Parvovirus B19 Associated Arthritis

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Abstract: Parvovirus B19 infection is common and widespread. The most well described presentations are transient aplastic crisis especially in patients with sickle cell anemia and erythema infectiosum in children. However, further studies showed that B19 infection could cause a variety of clinical presentations resembling rheumatic diseases. B19 associated arthritis shares a number of common features with rheumatoid arthritis. Accordingly, it can pose difficulty to rheumatologists to differentiate it from early rheumatoid arthritis. However, there is still no definite evidence to prove B19 infection is the causative agent for rheumatoid arthritis or other rheumatic diseases. Further studies focusing on the host interaction and the property of the virus are mandatory to give further information on this issue.

Keywords: Parvovirus B19, Rheumatoid arthritis, Rheumatoid factor

Introduction

Parvovirus B19 was first discovered in 1975 by Cossart and her colleagues in the human serum coded number 19, panel B. Hence, the virus was given the name B19. It was found to be associated with human disease in 1981. Subsequent clinical studies showed that parvovirus B19 infection could be the cause of several distinct clinical syndromes. The most well known disease is erythema infectiosum i.e. fifth disease, which is a febrile eruption with characteristic facial rash in children. In adults, the virus was found to be associated with transient aplastic crisis, especially in patients with sickle cell anemia. Recent researches have also indicated the possibility of development of connective tissue disease like syndromes in parvovirus infection. This review article summarizes the information about the pathogenesis and the clinical manifestations of parvovirus B19 associated arthritis.

Parvovirus B19 Virology

Parvovirus B19 is a member of the erythroviruses, which can replicate in the absence of any helper virus. It is a single stranded non-enveloped DNA virus and is one of the smallest viruses known to infect humans exclusively. It recognizes the P antigen, which is the cellular receptor expressed on mature erythrocytes and in particular, the erythroid precursor cells. Thus, it shows a pronounced tropism for these cells. P antigen has been identified in other cell types including megakaryocytes, endothelial cells, placental cells, fetal heart and liver cells. Therefore, individuals who lack the P antigen are not susceptible to parvovirus B19 infection.

The virus is genetically stable with a low variability for the three major proteins it encodes, including the structural viral capsid protein i.e. VP1 and VP2, and the nonstructural protein NS1. VP1 and VP2 are coded in the same open reading frame; therefore VP1 and VP2 are essentially identical except for an additional length of amino acids at the N terminal of VP1. The initial immune response against parvovirus B19 targets towards capsid protein VP2. During convalescence, antibody to the capsid protein VP1 develops and it is associated with neutralization of the virus in erythroid culture. Therefore VP1 is thought to protrude from the external virion surface and may play a role in cell attachment. Although the role of NS1 has not been clearly defined, antibody against NS1 is produced
in around 30% of individuals during infection and it has been associated with acute or chronic parvovirus B19 arthritis or persistent infection.6

Natural History of Parvovirus B19 Infection

Parvovirus B19 gains access to the human by aerosol transmission to the respiratory tract.7 Moreover, the virus can also be transmitted by infected blood products.8 During the incubation period, the virus replicates in the upper airway and subsequently leads to viraemia within 5 days of inoculation. The viraemic phase usually lasts for several days. During that time, the virus may be shed in the nasal or oral secretion and the person is infectious. There is infection of the erythroblasts in the bone marrow during the viraemic phase and it is associated with a temporary cessation of reticulocyte production and a mild drop in hemoglobin level. This may account for the aplastic crisis in patients with sickle cell disease. Otherwise majority of infected individuals remain asymptomatic or have minor flu like symptoms. Viraemic phase ends when there is production of IgM antibody to the virus, which usually appears 10 days after inoculation and lasts for 1 to 3 months. The production of IgM is associated with the onset of facial rash, polyarthralgia or polyarthritis. IgG antibody appears several days after the production of IgM antibody and persists lifelong.9

Clinical Features of Parvovirus B19 Related Arthritis

Joint symptoms occur in 10% of infected children but up to 60% of infected adults and they are more common in female patients (i.e. female to male ratio: 60% vs. 30%). The typical pattern in adults is acute onset of symmetrical polyarthritis predominantly involving the proximal inter-phalangeal joints and the metacarpo-phalangeal joints.10 Morning stiffness is common. However, arthritis in children may be asymmetrical and oligo-articular. The knees are predominantly affected.9 No erosion has been reported.11 Parvovirus B19 related arthritis is self-limiting. Resolution of joint symptoms usually occurs in 6 to 8 weeks. In a study recruiting children with acute parvovirus B19 infection with joint manifestations, 20 out of 22 patients had frank arthritis and the other 2 had arthralgia. The duration of symptoms was less than 6 weeks in 11 patients and resolved within 4 months in 14 patients. However, 6 patients had persistent arthritis up to 13 months.12 In another Scandinavian study, it showed that proximal interphalangeal joints and knees joints are the joints most commonly affected. Most of the patients had disease lasting from 2 weeks to 5 months. Of the 3 patients who had persistent arthritis, one developed rheumatoid arthritis and the other developed systemic lupus erythematosus.13

Diagnosis of Parvovirus B19 Infection

Current diagnosis of parvovirus B19 infection usually includes measurement of the IgG and IgM antibodies in the serum or B19 DNA in the serum or tissue sample. Specific IgM antibody directed against VP2 is produced soon after the infection but the titer declines gradually 3 months afterwards. Therefore, there is only a brief window of opportunity in which to make a diagnosis of B19 infection by IgM serology. Furthermore, caution should be made when interpreting the serology in immuno-deficient individuals and in pregnant women as they may not have an adequate immune response against the virus. Transfusion of blood products or treatment with immunoglobulins may yield false positive IgG serology. Serology test can be complemented by the use of PCR assay to detect the B19 DNA in the serum or tissue sample. Positive PCR test in the blood indicates ongoing acute or persistent infection whereas a positive PCR test in the bone marrow may indicate ongoing or remote infection.14 About 2% of healthy individuals may give positive result in the PCR test in the bone marrow or tissue sample. As a result, serial monitoring of the DNA titer may be helpful.

Pathogenesis of Parvovirus B19 in Arthritis

Immune Complex Deposition

Immune complex deposition is thought to be the cause of acute polyarthralgia or polyarthritis in parvovirus B19 infection as the occurrence of symptoms coincides with the development of specific IgG antibody.7 In addition, when chronically infected patients are treated with immunoglobulin, rash and joint symptoms may occur, suggesting an immune mediated process.15

Autoantibodies Production

Parvovirus B19 infection has been associated with the production of autoantibodies i.e. rheumatoid factor,16 antinuclear antibody, anti-mitochondrial antibody, anti-smooth muscle antibody and anti-parietal cell antibody.17
Antiphospholipid antibody produced during acute B19 infection seems to have similar specificity as those produced in patients with underlying connective tissue diseases. Further studies showed that anti-VP 1 IgG reacts specifically with human keratin, collagen type II, single stranded DNA, and cardiolipin. As type II collagen is thought to be the target antigen of both autoantibodies produced by B cells and clonally expanded T cells in the synovium from patients with rheumatoid arthritis, this may suggest the possible correlation between B19 infection and rheumatoid arthritis.

**Cytokine Upregulation**

Using both human hematopoietic cell lines and human endothelial cells to express NS1 protein is associated with the induction of IL6 production. Studies showed that NS1 functioned as a transacting transcriptional activator on the IL6 promoter. This finding further supports the role of B19 infection in the polyclonal B cell activation as the pathogenesis of rheumatoid arthritis. There are also scanty reports to suggest that B19 infection can cause systemic activation of monocytes, T cells, NK cells, or the release of other pro-inflammatory cytokines i.e. IL1 and TNFα. However, up till now, the profile of cytokine response to parvovirus B19 has not been elucidated. Therefore further studies are required to clarify the possible role of B19 in the cytokine upregulation process.

**Persistence of Parvovirus B19 in Human Body**

B19 virus DNA has been shown to persist in various sites of the human including bone marrow, synovium, and skin. However, the mechanism which allows this persistence is still unclear. One of the hypothesis to explain the persistence of B19 virus in human is made from the study of adeno-associated virus. It is a human dependovirus which can stably integrate its genome into human chromosome in a site specific manner. Actually the terminal sequence of adeno-associated virus and B19 are almost identical and it was shown to be crucial for viral integration. Therefore, B19 virus may integrate into human chromosome in the same manner to establish latency.

**Association with Parvovirus B19 Infection in Rheumatoid Arthritis**

Many studies have suggested the possible role of B19 infection in the pathogenesis of rheumatoid arthritis, as it usually shares the common clinical presentations of rheumatoid arthritis. Several indirect evidences support this hypothesis. In one study, patients with HLA DR4 antigen, which is thought to be the genetic predisposition for rheumatoid arthritis, were associated with more prolonged arthritis after B19 infection. Some studies have also reviewed the antibody level against B19 at the onset of rheumatoid arthritis. However, the incidence of IgM antibody remained low at the onset of rheumatoid arthritis. Findings on the incidence of IgG antibody are conflicting since the sero-prevalence of IgG increases with age.

DNA detection has also been evaluated in various studies. Generally, B19 DNA has not been found in the serum or synovial fluid in patients with rheumatoid arthritis. However, B19 DNA in the synovial biopsy was detected in 75% of patients with rheumatoid arthritis, compared with 17% of patients with other arthritides. Another study showed VP1 was expressed in all patients with rheumatoid arthritis with active synovial inflammation, but not in patients with osteoarthritis or in the control group.

On the other hand, B19 infection can be associated with the production of rheumatoid factor and an increase in IL6 and TNFα level in the synovial fluid. Incubation of synovial fibroblast cells with B19 containing serum showed more significant degradation of the cartilage membrane. Whether B19 infection is the cause of rheumatoid arthritis is still debatable. There is a lack of direct evidence to elucidate the pathogenic role of B19 in rheumatoid arthritis so far. Uncertainties including the difference in the host response to B19 virus in different ethnic groups, possible unrecognized reservoir for the virus, and unclear biologic effect of the viral proteins still require further investigations.

**Conclusion**

Parvovirus B19 infection is common and widespread. The most common presentations are transient aplastic crisis especially in patients with sickle cell anemia and erythema infectiosum in children. However, further studies showed that B19 infection could cause a variety of clinical presentations resembling rheumatic diseases. B19 associated arthritis shares a number of common features with rheumatoid arthritis. Accordingly, it can pose difficulty to rheumatologists to differentiate it from early rheumatoid arthritis. Although B19 associated arthritis normally does not result in erosive
arthropathy, it has been regarded as a trigger agent of rheumatoid arthritis. There have been ongoing researches to support this hypothesis. However, there is still no definite evidence to prove B19 infection is the causative agent for rheumatoid arthritis or other rheumatic diseases. Further studies focusing on the host interaction and the property of the virus are mandatory to give further information on this issue.

References