

Human parvovirus B19: a literature review and case study

Human parvovirus is ubiquitous. It affects human erythroid precursors causing their lysis and apoptosis, resulting in varying degrees of interference with red cell production. There is a range of clinical presentation from no obvious abnormalities, to the classic 'slapped cheek' and lacy body rash in a child, to fever and arthropathy in an adult. The level of haemoglobin may fall by 20g/dL or more precipitating anaemia in susceptible people. Amongst the most susceptible are unborn babies who suffer from a high rate of abortion if affected in the first trimester, anaemia that may result in non-immune hydrops in the second trimester, and *in utero* death in the third trimester. An illustrative case study of hydrops in the second trimester treated by *in utero* transfusion is presented, with a review of the literature.

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Parvovirus B19

Human parvovirus is a small (*parvus* in Latin means small) non-enveloped virus with a single strand of DNA, packaged with its three types of proteins into a particle with twenty sides (icosohedral symmetry)¹. Its limited amount of DNA requires it to join a mitotically active cell in order to reproduce and it attaches to several types of cells, but especially the erythroid progenitor cells. Platelet precursors may also be affected. This attachment is by means of a special protein on the surface of certain cells, the P antigen.

Parvovirus was discovered serendipitously in 1974 and is the only member of the family *Parvoviridae* known to be pathogenic in humans. It was identified while evaluating tests for hepatitis B virus surface antigen and named after the location of the laboratory sample in which it was found: number 19 in panel B². It was officially recognised in 1985 as a member of the *Parvoviridae* and given the name B19 by the International Committee on Taxonomy of Viruses³. At first, it was a virus without any obvious disease but an association with transient aplastic crisis in patients with sickle cell anaemia was noted in 1981⁴. Two years later it was linked to the childhood infection, erythema infectiosum (slapped cheek disease)⁵. It was then found to be associated with red cell aplasia and arthropathy in adults, myocarditis, neuropathies and perhaps even auto-

immune disease.

Due to the clinical similarity to rubella it was postulated that infection in pregnancy would result in structural defects in the offspring. However, while defects have not been confirmed, it has become recognised that *in utero* infection may result in abortion, hydrops and intrauterine death.

Case study

On a routine ultrasound at 20 weeks and 3 days of gestation, the fetus of a 32 year old gravida 3, para 2 lady was found to have signs of severe hydrops, including ascites, skin oedema, pericardial effusion, cardiomegaly, tricuspid regurgitation, hepatomegaly and placentomegaly. No other structural anomalies were found but the velocity of blood in systole in the middle cerebral artery was elevated suggesting reduced viscosity due to severe anaemia.

Blood samples from the mother on that day revealed elevated levels of IgM and IgG and the presence of parvovirus B19. It was apparent the baby was at severe risk of death from anaemia, resulting in cardiac failure and hydrops, and an intrauterine transfusion (IUF) of blood was undertaken (**FIGURES 1 and 2**).

Two cordocentesis and intrauterine blood transfusions plus one platelet transfusion were given to the fetus. Prior to the IUF fetal haemoglobin (Hb) was 3.3g/dL and 3.4g/dL, with a platelet count of 27,000; post IUF the Hb was 13.0g/dL

Keywords

Parvovirus B19; infection; fetal anaemia; hydrops fetalis; *in-utero* transfusion

Key points

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1. Parvovirus B19 is a common infection in humans.
2. It affects erythroid precursors resulting in decreased erythropoiesis.
3. It is usually spread by respiratory means but can pass vertically from mother to fetus.
4. It can lead to miscarriage, hydrops fetalis and intrauterine death.
5. Intrauterine blood transfusions can compensate until the effect of the virus passes.

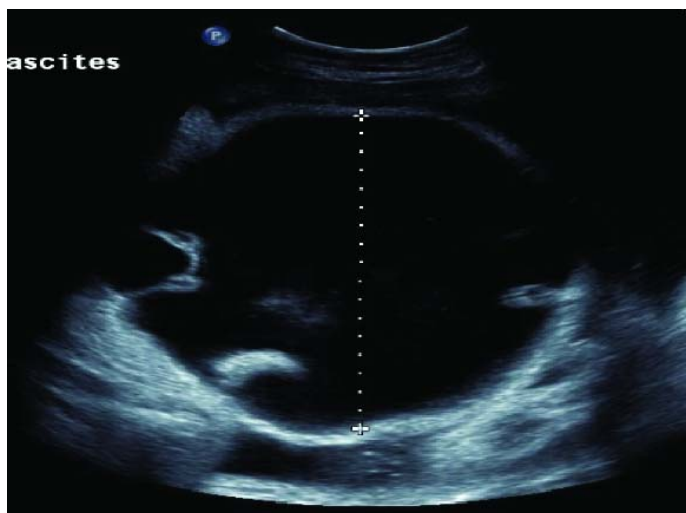


FIGURE 1 Transverse ultrasonography of the abdomen of the fetus revealing a huge amount of free fluid (black) in which a few loops of bowel are floating.



FIGURE 2 Transverse ultrasonography of the fetal chest revealing cardiomegaly and oedematous chest wall.

and 11.7g/dL respectively. The fetus stabilised, but there remained persistent fetal hydrops, gross ascites, scalp oedema and an enlarged heart.

A live female infant was born at 36 weeks' gestation by emergency lower segment caesarean section, for fetal hydrops and previous sections. Apgars were 6 at one minute and 8 at five minutes. She appeared pale and was suffering from respiratory distress complicated by a grossly distended and tense abdomen (**FIGURE 3**). She was intubated, and transferred to the neonatal intensive care unit as the consultant was concerned about diaphragmatic splinting and wanted to ensure that the baby was well oxygenated as soon as possible to avoid going into refractory persistent pulmonary hypertension. Left and right intraperitoneal drains were inserted; 870mL of ascites fluid was drained and sent for microscopy, culture, viral studies and albumin. Bloods were sent for FBC, LFTs, U&E, CRP, Coag, B/C, and virology.

Parvovirus B19 DNA was not detected in the ascitic fluid nor was specific IgM detected in the blood of the baby, although IgG levels were elevated. Echocardiography and ultrasonography of head, liver and kidneys revealed no abnormalities.

Enteral feeds were commenced on day one of life and the infant has tolerated feeds since.

She recovered quickly: was intubated within hours, fed enterally on the first day and discharged breastfeeding on day 5 with no evidence of congenital abnormalities.

She is now 15 months old and is generally well but is exhibiting significant

gross motor delay. She can only sit aided and cannot stand, but has reasonable hand control and is interested in her surroundings and communicates with about eight words. She has a lax abdominal wall.

Discussion

This case illustrates the danger of fetal infection and the value of intrauterine intervention in some babies. This baby must have been close to death.

The effect of parvovirus on the fetus is a result of the attachment and subsequent invasion by the virus of mitotically active cells bearing the specific attachment protein, P antigen, on their surface. Particularly affected are erythroid and megakaryocyte precursors and myocardial cells. The virus causes the erythroid precursors to lyse and to apoptose resulting in anaemia.

The virus spreads vertically from mother to fetus^{6,7} and if the mother is infected in the first trimester, about 10% of pregnancies are miscarried. If infected in the second trimester, there appears to be a 1% chance of developing hydrops and if infected in the third trimester, about a 1% chance of intrauterine death.

The most critical time of infection appears to be the 16th week of gestation⁸⁻¹¹ associated with the hepatic period of haematopoietic activity^{11,12} when the life span of the fetal red blood cell is shortened and red blood cell mass increases three to fourfold to meet the demands of fetal growth¹³. Fetal death usually occurs around 4-6 weeks post infection but has been reported up to 12 weeks after B19 infection¹⁴.

Hydrops fetalis appears to be a result of anaemia due to interruption of rapidly increasing erythropoiesis at that stage of pregnancy. The anaemia may cause high output cardiac failure which, in turn, may reduce the oxygenation of the endothelial cells of blood vessels, while increasing pressure within them, resulting in the characteristic leak of fluids into tissues and body spaces seen with hydrops fetalis. With parvovirus, direct infection of myocardial cells may contribute to the failure. Increased production of blood in the liver may interfere with the function of the hepatocytes, resulting in decreased production of albumin which will reduce the oncotic pressure within blood vessels, worsening the oedema. Hydrops may occur rapidly, usually within 2-4 weeks after maternal B19 infection¹⁵

Fortunately, the risk of developing hydrops after maternal infection is low: approximately 1%. The sero-prevalence of specific IgG denoting prior infection and life-long immunity increases with age from 2-15% of children from 1-5 years old, to 15-60% of children from 6-19 years of age to 30-60% in adults. Obviously many women are vulnerable, with an annual infection rate of 1.5%¹⁶. In these pregnancies, a vertical transmission rate of at least 33% has been established¹⁷.

Women are especially vulnerable if they care for school-aged children, particularly within the close family environment¹⁸. During outbreaks, transmission rates of 25% in schools and 50% at home have been reported¹⁹. Most pregnant women are asymptomatic though some experience malaise, arthropathy, fever and a rash¹⁵.

There is no correlation between the severity of the mother's illness and that of the fetus.

Whereas it was logical to fear a teratogenic effect of B19, none has been demonstrated in humans, including this case. The virus, however, has been associated with birth defects in animals, causing cerebellar hypoplasia and ataxia in cats, and anencephaly, microcephaly, facial defects and ectopic hearts in hamsters¹⁰.

In this case, the neurodevelopment of the baby is retarded, which may reflect tissue hypoxia but may also be due to infection of the fetal brain by the virus. There have been limited reviews of the outcome of fetal infection, but the rate of neuro-developmental abnormalities appears to be higher in cases of hydrops associated with parvovirus than with those associated with immune causes¹⁹.

Neurological complications are being reported with increasing frequency in association with parvovirus B19 but there is uncertainty as to whether they are due to infection *per se*²⁰, or secondary immune responses. Ultrasonography failed to reveal any abnormalities on several occasions in this infant and there was no suggestion of cerebral inflammation at any stage.

The patulous abdomen which will require surgical correction in this case appears similar to that of 'prune belly' syndrome. It is probably due to interference with development of the anterior abdominal wall musculature by sustained distension by ascites. This complication has not been widely reported but has affected another B19 baby treated by *in utero* transfusion in Brisbane. (Dr Glen Gardener, Maternal Fetal Medicine, personal communication. 2008.)

Diagnosis

Diagnosis depends on clinical signs, specific serology and detection of viral DNA by PCR. Acute infection can be detected by the presence of viral DNA and the development of specific IgM which appears about 10 days after exposure, at around the time of the development of symptoms and signs of infection, in more than 90% of immunocompetent patients. Levels begin to fall after two months and may be detectable for six months. IgG antibodies appear soon after the IgM and persist for life.

Thus, if IgG is negative but IgM is positive, recent infection is likely. If both are positive, infection has most likely

occurred within recent months. If IgG is positive but IgM is negative, past infection is likely. If both IgG and IgM are negative, infection is unlikely and the mother is vulnerable. Exceptions to these rules occur, unfortunately, because of the considerable individual variations. For example, the mother may not have detectable IgM at the onset of hydrops fetalis.

Elevated levels of specific IgM in the baby will denote its active infection because this immunoglobulin cannot pass through the placenta. IgG, however, can cross the placenta and elevated levels in the baby will usually denote past maternal infection.

B19 DNA can be detected in amniotic fluid and in fetal blood by PCR, confirming infection²².

Infection in this baby was confirmed by maternal positivity of IgM and IgG and the growth of parvovirus in her blood at 20 weeks' gestation. Virus was not isolated from the amniotic fluid but the baby's IgG was positive, denoting placental transfer. The baby's IgM was negative, consistent with the testing several months after the infection. In retrospect, it would have been wise for us to have looked for the virus in the baby's blood after birth.

Treatment

There is no specific treatment for human parvovirus and there is a need for a vaccine with similar effect to the one that protects dogs from the species of parvovirus that causes distemper. That vaccine is very effective and has been produced because of the relative ease of reproduction of the virus in tissue culture. In contrast, B19 is not easily cultured and, therefore, would be more expensive to produce. According to

the discoverer of B19, Yvonne Cossart (personal communication, 2008) wider studies on the implications of the infection for neurological, cardiac, haematologic and auto-immune disease would permit a better estimate of the overall effect of the virus in developed countries and provide impetus for the development of the vaccine. Studies in developing countries reveal a heavy disease burden, with B19 infection contributing as greatly to the development of severe anaemia as falciparum malaria²³.

There have been as yet unproved suggestions that immuno-globulin might ameliorate infection in pregnant women^{7,24}, otherwise, apart from trying to avoid infected people, there is no specific therapy for the mother. There may also be a role for immunoglobulin for the fetus and baby. (Cossart Y. Personal communication. 2008).

The fetus should be observed for signs of anaemia revealed by increased velocity of blood flowing in systole in the middle cerebral artery (MCA). This velocity increases with the decrease of viscosity as the blood thins in anaemia and has been shown reliably to correlate with the degree of anaemia²⁵. Levels of haemoglobin <5g/dL are considered to warrant *in utero* transfusion of blood, and are usually associated with hydrops. Platelets should be counted on the specimen of blood taken from the fetus and should be transfused if low. The complications of *in utero* transfusion include spontaneous rupture of membranes, bradycardia, immediate delivery, miscarriage, chorioamnionitis and intrauterine death. Velocity in the MCA should be repeated weekly and



FIGURE 3 Grossly distended abdomen at birth.

transfusions repeated as necessary.

This baby required two transfusions, even though the haemoglobin rose from 3.3g/dL to 13g/dL in the first week. It probably fell in the next week in association with restoration of the circulating blood volume and dilution of haemoglobin.

It is not clear why this baby had persistent ascites. Liver function tests were essentially normal after birth and there was no evidence of congestive cardiac failure. The ascites did not return after it was removed and the liver function has remained normal.

Conclusion

Parvovirus B19 is a common virus that usually does not damage the fetus but miscarriage, non-immune hydrops, and death may occur. Fetal demise is greatest in the first 20 weeks of gestation, and most losses will occur 4-6 weeks after exposure. Fetal blood transfusions have been shown to be effective. There is no specific treatment for the viral infection and human beings must await the development of a similar vaccine to that which protects their canine brethren from a cousin of the human parvovirus.

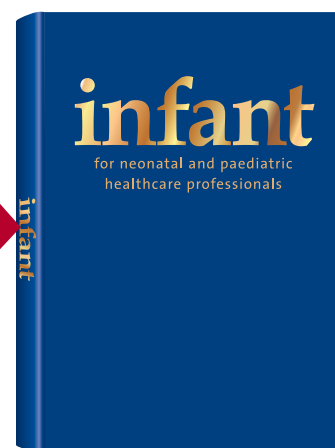
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