Series Editor: Camila K. Janniger, MD

Pediatric Parvovirus B19: Spectrum of Clinical Manifestations

Monica N. Valentin, MD; Philip J. Cohen, MD

Practice Points

- Parvovirus B19 (PVB19) infection in children most commonly presents as a self-limited erythematous exanthem isolated to the malar eminences following a mild prodromal illness.
- In healthy children, diagnosis is made clinically and treatment is supportive.
- Immunocompromised children and those with hemolytic anemia who are infected with PVB19 do not always present with the characteristic dermatologic findings and are at high risk for developing severe, life-threatening anemia.
- In high-risk groups presenting with anemia and fever, serologic testing is needed for diagnosis, and blood transfusions or high-dose immunoglobulins may be required for treatment.

Parvovirus B19 (PVB19) infection has a varied spectrum of clinical manifestations, ranging from subclinical infection to skin and joint symptoms to hematologic effects with potential fatality. The most common manifestation of PVB19 infection in children is erythema infectiosum (EI). Also known as fifth disease or slapped cheek syndrome, EI presents as an erythematous exanthem limited to the malar eminences that follows a mild prodromal illness. In healthy children, infection is self-limiting and has an excellent prognosis; however, in high-risk pediatric groups (eg, immunocompromised patients, children with hemolytic anemia or prenatal infection), clinical manifestations are hematologic in nature and typically are more severe. Diagnosis often is made clinically. Serologic testing can be confirmatory. Treatment is aimed at symptomatic relief, and a vaccine currently is under investigation.

Cutis. 2013;92:179-184.

From the Department of Dermatology, New Jersey Medical School, Newark.

The authors report no conflict of interest.

Correspondence: Philip J. Cohen, MD, Department of Dermatology, New Jersey Medical School, 185 South Orange Ave, Room H-576, Newark, NJ 07103-2714 (Philip.Cohen@va.gov).

Background and Epidemiology

Parvovirus B19 (PVB19), a member of the *Erythrovirus* genus of the Parvoviridae family, is a small, nonenveloped, single-stranded DNA virus that infects humans exclusively.[1] Its lack of a lipid membrane gives the virus stability and resistance to heat, cold, and detergents. Parvovirus B19 is highly selective for replication in erythroid progenitor cells. The receptor is blood group P antigen; without this antigen, an individual is immune to PVB19 infection.[2] The virus has 3 proteins: NS1, a nonstructural protein that gives the virus its cytotoxic properties, as well as VP1 and VP2, 2 structural proteins.[1,3]

Parvovirus B19 is ubiquitous worldwide but is more common in temperate versus tropical climates.[4] It is thought to occur in 4-year cycles, with 2 years of epidemic followed by 2 years of endemic.[1,4,5] Exindari et al[6] studied the distribution of PVB19 infection from 2006 to 2009 in northern Greece and demonstrated a statistically significant annual variation (P=.0002). Other temperate zones also have demonstrated this cyclic annual variation of PVB19 epidemics.[7,8] There also is a seasonal variation in PVB19 infections; elevated infection rates occur between December and July, with April accounting for 16% of infections.[8-10] Outbreaks most commonly occur in school environments, particularly in the

early school years, so much so that by 18 years of age, 50% of children have been infected by the virus.[11,12] In temperate areas, age-specific risk is highest in children aged 7 to 9 years and lower in adults; thus, seroprevalence of PVB19 increases with age.[7,13] By the first and second decades of life, 28% and 51% of patients are seropositive, respectively, and after 50 years of age, 78% are seropositive. Consequently, 30% to 40% of pregnant women are susceptible to PVB19 infection.[14]

Transmission

Parvovirus B19 can be transmitted in utero, as well as via respiratory droplets, blood, and bone marrow. On exposure, massive viremia follows a short replication in the nasopharyngeal lymphoid tissue.[15] The virus is then shed from nasal and oral secretions, which indicates the period of highest infectivity.[16] It spreads throughout the body and enters the bone marrow, attacking the erythroid progenitor cells.[15,17] There is a 50% transmission rate among those living with infected individuals; for those working in school environments with exposure to infected children, the transmission rate decreases to 20% to 30%.[13]

In approximately 30% of cases of maternal PVB19 infection, the virus is vertically transmitted to the fetus.[14] In pregnancy, the risk for transmission is highest during the first and second trimesters.[18] The precise mechanism of vertical transmission of PVB19 to the fetus is not fully understood. It has been suggested that PVB19 replicates in the placental villi and fetal capillaries, disrupting blood exchange and infecting the fetus.[19]

Parvovirus B19 infection may persist in the bone marrow in asymptomatic individuals for several years due to prolonged replication, allowing the virus to be transmitted via blood and bone marrow.[20] Parvovirus B19 is more commonly spread via donor blood versus donor bone marrow, but its infectivity is not fully understood.[1] Pooled plasma contains neutralizing immune antibodies; however, PVB19 infection from plasma with high levels of PVB19 DNA may occur.[21,22] In epidemic seasons, high levels of PVB19 antigen were found in a small percentage (0.58%) of blood donations from asymptomatic donors.[9,22,23] Infection from bone marrow transplantation is rare but also may occur.[24]

Clinical Findings

Parvovirus B19 infection has a varied spectrum of manifestations, ranging from subclinical infection to skin and joint symptoms to hematologic effects with potential fatality.[1] In healthy children, PVB19 infection presents as an asymptomatic infection in approximately 50% of patients and as nonspecific illness or benign erythema infectiosum (EI) in the other 50%.[18] Children younger than 4 years are less likely to display EI.[25] In adults, rheumatologic findings are more common than dermatologic ones.[13,17]

In one study, Anderson et al[15] inoculated 9 healthy adults intranasally and mapped the course of PVB19 infection. After 1 week of incubation, 4 patients developed mild illness with fever, itching, and myalgia associated with peak viremia. The following week, the same 4 patients developed transient reticulocytopenia with mild anemia. On days 17 to 18, a rash on the face and extremities and/or arthralgia lasting 3 to 4 days occurred in 2 of the 4 patients and was associated with IgG anti-PVB19 antibodies. Of the remaining 5 patients, 1 developed a 24-hour course of fever, malaise, and myalgia, and the other 4 patients remained generally asymptomatic with mild reports of transient headaches, malaise, or itching.[15]

Although arthralgia mainly is seen in adults, it also can be seen in children with a higher incidence in females.[26] In adults, arthralgia tends to be symmetric, affecting the small joints of the hands, wrists, and knees.[5,6,27] In children, arthralgia commonly is asymmetric, affecting the larger joints of the wrists, knees, and ankles.[28] Furthermore, arthralgia in children tends to occur later in the course of infection and is self-limiting but may recur in the same joints months later or may migrate to different joints.[27,29] A small number of children and adults may develop chronic polyarthritis that is clinically similar to rheumatoid arthritis, which begs the question of whether PVB19 infection causes chronic arthritis or is a precipitating factor of rheumatoid arthritis. Research shows that the joint destruction and erosions normally seen in rheumatoid arthritis are not seen in PVB19-associated arthropathy.[27]

The debate regarding the role of PVB19 in rheumatoid arthritis also extends to other autoimmune disorders, such as systemic lupus erythematosus, progressive systemic sclerosis, vasculitides, and antiphospholipid syndrome.[30,31] Some favor PVB19 as a causative agent of autoimmune disorders, while others believe it is a precipitating factor. Some hypothesize that the autoimmune response is driven by persistent viremia via molecular mimicry of host and virus proteins.[31]

Mild and transient hematologic effects (eg, anemia, lymphopenia, neutropenia, thrombocytopenia) may manifest in healthy individuals.[18] In cases of vertical transmission in newborns and infants, severe congenital anemia due to reduced red blood cell production may be the presenting symptom.[6] In children with underlying hemolytic anemia, PVB19 may cause an aplastic crisis.[5,18,32] The precipitous

drop in hemoglobin may prove self-limiting within a week or could be fatal.[1,33] In immunocompromised children with preexisting chronic anemia, PVB19 infection may cause aplastic anemia, myelodysplastic syndrome, prolonged pancytopenia, or pure red cell aplasia with or without a rash. In this patient population, the clinical course of the infection is prolonged and reinfection and reactivation are common.[34]

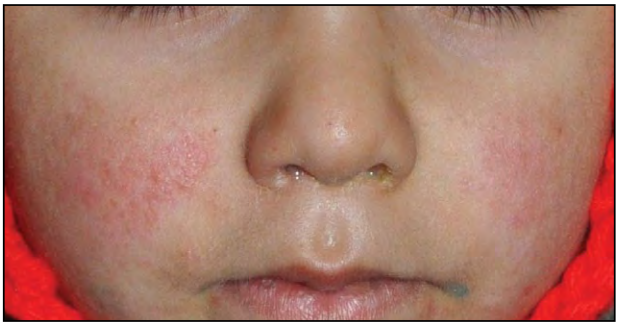
Vertical transmission to the fetus may result in congenital anemia, which can lead to nonimmune hydrops fetalis or fetal death in 2% to 5% of maternal PVB19 infections[14]; however, an American study showed higher incidences, with 12% (3/25) of maternal infections leading to hydrops fetalis and 16% (4/25) resulting in fetal death.[8] Pregnant women with asymptomatic PVB19 infections may experience more complications due to a weakened immune response that is unable to clear the replicating virus.[5,8] The developing fetus depends on a high level of erythropoiesis, which may be negatively impacted by the virus. Anemia in the fetus may be followed by aplastic crisis, cardiac failure, and hydrops fetalis. The virus also may cause fetal myocarditis, resulting in arrhythmia and cardiac arrest.[18]

Other disorders associated with pediatric PVB19 infection include glomerulonephritis,[35] acute pericarditis,[36] optic neuritis,[25] irritable bowel syndrome,[6] encephalopathy, stroke, epilepsy, meningitis, peripheral neuropathy, and dilated cardiomyopathy.[17,37,38] Parvovirus B19 may cause fulminant hepatitis, though the prognosis is more favorable in patients younger than 5 years.[39]

Dermatologic Manifestations

The most common clinical findings of PVB19 infection in children are EI, also known as fifth disease or slapped cheek syndrome, and papular-purpuric gloves and socks syndrome (PPGSS).[1]

Erythema infectiosum is the most widely known cutaneous finding and is most commonly seen in children aged 4 to 11 years.[6] Erythema infectiosum progresses in stages. Stage 1 consists of a mild prodromal illness with fever, coryza, gastrointestinal tract symptoms, and headaches. During this stage, there is depletion of erythroid progenitor cells, viremia with concurrent anti-PVB19 IgM production, and increased infectivity. After 3 to 7 days, stage 2 is characterized by malar erythema, which spares the nasal bridge and periorbital regions, hence the slapped cheek appearance, as well as pallor surrounding the mouth (Figure). On exposure to sunlight or heat, the exanthem becomes more pronounced.[1,26] During stage 2, clearance of the viremia occurs concurrent with the appearance of anti-PVB19 IgG, and the patient is no longer contagious.[6] Over the next 1 to 4 days, stage 3 involves the devolution of the malar rash into a lacy reticular pattern, while an erythematous maculopapular exanthem develops over the trunk and extremities. This exanthem may be pruritic and accompanied by arthropathy. In this last stage, the exanthem usually persists for 1 to 3 weeks before clearing but can last for months.[1,26] There are no long-term sequelae and the prognosis in children is excellent.[1,26]



Erythema infectiosum, or slapped cheek syndrome, demonstrating malar eminence erythema sparing the nasal bridge with concurrent circumoral pallor.

Papular-purpuric gloves and socks syndrome is an uncommon presentation of PVB19 infection. It typically is seen more in young adults than in children, with no particular predilection for males or females.[40,41] In 1990, Harms et al[41] first described PPGSS in 5 young adults who had a self-limited exanthem on the hands and feet with fever and oral mucous membrane lesions.

The exanthem of PPGSS is erythematous, monomorphic, and confined to the hands and feet, with sharp demarcations over the wrists and ankles, thereby producing a gloves-and-socks distribution. As it continues to evolve, the exanthem may gradually become purpuric and petechial and may progress to vesicles or bullae followed by sloughing of the skin of the palms and soles.[13,42] Characteristically, the exanthem of PPGSS is painful and pruritic and typically is accompanied by acral edema.[1,42,43] Mucosal involvement, which may include oral erosions, petechiae, and edema, is common in PPGSS and is referred to as acropetechial syndrome.[1,44] In 50% of cases, similar lesions occur in other sites, including the cheeks, elbows, glans penis, vulva, buttocks, thighs, and knees.[13]

Unlike EI, in which infectivity diminishes with the appearance of the rash, PPGSS is contagious when the exanthem is present, which occurs during the initial prodrome.[40,43] There may be mild leukopenia, neutropenia, thrombocytopenia, and eosinophilia, as well as elevation of transaminases,

erythrocyte sedimentation rate, and C-reactive protein levels.[42,43] Papular-purpuric gloves and socks syndrome generally resolves in 1 to 2 weeks with no long-term sequelae with an excellent prognosis.[43] Other viruses, such as hepatitis B, cytomegalovirus, Epstein-Barr virus, coxsackievirus B6, measles, human herpesvirus 6, and human herpesvirus 7, also have been linked to PPGSS.[1]

Parvovirus B19 infection also may manifest as an exanthem with a bathing trunk distribution as well as genital erythema and pustules.[45] The infection may result in many possible nonspecific cutaneous findings, such as reticular erythema, maculopapular eruptions, purpuric eruptions, petechial generalized rash, livedo reticularis, desquamation, vesiculopustular skin eruptions, pruritus without rash, and angioedema.[1,46] Additionally, PVB19 infection is linked with erythema multiforme, erythema nodosum, urticaria, and Gianotti-Crosti syndrome.[1] In a study of 14 patients with PVB19 infection, only 3 patients had the typical dermatologic manifestations of either EI or PPGSS. The other 11 patients had atypical findings, including an asymptomatic papular eruption, an eruption clinically resembling Sweet syndrome, myopathic dermatomyositis, lupus erythematosus–like syndromes, and palpable purpura of the lower extremities.[47]

Differential Diagnosis

Similar to its spectrum of clinical manifestations, the differential diagnosis of PVB19 infection is vast. Potential diagnoses include rubella, measles, scarlet fever, Gianotti-Crosti syndrome, Kawasaki disease, hand-foot-and-mouth disease, erythema multiforme, collagen-vascular disease, systemic lupus erythematosus, rheumatoid arthritis, erysipelas, roseola, sunburn, and drug reaction.[28,40] In a series of 906 patients who presented with fever and rash, 322 (36%) were found to be positive for PVB19 infection.[10] Thus, PVB19 should be considered when assessing a patient with a fever and rash of unknown etiology.[40]

Diagnosis

The diagnosis of PVB19 infection often is made clinically based on the combination of a rash, constitutional symptoms, arthropathy, and transient anemia.[1,6] Laboratory studies can assist in differentiating acute exanthems. These studies are especially important in assessing high-risk patients, such as those with hemolytic anemia. Screening for PVB19 also is suggested in measles- and rubella-negative sera.[10] Anti-PVB19 IgM levels have been positively correlated with PVB19 DNA levels.[48] Enzyme immunoassay for anti-PVB19 IgM and IgG with a sensitivity of 97% to 100% and specificity of 79% to 99% is used for diagnosis in immunocompetent individuals, as it is easier and more cost-effective than the polymerase chain reaction (PCR) assay.[13,49] Only the presence of anti-PVB19 IgM, which is detectable for up to 2 to 3 months after acute PVB19 infection, is diagnostic, as anti-PVB19 IgG seroprevalence is high.[16] In immunocompromised individuals, viral DNA must be tested through PCR or real-time PCR, as these individuals may fail to demonstrate an antibody response.[26,49]

In atypical skin eruptions, a punch biopsy may help to exclude other processes. Electron microscopy can be used in plasma and fetal tissues to detect infection, but this diagnostic modality is too technically sophisticated for regular use.[19] Parvovirus B19 is not routinely cultured, as the media needed for culture requires erythroid progenitor cells, such as human bone marrow, blood, and fetal liver.[1,3]

Pathogenesis

The pathogenesis of PVB19 infection still is not completely known.[18] In acute infection following inoculation, the virus is controlled by neutralizing antibodies, initially anti-PVB19 IgM and later IgG, which generally confers lifelong immunity.[14,20] It has been hypothesized that the skin and joint symptoms that occur with the production of anti-PVB19 IgG result from the deposition of immune complexes.[2,27] Alternatively, it has been proposed that these clinical manifestations may be due to the body's inflammatory response to viral antigens.[50] Cell-mediated immunity may play a role in PVB19 infection, as T_H1 and T_H2 helper T cells undergo clonal expansion in infected individuals.[51]

The molecular mechanism of latency and persistent replication of the virus is unknown. Polymerase chain reaction studies have demonstrated viremia 10 months to 5 years after infection.[18] Persistent viremia commonly occurs in immunocompromised patients but also may uncommonly be seen in immunocompetent individuals.[20] It is hypothesized that some human tissues may have the capacity to store *Erythrovirus* for more than 70 years or that the virus may integrate itself into the human genome.[18]

Treatment

As with many viral infections in humans, treatment is aimed at symptomatic relief because the infections tend to be self-limited and without long-term sequelae in immunocompetent individuals.[1] Nonsteroidal anti-inflammatory drugs may provide relief for arthralgia. Blood transfusions may be indicated in aplastic crisis. High-dose intravenous immunoglobulins have been used for immunocompromised patients. Intrauterine fetal blood transfusions have been used for hydrops fetalis.[14,26,52]

Because immunocompromised patients and those with hemolytic anemia may have nonspecific or atypical presentations, early monitoring for PVB19 infection may be indicated.[1] Weekly screening of the blood for PVB19 via PCR may be indicated for children undergoing intensive chemotherapy or following stem cell transplantation to facilitate earlier diagnosis.[32] At this time, there is no consensus on screening for blood donations used for hemotherapy in this high-risk group.[18]

Currently, a vaccine for PVB19 is being developed.[53] The vaccine consists of 25% VP1 and 75% VP2 with an adjuvant. In one study, 24 adults received 3 doses of the immunization over 6 months and all developed neutralizing antibody titers.[53] However, even with neutralizing antibodies, infectivity may not be reliably controlled.[54,55]

Conclusion

Parvovirus B19 is a self-limited and benign infection for most healthy children but may pose a considerable threat to high-risk populations such as immunocompromised patients or those with hemolytic anemia.

Acknowledgment—We thank Robert A. Schwartz, MD, MPH, Newark, New Jersey, for his contribution to this manuscript.

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