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Commentary

Parvovirus B19 infection in children: Is it more severe than expected?

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Human parvovirus B19 infection often manifests in the community as a mild exanthematous disease of childhood.[1] Complications such as headache, arthritis, and arthralgia occur less frequently in children compared to adults. However, certain populations including pregnant women, immunocompromised patients, and those with chronic hemolytic anemia, are at increased risk of developing serious complications due to parvovirus B19 infection.[2] It is of great importance to be aware of the potential outbreaks due to parvovirus B19 and the periodic increases in case numbers, especially in high-risk groups. Various outbreaks of parvovirus B19 have been reported worldwide at different times in non-tropical regions during winter and spring, typically lasting 3-6 months. Of the well-documented 30 erythema infectiosum outbreaks, 23 occurred between March and May, and these outbreaks affected 50 to 165 people. Furthermore, retrospective analysis of 50 years of data in North America has shown a cyclical pattern with increased disease activity approximately every 6 years, lasting for three years.[3,4]

In our center, cases identified have similarly occurred between March and May 2024, consistent with the literature (Table I). Outbreaks predominantly affect children aged 5-14 years and their close contacts, including parents and teachers.[5,6] Among the six patients, the age of the cases ranged from 15 months to 7 years. Although transmission primarily occurred via respiratory droplets, transmission through blood product transfusion, clotting factor concentrates, intravenous immunoglobulin (IVIG) infusion, and post-organ transplant donor transmission has also been reported.[7-9]

Parvovirus B19 infection can lead to erythema infectiosum, intrauterine infection with hydrops fetalis, transient aplastic crisis, myocarditis, vasculitis, hepatitis, and various neurological disorders.[10] Of our patients, two had erythema infectiosum, three had myocarditis, one had aplastic crisis, and subsequently developed hemophagocytic lymphohistiocytosis. All the patients, who presented to the clinic with various complaints between March 2024 and May 2024, required hospitalization for various reasons, and received a diagnosis of parvovirus B19 infection. There is no consensus on which symptoms warrant parvovirus PCR testing and when it is appropriate to perform this test. The patients underwent parvovirus PCR testing on the day of admission while the etiological investigations for their diagnosis were being planned.

One of the patients diagnosed with erythema infectiosum was a 5-year-old boy with T-cell acute lymphoblastic leukemia (T-ALL), presenting with fever persisting for 2 days, macular rash on the face and extremities, and swelling in the hands and feet. His parvovirus B19 PCR was markedly elevated at

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640,200,000,000 IU/mL. He received 2 g/kg of IVIG over 5 days and was discharged after a 10-day hospital stay. Follow-up parvovirus PCR testing three months later was negative. The patient also exhibited pancytopenia, but it was difficult to distinguish whether it was related to the chemotherapy he received 5 days prior or secondary to parvovirus B19 infection. Another patient presented to the hospital during the exanthematous phase of the disease with a rash noticed on the cheeks. We learned that a week before admission, the patient had non-specific complaints such as weakness, headache, and subfebrile fever during the initial viremic phase of the illness. This patient, aged 6.5 years with a diagnosis of thalassemia intermedia, also had anemia, and their parvovirus PCR resulted in 120,700,000 IU/mL. They received 2 g/kg of IVIG and were discharged after a 5-day hospital stay. Both patients were hospitalized primarily due to the need for a transfusion.

Three other patients, initially diagnosed with myocarditis, were transferred from other hospitals and admitted directly to the intensive care unit (ICU) due to signs of heart failure. These children, who had no previous health conditions, presented with acute heart failure symptoms, elevated troponin levels, and abnormal echocardiographic findings, confirming myocarditis. Upon admission, all three had elevated troponin-I and brain natriuretic peptide levels and required inotropic support, IVIG, and steroid therapy (Table I).

- The first patient, a 15-month-old girl, exhibited nasal discharge and poor appetite for ten days, followed by facial swelling and decreased urine output. Her echocardiogram showed a reduced ejection fraction (EF) of 35%. A parvovirus PCR test confirmed the diagnosis at 152,000 IU/mL. She was discharged after 18 days in the hospital, including 10 days in ICU.
- The second patient, a 5-year-old, presented with a recent onset of poor appetite, restlessness, and nocturnal episodes of crying. An echocardiogram revealed a low

Table I. Characteristics of the patients with parvovirus B19 infection

Patient no	Age	Sex	Underlying conditions	Presentation symptoms	Clinical diagnosis at admission	Parvovirus PCR (IU/mL)	Hematologic findings	Treatment	Outcome
1	5 years	M	T-cell acute lymphoblastic leukemia	Fever, macular rash, swelling in hands and feet	Erythema infectiosum	640,200,000,000	Pancytopenia	IVIG	Recovery
2	6.5 years	M	Thalassemia intermedia	Rash on the cheeks	Erythema infectiosum	120,700,000	Anemia	IVIG	Recovery
3	15 months	F	None	Facial swelling, decreased urine output	Myocarditis	152,000	Normal	IVIG and steroid	Recovery
4	5 years	M	None	Presyncope	Myocarditis	6,600	Normal	IVIG and steroid	Recovery
5	2 years	F	None	Edema in hands and feet	Myocarditis	27,480	Normal	IVIG and steroid	Recovery
6	7 years	M	Hereditary spherocytosis	Intermittent fever, palpitation	Aplastic crisis and HLH	157,000	Pancytopenia	IVIG and steroid	Recovery

F, female; HLH, hemophagocytic lymphohistiocytosis; ICU, intensive care unit; IVIG, intravenous immunoglobulin; M, male; PCR, polymerase chain reaction.

EF, and a parvovirus PCR test was 6,600 IU/mL. This patient spent five days in the ICU and an additional 10 days in the general ward.

- The third patient, a 2-year-old, had a two-week history of cough and intermittent fever, later developing edema in the hands and feet. Imaging showed bilateral pleural effusion and cardiomegaly, with an EF of 30% and a parvovirus PCR of 27,480 IU/mL. Despite treatment with IVIG and steroids, the patient had a prolonged recovery, requiring approximately 1.5 months of hospitalization, including five days in the ICU.

It is important to note that while the presence of the virus in the blood does not necessarily indicate that the myocardium is infected by the same pathogen, the clustering of parvovirus PCR-positive cases without other identifiable causes cannot be disregarded. It should also be noted that since our hospital is a tertiary referral center, myocarditis patients were referred from surrounding provinces. Therefore, it is possible that we encountered more severe cases of parvovirus B19 myocarditis within a short timeframe of two months. Due to the lack of data on how many of the myocarditis cases previously diagnosed and followed in our clinic were parvovirus PCR positive, it has not been possible for us to make comparisons with previous years.

Lastly, a 7-year-old patient with hereditary spherocytosis was admitted with intermittent fever and palpitations. The patient's diagnostic workup, prompted by pancytopenia, revealed a parvovirus PCR of 157,000 IU/mL, suggesting an aplastic crisis. Although an aplastic crisis is a known complication of parvovirus B19 in patients with chronic hemolytic anemia, persistent fever, worsening pancytopenia, and elevated ferritin levels raised concerns about hemophagocytic lymphohistiocytosis (HLH). After initiating IVIG treatment based on a preliminary diagnosis, further HLH-specific testing and bone marrow aspiration confirmed HLH. Steroids were added due to the patient's resistant fever, and the patient was discharged after 15 days without the need for intensive care.

Due to having 6 patients who tested positive for parvovirus B19 with various clinical presentations in the past few months, we organized an online meeting on May 29, 2024, to discuss the situation nationwide and share our experiences with other clinicians. Shortly after this meeting, the European Centre for Disease Prevention and Control (ECDC) issued an evaluation drawing attention to reports of increased frequency of parvovirus B19 cases in several European countries as of June 5, 2024.[11] The report highlighted significant increases in the number of pregnant women infected with parvovirus B19 in Denmark by the end of 2023 and early 2024 (higher than the increase observed in 2017), rising rates of parvovirus B19 infection among both pediatric age groups and pregnant women as well as blood donors in France, and an increased number of erythema infectiosum cases identified among pediatric populations in the Netherlands, alongside frequent detections among blood donors.[12,13] According to the report, the risk posed by parvovirus B19-related illness has been assessed across four different populations. While the infection is considered low-risk for the general population, it is deemed to be of moderate to high risk for immunocompromised individuals (such as those using immunosuppressive drugs, HIV-infected persons, cancer patients, and organ transplant recipients) and patients with chronic hemolytic anemia. Consistent with this risk assessment, the infection in patients diagnosed with hereditary spherocytosis as in one of our cases, has resulted in a more severe clinical impact compared to other patients.

In this assessment, considerations were also made regarding measures to protect populations at risk of developing severe complications due to parvovirus B19 infection. Priority was given to ensuring that healthcare workers are aware of the increasing prevalence of parvovirus B19 infection. Recommendations also include

monitoring the immunity of pregnant women working in high-risk professions, such as healthcare and teaching, where there is a heightened risk of exposure to parvovirus B19.[11]

It is important to note the periodic increases in parvovirus B19 infections and exercise caution regarding potential complications in at-risk patient groups. In the post-pandemic era, it is essential to determine whether the recent rise in parvovirus B19 infections mirrors the intermittent patterns observed prior to the pandemic or if it displays distinct characteristics. Such evaluations should be integrated into the ongoing process of diagnosing and monitoring patients over time, allowing for timely intervention and better management of potential outbreaks.

The lack of knowledge regarding the number of cases with positive parvovirus B19 PCR from previous years, the hospitalization rates due to parvovirus B19 infection, and the absence of comparisons with previous years are limitations of this study.

Ethical approval

The authors declare that they have obtained informed consent from the parents of the presented patients for their data to be included in this article.

Author contribution

The authors confirm contribution to the paper as follows: Letter conception and design: ÖY; literature review: EAÖ; draft manuscript preparation: OY, EOA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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