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PARTIAL C4 DEFICIENCY IN TWO CHILDREN WITH SYSTEMIC LUPUS ERYTHEMATOSUS*

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Systemic lupus erythematosus (SLE) is a rare disease in childhood. Here two cases with SLE are presented, both with C4 null alleles yielding a functional C4 deficiency. The first case, a 14-year-old girl with a C4A null allele only, had a mild disease course, whereas the second child, a seven-year-old boy with both C4A0 and C4B0, had a more relentless course leading to death in five years. We conclude that complement activation by the classical pathway might be an essential mechanism that protects against the emergence of autoimmune or immune-complex disases, and that the deficient state in our patients predisposed them to the early development of SLE. *Key words: systemic lupus erythematosus, C4 null allele, childhood.*

Systemic lupus erythematosus (SLE) has been reported in children of all ages, although it is very rare before the age of ten. The prevalence appears to be high in Turkey, since 56 children with SLE have been seen during the last ten years at our hospital. Various genetic and environmental factors may contribute to the initiation of the disease process. Among these factors are deficiencies of complement proteins of the classical pathway (C1q, C1r, C1s, C4, and C2)[1]. Such deficiencies also favor bacterial infections which may contribute to the initiation of the autoimmune process. A partial deficiency of C4 expression has also been reported in SLE[2]. Two forms of C4 are coded on chromosome 6-C4A and C4B-so that C4 synthesis is due to the expression of four genes (two for each). The two forms differ in their capacity to bind covalently to cell surfaces and proteins. Whereas C4B binds essentially to hydroxyl residues, C4A binds

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more efficiently to amino residues[3,4]. For example C4B is capable of inducing the lysis of erythrocytes five-to-ten-fold more efficiently than C4A, whereas C4A binds preferentially to immune complexes[5,6]. It was therefore of particular interest not only that SLE was associated with partial C4 deficiency, but also that C4A was the culprit for this association[2]. The presence of a C4AQ0 allele (lack of expression of one of the C4A gene products) is found in approximately 15 percent of normal individuals and in 30 percent of SLE patients. Even more striking is the observation that a double C4AQ0 (homozygous C4AQ0, i.e. no circulating C4A in plasma) is found in 11 percent of SLE patients and in only one percent of normal individuals[7-11].

We have recently begun to determine the C4 alleles in children with SLE and their families, and found a partial C4 deficiency in two patients studied because of their persistently low C4 levels.

Case Reports

Case 1

This 14-year-old girl presented with polyarthralgia, arthritis in the interphalangeal joints and a butterfly rash following a hepatitis A infection. She was the third child of the family, and her parents were distantly related.

Laboratory examinations were as follows: Hb 12.80 g/dl, white blood cell (WBC) 6400/mm^3, erythrocyte sedimentation rate 128 mm/hr, C3: 30 mg/dl, C4 < 5 mg/dl, C1q: 36 mg/dl (normal), C5: 11 mg/dl (normal), ANA:+, Anti DNA: 17 unit/ml (normal: 0-5). Urine examination was normal.

The child was diagnosed with SLE, and corticosteroid treatment was initiated at a dose of 2 mg/kg/day. At the end of six weeks, the patient was in clinical remission. The complement levels at the time were C3: 74 mg/dl, C4 < 5 mg/dl. The corticosteroid dose was lowered and hydroxychloroquine was instituted. Her C4 levels remained below 5 mg/dl although there was no activation of the disease for a year.

The C4 assays and HLA typing of the patient and the family were thus studied. The C4 functional assay (hemolytic) revealed a 28 percent function for C4. The patient as well as the father and one sister had C4AQ0 (Fig. 1). These three family members were the only ones with HLA-B8 antigen on a supratype of HLA-A1, B8, BfS, C4AQ0, B1,-DR4.

Case 2

This seven-year-old boy was diagnosed with SLE in 1987, when he presented with aphthous stomatitis, cutaneous lesions, Raynaud phenomenon and Coombs+ hemolytic anemia. The parents were first cousins.

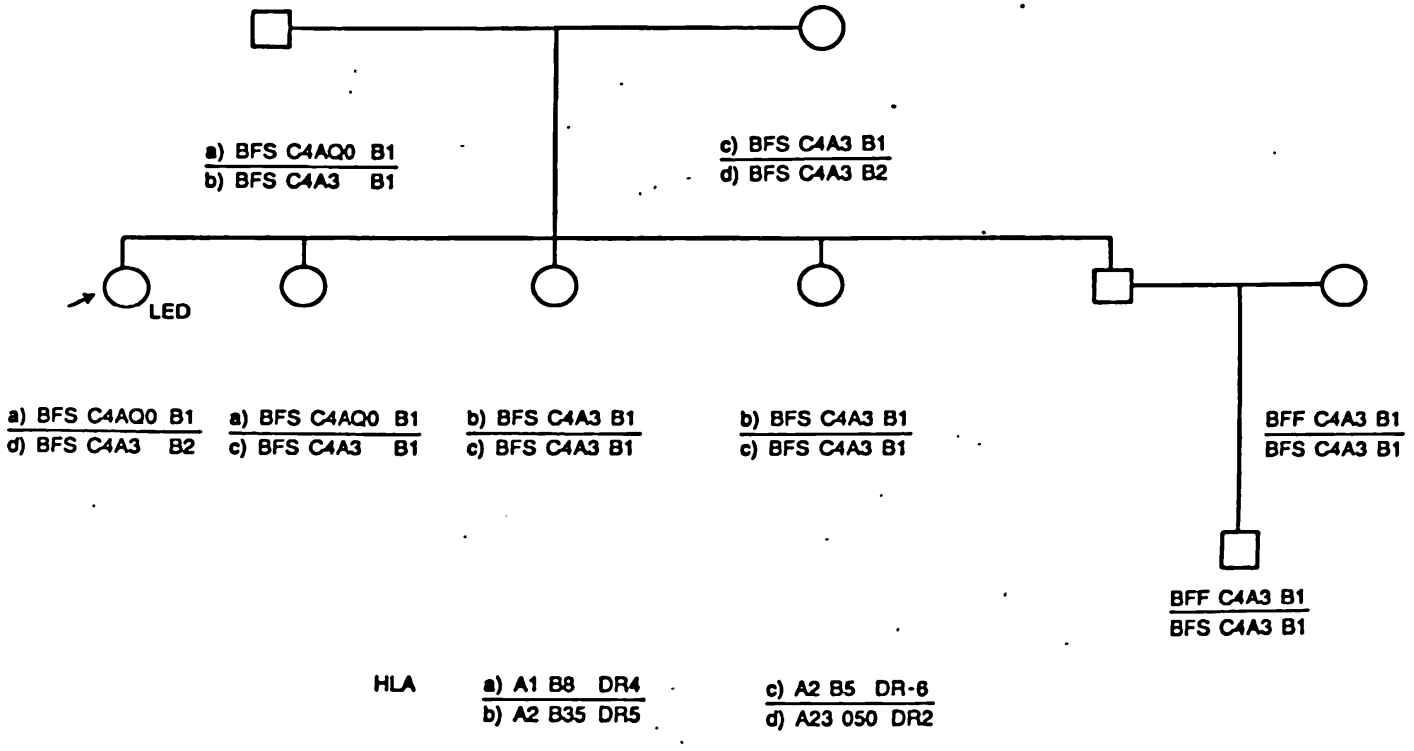

Fig. 1: The patient as well as the father and one sister had C4AQ0.

Laboratory studies revealed Hb 8.20 g/dl, WBC 3400/mm^3, sedimentation rate 22 mm/hr, C3: 48 mg/dl, C4: 8 mg/dl, ANA +, and Anti DNA: 48 unit/ml.

During the follow-up period, the patient developed cerebral involvement and showed a resistant disease course. He received oral and intravenous corticosteroids, and the disease activity was partially controlled after the addition of cyclophosphamide. During his five-year follow-up period, his C4 levels were consistently low although C3 reached normal levels a few times. Five years after the diagnosis he was admitted to the hospital with a secondary viral infection superimposed on his neutropenia and pulmonary edema. This time he was reevaluated because of his atypical facies, and his chromosomal analysis revealed him to be a mosaic Down syndrome. In spite of symptomatic treatment for his pulmonary edema and infection, he died a day after his hospitalization.

The C4 assays were performed and revealed a functional C4 level of 20 percent of normal. Null alleles were present at the C4A and C4B loci. HLA typing was as follows: A3, A23, B51 (5, w4), DRw15-(2, Qw1), DQw6 (Qw1).

Discussion

These two patients had partial C4 deficiencies and SLE. Christiansen et al.[12] have suggested a gene dose effect, starting with total C4 deficiency (C4AQ0, BQ0), which is associated in more than 90 percent of cases with an SLE-like

disease; i.e. total C4 deficiency appears to be associated almost invariably with the expression of autoimmunity and/or an immune complex disease. Double C4A null allele increases the likelihood of developing SLE approximately ten-fold, whereas the presence of only a single C4A null only doubles this likelihood[7-11]. In the young boy described here in whom two C4 gene products were lacking, SLE started before the age of ten, which is very rare.

The results of several series suggest that the association between C4 deficiencies and SLE is due to the lack of C4A or total C4 function[1,2]. However, a recent report provides evidence for the pre-dominant role of class I and II genes over C4, since the C4AQ0 allele was included in a haplotype which was itself a risk factor for SLE (HLA B9-C4AQ0-C4B1-DR3)[13]. This haplotype was also present in our first patient. Despite these latter epidemiological data, it is worth emphasizing that C4 function might be essential in many immune reactions including B-cell memory and the physiological clearance of bacteria, viruses, immune complexes and other substances such as DNA[1,14-17]. Thus complement activation by the classical pathway might be an essential mechanism which protects against the emergence of autoimmune or immune-complex diseases.

From the foregoing we might suggest that it is not the partial C4 deficiency which causes SLE, but an optimal C4 function which is a protective factor. This hypothesis is supported by the fact that 1 in 100 normal individuals are homozygous for C4AQ0. Without other factors predisposing to SLE, this partial C4 deficiency has no pathological consequences. There is a corollary to this hypothesis, namely that patients who are predisposed to develop SLE and who have a partial C4 deficiency will develop the disease earlier than those in whom C4 function is normal. The two children we studied had partial C4 deficiency in an environment (infections) which might be particularly efficient at triggering immune and possibly autoimmune responses. We plan now to compare in a prospective study the frequency of partial C4 deficiencies in childhood versus adult-onset SLE.

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