

Familial Discoid Lupus erythematosus Associated with Heterozygous C4 Deficiency

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Low levels of the fourth component of complement (C4) were found functionally and immunochemically in two sisters (17 and 22 years of age) suffering both from discoid lupus erythematosus. C4-typing of the family revealed that the two sisters and the mother had only two, and the father three of the four genes coding for C4 expressed. All carried the null allele C4B*QO. This observation adds to the increasing evidence that not only complete but also partial genetic complement deficiencies may predispose to lupus erythematosus. *Key words: Lupus erythematosus: Genetic risk factors; C4 deficiency.* (Received June 7, 1984.)

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Hereditary complement (C) deficiencies have been described for all components of the classical pathway activation (for review see 1). Their frequent association with systemic (SLE) and discoid lupus erythematosus (DLE) or lupus-like syndromes is now well established (2, 3). The complete absence of C4 has first been reported in an 18-year-old girl with SLE (4). In a further communication (5), the mother of two C4 deficient children with SLE, an obligate heterozygote, was found to have DLE. Recently, it has been postulated on the basis of 1730 patients studied, that a partial genetic deficiency of C4 is related to dermatologic diseases, especially DLE and urticaria/angioedema (6).

We report here on a family with heterozygous C4 deficiency, two members of which have DLE.

CASE REPORTS

The proband (M. M.), an 18-year-old girl, presented with an erythematous, scaly and partially atrophic "butterfly" eruption. Similar lesions were noted on the back of her fingers including the periungual areas. A biopsy of lesional skin was consistent with the diagnosis of DLE. Direct immunofluorescence showed deposits of IgM, C1q and C3 at the dermo-epidermal junction. ANA and anti-DNA-antibodies were negative. There were no signs of systemic involvement.

C determinations revealed low normal total hemolytic C (CH50). C4 was markedly reduced functionally (15% of normal) and immunochemically (50% of normal), as was the hemolytic activity of C2 (Table I). Hemolytic C1 was normal. The 23-year-old sister (B. M.) had DLE clinically (erythematous-squamous lesions on the face and back of fingers) and histologically. Interestingly, she complained about a pronounced sensitivity to cold on her hands and feet, a sign which has already been noted in individuals with homozygous C4 deficiency (7). ANA were positive (1:160) but anti-DNA-antibodies were within normal limits. Her complement status was comparable to her sister's with a still more significant reduction of functional and immunochemical C4.

The 22-year-old brother could not be examined but was said to be normal.

The 45-year-old mother (I. M.) and the 47-year-old father (K. M.) had no history of dermatological disease and were found to be free of skin lesions. C values were within normal limits with the exception of very low C4 levels and a low hemolytic C2 in the father (Table I).

C4 phenotyping was performed in the parents and the two sisters according to (8). All carried the null allele C4B*QO. In addition, the mother exhibited the null allele C4A*QO and the two sisters another C4B*QO (Fig. 1).

Analysis of histocompatibility antigens revealed that the sisters had the same haplotype HLA

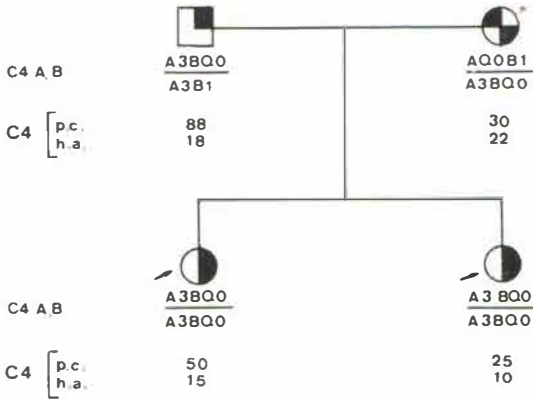


Fig. 1. Pedigree of the family M.; C4A,B allotypes and C4 levels (C4 p.c. = protein concentration, C4 h.a. = hemolytic activity). The levels are expressed as percentages of a pool of normal sera. Null alleles are shown as blackened quadrants. ↗ = affected with DLE.

A₃A₁₁Bw₄₄Bw₅₁Cw₂Dr₂Dr₄. The mother had HLA A₂A₁₁Bw₅₁Cw₁Dr₄Dr₇ and the father HLA A₃B₂₇Bw₄₄Cw₂Dr₁Dr₂.

DISCUSSION

Complement (C) deficiencies have been identified among the genetic risk factors for systemic lupus erythematosus (SLE) (9, 10). Furthermore, it becomes increasingly clear, that not only complete but also partial C deficiencies may predispose to lupus erythematosus, especially the cutaneous (discoïd) form (DLE). Thus, low levels of C components (mainly C4 and C2) in lupus diseases may be due to genetically determined defective synthesis and not necessarily to immune complex-induced classical C activation and C consumption. It appears, however, that the majority of individuals with a heterozygous C defect remains free of disease. The study of 204 heterozygous C2 deficient individuals revealed that only 16% suffered from an autoimmune disorder, predominantly SLE (11).

Complete absence of C4 seems to be an extremely rare event. However, partial defects of C4, represented by the null (silent) alleles C4A*QO and C4B*QO, are more common and have been detected in a high percentage in SLE patients (12, 9). In the family reported here the parents and the two sisters affected with DLE, were carriers of C4B*QO. The mother had also C4A*QO and the sisters were homozygous for C4B*QO (Fig. 1). Interestingly, all family members deficient only at the C4B locus had low functional C2 titers. From our findings it cannot be decided whether we deal with two associated genetic

Table I. Total complement (CH50) and complement components C4, C2 and C3 in family M.

h.a. = hemolytic activity, p.c. = protein concentration. Hemolytic C1 and C1-inactivator (p.c. and h.a.) were normal. Values are expressed as percentage of the concentrations in a normal serum pool

	CH50	C4 p.c.	C4 h.a.	C2 h.a.	C3 p.c.
Proband M. M.					
DLE	83	50	15	13	94
Sister B. M.					
DLE	34	25	10	11	62
Mother I. M.	74	30	22	95	86
Father K. M.	110	88	18	23	104

defects or an alteration of the C2 function in the classical pathway convertase by the C4B product. Further family studies are necessary to elucidate the contribution of partial C defects to the pathogenesis of lupus erythematosus.

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