

Human Parvovirus B19 Infection in Children: Uncommon Clinical Presentations

Judith Barash MD¹, Doron Dushnitzky MD¹, Dalia Sthoeger MD¹, Rita Bardenstein MSc² and Yigal Barak MD¹

Division of ¹Pediatrics and ²Microbiology Laboratory, Kaplan Medical Center, Rehovot, Israel
Affiliated to the Hebrew University-Hadassah Medical School, Jerusalem, Israel

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Abstract

Background: Human parvovirus B19 is responsible for a variety of clinical syndromes, such as erythema infectiosum, non-immune hydrops fetalis, transient aplastic anemia, and arthropathies. HPV is also suspected of playing a role in the pathogenesis of various chronic inflammatory and autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, Kawasaki disease and multiple sclerosis.

Objectives: To study the age distribution and clinical presentation of patients hospitalized for human parvovirus B19 infection.

Method: We reviewed the case records of all pediatric patients with serologic evidence of HPV infection who were admitted during a 20 month period to a major community hospital.

Results: Of 128 children tested for HPV, 48 had evidence of acute infection based on the presence of immunoglobulin M antibodies; 8 patients who also had positive IgM for other viruses were excluded, thus 40 case records were studied. The mean age of the patients was 5.21 years, but 22 patients were under 4. The clinical presentations included 25 patients with fever, either recurrent or prolonged, accompanied in some by enlarged spleen, liver and lymph nodes, skin rash and arthropathy; the remaining patients were investigated for anemia, skin rash, joint complaints and hepatitis. In addition, HPV infection was documented in several well-defined clinical conditions, such as SLE, vasculitic skin lesions, acute lymphoblastic leukemia, pure red cell aplasia, and optic neuritis.

Conclusions: In a group of 40 pediatric patients exhibiting anti-HPV IgM antibodies, a younger age and less common clinical presentations were observed, furthermore 5 patients had clinical syndromes in which the causative role of HPV infection was not clear.

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[2,3]. During the last decade HPV infection has been associated with various inflammatory diseases such as vasculitis [4,5], idiopathic thrombocytopenic purpura [6], Kawasaki disease [7], myocarditis [8], systemic lupus erythematosus [9] and diseases with an obscure origin such as multiple sclerosis [10], childhood acute lymphoblastic leukemia [11] and Diamond-Blackfan anemia [12]. This clearly widespread infection is transmitted primarily through respiratory secretion, or through infected serum. Infection is most common in children aged 4-11; the seropositivity among adult populations ranges from 50 to 70%. Outbreaks of the virus can occur, particularly in the winter or spring [13].

The aim of the present study was to evaluate the clinical presentations and epidemiologic data in a large group of pediatric patients with serologic evidence of acute HPV infection, who were investigated in the pediatric service of a regional Israeli hospital during a 20 month period. Naturally, since this was a hospital-based study mostly patients with less common presentations were investigated.

Patients and Methods

We reviewed the case records of all patients with serologic evidence of acute HPV infection, based on positive serology for serum IgM antibodies, from January 1999 to August 2000. Levels of serum anti-HPV IgG and IgM antibodies were determined using enzyme-linked immunosorbent assay for VP1 and VP2 specific protein respectively, manufactured by IBL-Hamburg and performed in the microbiology laboratory of the Kaplan Medical Center. This assay was evaluated and compared to indirect immunofluorescence assay and to polymerase chain reaction and was found to have 97% sensitivity and 96% specificity [14].

Results

HPV serologic tests were performed in 128 children admitted for various clinical presentations to the Pediatric Division of the Kaplan Medical Center during the designated period. The mean age of the patients, 18 males and 22 females, with acute HPV infection was 5.21 years (range 2 months to 15.5 years), but 22 (55%) were less than 4 years old.

Eighty children were found to be negative for IgM antibodies, of whom 29 (36%) were positive for IgG antibodies, indicating previous illness. We identified 48 patients with positive anti-HPV IgM antibodies; 14 (29%) also had positive HPV IgG antibodies. Of the 48 patients, 37 (77%) were tested for antibodies against both Epstein-Barr virus and cytomegalovirus. Four patients had positive

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The spectrum of diseases associated with human parvovirus is wide and constantly growing. Most commonly, it includes erythema infectiosum (fifth disease or "slapped-cheek" syndrome), intrauterine infections with hydrops, and pure red cell aplasia in patients with chronic hemolytic anemia or in immunocompromised individuals [1]. HPV infection may also lead to arthritic disorders, which are rare in children but frequent in adults (8% vs. 80% affected)

HPV = human parovirus

IgM = immunoglobulin M

SLE = systemic lupus erythematosus

IgM for CMV and 4 patients had IgM for EBV. These eight patients were excluded from the study since it is known that false positive results may be seen with other acute viral infections. In an assessment performed by Jensen and Vestergaard [15], 17% of sera positive for EBV were also positive for HPV IgM, and 20% of sera positive for CMV IgM were also positive for HPV IgM.

In 14 of the 48 patients positive for IgM antibodies the serologic test was repeated within 1 month, and the repeated testing showed that all 14 were positive for HPV IgM antibodies.

The seasonal variations of the time of diagnosis [Figure 1] reflect a significant rise in the incidence of HPV infection during autumn and winter (October to January), with a solitary peak in May (spring) and almost constant spread throughout the rest of the year.

Clinical presentations [Table 1]

- **Fever:** Twenty-five patients (62.5%) presented with fever, which was the sole cause for investigation in 12 of them. In the other 13 patients fever was accompanied by one or more of the following symptoms: hepatosplenomegaly in 4, lymphadenopathy in 2, rash in 4, joint complaints in 3, and cytopenia in 2 patients. Concerning the pattern of fever, 10 patients had recurrent fever, which was defined as at least four episodes of fever lasting more than 1 day during the preceding 2 months. The parents reported fever occurring once in 1 or 2 weeks, each time for 3–4 days and in most cases around 38.5°C. One patient had intermittent fever during 2 months and was febrile for 3–4 days every week. Fourteen patients had prolonged daily fever, about 38.5–39.5°C, for 2–3 weeks. Of the 25 patients presenting with fever, 19 (76%) were under the age of 4.
- **Anemia:** Six patients were investigated for unexplained or non-responding anemia. In two of them, either thrombocytopenia or leukopenia was also present. A 2 month old baby with red cell aplasia was evidently a case of Diamond-Blackfan syndrome.

CMV = cytomegalovirus
EBV = Epstein-Barr virus

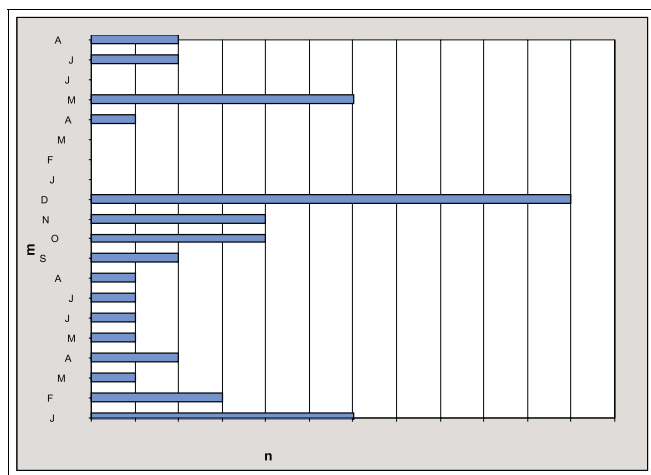


Figure 1. Seasonal distribution of the diagnosis of acute parvovirus B19 infection

Table 1. Clinical characteristics of patients with acute parvovirus B19 infection

Patient	Age (yr)	Gender	Presenting signs and symptoms
1	1	Female	Recurrent fever
2	8	Female	Recurrent fever, hepatosplenomegaly
3	2	Female	Recurrent fever
4	2	Male	Recurrent fever, left knee monoarthritis
5	2	Female	Recurrent fever
6	1	Female	Intermittent fever
7	1	Male	Recurrent fever
8	1	Male	Recurrent fever
9	2	Female	Recurrent fever
10	2	Male	Recurrent fever, prolonged fever for 1 month
11	1	Male	Recurrent fever
12	5	Female	Prolonged fever, backache, pancytopenia
13	14	Female	Prolonged fever, 3–4 week duration
14	3	Male	Prolonged fever, splenomegaly, cervical lymphadenopathy
15	3	Male	Prolonged fever, right hip synovitis
16	4	Female	Prolonged fever, thrombocytopenia
17	2	Male	Prolonged fever
18	11	Female	Prolonged fever for 3 weeks followed by rash
19	3	Female	Prolonged fever, rash, cervical lymphadenopathy
20	1	Male	Prolonged fever, intermittent rash
21	1	Female	Prolonged fever for 3 weeks hepatosplenomegaly
22	11	Female	Prolonged fever and rash
23	6	Male	Prolonged fever, splenomegaly
24	3	Male	Prolonged fever
25	2	Male	Prolonged fever
26	13	Male	Hip pain, anemia
27	11	Male	Left knee monoarthritis
28	10	Male	Recurrent right hip pain
29	15	Female	Polyarthralgia
30	6	Male	Right knee arthritis
31	1	Female	Vasculitic rash on face & extremities
32	12	Female	Rash
33	0	Female	Severe aplastic anemia
34	9	Female	Anemia, headache, fatigue
35	3	Female	Anemia, thrombocytopenia
36	3	Female	Anemia
37	15	Female	Anemia and leukopenia
38	10	Female	Anemia
39	13	Male	Hepatitis
40	10	Male	Optic neuritis

- **Rash:** In most of the patients the skin rash accompanied other symptoms and was compatible with erythema infectiosum. One 9 month old baby (patient no. 31) had vasculitic rash, which was identified as leukocytoclastic vasculitis on skin biopsy and was consistent with the diagnosis of acute hemorrhagic edema of infancy.
- **Arthropathy:** Eight patients presented with joint complaints. Three had monoarthritis of large joints without fever, one of whom revealed positive antinuclear antibody and positive anti-DNA. Another female patient had symmetric polyarthralgia of small and large joints.

- **Hepatitis:** Hepatitis was diagnosed in one patient, without any proven etiology.
- **Optic neuritis:** The only positive findings in a young boy with optic neuritis were significant levels of IgM and IgG anti-HPV antibodies. The patient responded well to pulse steroid therapy.

Discussion

In the normal host, HPV infection can be asymptomatic (20–50% of children and adults) and may cause erythema infectiosum or induce polyarthropathy syndrome. This retrospective study of 40 basically normal pediatric patients with acute HPV infection focuses on some other, less common, presentations of HPV infection.

The gender and seasonal distribution are consistent with previous data [13]; namely, more cases were admitted during early winter, with one small outbreak in May. On the other hand, the patients were much younger than shown in previous epidemiologic data. HPV is common among the age group 4–14 years [13], whereas in this study 55% of the patients were under the age of 4.

The presenting symptoms were variable, but in most cases (25/40), children had either prolonged or recurrent fever, sometimes accompanied by other signs such as anemia, or had a “mononucleosis-like” clinical picture with liver or spleen enlargement, lymphadenopathy, skin rash and arthropathy. We suggest, therefore, that serology for parvovirus should be included in the work-up of patients with unexplained fever or “mononucleosis-like” symptoms. Interestingly, of the 25 patients presenting with fever, 76% were less than 4 years old, suggesting the possibility that prolonged or recurrent fever is a more common presentation of HPV infection in younger children. Clinical syndromes consisting of anemia, skin rash and arthropathy are known to be associated with HPV infection. The data in the present study show that even in solitary unexplained anemia or joint symptoms that are not accompanied by the other constituents, HPV infection should be considered.

The occurrence of acute HPV infection in five unusual clinical presentations warrants special consideration. The first, patient no. 26, was a 12 year old boy who presented with clinical and serologic findings highly suggestive of SLE. Although HPV infection has been reported to induce SLE [9], it remains to be seen whether he will develop the full-blown clinical picture of SLE in the future. In patient no.12, a 5 year old girl investigated for fever, backache and pancytopenia, repeated bone marrow biopsy eventually disclosed the diagnosis of acute lymphatic leukemia. A causative relationship between parvovirus infection and childhood acute lymphatic leukemia has previously been proposed [11], and the present case might strengthen this association. In patient no. 33, a 2 month old female infant with prolonged severe red cell aplasia, the diagnosis of Diamond-Blackfan syndrome was suggested. It was previously shown [12] that some infants with this finding in fact had HPV infection, with a transient course and an excellent prognosis. A 9 month old girl (patient no.31) presented with vasculitic skin rash, proven on biopsy to be leukocytoclastic vasculitis, consistent with the diagnosis of acute hemorrhagic edema of infancy, which is a benign variant of Henoch-Schonlein purpura in young infants. Since various vasculitic syndromes have been associated with parvovirus infection [4,5,7], it is possible that this vasculitis was also caused by

HPV infection. A 10 year old boy (patient no. 40) who was admitted for severe optic neuritis responded favorably to intravenous pulse steroid treatment. Except for HPV infection, no other etiology for optic neuritis, including multiple sclerosis, was found at this stage. Since HPV was implicated in the pathogenesis of multiple sclerosis [10], its possible expression in this patient in the future should be seriously considered.

In conclusion, in addition to its common established clinical presentations, HPV infection in a previously healthy pediatric population may also be associated with a less common clinical presentation, especially in the younger age group. Therefore, a high index of suspicion is necessary to identify this infection within a large spectrum of inflammatory conditions.

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Correspondence: Dr. J. Barash, Director, Pediatric Day Care Unit, Kaplan Medical Center, Rehovot 76100, Israel.

Phone: (972-8) 944-1451

Fax: (972-8) 944-1145

email: barashj@inter.net.il