117 Parvovirus B 19

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Parvovirus B 19 (B19) is the only known human pathogenic parvovirus. It was discovered accidentally in 1974 during a study screening healthy blood donors for hepatitis B using panels of serum samples. One sample (coded 19 in panel B) gave a positive result in counterimmunoelectrophoresis (CIE) but negative results in more sensitive assays. Electron microscopic examination of the excised precipitin line from the CIE showed the presence of 23-nm particles resembling parvovirus. Since that time, serologic surveys have demonstrated that B19 is a ubiquitous agent. Thirty percent to 60% of adults have antibody to the new virus. Systematic search of blood samples to identify infected patients and possible clinical correlates resulted in 1981 in the discovery of B19 in the serum of sickle cell anemia patients with aplastic crises. The next major association was made in 1983 when B19 infection was found to be the causative agent of erythema infectiosum. Since then, the spectrum of illness with which B19 is associated has grown to include intrauterine infection with hydrops, arthritis, idiopathic thrombocytopenic purpura, transient erythroblastopenia of childhood, neutropenia, hemophagocytic syndrome, encephalitis, pseudoappendicitis, and purpura. This chapter reviews the present knowledge on Parvovirus B 19 virology and epidemiology and its associated clinical manifestations.

Virologic Aspects of B19 Infection

Parvovirus B 19 is a small (*parvum* is Latin for small), nonenveloped, single-stranded DNA virus that belongs to the family Parvoviridae and is a member of the genus *Parvovirus*. As result of its lack of envelope and limited DNA content, B19 is extremely stable to physical inactivation by such mechanisms as heat (60 min at 56°C) and lipid solvents. Parvoviruses are species specific, and no animal model has been identified that permits the replication of B19. In addition, although the virus can be grown in fresh human bone marrow cells, erythroid cells derived from fetal liver, and erythroid leukemic cells, there is no practical in vitro system for isolation of B19 from clinical specimens.

Epidemiology

Infection with B19 is common. The reported prevalence of immunoglobulin G (IgG) antibodies ranges from 2% to 15% in children 1–5 years old, from 15% to 60% in children 5–19 years old, from 30% to 60% in adults, and up to 90% in the elderly. Women of child-bearing age show an annual seroconversion rate of 1.5%. Viremia in the general population, however, is rare. A study of the prevalence in blood donors showed that 1:20,000–1:40,000 units of blood contain high titers of B19 during the epidemic season. This is important to consider when many thousands of units of blood are pooled to make factor concentrates used for treatment of patients with hemophilia.

The distribution of B19 is worldwide. Seroprevalence studies from the United States, Western Europe, and Japan show similar patterns. The prevalence rates are slightly higher in developing countries. Infection in temperate climates is common in late winter, spring, and early summer. Infection with B19 follows a cyclic pattern, with increased rates of infection occurring every 4–5 years. The infection may be either epidemic or sporadic. The major route of transmission is through respiratory secretions of viremic patients. Transmission may occur among family members, from patient to patient, and from patient to health care or day care provider. The secondary attack rate among household contact is approximately 50%, and during school epidemics 10–60% of schoolchildren will develop erythema infectiosum. Outbreaks of erythema infectiosum in schools may be prolonged over months, suggesting close contact transmission rather than an aerosol transmission mode. Patients with erythema infectiosum are beyond their period of infectivity and present a low risk for further transmission; therefore, they need not be isolated. The principal risk in clinical settings appears to come from patients with high-titer viremia, such as patients with sickle cell anemia and aplastic crisis, or those with chronic pure red cell aplasia, such as human immunodeficiency virus–infected patients. These patients should be in contact and respiratory isolation, and pregnant health care workers should not take direct care of such patients.

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Other routes of transmission include vertical and parenteral transmission and as an occupational hazard in medical laboratory workers. Vertical transmission may occur from mother to fetus in approximately one third of cases of serologically confirmed maternal infection. B19 has been shown to be transmissible in factor VIII and factor IX concentrates. B19 is heat resistant and can withstand the usual heat treatment (80°C for 72 h) used to destroy infectivity of factor concentrates. In addition, solvent detergent methods only inactivate lipid-enveloped viruses (B19 is a nonenveloped virus). B19 has been transmitted by steam- or dry-heated factor VIII and IX concentrates. The question of whether measures should be taken to reduce B19 infection by transfusion of blood components and clotting factor concentrates is eloquently discussed in a recent publication. Immunoglobulin products have not been associated with B19 transmission and may present a low risk because they contain high B19 antibody titer.

Pathogenesis

B19 has tropism for erythroid progenitor cells, including erythroid colony-forming and burst-forming units. The major receptor for B19 on erythroid target cells is the P antigen; B19 capsids bind to P antigen. B19 is critically dependent for its replication upon actively dividing cells. Virus replication occurs in the nuclei of the pronormoblasts. During its replication, B19 is cytotoxic to the infected cells.

The diverse clinical manifestations of B19 infection are the result of either erythroid progenitor (and/or possibly other hematopoietic progenitor cell) aplasia or host immune response. In the immunocompetent host, B19 infection typically results in a self-limited febrile illness characterized by asymptomatic red cell aplasia followed by a rash or arthropathy presumed to be immunologically mediated. Recovery is associated with the production of specific antibodies and probably lifelong immunity. Asymptomatic infection is common. In one study of a school outbreak, B19 caused asymptomatic infection in approximately 25% of adults. If the immunocompetent host has an underlying hematologic disorder (typically characterized by increased cell destruction) (*Table 117.1*), B19 may result in severe symptomatic anemia. However, in all such cases the aplastic anemia is transient. In contrast, B19 infection in immunocompromised patients may become persistent and results in chronic anemia. The fetus is particularly vulnerable because it might develop severe anemia and persistent infection due to its decreased red cell survival (about half that of a normal adult) and inability to mount an adequate immune response to clear the infection.

Table 117.1
Hematologic conditions predisposing patients to Parvovirus B 19–associated acute aplastic crisis

Hereditary disorders
Sickle cell anemia
Hereditary spherocytosis and stomatocytosis
Thalassemia
Glucose-6-phosphase dehydrogenase deficiency
Pyruvate kinase deficiency
Pyrimidine-5′-nucleotidase deficiency
Congenital dyserythropoietic anemia
Acquired disorders
Iron deficiency anemia
Chronic autoimmune hemolytic anemia
Cold antibody-mediated autoimmune hemolytic anemia
Malaria
Blood loss
Paroxysmal nocturnal hemoglobinuria
Normal host

The cause of transient neutropenia has not been well defined. Parvovirus has been detected in granulocytic- and erythroid-line cells in a patient with B19-induced pancytopenia. In addition, replicative forms of B19 DNA have been found in granulocyte-enriched fractions of human serum, suggesting a role for direct infection by B19. B19 has not been shown to replicate in megakaryocytes, but in vitro it inhibits megakaryocyte colony formation.

Diagnosis

For optimal diagnostic yield, the patient's clinical presentation, stage of disease at presentation, and the underlying hematologic and immunologic conditions must be considered when ordering a laboratory test. In a previously normal host who presents with erythema infectiosum or arthropathy, for example, a single immunoglobulin M (IgM) antibody assay is the only test required to confirm infection. IgM is detectable within 3 days after onset of disease, peaks in 2–3 weeks, and then begins to decline in 1–2 months. B19 IgM can be measured in patients' serum or saliva. Saliva can be a convenient alternative to

serum for the diagnosis of recent infection, particularly during outbreaks. Patients with chronic hematologic disorders, on the other hand, may present with aplastic crises before IgM or IgG antibodies are detectable. Furthermore, the fetus or patients with immune deficiency may have an unpredictable antibody response.

Serologic tests of viral infections can be confusing when more than one virus is sought as the cause of a particular set of symptoms. Some samples positive for *Parvovirus* IgM often give positive results for other viruses. In one study, of 25 initially B19 IgM-positive sera, 20% cross-reacted in an Epstein–Barr virus viral capsid antigen IgM test and 8% in a cytomegalovirus IgM test. Another report compared several enzyme immunoassays for the detection of parvovirus to a radioimmunoassay developed by the authors, which used baculovirus-expressed B19 protein. From 88 sera tested, approximately 50% agreement between tests was found. Test sensitivity ranged from 70% to 100% and specificity from 76% to 100%.

Tests of B19 DNA or viral antigens are most useful for patients with aplastic crises or immune deficiency states. The most sensitive assays for B19 DNA detection are polymerase chain reaction (PCR) and hybridization assays. Recent and rapid methods for detection of B19 DNA using a nested PCR reaction have been developed. PCR and hybridization assays have been applied successfully to a variety of clinical samples. B19 DNA may be detectable in serum of patients for several months even after an uncomplicated infection. Because of extreme sensitivity, meticulous care and adequate controls must be used to ensure reliable results. The PCR is often considered to be a specific and highly sensitive test for the viruses in clinical specimens. The nested PCR method for parvovirus was able to detect as low as 3–30 viral genome copies.

Assays for B19 antigens are available but are relatively insensitive. Electron microscopy can also be used to detect B19. In anemic patients, bone marrow aspirate examination shows giant cell proerythroblasts, which constitute strong evidence of B19 infection. In situ hybridization and immunohistochemical studies can be used to confirm the diagnosis. These studies can be used also on tissue obtained from other infected sites.

Clinical Overview of Nonhematologic Effects

In the normal host, B19 infection can be asymptomatic or causes disease such as erythema infectiosum, polyarthropathy syndrome, acute hepatitis, and Behçet's disease. Asymptomatic infection occurs in as high as 20–50% of children and adults. Most people with B19-specific antibody have no recollection of any specific symptoms.

Erythema Infectiosum (Fifth Disease)

Erythema infectiosum is the most common clinical manifestation of B19 infection. It is a moderately contagious disease affecting mainly children. It is called the fifth disease because it was the fifth of five illnesses described exhibiting somewhat similar skin rash. (The other four diseases were rubella, measles, scarlet fever, and Filatov–Dukes disease, the last of which is now considered a mild atypical form of scarlet fever.) Histopathologic changes of the skin include edema and lymphocytic infiltrate. The disease affects mainly children, is infrequently encountered in infants and adults, and is characterized by an initial nonspecific prodromal illness followed in 2–5 days with marked erythema of the cheeks sparing the circumoral and bridge of the nose regions (giving the child a slapped-cheek appearance) and a lacy rash on the trunk and extremities. The rash may involve the palms and soles. Infrequently the body rash may precede the facial one. It may be transient or recurrent over 1–3 weeks. Recrudescence may occur with exercise, warm baths, rubbing of the skin, or emotional upset. There may be great variation in the skin rash appearance. Pruritus may occur in as much as 70% of patients. The rash lasts from 2 to 39 days (mean, 11 days) and resolves without desquamation. Constitutional symptoms such as headache, pharyngeal pain, myalgia, arthralgia, and gastrointestinal disturbances are more frequent and more severe in adults. Less than 10% of children will have arthralgias or joint swelling.

Complications of erythema infectiosum are rare. Arthritis, hemolytic anemia, pneumonitis, and encephalopathy have been reported. No treatment is indicated and isolation is not required. Because the disease is mild and the duration of the rash is prolonged, affected children should be allowed to attend school.

Polyarthropathy Syndrome

The polyarthropathy syndrome in children is usually mild and of short duration. The role of viral infections in the etiology of acute and chronic arthritides of childhood is incompletely understood. There are several viruses that are known to cause acute arthritis, including rubella,

influenza, and B19. Among the many aspects of acute polyarthritis, B19 has been found associated with carpal tunnel syndrome, hepatic dysfunction, and possibly angioedema.

Myocarditis

Parvovirus has been identified as the cause of acute myocarditis and pericarditis in adults and children and may cause cardiac transplant rejection.

Hepatitis

Hepatic dysfunction has been noted in some children with erythema infectiosum. A retrospective investigation by PCR for *Parvovirus* in serum from 773 patients found four children with acute hepatitis of unknown origin who had B19 DNA. These four patients were between 7 months and 5 years old, and other common viral causes of hepatitis were excluded, including hepatitis A, B, or C viruses and Epstein–Barr virus.

Effects on Fetus

Seroprevalence studies have shown that 25–75% of pregnant women are seropositive and that the annual incidence of B19 infection in women of reproductive age is approximately 1.5%. Maternal infection during pregnancy, whether symptomatic or not, is usually followed by a successful outcome with delivery of a normal child. The risk of an adverse outcome in women with serologically confirmed B19 infection is less than 10%, and that in women with unknown immunity who are exposed in the household or in the school is 2.3% and 1.4%, respectively. Infection in the first 20 weeks of pregnancy is associated with the greatest risk of fetal loss, especially between weeks 10 and 20, which coincide with the development of erythroid precursors. The interval between maternal illness and fetal death is usually 3–5 weeks but may be as long as 11 weeks. All pregnancies complicated with nonimmune hydrops should be investigated by fetal blood sampling looking for the evidence of *Parvovirus* infection. Intrauterine transfusion should be reserved for hydropic fetuses with a low hematocrit.

A study of 618 pregnant women exposed to B19 found that 50% were immune to B19 and 259 remained susceptible after exposure, but only 52 (16.7% of all those susceptible) contracted B19 infection. None of the 52 fetuses of infected women developed nonimmune hydrops, and there were no fetal deaths attributable to B19 in this group. The relative risk of maternal B19 infection was 2.8 if the source was a related child living in the household, and the mother's occupation had no significant correlation. Symptoms reported by the women included polyarthralgia (46%), fever (19%), and nonspecific rash (38%) and were significantly more common ($p < 0.001$) in IgM-positive patients than in noninfected women. About one third of the IgM-positive women were entirely asymptomatic. The authors concluded that exclusion of pregnant women from the workplace during endemic periods with seasonal clusters of cases is not justified.

There is some controversy as to whether a child born to a mother with acute *Parvovirus* infection is at risk for developmental delay. A study of over 100 women who became seropositive for parvovirus during pregnancy revealed that there is no apparent increase in the frequency of developmental delays in children with exposure in utero to *Parvovirus*, but the authors stated that larger studies were needed.

The most common abnormality reported in the affected fetuses is hydrops fetalis. B19 infection accounts for up to one fourth of cases of nonimmune hydrops. The pathogenesis of B19-associated fetal damage is probably similar to that leading to aplastic crises in other conditions in which the red cells have a shortened life span. The resultant anemia is thought to cause cardiac failure and hydrops. However, anemia is not profound in all cases, and red blood cell lysis, myocarditis, and liver disease may contribute to the development of hydrops and fetal loss. Hydrops can resolve without treatment and result in the delivery of a normal infant. Intrauterine blood transfusion has been tried with successful outcome. However, this procedure is not without hazards, and the risk–benefit ratio must be calculated carefully before recommending such treatment.

B19 Infection in Patients with an Underlying Hematologic Disorder

The sudden onset of markedly lower red cell numbers in patients with sickle cell anemia and hereditary spherocytosis has been called "aplastic crisis" or transient aplastic crisis. An infectious etiology for aplastic crisis in sickle cell anemia patients had been hypothesized since the early 1980s because of clustering of cases and periodic epidemics. In 1981, two groups published evidence that linked acute parvovirus infection to the onset of aplastic

crisis in patients with sickle cell anemia. Since then, numerous additional chronic hemolytic anemias have been documented to have the same hematologic pathophysiologic findings (Table 117.1). B19 infection can occur, interestingly, without inducing an aplastic crisis even in patients with chronic hemolytic anemias. Recent transfusions could explain some of these cases.

The usual presentation includes a prodrome of fever and constitutional symptoms suggesting a viral illness from 1 to 17 days before the aplasia. Shortly afterward, the patient has extreme pallor and fatigue. More than half report abdominal pain, vomiting, or nausea. Nearly three quarters of the patients have aches and pains or distinct arthralgias. About one quarter of these patients also have faint maculopapular skin rashes. Patients with hepatic or splenic sequestration with the aplastic crisis have also been reported. Although life threatening and occasionally fatal, the aplastic episode is self-limited. Of considerable interest are the reports of aplastic crisis in individuals with previously undiagnosed and unsuspected compensated hereditary or acquired hemolytic anemia. Reticulocytopenia (reticulocyte counts 0–2.2%) and profound anemia with hematocrits as low as 7% are common. Bone marrow aspirates reveal marked erythroid hypoplasia with characteristic inclusions in the giant pronormoblasts. Reticulocytosis occurs from 2 to 14 days after presentation with the aplastic crisis. Most of these patients require red cell transfusions.

Any person with a chronic hemolytic anemia is at risk for aplastic crises because of the rapid turnover of their erythroid progenitors. It is important to note that occasional instances of aplastic crisis have been reported with pneumococcal, other streptococcal, and *Salmonella* infections. B19-associated aplastic crises have been reported in patients with hereditary spherocytosis, pyruvate kinase deficiency, autoimmune hemolytic anemia, thalassemia, and hereditary erythroblastic multinuclearity associated with a positive acidified serum test (Table 117.1).

Transient Erythroblastopenia of Childhood

Transient erythroblastopenia of childhood is a temporary failure of erythropoiesis in previously hematologically normal children. In the few cases that have been described with B19 infection, anemia was associated with thrombocytopenia, whereas in the classic transient erythroblastopenia of childhood the platelet count is high, suggesting that the two conditions are different. This entity does not appear to be caused by B19 infection.

B19 and Idiopathic Thrombocytopenic Purpura

Thrombocytopenia associated with B19 infection may occur before or after the rash appears in a patient with erythema infectiosum. In vitro studies have shown that B19 can suppress megakaryocyte formation and that B19 RNA may be found in the megakaryocytes. Typical immune thrombocytopenia (ITP) has been reported shortly after the onset of erythema infectiosum.

A longitudinal study to determine a possible role of B19 in ITP patients seen at one center over a 12-month period was reported. B19 DNA was detected by PCR in 17/35 ITP patients (49%). Of these, six had anti-B19 IgM titers and eight were seropositive for anti-B19 IgG. It was hypothesized that a chronic B19 infection would permit PCR detection of B19 DNA long after the acute viral infection, thus providing the association of IgG titers but no IgM anti-B19 antibodies. There has been some speculation that ITP patients have altered immune systems, but there are conflicting data on lymphocyte function and subsets. *Parvovirus* infection is known to induce anti-DNA and anti-lymphocyte antibodies in some individuals.

Neutropenia Secondary to Parvovirus Infection

Infection of normal individuals with B19 is accompanied by mild neutropenia 10–14 days after an intranasal injection; this is the time of fever, maximum viremia, and the IgM response to the viral infection. The neutropenia lasts for approximately a week. There have been several reports dealing with the effects of B19 infection and anemia, but also accompanied by lower numbers of myeloid precursors or mature neutrophils. Typically the neutropenia would only last a few days. One study found IgG antibodies to red cells, neutrophils, or platelets in four children with B19 infection. The neutropenia resolved within 10 days in all of these children, who were subsequently proven to have acute *Parvovirus* infection by elevated IgM titers. Interestingly, the anti-B19 IgM was detected after the neutropenia resolved in one patient.

Parvovirus has also been linked to autoimmune neutropenia in children. Typically the neutropenia lasts a median of 19 months (range: 6–64 months), with spontaneous recovery. IgM antibody to B19 has been found in a series of five patients with autoimmune neutropenia and accompanying anti-neutrophil NA-1 antibody. These authors failed to find the viral DNA by PCR analysis.

A larger study of children with chronic autoimmune neutropenia showed evidence of B19 DNA by PCR in the bone marrow of 15/19 children tested. Four of six sera specimens taken at the time of the bone marrow sample had IgG antibody to B19. None had IgM titers, although the immune response to B19 is often defective or delayed in chronic B19 infection. Since no control patients had evidence of B19 in their bone marrow, it is unlikely that contamination of the DNA specimens could be blamed for the 15/19 positives in the neutropenic patients.

B19 Infection in Patients with Congenital or Acquired Immunodeficiency States

In patients with either congenital or acquired immunodeficiency, B19 infection may become chronic, resulting in persistent viremia and chronic bone marrow failure. The clinical illness in such patients is usually characterized by acute anemia that is persistent, with or without neutropenia or thrombocytopenia; chronic viremia; and, on bone marrow examination, erythroid hypoplasia with giant vacuolated proerythroblasts similar to those described in acute B19 infection. Spontaneous recovery has been reported. Temporary cessation of immunosuppressive agents usually results in clearance of viremia and resolution of hematologic manifestations. Prompt decrease in viremia, increase in reticulocyte count, and increase in hemoglobin usually follow intravenous immunoglobulin (IVIG) administration. Long-term remissions have been documented, but repeated administrations are frequently necessary to sustain or reinduce remissions. Chronic B19 infection has been reported to occur in patients with a variety of underlying immunodeficiency states (*Table 117.2*).

Effective therapy of B19-induced pure red cell aplasia in immunocompromised patients consists of infusion of commercially available immunoglobulin preparations. These are good sources of neutralizing antibodies because most adult populations have been exposed to the virus. Patients with acquired immunodeficiency syndrome respond to a 5–10-day course of IVIG, but relapses are common. A second course or maintenance IVIG infusions may be required. In patients who are undergoing therapy with immunosuppressant drugs, temporary cessation of therapy may result in clearance of viremia and recovery of cytopenia. Measurement of serum virus can be helpful in determining optimal therapy and predicting relapse.

Table 117.2
Immunodeficiency disorders that have been associated with chronic Parvovirus B 19 infection

Congenital immunodeficiency
Nezelof syndrome
Common variable immunodeficiency
Severe combined immunodeficiency
Fetus
Others
Acquired immunodeficiency
Human immunodeficiency virus infection
Malignancy
Acute lymphoblastic leukemia
Acute myeloid leukemia
Non-Hodgkin lymphoma
Brain tumors
Wilms tumor
Rhabdomyosarcoma
Organ transplant recipients
Renal transplantation
Liver transplantation
Cardiac transplantation
Bone marrow transplant recipients
Collagen-vascular diseases
Systemic lupus erythematosus
Rheumatoid arthritis

Vaccine Development

Effective vaccines have been developed for animals, and the prospects for a human Parvovirus B 19 vaccine are good. The availability of a genetically engineered expression system capable of producing unlimited quantities of B19 viral capsid antigens has made it possible to consider vaccine development. Viable candidates for B19 vaccines are now available, and vaccines should be in human trials soon.

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