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A Case of Selective C_{1q} Deficiency

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Most of the deficiencies of the complement system studied until recently appeared to be due to genetically determined inborn errors of metabolism and they were often associated with serious diseases.[1] Within the past few years several unusual complement abnormalities have been reported during the course of systemic lupus erythematosus (SLE) and other collagen diseases.[2-14] C_{1q}, a subcomponent of the first component of complement has been observed to be deficient in patients with severe combined immunodeficiency,[15-17] to be decreased in hypogammaglobulinemia, myeloma and systemic lupus erythematosus,[18] and in lupus like syndromes associated with various cutaneous manifestations or vasculitis.[19-22]

Case Report

A 10 year old white male (H. I. I.) was admitted to the Hacettepe Children's Hospital on April 12, 1977 with complaints of fever, vomiting, convulsions and skin lesions. Ten days prior to admission he developed cough and fever. He began to vomit for the pat 3 days and had a generalized convulsion which was followed by drowsiness.

Physical examination revealed a thin underdeveloped, semicomatose boy, with a temperature of 38°C. He had hyperkeratotic, desquamative skin lesions which also involved the scalp. The skin over the abdomen and

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extremities had some hyperpigmented areas in sizes of 2x2 cm. There was peeling in the palmar and plantar areas. The eyes appeared to be exophathalmic with bilateral leukoma. There were scars over the eyebrows. The right ear drum was perforated and the ear canal contained pus. The oral mucosa and soft palate were covered with aphtous lesions and monilia. The finger and toe nails were deformed and seem to have monilia-like lesions.

The Kernig and Brudzinski signs were positive. A lumbar puncture showed a cloudy cerebrospinal fluid (CSF) with 1100 polymorphonuclear (PMN) cells/µl. Its protein and sugar contents were 252 mg/dl and 50 mg/dl respectively. The blood sugar was 100 mg/dl. The CSF cultures yielded no growth. The patient was treated with penicillin and chloramphenicol as a case of bacterial meningitis and he responded to this therapy with return of CSF and clinical findings to normal at the end of second week.

Laboratory studies including BUN, uric acid, creatinine, creatinine clearance, serum electrolytes, SGOT, SGPT, thymol turbidity, total lipids, cholesterol, zinc, fetal hemoglobin, ACTH stimulation, ASO, CRP alkaline phosphatase, quantitative NBT test, blood and urine aminoacids showed normal values. The LE cell, latex, direct Coombs tests, HBsAg, antibody for HBsAg, cryoglobulins and coproporphirine in urine were negative. Urinalysis showed negative to ++ albuminuria with an acid pH and specific gravity of 1006 to 1022. There were 8-10 WBC and a few RBC's in the initial urinary sediment which disappeared in the subsequent specimes. The hemoglobin varied between 4.5 and 13.2 mg/dl. The WBC varied between 4000 and 32400/µl with a predominance of PMN. Absolute lymphocyte count was 880 - 4900/µl. The serum calcium was between 7.4 and 8.8 mg/dl and the serum phosphorus varied between 2.7 and 5.7 mg/dl. Total protein and albumin varied from 5.2 to 6.8 gm/dl, and from 1.8 to 3 gm/dl. Serum electrophoresis showed the following values: albumin 39 %, alpha-1 globulin 3 %, alpha-2 globulin 18 %, beta-globulin 18 % and gammaglobulin 22 %. Immunological studies showed normal serum immunoglobulins (IgG 935 mg/dl, IgM 162 mg/dl, IgA 210 mg/dl, β_1 C 85 mg/dl). His blood group was B, Rh positive, Anti-A titer was 1/128. He gave a positive response to PHA at skin testing. The skin test response to other antigens (candida, SKSD, mumps and PPD) was negative. His lymphocytes showed a normal blastic transformation response to the stimulation with PHA, candida and allogeneic lymphocytes. The response to SKSD was low. His E rosettes were low (35 %) on two occasions (The values for the controls were 64 % and 68 %). Auto-antibody studies were negative for antinuclear antibody,

antireticulin, mitochondrial and smooth muscle antibodies. A skin and muscle biopsy was interpreted as chronic dermatitis and normal appearing muscle. Examination of the skin did not show staining with fluorescinated monospecific anti-serum for IgA or IgM. But with anti IgG, the upper dermis had much diffuse the lower dermis had moderate degree of staining. The basal layers of the epidermis showed granular staining with anti-β_1C. There was also strong staining with anti-β_1C on the walls of the blood vessels. Because of reduced cellular immunity (negative skin test responses, low E rosettes, low in vitro response to SKSD) and these peculiar skin lesions, an underlying collagen disease was suspected but unproven by the above described laboratory tests. The CH_{50} test showed no detectable hemolytic activity. Therefore the serum was analysed for the individual complement components. With the Mancini technique C3 was found to be normal with 85 mg/dl. All complement components tested were found to be within the normal range except C_1. The C_1 titers of the mother and the brother were lower than normal; they both had normal CH_{50} activity (Table I).

The absence of the C_1 activity in the patient serum was found to be due to the lack of the C_1 subcomponent C_{1q}. Immunochemically, C_{1s} was detectable as in control sera, but no C_{1q} was found confirming the results of the functional tests (Figure 1). Because of progressive skin lesions a plasmaphoresis was performed for three successive days by giving 15 ml/kg of plasma each day. The skin lesions improved following the plasma administration; but they returned 10 days later. As is seen in table-1, the CH_{50} values became normal 1.5 and 4 hours after plasma infusions, however, the C_1 titers were still low.

Addition of highly purified human C_{1q} to the patient serum restored the C_1 activity indicating the presence of the two other C_1 subcomponents, C_{1r} and C_{1s}. The titers of C_{1r} and C_{1s} were found to be in the normal range as compared to normal human serum. Titration of highly purified C_{1q} with patient serum as a source of C_{1r} and C_{1s} resulted in a linear dose response curve (Figure 2).

Comment

In this communication a case of selective C_{1q} deficiency associated with recurrent skin lesions and infections is described. The activies of the two other C_1 subcomponents C_{1r} and C_{1s} were found to be in he normal range. Addition of highly purified C_{1q} restored the hemolytic C_1 activity. The administration of fresh frozen plasma alleviated the skin lesions temporarily; during this time the CH_{50} values were found to be normal although the Cl titer was about 100 times lower than normal.

TABLE I

HEMOLYTIC TITERS OF COMPLEMENT COMPONENTS IN SERUM SAMPLES OF PATIENT H. I. I., HIS MOTHER AND BROTHER IN COMPARISON TO NORMAL HUMAN SERUM (NHS)[a]

	Patient							
	24.5.1977	31.5.1977	20.6.1977	1,5 hours after Plasma	4 hours after Plasma	Mother	Borther	NHS
CH50 (U/ml)	0	0	0	35.0	34.4	28.3	37.3	37.5
C1 eff. mol./ml x 10^{13}	0	0	0	6.4 x 10^{11}	2.2 x 10^{11}	1.2	1.4	2.0
C4 eff. mol./ml x 10^{13}	1.2	1.3	1.0					0.7
C2 eff. mol./ml x 10^{11}	7.8	7.7	6.5					2.7
C3 eff. mol./ml x 10^{12}	2.7	2.2	2.4					2.2
C5 eff. mol./ml x 10^{13}	1.4	0.9	0.9					1.1
C6 eff. mol./ml x 10^{12}	4.2	4.6	4.5					4.0
C7 eff. mol./ml x 10^{12}	6.2	6.7	7.0					3.5
C8 eff. mol./ml x 10^{12}	5.7	7.0	4.5					6.0
C9 eff. mol./ml x 10^{12}	3.1	3.7	4.4					1.2

a CH50 assay and molecular titrations of C1, C4 and C2 were performed according to Rapp and Borsos.[24] The results of the titrations were expressed as CH50 units/ml or effective molecules/ml (eff. mol./ml), respectively. Functional assays of the late-acting components were performed as described by Nelson et al.[25] in the modification recommended by Cordis Corporation.

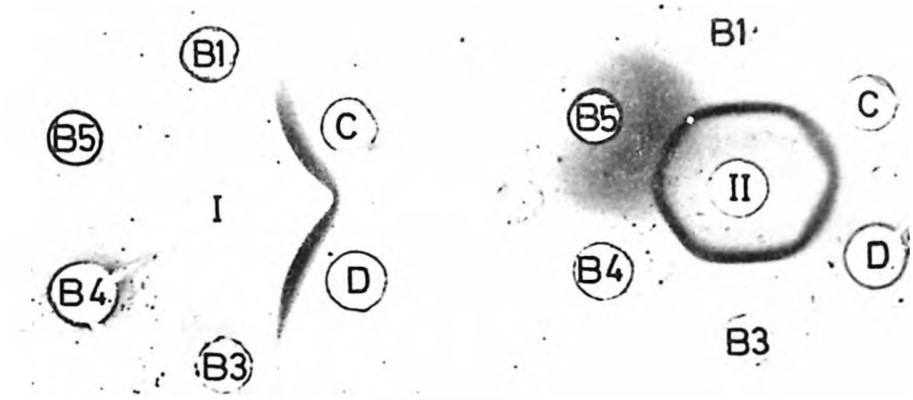

Figure 1

Immunodiffusion of serum of H. I. I. (B), mother of H. I. I. (C) and brother of H. I. I. (D) against an antiserum to human C1q (I) and an antiserum to human Cls (II). B1: H. I. I. 24.5. 1977; B3: H. I. I. 20.6. 1977; B4: H. I. I., 1.5 hours after plasma infusion; B5: H. I. I., 4 hours after plasma infusion.

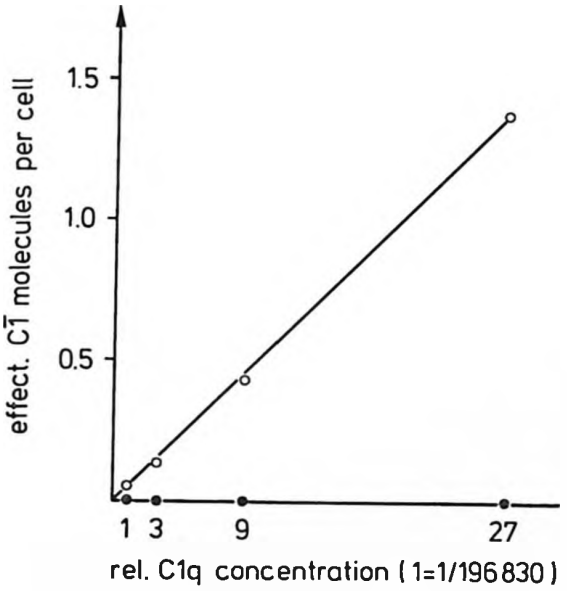

Figure 2

Dose response curve of highly purified Clq with H. I. I. serum as a source of Clr and Cls. EAClq4 were prepared by incubation EAC4 with different concentrations of Clq for 20 min. at 30°C in veronal buffered saline containing sucrose, Mg++–, Ca++–ions and gelatin (VBS-S; pH7.3; $\mu = 0.06$); afterwards the cells were washed and incubated with H. I. I. serum (1: 100 diluted in VBS-S) for 10 min. at 30°C. After washing, the formed EAC14 cells were lysed by successive addition of C2 and C-EDTA.

o—o EAClq4 + H. I. I. serum; .—.EAC4 + H. I. I. serum as control.

So far the published cases of C_{1q} deficiencies were either associated with severe combined immunodeficiency in infants[15-17] or in lupus erythematosus like syndromes associated with varieties of skin lesions or vasculitis.[19-22] C_{1q} levels were also found to be decreased in myeloma, adult common variable hypogommaglobulinemia and in agammaglobulinemic subjects.[18, 23]

In the presented case the lack of C_{1q} protein and C_{1q} activity can not be explained by hypogammaglobulinemia since the levels of IgG, IgM and IgA were found to be normal; an antigen antibody complex interaction with the components of the classical pathway of complement could be ruled out since C_{1r}, C_{1s}, C4 and C2 were found in the normal range. It was not possible to demonstrate systemic lupus erythematosus or other collagen diseases by the laboratory tests performed. All this data support the interpretation of a special case of a selective C_{1q} deficiency which is not described yet. Since the mother and the father are genetically related (second cousins) a hereditary deficiency of the C_1 subcomponent C_{1q} can not be ruled out; this possibility is presently under investigation.

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