Parvovirus B19 Infection in Patients with Rheumatoid Arthritis in Taiwan

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ABSTRACT. ***Objective.*** To investigate the role of human parvovirus B19 infection in the pathogenesis of rheumatoid arthritis (RA) in Taiwan.

Methods. Seventy-eight patients with RA and 55 unrelated controls (51 trauma and 4 osteoarthritis) were enrolled. Anti-parvovirus B19 IgG and IgM antibodies were detected in plasma of patients with RA and controls by the enzyme immunoassay method. These antibodies were also detected in the synovial fluid of 18 RA patients and 52 controls. B19 DNA was measured in the plasma of 72 patients with RA and 45 controls by nested polymerase chain reaction (PCR). It was also measured in the synovial fluid of 14 RA patients and 39 controls. Immunohistochemistry was performed to detect viral capsid protein VP1 of B19 in the synovial membrane of 7 RA patients and 32 controls. HLA-DR genotyping was performed by the sequence-specific primer PCR method. The interactions between B19 infection and HLA-DR genotype and susceptibility to RA were also analyzed.

Results. The prevalence of B19 infection was significantly increased in patients with RA compared with controls. The positive rates of B19 DNA in plasma and synovial fluid were significantly higher in RA patients than in controls. The odds ratio of DR4(+) B19 infection(+) was higher than that in DR4(+) B19 infection(–) or DR4(–) B19 infection(+) in comparison with DR4(–) B19 infection(–). A significant association was found between RA and DR4(+) B19 infection(+) in comparison with DR4(+) B19 infection(–). The odds ratio of DR4(+) plasma B19 DNA(+) was also higher than that of DR4(+) plasma B19 DNA(–) or DR4(–) plasma B19 DNA(+) in comparison with DR4(–) plasma B19 DNA(–). RA tended to be associated with DR4(+) plasma B19 DNA(+) compared with DR4(+) plasma B19 DNA(–).

Conclusion. The prevalence of parvovirus B19 infection was significantly higher in patients with RA than in controls. Synergistic effects were present between HLA-DR4 and parvovirus B19 infection or plasma B19 DNA for susceptibility to RA. Parvovirus B19 infection may play a role in susceptibility to RA. (First Release Mar 1 2006; J Rheumatol 2006;33:887–91)

Key Indexing Terms:
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Rheumatoid arthritis (RA) is a chronic inflammatory disease that may involve multiple joints and internal organs. The detailed pathogenesis is still obscure, whereas genetic and environmental factors including bacterial or viral infection may be involved in the development of RA[1]. Viral infection such as rubella, human T cell leukemia virus I, human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, and parvovirus B19 may induce acute arthritis[2-7]. The acute arthritis caused by parvovirus B19 infection may be symmetric and polyarticular, and usually involves proximal interphalangeal and metacarpophalangeal joints, resembling RA[4]. The arthritis may progress to be chronic and erosive, fulfilling the American College of Rheumatology (ACR) criteria for the classification of RA[6,8-13]. Thus, parvovirus B19 infection may play a role in the development of RA.

Parvovirus B19 is a small single-strand DNA virus. It is a member of the family *Parvoviridae*. Because replication occurs in erythrocyte precursors, B19 is classified as a member of the *Erythrovirus* genus. In immunocompetent children, B19 is the cause of erythema infectiosum or fifth disease. B19 has tropism for erythroid progenitor cells. B19 infection may induce transient aplastic crisis in patients with hemolytic diseases[14]. Immunocompromised individuals may fail to eradicate the virus, thereby generating a state of chronic anemia. Fetal death, hydrops fetalis, pure red cell aplasia, and congenital anemia may also develop after B19 infection[15].

The association of B19 infection with RA is still controversial. Takahashi, *et al* and Ishii, *et al* proposed that parvovirus B19 was a causative agent for RA[16,17]. In contrast,

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Peterlana, *et al* showed that the presence of parvovirus B19 DNA in the synovium was not correlated with RA[18]. We investigated the role of parvovirus B19 infection in the pathogenesis of RA in Taiwan.

MATERIALS AND METHODS

Seventy-eight patients with RA (63 women, 15 men) and 55 unrelated controls (51 trauma and 4 osteoarthritis; 37 women, 18 men) were enrolled. All patients and controls were Taiwanese. All patients fulfilled the ACR 1987 revised criteria for classification of RA[12].

Detection of anti-B19 antibodies. Anti-parvovirus B19 IgG and IgM antibodies were detected in the plasma of all patients with RA and controls by ELISA (parvovirus B19-IgG ELISA kit, parvovirus B19-IgM ELISA kit; IBL, Minneapolis, MN, USA). Synovial fluid analysis was available in a proportion of these patients and controls. These antibodies were also tested in the synovial fluid of 18 RA patients and 52 controls. Parvovirus B19 infection was defined as the presence of positive anti-parvovirus B19 IgG or IgM antibody.

Extraction of viral DNA. Because of insufficiency of samples, B19 viral DNA was extracted from the plasma of 72 RA patients and 45 controls using a viral DNA/RNA isolation kit (Maxim Biotech, Rockville, MD, USA). B19 viral DNA was also extracted from the synovial fluid of 14 RA patients and 39 controls. These patients and controls were subsets of the patients and controls with detection of anti-B19 antibodies noted above.

Nested polymerase chain reaction (PCR) of B19 VP1 gene. Parvovirus B19 DNA was detected using the nested PCR method as described[18]. The sequences of primers for the first-round PCR were 5'-CTT TAG GTA TAG CCA ACT GG-3' and 5'-ACA CTG AGT TTA CTA GTG GC-3'. PCR was carried out under the following conditions: 35 cycles of 1 min at 95°C (denaturation), 1.5 min at 55°C (annealing), and 1 min at 72°C (extension), and then a final elongation phase at 72°C for 7 min. The PCR product was used for second-round PCR. The sequences of primers for second-round PCR were 5'-CAA AAG CAT GTG GAG TGA GG-3' and 5'-CCT TAT AAT GGT GCT CTG GG-3'. Amplification conditions were the same as in the first-round PCR. The sequence of B19 DNA was also proved by direct sequencing.

Immunohistochemistry. Synovial membrane samples were obtained from 7 RA patients and 32 controls for immunohistochemical study, performed using a streptavidin-biotin method with a Dako LSAB2 system peroxidase kit (Dako Corp., Carpinteria, CA, USA) and a 3,3'-diaminobenzidine (DAB) substrate kit for peroxidase (Vector Laboratories, Burlingame, CA, USA) according to the manufacturers' instructions. Briefly, frozen sections were blocked with goat serum, and endogenous peroxidase was inactivated in 3% hydrogen peroxide, then the sections were labeled with mouse anti-human parvovirus B19 antibody (Chemicon International, Temecula, CA, USA) overnight at 4°C, incubated with a biotinylated-link antibody (goat anti-mouse IgG), followed by peroxidase-labeled streptavidin, and developed with DAB to produce a brown-colored precipitate at the antigen site. Then the sections were counterstained with hematoxylin.

HLA-DRB1 genotyping. Human genomic DNA extraction from peripheral blood mononuclear cells was performed using an Easy Blood Genomic DNA Purification kit (Genemark Co., Taiwan). HLA-DRB1 genotypes were determined in all patients and controls using a Dynal Allset SSP kit (Dynal Biotech, Wirral, UK).

Statistical analysis. Chi-square test with Yates' correction or Fisher's exact test was used for statistical analysis. The interactions between parvovirus B19 infection and HLA-DR4 for susceptibility to RA were also evaluated according to the method of Svejgaard, *et al*[19].

RESULTS

B19 infection was defined as individuals with positive anti-B19 IgG or IgM antibody. The prevalences of parvovirus B19 infection were significantly higher in the plasma and synovial fluid of RA patients than those in controls (Table 1). Sixty-three patients had anti-B19 IgG in plasma only, and 3 patients had anti-B19 IgM only. Four patients had both antibodies. Fourteen controls had anti-B19 IgG alone, and 2 patients had anti-B19 IgM alone. Two controls had both antibodies. Patients and controls were matched for age and sex.

Table 1. Human parvovirus B19 infection (positive anti-B19 IgG or IgM antibody) in RA patients and controls.

Sample	RA, n (%)	Controls, n (%)	OR (95% CI)	p
Plasma	73/78 (93.6)	18/55 (32.7)	30.0 (10.3–87.2)	< 0.0001
Synovial fluid	10/18 (55.6)	10/52 (19.2)	5.3 (1.7–16.7)	0.005

The positive rate of parvovirus B19 DNA was significantly increased in the plasma of RA patients in comparison with controls. A similar finding was evident with regard to synovial fluid (Table 2).

To investigate the role of B19 infection and HLA-DR on the development of RA, the interactions of B19 infection with HLA-DR4 for susceptibility to RA were analyzed. The odds ratio of DR4(+) B19 infection(+) was higher than that in DR4(+) B19 infection(–) or DR4(–) B19 infection(+) in comparison with DR4(–) B19 infection(–). A synergistic effect was present between HLA-DR4 and parvovirus B19 infection for susceptibility to RA (Table 3). A significant association was found between RA and DR4(+) B19 infection(+) in com-

Table 2. Human parvovirus B19 DNA in plasma and synovial fluid of RA patients and controls.

Sample	RA, n (%)	Controls, n (%)	OR (95% CI)	p
Plasma	22/72 (30.6)	4/45 (9.1)	4.5 (1.4–14.1)	0.005
Synovial fluid	8/14 (75.0)	8/39 (26.9)	5.0 (1.4–19.2)	0.015

Table 3. Interactions between parvovirus B19 infection and HLA-DR4 on susceptibility to RA.

	RA	Controls	OR	p
DR4(+) B19 infection(–)	4	13	2.8	0.2
DR4(–) B19 infection(–)	3	27		
DR4(–) B19 infection(+)	35	13	24.3	< 0.001
DR4(–) B19 infection(–)	3	27		
DR4(+) B19 infection(+)	36	2	162	< 0.0001
DR4(–) B19 infection(–)	3	27		
DR4(+) B19 infection(+)	36	2	58.5	< 0.001
DR4(+) B19 infection(–)	4	13		

parison with DR4(+) B19 infection(–). Similar findings could also be seen in the interactions between HLA-DR4 and plasma parvovirus B19 DNA (Table 4). The odds ratio of DR4(+) plasma B19 DNA(+) was higher than that for DR4(+) plasma B19 DNA(–) or DR4(–) plasma B19 DNA(+) in comparison with DR4(–) plasma B19 DNA(–). This finding suggested a synergistic effect between DR4 and plasma B19 DNA on susceptibility to RA. RA tended to be associated with DR4(+) plasma B19 DNA(+) in comparison with DR4(+) plasma B19 DNA(–).

DISCUSSION

In addition to the high prevalence of B19 infection in patients with RA, B19 DNA and VP1 protein were also detected in the synovial fluid and synovial membrane, respectively, of rheumatoid patients. We observed that parvovirus B19 infection may be associated with the development of RA in Taiwan.

Acute symmetric polyarthritis mimicking RA may develop after parvovirus B19 infection in adults. In children, the arthritis may be asymmetric and pauciarticular. Knee joints are the most often involved. Some cases have become chronic and the patients were diagnosed to have juvenile rheumatoid arthritis[20].

The association of human parvovirus B19 infection with development of RA is controversial[9,16,21-27]. Parvovirus B19-induced arthritis is usually transient, but it occasionally becomes chronic. Typical RA might be developed after B19 infection. Rheumatoid factor has also been detected in some cases. Takahashi, *et al* and Ishii, *et al* have argued that parvovirus B19 was a causative agent for RA[16,17]. Persistent infection with B19 and its induction of immunopathology might be associated with the initiation and perpetuation of RA. However, Peterlana, *et al* showed that the prevalence of B19 DNA was similar in RA and control synovial membrane samples[18]. Soderlund, *et al* also demonstrated that genomic B19 could persist in the synovial membranes not only in young patients with chronic arthropathy, but also in healthy immunocompetent individuals[28]. These findings suggested that the simple detection of viral DNA was not sufficient to confirm a link between virus and RA.

Table 4. Interactions of plasma parvovirus B19 DNA with HLA-DR4 on susceptibility to RA.

	RA	Controls	OR	p
DR4(+) B19 DNA(–)	24	12	2.2	0.08
DR4(–) B19 DNA(–)	26	29		
DR4(–) B19 DNA(+)	8	2	4.5	0.08
DR4(–) B19 DNA(–)	26	29		
DR4(+) B19 DNA(+)	14	2	7.8	0.004
DR4(–) B19 DNA(–)	26	29		
DR4(+) B19 DNA(+)	14	2	3.5	0.1
DR4(+) B19 DNA(–)	24	12		

Our study showed that the prevalence of parvovirus B19 infection was significantly higher in patients with RA than in controls. The positive rates of B19 DNA in synovial fluid and plasma of RA patients were also significantly increased compared with controls. VP1 is the primary target of anti-B19-IgG antibody in the convalescent phase. Although VP1 protein makes up only 4% of the total capsid protein, the unique region of VP1 is necessary for the virus to assume its mature capsid conformation. In our immunohistochemical studies of synovial membrane, the B19 viral capsid protein VP1 was detected in 4 of 7 (57.1%) RA patients and 5 of 32 (15.6%) controls. VP1 protein expression in synovial membrane was significantly higher in RA patients than in controls (OR 7.2, p = 0.037). However, the size of the rheumatoid synovial membrane sample in our study was small. A larger number of cases is required. Mehraein, *et al* also demonstrated replicative virus infection and expression of B19 VP1/VP2 protein in the synovial membrane of 90% of RA patients[22]. Their findings support the importance of B19 infection in the pathogenesis of RA.

We also detected B19 DNA in controls. This meant that B19 infection alone was not sufficient to induce arthritis. The risk for development of RA was higher in DR4-positive individuals combined with B19 infection. Therefore, B19 infection may be a trigger factor for the development of RA in the presence of DR4. Kerr, *et al* showed that the frequencies of HLA-DRB1*01, *04, and *07 alleles were significantly higher in patients with B19 infection than in controls[29]. HLA class I and II alleles were associated with symptomatic acute parvovirus B19 infection. Gendi, *et al* also demonstrated that HLA-DR4 might be associated with persistence of joint symptoms beyond one week[30].

The mechanism for B19-associated arthritis is still unknown. The mechanisms involved in the B19-associated diseases include local viral replication, non-structure protein (NS1) cytotoxicity, immune complex deposition, erythroblast apoptosis, autoantibody production, cytokine upregulation, altered immune function, and persistence of B19 in the human body[31]. NS1 can induce the upregulation of interleukin 6 (IL-6), as a transcriptional activator on the promoters of IL-6 gene[16,17,32-34]. NS1 also has cytotoxic and apoptotic effects resulting in cell lysis[14]. B19-infected lymphocytes and macrophage are associated with enhanced IL-6 and TNF-α production[16,34]. Immune complex deposition is thought to occur in the acute polyarthropathy of B19 infection. In experimental parvovirus infection, joint symptoms appeared during viremia and in the presence of specific IgG[35]. B19 infection has been associated with the development of rheumatoid factor[5,24,36] and various autoantibodies including antinuclear antibody and anti-DNA, anti-SSA/SSB, anti-mitochondria, anti-smooth muscle, anti-gastric parietal cell, and antiphospholipid antibodies[37-39]. B19 virus has been shown to infect and persist in T cells, B cells, dendritic cells, and macrophages, but not synovial lining cells in the synovium[16,40]. Together with NS1-mediated upregulation of IL-6

this may alter host cellular immunity. The synovial cells or lymphocytes would continuously secrete inflammatory cytokines with the persistent infection of B19 in joints, causing polyclonal B cell activation and synovial cell proliferation in RA synovium.

The hypothesis of molecular mimicry has also been suggested in the etiopathogenesis of RA[41]. The molecular mimicry mechanism is usually used to explain the role of exogenous agents in the pathogenesis of autoimmune diseases. Anti-VP1 IgG may crossreact with type II collagen, which is a target antigen of autoantibodies in the RA synovium[42,43]. Autoantibody activity against keratin, ssDNA, and cardiolipin can be induced after virus infection[42]. These findings suggest molecular mimicry or epitope spreading.

B19 infection might also cause a systemic lupus erythematosus-like syndrome[44,45] or SLE disease[10]. However, the relationship between B19 infection and SLE needs to be further elucidated[46]. The B19 infection-associated arthritis and lupus-like syndrome may also be due to molecular mimicry.

Our study revealed that parvovirus B19 infection may play a role in the pathogenesis of RA in Taiwan, especially in those individuals possessing HLA-DR4.

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