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Original Article MICROBIOLOGY

The role of parvovirus B19 infection in frequently ill children

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ABSTRACT

OBJECTIVE: Parvovirus B19 is a very common infection, especially in school-age children, with its rapid spread. In the present study, Parvovirus B19 infection was detected in frequently ill nursery children. The present study aimed to determine the seroprevalence value, to determine whether there is an active infection and to determine to what extent it affects the relevant immune system parameters, to determine whether the obtained data will contribute to the epidemiology of childhood Parvovirus B19 infections in our country and also, to determine whether it is a reason for children to become ill frequently.

METHODS: Parvovirus B19 DNA test results of 112 children aged 2–6 years who were grouped as frequently ill and infrequently ill and who went to nursery and kindergarten were examined quantitatively with the Real-Time PCR Method. Parvovirus B19 IgG and Parvovirus B19 IgM antibody presence was investigated with the ELISA Method. Flow Lymphocyte subgroups were analyzed with the Cytometry Method.

RESULTS: Among the 112 patients who were included in the study, 105 (93.7%) Parvovirus B19 DNA results were negative and 7 (6.3%) were positive. Parvovirus B19 IgG test results were negative in 108 (96.4%) patients and positive in 4 (3.6%). When the Parvovirus B19 IgM results were evaluated, 109 (97.3%) were determined as negative and 3 (2.7%) positive. Natural Killer Cells (NK) from patients with positive Parvovirus B19 DNA, Parvovirus B19 IgG, and IgM were detected outside the normal limit value ranges in CD25, CD19, HLA DR, CD3, CD45RO, and CD8 values.

CONCLUSION: No significant relationships were detected between frequent illness and Parvovirus B19 infection, the infection did not significantly affect the immunodeficiency parameters, and although it is already known that Parvovirus B19 infection peaks every 3–4 years, the study did not coincide with this period of Parvovirus B19 infection.

Keywords: Children; diagnosis; ELISA; flow cytometry; parvovirus B19.

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Human Parvovirus B19 (HPV B19) infection is a common infection on a global scale, with no geographical boundaries or ethnic origins, and is more common in childhood than in adults with adult seroprevalence rates between 70–85% [1]. HPV B19 is a single-stranded DNA virus that multiplies in erythroblasts in the bone marrow. In addition to causing acute infection, it can persist in different cell types throughout life [2].

HPV B19 is a respiratory virus that causes symptoms such as fever, headache, malaise, and myalgia as well as

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clinical manifestations such as Erythema Infectiosum (EI) (Fifth Disease, Slapped Cheek Syndrome) and oligoarthritis [3–5]. Infection is more common at the end of winter and the beginning of summer. Seroprevalence might vary between 2–10% in children under five years of age [4]. It has been reported that childhood rashes are frequently detected in schools and nurseries because of the easy spread of the virus, affecting approximately 50% of school children and 20% of school personnel [6, 7].

HPV B19 was first discovered in 1974 in England by Cossart et al. [8], who evaluated the tests for Hepatitis B Virus Surface Antigen (HBsAg) in the sera samples that were taken from 11 individuals and identified a novel virus similar to existing Parvoviruses under electron microscopy, which was described as a Parvovirus-Like Agent. The virus was later named Parvovirus B19 because it was discovered in the B19 well of the microtiter plate in the study. Initially described as a Parvovirus-Like Agent or Human Parvovirus, this virus was called Parvovirus B19 (PV B19) by the International Committee on Taxonomy of Viruses (ICTV) in 1985 when it was identified as a member of the Parvoviridae family [9]. HPV B19 is the only accepted member of the Erythroparvovirus genus that shows tropism with erythroid progenitor cells [10].

The seroprevalence range of IgG antibodies in HPV B19 infection commonly seen in humans is 2–15% in children aged 1–5 years and 15–60% in children aged 6–19 years [1, 11]. This rate is close to 60% in adults and increases with age [12]. Infection is more common in late winter and early spring. The infection rate reaches epidemic levels every 3–4 years, and transmission of the infection to seronegative individuals is quite common during outbreaks. For this reason, an increase in the number of children with EI and transient aplastic crisis may be detected in the community. The recurrence rate of HPV B19 infection outbreaks in school or home environments is approximately 50% in children and approximately 20–30% in teachers [13, 14]. The virus is usually transmitted through close contact. Although the transmission rate is 50% in household contacts, this is 10–60% in children with school or daycare contacts [15, 16].

Virus-specific IgM antibodies are found during the transient aplastic crisis when the reticulocyte count is at its lowest level and IgG is formed during the 10 days after the aplastic crisis [11]. IgM antibody begins to be produced 8–12 days after infection and plays an active roles in clearing viremia. The presence of IgM-type antibodies continues for 3–6 months [5, 17]. The production of IgG antibodies begins a few days after the production of IgM antibodies, after IgM antibodies. Although the level of IgM antibodies decreases after months or weeks, IgG antibodies continue to exist [18]. Virus-specific anti-HPV B19 IgG begins to be produced on the 16th day following the onset of infection, which is evidenced by the emergence of arthralgia and EI, which are partly mediated by the accumulation of antigen-antibody complexes. It is already known that IgG, which is specific to the virus, controls HPV B19 infection and restores erythroid cell production, might be detected in blood samples of individuals for a lifetime and protects the individual against a secondary infection [5, 18, 19]. Itching, rash, and arthralgia can be seen 17–18 days after the infection. The recovery process, which begins with the appearance of an IgM antibody 10–12 days after the infection, coincides with the period when the viral load is at its highest [11]. The humoral immune response occurs in healthy individuals who are infected with HPV B19 [20]. The reticulocyte count is quite low at the time of viremia during which a temporary decrease in hemoglobin level also occurs. Reticulocytes reach normal levels after 7–10 days [21]. With the use of PCR tests, HPV B19 DNA might be detected in blood samples for months or even years from the beginning of the infection in individuals with healthy immune systems, despite the presence of neutralizing antibodies [22–26].

Along with humoral immunity, cellular immunity also contributes to the control of infection [27]. After the infection, Classification determinant 8 (CD8) T lymphocytes, which present antigens and recognize the infected cell-like dendritic cells, are detected on the surface of the infected cell. Once activated, CD8 T cells serve as memory cells for a long time [28]. The activation of CD8 T-Cells against HPV B19 epitopes and their detection for up to 2 years following the infection contributes to the T-Cells keeping pathogenic cells un-

Highlight key points

- No significant relationships were detected between frequent illness and Parvovirus B19.
- Children with Parvovirus B19 infection had lower CD25 levels compared to those without the infection.
- The majority of children in the study (93.7%) tested negative for Parvovirus B19 DNA.

der control for a long time [29]. During the HPV B19 infection period, Classification determinant 36 (CD36) EPCs show cytopathic properties [30]. Although HPV B19 infects various tissues and cells, including erythroid Classification determinant 34 (CD34) cells, synovial tissue, hepatic tissue, myocardial endothelial cells, and tonsil tissue, it does not cause an active viral infection in these cells [31–35].

MATERIALS AND METHODS

The Istanbul University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 16.01.2022, number: 1411396) and this study was conducted in accordance with the Declaration of Helsinki.

In the present study, HPV B19 DNA presence was quantitatively investigated by Real-Time PCR method, HPV B19 DNA test was done using the Artus Parvo B19 RG PCR (QIAGEN GmbH, Hilden Germany) PCR kit on the ROTOR-GENE Q (QIAGEN GmbH, Hilden Germany) device in a total of 112 pediatric patients aged 2–6 years who applied to the General Pediatrics Clinic of the Department of Child Health and Diseases of Istanbul University, Istanbul Faculty of Medicine, were evaluated as frequently ill and infrequently ill, and who went to nursery and kindergarten in blood samples brought to the laboratory of the Department of Medical Microbiology, Virology and Basic Immunology, Istanbul University, Istanbul Faculty of Medicine. The presence of HPV B19 IgG and HPV B19 IgM antibodies was investigated with the ELISA Method using the SERION ELISA Classic Parvovirus B19 IgG/IgM (Serion GmbH, Würzburg, Germany) kit on the DiaSorin ETI-Max3000 (DiaSorin S.p.A. Saluggia, Italy) Device. Lymphocyte subgroups were analyzed with Flow Cytometry using Navios EX Software (Beckman Coulter, Brea, CA, USA). The data of the children were recorded in the anamnesis form during the interview with the parents. Frequent illness criteria in children were determined as fever over 38 degrees and 5 or more fevers per year.

Data Analysis

The IBM SPSS 21 for Windows (IBM Corp., Armonk, NY, USA) was used to analyze the study data. The p-value obtained was considered significant when it was less than 0.05.

Table 1. Percentage distribution of patients' HPV B19 DNA, IgG, and IgM results according to whether they become ill frequently or not

	Frequently ill (n=58)	Not frequently ill (n=54)	Percentage (%)
HPV B19 DNA			
Positive	3	4	6.3
Negative	55	50	93.7
HPV B19 IgG			
Positive	1	3	96.4
Negative	57	51	3.6
HPV B19 IgM			
Positive	1	2	2.7
Negative	57	52	97.3

DNA: Deoxyribose nucleic acid; HPV B19: Human parvovirus B19; n: Number of patients.

RESULTS

Patients who applied to the General Pediatrics Clinic and were included in the study had applied to the clinic with complaints of cough, fever, runny nose, sore throat, shortness of breath, rash on the body, redness on the cheeks, frequent illnesses, and itching on the face and trunk. Based on the clinical data, 11 of the 112 patients had allergies, 10 had a known disease (heart murmur, asthma, multicystic kidney, hepatosplenomegaly, meningitis 1 year ago, allergic rhinitis), and 14 patients had a history of previous hospitalization.

Among the children who were included in the study, 36 (32.1%) were girls and 76 (67.9%) were boys. Based on the information received from the parents, it was learned that 58 (51.8%) of the children had frequent infections and 54 (48.2%) did not have frequent infections.

When the HPV B19 DNA results of 112 patients were evaluated, 105 (93.7%) were negative and 7 (6.3%) were positive. The percentage distribution of the patients according to sex, whether they had frequent infections or not, HPV, B19 DNA PCR, HPV B19 IgG, and HPV B19 IgM results are given in Table 1.

As seen in Table 1, the analysis of whether there was a significant difference between the frequently ill and not frequently ill groups in terms of HPV B19 DNA positivity (Chi-Square) could not be done because of the in-

Table 2. The percentage distribution of those who had HPV B19 infection (n=112)

	Percentage
Negative	91.1
Positive	8.9
Total	100.0

HPV B19: Human parvovirus B19; n: Number of patients.

Table 3. The number of those who had HPV B19 infection according to the frequency of becoming ill

Frequent illness	Negative	Positive	Total
Yes	49	5	54
No	53	5	58
Total	112	10	112

HPV B19: Human parvovirus B19.

sufficient number of cases. The analysis of whether there was a significant difference between the frequently ill and not frequently ill groups in terms of HPV B19 IgG positivity (Chi-Square) could not be done because of the insufficient number of cases. The analysis of whether there is a significant difference between the frequently ill and not frequently ill groups in terms of HPV B19 IgM positivity (Chi-Square) could not be done because of the insufficient number of cases.

Patients with positive HPV B19 DNA, HPV B19 IgG, and HPV B19 IgM values were defined as those with HPV B19 infection. Information about these patients is given in Tables 2 and 3.

In the evaluation made by using the Chi-Square Test for children who were positive for any of the HPV B19 DNA, HPV B19 IgG, and HPV B19 IgM values (who had HPV B19 infection) and separated according to whether they had frequent infections or not, no statistically significant differences were detected (p=0.9). In this context, the fact that the children had the HPV B19 virus at any point in their lives did not cause them to have frequent infections.

Among the 112 patients, 105 (93.7%) had negative HPV B19 DNA results and 7 (6.3%) had positive HPV B19 DNA. When the HPV B19 IgG results of 112 patients were evaluated, 108 (96.4%) were negative and 4 (3.6%) were positive. Among the patients with HPV B19 IgG positivity, 3 were male and went to kindergarten and 1 was a female and went to daycare. When the HPV B19 IgM results of 112 patients were evaluated, 109 (97.3%) were negative and 3 (2.7%) were positive. Among the 3 patients with HPV B19 IgM positivity, 2 were male and went to kindergarten and 1 was a female and went to daycare. Only 1 of the 3 patients who had HPV B19 IgM positivity had a history of frequent illness. The female patient who had a positive HPV B19 IgM test and was going to nursery school had positive HPV B19 DNA and HPV B19 IgG tests. Three patients had positive HPV B19 IgG values and positive HPV B19 DNA. Two of these three patients were attending kindergarten and one was attending nursery school. Two of those who went to kindergarten were boys and the one who went to nursery school was a girl.

Lymphocyte subgroups of 112 patients were examined. The results outside the normal ranges were detected in natural killer cells (NK), Classification determinant 25 (CD25), Classification determinant 19 (CD19), Human leukocyte antigen DR isotype (HLA DR), Classification determinant 3 (CD3), Classification determinant 45RO (CD45RO), and Classification determinant 8 (CD8) values of patients with positive HPV B19 DNA, HPV B19 IgM, and IgG. These results are detailed in Tables 4, 5 and 6.

The Independent Samples T-test was used for frequently ill and not ill groups and no significant differences were detected between the ages. Frequent illness was not associated with age (p=0.33). The mean CD25 value of frequently ill children was 1.84±0.75 IU/mL. The mean CD25 value of children who do not frequently become ill was 1.94±0.76 IU/mL. No significant differences were detected between the groups in terms of CD25 (p=0.23). The mean IgG value in children who become ill frequently was 957.57±254.993 IU/mL. The mean IgG value in children who do not frequently become ill was 971.71±204.723 IU/mL. No significant differences were detected between the groups in terms of IgG (p=0.37). The mean IgM value among children who became ill frequently was 117.591±49.28 IU/mL. The mean IgM value among children who did not become ill frequently was 123.806±37.67 IU/mL. No significant difference was observed between the groups in terms of IgM (p=0.23).

Table 4. HPV B19 DNA-positive patients' lymphocyte subgroup results

	Sex	Frequent illness	NK (10–20)	CD25 (2–6)	CD19 (9–25)	HLA DR (18–38)	CD3 (50–75)	CD45RO (16–38)	CD8 (15–35)
P1	Male	No		1	27				
P2	Male	No				17			
P3	Female	No	3	1					
P4	Male	Yes	29			9			42
P5	Male	Yes		1		17			
P6	Female	No	2	1		17		13	
P7	Female	Yes		1					

NK: Natural killer cells; CD: Classification determinant; HLA DR: Human leukocyte antigen-DR isotype; HPV B19: Human parvovirus B19.

Table 5. HPV B19 IgM-positive patients' lymphocyte subgroup results

	Sex	Frequent illness	NK (10–20)	CD25 (2–6)	CD19 (9–25)	HLA DR (18–38)	CD3 (50–75)	CD45RO (16–38)	CD8 (15–35)
P6	Female	No	2	1		17		13	
P8	Male	Yes	6	1					42
P9	Male	No	7	1			76		

NK: Natural killer cells; CD: Classification determinant; HLA DR: Human leukocyte antigen-DR isotype; HPV B19: Human parvovirus B19.

Table 6. HPV B19 IgG-positive patients' lymphocyte subgroup results

	Sex	Frequent illness	NK (10–20)	CD25 (2–6)	CD19 (9–25)	HLA DR (18–38)	CD3 (50–75)	CD45RO (16–38)	CD8 (15–35)
P1	Male	No		1	27				
P2	Male	No				17			
P6	Female	No	2	1		17		13	
P10	Male	Yes	7				77	40	

NK: Natural killer cells; CD: Classification determinant; HLA DR: Human leukocyte antigen-DR isotype; HPV B19: Human parvovirus B19.

Based on the T-test results of the groups that had and did not have HPV B19 infection, the CD25 average of children with HPV B19 infection is 1.30±0.48 IU/mL. The CD25 average of children without HPV B19 infection is 1.95±0.75 IU/mL. In this context, the CD25 value was observed to be lower in children with HPV B19 infection than in children without HPV B19 infection. This difference was statistically significant ($p<0.05$).

DISCUSSION

In the present study, HPV B19 DNA was quantitatively evaluated in 112 patients by using the RT-PCR Method. A total of 112 patients were classified according to whether they became ill frequently and whether they went to nursery or kindergarten. HPV B19 DNA was detected as positive in seven of these patients (6.3%). One of the seven patients who were detected as HPV

B19 DNA positive went to nursery, and two went to nursery and became ill frequently. Only three (5.1%) of the 58 patients who became ill frequently had HPV B19. Since the number of cases in which HPV B19 DNA was detected between the patient groups who became ill frequently and those who did not become ill statistically was not suitable for the Chi-Square Test, this test could not be used.

In the present study, when the HPV B19 IgG and HPV B19 IgM test results of 112 patients were evaluated, only four (3.5%) had positive HPV B19 IgG, and three patients (2.6%) had positive HPV B19 IgM tests and only one patient (0.9%) had positive HPV B19 IgM and HPV B19 IgG at the same time. The seroprevalence rate of HPV B19 IgG antibodies (3.5%) in the present study was consistent with the literature data when age ranges were also taken into account [1, 11].

One of the four patients with positive HPV B19 IgG was a male who was frequently ill and went to kindergarten, one was a female who was not frequently ill and went to kindergarten, and the other two patients were male patients who were not frequently ill. Only one of the 60 patients who were frequently ill was positive for HPV B19 IgG (1.6%) and had had the infection before. Since the number of HPV B19 IgG positive cases between the patient groups who were frequently ill and those who were not, statistically, was not suitable for the Chi-Square Test, this test could not be used.

One of the 3 patients with positive HPV B19 IgM was a female patient who was frequently ill, attending kindergarten, the other two were male, one was a male patient who was frequently ill and attending nursery school, and the remaining male patient was a male patient who was not frequently ill and attending nursery school. Only one of the 60 patients with frequent illness was positive for HPV B19 IgM (1.6%) and was in the early stages of infection. Since the number of HPV B19 IgM-positive cases between the patient groups with frequent illness and those without illness was statistically inappropriate for the Chi-Square Test, this test could not be used.

Lymphocyte subgroups of 112 patients were evaluated by Flow Cytometry. The results of CD25 values in 7 patients with positive HPV B19 DNA were evaluated and the CD25 values of patients with HPV B19 infection were significantly lower than those without ($p<0.05$).

In a previous study that was conducted by Türk Dağı et al. [36] to determine the presence of HPV B19 IgG in children aged 0–17, they aimed to determine HPV B19 seroprevalence in children and healthy blood donors using the ELISA test. They found the seroprevalence rate to be 20.7% in children aged 0–17 and 36% in adults aged 18–60. They found the HPV B19 IgG seropositivity rate of pediatric patients aged 0–4 to be 15.8%. In this context, they suggested that the reason why the seroprevalence rate in children aged 0–4 was higher than in studies conducted both in the world and in Turkey and the rates in other age groups were lower was because of population differences.

In the study that was conducted by Vilibick-Cavlek et al. [37] in Croatia between 2010–2021, they aimed to determine HPV B19 IgG and IgM antibodies from blood samples taken from 1538 patients and to analyze the seroprevalence value of HPV B19 infection. They found the rate of HPV B19 IgG antibodies in the participants as 64.1%. They found the HPV B19 IgG positivity rate in children aged 6 months to 9 years as 30% and in adolescent and child patients as 42.4%. They found the HPV B19 IgM positivity rate as 4% in the youngest age groups. They also reported that the seroprevalence value increased with age.

In their study, Bouafsoun et al. [38] aimed to evaluate the seroprevalence of HPV B19 IgG and HPV B19 IgM antibodies in 257 children aged 7–15 years with fever and rash. They found the seroprevalence rates of HPV B19 IgG antibodies to be 38.2% in children aged 19 months-4 years and 53.5% in children aged 4.5–9 years. They found the seroprevalence rates of HPV B19 IgM antibodies to be 7.9% in children aged 19 months-4 years and 17% in children aged 4.5–9 years. They suggested that viral infection is acquired in early childhood and that the seroprevalence value increases with age. We believe that the reason why the HPV B19 IgG positivity rate was found to be 3.5% and the HPV B19 IgM positivity rate was found to be 2.6% in the present study is that they have not encountered the HPV B19 virus before or recently, the pediatric patients are young, and families and children do not come into contact with many people because of the isolation measures and mask use because of the pandemic we have recently experienced, which prevents the transmission of HPV B19 infection.

In their study conducted between 2006 and 2009, Exindari et al. [39] aimed to determine the epidemiological and clinical characteristics of HPV B19 infections seen

in the northern region of Greece. In their study in 2006, only three out of 17 patients (17.6%) and in 2007, 16 out of 29 patients (55.2%) were diagnosed with acute infection with HPV B19 DNA and HPV B19 IgM antibodies. In 2009, they determined this rate as 14.3%. In their study, they observed that the incidence of HPV B19 varies annually. We believe that the reason why HPV B19 IgM antibodies were detected in only three out of 112 pediatric patients (2.7%) in the present study is because of the attention paid to protective measures during the pandemic process and the small number of cases.

The present study suggests that children with HPV B19 infection may be prone to transmitting the infection if their CD25 value is significantly low. However, multicenter studies with a larger number of cases are needed to strengthen the level of evidence.

Isa et al. [40] made an immunological examination of individuals with acute HPV B19 infection to explain the persistence of the infection and to determine whether they suffered from immune deficiency. They detected low NK and CD19 cell levels in some patients. However, they could not reach conclusions indicating a general immune deficiency disorder in the patients as a result of this evaluation. In the present study, NK values were detected to be low in five patients with HPV B19 infection. When the literature studies conducted so far were reviewed, no literature study related to HPV B19 infection was found in children who became ill frequently and children who did not become ill frequently.

Conclusion

The present study was conducted to determine the seroprevalence of HPV B19 in children in kindergartens and nurseries who became ill frequently, to evaluate whether the virus was already present, and to determine whether this virus caused immune deficiency disorder. However, because of the single-center nature of the present study, the small number of cases, and the narrowness of our case group, limited data were obtained as a result of the study.

In conclusion, no significant relationships were detected between frequent illness and HPV B19 infection, the infection did not significantly affect the immune deficiency parameters, and although it is already known that HPV B19 infection peaks every 3–4 years, the study did not coincide with this period of HPV B19 infection. However, we believe that conducting studies with a large number of cases on the subject will contribute to obtaining better data to improve the results obtained.

Ethics Committee Approval: The Istanbul University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 16.01.2022, number: 1411396).

Informed Consent: Written informed consents were obtained from patients who participated in this study.

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