

parvovirus B19

Parvovirus B19 is an autonomous, wide spread (globally endemic) virus. There are other members of the parvovirus family that are called dependoparvoviruses; which means that they co-infect (only replicate in the presence of other viruses e.g. Adenoviruses) these are mostly non-pathogenic.

Transmission:

Mostly:

- Feco-oral
- Upper respiratory tract
- Via urine

Rarely:

- Blood spread → high risk in pooled blood products (from multiple donors).
- Transplacentally

Parvovirus B19 is very stable, its presence has been reported in pasteurized blood products i.e. it is resistant to heat & pressure, it also resists solvent detergent treatment, due to its high stability blood screening by nucleic acid testing e.g. by PCR is done to detect the presence of its nucleic acids.

Routs of entry:

Dividing epithelial or lymphoid cells of the:

- Upper respiratory tract
- Oropharynx
- Intestines

Parvovirus B19 replicates in mitotically active cells, & prefers cells of the erythroid lineage. Unlike EBV, Parvovirus B19 neither induces cells to proliferate nor manipulates the immune system's response.

Major sites for Parvovirus B19 replication are the sites of erythropoiesis

In adults → bone marrow

In the fetus → liver

Most Parvovirus B19 infections are asymptomatic; however, patients who present with the illness have mild nonspecific symptoms including Fifth Disease (Erythema Infectiosum), Arthropathy (joint symptoms), Transient Aplastic Crisis in patients with hemolytic disorders, Chronic Pure Red Cell Aplasia in immunocompromised patients.

Molecular biology of Parvovirus B19:

- Simpler than EBV
- Small single stranded genome
- Fewer genes than EBV
- Icosahedral (20 faces) protein capsid
- No lipid envelope

The simplicity and the absence of the lipid envelope is what makes this virus structurally stable i.e. resistant to pasteurization.

Access of the virus into cells:

The Parvovirus B19 receptor Globoside (P antigen) is present mostly on erythroid progenitors, in addition to being expressed on endothelial cells, cardiomyocytes, megakaryocytes & placental trophoblasts. Parvovirus B19 also uses integrins as co-receptors. Once the virus has gained access to the cell, the exact mechanism of how it reaches the nucleus via Clathrin or non-Clathrin vesicle is not fully understood. The virus uses microtubules to get to the nucleus, it also uses phospholipase A2 in its VP1 (Viral Protein 1), which is part of its capsid to modify membranes, in order to enable it to escape from the endocytic vesicle to the cytoplasm, so it can gain entry to the nucleus.

Once it has entered the nucleus viral replication, transcription, translation, as well as assembly, all occurs inside the nucleus.

Infection of non-erythroid lineage cells does not produce a lot of viruses; however, transcription of some viral proteins occurs, particularly NS1 (Non-Structural protein 1), which induces apoptosis; as a result, not only erythroid cells are being lost, but also

thrombocytopenia, neutropenia, etc... are resulting secondary to the infection of non-permissive cells & the induction of apoptosis.

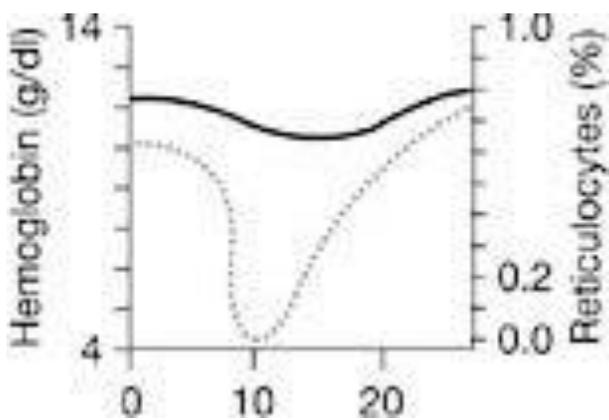
In addition to that, the virus can also induce the synthesis of NS1 in permissive cells, resulting in their destruction. Therefore both permissive and non-permissive cells are being destroyed by the infection.

Pathogenesis

There are three kinds of patients:

A. Normal patients

- Viral replication causes the lysis of cells
- Infection spreads by viremia (viral particles are present in the blood)
- Biphasic course of disease :
 - I. Phase 1 >> non-specific symptoms minor febrile prodrome about 7- 10 days after exposure (associated with viremia)
e.g. fever, myalgia, chills& headache.
 - II. Phase2>> is 2° to the activation of the Immune system>>classical facial rash &arthralgia after 2-3 days after phase1. (associated with immune response)
- Clinical symptoms :
 - Erythema Infetiosum (slapped cheek /Fifth Disease)
The rash may be in a lacy reticular pattern
In adults the arthralgia may present with or without rash, rarely with slapped cheek & it is usually symmetrical, affecting small joints mimicking RA, due to the fact that it is immune- complex mediated.



Key:

Solid line> Hb level

Broken line> Reticulocyte count

According to the graph:

Reticulocytes are being lost due to viremia, but

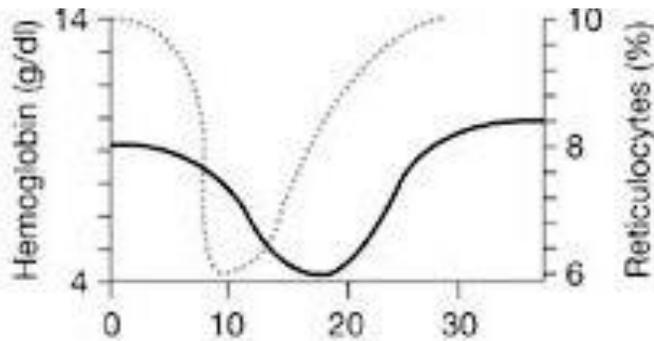
Because they are short lived the drop in the Hb level is insignificant, because in normal patients the RBCs have a normal life span.

B. Transient Aplastic Crisis patients:

- Occurs in patients with anemia e.g. Sickle Cell Anemia, Thalassemia, and Acquired Hemolytic Anemia.
- Disease course >> one phase
- Self-limited/ transient >> due to the fact that after mounting an immune response IgM & IgG antibodies targeted against VP1 will be produced >> killing the virus & preventing it from gaining access to the cells in addition to losing its phospholipase activity.
- Acute, patients cannot get oxygen & nutrients to their cells >> require transfusions
- Very bad worsening of their anemia due to the fact that their RBCs have shorter life span.

- Unlike in EBV infection where the immune response is mediated via cellular immunity, in Parvovirus B19 infection the immune response is mediated via antibodies (humoral immunity); however, there may be a contribution by the cellular immunity.
- Low rate of erythropoiesis due to the killing of the erythroprogenitor cells.
- Particularly in patients with Sickle Cell Anemia Parvovirus B19 infection may precipitate a risk for cardiovascular accidents.
- There may be variable degrees of thrombocytopenia & neutropenia due to the apoptosis of non-permissive cells.
- Bone marrow sample shows reticulocytopenia i.e. absence of erythroid precursors.

- Blood smear shows the presence of giant pronormoblasts
- Symptoms are typical of severe anemia e.g. pallor, fatigue, etc.....



Key:
 Solid line > Hb level
 Broken line > reticulocyte level

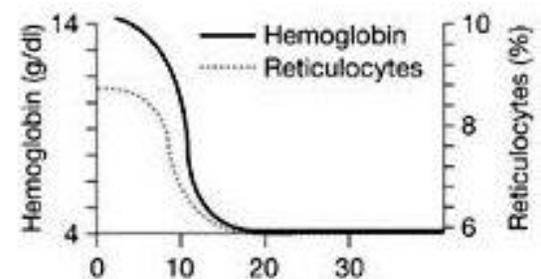
According to the graph:

Due to anemia, the reticulocytes will normally try to proliferate in order to compensate for the RBC loss. In the case of Parvovirus B19 infection the symptoms will be severe in anemic patients because their body depends on the reticulocytes for compensating the RBC loss 2° to anemia.

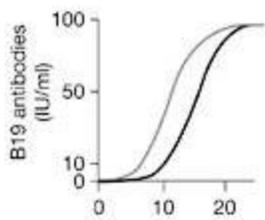
Therefore Hb level will drop severely, especially if the RBC life span is shortened, along with a step drop in the Reticulocyte level.

C. Chronic anemia/pure red cell aplasia patients

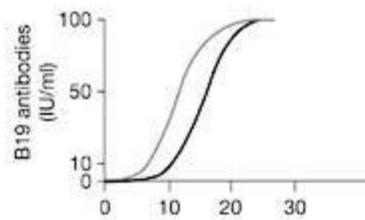
- Occurs in patients who cannot mount a neutralizing antibody response (immunocompromised)
- This immune deficiency may be congenital, or due to AIDS, lymphoproliferative disorders especially acute lymphocytic leukemia, or 2° to transplantation.
- Persistent anemia with giant pronormoblasts scattered in the bone marrow.
- Rarely, transient neutropenia, lymphopenia & thrombocytopenia.
- Reticulocyte level goes down (reticulocytopenia).
- Hb level goes down.
- As a result of not being able to elicit an immune response >>no immune complex mediated symptoms appear.
- The patient is dependent on transfusions.



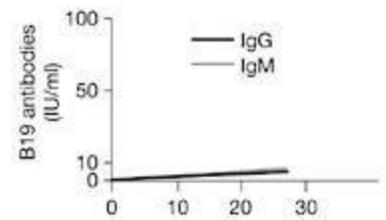
Note: in Parvovirus B19 infections IgM & IgG production are of similar peaks unlike in most other diseases.



In normal patients
PRCA patients



TAC patients



Fetal infection:

Parvovirus B19 infection is worse in fetus, due to the fact that the fetus is a big mass of proliferating cells, thus being an optimal site for Parvovirus B19 replication.

- In 30% of Parvovirus B19 maternal infections are vertically transmitted.
- Erythroblasts in the fetal liver are infected.
- Infection may lead to severe anemia leading to high output cardiac failure.
- Fetal infection may persist after birth as PRCA.

Unlike in EBV infection, Parvovirus B19 intrauterine infection is very serious.

Maternal immunity is protective to the fetus, therefore the fetus of a mother who has been previously infected with Parvovirus B19 is not susceptible to the infection; however, if the mother gets a primary infection & transmits it transplacentally to the fetus, both the mother and fetus in this case are not immunized, & in most cases the infection is severe especially if it was in the first two trimesters.

Diagnosis:

- IgM antibodies >> are present at the time the rash appears in Erythema Infectiosum and by day 3 in TAC pts
- IgG antibodies >> appear late approximately at day 7 & therefore are not used for the diagnosis in acute cases.
- PCR >> is the most specific & is detectable earlier than serology, it is used :
 - ✓ In immunocompromised patients (PRCA) e.g. in the case of acute lymphoblastic leukemia, since neither IgMs nor IgGs are produced.

✓ For early detection.

Treatment

- There is no available antiviral treatment for Parvovirus B19 infection.
- Treatment is usually supportive, treating the symptoms, e.g. patients with anemia>> blood transfusions.
- Patients who cannot mount an immune response IV immunoglobulins are given from immunized donors.
- Intrauterine blood transfusions may be useful to prevent the loss of the fetus.

Done by:

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