Association Between FcγR Ila and Iila Polymorphism and Clinical Manifestations in Korean Patients with Adult-Onset Still's Disease

High-dose intravenous immunoglobulins alter the disease activity of adult-onset Still's disease (AOSD). Because activation status of FcγR is possibly dependent on their genetic polymorphisms, we investigated whether the polymorphisms of FcγR Ila and Iila are risk factors, and affect the clinical features of AOSD. Genomic DNA was extracted from 36 patients and from 197 healthy controls. Polymerase chain reaction for FcγR Ila and Iila using the allele-specific primers and direct sequencing of FcγR Ila polymorphic site were performed. The frequencies of FcγR Ila/Iila genotype between patients with AOSD and controls were not different. The allelic frequencies of FcγR Ila/Iila between patients with AOSD and controls were not different, either. However, the FcγR Ila-R/R131 genotype was associated with a higher concentration of hemoglobin (p=0.04) and stable liver function (p=0.009) than the other genotypes. The FcγR Ila-F/F176 genotype was associated with significantly lower titers of serum ferritin (p=0.025), and higher serum albumin (p=0.037) and cholesterol (p=0.014) concentrations than the other genotypes. This study suggest that the FcγR Ila and Iila polymorphisms might not be genetic risk factors for AOSD in Korean, but contribute to the activity of disease. FcγR Ila-R/R131 and Iila-F/F176 genotypes, low-binding genotypes for IgG2a and G1, may have more protective effects in acute stage of the disease than the other genotypes.

Key Words : Still's Disease, Adult Onset; Polymorphism, Genetics

INTRODUCTION

Adult-onset Still’s disease (AOSD) is a systemic inflammatory disease, and its major clinical manifestations include high spiking fever, typical skin rash, polyarthritis, and neutrophilic leukocytosis. The common minor features are sore throat, serositis, lymphadenopathy, splenomegaly, liver dysfunction, and negative results for antinuclear antibodies (ANA) and rheumatoid factor (RF) assay (1). Although the pathogenesis of AOSD has been investigated from various aspects including infection, immune reaction, genetic factor, environmental factor, and pregnancy or hormonal effects, it has not been clearly identified yet.

Forty to eighty percent of patients with active stage AOSD show increased titers of immunoglobulin (Ig), most of which are IgG, and sometimes, detected as a form of immune complex (IC) (2-4). Ig or IC may influence the expression of Fc gamma receptors (FcγRs) on the surface of phagocytic cells such as monocytes, macrophages, natural killer (NK) cells, and neutrophils. Administration of high-dose intravenous immunoglobulins (IVIG) may induce remission of active AOSD by means of blocking FcγR or regulating humoral immune response (5-6). Patients with AOSD also have high serum levels of interleukin-6 (IL-6), interferon-γ (INF-γ), and tumor necrosis factor-α (TNF-α). IL-6 induced by FcγR triggering may stimulate the ferritin synthesis and B cell proliferation, but the ferritin inhibits Ig production of B cells (7-10). Previously, both the concentration of IL-6 and that of serum ferritin have been shown to rise and fall depending on the disease activities in juvenile chronic arthritis and AOSD (11, 12). Nakatani et al. recently reported that in Kawasaki disease, which has similar clinical features with AOSD in part, high level of Fcγ-R II and III expression on the surfaces of neutrophils and monocytes at active state fell after IVIG therapy (13).

The polymorphisms of FcγR Ila131R/H and Ila176V/F were also revealed as genetic risk factors for systemic lupus erythematosus (SLE), especially lupus nephritis, and as susceptibility and/or severity markers for SLE and rheumatoid arthritis (RA) in distinct ethnic groups (14-19). FcγR polymorphism might be associated with AOSD by means of IC handling, cytokine production, and binding ability to acute phase reactants, such as C-reactive protein (CRP). We investigated whether the polymorphisms of FcγR Ila131R/H and Ila176V/F influence the development and clinical manifestations of AOSD.
MATERIALS AND METHODS

Patients

Thirty-six Korean patients with AOSD and 197 Korean healthy controls were enrolled in this study. The patients were recruited between May 1998 and July 1999 at the Hospital for Rheumatic Diseases and Guri Hospital of Hanyang University. Diagnosis of AOSD was made by the criteria of Yamaguchi et al. (1). We excluded patients with occult infections, malignancy, or definite signs that fulfilled the criteria for other rheumatic diseases. Clinical manifestations and laboratory data at acute stage were collected by interview and retrospective review of medical records.

Disease duration was considered from initial clinical manifestation to September 1999. The clinical parameters included high fever (>39°C), arthritis (involvement of 4 or less joints for oligoarticular type and 5 or more joints for polyarticular type), skin rash, weight loss (>10% for 6 months), lymphadenopathy, hepatomegaly, splenomegaly, and sore throat in physical examination, serositis and renal involvement. The laboratory variables at active stage of the disease included serum concentrations of albumin, transaminase (ALT/AST), and erythrocyte sedimentation rate (ESR) followed by systemic remission, and the polycyclic-systemic type was defined as an initial single bout of systemic disease of variable duration, followed by systemic remission, and the polycyclic-systemic type referred to 2 or more episodes of systemic disease. The disease-course into 3 categories; the monocyclic-systemic type was defined as an initial single bout of systemic disease of variable duration, followed by systemic remission, and the polycyclic-systemic type referred to 2 or more episodes of systemic disease. The chronic destructive type referred to recurrent systemic manifestations, followed by bony erosion and deformities.

FcR IIa and IIIa genotyping

For genotyping of FcR IIa and IIIa, DNA was isolated from peripheral blood (Puregene kit, Gentra systems, Minneapolis, MN, U.S.A.). Polymerase chain reaction (PCR) was performed using allele-specific primers (Bioneer Co., Ltd., Cheongwon, Korea). Pan-primer of FcR IIa was 5’-TCA AAG TGA AAC AAC AGC CTG ACT AC-3’. Allele-specific primer of FcR IIa-131R was 5’-ATG GAA AAT CCC AGA AAT TCT CAC A-3’, and that of FcR IIa-131H was 5’-ATG GAA AAT CCC AGA AAT TCT CAC A-3’. Pan-primer of FcR IIIa was 5’-TCA CAT ATT TAC AGA ATG GCA ATG G-3’. Allele-specific primer of FcR IIIa-F136 was 5’-TCT CTG AAG ACA CAT TTC TAC TCC CTA A-3’, and that of FcR IIIa-V176 was 5’-TCT CTG AAG ACA CAT TTC TAC TCC CTA C-3’. The PCR was performed in a GeneAmp system 9600 (Perkin Elmer Biosystem, Norwalk, CT, U.S.A.) with 100 ng of genomic DNA, 10 μM of each primer, 100 mM of Tris-HCl, 500 mM of KCl, 15 mM (for IIa) or 25 mM (for IIIa) of MgCl2, 20 mM dNTPs, and 1 unit of Taq DNA polymerase (Boeringer Mannheim Biochemicals, Germany) in a 50 μL reaction volume. For FcR IIa, PCR was started with 94°C for 5 min, 62°C for 30 sec, and 72°C for 3 min, followed by 35 cycles of 94°C for 45 sec, 62°C for 30 sec, 72°C for 45 sec, and ended with an extension step at 72°C for 10 min. For FcR IIIa, PCR was started with 94°C for 5 min, 62°C for 30 sec, and 72°C for 3 min, followed by 35 cycles of 94°C for 30 sec, 55°C for 30 sec, 72°C for 30 sec, and ended with an extension step at 72°C for 7 min. Fifteen microliters of each amplified PCR product was analyzed by gel electrophoresis for 40 min (100 V) on 2% agarose gel containing ethidium bromide. The appearance of 378 bp (FcR IIa) or 138 bp (FcR IIIa) base pair PCR product in each allele-specific reaction indicate the presence of the allele (15-18).

Sequencing of FcR IIIa genomic DNA

Direct sequencing was performed to confirm the FcR IIIa genomic sequences for the samples that did not produce definitive patterns on PCR. We amplified a portion of exon 4 that corresponds to the second extracellular Ig-like domain (EC2). The forward primer was 5’-TGT AAA ACG ACG GCC AGT TCA TCA TAA TTC TGT CTT C-3’, corresponding to nt 486-505. The reverse primer was 5’-CAG GAA ACA GCT ATG ACC CT TGA TGG TGA TGG TGA TGG TGA TCT-3’. The size of the PCR product containing the nt 559 polymorphic site was 162 bp. FcR IIIa PCR products for sequencing were clarified with 2% agarose gel electrophoresis, and the products were purified with Qiaquick PCR clean-up kit (Qiagen, Germany). Using ABI Prism BigDye™ Terminator Cycle Sequencing Ready Reaction KIts (PE Biosystem, CA, U.S.A.), the purified product was prepared for sequencing. The PCR for BigDye™ adhesion to the purified PCR products was performed by 25 cycles of 96°C for 30 sec, 50°C for 15 sec, and 60°C for 4 min followed by an addition of 2 μL of 3 M Na acetate (pH 4.6) and 50 μL of 95% ethanol. The samples were mixed carefully and incubated on ice for 10 min. The mixture was then centrifuged for 30 min at 12,000 × g, followed by washing with 70% ethanol. The product was resuspended in 25 μL of templates suppression reagent (supplied with Ready Reaction KIts), heated at 95°C for 2 min, then chilled on ice. The samples were read with ABI Prism 310 Genetic Analyzer (PE Biosystem, CA, U.S.A.).

Statistical analysis

The distribution of FcR IIa and IIIa genotypes between 2 groups (AOSD patients vs. healthy controls) was compared using the Chi-square test (2 × 2, 2 × 3 contingency table). A probability of 0.05 (two-tailed) was used to reject the hypothesis that there was no significant difference in the distribution of genotypes between the groups. χ² test was also used to compare the frequency of FcR IIa-R/R131 (2 × 2, 2 × 3 contingency table)
contingency table: R/R131 vs. R/H131 and/or H/H131) and Fc R IIa-F/F176 (F/F176 vs. V/F176 and/or V/V176), and alleles (R131 vs. H131, F176 vs. V176) in each group. The odds ratios (OR) and 95% confidence interval (95% CI) were calculated to provide an estimate of the risk of AOSD in Fc R IIa and IIIa genotypes or allotype compared with the disease-free controls. The clinical parameters or laboratory variables at active stage of disease were compared using independent sample t-test or ANOVA. We used SPSS version 8.0 for Windows for the statistical analysis.

RESULTS

Clinical features of patients with AOSD

Of the 36 patients with AOSD, 4 were men and 32 were women. The mean age at diagnosis was 31.3 ± 10.4 yr, the mean duration from initial manifestation to diagnosis was 20.0 ± 16.5 months, and the duration of follow-up was 33.6 ± 26.1 months. There was no significant difference between the two sexes. During the disease course, 15 patients were classified as oligoarticular type, 16 as polyarticular type, and 3 had no arthritis. Two patients could not be classified because of short disease duration (Table 1). The frequency of clinical features were as follows: high fever 97.2%, arthritis 88.9%, skin rash 88.9%, sore throat 55.6%, hepatomegaly 44.4%, lymphadenopathy 41.7%, splenomegaly 33.3%, serositis 27.8%, renal involvement 13.9%, and weight loss 13.9%. The mean values of laboratory data at the time of active disease were as follows; leukocyte 17,294/μL, platelet 429,694/μL, hemoglobin 9.5 g/dL, erythrocyte sedimentation rate 55 mm/hr (Wintrobe method), C-reactive protein 7.8 mg/dL (normal <0.8 mg/dL), serum ferritin 4,986 ng/dL, serum albumin 3.6 g/dL, and serum cholesterol 182 mg/dL. Positive results of ANA and RF were found in 30.6% and 19.4%, respectively, at very low titers.

The distribution of Fc R IIa and IIIa genotypes, and its relationship with clinical features

The Fc R IIa and IIIa genotypes and alleles did not show a significant difference between patients with AOSD and healthy

Table 1. Characteristics of patients with AOSD and healthy controls

| AOSD patients (n=36) | Healthy controls* (n=197) |
|---------------------|---------------------------|
| Age at diagnosis (yr) | 31.3 ± 10.4 | 20.0 ± 16.5 |
| Duration of diagnosis (months) | 20.0 ± 16.5 | 16.5 ± 26.1 |
| Sex (M/F) | 4/32 | 99/98 |
| Follow-up duration (months) | 33.6 ± 26.1 | 33.6 ± 26.1 |
| Disease course: No. of patients | | |
| Monocyclic-systemic type | 7 | 16 |
| Oligoarticular type | 5 | 32 |
| Polyarticular type | 1 | 32 |
| Polycyclic-systemic type | 24 | 51 |
| Oligoarticular type | 9 | 16 |
| Polyarticular type | 11 | 16 |
| Chronic destructive type | 5 | 51 |
| Oligoarticular type | 4 | 4 |
| Polyarticular type | 4 | 4 |

Healthy controls (n=197) were consisted of 99 males and 98 females. *3 cases had no arthritis, and 2 cases could not be classified due to the short duration of follow-up.

Table 2. Distribution of Fc R IIa and IIIa genotypes and alleles in AOSD and healthy controls

| Fc R IIa & IIIa | AOSD patients (n=36) | Healthy controls* (n=197) |
|----------------|---------------------|---------------------------|
| Genotype no. (%) | | |
| Ila-131RR | 4 (11%) | 16 (8%) |
| Ila-131RH | 17 (47%) | 99 (50%) |
| Ila-131H/H | 15 (42%) | 82 (42%) |
| Ila-176VV | 3 (8%) | 22 (11%) |
| Ila-176VF | 22 (61%) | 104 (53%) |
| Ila-176FF | 11 (31%) | 71 (36%) |
| Allele frequencies | | |
| Ila-131R | 0.347 | 0.331 |
| Ila-131H | 0.653 | 0.669 |
| Ila-176V | 0.389 | 0.378 |
| Ila-176F | 0.611 | 0.622 |

Table 3. Relationship between laboratory data and Fc R IIa genotypes in patients with AOSD

| Patients (n=36) | Fc R IIa-RR | Fc R IIa-RH | Fc R IIa-H/H |
|----------------|-------------|-------------|-------------|
| Leukocytes (×10³/L) | 17,294 ± 7,377 | 23,900 ± 11,625 | 16,499 ± 5,493 | 16,433 ± 7,654 |
| Hemoglobin (g/dL) * | 9.5 ± 1.8 | 11.2 ± 1.6 | 9.3 ± 2.0 | 9.2 ± 1.4 |
| Platelets (×10³/L) | 429,694 ± 135,523 | 454,750 ± 198,807 | 431,882 ± 157,602 | 420,533 ± 93,732 |
| ESR (mm/hr) | 55.2 ± 21.4 | 40.5 ± 24.4 | 53.5 ± 21.2 | 61 ± 20 |
| CRP (mg/dL) | 7.8 ± 5.0 | 3.9 ± 4.1 | 8.1 ± 4.7 | 8.6 ± 5.5 |
| Serum albumin (mg/dL) | 3.6 ± 0.6 | 4.0 ± 0.4 | 3.5 ± 0.6 | 3.7 ± 0.6 |
| ALT (unit) | 93 ± 123 | 38 ± 32 | 88 ± 93 | 113 ± 163 |
| AST (unit) | 70 ± 77 | 33 ± 8 | 62 ± 75 | 88 ± 88 |
| Serum cholesterol (mg/dL) | 182 ± 51 | 187 ± 51 | 189 ± 58 | 172 ± 45 |
| Serum ferritin (ng/dL) | 4,986 ± 6,968 | 3,310 ± 4,116 | 7,209 ± 9,235 | 2,914 ± 2,977 |

*p=0.009 IIa-RR vs. Ila-RH/HH genotype, ′p=0.04 IIa-RR vs. Ila-RH/HH genotype. Values are expressed as mean ± standard deviation.
controls (Table 2). There was no significant difference between FcR IIa and IIa alleles and the clinical parameters (data not shown). The patients with AOSD with the FcR IIa-R/R131 genotype showed significantly higher concentrations of hemoglobin (p=0.009), and lower concentrations of serum AST (p=0.04) than those with the FcR IIa-RH/H genotype (Table 3). The FcR IIIa-V176 genotype was also revealed to be associated with significantly lower titers of serum ferritin (p=0.025), and higher serum albumin (p=0.037) and cholesterol (p=0.014) concentrations than the other genotypes (Table 4).

The patients with polyarticular type showed lower concentrations of serum albumin (p=0.025, 3.4±0.5 vs. 3.9±0.6), higher concentrations of serum ferritin (p=0.078, 7.179±8,907 vs. 2,628±2,858) than those with oligoarticular type. During the disease course, patients with the polycyclic-systemic type revealed higher titers of serum ferritin (p=0.013, 6,657±8,135 vs. 1,735±1,994) than those with the monocyclic-systemic type. The patients with the chronic destructive type marked higher platelet counts (p=0.001, 618,750±134,772 vs. 380,326±94,522), and were much more anemic (p=0.04, 8.3±1.2 vs.10.3±1.5) than the other two types. However, we could not find any statistically significant correlation between the genotypes and the clinical course due to the small number of patients in each group.

**DISCUSSION**

FcRs play important roles in immune regulation, as they link antibody-mediated immune responses with cellular effector function. FcRs have three distinct types: FcRI, FcRII, and FcRIII, with different IgG binding affinities and IgG subclass specificities (20). The structural heterogeneity of FcR is reflected in a wide range of biologic activities, including phagocytosis, antibody-dependent cell-mediated cytoxicity, and release of inflammatory mediator, as well as clearance of antigen/antibody immune complex and regulation of antibody production (21). Additional diversity of individual Fc-receptor-mediated function is related to genetically determined polymorphisms (21). FcR IIa alleles (R131 and H131) differ in their capacity to bind IgG2, and FcR IIIa alleles (V176 and F176) differ in IgG1 and IgG3 binding. In some ethnic populations with lupus, FcR IIa-R131 and FcR IIIa-F176, the alleles with a lower binding capacity, were known to be associated with nephritis, whereas FcR IIa-H131 and FcR IIIa-V176, the alleles with a high binding capacity, seemed to be protective (14-17, 22, 23).

Although the pathogenesis of AOSD has not been clearly defined, we speculate that FcRs may play a role in the pathogenesis based on the following evidences.

First, the IVIG treatment was effective in steroid-resistant cases of AOSD (5, 24, 25). The mechanism of action could be IVIG-mediated Fc receptor blockage and modulation. IVIG bound to the FcR on the surface of B cell induce apoptosis and inhibit the production of Ig or B cell proliferation (26). In the acute stage of Kawasaki disease, which has similar clinical manifestations with AOSD, the expression of FcR II and III was modulated by the infusion of IVIG (13, 27). These findings suggest that the immune system in patients with AOSD could be regulated by modulation of FcR II and III. Second, 40% to 80% of patients with AOSD have increased IgG level, sometimes in a form of IC (2-4). The abundant IgG in AOSD might bind to auto-antigens or to foreign antigens and then, induce FcR-mediated immune reactions. Third, AOSD patients in active stage had increased concentrations of IL-6, TNF-α, or INF-γ (11). FcR ligation may trigger the release of IL-1α, IL-6, and TNF-α (8, 28). FcR IIIa ligation of human macrophages in RA patients induces production of both TNF-α and IL-1α by immune complexes containing IgG RF (29). FcR IIIa engagement on the NK cell from V/F high-binding homozgyotes led to a larger rise in the concentration of CA2+ influx ([Ca2+]i), a greater level of NK cell activation, and a more rapid induction of activation-induced cell death than F/F low-binding homozgyotes (16). FcR IIa is a receptor for C-reactive protein on human monocytes and polymorphonuclear leukocytes. FcR IIa-R131 homozgyote binds CRP with a higher affinity and initiates higher increase in

**Table 4. Relationship between laboratory data and FcR IIIa genotype in AOSD**

| Patients (n=36) | FcR IIIa-V/V | FcR IIIa-V/F | FcR IIIa-F/F |
|----------------|-------------|-------------|-------------|
| Leukocytes (×10³/L) | 17.294±7.377 | 14.633±1.159 | 17.504±5.474 | 17.599±1.1178 |
| Hemoglobin (g/dL) | 9.5±1.8 | 9.6±1.9 | 9.4±1.9 | 9.5±1.8 |
| Platelets (×10³/L) | 429,694±135,523 | 521,000±170,853 | 423,681±127,404 | 416,828±146,954 |
| CRP (mg/dL) | 7.8±5.0 | 7.0±0.7 | 8.0±4.6 | 7.7±6.6 |
| Serum albumin (mg/dL) | 3.6±0.6 | 3.7±0.3 | 3.4±0.5 | 3.9±0.7 |
| ALT (unit) | 93±123 | 21±9.0 | 95±89 | 108±187 |
| AST (unit) | 70±77 | 32±11 | 76±76.8 | 67±89 |
| Serum cholesterol (mg/dL) | 182±51 | 151±51 | 181±46 | 192±64 |
| Serum ferritin (ng/dL) | 4,968±6,968 | 3,114±2,573 | 6,660±8,381 | 2,147±2,240 |

*p=0.037 IIIa-FF vs. IIIa-VV/VF genotype, †p=0.014 IIIa-VV vs. IIIa-V/F/F genotype, ‡p=0.025 IIIa-FF vs. IIIa-VV/VF genotype.

Values are expressed as mean±standard deviation.
[Ca++]i (30) than Fc R IIa H-131 homozygote. Therefore, the production of proinflammatory cytokines and activation of cells in AOSD may be influenced by Fc R polymorphisms. Fourth, the serum ferritin concentration in active AOSD was also significantly higher than that in inactive AOSD (31). Ferritin has an inhibitory effect on the in vitro proliferation of T lymphocytes and on the differentiation of human B lymphocytes (10). IL-6 increased the transferrin uptake and production of ferritin (32). TNF, which can be induced by Fc R ligation, may also stimulate the ferritin synthesis (7). Collectively, Fc R polymorphism may influence the serum concentration of ferritin through the cytokine-mediated inflammatory pathway.

Although this study was too underpowered to test the hypothesis due to small sample size, Fc R IIa-R/H131 and IIIa-V/F176 polymorphisms might not be genetic risk factors for AOSD. However, Fc R IIa-R/R131 genotype was associated with a higher hemoglobin concentration and lower serum transaminase concentration, and Fc R IIIa-F/F176 was associated with a higher concentration of serum albumin and a lower concentration of serum ferritin than the other genotypes. These data suggest that Fc R IIa-R/R131 and Fc R IIIa-F/F176 genotypes could be protective during the active stage of AOSD, and the difference in cell activation induced by the Fc R polymorphism may influence the concentration of ferritin and albumin, which reflect the level of cytokine release according to the Fc R polymorphisms. The patients with the Fc R IIIa-V/V176 genotype had a higher titer of serum ferritin, which has been known as a marker of disease activity in AOSD, and a lower concentration of serum albumin in the acute stage. These findings are consistent with our previous clinical report (2), which emphasized that the patients with lower concentrations of serum albumin in the early stage had a recurrent and chronic disease course. However, we could not find any difference in the clinical course by the Fc R polymorphism due to the small number of patients in each group. Fc R polymorphism may affect the level of activation of phagocytic cells in AOSD, whereas it contributes to the lupus pathogenesis as a genetic risk factor by the different capacity to handle IgG-containing immune complex.

In conclusion, there was no significant skewing in the distribution of the Fc R IIa and IIIa genotypes and alleles between the patients with AOSD and disease-free controls. However, Fc R IIa and IIIa polymorphisms might contribute to the process of active disease. Fc R IIa-R/R131 and IIIa-F/F176 genotypes or alleles may provide more protective effects in acute stage of the disease than the other genotypes. Therefore, compared with the defective scavenging of IC in SLE, especially lupus nephritis, Fc R IIa and IIIa polymorphism may affect the effector cell activation via Fc R triggered by Ig or IC in AOSD. It will be valuable to assess the relationship between AOSD and Fc R polymorphism with more AOSD patients to confirm our observation.

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