Complete Inherited Deficiency of the Fourth Complement Component in a Child with Systemic Lupus Erythematosus and His Disease-Free Brother in a North African Family

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Although null alleles of complement C4 genes (C4A*Q0 and C4B*Q0) are frequent in the normal population, the occurrence of two null alleles on the same chromosome is very rare and therefore complete C4 deficiency is exceptional. We describe a 16-year-old North African boy who presented with systemic lupus erythematosus with renal involvement and persistent undetectable classical pathway activity and C4 protein and hemolytic activity in plasma, with normal C3 levels. Similar complement abnormalities were observed in his healthy 12-year-old brother. Complete C4 deficiency was documented in the two brothers by investigation of the family and the lack of C4A and C4B bands upon phenotyping of C4. Southern blot analysis of the C4/CYP21 gene organization in the family indicated that the deficiency resulted from a deletion of the C4B/CYP21A genes associated with nonexpression of a C4A gene. The double-null haplotype was found to be associated with homozygous A2 B17 C2C BFF C4 AQ0 BQ0 DR7 HLA haplotype. Thus, similar C4 deficiencies with HLA identity may lead to different clinical presentations.

KEY WORDS: C4 deficiency; complement; systemic lupus erythematosus.

INTRODUCTION

The fourth component of human complement, C4, is a three-chain glycoprotein of M, 200 kDa that is essential to the function of the classical pathway of complement activation (1). Human C4 is usually encoded by two closely linked loci, C4A and C4B, located together with the genes coding for the cytochrome P450 steroid 21-hydroxylase (CYP21A and B) within the major histocompatibility class (MHC) III region on chromosome 6 (2, 3). The C4A and C4B isotypes differ by antigenicity, electrophoretic mobility, and hemolytic activity (4, 5). A large number of structural alleles of C4A and C4B has been defined by electrophoretic analysis of serum C4 proteins (6).

Null alleles of C4 genes, termed C4A*Q0 and C4B*Q0, are frequent in the normal population. The relative frequency of C4A*Q0 and C4B*Q0 in the Caucasian population is 0.126 and 0.138, respectively (7). A double-null haplotype, i.e., two null alleles on the same chromosome (C4AQ0BQ0 haplotype), is very rare so that complete deficiency is exceptional and occurs mostly in consanguineous families. Eighteen cases of complete inherited C4 deficiency have been described so far in the literature (reviewed in Ref. 7) (8).

In the present study, we report two brothers with complete C4 deficiency in a North African family. The propositus was a 16-year-old boy presenting with systemic lupus erythematosus (SLE) and renal involvement. One of his brothers who was also...
MATERIALS AND METHODS

Patients

The propositus (Ham.) was the first of four children born to consanguineous parents (calculated consanguineous factor of 1:32). The mother has no clinical history of disease. The father died of liver cancer. Both parents were born in Algeria. At the age of 6, Ham. presented with a malar rash exhibiting typical histological features of lupus upon lesional skin biopsy. The cutaneous lesions had disappeared with local steroid therapy. The boy was lost for follow-up until the age of 14, when he experienced three episodes of macroscopic hematuria. Clinical examination at that time revealed a butterfly lesion of the face with marked photosensitivity associated with asthenia, anorexia, and arthralgias. Blood pressure was 120/70 mm Hg. Laboratory evaluation showed the following: hemoglobin, 14 g/dl; white blood cell count, 9.2 x 10^9/L; lymphocytes, 3.4 x 10^9/L; platelets, 400 x 10^9/L; erythrocyte sedimentation rate, 17 mm/hr; a normal electrophoretic pattern of serum proteins— IgG, 1140 mg/dl (normal range, 640–1350); IgA 180, mg/dl (normal range, 70–310); and IgM, 160 mg/dl (normal range, 56–350); the presence of circulating immune complexes as measured using a solid-phase Clq-binding assay; the absence of antinuclear antibodies and anti-native DNA antibodies (as assessed by ELISA); and the presence of antibodies to Ro/SS-A as detected in a double-agar gel immunodiffusion using thymic extracts as source of antigens and positive reference sera (Clonatec, Paris, France). No antibodies to La/SS-B, Sm, RNP, or phospholipid and no circulating lupus anticoagulant were detected. Urinary analysis showed moderate proteinuria (1 g/24 hr) and microscopic hematuria (250,000 red cells/ml). Renal function was normal, with a creatinine clearance of 100 ml/min/1.73 m². A percutaneous renal biopsy showed the presence of focal proliferative glomerulonephritis with thickening of capillary walls and a wire loop appearance. Immunofluorescence examination revealed the presence of mesangial deposits of IgG and C1q but no deposits of C3. The boy was treated with intravenous pulses of methylprednisolone (3 x 750 mg) followed by oral prednisone (60 mg/day) and hydroxychloroquine (300 mg/day). Asthenia, anorexia, arthralgias, and hematuria disappeared. The cutaneous lesions improved and proteinuria decreased to 0.3 g/24 hr. After 1 month of treatment, prednisone was tapered to alternate doses. A second renal biopsy, performed after 15 months of treatment, demonstrated a decrease in endocapillary proliferation and immune deposits. After 2 years of follow-up, the boy received 15 mg of prednisone every second day. He presented no clinical symptoms; urinary and blood analysis were normal except for the presence of a mild proteinuria, 0.2 g/24 hr, and the persistence of anti-Ro/SS-A antibodies in the serum.

The mother (Fat.), the only sister (Ilh.) of the propositus, and his two brothers (Yas. and Abd.) were healthy upon clinical examination. Urinary analysis revealed no abnormality. No serum antinuclear or anti-ENA antibodies, including anti-Ro/SS-A antibodies, were found.

Complement Assays

Freshly drawn EDTA plasma was obtained from the propositus and his mother, sister, and two brothers. Measurement of CH50 activity and hemolytic assays for C4 and C2 were performed as described previously (9). Results were expressed as the percentage of mean values obtained with a reference plasma pool prepared from 100 healthy donors. The range of normal values was 100 ± 25% for CH50 and 100 ± 30% for hemolytic levels of C2 and C4. Plasma concentrations of C3, C4, B, and Cl-inh were measured by nephelometry (Beckman, Gagny, France). Normal concentrations ranged between 85 ± 20 and 24 ± 12 mg/dl for C3 and C4, respectively. Functional levels of Cl-inh were measured in the plasma of the propositus using a hemolytic assay (9).

HLA Typing

HLA-A, -B, -C, and -DR typings were carried out by standard lymphocyte microcytotoxicity and oligotyping techniques (10, 11).

C2, C4, and Factor B (BF) Protein Allotyping

BF typing was performed by high-voltage agarose electrophoresis and immunofixation using a polyclonal anti-factor B IgG (Atlantic Antibodies, Stillwater, OK) (12). The C2 polymorphism was analyzed by isoelectric focusing and immunoblotting using a specific polyclonal anti-C2 antisera (SeroTec, Oxford, UK) (13). C4 allotypes were detected in neuramin-