

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ



HEMATOPOIETIC & LYMPHATIC SYSTEM

SUBJECT : MICROBIOLOGY

LEC NO. : 1

DONE BY : ALI ABUGHAZLEH



وَقُلْ رَبِّ زِدْنِي عِلْمًا

1- Epstein-Barr Virus and Parvoviruses B19

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Objectives

- Describe the virology, epidemiology, pathogenesis, clinical presentation and management of Epstein-Barr Virus
- Describe the virology, epidemiology, pathogenesis, clinical presentation and management of Parvovirus B19



Epstein-Barr Virus (EBV)

رح نبدا اليوم بالحديث عن اشهر الفيروسات بالجهاز الدموي الليمفاوي اول فايروس هو EBV الي بسبب مرضين هما

1- infectious mononucleosis (infections come from that they cause infection / mononucleosis come from they risk the monocytes and lymphocytes of infected individuals)

2- African Burkitts lymphoma (they are common on Africa and Burkitts du to scientist that discover it)

Lymphoma is a malignant tumour of the lymphatic system

يتكون هذا الفيروس من مادة وراثية صغيرة بالمقارنة مع انواع الهيريس الاخرى تكون المادة الوراثية مغلقة بطبقة بروتينية تسمى capsid ثم بطبقة بروتينية اخرى تسمى tegument ثم الغلاف الخارجي الاخير ال envelope ويتكون من الدهون على سطح هذا الغلاف هناك بروتينات صغيرة تسمى glycoproteins لها اهمية كبيرة في حدوث الاصابة مسؤولين عن ال attachment

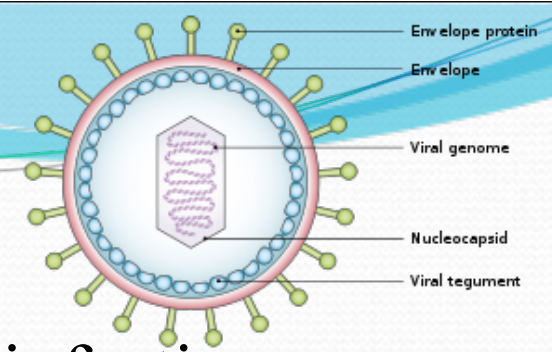
يرتبط هذا الفيروس مع نوعين من الخلايا الاولى هي الخلايا البائية المناعية والاعلى خلايا ال epithelial of upper respiratory tracts

TABLE 1. Types of virus and associated clinical features

VIRUS	CLINICAL FEATURES
HSV-1	Cold sores, mouth ulcers, genital sores
HSV-2	Genital sores, mouth ulcers
VZV	Chicken pox, shingles
EBV	Glandular fever
CMV	Fever and hepatitis
HHV 6	Roseola infantum in children
HHV 7	Exanthema subitem in children
HHV 8	Kaposi sarcoma (in HIV patients)



Virology



- Epstein-Barr virus is the etiologic agent of infectious mononucleosis and African Burkitt's lymphoma
- Its complete nucleotide sequence of 172 kbp is smaller than other herpes viruses
- The virus is approximately 120 nm to 180 nm in diameter and is composed of a double helix of DNA wrapped in a protein capsid. The capsid is surrounded by a tegument made of protein, which in turn is surrounded by an envelope made from lipids. The viral envelope contains glycoproteins, which are essential to infection of the host cell
- In vivo, EBV is tropic for both human B lymphocytes and epithelial cells

تأتي التسمية لهذا الفيروس من أسماء العلماء الذين ساهموا في اكتشافه
فالعالم Epstein حضر محاضرة لعالم آخر اسمه Burkitt وهو جراح مهتم في السرطانات التي تصيب
الأطفال خلال المحاضرة وهو يشرح كان يحكي في عن نوع من السرطان يصيب الأطفال كثير في أفريقيا
ومجهول سببه ، اجى عليه العالم Epstein وبعد المحاضرة قلو خليتنا نوخذ عينات ونرسلها للمختبر في
بريطانيا هناك وجدو الفايروس بالتالي سبب هذا السرطان

History



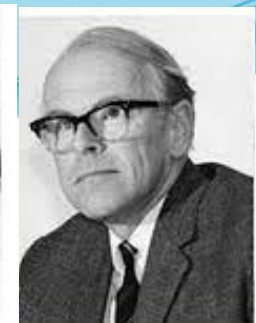
Tony Epstein



Bert Achong



Yvonne Barr



Denis Burkitt

- The Epstein–Barr virus is named after **Epstein**, a professor emeritus at the University of Bristol, and **Barr** a PhD graduate from the University of London
- Epstein attended a lecture on Children's Cancer in Tropical Africa by **Burkitt**, a surgeon practicing in Uganda
- Specimen was sent from Uganda to be cultured and virus particles were identified
- Later on, a technician in their laboratory developed mononucleosis and they were able to compare a stored serum sample, showing that antibodies to the virus developed and the virus was linked to mononucleosis

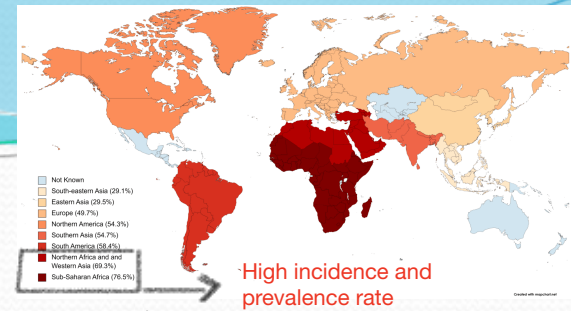
لحظ الصدفة في عامل بالمختبر صار معو mononucleosis (كان معروف ويشخصون بس السبب تبعه مجهول) فحصوا الدم تبعوا لقوا انو كون اجسام مضادة ضد فايروس EBV فاستنتجوا انو المسبب
لهذول المرضين واحد ومشان يحفظوا حقوقهم كل واحد حطوا اسمو باشي الو علاقة بالفايروس

بنحكي هون عن نسبة انتشار المرض وعن طريقة انتقاله

Epidemiology

Why respiratory viruses are very common ?

لانه سرعة انتشاره عالية ، عن طريق النفس عن طريق الرذاذ ... الخ



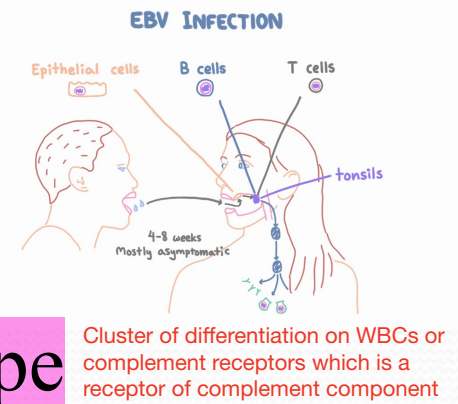
- EBV is one of the most common viral infections to human
- EBV can be cultured from saliva of **10 to 20%** of healthy **adults** and is intermittently recovered from most seropositive individuals
يعتبر هذا الفيروس ليس سريعاً جداً بالانتقال لذلك حتى ينتقل يجب ان يكون هناك contact اكثر من مرة (يعني يقعد معهم مرتين ثلاث حتى ينصاب) مع الشخص المصاب يعني عيلته ، اصحابه ، ومع ذلك يعتبر common
- It is of low contagiousness, and most cases are contracted after repeated contact between susceptible persons and those asymptotically shedding the virus (**by respiratory droplets**)
- Secondary attack rates of infectious mononucleosis are low (<10%), because most family or household contacts already have antibody to the agent
الاصابة للمرة الثانية غير شائعة لانه الجسم يكون كون مناعة ضده
- Worldwide **90-95%** of adults are seropositive
laboratory test result that shows the presence of a specific marker, usually an antibody, in the blood. Meaning the person are infected with virus and developed immunity against it
- Infectious mononucleosis has also been transmitted by blood transfusions
ينتقل عن طريق الدم ايضا طيب ليه لانه من الاهداف تبعو الي يرتبط فيها هي B LYMPHOCYTES وغالبا انه ما يصيب الجهاز التنفسي لفترة مؤقتة ثم يذهب ليصيب الخلايا البائية و يستقر فيها خلال نقل الدم من شخص لآخر ممكن ينتقل الفايروس

اعراض هذا الفايروس عادة يدخل على respiratory system ويعمل حرارة مع التهاب حلق وينتهي هناك ما يدخل على الخلايا البائية اسمو هون mononucleosis فغالبا تشخيصه يكون خاطئ مع التهاب الحلق البكتيريا ف بقول الطبيب التهاب حلق وما حدا بعرف انو الي صابك فايروس

CD21 receptor يرتبط الغلايكوبروتين مع B cell خلايا ال epithelia قبل شوي بالبداية خلايا ال
و يدخل الخلية ببلش يشغل الخلية لصالحوا يصنع مادة وراثية، بروتينات، دهون الخ مشان يتكاثر وينتج فيروسات جديدة

Pathogenesis

Most of the virus infection are asymptomatic and selflimiting



- EBV initially infects epithelial cells
- The virus enters B lymphocytes by envelope glycoprotein binding to a surface receptor CD21, which is the receptor for the C36 component of complement
- 18 to 24 hours later, EBV nuclear antigens are detectable within the nucleus of infected cells
- EBV has been associated with several lymphoproliferative diseases, including African Burkitt's lymphoma, nasopharyngeal carcinoma, and lymphomas in immunocompromised patients
- The distribution of EBV infections in Africa has suggested an infectious cofactor, such as malaria, which may cause immunosuppression

هناك نظرية تربط بين وجود الملاريا في مناطق معينة وانتشار هذا
الفايروس بالتالي نتائج كارثية اهمها هبوط المناعة وحدوث السرطان

اذا الفايروس قدر يطلع من الجهاز التنفسي ويوصل للدم هون المصيبة
بصيب خلايا B ويعمل خريطة فيها ويدخل الشخص ب Lymphoma

دليل وجود مناعة ضد هذا الفيروس هو الاجسام المضادة

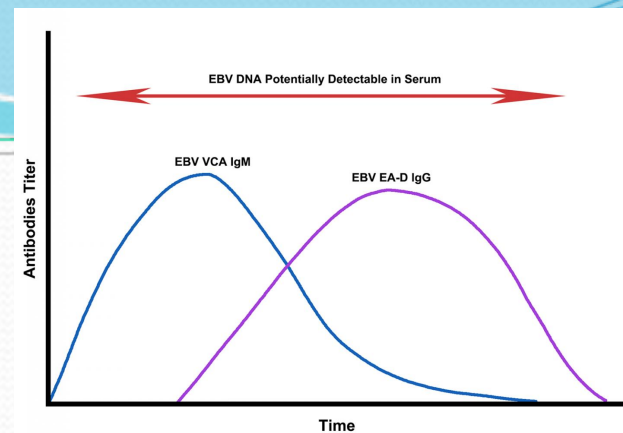
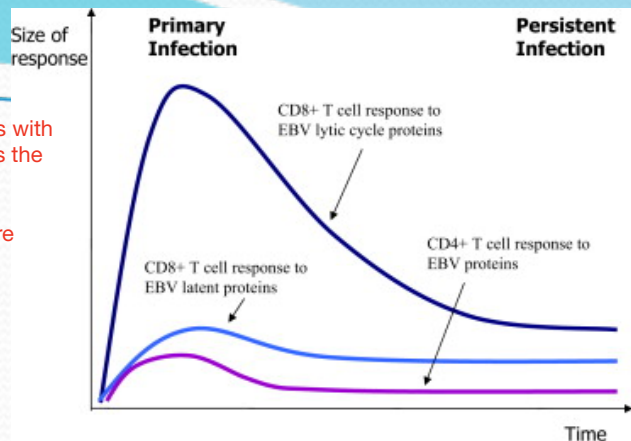
Antibody are the products of activation of immune response

وكمان قبل شوي حكينا انه نسبة الاصابة بهذا المرض للمرة الثانية اقل من ١٠٪

“atypical” lymphocytosis meaning there is an increase number of lymphocytes with abnormal shape this du to reacting from body to intracellur pathogens which is the virus and the mononuclear cells such macrophages can't destroy so there's activation of B cell

lymphocytes that activate as part of the body's response to infections. They are larger than normal lymphocytes, with varying sizes and shapes

Immunity



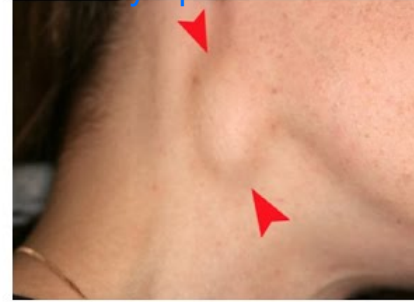
- Virus-induced infectious mononucleosis is associated with circulating antibodies against specific viral antigens
- The “atypical” lymphocytosis associated with infectious mononucleosis is caused by an increase in the number of circulating T cells, which appear to be activated cells developed in response to the virus-infected B lymphocytes
- With recovery from illness, the atypical lymphocytosis gradually resolves, and cell-mediated immune functions return to preinfection levels, although memory T cells maintain the capacity to limit proliferation of EBV-infected B cells

IgM are related to acute phase of infection but IgG related to past exposure with developing immunity

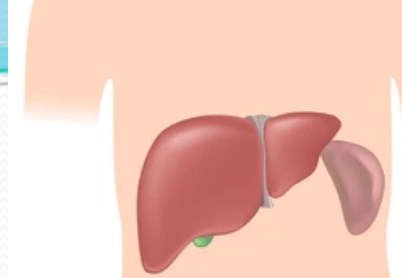
Pharyngitis



Lymphadenitis



Hepatosplenomegaly



Clinical Manifestations

1. Infectious Mononucleosis (Glandular fever)

Associated with fever and enlargement of gland

Most primary EBV infections are asymptomatic
Clinically apparent infectious mononucleosis is characterized by fever, malaise, pharyngitis, tender lymphadenitis, and splenomegaly

كيف يتم تمييز التهاب الحلق العادي عن الالتهاب الذي يسببه الفايروس بس عن طريق تضخم الطحال

تعب ،حرارة طفيفة ، التهاب حلق ، التهاب القعد اللمفاوية المؤلمة ، تضخم الطحال
وقبل شوي حكينا انه الفيروس بوصل الدم Spleen is the filter of blood
ومنه للطحال لانه الخلايا البائية خلال دورة حياتها بتمر بالطحال

These symptoms persist for days to weeks; they slowly resolve

Especially on children

Complications such as laryngeal obstruction, meningitis, encephalitis, hemolytic anemia, thrombocytopenia, or splenic rupture may occur in 1 to 5% of patients

2. Lymphoproliferative Syndrome

- Patients with **primary or secondary immunodeficiency** are susceptible to EBV-induced lymphoproliferative disease
- The risk is greatest in patients experiencing primary EBV infection rather than reactivation
- Most characteristic is **persistent fever**, lymphadenopathy, and hepatosplenopathy تستمر الاعراض لفترة طويلة جدا

The development of Burkitt lymphoma in individuals affected by malaria is influenced by chronic immune stimulation, co-infection with Epstein-Barr virus (EBV), genetic predisposition, and environmental factors. Malaria triggers persistent immune activation, potentially promoting genetic mutations and cellular changes leading to lymphoma. Co-infection with EBV, prevalent in malaria-endemic regions, exacerbates immune dysregulation and increases lymphoma risk.

يعني هون بحكي عن علاقة الملاريا التي بتسبب chronic stimulation of the immune system
والفيروس بقلك هذا التحفيز رح يزيد عدد خلايا B cell النشطة بشكل هائل بالتالي بسبب سرطان اسمه Lymphoma ويبيجي الفيروس بصيب خلايا B cell ف بادي لحدوث هذا المرض

HLS cancer are more related to children and young
(Leukaemia ,Lymphoma)

علاقة الملاريا والفيروس
والربط بينهما

Lymphadenopathy
Tendency enlargement of
cervical lymph node with
secondary infection and
ulceration

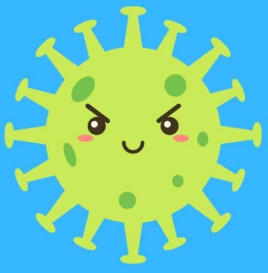
The persistence of
symptoms is the differential
diagnosis



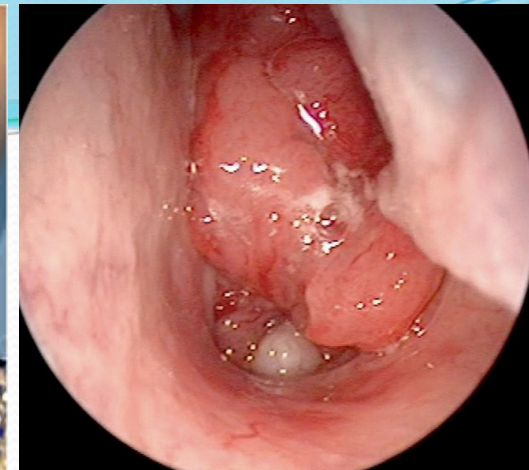
3. Burkitt 's lymphoma

- In sub-Saharan Africa, Burkitt's lymphoma is the most common malignancy in young children
- The risk is greatest in equatorial Africa, where there is a high incidence of malaria
- Burkitt's lymphoma is thought to result from an early EBV infection that produces a large pool of infected B lymphocytes
- Malarial infection may further increase the size of this pool and provide a constant antigenic challenge
- Serologic screening for increased IgA antibody levels can be used for early diagnostic purposes

المنطقة الجغرافية تلعب دور ايضا في التشخيص فمثلا
افريقيا التشخيص شائع جدا



This is the epithelium not
the lymph node



4. Nasopharyngeal Carcinoma

- Nasopharyngeal carcinoma (NPC) is endemic in **southern China**, where it is responsible for approximately 25% of the mortality from cancer
- The high incidence of NPC among the southern Chinese people suggests that genetic or environmental factors in addition to EBV may also be important in the pathogenesis of the disease

Nasopharyngeal cancer is a disease in which malignant (cancer) cells form in the tissues of the nasopharynx. Ethnic background and being exposed to the Epstein-Barr virus can affect the risk of nasopharyngeal cancer. Signs of nasopharyngeal cancer include trouble breathing, speaking, or hearing.

سبب الاختلاف في حدوث هذه الامراض الاربعة قد يعزى الى عوامل اخرى بالاضافة الى الفيروس

Other risk factors include genetic predisposition, consumption of salt-preserved foods, smoking, and exposure to certain environmental toxins.

مثلا اجاك واحد عنده sore throat, fever, splenomegally
وفي حدا بالعيلة كمان عنده نفس الاعراض او مر فيها هسا بتفكر انه EVB
وبدك تبيلش تشخص بشكل دقيق

Diagnosis

We need to do the ultrasound / imaging (CT scan , MRI) test because we the spleen need 10x enlargement to be palpable

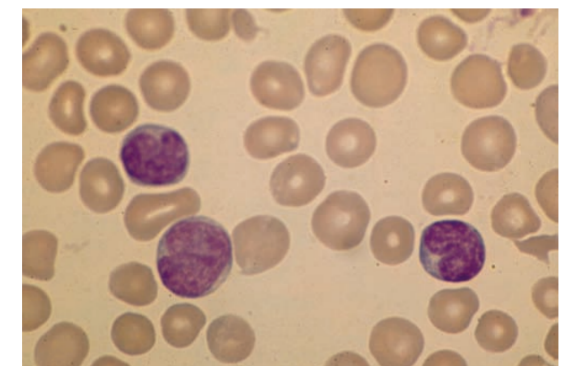
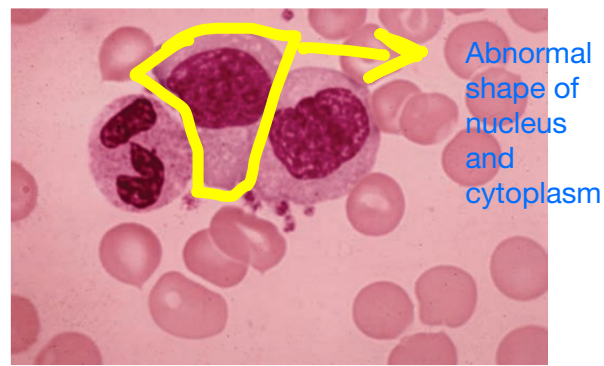


FIGURE 14-9. A. Atypical lymphocytes (Downey cells) in blood smear from a patient with infectious mononucleosis. Note indented cell membranes. Polymorphonuclear leukocyte is adjacent to the two affected cells. **B.** Normal lymphocytes contrast sharply with those in A.

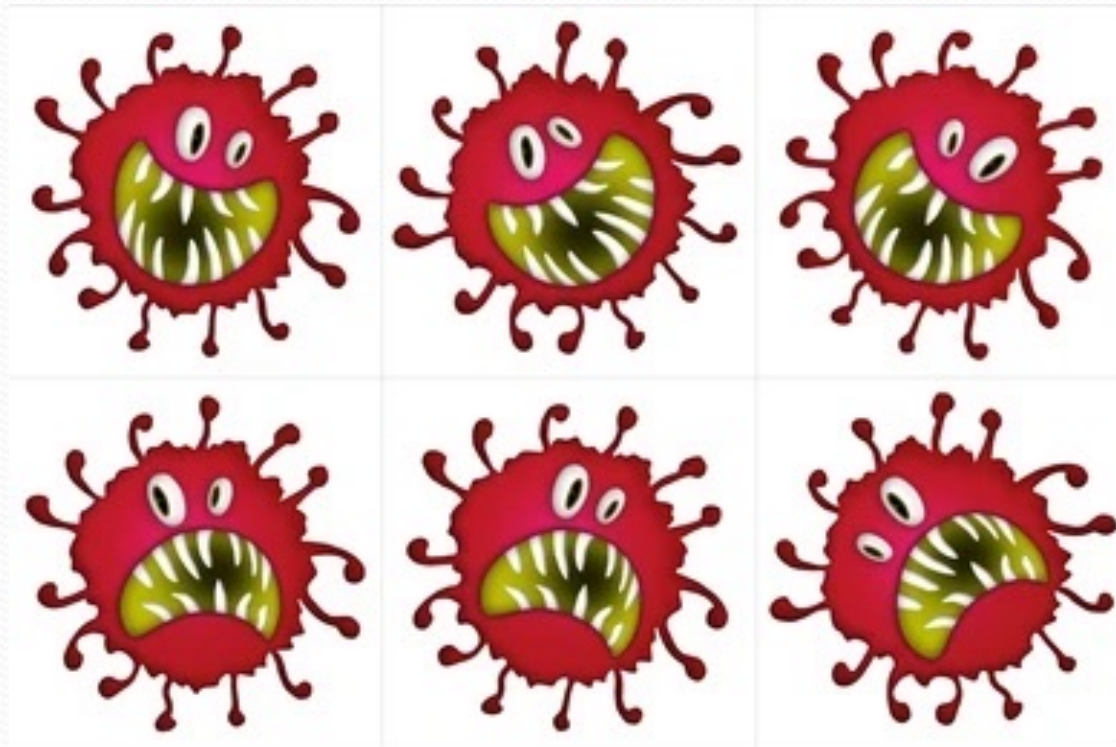
- Positive EBV- specific serologic findings CBC look for Lymphocytosis
- PCR studies is confirmatory Look for the genetic material of the virus
- Hematologic examination reveals a markedly raised lymphocyte and monocyte count with more than 10% atypical lymphocytes
- Atypical lymphocytes, although not specific for EBV, are present with the onset of symptoms and disappear with resolution of disease
- Alterations in liver function tests may also occur, and hepatosplenomegaly is a frequent finding

Treatment and Prevention

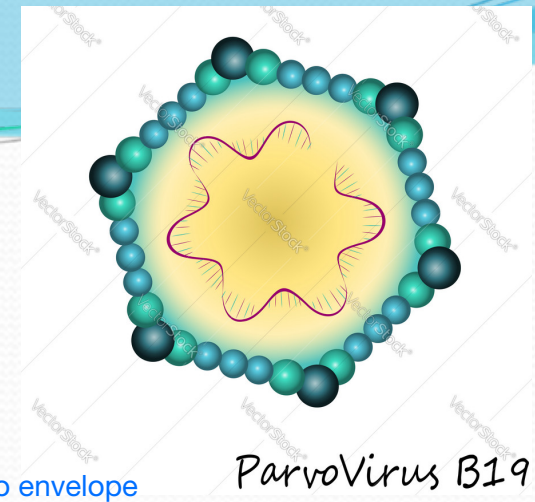
There's no vaccine approved

- **Treatment** of infectious mononucleosis is largely **supportive**. More than 95% of patients recover uneventfully
- **In a small percentage of patients, splenic rupture may occur;** restriction of contact sports or heavy lifting during the acute illness is recommended من الصعب جدا اصلاح الطحال اذا صار له rupture فاذا صار رح نستأصل الطحال نهائياً
- **Systemic acyclovir makes little or no impact on the clinical illness**
- **Laryngeal obstruction** should be treated with **corticosteroids**
- Immunization with virus specific antigen have shown to be effective against Burkitt's lymphoma and nasopharyngeal carcinoma in animal model and the **vaccine is under development**

Parvovirus B19 Infections



Virology

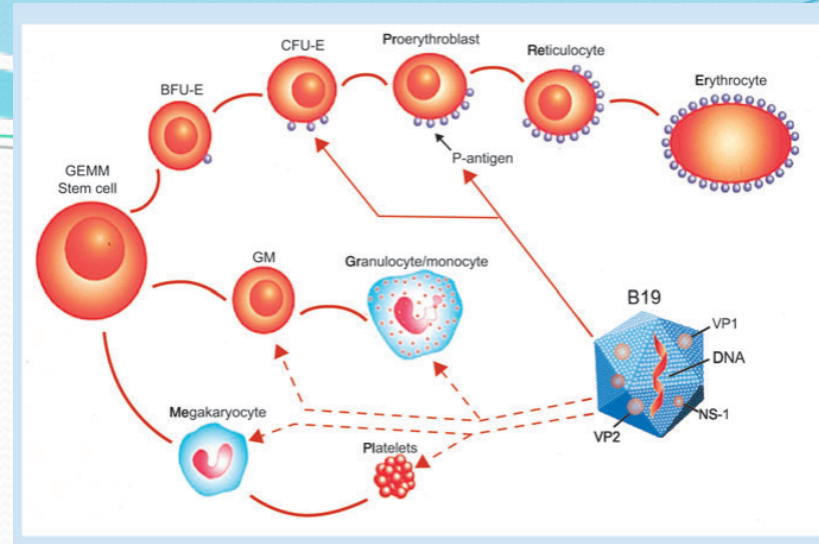


- Parvoviruses are very small (18 to 26 nm), naked virions that contain a linear single-stranded DNA molecule
- The major cellular receptor for the virus is globoside (also known as blood group P antigen, which is commonly found on erythroid progenitors, erythroblasts, megakaryocytes, and endothelial cells)
- A primary site of replication appears to be the nucleus of an immature cell in the erythrocyte lineage. Such infected cells then cease to proliferate, resulting in an impairment of normal erythrocyte development

The major target of this virus is immature RBCs thereby they are results on ANEMIA

بشكل عام الشخص السليم الي ما عنده انيميا ما بتاثر
كثير بتكسر شوية خلايا دم بس لو عندك مشاكل مثلا
ثلاسيميا وخلايا الدم قاعدة بتتكسر بيحي الفيروس
بخلص على الباقي فيصير عنده اعراض شديدة

Pathogenesis



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

Primary infection in such individuals often produces an acute, severe, sometimes fatal anemia manifested as a rapid fall in RBC counts and hemoglobin

Patients may present initially with no clinical symptoms other than fever, and is commonly referred to as aplastic

crisis

Aplastic crisis is a condition characterized by a sudden drop in the production of red blood cells, white blood cells, and platelets by the bone marrow. It is most commonly associated with infections by the parvovirus B19, which is responsible for causing fifth disease (also known as erythema infectiosum).

Epidemiology

- The viral infection is common among **children 5-15 years old**
- Epidemiologic evidence suggests that spread of the virus is primarily by the **respiratory route**, and **high transmission rates occur in households**
- Once **skin rash appears** 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 30 to 60% of adults

لا يطلع الطفح الجلدي
ببطل معدي عن طريق
التنفس

غالبا ينشوفه بالاماكن المغلقة والصغيرة مثل حضانه فيها ٥٠ طفل بغرفة وحدة
الغرف الصفية

It is common but less than EBV

Clinical Manifestations

زي كانك صافع
واحد كف ومعلم
على وجهو

خاصی فیروس بسبب skin rash

- Erythema infectiosum (also referred to as fifth disease, slapped check, apple face, or academy rash) is attributable to parvovirus B19
↓
حجر خردودا كل المدرسة بتلاقيهم امامه
- After an incubation period of 4 to 12 days, a mild illness appears, characterized by fever, malaise, headache, myalgia, and itching in varying degrees
- 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

ما قرأها الدكتور نهائي

- 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
- like rubella, active transplacental transmission of parvovirus B19 can occur during primary infections in the first 20 weeks of pregnancy, sometimes resulting in stillbirth of fetuses that are profoundly anemic



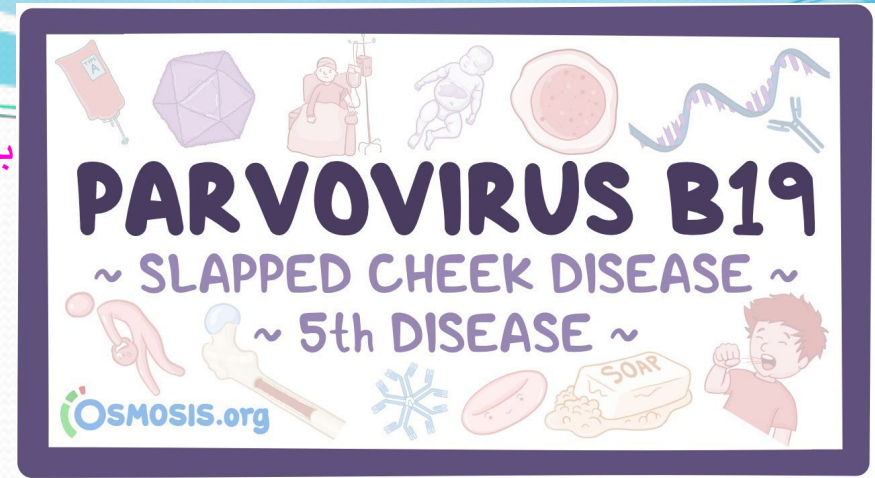
haemolytic anemia يعني thalassemia كان عنده اذا الشخص

بيجي الفيروس بكمال على باقي ال RBCs

بس بشكل عام اذا انتا شخص صحي ما عندك انيميا ما بسبب اعراض

خطيرة ، ما في داعي للادوية فقط علاج الاعراض مثل البنادول

Diagnosis



- Viremia usually lasts 7 to 12 days but can persist for months in some individuals
- CBC (low Hb)
- It can be detected by specific DNA probe or polymerase chain reaction (PCR) methods
- Alternatively, the presence of IgM-specific antibody late in the acute phase or during convalescence strongly supports the diagnosis

