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HUMAN B19 PARVOVIRUS INFECTION: AN EXAMPLE OF MULTIPLE PATHOGENIC EFFECTS DETERMINED BY DIFFERENCES IN HOST SUSCEPTIBILITY

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B19 infection offers some general lessons about human viruses and their possible effects on the human host, as follows: (1) Ubiquitous apparently benign viruses may have severe effects on a compromised host. The virus may be invariable but the host can have diverse susceptibilities. (2) B19 and some other human viruses (though for none is the evidence so clear as for B19) have narrowly targetted effects. The host cell of B19 is a specialised progenitor of mature red cells: impairment of the function of this cell by B19 may cause profound anaemia. (3) The 'normal' host response to B19 may also cause disease, though this is self limiting. (4) The effects of malfunction of the virus' target cell are exacerbated when the immune response is impaired by congenital or acquired immunodeficiency, immunosuppressive therapy or, in the case of the fetus, developmental immaturity that allows the virus to persist.

Key words: Parvovirus B19 – pathogenesis – host susceptibility – giant pronormoblast – fifth disease – aplastic crisis – hydrops fetalis

Medical virologists are not accustomed to think of themselves as parasitologists, whom they associate with disease due to larger life forms than viruses that infect or infest human and other hosts. They have, nevertheless, a contribution to make to this meeting. The organisms with which they work are strictly intracellular and most are fastidious in their choice of hosts. Viruses are, in common parlance, highly parasitic. The human parvovirus B19, for instance, infects only man. It has a peculiar cell tropism for an early erythrocyte progenitor, the giant pronormoblast, and this cell can be regarded as its host (Mortimer et al., 1983). *In vitro,* the virus can only be propagated in systems that contain the cell: marrow explants, peripheral blood cultures and fetal liver cultures. In all cases the cell must be stimulated into mitosis by addition of erythropoietin. In vivo most of the virulent effects of B19 infection are ascribable to its destructive tropism for this red cell progenitor leading to anaemia in hosts who have an impaired red cell reserve or are unable rapidly to eliminate the virus because of congenital or acquired immune paresis (CDC, 1989). It is these host factors rather than any variability in the virulence of the infecting virus strains that determines the outcome of B19 infection.

RECOGNITION AND DIAGNOSIS OF B19

Although parvovirus B19 is ubiquitous in human populations its existence was not recognised until 1975, and then only by chance (Cossart et al., 1975). It is mainly an infection of young children and their family contacts, and it usually spreads by the respiratory route. However, it is less infectious than, for instance, measles and chickenpox, and many adults – as many as 30% – are susceptible to it. Serological and genomic assays for B19 infection were developed during the 1980s and have been used to elucidate the range of its pathogenic effects in man (Cohen et al., 1983). It is possible to detect circulating virus and antigen by electron microscopy and serologically, and to measure specific IgM and IgG class antibody responses in acute infection. B19 DNA can be directly measured in plasma and serum by 'dot blot' hybridisation and, *in situ*, in target tissues such as bone marrow, liver and placenta. Recently, viral DNA has been amplified by PCR, though in most cases this is unnecessary for diagnosis as the DNA is abundant in those clinical circumstances where investigation is required

PATHOGENIC EFFECTS OF B19

The effects of B19 virus on the immunologically mature human host are largely benign and indeed infection is often (perhaps 50% of all cases) subclinical. The typical disease in childhood is called fifth disease or,

more descriptively, slapped cheek syndrome. In adults, particularly young women, B19 infection may cause a polyarthropathy which is sometimes severe and disabling, and may persist for a month or more (Woolf et al., 1989). However, it seems always to resolve and there is no firm evidence to link B19 to rheumatoid or other chronic arthritides.

The special interest of B19 as a parasite does not lie in the manifestations of disease in the normal host, but it in its effects on the compromised host. What makes the human host vulnerable is (i) a too heavy burden on the erythropoietic mechanism, (ii) an inability to eliminate the virus because of immune deficiency or (iii) a combination of both of these factors. It can be predicted that where either or both factors is present B19 infection will be severe and often persistent in its clinical effects, sometimes threatening life.

Severe B19 related illness was first reported as an effect of B19 infection in children with sickle cell disease (Pattison et al., 1981). 'Aplastic crisis' ensues when the bone marrow cannot, because of B19 virus infection of pronormoblastic cells, continue to replace haemolysing red cells at the necessary rate. This is an acute, profound anaemia that is only reversed when the normal immune response eliminates the virus. The crisis may also arise in other forms of congenital or acquired haemolytic anaemia and in anaemia due to chronic blood loss, nutritional deficiencies and other avitaminoses.

The normal process of red cell replacement can also be disturbed when immunodeficiency prolongs the usually short lived impact of B19 infection on erythropoiesis. Once AIDS had been recognised as a new disease, it was possible to predict that patients with it who were exposed to B19 infection would become chronically infected and develop anaemia. In these cases the drug zidovudine, not B19 virus, the true culprit, has often been blamed for a fall in haemoglobulin. Similarly, children with leukaemia, especially those receiving cytotoxic therapy, may fail to eliminate B19 quickly and become anaemic, more because of the effect of the virus on its host cell than because of chemotoxic suppression of haematopoiesis. This may be demonstrated by the ability of heterologous antibody to B19 in the form of immunoglobulin or plasma to cause a reticulocytosis and reverse the anaemia in these patients (Kurtzman et al., 1988).

IMMUNOPATHOLOGICAL ASPECTS OF B19 INFECTION

The immune response, although essential in preventing persistent infection and disease, is probably responsible for the rash and the arthropathy associated with B19 infection. Infection in leukaemic children and AIDS patients is often asymptomatic ie without rash or arthropathy until anaemia presents itself. In pregnancy, too, the mild physiological immunoparesis may both prolong infection (increasing risk to the fetus) and, by preventing rash or joint symptoms developing, allow the risk to go unrecognised. It is a sign of the role of circulating antibody in provoking the rash of B19 infection that leukaemic carriers of B19 infection develop a rash when they receive immunoglobulin treatment to reverse their anaemia.

FETAL DISEASE

In some other clinical circumstances, notably in the middle trimester of pregnancy, the effect of the virus in preventing its target cell from fulfilling its physiological role and the immunological tolerance due to fetal immaturity combine to cause severe disease. B19 infection crosses the placenta in up to a third of maternal infections and the fetus is most vulnerable between 16 and 24 weeks of gestation when the red cell 'compartment' is expanding rapidly (PHLS Working Party, 1990). At this time hydrops fetalis can develop. There is severe anaemia, effusion into cavities, heart failure and perhaps myocarditis, ie a direct viral effect on cardiac muscle. Many of these pregnancies end in miscarriage and stillbirths. Intra-uterine transfusion has been attempted to correct the fetal anaemia but it is probable that those fetuses that survive do so because of their growing immune competence and ability to eliminate the virus. It is unclear whether the benefits of intra-uterine transfusion in this situation outweigh its risks.

VIRUS STABILITY

The effects of B19 virus on the host described above are direct and often severe, but they depend on underlying disease or immaturity for their virulence. The virus itself does not appear to vary in the range of effects it can produce and the same outbreak of B19 infection may manifest any or all of the clinical complications described above. This is consis-

tent with the relatively stable restriction enzyme patterns found when viral DNA from specimens collected in different parts of the world at different times have been analyzed (Mori et al., 1987). Unlike other, especially RNA viruses, and most other parasites, B19 virus isolates are almost uniform.

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