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Evaluation of Lymphocyte Subgroups in Children with Glucose-6-Phosphate Dehydrogenase Deficiency

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Glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency is an inherited disease estimated to be carried by 400 million people. Although it is more common in boys, it can also be seen in girls.[1] Glucose-6-phosphate dehydrogenase catalyzes the first reaction in the pentose phosphate pathway, takes part in the formation of reduced nicotinamide adenine dinucleotide phosphate (NADPH), and protects cells from oxidative stress. The pentose phosphate pathway is the only source of NADPH for erythrocytes. Erythrocytes need G6PD to be protected from oxidative damage and hemolysis.[2] Glucose-6-phosphate dehydrogenase is also necessary for other blood cells, and in case of deficiency, these cells are also affected. There are few studies on this subject and its clinical results in the literature, and some of them contain conflicting results.

In G6PD-deficient mice, mortality increases with cytokine release in severe inflammation due to endotoxemia, but mortality is not affected in the severe sepsis model.[3] In addition to studies that have a higher prevalence and incidence of G6PD deficiency in newborns followed up with a diagnosis of sepsis and consider G6PD deficiency as a risk factor for sepsis, there are also studies that found the rate of sepsis to be similar to the control group.[4,5] Glucose-6-phosphate dehydrogenase enzyme levels also affect the severity of coronavirus disease 2019 infection.[6]

As a result of hemolysis, immune system cells may differentiate, and their functions may change. In patients with chronic hemolysis, the phagocytosis ability of neutrophils and macrophages is also reduced. Increased free heme in plasma can affect proinflammatory or anti-inflammatory cell differentiation.[7] In patients with G6PD deficiency, the enzyme level in neutrophils and, as a result, the formation of reactive oxygen radicals were found to be lower than in healthy individuals. However, the bactericidal activity of neutrophils is not affected, probably because of the diurnal fluctuations of the G6PD level during the day and thus sufficient NADPH production.[8] Glucose-6-phosphate dehydrogenase deficiency also affects monocyte/macrophage polarization in humans.[9] Schilirò et al[10] reported that the T-lymphocyte subpopulation changes and the ratio of CD4/8 during hemolysis in children with G6PD deficiency reverses.

In this retrospective study, we investigated the difference in cellular immunity by identifying lymphocyte subgroups in children with G6PD deficiency. Twenty-three children aged 0-18 years were included in the study. The lymphocyte subgroup levels of 23 cases, including 16 favism, 4 neonatal hyperbilirubinemia, 1 acute hemolytic attack due to infection, and 2 asymptomatic cases, were evaluated according to the age-appropriate reference range.[11] In 3 patients, lymphocyte subsets were measured during acute hemolytic attack and the values were within the normal reference range. In the remaining 20 patients, the values were measured outside the attack. Among these, an increase in CD8-positive cells was detected in 4 patients and a decrease in CD4-positive cells was detected in 4 patients. Two of them had both CD8 increase and CD4 decrease. The number of CD19-positive cells was low in 5 patients. Among patients with acute hemolytic anemia, CD8-positive cells in 3 patients, natural killer cells in 2 patients, and CD4/CD8 ratio in 3 patients were below normal values.

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Table 1. Lymphocyte Subgroups of the Patients

Patient	Age (years)	Gender	WBC (/μL)	NEU (/μL)	CD3 % (n)	CD4 % (n)	CD8 % (n)	CD4/8 (n)	CD19 % (n)	NK % (n)
1	4.5	Male	6759	3550	75 (43-76)	34 (23-48)	25 (14-33)	1.4 (0.9-2.9)	22 (14-44)	12 (4-23)
2	7	Male	6470	3290	**86** (55-78)	32 (27-53)	**17** (19-34)	1.9 (0.9-2.6)	14 (10-31)	22 (4-26)
3	4.5	Male	6570	4470	**77** (43-76)	**12** (23-48)	**48** (14-33)	**0.2** (0.9-2.9)	**5** (14-44)	14 (4-23)
4	6.5	Male	9200	3480	N/A	29 (27-53)	**17** (19-34)	1.7 (0.9-2.6)	N/A	19 (4-26)
5	1.5	Male	10 430	2085	73 (39-73)	45 (25-50)	23 (11-32)	1.9 (0.9-3.7)	20 (17-41)	**2** (3-16)
6	1	Male	11 100	3490	55 (54-76)	**30** (31-54)	21 (12-28)	1.4 (1.2-3.9)	39 (15-39)	4 (3-17)
7	6	Male	7160	3140	79 (55-78)	36 (27-53)	32 (19-34)	1.1 (0.9-2.6)	**9** (10-31)	7 (4-26)
8	9.5	Male	7680	5020	**83** (55-78)	38 (27-53)	**39** (19-34)	0.9 (0.9-2.6)	**9** (10-31)	7 (4-26)
9	5.5	Male	9040	4400	59 (55-78)	38 (27-53)	**15** (19-34)	2.5 (0.9-2.6)	25 (10-31)	5 (4-26)
10	15	Male	4740	1910	**51** (52-78)	**21** (25-48)	20 (9-35)	1.0 (0.9-3.4)	12 (8-24)	22 (6-27)
11	3	Male	12 400	4310	68 (43-76)	36 (23-48)	25 (14-33)	1.4 (0.9-2.9)	31 (14-44)	10 (4-23)
12	1.5	Male	8510	2110	**84** (39-73)	34 (25-50)	19 (11-32)	1.7 (0.9-3.7)	28 (17-41)	8 (3-16)
13	3	Male	7590	3400	63 (43-76)	38 (23-48)	21 (14-33)	1.8 (0.9-2.9)	15 (14-44)	10 (4-23)
14	3	Male	5400	1950	72 (43-76)	43 (23-48)	22 (14-33)	1.9 (0.9-2.9)	22 (14-44)	**2** (4-23)
15	16	Male	7410	3970	81 (55-83)	45 (28-57)	35 (10-39)	1.2 (1-3.6)	6 (6-19)	22 (7-31)
16	2.5	Male	7580	3050	68 (43-76)	40 (23-48)	22 (14-33)	1.8 (0.9-2.9)	19 (14-44)	5 (4-23)
17	7	Male	5750	2430	73 (55-78)	42 (27-53)	27 (19-34)	1.5 (0.9-2.6)	**8** (10-31)	12 (4-26)
18	8.5	Male	6360	2630	70 (55-78)	40 (27-53)	27 (19-34)	1.4 (0.9-2.6)	11 (10-31)	16 (4-26)
19	1.5	Male	5920	2080	57 (39-73)	41 (25-50)	12 (11-32)	3.5 (0.9-3.7)	24 (17-41)	14 (3-16)
20	5	Male	7820	4660	62 (55-78)	**19** (27-53)	**37** (19-34)	**0.5** (0.9-2.6)	19 (10-31)	8 (4-26)
21	3	Female	10 200	4980	**77** (43-76)	25 (23-48)	**41** (14-33)	**0.6** (0.9-2.9)	**7** (14-44)	12 (4-23)
22	1	Male	10 600	2720	64 (54-76)	33 (31-54)	26 (12-28)	1.2 (1.3-3.9)	25 (15-39)	8 (3-17)
23	2	Male	8560	2880	55 (43-76)	27 (23-48)	23 (14-33)	1.1 (0.9-2.9)	34 (14-44)	8 (4-23)

N, normal range; N/A, not available; NEU, neutrophil; NK, natural killer cell; WBC, white blood cell. Bold values signify the values outside the normal range.

CD3-positive cells increased in 5 patients and decreased in 1 patient (Table 1). In the correlation analysis performed between lymphocyte subgroups and G6PD levels, no statistically significant relationship was found between the groups.

As a result, in 56.5% of the children with G6PD deficiency, the lymphocyte subgroup values measured outside the acute hemolytic attack were lower or higher than the normal reference values. The lack of a healthy control group, one-time measurement of lymphocyte subsets, and the lack of immunoglobulin values are the limitations of the study. It should be kept in mind that lymphocyte subset changes can be seen even outside of hemolytic attack in children with G6PD deficiency. These children should be evaluated for accompanying cellular and humoral immune abnormalities, even outside the hemolytic attack.

Ethics Committee Approval: Ethical Committee Approval was obtained from the Sakarya University Faculty of Medicine Ethics Committee for the study (Approval date: 05.03.20. Issue: 71522473/050.01.04/60).

Informed Consent: Informed consent was not obtained because it was a retrospective study.

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