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# Epstein–Barr Virus Infection in Children Following Acute SARS-CoV-2 Infection

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ABSTRACT

BACKGROUND.
Epstein–Barr virus (EBV), a human herpesvirus with potent B cell growth transforming ability, induces multiple cellular immune responses in the infected host. According to the most recent evidence, the Epstein-Barr virus is characterized by lifetime latency in B cells and intermittent recrudescence of lytic infection triggered by stresses. Furthermore, several investigations have hypothesized that autoimmune mechanisms and the persistence of SARS-CoV-2 virus fragments induce the development of long-term COVID-19. Therefore, other latent host viruses, such as Epstein-Barr virus, play an important role.

OBJECTIVES
The present study aimed to provide insight into clinical-laboratory aspects in pediatric patients with EBV after COVID-19.

METHODS
This prospective study was conducted from November 2021 to November 2022 at the Tbilisi state medical university G. Zhvania Pediatric Academic Clinic. 1- 3 years old, 81 outpatients with EBV infection (male 42 [51,8%] and female 66 [48,1%]) were distributed into basic (42 patients after acute SARS-CoV-2 infection) and control groups (32 patients without a history of COVDI-19). All study subjects had EBV infection markers, and conventional clinical/laboratory indices evaluated.

RESULTS
The incidence of EBV infection is high (60.4%) in the post-COVID-19 period. Tonsil enlargement, cough, and splenomegaly were more prevalent in the basic group than in the control group: 85,7% vs. 40,6%, 81,6%, 85,7% vs. 20,5%, and 79,5% vs. 25,6%, respectively.

CONCLUSIONS
The increased incidence of EBV infection in children after the COVID-19 pandemic is a challenge requiring optimized clinical care strategies.

KEYWORDS
COVID-19; EBV infection; SARS-CoV-2 infection.

## BACKGROUND

Epstein–Barr virus (EBV), a human double-stranded DNA herpesvirus with potent B cell growth transforming ability, induces multiple cellular immune responses in the infected host.[1-3]

According to the latest data, the Epstein–Barr virus is characterized by lifelong latency in B cells and intermittent recrudescence of lytic infection caused by stressors.[4] Some studies have suggested that autoimmune factors and the persistence of viral fragments of the SARS-CoV-2 virus cause the development of long-term COVID-19.[5] The role of other latent host viruses, such as Epstein–Barr virus, is significant.

The COVID-19 pandemic is one of the biggest challenges that has emerged concerning the health of children. As of February 7, 2023, there have been 754,816,715 confirmed cases and 830,232 deaths globally.[6] Since the beginning of the epidemic until February 2023, about 15.4 million children in the United States have tested positive for COVID-19.[7]

The first case of COVID-19 in Georgia was confirmed on February 26, 2020.[8] COVID-19 was the leading cause of morbidity in children under 15 in 2021 (1025.6 per 100,000) with high hospitalization and mortality rate (1%).[8]

According to accessible data, acute SARS-CoV-2 infection can contribute to the development of other diseases, including Epstein-Barr virus infection.[5]

In the present study, we aimed to provide insight into clinical-laboratory aspects in pediatric patients with EBV after COVID-19.

## METHODS

This study was conducted from November 2021 to November 2022 at the Tbilisi state medical university G. Zhvania Pediatric Academic Clinic. 1- 3 years old, 81 outpatients with EBV infection (male 42 [51,8%] and female 66 [48,1%]) were distributed into basic (42 [60.4%] patients

after acute SARS-CoV-2 infection) and control groups (32 [39.5%] patients without a history of COVDI-19).

The following investigations were performed in all study patients: full blood count (FBC), C-reactive protein (CRP), EBV serology (anti-viral capsid antigen IgM and IgG [anti-VCA IgM and anti-VCA IgG]), heterophile antibodies IgM [HA-IgM], anti-EBV nuclear antigen IgG [anti-EBNA IgG], and anti-early antigen IgG [anti-EA IgG]), and abdominal ultrasound.

Descriptive statistics and T-tests were used for statistical analysis of data. A p-value under 0.05 was considered statistically significant.

## RESULTS

The clinical characteristics of study patients are represented in Table 1.

TABLE 1. Clinicall characteristics of all study patients

| Symptoms/signs | *Basic group N=49* | *Control group N=32* |
|---|---|---|
| Fever, n, (%) | 49 (100) | 32 (100) |
| Nasal obstruction, n, (%) | 37 (94.8) | 30 (61.2) |
| Neck lymphadenopathy, n, (%) | 44 (89.7) | 13 (40.6) |
| Enlarged tonsils/tonsil stones, n, (%) | 42 (85.7) | 13 (40.6) |
| Cough, n, (%) | 40 (81.6) | 8 (20.5) |
| Splenomegaly, n, (%) | 39 (79.5) | 10 (25.6) |
| Snoring during the sleep, n, (%) | 32 (63.3) | 20 (51.2) |
| Fatigue, n, (%) | 24 (48.7) | 20 (51.2) |
| Hepatomegaly, n, (%) | 22 (44.8) | 7 (21.8) |
| Abdominal pain, n, (%) | 21 (42.8) | 7 (21.7) |
| Rash, n, (%) | 20 (40.8) | 5 (15.6) |
| Headache, n, (%) | 11 (22.4) | 6 (18.7) |
| Eyelid edema, n, (%) | 7 (14.2) | 1 (3.1) |

Table 2 presents the laboratory test results in the comparator groups.

TABLE 2. Laboratory test results of studi patients

| Test | Basic group N=49 | Control group N=32 | P-vaue |
|---|---|---|---|
| WBC, x$10^9$/L, M±SD | 11.95 ± 2.48 | 10.91 ± 1.48 | <0.05 |
| Neutrophis, (%), M±SD | 35.87 ± 1.13 | 32.29 ± 0.13 | <0.05 |
| Lymphocytes, (%), M±SD | 62.0± 1.03 | 64.0± 1.21 | <0.05 |
| Atypical lymphocytes, (%), M±SD | 10.0 ± 2.2 | 9.2 ± 1,8 | <0.05 |
| Monocytes, (%),M±SD | 14 ± 1.22 | 11 ± 1.13 | <0.05 |
| Platelets, x109/L, M±SD | 243.0 ± 90 | 221.0 ± 88 | >0.05 |
| Hemogobin, g/dL, M±SD | 106 ± 10,1 | 100 ± 10,0 | <0.03 |
| CRP, mg/L, M±SD | 10.9± 12,2 | 10.7± 11,6 | <0.05 |

*Abbreviations: CRP, C-reactive protein; M±SD, mean ± standard deviation; WBC, white blood cells.*

Table 3 contains the results of EBV serological testing.

TABLE 3. Results of EBV serological testing of study patients

| Serological Markers | Basic group N=49 | Control group N=32 | P-vaue |
|---|---|---|---|
| Positive HA IgM, anti-VCA IgM, and anti-VCA IgG, n, (%) | 32 (65.3) | 27 (84.3) | <0.05 |
| Positive anti-VCA IgM, and anti-VCA IgG, n, (%) | 17 (34.6) | 5 (15.6) | <0.05 |

*Abbreviations: anti-VCA IgG, anti-viral capsid antigen IgG; anti-VCA IgM, anti-viral capsid antigen IgM; HA IgM, heterophile antibodies IgM.*

## DISCUSSION

According to the existing evidence, the incidence of EBV is high after the resolution of acute SARS-CoV-2 infection.[4] The results of the present study corroborate the trend mentioned above; we found that EBV exposure is 60.4% in patients after acute COVID-19 disease ($p<0.05$).

The distribution and frequency of clinical symptoms and signs of EBV infection in our study subjects follow the previously reported evidence.[1] Tonsil enlargement, cough, and splenomegaly were more prevalent in the basic group than in the control group: 85,7% vs. 40,6%, 81,6% vs. 20,5%, and 79,5% vs. 25,6%, respectively.

All laboratory test (hemoglobin, total white blood cells and their subtypes, and C-reactive protein) results were significantly higher in EBV-infected patients following the acute COVID-19, except platelet count. These findings back up the findings of Yanming Wu et al.[3]

EBV serological testing results were also different between comparators. The positive heterophile antibodies IgM (HA IgM) cases were significantly higher in EBV-infected patients after acute SARS-CoV-2 infection ($p<0.05$). There is no relevant literature data concerning EBV serology in children after COVID-19.

## CONCLUSIONS

The increased prevalence of EBV infection in children after the COVID-19 pandemic is an issue that requires enhanced treatment measures.

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