8.5.20 Parvovirus B19 886

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886 section 8 Infectious diseases 8.5.20 Parvovirus B19 Kevin E. Brown ESSENTIALS Parvovirus B19 (B19V) is a small DNA virus that replicates in eryth- roid progenitor cells, with virus-induced cytotoxicity stopping red cell production. It only infects humans, is endemic in most places, and is transmitted predominantly by the respiratory route. In healthy people it causes the rash illness, erythema infectiosum, also known as ‘fifth disease’ or ‘slapped cheek disease’, associated with minimal drop in haemoglobin, but in patients with increased red cell turnover (e.g. haemolytic anaemia or haemoglobinopathy), it causes transient aplastic crisis; in immunocompromised patients it causes chronic an- aemia; and following maternal infection it leads to hydrops fetalis or fetal loss. Treatment is supportive in most instances, but reduction in iatrogenic immunosuppression and/or intravenous immunoglobulin may be appropriate in some cases. No vaccine is available. Introduction Parvovirus B19 (B19V) is a member of the Parvoviridae, small (c.22 nm), nonenveloped, icosahedral-shaped viruses (Fig. 8.5.20.1), with a linear single-stranded DNA genome of about 5000 nucleo- tides. At least five types of parvovirus infect humans: B19V; adeno- associated viruses; human partetraviruses (Parv4/5) and bocaviruses, and the recently described human bufavirus. To date, only B19V and human bocavirus 1 (HBoV1) have definitively been shown to be a human pathogen. HBoV1 is a respiratory pathogen, associated with respiratory infections and wheezing in young children. Aetiology, pathogenesis, and pathology Based on viral sequence, B19V can be divided into three distinct genotypes (1, 2, and 3). Genotypes 2 and 3 are infrequently detected in Europe or the United States of America. No differences in patho- genicity are observed between the different genotypes, and they are all a single B19V serotype. B19V replication occurs primarily in erythroid progenitors, with the specificity in part due to the limited tissue distribution of the B19V receptor, blood group P antigen (globoside). Infection leads to high titre viraemia (>1012 virus particles/ml or IU/ml) (Fig. 8.5.20.2), and the virus-induced cytotoxicity stops red cell production. In immunocompetent people, viraemia and arrest of erythropoiesis is transient, and resolves as the antibody response is mounted. In those with normal erythropoiesis, the drop in haemoglobin is minimal, but in patients with increased red cell turnover, infection induces a transient crisis with severe anaemia (Fig. 8.5.20.2b). Similarly, in the fetus or anyone who does not mount a neutralizing antibody response which halts the lytic infec- tion, erythroid production is compromised and patients develop chronic anaemia (Fig. 8.5.20.2c). The immune-mediated phase of illness begins 2–3 weeks postinfection as the IgM response peaks, and the rash of fifth dis- ease, arthralgia, and/or frank arthritis appear. The B19 receptor is found on other cell types, including megakaryocytes, endothelial cells, placenta, myocardium, and liver. B19 infection at these sites may be responsible for some of the more unusual presentations. Rare people who lack P antigen are naturally resistant to B19V. Epidemiology B19V exclusively infects humans, and

the virus is endemic in virtually all parts of the world. Transmission is predomin- antly via the respiratory route, prior to the onset of the rash or arthralgia. About 50% of 15-year-old children have detectable IgG, increasing to more than 90% of older people. In pregnant women there is an estimated annual seroconversion rate of ap- proximately 1%. The secondary infection rate within households approaches 50%. Prevention High titre B19V is not unusual in blood, and transmission occurs via transfusion, particularly of pooled components. B19V is resistant to heat and solvent/detergent inactivation. Plasma pools Fig. 8.5.20.1 Typical appearance of parvovirus B19, with characteristic 22 nm icosahedral particles. Courtesy of Dr Hazel Appleton, Virus Reference Department, Public Health England.

8.5.20 Parvovirus B19 887 are currently screened by nucleic acid testing and high titre pools are discarded. Clinical features The clinical manifestation of B19V infection varies widely, depending on the host (Table 8.5.20.1). Most of these infections are asymptomatic. In healthy, immunocompetent people, B19 in- fections causes erythema infectiosum, also known as ‘fifth disease’ or ‘slapped cheek disease’ due to the characteristic facial rash which appears several days after a minor febrile prodrome. The rash may spread and develop a lacy reticular appearance, but the intensity and distribution of the rash varies and is difficult to distinguish from other viral exanthems. Rarely the rash can present as papular- purpuric gloves and socks syndrome; see Fig. 8.5.20.3. (a) 15 13 11 9 7 5 3 1 B19 virus 100 Clinical manifestations Clinical manifestations Clinical manifestations 10 8 6 4 14 Haemoglobin (g%) Reticulocytes (g%) 10 8 6 4 14 Haemoglobin (g%) Reticulocytes (g%) 10 0.2 0 4 14 Haemoglobin (g%) Reticulocytes (g%) 10 10 10 Days Fever, chills headache myalgia Rash arthralgia Inoculation or infection 6 2 20 Normals 10 Days Infection 6 2 20 TAC 10 Days Symptoms of anaemia Symptoms of anaemia Infection 6 2 20 PRCA 10 IgM and IgG IgG IgG (b) 15 13 11 9 7 5 3 1 B19 virus (c) 15 13 11 9 7 5 3 1 B19 virus IgM IgM 0 10 50 B19 antibodies 0 10 50 100 B19 antibodies 0 10 50 100 B19 antibodies Fig. 8.5.20.2 Schematic of the time course of B19 infection in (a) erythema infectiosum (EI), (b) transient aplastic crisis (TAC), and (c) pure red cell aplasia (PRCA) or chronic anaemia. The B19 virus titres are given in log 10 IU/ml. From Young NS, Brown KE (2004). Parvovirus B19. N Engl J Med, 350, 586–97. Copyright © 2004 Massachusetts Medical Society. Reprinted with permission. Table 8.5.20.1 Diseases associated with parvovirus B19 infection and methods of diagnosis Disease Host(s) Pathogenesis IgM IgG Quantitative PCR Fifth disease Healthy children Immune-mediated Positive Positive

> 104 IU/ml Polyarthropathy syndrome Healthy adults (especially women) Immune-mediated Positive within 3 months of onset Positive 104 within 3 months of onset Transient aplastic crisis (TAC) Patients with increased erythropoiesis Erythroid cytotoxicity Often >1012 IU/ml, but rapidly decreases Persistent anaemia/ pure red cell aplasia Immunocompromised patients Impaired neutralizing antibody Negative/weak positive Negative/weak positive Often >1012 IU/ml, but should be >106 IU/ml in the absence of treatment Hydrops fetalis Fetus Erythroid cytotoxicity and impaired neutralizing antibody Positive amniotic fluid or tissue

888 section 8 Infectious diseases In adults, the ‘slapped cheek’ may not be apparent. Although uncommon in children, a symmetrical polyarthropathy, affecting the small joints of the hands and occasionally the ankles, knees, and wrists occurs in c.50% of adults, more often in women than

men. Resolution usually occurs within a few weeks, but recurring symptoms can continue for months. Patients with increased erythropoiesis (i.e. those with haemo- lytic anaemia or haemoglobinopathy) develop transient aplastic crisis, with symptoms of acute anaemia. Bone marrow examin- ation reveals an absence of erythroid precursors and the presence of characteristic giant pronormoblasts. In the immunocompromised (i.e. patients with HIV, leukaemia, and following transplantation), B19 infection may lead to chronic anaemia or pure red cell aplasia. Patients have persistent anaemia with reticulocytopenia, absent or low levels of B19 IgG, high levels of B19 DNA in serum, and often scattered giant pronormoblasts in the bone marrow. Transient neutropenia, lymphopenia, and thrombocytopenia may be seen, and B19V occasionally causes a haemophagocytic syndrome. Infection with B19V during pregnancy can lead to hydrops fetalis and fetal loss. The risk of transplacental fetal infection is about 30%, and the risk of fetal loss, predominantly in the second trimester, 9%. The risk of congenital infection is less than 1%. Although B19V does not appear to be teratogenic, there are anecdotal reports of eye damage and central nervous system abnormalities. Cases of con- genital anaemia have also been described. B19V probably causes 10–20% of all cases of nonimmune hydrops. B19V infection is rarely associated with hepatitis, vasculitis, myocarditis, glomerulosclerosis, and central nervous system disease. Diagnosis In immunocompetent people, B19V infection is usually diag- nosed by the detection of B19 IgM antibodies (Table 8.5.20.1). IgM can be found at the time of rash in erythema infectiosum and by the third day of transient aplastic crisis in patients with haem- atological disorders. IgM remains detectable for about 3 months. B19 IgG appears by the seventh day of illness and remains for life. Detection of B19 DNA should be used for the diagnosis of early transient aplastic crisis or chronic anaemia. Although levels fall rapidly with the development of the immune response, low levels of DNA (103 IU/ml or less can be detectable by polymerase chain reaction (PCR) for months and even years after infection, even in healthy people), so a quantitative PCR should be used for diag- nosis. At the height of viraemia, more than 1012 B19 DNA IU/ml of serum can be detected, but titres fall rapidly within 2 days. Patients with aplastic crisis or B19-induced chronic anaemia generally have more than 105 IU/ml B19 DNA. Treatment No antiviral drug is available, and treatment is often only symptomatic. B19-induced transient aplastic crisis may require blood transfusions, and intrauterine blood transfusion can prevent fetal loss in some cases of fetal hydrops. In patients on chemotherapy, stopping treat- ment temporarily may result in an immune response and resolution, but if unsuccessful or inapplicable, intravenous human normal im- munoglobulin may cure or improve persistent B19 infection. These patients and those with transient aplastic crisis should be considered infectious. Administration of immunoglobulin is not beneficial for erythema infectiosum or B19-associated polyarthropathy. Prevention in the future No vaccine is currently approved for parvovirus B19. A vaccine based on viral-like particles expressed in yeast cells is in develop- ment and may overcome some of the problems with the earlier insect-cell based vaccine. FURTHER READING Brown KE, et al. (1994). Resistance to parvovirus B19 infection due to lack of virus receptor (erythrocyte P antigen). N Engl J Med, 330, 1192–96. Chandramouli S, et al. (2013). Generation of a parvovirus B19 vaccine candidate. Vaccine, 31, 3872–78. Kurtzman GJ, et al. (1987). Chronic bone marrow failure due to per- sistent B19 parvovirus infection. N Engl J Med, 317, 287–94. Maple PA, et al. (2014). Identification of past and recent parvovirus B19 infection in immunocompetent individuals by quantitative PCR and enzyme immunoassays: a dual-laboratory study. J Clin Microbiol, 52, 947–56. Young NS, Brown KE (2004). Parvovirus B19. N Engl J Med, 350, 586–97. Fig. 8.5.20.3 A very unusual presentation of parvovirus B19 infection

is papular-purpuric gloves and socks syndrome. From Gutermuth J, et al. (2011). Papular-purpuric gloves and socks syndrome. Lancet, 378, 198, Copyright © 2011, with permission from Elsevier.

Revision #1
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