PARVOVIRUS B19

A MALEVOLENT INFECTION IN PREGNANCY

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Parvovirus B19 infection is a common viral infection that generally results in an innocuous illness during childhood. However, in pregnant women, parvovirus B19 infections can cause serious complications such as foetal anaemia, hydrops fetalis and spontaneous abortion. Parvovirus B19 can also trigger sequelae such as reactive arthritis and anaemia, particularly in adults. Since clinical symptoms are often absent or ambiguous, serology together with direct pathogen detection plays an important role in diagnosis and prenatal healthcare.

Parvovirus B19

Parvovirus B19 is among the smallest known viruses. It is a single-stranded DNA virus from the family of Parvoviridae with a genome length of 5000 to 5500 base pairs and a diameter of 21 to 23 nm. It was first discovered in 1974, and its designation B19 derives from the code of the sample in which it was coincidentally found. Up until now three different genotypes have been identified, which show low sequence variability. The virus has a very high stability with regards to environmental factors and detergents. Parvovirus B19 replicates predominantly in haematopoietic cells.

Epidemiology

Infections with parvovirus B19 occur worldwide, predominantly in the spring. They spread in local epidemics, mainly in child day care centres, schools and hospitals. In central Europe they can be described as endemic. Primary infections can occur in all age groups, whereby acute cases are found most frequently in six to 15-year-olds. The prevalence of antibodies (IgG) against parvovirus B19 increases with age, amounting for example in Germany to around 35% in four to six year olds, 58% in 10-15 year olds, 70% in 25-29 year olds and 79% in 65-69 year olds. The virus is transmitted by droplets, via blood or blood products or diaplacentally and has an incubation period of four to 14 days.

Clinical Symptoms in Children

Infections with parvovirus B19 manifest in children as fifth disease, also known as slapped cheek syndrome, erythema infectiosum or Sticker's disease. In the prodrome phase the infection typically causes headaches, itching, myalgia and fever. This is followed by exanthema. When the rash appears the patient is no longer infectious. The exanthema begins with an intense redness and swelling on the cheeks with individual areas on the forehead and around the ears. It extends to the arms, buttocks, legs and extremities. The exanthema is characteristically garland-shaped or net-like and lasts for six to 21 days. Lymph node swelling and flu-like symptoms often accompany the rash. Pruritus, subfebrile temperature and arthralgia may also occur. Symmetrical arthritis can occur as a complication in children. Fifth disease may be difficult to differentiate clinically from other diseases such as chicken pox, rubella, measles, scarlet fever or drug-induced exanthema.

Clinical Symptoms in Adults

In adults, symptoms are more intense and the infection can trigger acral erythema and arthritis (acute symmetrical polyarthropathy), which is difficult to distinguish clinically from rheumatoid arthritis. Further, 17 to 33% of all heart muscle inflammation can be attributed to parvovirus B19. Since it multiples in erythroblastocytes, it can cause temporary anaemia. Patients with reduced erythrocyte production, e.g. patients with leukaemia or anaemia, may suffer transient aplastic crisis. In immunocompromised patients complications can be severe and even fatal.

Infections in Pregnant Women

Parvovirus B19 infections are a big threat for pregnant women. Diaplacentally transmitted parvovirus B19 disrupts the foetal blood system, leading to anaemia, hypoxia and in extreme cases to hydrops fetalis and foetal death. Around 5% of acute maternal infections result in spontaneous abortion in the first trimester. From the second trimester the virus attacks the erythroid precursor cells in the liver, interrupting erythrocyte synthesis. Hydrops fetalis develops in around 3-4% of acute infections, manifesting six to eight weeks or more after infection of the mother. Myocardial cells are also probably infected, resulting in heart insufficiency, which intensifies the symptoms of hydrops. Hydrops fetalis is fatal in around 30% of cases.

Diagnostics

The main laboratory methods used for parvovirus B19 diagnostics are viral DNA detection by PCR and serological analysis of specific antibodies. Serology complements the direct detection and is particularly valuable for identifying infections beyond the viraemic phase.

In an acute infection, antibodies of class IgM against the viral proteins VP1 and VP2 are detectable towards the end of the viraemic phase, around 10 days after infection (Figure 1). This is followed at the end of the third week by seroconversion with antibodies of class IgG against the same antigenic structures. After recovery IgM antibodies are generally no longer detectable, while the IgG immune response varies. Typically, the IgG titer against linear epitopes of VP2 drops. Thus a positive response against denatured VP2 is an indicator of a fairly recent infection. The titers against conformational epitopes of VP2 (virus-like particle, VLP) and against VP1 remain. Persons with a positive IgG result against these antigens are considered immune, regardless of the titer.

In a persistent infection, the complete elimination of the virus is delayed. Serologically, the detection of antibodies of class IgG against the non-structural protein 1 (NS1) can indicate a persistent infection, for example in patients with reactive arthritis.

Serological Assays

Anti-parvovirus B19 antibodies can be determined using enzyme immunoassays such as ELISA or immunoblot. The Anti-Parvovirus B19 ELISA utilises microplates coated with highly specific recombinant structural VP2 antigen. The ELISA allows reliable determination of the infection status, as demonstrated by a titer course study in 10 patients with suspected acute parvovirus B19 infection. At the first blood withdrawal IgM antibodies could be detected in all samples, whereas IgG antibodies occurred only at low concentrations or not at all. Ten days later the serological investigation demonstrated IgG seroconversion in three samples, while a significant increase in IgG titer was detected in the other seven sera (Figure 2). In a panel of blood donors the ELISA demonstrated an IgG seropositivity of 68%, in agreement ▷

with the known infection level in adults. In quality assessment schemes the ELISA yielded an agreement with the designated results of 99% for IgG and 98% for IgM. The ELISA can be fully automated and is highly suited to screening large numbers of patient samples.

Line immunoblots allow multiparametric serological determination of the infection status using both linear and conformational epitopes. EUROLINE Anti-Parvovirus B19 test strips are fitted with chips containing four highly specific recombinant antigens (Figure 2): the linear antigens VP1 and VP2, the conformational antigen VLP and the NS1 antigen. With this complete spectrum of antigens, relevant anti-parvovirus B19 antibodies (IgM and IgG) can be determined simultaneously at different stages of infection. In quality assessment schemes the EUROLINE provided 99% agreement with the target results from serologically and/or clinically characterised patient samples. Automated incubation and digital evaluation of results enhances the convenience of the analysis.

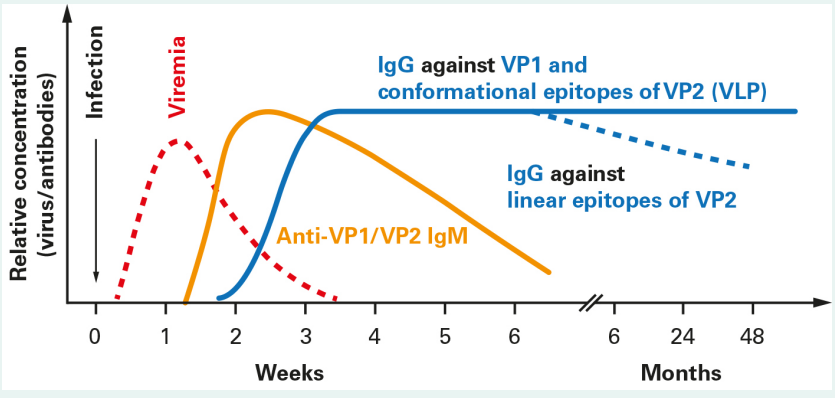
Perspectives

Serological diagnostics for parvovirus B19 are indispensable in pregnant women and in persons suffering from reactive arthritis. Pregnant women exposed to parvovirus B19 should be tested as soon as possible to establish if immunity already exists or if the patient has recently acquired an infection, which poses a risk to the foetus. If an acute parvovirus B19 infection is identified, the foetus must be monitored for anaemia, which can be treated with intrauterine transfusions if necessary. Serological screening as part of prenatal care can, moreover, help to identify seronegative women, who can then be advised on exposure prophylaxis, for example avoidance of nurseries, schools and communal facilities during pregnancy.

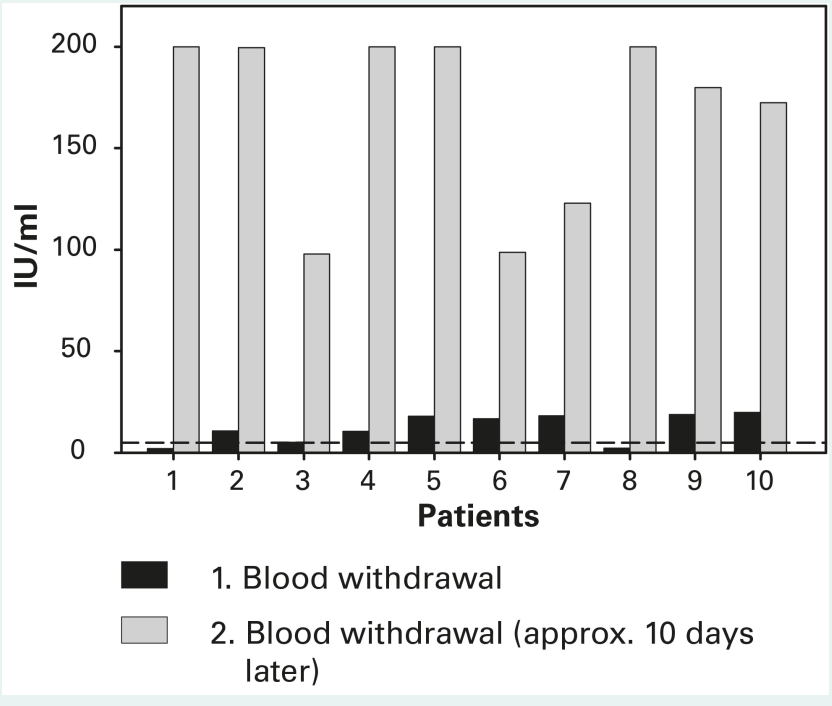
In patients with arthritis the differential identification of an infectious as oppose to an autoimmune origin (e.g. rheumatoid arthritis) aids decision-making regarding therapy. Parvovirus B19 is among the most common viral causes of reactive arthritis and should be tested alongside other frequent infectious triggers such as Borrelia.

A further important application for parvovirus B19 serology is the screening of donated blood and bone marrow products. High-risk patients should only be given blood that has tested positive for anti-parvovirus B19 IgG antibodies to avoid potential virus transmission from acutely infected but asymptomatic donors. ML

▽**Figure 1.** Course of antibodies in an acute parvovirus B19 infection



▽**Figure 2.** IgG titers in acutely infected persons



▽**Figure 3.** Anti-Parvovirus B19 EUROLINE test strip