MICROBIOLOGY

بسم الله الرحمن الرحيم

MID – Lecture 6

Parvoviruses

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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4- Parvoviruses

DNA- based virus

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Objectives

- Describe general structure, properties, replication and control of Parvovirus
- Describe the virology, epidemiology, pathogenesis, clinical presentation and management of Parvovirus B19

→ Parvoviruses are a big family of viruses with similar characteristics, one of them is a mostly human pathogenic virus (parvovirus B19) while the rest usually infect animals & insects.

Structure

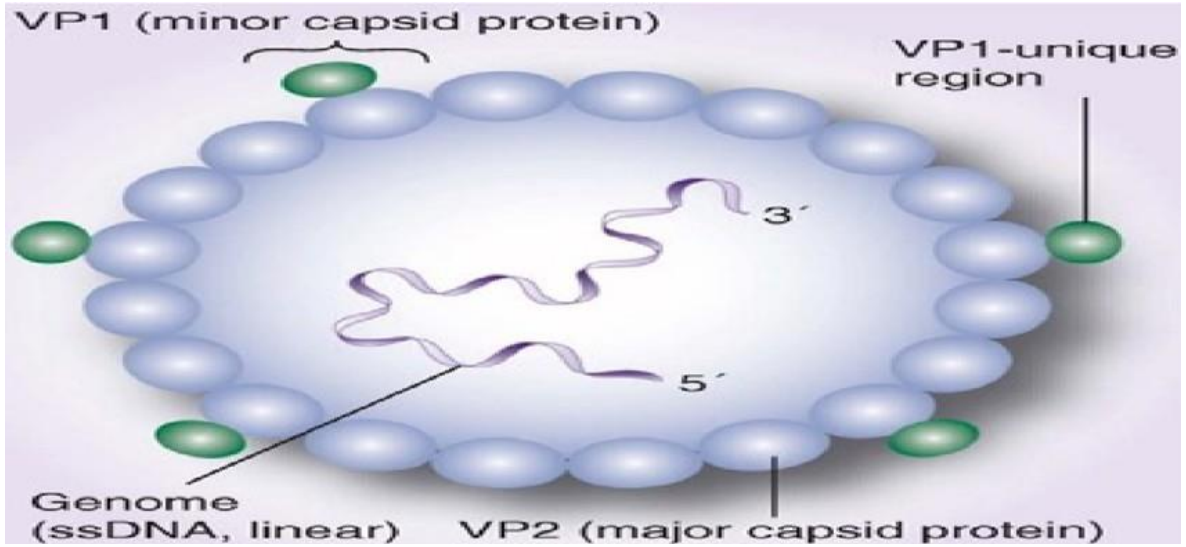
Normal range from 20nm to 450 nm No envelope

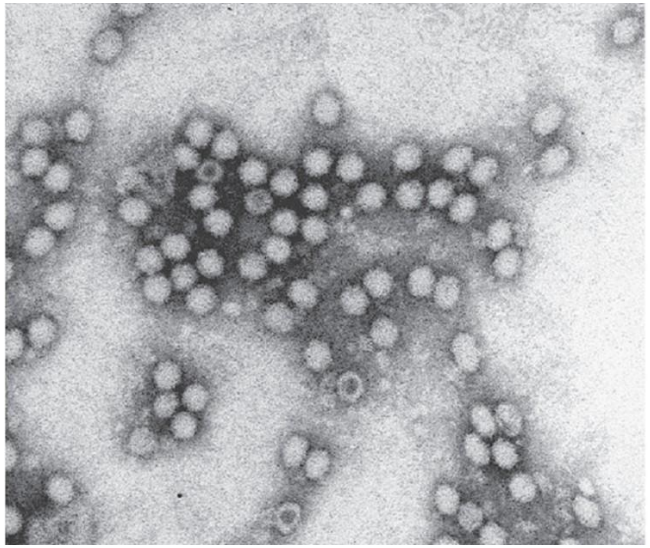
- Parvoviruses are very small (18 to 26 nm), naked virions that contain a linear single-stranded DNA (the smallest DNA animal viruses)

Limited number of capsomeres (remember, small virus)

- Icosahedral with 32 capsomers and 2 protein coats (VP2 and VP1)
- Parvovirus B19 is pathogenic for humans

VP: viroprotein
VP2 more abundant





Replication and control

- Because of the limited coding capacity of their genome, viral replication is dependent on functions supplied by replicating host cells or by coinfecting helper viruses
- Autonomously replicating and defective parvoviruses that require a helper virus for replication.
- It is difficult to culture human B19 parvovirus
- Viral DNA replication occurs in the nucleus
- Viral replication results in cell death
- Virions are extremely resistant to inactivation.
  - They are stable between a pH of 3 and 9
  - Withstand heating at 56°C for 60 minutes Most viruses dead in 15-30 min
  - Can be inactivated by formalin, and oxidizing agents

- → All viruses use machinery & metabolism of host cells, but some viruses carry essential enzymes. Parvovirus B19 is extremely small, so it does not carry polymerase or glycoproteins or anything at all ~basically too small for that~ which makes it weak in that aspect -replication weak- and sometimes even need co-infection with another virus.
- → Co-infection in which two viruses infect one host which can allow weaker virus -parvovirus here- to replicate more.
- → BUT B19 can still replicate by itself, other animal & insect parvoviruses usually require helping virus.
- → Some parvoviruses are defective, doesn't even have essential structures which makes them in need of support from another virus.
- → As mentioned previously, not all viruses cause cell death. Some can cause cytopathological effects, some cause minimal effect, etc.
- → Many factors can cause inactivation of virus: heat, salt, detergents, etc. Enveloped viruses being being more sensitive.

IMPORTANT

~Happy memorising

TABLE 31-1 Important Properties of Parvoviruses

Virion: Icosahedral, 18–26 nm in diameter, 32 capsomeres
Composition: DNA (20%), protein (80%)
Genome: Single-stranded DNA, linear, 5.6 kb, MW 1.5–2.0 million
Proteins: One major (VP2) and one minor (VP1)
Envelope: None
Replication: Nucleus, dependent on functions of dividing host cells
Outstanding characteristics:
Environmentally stable
Human pathogen, B19, has tropism for red blood cell progenitors.

Adhesion –first step in virus infection– requires receptor attachment on cell surface, specific attachment is called **tropism.**
Gives virus ability to target cell with certain affinity.

Immature RBCs

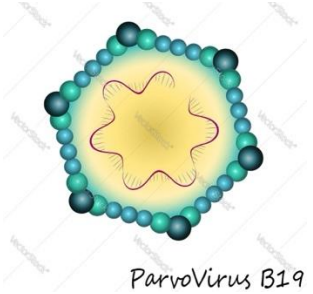
Parvovirus B19 Infections

Of course B19 also has same characteristics that are previously mentioned in regard to parvovirus family.

«اللَّهُمَّ اغْفِرْ لِي مَا قَدَّمْتُ وَمَا أَخَّرْتُ، وَمَا أَعْلَنْتُ وَمَا أَسْرَرْتُ، وما أنت أعلم به مني، أَنْتَ المُقَدِّمُ وَأَنْتَ المُؤَخِّرُ لا إِلَهَ إِلاَّ أَنْتَ»

Viral target

-Most famous blood groupings are ABO & Rh.
Ex. Blood group A → antigen A on blood cell
-Any antigen on RBC can be a blood group (almost 40)



Blood group: antigen on RBC surface

- The cellular receptor for B19 is blood group P antigen (globoside). P receptor is parvovirus B19 receptor.
- P antigen is expressed on mature erythrocytes, erythroid progenitors, megakaryocytes, endothelial cells, placenta, and fetal liver and heart, which helps explain the narrow tissue tropism of B19 virus

Mature & immature RBC

→ If the mother was affected, the virus can reach placenta & then reach fetal heart or liver

- the major sites of virus replication in patients are assumed to be the adult marrow, some blood cells, and the fetal liver
- A primary site of replication appears to be the nucleus of an immature cell in the erythrocyte lineage.

→ Remember, B19 is DNA- based virus which means it needs a nucleus, this is why it usually targets progenitor RBC more (they have a nucleus)

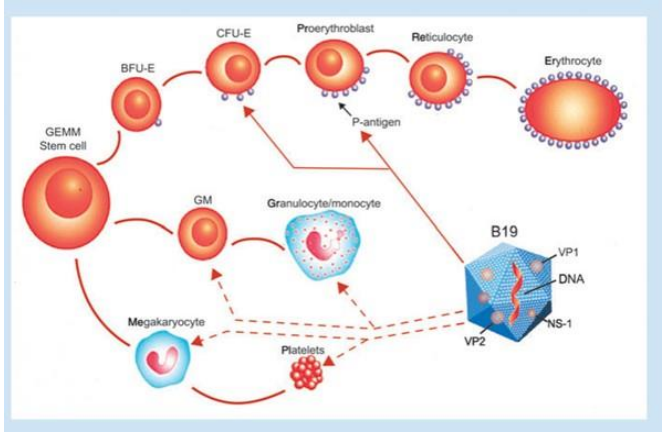
Epidemiology

- The viral infection is common among children 5-15 years old
  → As you grow older, you form immunity which decreases B19 transmission
- Epidemiologic evidence suggests that spread of the virus is primarily by the respiratory route, and high transmission rates occur in households
  → Enters through respiratory system although B19 doesn't stay there → travels to blood, bone marrow, fetal liver, etc.
- Once skin rash appear the virus is no more contagious
- Outbreaks tend to be small and localized, particularly during the spring months, with the highest rates among children and young adults
- Seroepidemiologic studies have demonstrated evidence of past infection in up to 60% of all adults and 90% of elderly people (seropositive IgG)
  One specific for parvovirus B19

-Seroepidemiology is the systematic collection and testing of blood samples from a target population to identify current and past experiences with infectious diseases by means of biological markers.
-A seropositive test result usually means that a person has been exposed to or infected with a virus or other infectious agent and has made antibodies against it

→ A lot of past infections most being asymptomatic/subclinical
→ Allowed formation of good immunity against B19
→ High percentage of IgG suggests virus being common with high transmission but mostly subclinical

Pathogenesis



- Viral replication causes cell death interrupting red blood cell production (anemia)
- Bone marrow biopsies from infected patients show erythrocyte maturation arrest, with erythroblast intranuclear inclusions
- Both virus-specific IgM and IgG antibodies are made after B19 infections which form immune complex
- The clinical consequences of the viral effect on erythrocytes are generally trivial, unless patients are already compromised by a chronic hemolytic process, such as sickle cell disease or thalassemia or in immunocompromised patients

Why does B19 virus not cause chronic anaemia considering it kills progenitor RBCs?
Because it is a **transient** process, also it kills progenitor cells and not stem cells.
-Of courses this is in the case that the infected person has healthy immunity & bone marrow-

~ More on each point next slide

- → RBCs are produced in bone marrow where they live 120 days in circulation then get destructed, virus interrupts this process by making bone marrow's ability to produce new RBCS weak & cells stay in immature state (erythroblasts). Also, inclusion bodies form in the nucleus.

- → B19 virus has great ability to activate immune system to produce IgG & IgM BUT at the same time, these can form complexes and depositions in some tissue.

- → The process is mild & transient, virus enters through respiratory system and keeps searching until it finds its target cells and stars breaking them but because our bone marrow is always producing new RBCS, the drop in RBC hemoglobin is minor (if hemoglobin was 14 g\dl it might drop to 13-13.5g\dl). The effect goes away -transient- after body forms appropriate immunity against it.

- → BUT if the patient infected has sickle cell anaemia or thalassemia; the effect will be more dangerous considering those cases already have low hemoglobin (if hemoglobin was 8g\dl in sickle cell anaemia patient for example, it may reach 4-3g\dl or even less).

- → Also, immunocompromised patients can't get rid of the virus easily, instead of a week time period before IgG clears the virus it takes longer time. This causes them to suffer greater loss in RBC -more cells destructed- which causes bone marrow exhaustion & increases the severity of the virus effect.

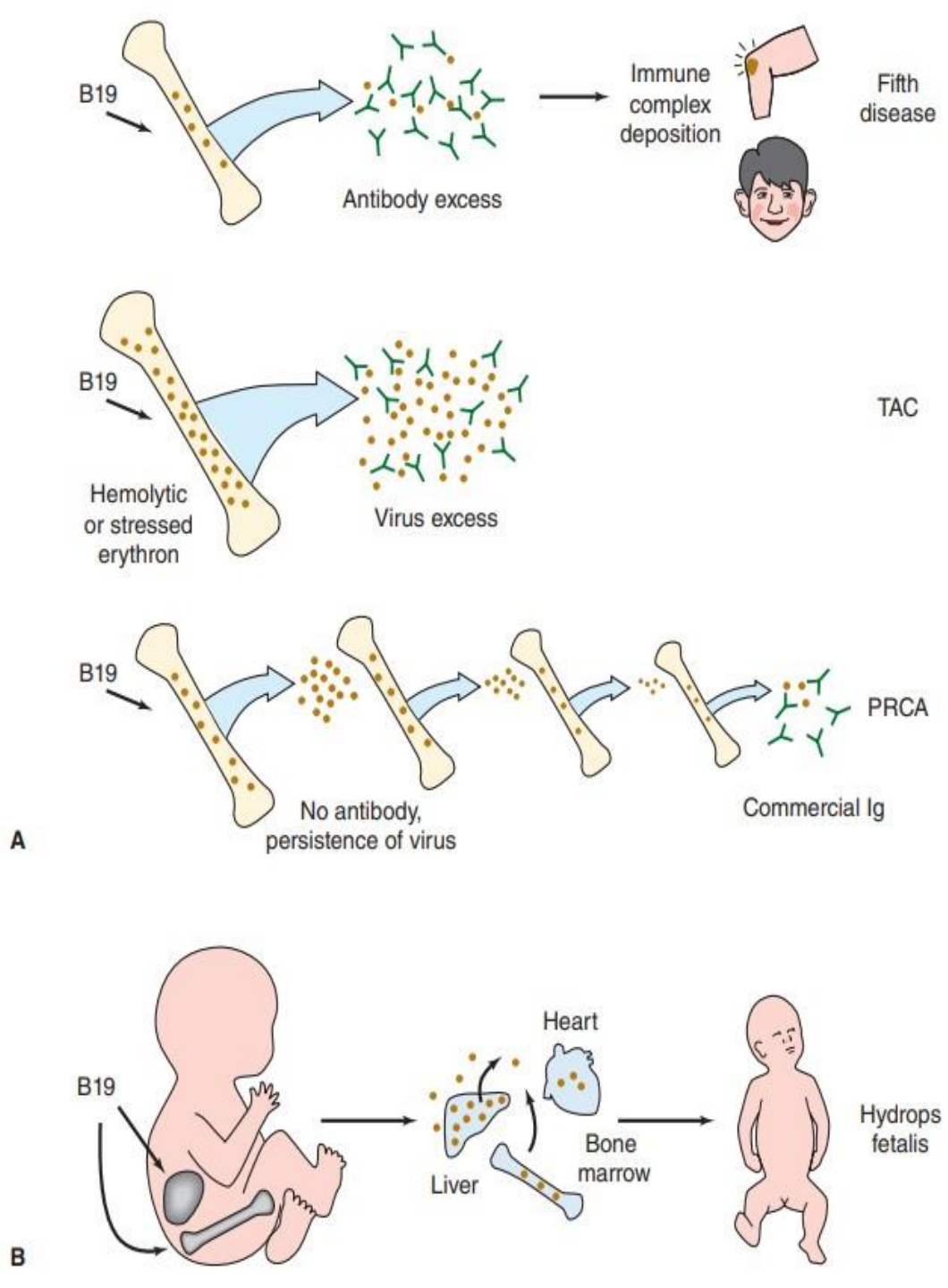
Normal hemoglobin levels are different for men and women. For men, a normal level ranges between 14.0 grams per deciliter (gm/dL) and 17.5 gm/dL. For women, a normal level ranges between 12.3 gm/dL and 15.3 gm/dL.

Virus reaches bone marrow and antibodies start forming, some kill the virus but some complexes reposition to the skin which causes a rash -main clinical finding-

B19 start causing hemolysis, bone marrow gets tired -transient state-

Immunocompromised patient, virus destructs & weakens bone marrow → no antibodies to clear virus

If a pregnant woman gets infected she could suffer from 1,2&3 and it could affect the baby as well since it's vertically transmitted.



1. Erythema infectiosum

Erythema: skin redness
Infectiosum: course of erythema is a virus skin erythema has many causes and some are not infectious like eczema.

2. transient aplastic crisis

-Not only skin manifestations, hemoglobin decreases & blood hemolysis markers increases
- (3-4) weeks at most then immunity stops virus

3. pure red cell aplasia

Aplasia: shut down of bone marrow cells, can be specific.
Ex. Red cell aplasia → shut down of red cell formation

4. Hydrops fetalis

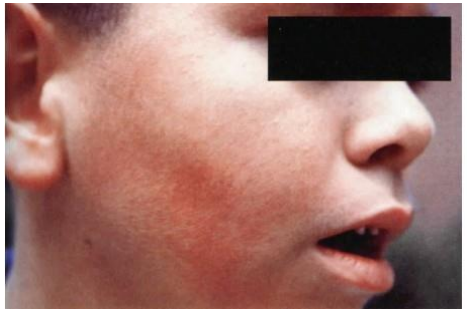
The baby's RBC production will be even weaker since it already depends on the mother for blood, and its immune system is weak and can't produce antibodies and the infection can lead to death.
Hydrops= anaemia leads to fluid accumulation/ Edema/ swelling

TABLE 31-2 Human Diseases Associated with B19 Parvovirus

Syndrome	Host or Condition	Clinical Features
Erythema infectiosum	Children (Fifth disease) Adults	Cutaneous rash Arthralgia–arthritis
Transient aplastic crisis	Underlying hemolysis	Severe acute anemia
Pure red cell aplasia	Immunodeficiencies	Chronic anemia
Hydrops fetalis	Fetus	Fatal anemia

Just remember it can be asymptomatic.
The antibodies fight it upon entry in case of previous exposure.

1- Erythema infectiosum



- Erythema infectiosum (also referred to as fifth disease, slapped check, apple face, or academy rash)

Academy rash= it spreads in schools, nurseries...
Fifth disease= it was the 5th disease discovered that led to skin rash.

- After an incubation period of 4 to 12 days, a mild illness appears, characterized by fever, malaise, headache, myalgia, and itching in varying degrees

Non-specific viral syndrome, accompanied by most viral infections.

- Viremia occurs 1 week after infection and persists for about 5 days
- A confluent, indurated rash appears on the face, giving a "slapped-cheek" appearance. The rash spreads in a day or two to other areas, particularly exposed surfaces such as the arms and legs, where it is usually macular and reticular

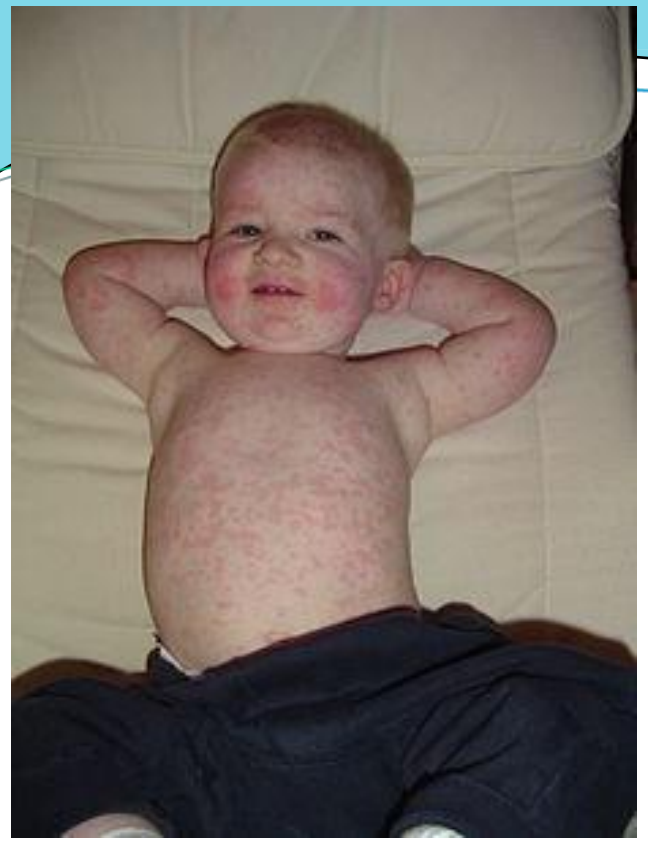
It's not contagious if it reaches the rash stage.

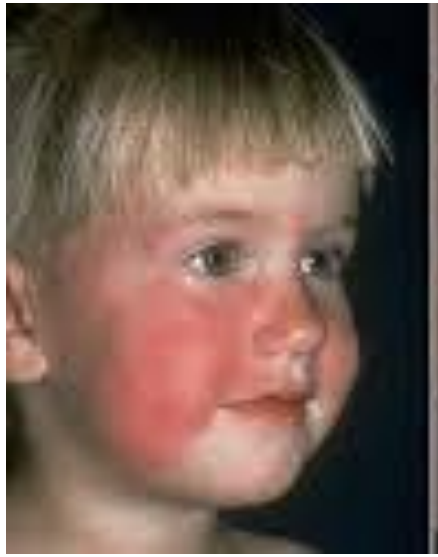
- During the acute phase, generalized lymphadenopathy or splenomegaly may be seen, along with a mild leukopenia and anemia

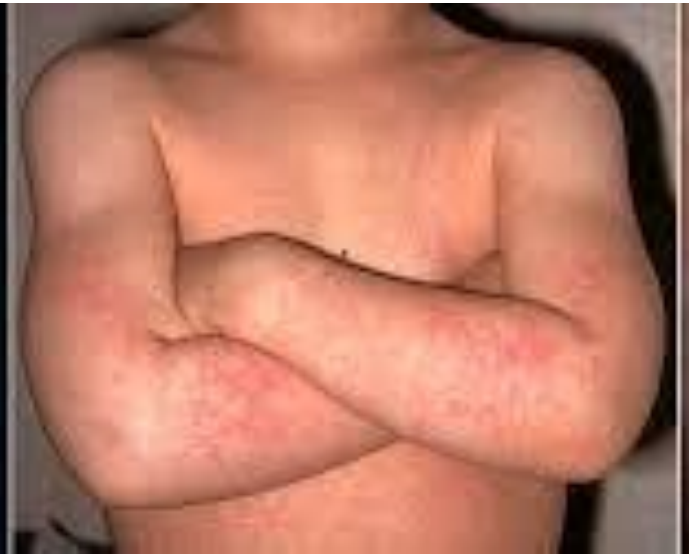
1- Erythema infectiosum

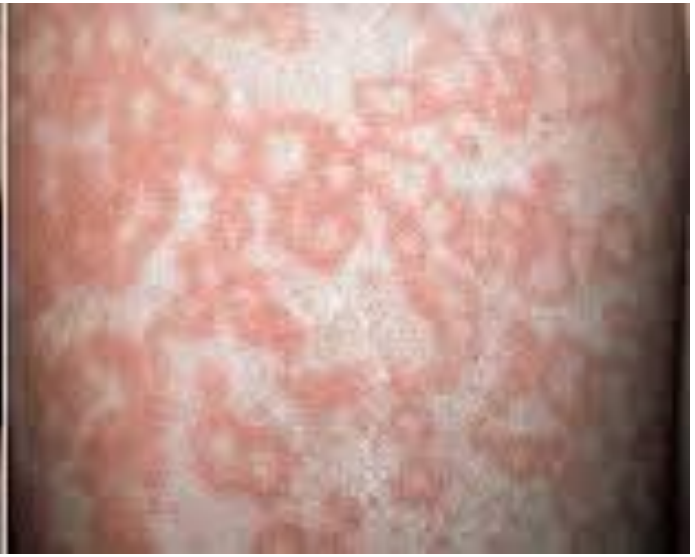
Lymphadenopathy; to transmit the Ag to the lymph nodes to activate the T and B cells and release AB
Splenomegaly; hemolysis leads to it because of excessive turnover(RBCs die in the spleen).
The virus could target progenitor cells.

- A confluent, indurated rash appears on the face, giving a "slapped-cheek" appearance. The rash spreads in a day or two to other areas, particularly exposed surfaces such as the arms and legs, where it is usually macular and reticular
- During the acute phase, generalized lymphadenopathy or splenomegaly may be seen, along with a mild leukopenia and anemia
- The illness lasts 1 to 2 weeks, but rash may recur for periods of 2 to 4 weeks thereafter, exacerbated by heat, sunlight, exercise, or emotional stress
- Arthralgia sometimes persists or recurs for weeks to months, particularly in adolescent or adult females
- Serious complications, such as hepatitis, thrombocytopenia, nephritis or encephalitis are rare

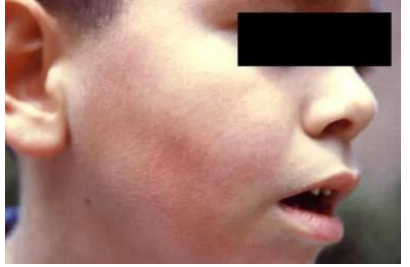








2- Transient Aplastic Crisis



- Transient aplastic crisis may complicate chronic hemolytic anemia (sickle cell disease, thalassemias), acquired hemolytic anemias in adults, and after bone marrow transplantation.

The Most critical question
Does the child have chronic hemolytic anemia or an immune deficiency?

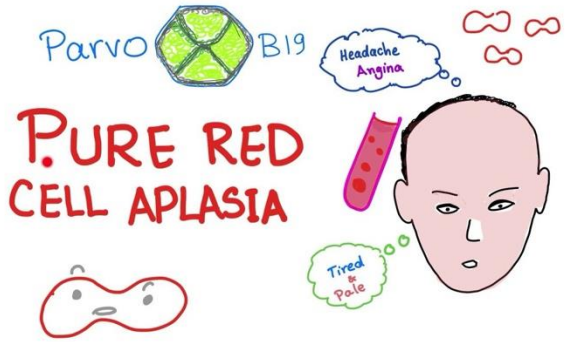
- Abrupt cessation of RBCs synthesis in the bone marrow (reduction of erythroid precursors), accompanied by a rapid worsening of anemia.
- The infection lowers production of erythrocytes, causing a reduction in the hemoglobin level.

Destructed RBC-> lower in its content= Hb

- The temporary arrest of production of RBCs becomes apparent only in patients with chronic hemolytic anemia because of the shortened life span of their erythrocytes

Erythrocytes' t1\2 is 20 days
In thalassemias it's 7 days, so the patient's Hb levels could get as low as 8
And when infected the t1\2 is 1-2 days-> even lower Hb
It's treated by blood transfusion.

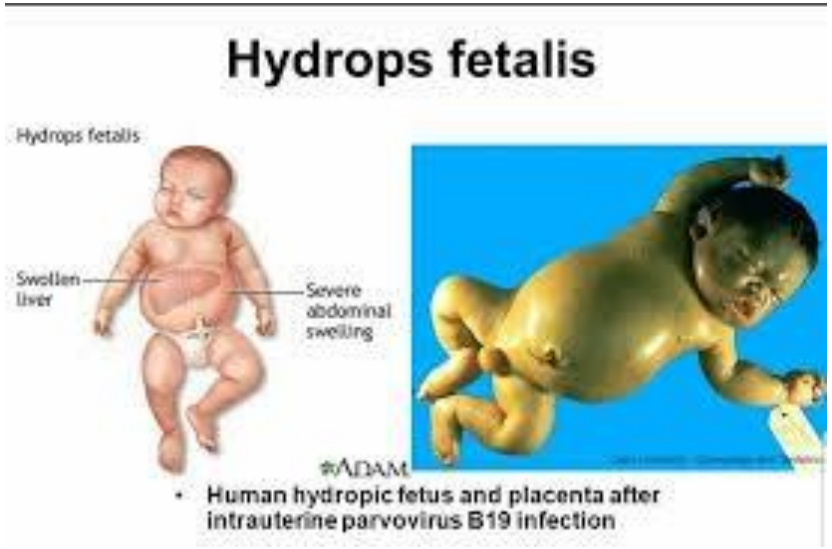
3. Pure red cell aplasia



- B19 may establish persistent infections and cause chronic suppression of bone marrow and chronic anemia in immunocompromised patients.
- The disease is called pure red cell aplasia.
- The anemia is severe, and patients are dependent on blood transfusions.
- It has been observed in patient populations with congenital immunodeficiency, malignancies, AIDS, and organ transplantation

Malignant because
They're considered immune suppressant
-> The immune system is focused on fighting cancer

4. Hydrops fetalis

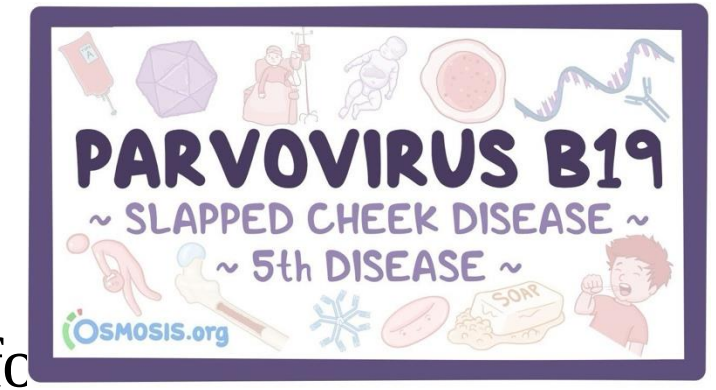


- Maternal infection with B19 virus may pose a serious risk to the fetus, resulting in hydrops fetalis and fetal death due to severe anemia.
- The overall risk of human parvovirus infection during pregnancy is low; fetal loss occurs in fewer than 10% of primary maternal infections.
- Fetal death occurs most commonly before the 20th week of pregnancy.

It has other causes technically anything that causes anemia in the fetus ends with it(Rh incompatibility)

how likely for the mother to get infected?
Very unlikely: 1. she's an adult
2. She might be immune due to previous exposure
3. even if she isn't immune and even with her compromised immunity, her system will still fight it before it's transmitted to the baby.

Diagnosis



- Viremia usually lasts 7 to 12 days but can persist fo
  months in some individuals
- CBC (low Hb)

To check anemia levels

- Polymerase chain reaction (PCR)

Aplastic anemia/ blood cell aplasia could require it as well as bone marrow biopsy to ensure that the virus is the main cause of the disease

- IgM-specific antibody late in the acute phase or during
  convalescence strongly supports the diagnosis
- Antigen detection assays
- Bone marrow biopsy

Management

- Fifth disease and transient aplastic crisis are treated symptomatically(self-limited)
- Severe anemia due to the latter may require transfusion therapy
- Commercial immunoglobulin preparations contain neutralizing antibodies to human parvovirus. These can sometimes ameliorate persistent B19 infections in immunocompromised patients and in those with anemia

passive immunization; antibodies from a healthy previously infected person are collected and given to an anemic person to help its immune system fight it off, when they all die(AB) the immunity ends with it as well

- There is no vaccine against human parvovirus
- There is no antiviral drug therapy

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

رزقكَ لن يأخذه غيركَ،

ولكن عبادتكَ لن يقوم بها غيـــــركَ،

إنَّ الله سبحانه قد تكفَّل لكَ بالرزق،

وطلبَ منكَ العمل!

فلا تنشغل بما تكفلَّ لكَ به،

وتنسَ الذي طـــالبـــــكَ به!

لا تنسوا اخوانا المستضعفين من دعائكم