Mod Rheumatol (2005) 15:69–72
DOI 10.1007/s10165-004-0365-7

CASE REPORT

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Systemic lupus erythematosus in identical twins: a case report

Received: May 7, 2004 / Accepted: November 1, 2004

Abstract In this report we describe the case of identical twin sisters that developed systemic lupus erythematosus (SLE). These patients have in common major histocompatibility complex class I and class II alleles and identical red blood cell antigens, which is a clear indication of monozygotic twins. Both twins showed high titers of anti-dsDNA antibody. However, only one of them manifested signs of lupus psychosis and was positive for the LE test, rheumatoid factor, anti-Scl 70, anti-SSA, and antiribosomal P antibodies. Both sisters lived together; therefore, the environmental factors were considered to be the same. Interestingly, these patients expressed different types of autoantibodies and the manifestation of disease was also quite different. When one of the twins was diagnosed with SLE, we began to closely follow up signs of the disease in the other twin periodically. This enabled us to promptly diagnose the second twin with SLE and she was successfully treated without progression of the disease. It is important to mention that following up the subsequent history of an identical twin diagnosed with SLE allowed early detection of the disease in the other twin.

Key words Histocompatibility leukocyte antigen (HLA) · Identical twins · Systemic lupus erythematosus (SLE)

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Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease characterized by the production of non-organ-specific autoantibodies including antinuclear, anti-double-stranded DNA and antiphospholipid antibodies. Significant health consequences include renal failure, vasculitis, arthritis, seizures and other neurologic complications, and increased risk of infection.[1]

Systemic lupus erythematosus is regarded as a complex disease with an etiology that appears to be the interplay of genetic and environmental factors.[2] To a great extent there is plenty of evidence that favors an important role for genetic factors in SLE. The level of genetic contribution can be measured by comparing the concordance rate between identical and dizygotic twins. In SLE, the monozygotic twin concordance rate for clinical expression of the disease has been found to be 25%–69%, whereas the presence of serum autoantibodies can be as high as 92%.[3–7] For comparison purposes, only 1%–2% of siblings and dizygotic twins are concordant for SLE. In addition, only 10%–12% of all SLE patients have first- or second-degree relatives with the disease.[8,9]

In previously reported serological studies, the dominant role that genetic factors played in determining specific autoantibody profiles was shown.[10] To help clarify the association between the genetic and environmental factors in the development of SLE is necessary to study case reports that bridge these two factors. In this report, we describe monozygotic twins with SLE. These patients have in common major histocompatibility complex class I and class II alleles: A26, A31, B51, B60, and DR14, DR15, DQ1, DQ7, respectively. They also have identical red blood cell antigens, which is a clear indication of monozygosity. However, their autoantibody profiles and disease progression were quite distinct.

Case reports

Twin A

A 19-year-old Japanese woman was admitted to our hospital in February 1999 with fatigue, arthralgia, oral aphtha, hair loss, and pretibial edema. Her family history showed no marriage of consanguinity. She appeared well until September 1998 when fatigue and arthralgia developed. Neither dry eye nor dry mouth was observed. On physical examination, her blood pressure was 138/90 mmHg with a regular heartbeat of 93 beats/min, and a temperature of 37.4°C. Her skin did not show malar rash, discoid rash, or skin sclerosis, but arthritis and oral aphtha were observed. Cardiac examination discovered enlargement of limit of cardiac dullness, and lung and abdominal examination revealed no abnormalities. During a neurological examination, no abnormalities were observed. However, the patient suffered from depression, appetite loss, and apathy. Laboratory studies revealed a leukocyte count of 3610/mm^3, hemoglobin of 9.0 g/dl, platelet count of 16.6×10^4/mm^3, and erythrocyte sedimentation rate (ESR) of 113 mm/h (Westergren method), but negative C-reactive protein (CRP). Electrolytes and renal function were normal with albumin levels of 3.3 g/dl, but hypergammaglobulinemia was observed (26.9%). Urinalysis revealed proteinuria (1.8 g/24 h) and microscopic hematuria, and creatinine clearance (Ccr) was normal (108.4 ml/min). Room air arterial blood gases revealed PaO_2 of 97.9 mmHg, $PaCO_2$ of 38.4 mmHg, and a pH of 7.39. Her C3 levels were 21.2 mg/dl (normal: 65–135 mg/dl), the C4 was 1.4 mg/dl (normal: 13–35 mg/dl), and total serum hemolytic component (CH_{50}) was 14 U/ml (normal: 28–53 U/ml). She tested positive for antinuclear antibody (ANA) with an index of more than 200 (normal: <20), anti-dsDNA was more than 400 IU/ml (normal: <12 IU/ml), rheumatoid factor (RF) was 81.9 IU/ml (normal: <10 IU/ml), anti-Scl-70 was positive with an index of 35.9 (normal: <24), and anti-Ro (SSA) was positive with an index of 68.6 (normal: <30). Anti-La (SSB), anti-Sm, anti-RNP, and anti-Jo-1 antibodies were undetectable as measured by enzyme-linked immunosorbent assay (ELISA), but her LE test was positive. False-positive serology for syphilis was not observed in this patient. Lupus anticoagulant, anticardiolipin antibodies, and anti-β2GPI antibody were not detected. Chest X-ray revealed cardiomegaly and an echocardiogram revealed moderate pericardial effusion. Because of the psychological symptoms, *N*-isopropyl-*p*-[^{123}I]iodoamphetamine brain single-photon emission computed tomography (SPECT) was performed. A diffuse decrease of cerebral blood flow was observed. The color of the cerebrospinal fluid was normal and the number of cells, the concentration of protein, the levels of interleukin-6, and IgG index were within normal ranges. Antiribosomal P antibody was positive with an index of 17.6 (normal: <10) as determined by ELISA. A diagnosis of lupus psychosis was made, and high-dose corticosteroids (prednisolone 60 mg daily) was started in February 1999 and tapered to 10 mg every 4 weeks. Additionally, pulse methylprednisolone therapy (1 g/day) was performed three times. This treatment relieved her symptoms and improved her abnormal data gradually until she was in complete remission. Prednisolone was tapered to 30 mg daily in July 1999 and the patient was discharged. Because of the arthritis, proteinuria, and serological data, her disease was considered to be active. Azathioprine (50 mg daily) administration was added in July 2001. Prednisolone was tapered to 17 mg in June 2003. Although her symptoms disappeared, SLE was considered to be moderately active, based on serology tests. The complement data were as follows: C3 was 70.9 mg/dl, C4 8.5 mg/dl, and CH_{50} 25 U/ml. Her ANA was positive with an index of 50.9 and anti-dsDNA levels were 72 IU/ml in June 2003.

Twin B

Clinical findings of SLE were negative in the monozygotic twin sister. There was no serological abnormality such as hypergammaglobulinemia or elevation of anti-dsDNA, except for a false-positive serologic test for syphilis in February 1999. We checked the serologic data of this patient every 6 months. Signs of arthritis were observed in September 2002. Then in October, she was positive for ANA with an index of 38, anti-dsDNA of 140 IU/ml, abnormality of complement (C3: 57 mg/dl; C4: 6 mg/dl; CH_{50}: 24 U/ml), and leukopenia of 3200 mm^3. The diagnostic criteria of SLE were fulfilled (arthritis, leukopenia, abnormal titers of anti-DNA and ANA). She was admitted to our hospital in November 2002. Neither dry eye nor dry mouth was observed. On physical examination, she had a blood pressure of 112/60 mmHg, a regular heartbeat of 60 beats/min, and a temperature of 36.9°C. Her skin showed no signs of malar and discoid rash; however, arthritis was observed. Cardiac, lung, and abdominal examination did not reveal any abnormalities. No abnormalities were observed after a neurological examination. Laboratory studies revealed a leukocyte count of 2990/mm^3, hemoglobin 12.4/dl, a platelet count of 21.1×10^4/mm^3, ESR of 11 mm/h, and negative CRP. Electrolytes and renal function were normal with albumin levels of 4.8 g/dl and hypergammaglobulinemia was not observed (18.8%). Urinalysis revealed no proteinuria and no hematuria. Her Ccr was normal (125.0 ml/min). The C3 was 51.6 mg/dl, C4 5.4 mg/dl, and CH_{50} 14 U/ml. Her ANA had an index of 43.7, anti-dsDNA levels were 199 IU/ml, but RF was negative. Testing of anti-Scl-70, anti-Ro (SSA), Anti-La (SSB), anti-Sm, anti-RNP, anti-Jo-1, and antiribosomal P antibody were found to be negative as measured by ELISA, and her LE test was also negative. A false-positive serological test for syphilis was observed in this patient. Lupus anticoagulant, anticardiolipin antibodies, and anti-CLβ2GPI antibody were negative. Chest roentgenogram was normal. A moderate dose of corticosteroids (prednisolone 40 mg daily) was started in December 2002 and tapered to 10 mg every 4 weeks. Prednisolone was tapered to 30 mg daily in January 2003 and she was discharged. Prednisolone was further tapered to 15 mg in December 2003 and her symptoms disappeared. Serological test results were C3 97.0 mg/dl, C4 11.8 mg/dl, and CH_{50} 38 U/ml. Her ANA was

negative and anti-dsDNA levels were 22.8 IU/ml in December 2003. Treatment with corticosteroids relieved her symptoms and improved her abnormal data gradually, and she is now in complete remission.

Discussion

Recently, investigators have begun to realize that genetic effects in SLE could be highly associated with histocompatibility leukocyte antigen (HLA) genes in addition to other genes. Therefore, it is possible that these two factors could be linked in the development of SLE.

The association between SLE and HLA typing, specifically, the HLA class I B8, has previously been reported.[11] Later studies have then described that the association is stronger with HLA class II DR2 and DR3 (DRB1*0301), the latter being in linkage disequilibrium with B8.[12–14] Several studies have also suggested that the contribution of HLA class II genes in SLE exists predominantly at the level of production of specific autoantibodies rather than with SLE itself.[15–18] In contrast, Grennan et al. demonstrated that most of the genetic predisposition to SLE is attributable to genes outside the HLA region.[19]

Complement deficiency of the early components C1q, C2, and C4 of the classical pathway of complement are associated with high risk for the development of SLE.[20–22] C4A deficiency is probably the most commonly inherited complement deficiency, occurring in varying frequency in different populations.[23] The most common C4A deficiency allele in Caucasians is a 28-kb deletion removing both the C4A and 21-OHA genes, which occur in the HLA B8-DR3 haplotype.[23–25] A C2 deficiency is associated with a low frequency of SLE and milder manifestation of disease when compared with deficiency of C1q and C4. In our case report, serum levels of C4 were low because of activation of complement and not due to C4A deficiency. It's important to note that the levels of complement in both patients improved with prednisolone therapy.

A recent study revealed that interleukin 10 (IL-10) plays a role in the regulation of both cellular and humoral immune responses and is a likely candidate as a mediator in autoimmune disease.[26] Elevated levels of IL-10 have been reported to be associated with several autoimmune diseases, including SLE.[27] A correlation between in vitro IL-10 production and the promoter genotypes has also been reported.[28] Most notably, the G allele of the G/A polymorphism at nucleotide position 1082 has been associated as a "high producer" phenotype when compared with the A allele.[28] Moreover, tumor necrosis factor (TNF) was suggested to be protective against SLE.[26] The biological actions of TNF are mediated via two distinct TNF receptors (TNFR): 55 kDa TNFRI and 75 kDa TNFRII. TNFRII mediates a wide spectrum of cellular responses ranging from cellular proliferation to apoptosis. Interestingly, in SLE patients the level of soluble TNFRII was found to correlate with disease activity. A polymorphism in exon 6 of the TNFRII receptor, which consists of either methionine or arginine at amino acid position 196, revealed an association with SLE in Japanese patients. In addition, an association of Fcγ receptor (FcγR) polymorphism with SLE has been shown to occur in various populations. There are two classes of low-affinity FcγRs: FcγRII and FcγRIII. Three FcγRII genes (FCGR2A, FCGR2B, and FCGR2C) and two FcγRIII genes (FCGR3A and FCGR3B) from a clustered gene family are located on chromosome 1q23.[29] Earlier studies revealed an association of susceptibility to SLE in the Japanese population with polymorphisms of FCGR2B and FCGR3B alleles but not of FCGR2A and FCGR3A.[30] In this study we were not able to investigate a linkage between our patients and polymorphisms of IL-10, TNF, and FcγR.

A specific inheritance trait associated with a single HLA genotype was not observed in the identical twins when HLA testing was performed. Despite this lack of association, this could be attributed to only one of the individuals studied. In our case, clinical features and serological data suggested that a variety of factors appear to influence the development of the disease.

Serological studies of monozygotic twins with SLE have been performed previously. Autoantibodies to Ro/SS-A, La/SS-B, U1-RNP, and Sm were detected, and ANF patterns in HEp-2 cells were also studied. In monozygotic twins concordant for SLE, titers of autoantibodies, and ANF pattern of HEp-2 cells were similar and especially with anti-U1-RNP; 36% of monozygotic twins showed anti-U1-RNP antibody, whereas in SLE patients who were not twins the frequency of such an antibody profile was 10%. These data suggested that a dominant role for genetic factors determined a specific autoantibody profile.[31]

In our study, both twins were positive for anti-dsDNA antibodies with very high titers. On the other hand, RF, anti-Scl 70, and anti-SSA antibodies were positive in twin A but were negative in twin B. The LE test was positive in twin A but negative in twin B. Moreover, both of them were negative for anti-La (SS-B), anti-Sm, anti-RNP and, anti-Jo-1 antibodies.

Recently it was reported that serum antiribosomal P antibody levels were significantly elevated in patients with lupus psychosis, including those with organic brain syndrome and nonorganic psychosis, using an established ELISA system to measure antiribosomal P antibody.[32] Interestingly, Twin A manifested the psychological symptoms and was diagnosed with lupus psychosis. Antiribosomal P antibodies were also detected and this facilitated an association with lupus psychosis. In contrast, twin B did not show psychological symptoms and was negative for antiribosomal P antibodies.

It is possible that autoantibody levels between twin A and twin B were different because twin B was diagnosed with SLE at the early stage of the disease. In our case, twins A and B were living together, thus the environmental factors were considered to be quite similar. When twin A was diagnosed with SLE, we started to follow up twin B periodically. We were able to diagnose twin B with SLE promptly, and she was successfully treated for SLE without progression of the disease. Therefore, this observation indicates

that it is of importance to follow up the subsequent history of the other sibling in cases of monozygotic twins when one twin has already been diagnosed with SLE.

We consider that genetic factors in SLE play an important role on the onset of SLE. Genetic factors play the dominant role in determining the outcome of autoimmune responses and other genetic, and in some instances nongenetic factors can determine the specificity of autoimmunity. In our study, other genetic factors except HLA may have contributed to the onset of SLE and, if one of the twins succumbs to SLE, it is critical to carefully monitor the other sibling for signs of this disease.

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