HUMAN PARVOVIRUS B19 INFECTION

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THE VIRUS.

Parvoviruses are among the smallest of the DNA viruses (1). Members are unique for their requirement for dividing cells for replication (1). Individual members are species specific and exhibit limited tissue tropism among various species (2). In animals, they are known to cause a variety of diseases including an often fatal enteritis in cats, dogs and mink, infertility and fetal death in pigs and immune complex glomerulonephritis in mink (2). The only member of the genus *parvovirus* known to cause human disease is Parvovirus B19 (2, 3). Two other members of this family, the fecal parvovirus and the RA1 virus, are reported to be potential human pathogens.

Parvovirus B19 contains single stranded DNA encapsulated by two structural proteins (VP1 and VP2), that are 58 and 77 kDa proteins (4-6). The 5. 5 kilobase genome also encodes for at least one other protein an 84 kDa protein, that is present during intracellular viral replication, but not in mature virions (4, 7, 8). This protein, called NS1, is required for encapsulation of viral DNA and is itself cytotoxic (8). The genome is contained in an nonencapsulated icosahedral protein coat (1). The single stranded DNA contains terminal hairpin palindromic ends that are identical terminal repeats 383 bases in length (9, 10). B19 has been grown in vitro in erythroid precursor cells, but not in a host of other cell types. This tissue predilection is consistent with the clinical observation that the viral infection inhibits erythropoiesis (11). Among Parvovirus B19 isolates, variations in restriction enzyme sites has been detected, but antigenic differences have not been detected (12). Viral replication is dependent on host enzymes and occurs in the cell nucleus of rapidly dividing cells (1). Parvovirus B19 is a heat stable enzyme that can survive at 60 °C for up to 12 hours.

HISTORICAL PERSPECTIVE

In 1975, Cossar et al. (13) reported the identification of parvovirus-like particles in human serum. During routine screening for the presence of hepatitis B antigen, they found several specimens with a positive immunoelectrophoresis result, but negative hemagglutination and radioimmunoassay results. In 11 of these serum specimens, one of which was encoded B19, a novel virus was identified. Electron microscopy detected spherical 20 to 25 nm viral particles with many disrupted fragments and empty shells and serological reactions demonstrated that the antigen was distinct from hepatitis

B. The authors speculated that this new virus could be an infectious agent, noting that 30% of adults had preexisting antibody to the antigen. The virus was later identified as a Parvovirus and given the label B19.

Table I

Age (years)							
1-5	6-10	11-20	21-30	31-40	41-50	51-60	61-68
2/24 (8%)	5/26 (19%)	29/71 (41%)	96/205 (46%)	48/139 (34%)	53/147 (36%)	34/88 (39%)	28/68 (41%)

EPIDEMIOLOGY.

The prevalence of anti-Parvovirus B19 IgG antibodies in 76 children and 692 adult blood donors is illustrated in Table I (14). Evidence of prior infection was uncommon in 1-5 years olds and increased to 40% in 11-20 years olds. Therefore, infection with Parvovirus B19 is common. It has been suggested that the incidence of infection with Parvovirus B19 is highest in the spring and summer. Evidence supporting this claim was obtained from a review of the monthly incidence of Parvovirus B19 infections that were reported in Great Britain between 1984 and 1986 (15). It is clear from figure 1 that the incidence is highest in the spring and summer.

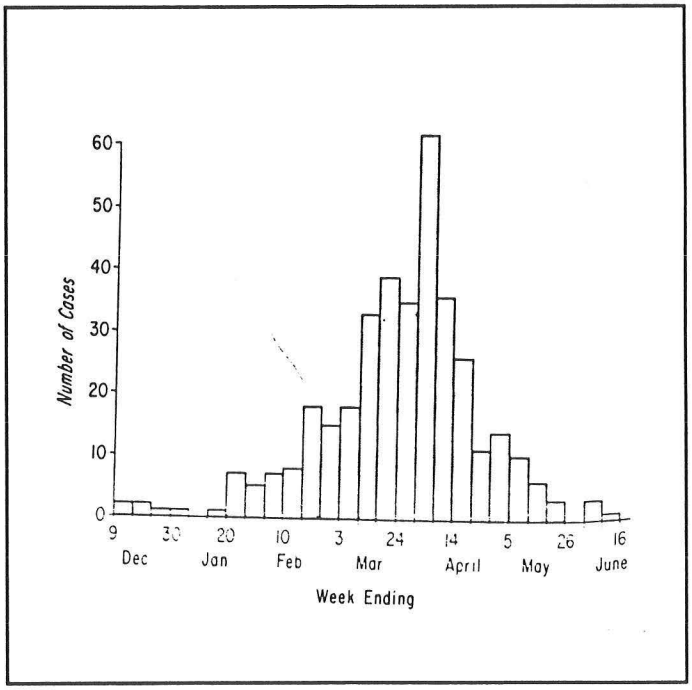

Figure 1

Parvovirus B19 DNA has been

Table II

PRESENCE OF B19-SPECIFIC IGM IN SUSCEPTIBLE HOUSEHOLD CONTACTS OF IGM-SEROPOSITIVE PATIENTS WITH APLASTIC CRISIS OR ERYTHEMA INFECTIOSUM

Age of household contact	Aplastic Crises	Erythema infectiosum	Total
	% susceptible individuals with IgM anti-B19		
< 20	37	74	56
≥ 20	31	55	41

found in urine and respitory secretions in viremic patients (16), which suggests that these secretions may be involved in transmission. Moreover, experimental intranasal inoculation of virus leads to infection (11). Whatever the mode of transmission, the virus can be effectively transmitted by household contact (16). The secondary attack rate for infection among susceptible household contacts is about 50% (Table II, 16, 17). In school outbreaks, 10-60% of students may develop erythema infectiosum (16, 18). In outbreaks in which student involvement is widespread, preliminary data suggest that 20-30% of susceptible staff may develop serologic evidence of infection during the course of infection (Table III, 19). The incubation period of secondary cases has been estimated to be 13 to 18 days (16).

The virus can also be transmitted parenterally via blood transfusions. In one study of hemophiliacs, the prevalence of antibody to Parvovirus B19 was 55. 5% in first transfused subjects and 93. 3% in hemophiliacs treated with multiple transfusions (20). Tattooing was suspected as the source of infection in two cases (20).

Numerous reports of epidemics of infection with Parvovirus B19 have led to the conclusion

Table III

PARVOVIRUS B19 INFECTION AMONG SCHOOL AND DAY CARE PERSONNEL

Employment	Total No.	Preoutbreak Prevalence No. (%)	No. Susceptible During Outbreak	Outbreak Incidence No. (%)
Day-Care Ctr.	50	34 (68)	16	5 (31)
Elementary Sch.	255	153 (60)	102	20 (20)
Middle Sch.	98	48 (49)	40	11 (28)
High Sch.	117	59 (50)	58	6 (10)

Wide spread outbreak of erythema infectiosum in school aged children in Ohio (Chorba et al. J. Infect. Dis. 1986).

that these infections occur largely within epidemics, but sporadic cases also appear to occur. Epidemics have tended to involve school aged children and those exposed to infected school aged children such as day care workers or hospital staff involved in caring for children of patients with aplastic crises.

Finally, recent reports have claimed that 7 laboratory workers acquired the virus through activities in a clinical laboratory (21) suggesting that laboratory workers are also at increased risk for exposure to Parvovirus B19.

CLINICAL MANIFESTATIONS

Human volunteers have provided basic information about the characteristics of this infection (11). In two studies, volunteers received intranasal inoculum of parvovirus B19. These studies are depicted in Figure 2. Viremia was detectable at 5 days and reached a peak at 9 days following inoculation. All of the seronegative volunteers developed fever and constitutional symptoms for several days. Viremia disappeared 10-15 days following the inoculation coinciding with the

development of IgM antibody to HPV. IgG antibody to HPV developed 4-5 days later. 3 of 7 seronegative volunteers developed a second illness on day 17 that lasted two to three days. This illness included rash, arthralgia in all three patients and frank arthritis in at least one patient. Joint symptoms persisted until day 24.

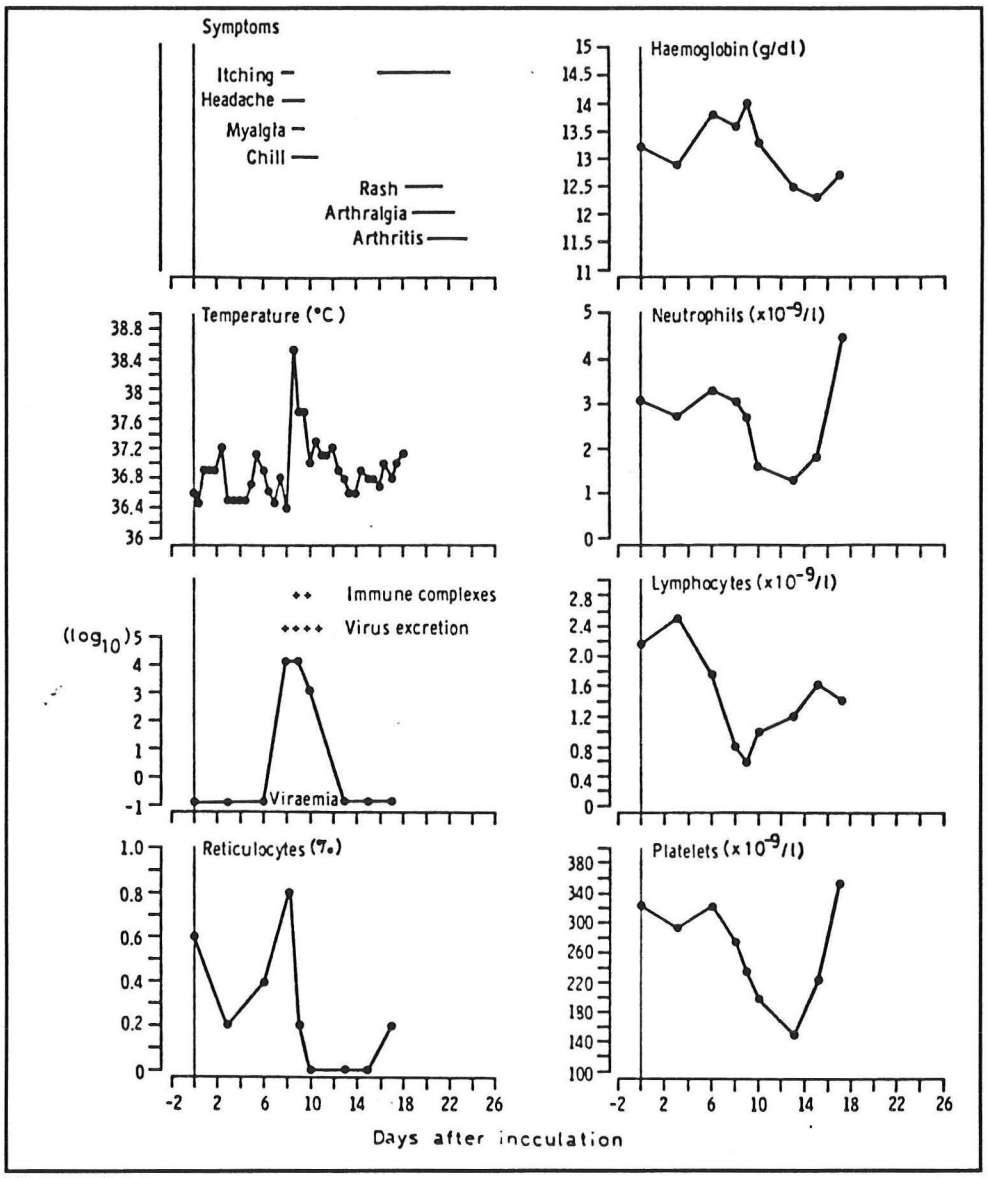

Figure 2

Reticulocytopenia developed in all seronegative volunteers as did a clinically insignificant drop in hematocrit. In addition, neutropenia, lymphopenia and thrombocytopenia also developed in many of the patients. Neutropenia was the least common hematologic manifestation.

Erythema Infectiosum. This benign illness occurs most commonly in school aged children who present with rash which begins on the cheeks giving a slapped cheek appearance (3, 22-24). When the facial rash clears a variable rash appears on the trunk and extremities that has a morbilliform,

confluent circinate or annular appearance (3, 22-24). Central clearing often gives a lace-like appearance. Papular, vesicular, and purpuric skin eruptions have also been reported (25-29). The rash frequently remits and recurs with stress, exercise, sunlight or bathing and usually disappears within 2 weeks (30, 31). Although adults can present with the classic symptoms of erythema infectiosum, they are particularly prone to arthropathy (see below) associated with infection (22, 31-33). Nonspecific complaints such as fever and coryza are reported to be uncommon (22). The illness is reported to occur in epidemics in the spring (22). Erythema infectiosum is also known as fifth disease because it was the fifth childhood exanthem that was described.

Table IV

CLINICAL FEATURES OF 162 CHILDREN INVOLVED IN AN OUTBREAK OF ERYTHEMA INFECTIOSUM

Symptom	%
Rash	100
Red cheeks	85
Recrudescent	67
Lacy	60
Cheeks	87
Sore throat	32
Fever	28
Cold	19

Evidence that erythema infectiosum was caused by Parvovirus B19 was obtained by a study of an outbreak of erythema infectiosum in England in 1983 (23). The outbreak occurred in a school with 430 children. 162 children developed an erythematous rash. The characteristics of the rash and associated illness are depicted in Table IV. The vast majority of the children developed a facial rash and fever and symptoms of an upper respitory illness were less common. The serum of 36 children was examined for evidence of antibodies to Parvovirus B19. As can be seen in figure 3, each of the children had IgM antibodies to B19 whereas none of the household contacts, control children or

control adults had these antibodies. Of interest was the finding that IgG antibodies to Parvovirus B19 was not only detected in the children, but was also present in 3 of 22 children and 16 of 19 control adults suggesting that prior exposure to the virus was somewhat uncommon in children, but common in adults. This study strongly supported the hypothesis that exanthem infectiosum was caused by Parvovirus B19 and suggested that infection with the virus was a common occurrence.

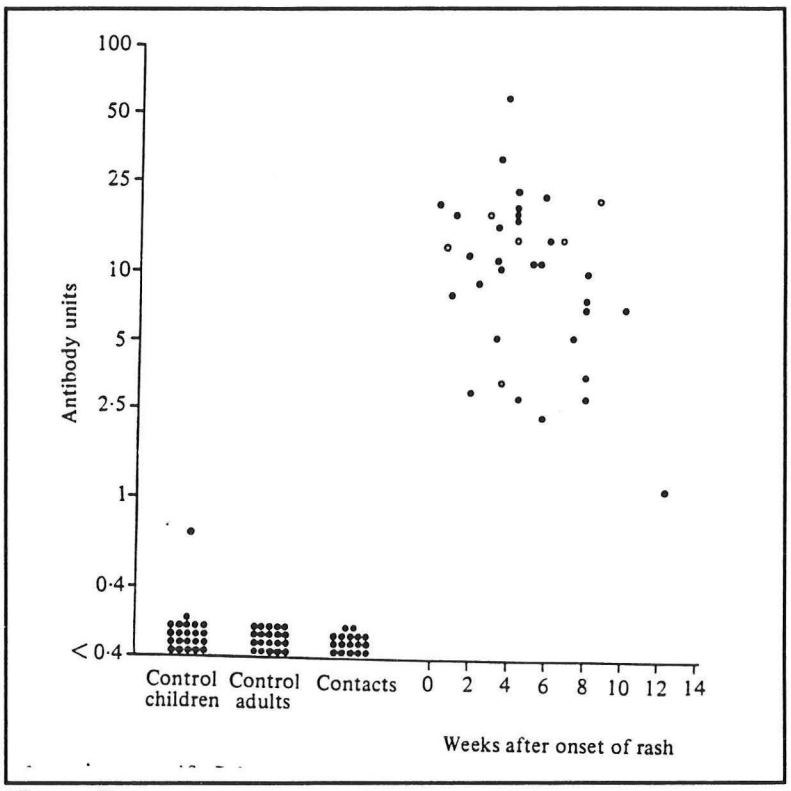

Figure 3

Asymptomatic infection can also occur. In outbreaks of Parvovirus B19-related illness, no symptoms were reported in about 20% of serologically confirmed cases (16, 18).

Aplastic crises Aplastic crises in sickle cell disease was long thought to be caused by an infectious agent, because of the symptoms of infection often preceding crises, the occurrence of family outbreaks in affected siblings and the absence of recurrent crises within the same patient. In 1981, investigators identified a parvovirus in the serum of two children with aplastic crises (34). Later studies demonstrated that 60 of 67 and 24 of 26 patients with aplastic crises (16, 35), had evidence of recent infection with Parvovirus B19 (either virus or IgM antibody). From these and many more recent studies, it is clear that the vast majority, if not all, aplastic crises in individuals with chronic hemolytic anemias as well as other conditions such as anemia from loss of blood, that require an increased red cell production to maintain normal red cell volume are caused by infection with Parvovirus B19. Symptoms of aplastic crises are those associated with acute anemia and include

pallor, weakness, and lethargy. Patients may report nonspecific symptoms several days before presentation, but these symptoms are often not present. Reticulocyte reappear 7 to 10 days after their disappearance (11).

Patients with aplastic crises usually present acutely at the nadir of their reticulocyte count which occurs before the development of rash and high titers of antibody to Parvovirus B19 (16). Therefore, they are usually viremic and infectious. Viral titers in patients with hemolytic anemias and aplastic crises are several orders of magnitude greater than those observed in normal individual infected with Parvovirus B19. Serum from these individuals is one of the best sources of Parvovirus B19. Patients with aplastic crises may have increased titers of Parvovirus B19 in the serum for another reason as well. The virus has a predilection for red cell precursors that are rapidly dividing (1). Since patients with chronic hemolytic anemias are likely to have many more of these cells than normal individuals, this may serve to facilitate virus replication in these patients.

Infection with Parvovirus B19 in patients with chronic hemolytic anemia does not always result in aplastic crises. Thus, in one study of patients with sickle cell anemia that had no history of previous aplastic crises, 17 of 63 patients had high titer IgG antibody to Parvovirus B19 (36).

Persistent B19 infection. Patients with immunodeficiencies resulting from HIV, leukemia, congenital immunodeficiency, therapy for systemic lupus erythematosus or bone marrow transplantation have been observed to develop persistent infection with Parvovirus B19 infections associated with life threatening chronic anemia (37-43). Persistent infection has been documented by detecting Parvovirus B19 DNA by dot blot or PCR techniques (37-43). In one case, a 30 year old white male with acute myeloid leukemia received T-lymphocyte depleted bone marrow from his HLA-identical sister (38). Prior to transplant, he had IgG antibody to Parvovirus B19. Following the transplant, his blood counts returned to normal and his IgG antibodies to Parvovirus B19 disappeared. He developed mild acute and chronic GVH and was treated with prednisone. One year following BMT the patient developed pancytopenia. Bone marrow revealed hypocellular marrow with a marked decrease of myelopoiesis and total absence of erythropoiesis. Parvovirus B19 was detected by electron microscopy, dot blot and PCR techniques. The patient developed only low titer of IgM and IgG

antibodies to Parvovirus B19 and DNA could be detected in his serum for the remainder of his life. Immunocompromised patients that develop persistent infection with Parvovirus B19 may also develop thrombocytopenia, and neutropenia.

In addition to reports of persistent infection in immunocompromised hosts, there are reports of patients developing this syndrome with apparently normal immune systems. One of these patients had an anemia requiring transfusions for 10 years (39). The infection was controlled and eventually cured by intravenous immunoglobulin therapy. In a similar example, two brothers developed pure red cell aplasia for years without obvious immunodeficiency (43). Parvovirus B19 DNA was detectable in the blood, bone marrow and spleen. One brother died and a diagnosis was established postmortem. The other brother was diagnosed antemortem and treated with intravenous immunoglobulin. Immunoglobulin therapy eliminated virus from the blood and restored red blood cell counts to normal. The patient was found to have some in vitro abnormalities in his immune response in vitro, but no history of recurrent infections. Of interest was the finding that the later patient produced IgM, but not IgG antibodies to Parvovirus B19. This finding suggests that only the production of IgG antibodies provide protective immunity from this virus. Treatment of the patient with IV immunoglobulin resulted in the appearance of host IgG anti-Parvovirus B19 antibodies. Since isotype switching is thought to be under the control of T cell lymphokines, this observation suggests the possibility that the mechanism whereby immunoglobulin therapy controls or cures Parvovirus B19 infection is by its ability to promote T cell responses, possibly by facilitating antigen uptake by antigen presenting cells. Improvement following intravenous immunoglobulin therapy has been reported in some, but not all immunocompromised patients as well.

Although the incidence of persistent infection in immunocompetent and immunodeficient individuals is not known, one report claimed that 15% of patients with pure red cell aplasia have Parvovirus B19 DNA in their serum (43).

Serologic studies suggest that persistent infection can develop in the absence or presence of IgG or IgM antibodies to Parvovirus B19. The finding that intravenous immunoglobulin therapy controls the infection in many of these patients suggests that anti-Parvovirus B19 antibodies provide protection from infection and suggest that antibodies detected in those patients with persistent

Parvovirus B19 infection may be of low titer or low affinity. The lack of antibodies in many patients with persistent infection makes diagnosis difficult. Diagnosis rests on the ability to demonstrate virus in the blood or tissue using PCR techniques. Because of the public health implications and the implications for therapy Parvovirus B19 should be considered in all patients with unexplained chronic anemia especially in those patients with deficient immune systems.

Fetal abnormalities Since porcine parvoviruses had been implicated in fetal infection and death (2), it was not surprising that human parvoviruses might have similar effects. Initial support for this hypothesis came from studies and case reports demonstrating that Parvovirus B19 DNA could be detected in a variety of tissues from spontaneous abortuses accompanied by a consistent picture of hydrops fetalis (44-57).

Several studies have attempted to provide reliable estimates of the risk of maternal infection to the fetus. In one study, the prevalence of recent infection with Parvovirus B19 was about 1% in normal women and 1% in women with pregnancies resulting in fetal death (49). These data suggest that Parvovirus B19 infection does not account for a substantial proportion of fetal deaths in the general population. It appears to play a more important role in nonimmune fetal hydrops, however,

Table V

DETECTION OF *PARVOVIRUS* B19 DNA IN UNEXPLAINED FETAL HYDROPS

Group	No.	No. (%) with *Parvovirus* B19 DNA
Unexplained fetal hydrops	13	4 (31)
Explained fetal hydrops	13	0 (0)
Fetal death without hydrops	13	0 (0)

where in one study of 13 cases of unexplained fetal hydrops(58), 4 (33%) were positive for Parvovirus B19 DNA (Table V).

The Public Health Laboratory Service Working Party on Fifth Disease in the United Kingdom has recently reported the largest series to date of Parvovirus B19 infection in pregnancy (59). This study prospectively follow a cohort of 193 women with anti-IgM anti-Parvovirus B19 antibodies. These women were identified either because of rash or contact with infected children. The source of the infection was unknown in 73%, household contact with infected children in 16%, or working with infected children in 9%. Three of the women were lost to followup. 63% of the women were within the first 12 weeks of gestation, 26% were 13-26 weeks since conception and only 10 % of the infections were reported in women in the last trimester of gestation. This tendency for infection to occur in the first 20 weeks of infection may relate to concern among practitioners about rashes in early pregnancy. Four of the women had therapeutic abortions. Of the remaining 186 women 84% had liveborn infants and 16% had fetal deaths. The fetal loss rate was 17% for women infected within the first trimester and 6% (1/17) for those infected afterwards. One infant was diagnosed with hydrops and treated with intrauterine transfusion and survived to term. Other than

Table VI

OUTCOME OF INFECTION WITH *PARVOVIRUS*[1] B19 IN 236 PREGNANT WOMEN

Outcome	Number (n=236)	%
Normal Fetus	194	82
Hydrops Fetalis (survival[2])	3	1
Hydrops Fetalis (death)	39	17

[1] Diagnosis of *Parvovirus* B19 infection based on the presences of an anti-IgM anti-*Parvovirus* B19 antibody.
[2] Treated with intrauterine transfusions. Fetus was normal in 2 and one had cardiac septal deviation. Compilation of data from Anand, Mortimer, Public health, and Schwarz.

2 with hypospadias, all liveborn infants were normal. Of the fetal deaths, tissue was available from 14 cases, 6 were positive for B19-DNA by hybridization, 2 were equivocal, 6 negative. Assuming that the 14 fetuses were representative of the 30 deaths and considering equivocal cases as positive, then 17 or 9% of the 186 women might have had a Parvovirus B19-associated fetal loss. A compilation of this study together with several other studies (45, 48, 60) is provided in Table VI. Whereas fetal death may occur as a consequence of maternal infection with Parvovirus B19, fetal anomalies seem to be uncommon. In over 236 liveborn infants of B19-infected mothers reported in the literature only 2 cases of hypospadias and one deviated cardiac septum have been described (45, 48, 59, 60).

An estimate of the transplacental transmission rate was made by assuming that, in addition to the one case with prenatal confirmation of fetal infection, the occurrence of at least one of the following signified intrauterine infection: a) an adverse outcome; b) IgM anti-Parvovirus B19 in cord or neonatal blood; c) persistent IgG anti-Parvovirus B19 antibodies in infants > 1 years old. The transmission rate was estimated to be 30 % using these criteria of infection (59).

The British study discussed above did not include a control group of women that were not infected with Parvovirus B19. Preliminary data from a recent study suggest that there is a 2 to 3% increase in the rate of fetal deaths among infected women compared with controls and that this difference occurs during the first 20 weeks of pregnancy (61).

To summarize, the overall risk of fetal death after maternal infection is probably < 10%, is less in the second half of pregnancy and does not carry an increased risk of birth defects over background. If we extrapolate to the case of the woman with unknown serologic status and assume about 50% of these women are immune and that the secondary attack rate is 50% in the household setting and 30% in a work setting with intense exposure, then we estimate that the risk of fetal death is <2. 5% after household exposure and <1. 5% after a significant work exposure.

Prenatal diagnosis generally rests on the demonstration of IgM antibodies or virus in the maternal circulation. Recent studies have demonstrated that PCR techniques can identified Parvovirus B19 DNA in the amniotic fluid of infected infants prenatally (61). One unexpected finding from these studies is that in some infected women, hydrops was documented by ultrasound and shown to resolve without intervention.

Arthritis Evidence that infection with Parvovirus B19 leads to inflammatory arthritis comes from several observations. First, the relatively common occurrence of inflammatory arthritis/arthralgias (56%) in patients with erythema infectiosum (22). Second, the finding of Parvovirus B19 DNA in the synovial fluid of a patient with inflammatory arthritis of the knee that lasted 3 months (62). Third, the occurrence of frank arthritis 17 days after nasal inoculation of Parvovirus B19 in human volunteers (11). Fourth, the finding that 15% of patients presenting to an early synovitis clinic had IgM antibodies to Parvovirus B19 (33). Finally, a large number of case reports of the occurrence of inflammatory arthritis in patients with IgM antibodies to Parvovirus B19 (32, 63-67).

In one study of 30 patients with positive IgM antibodies to Parvovirus B19 and inflammatory arthritis documented by physical exam, 22 of the patients were female and only 3 were children suggesting that the arthritis is uncommon in children and more common in women then men (32). This conclusion was supported by a similar study of 21 patients, in which 19 were female and all were adults (65). While one interpretation of these findings is that women get arthritis more commonly than men, an alternative explanation is that adult infection is more common in women due to their increased exposure to children.

Prodromal symptoms are not always present in patients with arthritis-associated Parvovirus B19 infection. In one study of 27 patients only 48% suffered prodromal symptoms such as rash, coryza or fever (32). When rash occurred it generally preceded the arthritis by 1-5 days.

The most common joints involved were the proximal interphalangeal and metacarpophalangeal joints of the hands (47%), followed by the knees (20%), wrists (19%), and ankles (14%) (32). Involvement of other joints is less common. Joint involvement typically lasts 7 to 28 days, but chronic involvement for up to 2 years has been described in over 10 cases.

The incidence of arthritis in adults infected with Parvovirus B19 is unclear. In one study 8 of 9 adults with fifths disease developed joint symptoms (65). 4 of the affected patients developed only arthralgias, but 4 developed frank arthritis. In a large study of patients with erythema infectiosum prior to the discovery of Parvovirus B19, arthritis/arthralgia was found to occur in 59% of adults with erythema infectiosum (22).

The relationship between parvovirus and rheumatoid arthritis is somewhat controversial. One study found that 93% of patients with rheumatoid arthritis, but only 61% of a control group had IgG antibodies to Parvovirus B19 (64). These authors suggested the possibility that Parvovirus B19 caused rheumatoid arthritis (68). Another study was unable to confirm an increase in the frequency of these antibodies in patients with rheumatoid arthritis. Moreover, although rheumatoid factor has developed in some patients with chronic arthritis, most patients are rheumatoid factor negative (32, 33, 65).

The duration of arthritis appears to depend on the patients population studied. Studies following patients that presented to arthritis clinics found that the arthritis lasts months to years (33, 65). In contrast, patients presenting with fever and rash to a general practitioner and are found to have arthritis generally have a self-limited disease that lasts days to weeks (32, 65). My interpretation of these studies is that the vast majority of patients have a mild arthritis/arthralgias that last days, but that a few patients develop a more significant arthritis that last months or even years. Recurrence of the arthritis is not uncommon. Whether chronic destructive arthritis lasting years is the result of Parvovirus B19 infection is not clear. Patients have been reported that develop a chronic rheumatoid arthritis-like disease following infection (33, 65, 69). Many of these patients appear to develop rheumatoid factor positivity (63-65, 69). Whether this is the chance occurrence of rheumatoid arthritis and Parvovirus B19 infection or a causal relationship is not clear.

Other Mesenteric adenitis (70), Henoch-Schonlein purpura (27), vasculitis (71) and hemophagocytic syndrome (72) havealso been reported in individuals with IgM antibodies to Parvovirus B19.

DIAGNOSIS

Antibody detection. The cornerstone of Parvovirus B19 diagnosis has been IgG and IgM antibody assays and the IgM assay is the most sensitive way to diagnose acute infection in the normal host (73). The capture antibody method, either as a radioimmunoassay or enzyme-linked immunoassay, has been the most commonly used. With this method, IgM is detected within a few days of illness onset in about 90% of outbreak-related cases of erythema infectiosum (13, 74, 75). The level of antibody begins to fall 30 to 60 days after the onset, but can be detected in some

patients for over 4 months after the onset of illness. The availability of antigen for this test has been limited, until recently, to serum obtained from patients with aplastic crises that have high titers of antigen. More recently, antigen has been synthesized from cloned genes or prepared from virus grown in fetal liver (76-78). These antigens have been used to develop Western blot and antibody capture assays.

Detecting the virus. The most sensitive method of detecting viral DNA is PCR techniques (79-82). Less sensitive techniques using nucleic acid hybridization for Parvovirus B19 DNA have also been employed. Still less sensitive assays employ EIAs to look for viral proteins (41, 74). The PCR and hybridization techniques are the tests of choice for diagnosing infection in immunocompromised hosts. Infection can also be suspected by demonstrating parvovirus-like particles in cells or giant pronormoblasts with marginated chromatic and nuclear inclusions (39).

PATHOGENESIS

Fetal Death. Parvovirus tends to infect and destroy rapidly dividing cells (1). In adults the virus has a predilection to infect hematopoietic precursors, but in the fetus they may infect liver and myocardial cells as well leading to hepatic and myocardial damage.

The pathogenesis of fetal hydrops is somewhat controversial. Infected fetuses clearly develop severe anemia (54) and anemia is known to result in hydrops in other clinical settings. This finding together with a number of reports that fetuses with hydrops survived following intrauterine transfusion (60, 83) have suggested that the virus stimulates hydrops by inducing anemia. However, a number of reports have demonstrated virus and inflammation in the myocardium and have suggested that at least part of the pathogenesis may relate to the capacity of the virus to induce myocarditis in the fetus (73, 84).

It seems likely that the fetus is particularly vulnerable to Parvovirus B19 infection, because of its need to rapidly expand its blood volume and because of its poorly developed immune system. Persistent viremia has been documented in a number of infants and IgM production does not occur in many infected infants (59). The finding that fetal death associated with Parvovirus B19 infection is less common in the last trimester of gestation suggests that these more mature fetuses are more able to tolerate an arrest of erythropoiesis and/or clear the infection.

Aplastic crises It is clear that Parvovirus B19 infects and is cytotoxic for erythroid progenitor cells leading to arrest at the normoblast stage of development. Moreover, serum from viremic individuals inhibits erythroid colony forming units in vitro (85, 86). Thus, it is not surprising that reticulocytopenia and anemia are uniformly present during infection. The mechanism responsible for the decrease in platelets, lymphocytes and neutrophils seen in infected patients is less clear. One study demonstrated that Parvovirus B19 infection impaired megakaryocytopoiesis in vitro (87). Moreover, they reported that, although megakaryocyte progenitor cells were infected with Parvovirus B19, the cells were nonpermissive for viral replication. Thus, infection of megakaryocyte precursor cells with subsequent cytolysis may be the mechanism responsible for thrombocytopenia.

Arthritis. The pathogenesis of the acute arthritis is not known. The finding of viral DNA in the synovial fluid (62) suggests a direct viral infection of the joint. However, the observation that the arthritis occurs co-incident with the development of IgG antibodies suggests the possibility that the disorder is caused by immune complexes (11). As discussed earlier, it is not clear that Parvovirus B19 is involved in the pathogenesis of a chronic arthritis. However, it is interesting to speculate that certain predisposed individual develop chronic arthritis much as is seen in Reiter's syndrome where predisposed individual develop chronic arthritis following infection with specific bacterial organisms.

INFECTION CONTROL MEASURE IN THE HOSPITAL SETTING

Several findings have suggested that measures should be taken to prevent nosocomial infection with Parvovirus B19. First outbreaks of Parvovirus B19 infection have occurred in hospital staff caring for infected patients. Second, nosocomial infection has been reported. Finally, as discussed above, infection with Parvovirus B19 causes significant morbidity and mortality in selected subgroups of patients. The following recommendations were taken from an earlier publication (88).

Patients with fifth disease. Since most people with rash are no longer viremic, the risk of transmission is low (89). It has been suggested that secretion precautions be used in these patients for at least the first 24 hours, because of rare case reports of transmission from

patients with rash. I think it would be prudent to keep patient in a private room or at least make sure that roommates do not have a hemolytic anemia, and are not pregnant or immunocompromised.

Patients likely to be viremic. This includes patients who develop aplastic crises. These patients have viremia several logarithmic orders of magnitude greater than those with fifth disease (16). It seems prudent to isolate the patient with secretion precautions. Moreover, if the patient is coughing, respitory isolation may be appropriate as the mechanism of transmission is not known. As with fifths disease, roommates that are likely to develop complications of infection are not appropriate.

Parturients of infected babies. Human Parvovirus B19 DNA is readily detected in placenta and fetal blood from hydropic fetuses. Detection of Parvovirus B19 DNA from a surviving neonate has also been reported. The need for secretion precautions and decontamination of the delivery room is obvious. Isolating the fetus with secretion precautions seems wise. In addition, it seems prudent to instruct parents to avoid contact with other infants and to use proper hand washing techniques.

Household contacts of viremic patients. The secondary attack rate of household contacts is 50% in susceptible individuals (16, 23). Since 50% of normal adults are susceptible (14, 23), the chance that an adult household contact would become viremic is 25%. It has been suggested that these patients be isolated by secretion precautions from 7 to 18 days following exposure.

Employees, visitors and patients who are pregnant. Avoid contact with patients who have fifths disease, are likely to be viremic or who are household contacts with either of these.

TREATMENT

Hydropic fetuses. Intrauterine transfusions have been used to treat hydropic fetuses in cases of maternal infection with Parvovirus B19 (59, 60, 83). No controlled trials demonstrate that they are effective. Moreover, the balance between safety and efficacy of this high risk procedure has not been examined.

Persistent infection. Intravenous immunoglobulin therapy has controlled and even cured infections in immunocompromised hosts (39, 43) and is relatively safe and should be considered in treatment of persistently infected individuals although no controlled trials demonstrate its efficacy.

Arthritis. Should be managed conservatively with nonsteroidal antiinflammatory agents. In cases of chronic arthritis therapy should be similar to that given other patients with seronegative arthritis.

Aplastic crises. Supportive management is indicated. The infection is self-limited and reticulocytes will reappear in a few days without additional therapeutic maneuvers.

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