia and the serious long-term consequences of chronic bilirubin encephalopathy has been well documented (5-9). The global burden of infant mortality due to G6PD-associated neonatal jaundice is estimated in the range of 0.7-1.6 per 1000 of all births according to World Health Organization (WHO) data (10).

In the Republic of North Macedonia (RNM), the deficit of glucose-6-phosphate dehydrogenase has been sparsely

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investigated. Fraser et al. estimated an average prevalence of G6PD deficit in Yugoslavia of 1% based on the examinations performed on 144 samples from the then FR Macedonia and 512 samples from the area of Dalmatia (11). Andreeva et al., reported a G6PD deficit prevalence of 1.02% among children of Macedonian nationality and 6.63% among Roma children (12). To our knowledge, there have not been studies so far relating to the deficit of G6PD in the newborns from the Republic of North Macedonia. Also, no reports exist on the implementation of quantitative testing for G6PD in the newborns from the RNM. The aim of our study was to determine the reference values for the level of G6PD in the erythrocytes of the newborns from the Republic of North Macedonia.

MATHERIALS AND METHODS

Participants

Eighty-two healthy newborns without hyperbilirubinemia were selected for testing of G6PD. The examinees were selected from the hospitalized and outpatient patients of the Department of Neonatology at the University Pediatric Clinic in Skopje, RNM. The following data from the perinatal history were recorded: gestational age (GA), birth weight (RW), birth length (BL), Apgar score (AS), mode of delivery (spontaneous, instrumental, or caesarean section), perinatal risk factors, intrauterine growth expressed as a percentage of the growth curve (13). Also, age, gender, and nationality were recorded. The criteria for inclusion were the following:

- Term and near-term gestational age (≥ 36).
- Breast or formula feeding.
- Absence of accompanying pathology.
- Absence of clinically obvious and significant jaundice, i.e., the intensity of jaundice for the appropriate day and hour did not meet the criteria for phototherapy treatment (9).

Laboratory analyses

Blood samples were taken for full blood count, blood smear and reticulocytes (200 µl) and additional 200 µl of capillary blood for quantification of G6PD using the spectrophotometric method. In the examinees who would eventually be diagnosed with G6PD deficiency by the spectrophotometric method, it was planned to take another test-tube of anticoagulated blood for genetic testing of G6PD. The parents of the children signed an informed consent for the participation in the study. Consent to perform these analyses was also obtained from the Institutional Ethics Commission in accordance with the Helsinki Declaration.

Sysmex K-4500 Automated Hematology Analyzer Minnesota, USA) was used for complete blood count analysis. Light microscopy was used to analyze blood smears and reticulocytes. Blood smear analysis was performed to rule out possible congenital erythrocyte membrane defects (14, 15). Reticulocytes are young forms of erythrocytes whose presence in the circulation indicates active hematopoiesis (16). Higher G6PD levels are expected in reticulocytes because the enzyme levels decrease as the erythrocyte ages. The presence of the elevated reticulocyte count may be associated with falsely high G6PD values.

Quantitative spectrophotometric testing for G6PD

The enzyme activity was determined by measuring the increase in light absorption at 340 nm following a reduction of NADP to NADPH when the sample was incubated with G6P. G6PD activity was determined in relation to erythrocyte count and expressed as mU/10^9 erythrocytes (Er) (17). A spectrophotometer (Human Analyzer 3000, Germany) was used for this purpose. Commercially available kits (AMS U.K. Ltd, East Sussex, U.K.) were used to perform the test (86,114). Values of 245 to 299 (272 ± 27) mU/10^9 erythrocytes were considered normal (18, 19).

The results are interpreted in absolute values and as a percentage of the normal G6PD activity. Deficient individuals have less than 60% of the normal activity. Enzyme activity less than 10% of the normal activity is classified as severe deficiency, and activity between 10 and 60% is a moderate deficit (5-7, 20-22). The normal value of G6PD in neonatal age is one third higher than the normal enzyme values in other age groups due to the physiological polycythemia present at this age (23).

Statistical analysis

All data analyses were performed using the statistical package Statistical Package for the Social Sciences (SPSS) 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Distribution of examinees by gender and nationality is represented in Table 1. Almost equivalent gender distribution was noted with 40 (48.78%) male and 42 (51.22%) female subjects. The ethnic structure of the examinees consisted of 34 (41.46%) newborns of Macedonian, 38 (46.34%) of Albanian and 10 (12.2%) of Roma nationality.

The examinees were born at gestational age of 36-41 gestation week (GW), with median at the 40th GW, the group consisted of mainly eutrophic newborns, mean ± SD of birth weight

Table 1.
Gender and nationality of the examined group.

Gender	N (82) (percentage)	Nationality	N (82) (percentage)
Male	40 (48.78%)	Macedonian	34 (41.46%)
Female	42 (51.22%)	Albanian	38 (46.34%)
		Roma	10 (12.2%)

Table 2.
Perinatal and growth characteristics of the examined group.

Number of examinees 82

	mean ± SD	min - max	median
Gestational age	39.32±1,4	36 - 41	40.0
Birth weight	3267.26±436.9	1960 - 4260	3270
Birth percentile	40.58±23.4	2 - 96	40.0
Apgar score at 1. minute	8.09±0.5	7 - 10	8.0
Apgar score at 5. minute	8.88±0.9	4 - 10	9.0

Table 3.
Hematological parameters (descriptive analysis) of the examined group.

Number of examinees 82

	mean ± SD	min - max	median
Hb (g/L)	164.17±30.9	91 - 215	168.0
Le (x10^9/L)	15.09±5.6	3.9 - 28.3	15.1
Tr (x10^9/L)	272±73.5	135 - 487	260
Er (10^{12}/L)	5.07±0.9	3.29 - 6.87	5.22
Htc (%)	0.49±0.1	0.28 - 0.69	0.43
Ret	10±6.9	1 - 40	10.0

Legend: Hb - hemoglobin, Er - erythrocytes, Le - leucocytes, Tr - thrombocytes, Htc - hematocrit, Ret - reticulocytes

Table 4.
G6PD relative and absolute values.

Number of examinees 82

	mean ± SD	min - max	median
G6PD relative value	0.84±0.1	0.7 - 1.06	0.84
G6PD quantitative value (mU/10^9Er)	229.12±24.2	191.7 - 288	228.0

was 3267.26±436.9 and median 3270 g (Table 2.). Estimation of the percentile curve on the growth chart showed distribution around the 40th centile. Median Apgar scores were 8 in the 1. minute and 9 in the 5. minute (Table 2.).

Table 3. shows descriptive analysis of all hematological parameters: hemoglobin (Hb), erythrocytes (Er), leucocytes (Le), thrombocytes (Tr) hematocrit (Htc) and reticulocytes (Ret) respectively.

The relative and absolute values of the G6PD enzyme are represented in Table 4. The mean ± SD of the G6PD quantitative value in the examined group was 229.12 ± 24.2 mU/10^9Er ranging from a minimal value of 191.7 to a maximum value of 288, and a median of 228.0 mU/10^9Er. The average value of the enzyme G6PD expressed as a percentage of normal enzyme activity was calculated according to the reference range of the used diagnostic test. The reference values of the commercial diagnostic test ranged from 245 to 299 (272 ± 27) mU/10^9 erythrocytes; values that were significantly higher than those obtained in our patient population (19, 20). It would therefore be more appropriate to establish population-specific reference value (range) for the appropriate diagnostic test and to compare the results with this value.

We propose the average activity of the enzyme G6PD in the examined group of healthy newborns to be taken as a reference value (range) for the newborn population in the Republic of North Macedonia. This range is 229 ± 24 (205-253) mU/10^9Er.

DISCUSSION

G6PD deficiency has not been studied extensively in the Republic of North Macedonia. Fraser et al. in 1966 reported an average prevalence of the deficit in Yugoslavia of 1% based on samples acquired from the then FR Macedonia and the Dalmatia region (11). Thereaf-

ter, Andreeva et al., performed two subsequent studies estimating the G6PD deficiency prevalence in the south-eastern area of Macedonia and in the city of Skopje. A frequency of 1 to 2% was shown for the south-eastern part of the Republic (12). By processing samples of 1196 male school children from the territory of Skopje, a prevalence of the deficit of 1.02% was reported among children of Macedonian nationality and 6.63% among Roma children (12). Qualitative tests were used in all three studies. The qualitative test that was in use at the University Pediatric Clinic in Skopje, RNM could not meet the requirements for detection of G6PD deficiency in the neonatal period taking into consideration the higher reticulocyte count and the higher values of G6PD in the neonatal period in general. Moreover, in newborns, the use of a quantitative method is recommended as the preferred method for G6PD deficiency screening (24). G6PD deficiency as an X-linked inherited disease is expected to be more common in males (25).

Due to different X-chromosomal inactivation, the erythrocytes of G6PD heterozygous female individuals are a random mosaic of normal and deficient clones of cells with a wide range of enzyme activity (23, 24). Therefore, in heterozygotes, various options are probable, from significant deficits to normal findings. Republic of North Macedonia is marked in most of its territory as a former hyperendemic area for malaria (11). Due to the high selection pressure of malaria, it can be assumed that a high incidence of G6PD deficiency is maintained in Macedonia, comparable to that of the neighboring countries and the nearby countries in the Mediterranean region (22, 26). To our knowledge, no reports exist on implementation of the quantitative testing for G6PD in newborns from the RNM.

The aim of our study was to determine the reference values for the level of G6PD in erythrocytes in newborns and in RMN. We assumed that by obtaining the population-specific levels for the enzyme G6PD in newborns, we could ease and improve detection of this enzyme deficit in the newborn period, especially in infants with extensive or prolonged jaundice of undefined etiology (18). Also, we expected to gain improved detection of heterozygous female carriers who would have been missed by the less accurate qualitative method (23, 24).

The average value of G6PD enzyme in erythrocytes obtained by the quantitative spectrophotometric method was 229.12 ± 24.2 mU/10^9Er in the examined group of the healthy newborns. The median value of the enzyme determined by this method was 228 mU/10^9Er. The average value of the enzyme G6PD, expressed as a percentage of the normal enzyme activity, was 0.84 ± 0.1%. The reference values of the commercial diagnostic test used in the quantitative spectrophotometric method ranged from 245 to 299 (272 ± 27) mU/10^9Er (18, 19). Compared with the activity of the enzyme registered in the population of the healthy newborns from the Republic of North Macedonia, a significant difference has been noticed. We could assume that the reference values of the commercial test had been set too high. It would therefore be more appropriate to establish a specific reference value (range) for this target population and for the appropriate diagnostic test to serve as a standard for further comparison of the results obtained from the G6PD testing. The advantage of establishing a population-specific reference value (range) is in increasing the sensitivity of the test. Namely, by adjusting the reference values to the average values of enzyme activity in the target newborn population, we get the opportunity to detect borderline enzyme deficiencies that would be missed by using higher reference values. Such borderline deficits are expected in hemizygote individuals with class 3 variants characterized by moderate to mild deficiency of enzyme activity, as well as in heterozygous female individuals (5-7, 20, 23, 24).

CONCLUSIONS

Based on our results, we propose an enzyme activity of 229 ± 24 (205-253) mU/10^9Er to serve as a reference value (range) for the appropriate diagnostic test and for the appropriate newborn population of the Republic of North Macedonia. We expect our study results to improve detection of the G6PD deficiency in the newborn population in the RNM, especially in the undefined neonatal jaundice group.

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Sažetak

REFERENTNE VRIJEDNOSTI ZA KVANTITATIVNO ISPITIVANJE G6PD DEFICITA KOD NOVOROĐENČADI IZ REPUBLIKE SJEVERNE MAKEDONIJE

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Glukoza-6-fosfat dehidrogenaza je ključni regulatorni enzim u pentoza-fosfatnom ciklusu koji sudjeluje u stvaranju reduciranih ekvivalenata za održavanje staničnog redoks statusa. Aktivnost enzima G6PD ključna je u zaštiti stanica od oksidativnog stresa. Deficit glukoza-6-fosfat dehidrogenaze (G6PD) prepoznat je kao najčešća nasljedna enzimopatija u svijetu. U Republici Sjevernoj Makedoniji (RSM) deficit glukoza-6-fosfat dehidrogenaze je rijetko istraživan. Štoviše, iz RSM-a ne postoje izvješća o kvantitativnom ispitivanju G6PD u novorođenčadi.

Cilj: Cilj našeg istraživanja bio je odrediti referentne vrijednosti za razinu G6PD u eritrocitima novorođenčadi iz Republike Sjeverne Makedonije. U tu svrhu odabrano je osamdeset i dvoje zdravih novorođenčadi i testirano na G6PD kvantitativnom spektrofotometrijskom metodom.

Rezultati: Srednja vrijednost ± SD kvantitativne vrijednosti G6PD u ispitivanoj skupini bila je 229,12 ± 24,2 mU/10^{9}Er u rasponu od minimalno 191,7 do maksimalno 288 te medijan od 228,0 mU/10^{9}Er, vrijednosti koje su bile znatno niže od unaprijed postavljenih referentnih vrijednosti dijagnostičkog testa u uporabi.

Zaključak: Pretpostavili smo da ćemo uspostavljanjem specifične referentne vrijednosti (raspona) za ciljnu populaciju i za odgovarajući dijagnostički test dobiti povećanu osjetljivost testa. To bi pomoglo optimizirati otkrivanje novorođenčadi s nedostatkom G6PD, hemizigota za blage varijante deficita i ženskih heterozigota na deficit G6PDa.

Ključne riječi: DEFICIT GLUKOZA-6-FOSFAT DEHIDROGENAZE, KVANTITATIVNO ISPITIVANJE, REFERENTNE VRIJEDNOSTI, REPUBLIKA SJEVERNA MAKEDONIJA

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