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"Fifth Disease: A review"

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Abstract
The fifth disease, which is known by many other names, is characterized by fever, rash and redness of the skin. It is caused by a small DNA virus named Parvovirus B19.The disease occurs more frequently in children and usually self controlled. Sometimes the symptoms may not be even manifested. The disease usually outbreaks in winter and spring and there is no vaccine available till today. The virus can cause aplastic crisis in chronic hemolytic anemia patients. Infection during pregnancy is also fatal. The spread is usually through respiratory droplets and infected blood transfusion. Correct diagnosis can be only made by ELISA technique. Treatment is symptomatic including increase in fluid intake and acetaminophen but aspirin should be avoided as it may increase chance of hemorrhage and thereby may worsen the condition.
Keywords: Turkey Slap Disease, slapped cheek, Parvovirus B19, Hydrops fetalis

Introduction:

Fifth disease is a mild childhood illness caused by the human parvovirus B19 that causes flu-like symptoms and a rash. It is called fifth disease because it was fifth on a list of common childhood illnesses that are accompanied by a rash, including measles, rubella or German measles, scarlet fever (or scarlatina) and scarlatinella, a variant of scarlet fever. Erythema infectiosum or fifth disease is one of several possible manifestations of infection by erythrovirus previously called parvovirus B19. The disease is also referred to as slapped cheek syndrome, Turkey Slap Disease slapcheek, slaps face or slapped face. In Japan the disease is called 'apple sickness' or 'ringo-byou' in reference to the symptom of facial redness. [1]

Description:

The Latin name for the disease is erythema infectiosum meaning infectious redness. It is also called the "slapped cheek disease" because when the bright red rash first appears on the cheeks, it looks as if the face has been slapped. Anyone can get the disease, but it occurs more frequently in school-aged children. The disease is usually mild and both children and adults usually recover quickly without complications. In fact, some individuals exhibit no symptoms and never even feel ill. Outbreaks most often occur in the winter and spring. Slapped cheek syndrome is caused by a virus called parvovirus B19. Slapped cheek syndrome is a virus that only affects humans. It is also known as erythema infectiosum or fifth disease, because it is the fifth most common disease it is characterized by a rash in children. Slapped cheek syndrome is caused by a virus called parvovirus B19. The symptoms of slapped cheek syndrome can vary from a minor illness, possibly with headache, mild fever and sore throat, to erythema infectiosum, which is usually produces a rash on the cheeks, hence its name 'slapped cheek'. It is thought that 60% of all people in the UK have been infected with parvovirus B19 at some point. It usually affects children, between the ages of four and 12. An increase in the number of infections occurs every three to four years, usually in schoolchildren. Once you have had the infection, it is likely you will be immune to the virus. Although parvovirus B19 can affect animals (canine parvovirus and feline panleukopenia virus), slapped cheek syndrome is only known to affect humans. The virus cannot pass from human to animal or vice versa. [2]

Epidemiology:

A significant increase in the number of cases is seen every three to four years; the last epidemic year was 1998. Outbreaks can

History [3, 4]

Table I- History of Fifth Disease

1905	The name "fifth disease" originated in 1905, when a French physician assigned numbers to the common childhood diseases characterized by rashes. For example, measles was "first disease," scarlet fever was "second disease," rubella was "third disease,"
1981	The disease was spread through Bend this winter. The health department received 20 reports of the viral infection in 1980 However; the incidence of Fifth Disease has decreased since Christmas.
1989	We know it now as a viral illness caused by what is called a parvovirus. It begins with a redness of the cheeks (slapped cheek syndrome), the rash eventually traveling down the arms and legs and onto the chest.
1998	Since Elaine J. Fricke's infant son, Shawn, died of the effects of fifth disease, she has desperately wanted to inform pregnant women of the possible dangers of Weisberger said Shawn's history is even more unusual because most babies who die as a result of the virus are stillborn.
2000	Close to 60 students at a local elementary school have been sent home with "Fifth Disease" over the past month. Fifth Disease is a highly contagious but relatively harmless illness.
2001	That's because viruses such as fifth disease are so easily transmitted. Last winter, scarlet fever spread across the Washington region
2002	Fifth disease so named because it once was considered one of the five main childhood diseases, is usually mild, according to the National Center.
2003	The lesson is part of the school nurse s plan to manage the school s current bout with fifth disease. As of Nov. 7 the Olathe School District has recorded 42 cases of fifth disease at four of its elementary schools and one at a junior high school.

arise especially in nurseries and schools. Parvovirus B19 causes an infection in humans only; cat and dog parvoviruses do not infect humans. In contrast with small animals, there is no vaccine available for human parvovirus B19. B19 virus is present throughout the year; in temperate climates outbreaks of infection are more common in the spring and summer. These outbreaks are centered on primary schools where up to 40% of pupils may be infected. Infection is commonest amongst 4 - 10 yr olds. By adulthood 60% of the populations are seropositive. Respiratory spread is the usual route of transmission of the virus. Blood borne spread can occur (1 in 40000 blood donations have virus present) in recipients of whole blood and factor VIII. The frequency of seropositivity among haemophiliac children is significantly higher than normal. [5, 6].

Occurrence:

Disease occurs worldwide. It is recognized most commonly during epidemics, usually occurring in spring, peaking in March, April or May. Secondary attack rate in households is approximately 50%. It is estimated that >50% of all adults have antibody to HPV-B19. [8]

Virology:

The B19 virus, generally referred to as parvovirus B19 [7] or sometimes erythrovirus B19 was the first (and until 2005 the only) known human virus in the family of parvoviruses, genus erythrovirus. B19 virus causes a childhood rash called fifth disease or erythema infectiosum which is commonly called slapped cheek syndrome. The virus was discovered by chance in 1975 by Australian virologist Yvonne Cossart. It gained its name because it was discovered in well B19 of a large series of petri dishes apparently numbered in

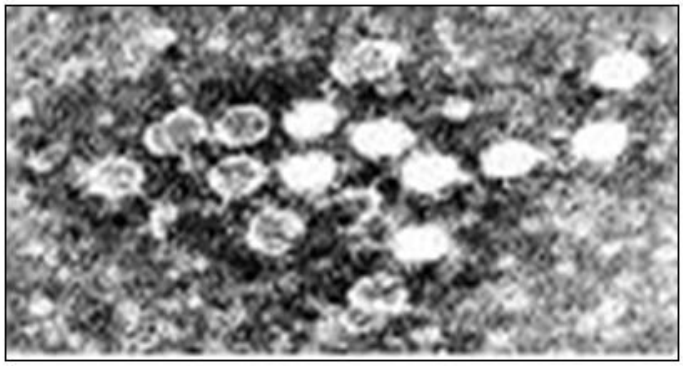

Figure I-Virology of B19 virus

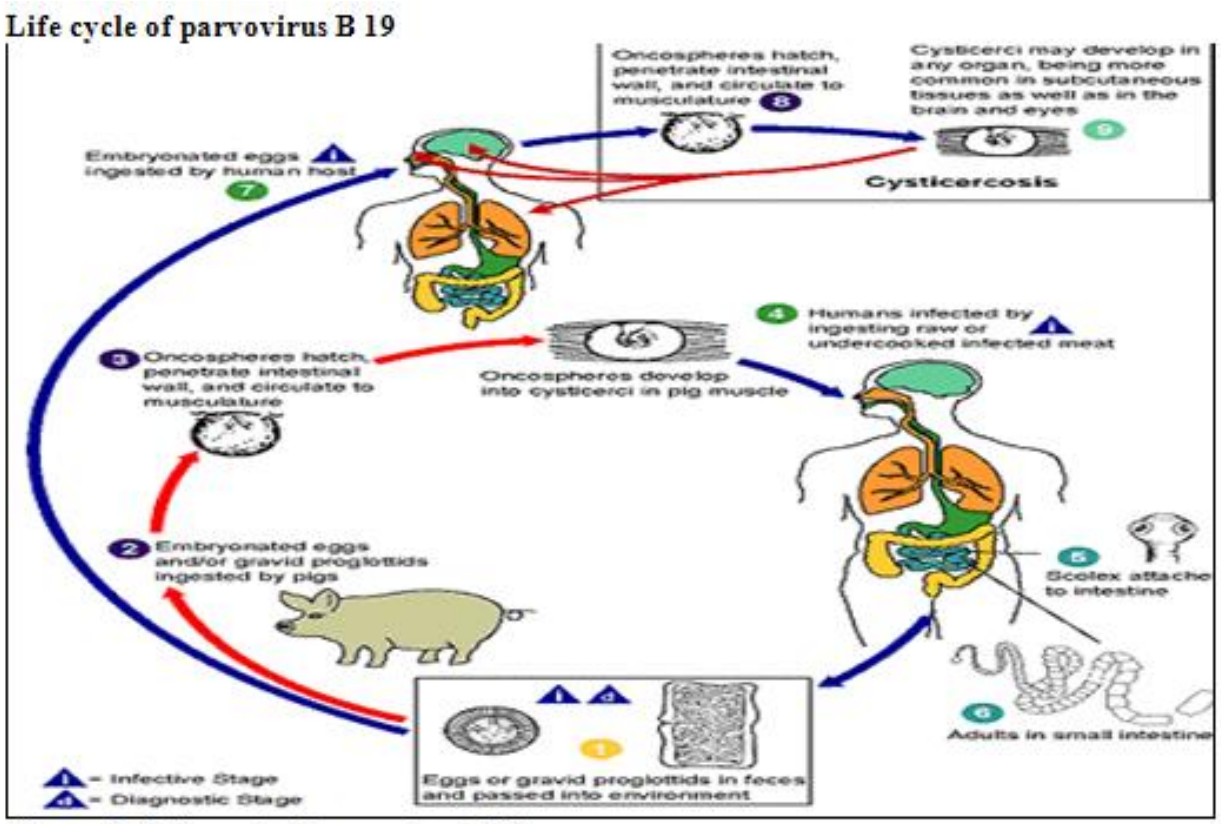

Figure II- Life cycle of parvovirus B 19

this way. Erythroviruses belong to the Parvoviridae family of small DNA viruses. It is a non-enveloped, eicosahedral virus that contains a single-stranded linear DNA genome. Approximately equal proportions of DNA of positive and negative sense are found in separate particles. At each end of the DNA molecule there are palindromic sequences which form "hairpin" loops. The hairpin at the 3' end serves as a primer for the DNA polymerase. It is classified as erythrovirus because of its capability to invade red blood cell precursors in the bone marrow. [8]

Description of Life Cycle:

1. Eggs or gravid proglottids in feces and passed into enviroment.
2. Embryonated eggs and/or gravid proglottids ingested by pigs.

3. Oncospheres hatch penetrate intestinal wall and circulate musculature.
4. Humans infected by ingesting raw or undercookd infected meat.
5. Scolex attaches to intestine.
6. Adults in small instetine.
7. Embryonated eggs ingested by human host.
8. Oncospheres hatch penetrate intestinal wall and circulate to musculature.
9. Cybcerci may develop in any organ been more common in subcutaneous tissues as well as in brain and tissues.[9]

Global scenario [10]

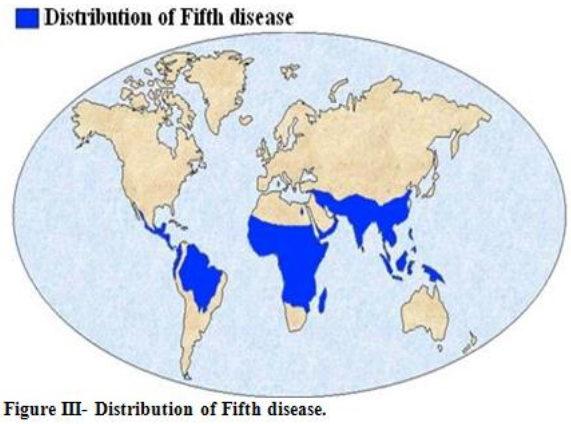

Figure III- Distribution of Fifth disease.

Pathophysiological:

The only known natural host cell of parvovirus B19 is the human erythroid progenitor

Small amounts of parvovirus B19 dramatically inhibit colony formation by early and especially by late erythroid progenitors without affecting myeloid colony. [11, 12] (See Figure IV)

B19 is associated with the following

1. Erythema infectiosum
2. Aplastic crisis in patients with chronic haemolytic anaemias.
3. Infection in Pregnancy
4. Persistent infection in immunocompromised patients

Mode of transmission:

The virus is primarily spread by infected respiratory droplets; blood-borne transmission, however, has been reported.The secondary attack risk for exposed household persons is about 50%and about half of that for classroom contacts.Fifth disease is transmitted primarily by respiratory secretions (saliva, mucous etc.) but can also be spread by contact with infected blood. The incubation period (the time between the initial infection and the onset of symptoms) is usually between 4 and 21 days. Individuals with fifth disease are most infectious before the onset of symptoms. Typically, school children, day-care workers, teachers and mothers are most likely to be exposed to the virus. When symptoms are evident, there is little risk of transmission therefore; infected individuals need not be isolated. [13]

Incubation Period

The incubation period is normally from 4-14 days, but can be as long as 20 days. [13]

Period of Communicability

An infected person can spread fifth disease during the week prior to the appearance of the rash. When the rash appears, a person can no longer spread the virus to others. [14]

Diagnostic tests:

Presence of IgG on enzyme-linked immunosorbent assay (ELISA) indicates previous infection and immunity and if present in maternal blood, protects mother and fetus from becoming infected. The easiest way to detect infection in healthy people is to evaluate B19 IgM-specific antibody status; its presence confirms infection within the past several months. Pregnant women who are IgG and IgM negative are susceptible to infection and should be counseled to reduce their exposure to sick children, especially if they are schoolteachers or day-care staff and more so during a Fifth disease epidemic. If they have already been exposed and the child is

Table II - Pathophysiology

Erythema Infectiosum	7 days after inoculation, a prodrome consisting of fever, headache, chills, malaise and myalgia is common which accompanies the viraemic phase of infection. There is a period of 7 before the onset of the rash. The classical rash of Fifth disease occurs in 3 stages. Firstly the rash appears on both cheeks (slapped cheek appearance). The second stage appears 1 to 4 days afterwards with the appearance of an erythematous maculopapular rash on the trunk and limbs. The third stage of the rash is highly variable in duration, lasting from 1 to 3 weeks and is characterized by marked changes in the intensity of the rash with periodic complete evanescence and recrudescence. The rash is often pruritic and is more prominent on the extensor surfaces. Subclinical infection can occur especially in children. Reinfection has been documented. There is wide variation in the form of the rash; in many cases the rash is indistinguishable from rubella. The most common complication is joint involvement. Symptoms commence 1 to 6 days after the onset of the rash but may also occur in the absence of the rash. Joint involvement is rare in children but occurs in 80% of adult females with a rash. In children, both sexes are equally affected and symptoms seem to be more severe than adults and of longer duration. In adults females are much more likely to be affected. The most common presentation is arthritis affecting the small joints of the hand, followed by wrists, ankles, knees and elbows. Shoulders, cervical and lumbar spine as well as the hips may be involved. There is pain and stiffness in the joints which may be accompanied by minor swelling. Two thirds of the cases resolve by 2 weeks and the majority by 4 weeks. [12]
Aplastic Crisis	The aplastic crisis which occurs in patients with chronic haemolytic anaemia (such as sickle-cell disease, hereditary spherocytosis, B-thalesessaemia, pyruvate kinase deficiency) has been recognized for several decades. Typically, the patient has a viral-like illness with fever and constitutional symptoms, followed by the onset of fatigue and anaemia. The Hb level may fall as low as 4g and reticulocytes are undetectable, but the leucocytes and platelet counts usually remain normal. Bone marrow aspiration shows a marked reduction in the numbers of erythrocytic precursors present with other cell lines being normal. A transfusion of packed cells may be necessary to correct the severe anaemia. However the patient usually quickly recovers within a week, with the Hb recovering to normal levels. Such crises generally occur in children, tend to cluster both in time and location and do not usually recur in an affected individual. It was suggested as early as 1960 that aplastic crises may be caused by an infectious agent but it was not until the early eighties that B19 became associated with aplastic crises. In individuals with chronic haemolytic anaemias, B19 infection causes a profound reticulocytopenia may result in the depression of Hb levels to critical levels. Reports of erythematous rash after aplastic crisis are rare. B19 infection does not invariably result in aplastic crisis in patients with chronic hemolytic anaemias. Although it may be responsible for up to 90% of aplastic crisis. [12]

Infection in Pregnancy	Infection by parvovirus during pregnancy is not associated with increased risk of fetal malformation. However infection during pregnancy is associated with increased fetal loss. This may be due to the fact that parvovirus attacks reticulocytes which may lead to anemia in the fetus and death. Indeed fetal hydrops (which is recognized as the most severe manifestation of rhesus incompatibility disease, with IUD, anaemic heart failure, pleural effusion, hepatoslenomegaly and as cites) is a consistent feature in still born infants. Infection in the first trimester is associated with a 5 - 10% fetal loss. Infection in the second trimester 12.5%. Clearly the majority of pregnancies proceed to term with delivery of normal infants. However fetal hydrops as a result of second and third trimester infection is seen in the newborn. Maternal infection occurs 2 to 12 weeks prior to the diagnosis of fetal hydrops. A diagnosis of fetal hydrops may be made by ultrasound. In a PHLS prospective study in pregnancy. 190 women known to be infected with B19 during pregnancy were followed up. A satisfactory outcome in 84% of women. No congenital abnormalities were observed. There was substantial risk of fetal loss especially in the 2nd trimester. The transplacental transmission rate was 33%. The fetal death rate was 9%. B19 appears to be responsible for a 20 fold increase in fetal loss during the 2nd trimester of pregnancy. B19 does not cause recurrent abortions. [12]
Persistent infection in immunoco-mpromised patients	B19 can cause persistent infection resulting in severe anemia in the immunocompromised particularly in children having immunosuppressive therapy. Patients with congenital immunodeficiency and AIDS may also develop this syndrome. Patients with this syndrome who have been given HNIG often show a beneficial response. However, improvement is usually seen when immunosuppressive therapy is relaxed. [12]

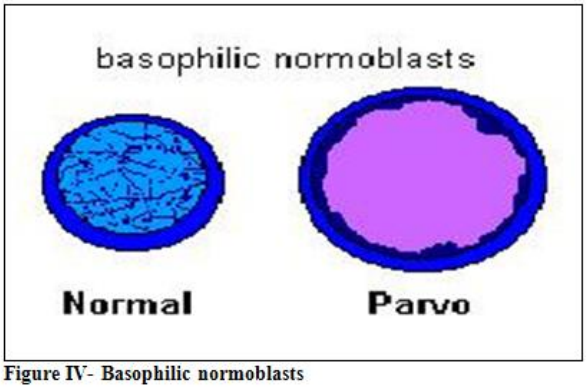

Figure IV- Basophilic normoblasts

diagnosis has been serologically confirmed, they should be evaluated for immune status. Specific IgM antibodies begin to appear within 3 days of onset of illness and are relatively short-lived, persisting only 30 to 60 days. Elevated maternal serum β-fetoprotein (MSAFP) has been suggested to indicate development of hydrops. This could serve as an indirect indicator of fetal infection, with elevated levels probably arising from damage to fetal liver cells. The authors speculated that the increase in β-fetoprotein preceded ultrasonographic detection of fetal hydrops by 4 weeks. The sensitivity of this test, however, is unknown because, in several cases, MSAFP level was normal despite severe fetal infection. Elevated MSAFP levels on routine maternal serum screening for Down syndrome and spina bifida should suggest a parvovirus infection rather than an open neural tube defect. An ultrasound study should be able to differentiate between the two conditions. Parvovirus B19 cannot be cultured on traditional tissue culture media. Torok et al [15] reported use of a polymerase chain reaction (PCR) to diagnose in utero fetal infection with human parvovirus B19. Specimens from fetal fluid samples

Role in disease

Table III- Role in disease

AIDS	Parvovirus B19 is a frequently overlooked cause of chronic anemia in individuals who have AIDS. Treatments with erythropoetin or intravenous immunoglobulin have been helpful in some patients. The parvovirus infection may trigger an inflammatory reaction in AIDS patients who have just begun antiretroviral therapy. [19]
Arthritis	In adults (and perhaps some children), parvovirus B19 can lead to a seronegative arthritis which is usually easily controlled with analgesics. Women are approximately twice as likely as men to experience arthritis after parvo virus infection. Possibly up to 15% of all new cases of arthritis are due to parvovirusand a history of recent contact with a patient and positive serology generally confirms the diagnosis. This arthritis does not progress to other forms of arthritis. Typically joint symptoms last 1-3 weeks, but in 10-20% of those affected; it may last weeks to months.[20]
Aplastic crisis	Although most patients have an arrest of erythropoiesis (production of red blood cells) during parvovirus infection, it is most dangerous in patients who have sickle cell anemia or hereditary spherocytosisand are therefore heavily dependent on erythropoeisis due to the reduced lifespan of the red cells. This is termed "aplastic crisis" (also called reticulocytopenia). It is treated with blood transfusion.[21]
Hydrops fetalis	Parvovirus infection in pregnant women is associated with hydrops fetalis due to severe fetal anemia, sometimes leading to miscarriage or stillbirth.The risk of fetal loss is about 10% if infection occurs before pregnancy week 20 (esp. between weeks 14-20), but minimal after then. Routine screening of the antenatal sample would enable the pregnant mother to determine the risk of infection. [22] Knowledge of her status would allow the mother to avoid the risk of infection.The risk to the fetus will be reduced with correct diagnosis of the anemia (by ultrasound scans) and treatment (by blood transfusions). There is no evidence to suggest that Parvovirus B19 leads to developmental abnormalities in childhood.[23,24]

(amniotic fluid, ascites, pleural effusion, fetal blood) might show viral DNA. Direct identification of viral particles or genome is possible only in the viremic stage. Fetal tests for IgM are not reliable because IgM appears in fetal circulation only after 22 weeksí gestation. Proven DNA isolation has been associated with negative results of antibody studies. Electron microscopy might be able to identify viral DNA particles and viral B19 antigens can be detected by radioimmunoassay or enzyme immunoassay but these methods are generally insensitive.[16]

Treatment for fifth disease:

Specific treatment for fifth disease will be determined by your child's physician based on,

- Child's age, overall health and medical history
- Extent of the disease
- Child's tolerance for specific medications, procedures, or therapies
- Expectations for the course of the disease.
- Opinion or preference

The goal of treatment for fifth disease is to help decrease the severity of the symptoms. Since it is a viral infection, there is no cure for fifth disease. Treatment may include,

- Increased fluid intake
- Acetaminophen for fever (DO NOT GIVE ASPIRIN) [17]

Prevention/Care:

Inform high risk people within the school when a case of fifth disease has been identified, persons with chronic hemolytic anemia, congenital or acquired immunodeficiencies and pregnant women. Pregnant women should consult with their health care provider if exposed to a positive case.

Encourage frequent hand washing and prompt disposal of used tissues. [18]

Signs and Symptoms:

Fifth disease begins with a low-grade fever, headache and mild cold-like symptoms (a stuffy or runny nose). These symptoms pass and the illness seems to be gone until a rash appears a few days later. The bright red rash typically begins on the face. Several days later, the rash spreads and red blotches (usually lighter in color) extend down to the trunk, arms and legs. The rash usually spares the palms of the hands and soles of the feet. As the centers of the blotches begin to clear, the rash takes on a lacy net-like appearance. Kids younger than 10 years old are most likely sometimes complain that the rash itches, but most children with a rash caused by fifth disease do not look sick and no longer have fever. It may take 1 to 3 weeks for the rash to completely clear and during that time it may seem to worsen until it finally fades away entirely. Certain stimuli (including sunlight, heat, exercise and stress) may reactivate the rash until it completely fades. Other symptoms that sometimes occur with fifth disease include swollen glands, red eyes, sore throat, diarrhea and rarely, rashes that look like blisters or bruises. In some cases, especially in adults and older teens an attack of fifth disease may be followed by joint swelling or pain, often in the hands, wrists, knees, or ankles. [25, 26] (See Figure – V and VI)

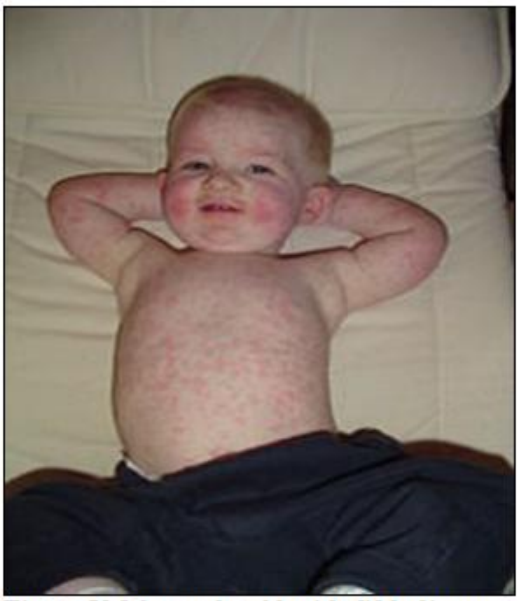

Figure V-16 months old with fifth disease

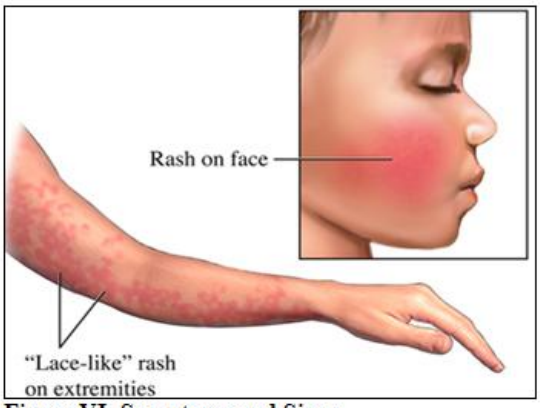

Figure VI- Symptoms and Signs

Demographics:

Fifth disease is very common in children between the ages of five and 15. Studies show that although 40 percent to 60 percent of adults worldwide have laboratory evidence of a past parvovirus B19 infection, most of these adults cannot remember having had symptoms of fifth disease. This fact leads medical experts to believe that most people with parvovirus B19 infection have either very mild symptoms or no symptoms at all. Fifth disease occurs everywhere in the world. Outbreaks of parvovirus tend to occur in the late winter and early spring, but there may also be sporadic cases of the disease any time throughout the year. In households where a

child has fifth disease, another family member who has not previously had fifth disease has about a 50 percent chance of also getting the infection, while classmates of a child with fifth disease have about a 60 percent chance of getting the disease. [27, 28]

Effects on the pregnancy and the fetus:

Despite earlier reports of high rates of vertical transmission and morbidity and mortality, more recent reports demonstrate that in most cases, no adverse effects on the fetus are evident. 37 cases of women exposed and infected during pregnancy; 14 (38%) of the pregnancies had adverse outcomes including miscarriage, fetal death and congenital anomalies. The vertical transmission rate (confirmed by IgG positivity in children at 1 year of age) is reported as 16% when mothers are infected during the first 20 weeks gestation and 35% when mothers are infected after 20 weeks gestation. In this prospective study, 1610 women were enrolled and 60 (3.7%) seroconvert during pregnancy. Only 30% of these 60 women reported signs or symptoms of the disease; five had spontaneous miscarriages, but evidence of the virus was found in the fetal tissue of only one of the aborted fetuses. The remaining 55 infected women delivered 56 healthy infants [29]. Out of 334 cases, fetal death occurred in 22 (6.6%) and hydrops fetal is in two (0.6%). In a prospective cohort study. Rodis et al [30] investigated the risk of fetal loss and congenital abnormalities after maternal parvovirus B19 infection among 427 pregnant women with B19 infection and 367 surviving infants, of whom 129 were followed up at 7 to 10 years of age. Fetal loss occurred only in the first 20 weeks of pregnancy and was around 9%. Seven cases of fetal hydrops followed maternal infection between 9 and 20 weeks gestation. No abnormalities attributed to B19 infection were found at birth in the surviving infants and no late effects were found at 7 to 10 years. Most cases of fetal death occurred within 3 to 6 weeks of maternal infection, but one was reported to have occurred as late as 12 weeks after infection. Thus, while parvovirus infection during pregnancy can cause miscarriage and hydrops fetal is that can deteriorate to fetal death, in most cases no adverse fetal effects occur. Due to the low incidence of fetal effects. Harger et al [31] questioned the need for serologic and ultrasound surveillance. In their assessment of 618 pregnant women exposed to parvovirus, 52 (8.4%) contracted B19 infection. None of the 52 fetuses of the infected women developed NIHF. Relative risk of maternal B19 infection was 2.8 if the source was a related child living in the household. Risk of B19 infection could not be predicted by pregnant women is occupations. The authors concluded that excluding pregnant women from the workplace during endemic periods is unjustified and that weekly fetal ultrasound evaluation yields little [32].

Conclusion:

The fifth disease although not a fatal or a serious one, still needs to be paid attention as it can worsen the condition. School children are more prone to infections and proper counseling is necessary regarding hygiene of children as well as teachers and other staff. The disease is contagious and treated symptomatically but prevention would be always better than cure to avoid drug borne complications.

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