Lupus Erythematosus Associated With Genetically Determined Deficiency of the Second Component of the Complement

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Background: The gene deletion responsible for the type I human complement C2 deficiency was reported in 1992. The purpose of our study is to evaluate clinical and immunological characteristics of 11 patients with lupus erythematosus and type I C2 deficiency.

Observations: We observed 5 patients with a homozygous C2 deficiency and 6 with a heterozygous C2 deficiency. Eight patients had systemic lupus erythematosus, 2 had subacute cutaneous lupus erythematosus, and 1 had chronic lupus erythematosus. Photosensitivity was present in 73% of the patients, and 64% tested positive for anti-Ro (SSA) antibodies. Renal involvement that required immunosuppressive therapy was present in 54% of the patients. Ninety percent of the patients tested positive for antinuclear antibodies, and 54% tested positive for anti–double-stranded DNA antibodies. Phenotyping of the fourth component of the complement was performed in 82% of the patients and showed a C4A4B2 phenotype, which is suggestive for the type I C2 deficiency.

Conclusions: Most patients with lupus erythematosus associated with C2 type I deficiency are photosensitive, and this is probably related to the presence of anti-Ro (SSA) autoantibodies. The prognosis for those patients is not better than that for patients with lupus erythematosus in general.

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UPUS ERYTHEMATOSUS (LE) is a multifactorial systemic disease. Its genetic component has been suggested by familial aggregation and twin studies.1 Deficiencies in proteins of the complement system were among the first identified genetic risk factors. Indeed, deficiencies in early components of the complement system are significantly associated with LE.2-6 This has been particularly well established for C4 deficiencies, the prevalence of homozygous C4A deficiency being approximately 10 times higher in patients with LE than in normal controls.7,8

The complete deficiency of C2 is the most frequently occurring homozygous complement deficiency in humans.9-12 The molecular abnormality of the most common type of C2 deficiency, the C2 type I deficiency, was identified in 1992.13 This deficiency results from a 28–base pair (bp) gene deletion, which causes a premature termination codon and a lack of synthesis of the C2 protein.

Patients with LE associated with complement C4 or C2 deficiencies are said to have a better prognosis than individuals with LE without inherited complement deficiencies.4,5,9,10 Cutaneous and articular involvement is prominent, but pleuropericardial, neurologic, and renal involvement is absent or mild. Usually, patients with LE with complement deficiencies have low (or absent) antinuclear antibody titers.12,14,15 In contrast, the prevalence of anti-Ro (SSA) antibodies is reported to be much higher than in non–C2-deficient patients with LE.14-16 Most information on C2-deficient patients with LE was reported before the identification of the molecular abnormality responsible for the type I deficiency.17-24 The aim of this study is to assess clinical and biological characteristics as well as the prognosis of patients with LE with genetically determined deficiency of C2. To avoid specialty-related disease subsets, we designed this as a laboratory-based study including 72 subjects with a C2 deficiency determined by direct genomic analysis. Among the subjects, 11 with LE were observed in detail.

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PATIENTS AND METHODS

This is a retrospective study in which all patients with type I C2 deficiency diagnosed at the Immunology Laboratory of the Strasbourg University Hospital, Strasbourg, France, between 1997 and 1998 were included. In all patients, type I C2 deficiency was diagnosed by detection of a 28-bp deletion in the C2 gene after polymerase chain reaction (PCR) amplification. During this period, 234 blood samples were submitted to the laboratory for analyses.

POLYMERASE CHAIN REACTION C2

Genomic DNA was extracted from a whole-blood EDTA sample with a standard phenolchloroform procedure. Genomic DNA was then amplified by PCR using the following primer sets: 5’GCCTGGGCGTAAAATCCAAATCCA-3’ and 5’GACAGGAGGCCTCCTGCGAGCC-3’

The PCR products were electrophoretically analyzed (3% agarose Nusieve 3:1; FMC Bioproducts, Rockland, Me). The normal, wild-type C2 allele appeared as a 180-bp band, while the 28-bp deleted gene product was represented by a 152-bp band. Positive and negative controls were systematically comitted with each set of samples tested.13

PHENOTYPING OF FACTOR B AND C4; COMPLEMENT ASSAYS

Factor B and C4 allotypes were determined by high-voltage gel electrophoresis followed by immunofixation.25,26 We measured total hemolytic complement (CH50) by a standard procedure in serum samples. Serum concentrations of C3 and C4 antigens were determined by nephelometry (Beckmann, Gagny, France).

ANTINUCLEAR ANTIBODIES

Antinuclear antibodies were detected on Hep2 cells by indirect immunofluorescence. The presence of antibodies to extractable nuclear antigens was determined by a standard technique of double immunodiffusion (Ouchterlony). Anti-DNA antibodies were measured using a Farr assay or with an enzyme-linked immunosorbent assay.

A standardized questionnaire was sent to each physician in charge of a patient with a proven C2 deficiency to establish clinical and biological characteristics. The diagnosis of systemic LE (SLE) was based on American Rheumatism Association criteria.27 The diagnosis of subacute cutaneous LE (SCLE) was based on history and clinical course according to Sontheimer et al.28 The diagnosis of discoid LE (DLE) was established at a mean age of 35.5 years. Three patients had SLE (patients 1, 3, and 5); 1 patient (patient 4) had LE and homozygous C2 deficiency also had recurrent infections; 1 patient had SCLE and Sjögren syndrome; 1 patient had glomerulonephritis and deafness.

RESULTS

Two hundred thirty-four blood samples from French, German, Swiss, Hungarian, and Austrian patients were submitted to complement analysis during the reference period. The patients had been in the Departments of Internal Medicine, Rheumatology, Dermatology, Nephrology, Clinical Immunology, Gastroenterology, and Pediatrics. A C2 deficiency was diagnosed in 72 patients (50 women and 22 men). Fifty-six subjects had homozygous C2 deficiency and 16 had homozygous C2 deficiency. We obtained exhaustive and analyzable data from 47 of the 72 patients with C2 deficiency (Table 1). Eleven of these 47 had LE. Phenotyping of C4 was performed in 40 of these 47 subjects and showed the C4A4B2 phenotype, which is usually associated with C2 deficiency, in 85% of patients.

Five unrelated patients (1 man [patient 1] and 4 women [patients 2-5]) had LE and homozygous C2 deficiency (Table 2). Two of them also had recurrent infections (patient 1, meningitis; patient 2, pneumonia). The first symptoms related to LE appeared at a mean age of 28.5 years (age range, 15-63 years), and the diagnosis of LE was established at a mean age of 35.5 years. Three patients had SLE (patients 1, 3, and 5); 1 patient (patient 2) had SCLE; and 1 patient had disseminated DLE (patient 4). The patients with SCLE and DLE had no systemic involvement.

Skin findings were present for all patients. Four patients were photosensitive (patients 1, 2, 4, and 5); 2 had the typical malar-shaped butterfly rashes of systemic LE (patients 1 and 5); 1 had a photodistributed erythematous-squamous eruption that corresponded to SCLE (patient 2) (Figure 1); and 1 (patient 4) had widespread DLE of
the face, neck, trunk, hands, and lips (Figure 2 and Figure 3). Histological findings specific for LE were obtained in 3 of these 4 photosensitive patients. Patient 3 had purpura and ecchymoses related to an autoimmune thrombocytopenia. Patient 1 had Raynaud phenomenon.

Four patients had joint pain (patients 1, 3, 4, and 5), and 3 of them had arthritis (patients 3, 4, and 5); 2 had epilepsy (patients 3 and 4), which was considered related to LE in 1 (patient 3). One patient (patient 1) had World Health Organization (WHO) stage V diffuse membranous glomerulonephritis, which manifested as renal failure, proteinuria, and hematuria. This patient also had LE-related antiphospholipid antibody syndrome with postembolic lung fibrosis, ischemic cardiomyopathy, and livedo.

Four patients (patients 1, 2, 4, and 5) tested positive for antinuclear antibodies, and 2 had anti–double-stranded DNA (dsDNA) antibodies (patients 1 and 3). Four patients (patients 2, 3, 4, and 5) had antibodies directed against the extractable nuclear antigen Ro (SSA), but only patient 5 had antibodies directed against the La (SSB) antigen. One patient had antiphospholipid antibodies (patient 1); 1 had autoimmune pancytopenia (patient 3); and 3 had moderate leukopenia (patients 2, 4, and 5). All patients had decreased CH50 levels, which contrasted with normal C3 and C4 levels in 3 patients, while patients 4 and 5 had also decreased C4 levels. In all cases, C2 was undetectable. Patients 3 and 5 had an associated partial C4 deficiency. In 4 patients, C4 and HLA phenotyping were performed and gave the following results: C4A4A4B2B2 in 2 patients (patients 1 and 2), C4A4AQ0B2B2 in 1 patient (patient 3), and C4A3A4B2BQ0 in 1 patient (patient 5); A10A32B18B18BFSBFSDR2DR2,1 A25A25B18B18DR2DR2,1 A11A11B18B18BFSBFSDRB1DRB1.1

Patients with SCLE and DLE were treated exclusively with antimalarial agents and the cutaneous lesions resolved only partially. The 3 patients with SLE responded favorably to immunosuppressive therapy.

### Patients with LE Associated with Heterozygous C2 Deficiency

Six women had heterozygous C2 deficiency (Table 2): 5 had SLE, and 1 had SCLE and Sjögren syndrome (patient 11). Mean age of diagnosis was 27.5 years (age range, 11-67 years). Five patients had specific skin involvement (patients 6, 7, 8, 9, and 11); 2 had a butterfly rash of SLE (patients 6 and 9); 2 had SCLE in 1 patient (patient 3), and C4A3A4B2BQ0 in 1 patient (patient 5); A10A32B18B18BFSBFSDR2DR2 (1 patient), A25A25B18B18DR2DR2,1 A21A10B37B18DR2DR2,1 and A11A11B18B18BFSBFSDRB1DRB1.1

Patients with SCLE and DLE were treated exclusively with antimalarial agents and the cutaneous lesions resolved only partially. The 3 patients with SLE responded favorably to immunosuppressive therapy.

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**Table 2. Clinical Characteristics and Autoantibody Profiles of Patients With Lupus Erythematosus and C2 Deficiency**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>LE Subset</th>
<th>ANA</th>
<th>ANA Specificity</th>
<th>GN (WHO Stage)</th>
<th>Photosensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Homozygous deficiency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>SLE</td>
<td>1/640</td>
<td>ds-DNA</td>
<td>Yes (V)</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>SCLE</td>
<td>Absent</td>
<td>Ro</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>SLE</td>
<td>1/2000</td>
<td>ds-DNA, Ro</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>DLE</td>
<td>1/160</td>
<td>Ro</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>SLE</td>
<td>1/1280</td>
<td>Ro, La</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Heterozygous deficiency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>SLE</td>
<td>1/1000</td>
<td>ds-DNA</td>
<td>Yes (IV)</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>SLE + DLE</td>
<td>1/1000</td>
<td>ds-DNA, Ro</td>
<td>Yes (III)</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>SLE + SCLE</td>
<td>1/1280</td>
<td>Ro, La</td>
<td>Yes (IV)</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>SLE</td>
<td>1/1600</td>
<td>ds-DNA</td>
<td>Yes (IV)</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>SLE</td>
<td>1/1600</td>
<td>ds-DNA, Sm, RNP</td>
<td>Yes (IV)</td>
<td>NA</td>
</tr>
<tr>
<td>11</td>
<td>SCLE</td>
<td>1/1280</td>
<td>Ro, La</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

*LE indicates lupus erythematosus; ANA, antinuclear antibody; GN, glomerulonephritis; WHO, World Health Organization; SLE, systemic LE; dsDNA, double-stranded DNA; SCLE, subacute cutaneous LE; DLE, discoid LE; NA, not applicable; and RNP, ribonucleoprotein.*
livedo (patients 9 and 11), and 1 patient (patient 8) who had SLE and SCLE lesions also developed histologically proven rheumatoid nodules. Five patients (patients 6, 7, 8, 9, and 11) had joint pain, and 2 of them (patients 6 and 11) had recurrent attacks of inflammatory and swollen joints. Two patients (patients 9 and 11) had a sicca syndrome, and 1 (patient 11) had an authentic Sjögren syndrome, which evolved into a fatal systemic diffuse large cell B lymphoma. Five patients had renal involvement (patients 6, 7, 8, 9, and 10). Four patients had WHO stage IV diffuse glomerulonephritis, and 1 had WHO stage III focal segmental glomerulonephritis. One of those patients (patient 6) had renal failure, which evolved favorably under immunosuppressive therapy. One patient had polynuertis (patient 8); another, ischemic stroke (patient 11); and a third (patient 7) was subject to depression.

All patients tested positive for antinuclear antibodies, and 4 had anti-dsDNA antibodies (patients 6, 7, 8, and 9). One patient (patient 10) had anti-Sm antibodies. Three patients (patients 7, 8, and 11) had anti-Ro (SSA) antibodies; and 2 (patient 8 and 11), anti-La (SSB) antibodies. One patient had anti-RNP (ribonucleoprotein) antibodies (patient 10). For 1 patient (patient 9), we obtained no information about the presence of antibodies against extractable nuclear antigens. One patient (patient 11) had antiphospholipid antibodies; 1 (patient 8) had type III mixed cryoglobulinemia; 5 (patients 7, 8, 9, 10, and 11) had lymphopenia; 4 had anemia (patient 6, 8, 9, 11) (with a positive Coombs test finding in 1 case); and 1 (patient 11), moderate thrombopenia.

All patients had decreased, but still detectable, C2 levels. C3 and C4 levels were also decreased in 4 patients. A hemolytic C2 assay was performed in 3 patients (patients 6, 7, and 9) and showed decreased values. C4 phenotyping was performed in 5 patients (patients 7, 8, 9, 10, and 11) and showed the C4A4B2 phenotype in all cases. Three patients (patients 7, 8, and 9) had an associated C4A deficiency (C4A4AQ0) and 1 (patient 10) had an associated C4B deficiency (C4B2BQ0). Haplotyping for HLA was performed in 3 patients and showed the A1B18F5SDR2 haplotype.

All patients were treated with antimalarial agents, and cutaneous lesions resolved only partially. The 5 patients with SLE responded favorably to immunosuppressive therapy. The sixth patient died of her Sjögren syndrome–related systemic lymphoma.

**COMMENT**

This study shows that cutaneous findings, most notably photosensitivity, are prominent among patients with LE and C2 deficiency. This could be related to the frequent presence of anti-Ro (SSA) autoantibodies. The prognosis of patients with LE and C2 deficiency, however, is no better than the prognosis of those with LE in general, with severe renal involvement occurring in 54% of cases.
Although homozygous C2 deficiency is the most common complete deficiency of a complement system component in humans, it is still rare and affects approximately 0.01% of the individuals in the general population. Although homozygous C2 deficiency is the most common complete deficiency of a complement system component in humans, it is still rare and affects approximately 0.01% of the individuals in the general population.4,29,30 However, the prevalence of homozygous C2 deficiency is significantly higher in patients with LE, varying between 0.4% and 2%.5,12,29,31,32 Heterozygous C2 deficiencies occur in approximately 0.7% to 1% of individuals in the general population, and its prevalence in patients with LE is about 2.4% to 5.8%.29,31

This study concerns exclusively patients with LE and a C2 type I deficiency confirmed by direct genomic analysis. The patients in this study were from a group of patients who were diagnosed with C2 complement deficiencies in a reference laboratory. Therefore, patients were not disease-subset or specialty restricted. However, there was a bias in ascertaining these patients because the search of C2 deficiency was only performed in patients in whom a deficiency was suspected based on clinical or biological grounds. This explains the high percentage of C2 deficiencies among the samples tested and the high homozygous-heterozygous ratio. Furthermore, very few laboratories routinely perform the search for the C2 gene deletion, and this fact explains why the analyzed blood samples were collected from different European countries.

A comparison between C2-deficient patients with LE and a large cohort of unselected patients with LE is given in Table 3. Photosensitivity, SCLE lesions, and anti-Ro (SSA) antibodies are more frequent among C2-deficient patients.

### Table 3. Comparison* Between C2-Deficient Patients With LE and a Large Cohort of Unselected Patients With LE (33)

<table>
<thead>
<tr>
<th>Clinical or Biological Sign</th>
<th>C2-Deficient Patients</th>
<th>Unselected Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Photosensitivity</td>
<td>8 (73)</td>
<td>453 (45)</td>
</tr>
<tr>
<td>Malar rash</td>
<td>4 (36)</td>
<td>579 (58)</td>
</tr>
<tr>
<td>SCLE lesions</td>
<td>3 (27)</td>
<td>56 (6)</td>
</tr>
<tr>
<td>DLE lesions</td>
<td>2 (18)</td>
<td>104 (10)</td>
</tr>
<tr>
<td>Joint involvement</td>
<td>8 (73)</td>
<td>840 (84)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>6 (54)</td>
<td>393 (39)</td>
</tr>
<tr>
<td>Sicca syndrome</td>
<td>2 (18)</td>
<td>161 (16)</td>
</tr>
<tr>
<td>ANA</td>
<td>10 (91)</td>
<td>963 (96)</td>
</tr>
<tr>
<td>Anti-dsDNA antibodies</td>
<td>6 (54)</td>
<td>779 (78)</td>
</tr>
<tr>
<td>Anti-Ro (SSA) antibodies†</td>
<td>7 (64)</td>
<td>254 (25)</td>
</tr>
</tbody>
</table>

* All data are given as the number (percentage) of patients. LE indicates lupus erythematosus; SCLE, subacute cutaneous LE; DLE, discoid LE; ANA, antinuclear antibody; and dsDNA, double-stranded DNA.
†P = .01.

Photosensitivity was a prominent feature, affecting at least 73% of the patients, although this percentage might even be higher since the data were collected retrospectively. This photosensitivity is probably related to the presence of the anti-Ro (SSA) autoantibody in most patients. Indeed, a correlation between photosensitivity and the presence of anti-Ro (SSA) autoantibodies has already been established and it is known that UV radiation increases binding of Ro (SSA) autoantibodies on the surface of keratinocytes. It is notable that both C2- and C4-deficient patients with LE are photosensitive and test positive for anti-Ro autoantibodies. However, these characteristics might be related to the associated HLA A10B18FSDR2 haplotype, which was present in 6 of 7 patients tested, and not specifically to the C2 gene deletion.

Lupus erythematosus—specific cutaneous involvement was another prominent feature, present in 9 of 11 patients. Five patients had either DLE or SCLE. Involvement of hands or hands and feet was a noteworthy finding in these patients and difficult to treat. Involvement of hands has already been reported in C1q-deficient patients and it is a common finding in C4-deficient patients (D.M.L. personal observation, 1995). Thus, hand involvement seems to be a clinical sign suggestive of complement deficiency associated with LE. Other cutaneous findings have also been reported in C2-deficient patients with LE: diffuse maculopapular rash of SLE, diffuse nonscarring alopecia,24 buccal ulcerations,20 cheilitis,16 palmar petechias,24 angioedema,37 and LE panniculitis.30

All tested patients but 1 had antinuclear antibodies on Hep2 cells; they also often had a high titer of anti-dsDNA antibodies. This autoantibody profile, which is common in SLE, is unusual in C2-deficient patients with LE. Studies have described C2-deficient patients with low (or absent) antibody–native DNA titers.4,10,22,39 Also, 54% of the patients in our study had severe renal involvement requiring immunosuppressive therapy. The prognosis associated with the C2 deficiency–associated LE in this patient group seems no better than that for patients with LE in general.

This latter point is not in accord with previously reported data, where renal involvement occurred in only 23% of the more than 50 described C2-deficient patients with LE.4 Although the difference in percentage of patients with renal involvement compared with our study group does not reach significance (P = .08), most patients in the earlier reports had “mild” renal involvement (mostly WHO stage II or III glomerulonephritis), while patients in our study had more severe stage IV or V glomerulonephritis.

There are 2 possible reasons for this difference. (1) In our study, only patients with a C2 deficiency confirmed by direct genomic analysis were included, which was not possible in studies published before 1992. (2) Our patients were included on the basis of laboratory results, not clinical findings. Hence patients had LE with different initial complaints (eg, cutaneous LE, nephritis, and arthritis), whereas most published cases of C2 deficiency associated with LE were dermatological patients with SCLE or DLE.16,19,23,30,41,47 It is well known that the prognosis for patients with SCLE or DLE is better than that for patients with LE, regardless of the association with C2 deficiency. Earlier reports therefore reflected the better prognosis in the LE cases than in the cases specifically related to C2 deficiency. It is possible that complement deficiencies are more readily investigated in patients without systemic involvement, because low complement is more unusual in these patients than in patients with systemic symptoms and complement consumption. This applies especially to all patients investigated before 1992 when it was not possible to diagnose

*References 4, 10, 12, 16, 17, 19, 21-24, 37, 38, 40-42.
C2 deficiency in a patient in whom the complement cascade was activated. Therefore, the patient group of our study might better reflect the real prognosis for patients with C2 deficiency associated with LE, which seems no better than the prognosis of LE in general.

The major difference between homozygous and heterozygous C2-deficient subjects with LE was the presence of severe infections. Forty percent of the patients with homozygous C2 deficiency had infectious complications, while none of the patients with heterozygous C2 deficiency experienced infection. The prognosis related to LE in both patient groups seemed equivalent.

It is difficult to assess the exact role of the deficiency of the C2 component in the pathogenesis of LE. Indeed, although patients with LE and C2 deficiency are unique in regard to the prevalence of specific cutaneous involvement, photosensitivity, and presence of anti-Ro (SSA) antibodies, they have the same prognosis as patients with LE in general. It is possible that their particular characteristics do not result from the C2 deficiency but from the C2 deficiency–associated HLA haplotype.43,44 Furthermore, cases of C2-deficient LE are exceptional before puberty,45 suggesting that the C2 deficiency plays only a minor role in the pathogenesis of LE. Nevertheless, C2 deficiency might be directly implicated in the pathogenesis of LE by lowering immune complex clearance. Indeed, Davies et al45,46 showed that splenic uptake of immune complexes was complement dependent, and immune complex clearance was reduced in C2-deficient subjects with SLE. It has recently been suggested that early complement components could be important co-signal in the negative selection of autoreactive B cells.47 These components’ deficiency, therefore, would be responsible for the negative selection of autoreactive B cells. Furthermore, Steinsson et al48 and Hudson-Peacock et al49 showed that SLE complicating C2 deficiency could be successfully treated with fresh frozen plasma. It is therefore tempting to postulate that persistence of autoantigens as a result of impaired clearance in the reticuloendothelial system might result in the presentation of antigen to “nonprofessional” antigen–presenting cells, resulting in an abnormal cellular or humoral response. However, this has not been proven.

In summary, in this study we showed that patients with LE and C2 type I deficiency are often photosensitive and have antibodies directed against the Ro (SSA) autoantigen. The prognosis for these patients is the same as the prognosis for those with LE in general, depending on renal involvement. Patients with homozygous C2 deficiency are prone to serious and recurrent infections.

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