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Parvovirus B19 infection

Thomas Tolfvenstam*, Kristina Broliden

Department of Medicine, Solna, Unit of Infectious Diseases, Center for Molecular Medicine, Karolinska Institutet, Karolinska University Hospital, B2:00, SE-17176 Stockholm, Sweden

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SUMMARY

Human parvovirus B19 (B19) is common in society. Among adults, more than 50% have contracted the infection and immunity is believed to last lifelong. Infection occurs in a few percent of pregnancies, and albeit rare it can then cause fetal anemia, non-immune fetal hydrops and fetal death. Among cases with fetal demise, B19 is found in significant numbers, especially in the second and third trimesters of pregnancy. There is no specific treatment or prophylaxis available against B19 infection, but counseling of non-immune mothers and active monitoring of confirmed maternal infections with intervention to correct fetal anemia is likely to decrease mortality. Passive immunization also has potential to resolve fetal complications, but needs further study.

1. Introduction

Parvovirus B19 (B19) is a common infection in humans and more than 50% of adults have contracted the virus.[1] It was discovered by Yvonne Cossart in 1975 and received its peculiar name as it was identified in sample 19 of panel B in a project surveying hepatitis B.[2] The virus was later shown bearing features of the Parvoviridae family. B19 infection during pregnancy can cause several serious complications to the fetus, such as fetal anemia, hydrops fetalis and fetal death. Teratogenic effects are rarely described. There is currently no specific prophylaxis or treatment against B19, but fatal outcomes can be prevented when maternal infection is detected by active management and symptomatic treatment of the fetus.

2. The virus

B19 is a member of the Parvoviridae family and belongs to the genus *Erythrovirus*, named so because of a pronounced tropism for erythroid precursor cells. The virus causes pathology through blocking erythropoiesis and causing inflammation.[3] B19 is a single-stranded, non-enveloped DNA virus and one of the smallest viruses known to infect mammalian cells.[4] B19 is physically and genetically stable, and differences in clinical manifestations of B19 infection have not been explained by B19 sequence variability.[5]

In addition to B19, two other similar genotypes are described in the same genus, but these variants are not readily discriminated by available B19 serology and polymerase chain reaction (PCR) assays, and the potential pathology has yet to be established.[6] Recently, a novel persisting virus, parvovirus 4 (PARV4), comprising two genotypes has been identified and suggested to transmit through parenteral or sexual routes.[7,8] The only other human-infecting virus in the family, bocavirus, was identified in 2005 and associated with respiratory infection and gastroenteritis in children.[9]

3. Epidemiology and transmission

B19 is transmitted through the respiratory route, but can also be transmitted vertically from the mother to the fetus, through bone marrow (BM) and organ transplantations, and via transfused blood products.[10–12] It is common worldwide, and the seroprevalence increases with age, so that 15% of preschool children, 50% of younger adults and about 85% of the elderly show serologic evidence of past infection.[13] In developing countries the seroprevalence has been shown to be a little higher, whereas in isolated communities seroprevalence is below 10%.[14–16] Infection appears to confer lifelong immunity in immunocompetent hosts. Although the seroprevalence is high, viremia or presence of viral DNA in peripheral blood is rare in healthy individuals. The frequency of B19 viremia in voluntary blood donors has been estimated at rates of 1:100 to 1:35 000.[17–20] The frequency varies greatly depending on the immune status of the host, epidemic periods and sensitivity of the methodology used. Presence of B19 DNA in BM samples can be found by PCR in 2% of healthy individuals and in up to 15% of children with hematologic malignancies without concomitant viremia.[21–24] The persistency of B19 DNA may represent both infectious virus and residual DNA from remote infection.

The incidence of infection shows a seasonal variation in temperate climates, being more common during winter and early

* Corresponding author. Tel.: +46 8 51770000; fax: +46 8 51771806.
E-mail address: Thomas.tolfvenstam@ki.se (T. Tolfvenstam).

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spring.[25] Epidemics are noted at intervals of about 3–4 years, with outbreaks of erythema infectiosum (EI) and B19-related disease. Most infections occur in children; adults at risk are household contacts, or those working at daycare centers or schools.[26–29] The secondary attack rate during epidemics of EI is about 50% in susceptible children and 25% in susceptible teachers.[28–30] Nosocomial transmission may occur, and is a potential risk in pediatric and neonatal wards during the acute phase of the disease when viral titers are high. In pregnancy, the risk of vertical transmission to the fetus when the mother becomes infected is ~30%.[10,31]

4. Symptoms and complications

About 30–50% of pregnant women are susceptible to B19 infection, and maternal infection is reported to occur in a few percent of pregnancies.[32–35] The incubation period to maternal symptoms when they occur is 4–14 days after exposure. In 25% of infected adults, the infection passes without symptoms, but transmission to the fetus may still occur with clinical symptoms evident from the fetus weeks to months later. Clinical symptoms in adults in general include a prodromal unspecific phase of fever, myalgia, coryza, headache and nausea which coincides with contagiousness. This phase may be followed after about a week by an erythematous maculopapular exanthema on the trunk and limbs. Arthropathy - arthritis are common in women and adolescents and may be the only clinical manifestation of the infection. Maternal B19 infection follows a seasonal and annual variation, and during epidemics the incidence of fetal infections rises.[35,36] Most cases of fetal B19 infections are asymptomatic and resolve spontaneously. Infants can thus be born healthy despite evidence of intrauterine infection diagnosed by the presence of IgM in umbilical cord blood.[33] Malformations as a consequence of intrauterine B19 infection have been reported in a few isolated cases, but have not been concluded to be a common feature of this infection.[37,38]

4.1. Hydrops fetalis

The association between fetal B19 infection and the development of non-immune fetal hydrops was first proposed by Brown et al., and it is estimated that about 15–20% of cases of non-immune hydrops fetalis are caused by B19.[31,39,40] The infection causes anemia, hypoalbuminemia, inflammation of the liver and possible myocarditis, leading to cardiac failure and subsequent development of fetal hydrops.[41] The condition most often resolves spontaneously but can also result in fetal death, with a mean timespan between maternal infection and fetal symptoms of six weeks, but it may be several months in rare cases.[31,42–44]

4.2. Fetal death

B19 infection during pregnancy is associated with fetal death, mainly in combination with fetal hydrops. The overall fetal loss rate after infection has been estimated at 5–10%, although detection frequencies vary substantially, likely depending on study inclusion criteria, current epidemics and detection methods.[35,45–51] Investigations have shown B19 associated fetal death mainly occurring during the second trimester, but B19 has also been associated with intrauterine fetal death (IUFD) in late gestation, in some studies without signs of fetal hydrops at time of death. B19 DNA has only been found in 3% of cases of spontaneous abortion in the first trimester.[52]

4.3. Pathogenesis of fetal complications associated with B19 infection

The mechanisms underlying clinical outcomes at various times of gestation are not known, but could be the result of different factors; in the second trimester, P-antigen is present on the trophoblast layer in the placenta and allows vertical transmission of B19 to the fetus from the infected mother.[53] The hematopoiesis is at this time located in the liver and is extremely active to increase the erythrocyte cell mass 34-fold to match the raised demand from the growing fetus. At the same time, the lifespan of the red blood cells is decreased to 45–70 days, making the fetus very vulnerable to any pause in the hematopoietic production.[54] The destruction of late erythroid precursors, caused by the B19 infection, leads to severe anemia. In combination with the hepatic inflammation and possibly myocarditis due to B19 infection of cardiac myocytes, these events may result in heart failure and the development of hydrops fetalis. By contrast, in the third trimester, the hematopoiesis migrates to the bone marrow, the need for a quickly increasing red blood cell mass is relieved, and the lifespan of the erythrocytes is increased. The cellular receptor P-antigen is virtually non-present in the third trimester.[53] Taken together this would make development of hydrops fetalis less likely. However, a low-grade persistent fetal and/or maternal infection may also cause IUFD at a later timepoint, and in the case of placental dysfunction even without fetal infection. Degenerative lesions have been shown in the placenta due to the inflammatory response to B19 infection.[41,55–57] In the fetus, myocarditis may be the cause of death due to arrhythmia or cardiac arrest without the development of anemia or hydrops.[41,58] Indeed, investigation of endomyocardial biopsy specimens revealed B19-associated inflammatory changes in 15% of cases of peripartum cardiomyopathy.[59]

5. Diagnosis

Laboratory diagnosis of B19 can be performed using serology, PCR, histopathologic examination and immunohistochemistry. Optimally, several methods are applied to increase the interpretability of the results. B19 IgM is usually present 10–12 days after infection and persists for 3–4 months, sometimes longer.[60] B19 IgG appears shortly after IgM and persists lifelong with slowly decreasing titers unless boosted by subsequent encounters with the virus. In pregnant women and immunocompromised individuals, serological responses must, however, be interpreted with caution as they are not always able to mount a clear antibody response to pathogens.[61,62] A positive PCR test in serum indicates ongoing acute or persistent infection. In cases of intrauterine fetal complications it can be very useful to extend routine analysis of maternal samples with analysis of amniotic fluid or cord blood for viral DNA or RNA by PCR for differential diagnostic purposes including B19.[63–67] Supplementary measurement of B19 antibody avidity and epitope-type specificity in B19 PCR-positive, IgM-negative pregnant mothers can help to non-invasively delineate acute infections.[45,68] Quantitatively, the clinical significance of different serum-titers of B19 DNA is not fully established. In healthy individuals with acute B19 infection, viral titers as high as 10^{12} geq/mL are detectable in blood.[69] However, a marked drop is seen at time of immunoglobulin production and onset of symptoms and titers remain at about 10^3–10^5 for months and even a few years following acute infection.[70,71] In pregnant women, initial viral load was high (mean value: 10^8 geq/mL). During follow-up low level (mean 10^5 geq/mL) persisted for at least 18 weeks in the majority of patients.[62] Future studies will hopefully determine the concentrations of viral load in different tissues and clinical settings to guide the clinicians in therapeutic choices.