

Parvovirus B19 and the New Century

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(See the article by Lindblom et al. on pages 528–36)

Since the discovery of parvovirus B19 by Ivonne Cossart 25 years ago, the knowledge of infection due to this virus has evolved from self-limiting erythema infectiosum in immunocompetent children to lethal cytopenia in immunocompromised patients. Now, it is possible to prevent these life-threatening parvovirus B19-mediated diseases [2, 3].

In this issue of *Clinical Infectious Diseases*, Lindblom et al. [1] comment on how parvovirus B19 infection causes severe cytopenia and can mimic a leukemic relapse or therapy-induced pancytopenia in children with acute lymphoblastic leukemia, causing significant longer periods without chemotherapy and a higher number of blood transfusions in parvovirus B19 DNA-positive children, compared with parvovirus B19 DNA-negative patients ($n = 99$). In their cohort of 99 patients, 18 were parvovirus B19 DNA positive at the time of diagnosis or during therapy, and only 1 child was infected after chemotherapy. The number of days of unwanted treatment interruption was significantly higher for parvovirus B19-positive

patients than for parvovirus B19-negative patients and was associated with poor prognosis.

The parvovirus B19-positive patients, who received multiple courses of systemic chemotherapy, required longer hospital stays, frequent blood sampling, obtainment of multiple bone marrow specimens, multiple transfusions of RBCs or platelets, and cessation of maintenance chemotherapy for ≥ 3 weeks. To avoid subsequent uncertain diagnoses, an assay to detect parvovirus B19 should be performed at diagnosis of leukemia and during treatment of parvovirus B19-seronegative patients who exhibit unexplained cytopenia.

Modern diagnostic analysis of parvovirus B19 infection usually includes measurement of parvovirus B19 IgG and IgM antibodies in blood samples and parvovirus B19 DNA in blood or tissue samples and especially in bone marrow samples (by quantitative PCR [4]). Morphologically, bone marrow aspirate samples do not show mature erythroid precursors but do show characteristic giant pronormoblasts at the time of acute infection [2].

In the past, parvovirus B19 was identified as an uncommon virus (with very little interest for the medical studies) and has attracted relatively little attention from clinicians and immunologists. Usually, adults presenting with symptomatic parvovirus B19 infection rapidly develop cellular immune responses with multiple specificities which rise to high levels and are maintained for many months. In a few

cases, parvovirus B19 DNA was detected in peripheral blood cells for >6 months [5].

It is also possible that viral antigen is retained (e.g., on skin and follicular dendritic cells) following the extremely high burden that appears during acute infection. Alternatively, subgenomic particles may be generated after the acute period, in the absence of full viral replication. The humoral response plays a well-documented role for viral neutralization, but there is also evidence that low-level persistence can occur in certain cases.

Parvovirus B19 is not classically persistent in normal infection and is present in only $\sim 2\%$ of bone marrow samples from healthy subjects [5, 6]. However, it seems that 10% of the children with hematologic malignancies but without concomitant viremia may have both infectious virus and residual DNA from remote infection.

Parvovirus B19 infection has been recognized as an important cause of severe anemia in immunocompromised patients, including organ transplant recipients, patients with congenital and acquired immunodeficiencies and leukemic patients receiving maintenance or consolidation chemotherapy [7–11]. Lindblom et al. [1] included in their study patients who had at least 1 bone marrow sample available for parvovirus B19 analysis (497 total samples). The authors also identified parvovirus B19 DNA in samples from 15% of these patients over 5.5 years.

Cases of parvovirus B19 have been re-

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ported in many different countries of Europe, in Ghana, in Brazil, and in other countries, making the infection a worldwide public health problem [12]. It is possible that this virus has a high mutation rate, because it is a characteristic form of the family *Parvoviridae*.

It is possible that an erythrovirus (V9) that is markedly different from parvovirus B19 and other human viruses provisionally named bocaviruses, with poorly understood epidemiological characteristics and disease associations, can be newly discovered [13, 14]. Recent advances in diagnosis and pathogenesis, new insights in the cellular immune response, and newly discovered genotypes of human parvoviruses form a platform for the development of modern therapeutic and prophylactic alternatives [2, 3, 5, 6].

There is no specific antiviral drug against parvovirus B19 infection, but a number of alternative options to eliminate the virus can be recommended, including blood transfusion, anti-inflammatory drugs, and intravenous immunoglobulin. No vaccines for the virus are currently approved.

Most studies have previously reported that treatment of persistent parvovirus B19 infection with intravenous immunoglobulin may provide resolution of abnormal blood counts [15, 16]. However, reports of complications, including acute myocardial infarction, acute renal failure, and, more rarely, thrombotic events, have emerged.

Previous reports seem to suggest that sucrose-based products are commonly associated with acute renal failure, which is caused by sucrose uptake in renal proximal tubule cells, with subsequent cellular swelling and occlusion of the tubular lumen (osmotic nephrosis). This is one of the most serious and potentially lethal toxicities of intravenous immunoglobulin [17–20]. A search of the literature has revealed up to 114 cases of intravenous immunoglobulin-related acute renal failure, with 17 reported deaths.

Recently, several studies [21–24] (in-

cluding a randomized, double-blind, phase 1 trial) have reported on a recombinant human parvovirus B19 vaccine composed of the VP1 and VP2 capsid proteins and formulated with MF59C.1. All volunteers became parvovirus B19 seropositive after receiving at least 2 doses of vaccine. There were no deaths or serious adverse events during the study [24].

In September 2007 in the United States, the National Institute of Allergy and Infectious Diseases initiated a phase I/II study of the safety and immunogenicity of a recombinant human parvovirus B19 vaccine [25]. Perhaps, in the near future, the vaccine could be used to prevent transient aplastic crisis in patients with sickle cell disease or other hemolytic anemias and in immunodeficient patients with pure red cell anemia [3] and to prevent persistent arthropathy in adults or in parvovirus B19-seronegative women with hydrops fetalis (when inoculated early during pregnancy).

In addition, a vaccine may have important therapeutic function in the context of the following diseases (coexisting morbidities):

1. A role of parvovirus B19 in rheumatoid arthritis has not been proven. Many viral infections, including parvovirus B19 infection, induce the production of autoantibodies. For example, parvovirus B19 infection could induce antibodies to double-stranded DNA, antinuclear soluble antigens, cardiolipin, and rheumatoid factor. The autoantibody production most likely results from both polyclonal stimulation of immune responses and production of polyspecific anti-B19 antibodies [26].

2. Symptomatic parvovirus B19 infection associated with severe chronic anemia is an uncommon problem in HIV-infected children who live to up to 2 years of age and are not severely immunocompromised. Parvovirus B19 infection should continue to be considered in the differential diagnosis of anemia in HIV-infected children [27].

3. In 1990, it was suggested that B19

infection might be a causative factor in some cases of severe anemia among young children in areas where malaria is endemic. *Plasmodium falciparum* infection is an important risk factor for severe anemia. The analysis of the results revealed that the association of parvovirus B19 infection in the context of severe anemia is not altered by malarial infections and that the effects of both are additive. The World Malaria Report in 2005 showed that ~1 million people die each year due to malaria, mostly in African countries south of the Sahara [28, 29].

4. In Nigeria, 45,000–90,000 newborns per year are born with sickle cell disease, and in the United States, up to 70,000 persons per year experience this disorder [30].

Further investigations of the relationship between parvovirus B19 infection and children undergoing chemotherapy for hematological malignancies is warranted. Factors that predispose this population to complications of parvovirus B19 infection include impaired immune response and, possibly, deficient erythropoietin production and decreased erythrocyte count [31, 32].

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