

Hematology



Histology

Dr. name : **Dr. Sameer Naji**

Biochemistry

Pathology

lecture number : **5 (2-virology)**

Pharmacology

Physiology

Microbiology

Done BY : **Ali Karesat**

Handout

Sheet

Slide

Parvoviruses

History

-Diseases caused by parvoviruses has been recognized among non-human hosts for a number of years . the first viruses to be discovered are **canine parvovirus** and **feline panleukopenia** , these two viruses cause infections in dogs and cats respectively, and they don't cross the species barrier.

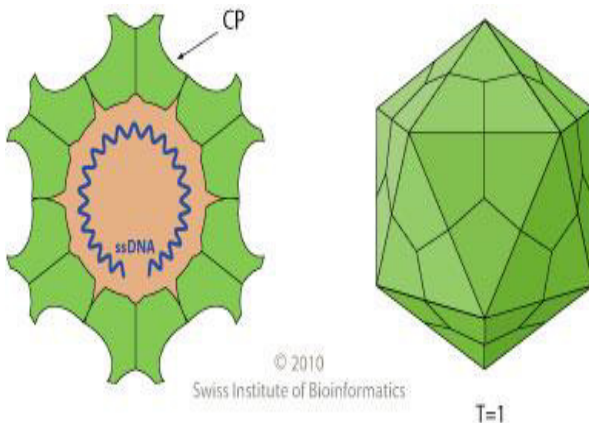
- what does the word canine and feline means ?

Canine came from **carnivores** which means "meat eaters " while feline is an animal family that includes wild and domestic cats .

-the most important virus among the parvoviridae family is **human parvovirus B19** which infects humans . The origin of this virus is not known yet .

Structure

-The word "parvo " means **very small** and because these viruses are among the smallest viruses , they are called parvoviruses . This idea of naming was also applied on bacteria , there is a group of bacteria called **parvobacteria** which includes H-influenza , brucella .. etc and they are also small in size .



-These viruses are **naked (non-enveloped)** , **single stranded DNA with an icosahedral capsid and a size of (18- 26) nm** .

Note : from last year you remember that the size of viruses range from 10- 400 nm and viruses are either DNA or RNA viruses , these DNA or RNA in viruses can either be single or double stranded.

- Parvovirus B19 encodes 3 capsid proteins , this virus forms primary cultures in human bone marrow cells , fetal liver cells , hematopoietic progenitor cells and megakaryotic cell line .

Classification

- Parvoviruses belong to parvoviridae family , this family is divided to parvovirinae subfamilies .
- There are many classifications in the parvoviridae family but we only care about parvovirus B19 .

Note : when we say " viridae " it refers to the **whole family** of the virus , but we say "virinae " we refer to the **subfamily** .

- There is another virus in the parvoviridae family called **dependoparvovirus**. This virus is called an **incomplete virus** because it depends on other viruses to complete its life cycle ,this is similar to Hepatitis D virus which needs hepatitis B to cause infection.

Transmission

The virus is transmitted through three major ways :

- 1- Transmission through infected respiratory droplets (mainly)
- 2- Blood-borne transmission
- 3- Vertical transmission (from the mother to the fetus through the placenta)

- Parvovirus B19 infection is common world wide, mostly infect persons who are 15 years of age, infection is most common in late winter and early spring.
- The virus is mainly transmitted from infected children to adults .The transmission rate is about 50% for those living with an infected person and about 20-30% for susceptible teachers or health care workers who are exposed to the infected children.
- The virus can be transmitted nosocomially during hospital time ranging from 4-14 days but can last as long as 21 days .
- **Patients infected with parvovirus B19 are no longer contagious when the rash starts to appear on the skin because the virus has been cleared from the blood .**

Note : in most of the viral infection , when there is **viremia** (the presence of the virus in the blood) the person is contagious , however when the virus is cleared from the blood the patient is no longer contagious .

Infectivity

***The cellular receptor for Parvovirus B19 is a Globoside which is known as blood group P-antigen , whenever there is a cell with a P-antigen ,it is considered a good target for this virus (important) .**

-This P-antigen is found on erythroid progenitors , erythrocytes, megakaryocytes and endothelial cells , all these are potential targets of the virus because they contain this P-antigen .

- the primary site of replication appears to be the **nucleus** of immature progenitor cells of the erythroid lineage, this will affect their proliferation, so impairment of erythrocytes development . this virus replicates in those cells and eventually lead to cell lyses consequently affecting the production of RBC'S .

-most of the symptoms that appear during the infection are caused from the formation of **immune complexes** (antigen-antibody reactions) which are harmful to the body .

Role in diseases

- Most people with parvovirus B19 infections are symptomatic and exhibit mild non-specific cold like symptoms (**coryza**)that are never linked to the virus itself.
- There are many clinical presentations associated with parvovirus B19 infections and we will go through each one of them in details :

1- Erythema infectiosum

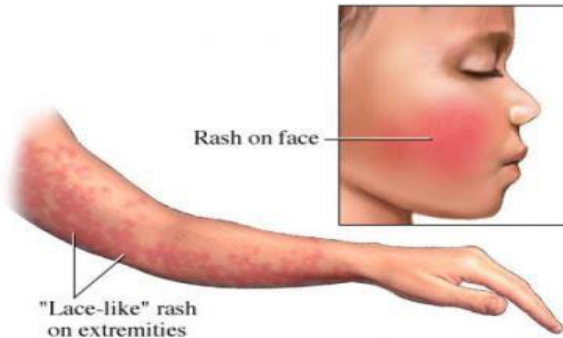
It is the most recognizable presentation of parvovirus B19 infection ,this disease is also referred to as "**Fifth disease** " or "**slapped check syndrome** " or "**Academy rash**".

This disease affects children up to 10 years of age . infection in adults causes mild symptoms of less pronounced rash , coryza , headache and nausea (not important for the exam) .

The disease progression is divided into stages :



- First stage : the rash appears as **erythema** of the cheeks mimicking the appearance of a **slapped cheek** .
- Second stage : after 1-4 days this stage appears as a maculopapular rash of the extremities and trunk , this rash has a lace –reticular pattern (lace : خيط ,reticular : شبكة)
- Third stage : continue for the next 1-3 weeks , the rash persist and it is exacerbated by sunlight or heat . eventually the rash will go away with no permanent damage so this disease is **self-limited** .



Note : keep in mind that the child which exhibit rash is NOT contagious because there is no viremia . The child is only contagious when he show cold like symptoms initially which can transmit the virus through droplets .

2- Arthralgia (Joint pain)

- Arthralgia is either a complication of erythema infectiosum or it is appears as a primary presentation of parvovirus B19 (it either appears first or later)
- Arthralgia affects women twice as often as men .
- Arthralgia generally resolves within 3 weeks but can last from months to years especially in women . In children the pattern of arthralgia can either be symmetric or asymmetric and usually involves the knees and ankles .
- Some patients with arthralgia test positive for rheumatoid factor and anti-nuclear antibodies .What are those ? rheumatoid factor is an IgM , these factors are seen in rheumatoid arthritis and other autoimmune diseases .

3- Transient aplastic crisis

- Because the virus replicates in RBC progenitor cells "they have the P-antigen" and affects RBC'S production . Any person suffering from anemia caused by iron deficiency anemia, HIV, Hereditary spherocytosis , sickle cell anemia , thalassemia may suffer from transient aplastic crisis during parvovirus B19 infection . " any cause of anemia will be aggravated in response to this virus resulting in aplastic crisis "

- The viruses causes cessation of erythrocytes production and in combination with the previous anemia in those patient this will cause crisis .
- Multiple blood transfusions are needed initially during the crisis .
- The apparent drop in hemoglobin may cause congestive heart failure and cerebrovascular accident..
- WBC and platelet count my also drop during the crisis . Patients are highly contagious during aplastic crisis and should be isolated to prevent transmission of the virus .

4- Infection in immunocompromised patients

- The main presentation in those patients is **persistent chronic anemia** , so they will present with fatigue , pallor and other signs of anemia .
- Reticulocytosis is **absent** because erythroid progenitor cells are damaged by the virus .
- Since immunocompromised patients lack the ability to form adequate antibodies against parvovirus B19 no immune complexes will be form and consequently those patients do not experience rash nor arthralgia (remember that rash and arthropathy are caused by the formation of immunocomplexes which are harmful to the body)
- This condition is treated by intravenous immunoglobulins which usually resolve the anemia .

5- Gloves and socks syndrome

- It is called papular purpuric gloves and socks syndrome , it mainly affect young adults (while erythema infectiosum affects children)
- The mechanism by which parvovirus B19 cause this syndrome is not known yet .
- **The patient presents with symmetric , painful erythema and edema in the feets and hands mimicking the appearance of gloves and socks .**



FIGURE 1: Papular-purpuric exanthem involving the distal extremities in a "gloves and socks" pattern

- The hallmark of the syndrome is sharp demarcation of the rash at the wrist and ankles , however other areas like the cheeks , elbows , buttock , inner thigh , vulva maybe involved as well .
- This condition gradually progresses to **petechia** which is bleeding under the skin in the form of dots caused from damaged blood capillaries . this petechia may develop to vesicles which will eventually be sloughed .
- Gloves and socks syndrome has been also associated with hepatitis B , EBV , CMV , Human herpes virus 6 (all these viruses are latent viruses) also measles .



6- Hydrops fetalis



-parvovirus B19 is transmitted from infected mother to the fetus through the placenta causing hydrops fetalis .

-the virus infect fetal liver and bone marrow erythroid progenitor cells which inhibits erythropoiesis which leads to fetal anemia due to the decreased lifespan of RBC's , also the virus infect the myocardium of the heart leading to myocarditis .

-the combination of severe anemia and myocarditis eventually leads to **congestive heart failure** which leads to fetal death .

-the estimated risk of trans-placental infection is **30%** with **2-6 % of fetal loss** , many infants are born without symptoms .

-the most vulnerable fetal period is the **2nd trimester** because of increase risk of reducing liver hematopoiesis . Why infection in the 1st trimester has lowest risk even though the placenta has a lot of P-antigens ?for 3 reasons :

1- Because there is no hematopoiesis in the liver cells at this period

2-Because there is no antigen-antibody interactions in the fetus due to the inability of the fetus to produce IgM pentamers that interact with the virus

3-Because of the inability of maternal IgM to pass through the placenta due to its large size .

Diagnosis

- Erythema infectiosum can be diagnosed based on clinical presentation (slapped cheek , arthralgia)without the need of laboratory investigations .
- If diagnosis could not be reaches based on clinical appearance , two main laboratory diagnostic tools are used :
 - 1- Polymerase chain reaction PCR , this test is mostly useful during viremia ,otherwise from bone marrow tissue biopsy if viremia was not there .This is the most sensitive test to diagnose parvovirus B19 infection .
 - 2- Serological testing for IgM against parvovirus B19 :because the presence of IgM indicates recent infection .In contrast IgG indicates previous infection therefore testing for IgG is not informative .

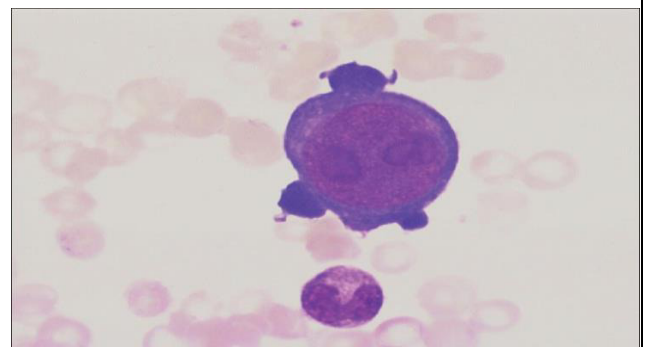
Table 1: Laboratory Diagnosis of Parvovirus Infection

	IgM	IgG	PCR for DNA
Unexposed	--	--	--
Acute Infection (3-7 days)	+++	--	+++
Acute Infection (7-14) days	+	++++	++
Previous Infection	-- ¹	+	-- ¹
Immuno compromised patient	--	--	++ ²

¹Increased IgM may be detectable for up to 9 months post-infection; positive PCR results have been observed up to 9 months post-infection as well

²Recent versus reactivated versus previous infection with parvovirus in an humorally compromised patient will rely greatly on the clinical history for proper interpretation of nucleic acid testing for parvovirus.

- 3- Microscopic evaluation of a bone marrow smear or peripheral blood smear may show **giant pronormoblasts** which are suggestive for parvovirus B19 infection but are not diagnostic .



Epidemiology

- The virus is common and wide spread all over the world

- Most adults have been infected in a certain stage in their life with a positive IgG serology so most healthy people have IgG antibody against parvovirus B19 because IgM will disappear within 1-2 weeks .
- Most infections are subclinical (except aplastic crisis) .
- Sporadic outbreaks among children happen each year , nosocomial transmission also happens .

Treatment

- 1- Erythema infectiosum is self limited and doesn't require specific treatment.
 - 2- Patients with arthralgia require NSAID (non-steroidal anti-inflammatory drugs)
 - 3- Patients in transient aplastic crisis may require blood transfusion while the bone marrow recovers .
 - 4- Patient with chronic red cell aplasia as in immunocompromised patients may require IV immunoglobulin administration . these immunoglobulins may correct the anemia symptoms however it could worsen the arthralgia due to complex formation .
 - 5- A vaccine has been developed but it is not commercially available yet .
-

The end

