Korean Journal of Pediatrics Vol. 52, No. 5, 2009
DOI : 10.3345/kjp.2009.52.5.611
■ Case report ■

Familial systemic lupus erythematosus in two Korean male siblings

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= Abstract =

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease characterized by the production of a wide range of autoantibodies, resulting in tissue damage. Although the susceptibility to SLE has been attributed to complex interactions between genetic and environmental factors, the influence of a genetic predisposition to SLE is supported by observations of familial aggregations. Family studies have found that siblings with an SLE-affected relative have a 20-fold higher risk of developing SLE compared with the general population. Here, we present a rare case of two male siblings with SLE. The clinical, laboratory, and histopathological findings of these individuals showed the characteristic features of SLE. Human leukocyte antigen (HLA) typing revealed that the brothers and their mother shared the common HLA haplotype of DRB1*1501 and DQB1*0602, which is significantly associated with disease susceptibility in both family-based and casecontrol studies. This report provides an opportunity to reveal the role of genetic factors in the development of SLE. **(Korean J Pediatr 2009;52:611-614)**

Key Words : Familial systemic lupus erythematosus, Children, Male, Sibling, Human leukocyte antigen

Introduction

Systemic lupus erythematosus (SLE) is a multi-system autoimmune disease that is characterized by the production of a wide range of autoantibodies directed mainly against nuclear antigens, which may result in damage to tissues[1]. Although susceptibility to SLE has been attributed to complex interactions between multiple genetic and environmental factors, the influence of genetic predisposition on susceptibility to SLE is supported by observations of familial aggregations[1]. Twin studies have confirmed concordance for SLE in 20-30% of monozygotic twins, as opposed to less than 2% concordance for SLE in dizygotic twins[2]. In SLE-affected families, siblings have a 20-fold higher risk of developing SLE, as compared with the general population[3].

To our knowledge, the previous reports on familial SLE in Korea have showed mother-son pair and sister-sister pair[4, 5]. We present the first case of male siblings with SLE. This report provides an opportunity to uncover the role of genetic factors in the development of SLE.

Received : 9 October 2008, Revised : 10 November 2008
Accepted : 5 December 2008
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Case report

A boy aged 11 years and 4 months was referred to Cheju National University Hospital for a facial rash and pain in multiple joints. Upon physical examination, he had an erythematous, facial rash that involved the cheeks bilaterally and the nasal bridge. He complained of pain in both the hands and lower legs, although his joints were quiescent. A complete blood cell (CBC) count showed a white blood cell (WBC) count of 4,500 per mm^3, hemoglobin (Hb) level of 12.4 g/dL, and platelet count of 85,000 per mm^3. Urinalysis revealed an absence of protein but there was hematuria (18-20 red blood cells [RBCs]/high power field [HPF]). His chemistry profile at presentation was normal, except for alanine aminotransferase (ALT) (74 U/L). He had an antinuclear antibody (ANA) titer of >1:640 (homogenous pattern) and anti-double-stranded DNA (anti-dsDNA) antibody level of 40.36 IU/mL. The subject was negative for antibodies to RNP, SSA/ Ro, and SSB/La. The complement levels were as follows: C3, 81 mg/dL; C4, 5 mg/dL; and CH50, 10.2 U/mL. A biopsy of the facial lesion showed features characteristic of SLE. The boy was treated with oral prednisolone (40 mg/day, 1 mg/ kg/day) and hydroxychloroquine (100 mg/day). He showed gradual clinical improvement and was discharged with 10 mg/day

prednisolone and 100 mg/ day hydroxychloroquine.

The elder brother of this boy subsequently presented with SLE, having developed symptoms 2 years after his brother, at 14 years of age. He was referred for generalized edema and oliguria. He had a history of Evans syndrome, which had been diagnosed 3 years previously in another hospital. The laboratory findings at that time showed a WBC of 4,500 per mm^3, Hb level of 9.0 g/dL, and platelet count of 2,000 per mm^3. The patient was ANA-positive with a homogenous pattern. He was negative for both anti-platelet and anti-dsDNA antibodies, and hypocomplementemia was not observed. This patient was treated with high-dose prednisolone (4 mg/kg/day). Over the following 3 months, his platelet counts normalized and the prednisolone treatment was successfully tapered. Six months before the referral, his CBC count was as follows: Hb level, 11.4 g/dL; WBC count of 5,600 per mm^3; and platelet count of 216,000 per mm^3.

On admission, the patient had an erythematous facial rash involving the cheeks bilaterally and the nasal bridge, and there was bilateral pretibial edema. The CBC revealed a WBC count of 4,600 per mm^3, Hb level of 11.4 g/dL, and platelet count of 216,000 per mm^3. Urinalysis showed 3+ protein, 2+ blood, 5-7 RBCs/HPF, and 4.2 g/day protein excretion for a 24-hour urine collection. His chemistry profile included elevated levels of blood urea nitrogen (BUN; 29.7 mg/dL), creatinine (1.6 mg/dL), and ALT (54 units/L), and decreased levels of total protein (5.8 mg/dL), serum albumin (2.6 mg/dL), and total calcium (6.3 mg/dL). He had an ANA titer of 1:80 (homogenous pattern) and anti-dsDNA antibody level of 77.75 IU/mL. He was negative for antibodies to RNP, SSA/Ro, and SSB/La. His complement levels were diminished as follows: C3, 56 mg/dL; C4, 3 mg/dL; and CH50, 3.6 U/mL. A renal biopsy showed class III focal segmental proliferative glomerulonephritis (World Health Organization classification of lupus nephritis). Triple therapy, which consisted of intravenous long-term methylprednisolone pulses (1 g/pulse), oral prednisolone (60 mg/every other day), and oral cyclophosphamide (50 mg/day), was initiated, to maintain renal remission. The patient was in the hospital for almost 2 months, and oral prednisolone was successfully tapered to 10 mg/day. In addition, the levels of proteinuria and serologic markers of disease activity improved as follows: proteinuria, 0.45 g/day; total protein, 5.6 mg/dL; serum albumin, 2.9 mg/dL; C3, 120 mg/dL; C4, 16 mg/dL; CH50, 37.4 U/mL; and anti-dsDNA antibody, 19.54 IU/mL. Renal function was restored, and the serum creatinine level was normalized (BUN, 11.6 mg/dL; creatinine, 1.2 mg/dL).

Currently, both brothers are doing well. The younger brother is no longer taking hydroxychloroquine but is still receiving prednisolone (10 mg once a day). The elder brother is currently receiving prednisone (15 mg once a day), calcium carbonate (500 mg once a day), cyclophosphamide (25 mg once a day), and ramipril (5 mg once a day).

Human leukocyte antigen (HLA) typing was performed, and the two brothers and their mother were found to share the haplotype of the DRB1*1501, DPB1*0201, and DQB1*0602 alleles (Table 1).

Discussion

Family studies have revealed a higher than expected prevalence among the relatives of patients with SLE[1]. Although the precise prevalence of familial SLE is not known, approximately 10% of patients with SLE have a first-degree relative with SLE, as compared to 1% of patients in control families[6-9]. In familial SLE, the most frequent mode of familial intra-aggregation is affected sibling pairs[8], and females predominate, with mother-daughter and sister-sister pairs being the most common and father-son pairs occurring relatively rarely[9].

In the present case, the brothers shared similar clinical manifestations, including malar rash, abnormal urinalysis, and thrombocytopenia. Thrombocytopenia, which is a component of the widely accepted classification criteria for SLE

Table 1. Human Leukocyte Antigen Typing of the Subjects

Locus	Mother	Older brother	Younger brother
A	A*02, A11	A*02, A24	A*02, A02
B	B*15, B40	B*15, B40	B*15, B56
C	Cw*08, Cw08	Cw*08, Cw08	Cw*04, Cw08
DR	DRB1*0901, DRB1*1501	DRB1*1201, DRB1*1501	DRB1*0901, DRB1*1501
DP	DPB1*0201	DPB1*0201, DPB1*0202	DPB1*0201, DPB1*0402
DQ	DQB1*0303(DQ9), DQB1*0602	DQB1*0301(DQ7), DQB1*0602	DQB1*0303(DQ9), DQB1*0602

proposed by the American College of Rheumatology (ACR), is associated with mortality and other serious clinical manifestations[10, 11]. Thrombocytopenia is categorized into: 1) an acute form that appears in association with severe, multisystemic disease flares; and 2) a chronic condition that is present even when the disease is otherwise quiescent[11]. The combination of idiopathic thrombocytopenic purpura and acute hemolytic anemia may occur in isolation or in SLE patients[11]. Moreover, thrombocytopenia is a component of a severe familial form of SLE, and SLE is more severe in families that have a thrombocytopenic SLE patient[12]. Therefore, in the case of the older brother, Evans syndrome may have been an initial manifestation of SLE.

HLA class II genes have received significant attention as genetic risk factors for many autoimmune diseases, and there is evidence to support the assignment of specific HLA class II haplotypes as genetic risk factors for SLE in several populations. In Koreans, HLA-DRB1*15 and DQB1*06 have been associated with genetic susceptibility in SLE patients[13, 14]. A recent study using a large cohort identified three distinct SLE-associated haplotypes that contained the DRB1*1501/ DQB1*0602, DRB1*0801/DQB1*0402, and DRB1*0301/DQB1* 0201 alleles, respectively[15]. In addition, haplotypes bearing the DRB1*1501/DQB1*0602 and DRB1*0301/DQB1*0201 alleles were detected in almost two-thirds of SLE patients, and were significantly associated with disease susceptibility in both family-based and case-control studies[16].

We performed HLA typing of the two brothers and their mother. Unfortunately, their father refused to undergo HLA haplotyping. The two brothers and their mother shared the common haplotype of DRB1*1501, DPB1*0201, and DQB1*0602. There is one interesting report about the sharing of common HLA haplotypes between mother and son: Stevens and et al. reported a significant increase in the frequency of identical HLA class II alleles for male SLE patients and their mothers, as compared with the frequencies for healthy men and their mothers, and they proposed that the mother-son HLA relationship affects the sons risk of developing SLE. Moreover, the increase in mother-son HLA haplotypes was most marked for the DRB1 locus in patients with SLE-associated DRB1 alleles[17].

In summary, in the present study, we describe male siblings who developed SLE, and we hypothesize that genetic predisposition plays an important role in the SLE susceptibility of these subjects.

한 글 요 약

형제에서 발병한 가족성 전신 홍반 루푸스

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전신 홍반 루푸스는 자가 항원에 대한 자가 항체를 생성하여 염증을 일으켜 다양한 기관에 손상을 주는 자가 면역 질환이다. 발병 원인은 잘 알려져 있지 않으나, 전신 홍반 루푸스 환자의 가족 중에 전신 홍반 루푸스가 일반인보다 20배 이상 발병 위험이 높아 유전적인 요인이 관련되어 있을 것으로 생각된다. 저자들은 형제에서 발병한 가족성 전신 홍반 루푸스 증례를 경험하였고, 전신 홍반 루푸스와 연관된 조직적합 유전자인 HLA DRB1*1501과 DQB1*0602 유전자를 환아모와 형제들이 공유한 것을 발견하였기에 문헌 고찰과 함께 보고하는 바이다.

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