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Correlation of disease activity with circulating immune complexes (C_{1Q}bA) and complement breakdown products (C_{3D}) in patients with systemic lupus erythematosus

A prospective study

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Summary. Most biologic effects of immune complexes are mediated through the activation of the complement system. The relationship between lupus disease activity and the presence of C_3 breakdown products (C_{3d}) and circulating immune complexes (CIC) as demonstrated with the C_{1q} binding assay (C_{1q}bA), was evaluated. Nearly all 13 systemic lupus erythematosus (SLE) patients had a stable disease course in this prospective study, nevertheless, in each patient the profiles of the serologic parameters were quite different. Despite the small number of investigated patients (13), it is concluded that irrespective of the disease activity, the serologic parameters could be either positive or negative. No relationship could be obtained between disease activity and the presence of C_{3d} and/or CIC. Nor was there any evidence that the presence of CIC would indicate increased levels of C_3 breakdown products (C_{3d}). This observation argues against a pathogenetic significance of CIC detected by the C_{1q}bA in SLE. In conclusion, the supposed link between the presence of CIC, consumption and activation of the complement system, and the activity of SLE needs further study.

Key words: Systemic lupus erythematosus – C_3 breakdown products – C_{3d} – Circulating immune complexes – C_{1q} binding assay (C_{1q}bA)

Introduction

The role of immune complexes in the pathogenesis of vasculitis in both man and animals is recognised. This conclusion is based on the detection of immune complexes in the circulation of patients with systemic vascular diseases [1–3], and the demonstration of antibodies, antigens, and complement components within the lesions [4, 5]. Systemic lupus erythematosus (SLE) is considered to be a prototype of an immune complex disease. Evidence for this is due to the presence of circulating DNA [6, 7]; antibodies to DNA [7]; immune complexes composed of DNA and anti-DNA antibodies [8, 9]; usually decreased serum complement components [10, 11]; and deposition of DNA, anti-DNA, and complement components in tissues [12, 13]. As well as the anti-dsDNA–DNA immune complexes, using a variety of methods for detecting circulating immune complexes, the existence of other kinds of immune complexes in SLE is demonstrated. In these studies it is shown that the detection of CIC is quite specific for SLE; correlations with disease activity were, however, inconsistent, depending on the method used for detecting CIC [14, 15]. Demonstration of CIC in patients will not always prove their pathogenic role in the disease. Most of the biologic effects of CIC will be mediated through the activation of the complement system. Activaprospective longitudinal manner between the complement breakdown products. By studying the relationship in a prospective langitudinal manner between the complement profiles (C_{1q} and C_3), CIC (C_{1q} binding activity), C_3 breakdown products (C_{3d}), and the disease activity in SLE patients, we tried to determine the role and maybe the pathogenic significance of the C_{1q}-binding immune complexes and C_3 breakdown products.

Materials and methods

Patients. Thirteen patients (10 women, 3 men, aged 30–79 years) fulfilling four or more of the American Rheumatism Association criteria for the classification of SLE [16] were followed at the Department of Rheumatology of the Dr. Daniel den Hoed Clinic, Rotterdam, for 10 to 46 months. Blood samples (sera and plasma) from these patients were usually obtained at 6 week intervals. After coagulation and centrifugation the sera were stored at –70 °C prior to determination of CIC, C_{3d}, C_{1q}, C_3, and anti-dsDNA. Disease activity was recorded by one of us (AJGS) without knowledge of the serologic parameters. Prior to initiating the study, criteria were established for scoring disease activity. On standard clinical record sheets signs of disease activity, medication dosages, indication for dosage alterations and routine clinical laboratory results were recorded. During the study neither physician had knowledge of any of the results of the special serologic tests.

Determination of clinical score. Disease activity was divided into minor and major symptoms as described earlier [17, 18]; to major symptoms 3 points were given, to minor symptoms 1 point

(Table 1) according to the method of Hurd et al. [19]. Because of the prospective character of this study, the level of anti-dsDNA or levels of the complement components made no contribution to the disease score. All scores were based on manifestations present at the time the blood sample was drawn.

Correlations between the presence of manifestations of SLE and serologic results were determined by analysis of coincident data. Special attention was paid to changes in disease activity score with changes in the serologic data (C_{1q}bA, C_{3d}, anti-dsDNA, C_{1q}, and C_3).

Determination of anti-dsDNA. Anti-dsDNA was determined by the Fass assay modified as described by Aarden [20]. All sera were studied until DNA binding was about 30% of the added DNA. Anti-dsDNA activity is expressed in terms of units per ml. One unit of anti-dsDNA is defined as the amount of anti-dsDNA that precipitated 30% of the added DNA.

Measurement of C_{3d}, immune complexes, C_{1q}, and C_3. Plasma levels of C_{3d} were determined according to the method of Perrin et al. [21]. In 45 normal controls the mean value (±2SD) for C_{3d} was 1.25–7.75 μg/ml. Circulating immune complexes were detected using the C_{1q} binding assay according to the method of Zubler et al. [22]. In a group of 98 healthy blood donors the upper limit was (mean+2SD) 7% C_{1q} binding. The C_{1q} and C_3 levels were measured by radial immunodiffusion with anti-C_{1q} and anti-C_{3c} antisera and expressed as a percentage of the human serum pool of 250 blood donors. The normal range of C_{1q} amounted to 69–128% (mean±2SD) and C_3 66–124% (mean±2SD).

Results

Patient characteristics

In this follow-up period (Table 2) two patients (6 and 9) were studied in an active stage of their disease (disease score 4), and two patients (3 and 5) showed no signs of activity during the follow-up. Most patients had arthritis, c.q. arthralgia, and/or skin involvement. The two patients with a disease activity score of 4 had arthritis, fever, skin involvement and hematologic abnormalities. Clear changes in the anti-dsDNA course were only observed in patients 7, 8, 9, and 11. During the whole follow-up period the SLE patients had a stable disease course.

As shown in Table 2 no clear relationship could be demonstrated between the level of C_3 and the presence of a positive C_{1q}bA or C_{3d}, or vice versa. In 41 sera samples elevated C_{3d} values were found, and only in two sera decreased C_3 levels were detected. In 17 of these 41 sera the C_{1q}bA was positive (41%). Of the remaining 144 sera, the C_3 levels in 123 sera were normal and in 55 out of the 144 sera the C_{1q}bA was positive (38%). This demonstrates the lack of correlation between these three serologic parameters (C_3, C_{3d}, and C_{1q}bA).

In Table 3 the relationship between the disease activity score and the presence of C_{3d} in the circulation and/or a

Table 1. Clinical activity score. All cases in which the symptoms were explained by other causes than SLE were excluded

One point minor symptoms	Three points major symptoms
Polyarthralgia, arthritis	Serositis
Fever	Neurologic signs
Skin rash and active cutaneous lesions	Renal involvement
Anemia (< 7 mMol/l)	
Leucocytopenia (< 3 × 10⁹/l)	
Thrombocytopenia (< 100 × 10⁹/l)	

Table 3. Disease activity in relation to elevated levels in C_{3d} or a positive C_{1q}bA

Disease activity score	Number of patients	Patients positive for		
		C_{3d}	C_{1q}bA	$C_{3d}+C_{1q}$bA
0	2	1	2	1
1	7	3	4	1
2	2	–	1	–
3	–	–	–	–
4	2	1	2	1

Table 2. Relationship between disease activity score with the serologic parameters (anti-dsDNA, C_{1q}, C_{3d} and C_{1q}bA) in the different SLE patients during the observation period

Patient nos.	Follow-up duration (months)	Disease activity score	Number of blood samples examined	Number of blood samples positive for			Amount of sera with anti-dsDNA levels (units/ml)			Amount of sera with decreased levels	
				C_{1q}bA	C_{3d}	C_{1q}bA+C_{3d}	< 20	20–50	> 50	C_{1q} < 69%	C_3 < 66%
1. Lan	30	1	18	0	2	0	18	0	0	0	0
2. Boe	12	1	11	0	11	0	11	0	0	0	0
3. Kui	42	0	11	5	5	4	11	0	0	0	0
4. Sla	32	1	9	6	0	0	0	1	8	0	0
5. Ope	8	0	8	8	8	0	8	0	0	0	0
6. Hoe	16	4 → 0	9	4	0	0	9	0	0	0	0
7. Kwa	13	1	9	8	8	8	8	1	0	1	0
8. Kru	24	2	18	18	1	1	1	7	10	0	7
9. Lue	13	4 → 2	27	10	13	4	18	4	5	0	0
10. Jan	36	1	19	0	0	0	19	0	0	0	0
11. Gro	25	2	29	0	1	0	6	8	15	1	16
12. Sch	20	1	11	11	0	0	11	0	0	0	0
13. Wel	10	1	6	2	0	0	6	0	0	0	0

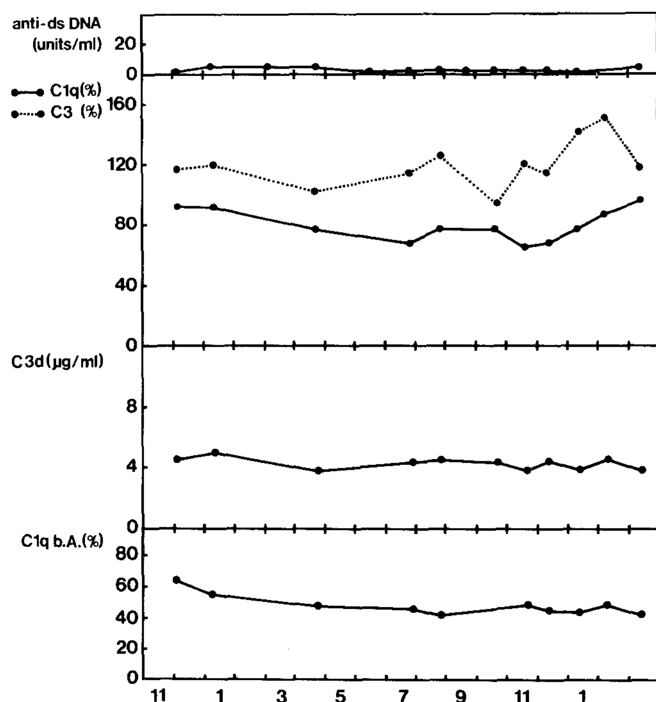

Fig. 1. The profiles of the serologic parameters (anti-dsDNA, C_{1q}, C_3, C_{3d}, and $C_{1q}bA$) in Patient 12, a woman born in 1950. The first manifestation of SLE developed in 1968; at that time she complained of exanthema and polyarthralgia. In 1972 exacerbation with signs of renal involvement (proteinuria), thrombocytopenia, and leukocytopenia was observed. From the end of 1978 she was followed, the only clinical manifestation of her disease was slightly changing skin rashes. In this observation period she took 5 mg prednisolone/day

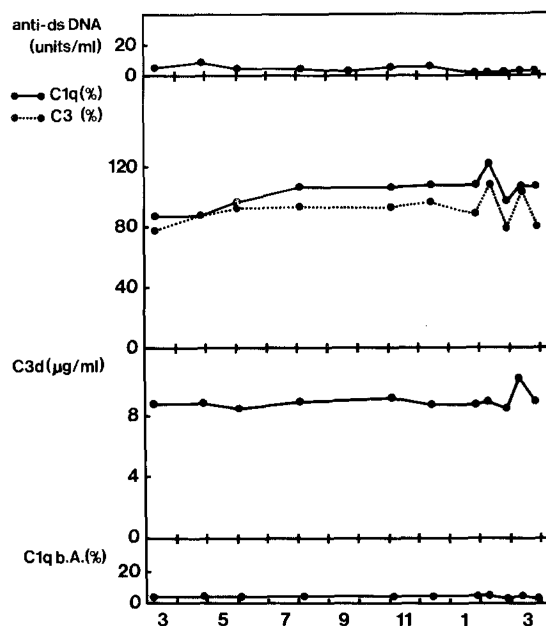

Fig. 2. The profiles of the serologic parameters (anti-dsDNA, C_{1q}, C_3, C_{3d}, and $C_{1q}bA$) in Patient 2, a woman born in 1946. In 1977 she was admitted to the hospital for the first time with increasing complaints of polyarthralgia, thrombocytopenia, and a myelitis transversus. Laboratory examinations revealed a positive lupus erythematosus cell preparation and a false positive lues serology. From that time on she had only periods of polyarthralgia or skin rashes. The prednisolone doses were decreased and changed to Plaquenil. In the observation period she had varying periods of only skin rashes

Table 4. Raised levels of C_{3d} and/or a positive $C_{1q}bA$ positive in relation to the anti-dsDNA levels

Anti-dsDNA levels (units/ml)	Number of sera	Number of sera positive for		
		C_{3d}	$C_{1q}bA$	$C_{3d}+C_{1q}bA$
	nos			
<20	126	34 (26%)	45 (36%)	14 (11%)
20–50	21	4 (19%)	8 (38%)	1 (5%)
>50	38	3 (8%)	19 (50%)	2 (5%)

positive $C_{1q}bA$ is shown. Overall no clear relationship could be seen. For example, two patients with a disease activity score of 0, both had a positive $C_{1q}bA$; as did the two patients with a disease activity score of 4.

In trying to find a correlation between the anti-dsDNA levels and the $C_{1q}bA$ and/or C_{3d} levels, the 185 investigated sera samples were grouped according to their anti-dsDNA levels (Table 4). However, the majority of sera had an anti-dsDNA level of less than 20 units, but 26% of the sera had C_{3d} and in 36% a positive $C_{1q}bA$ was detected. In contrast the 38 sera with an anti-dsDNA level of more than 50 units, in 8% of the sera C_{3d} was elevated and in 50% a positive $C_{1q}bA$ was found.

Correlations between longitudinal serologic measurements and disease activity

Taking the patients together no clear correlation exists between the clinical course of the disease and the serologic parameters (C_{3d} and $C_{1q}bA$). Two contrasting follow-up profiles are shown in Figs. 1 and 2. Both patients had nearly the same manifestation of the disease (skin rashes), however, Patient 12 had a constant elevated $C_{1q}bA$, normal complement profile, and C_{3d}. Patient 2 had a negative $C_{1q}bA$, normal complement profile (C_{1q} and C_3), but increased levels of C_{3d}. Another longitudinal course is shown in Fig. 3. In the period of pericarditis the $C_{1q}bA$ was positive and the C_{3d} which was elevated, decreased. After that period the disease activity subsided and $C_{1q}bA$ became negative. The C_{3d} content increased and remained stable and more or less elevated. At the end of the study the $C_{1q}bA$ increased. In this period and after the study no remarkable changes took place in the course of the disease.

Discussion

The presence and levels of CIC in patients with SLE have been described by many investigators using a variety of assay techniques [14, 15]. Depending on the assay, correla-

Table 5. Reported correlations between levels of Clq binding material ($C_{1q}bA$) with disease activity in systemic lupus erythematosus

Authors	Reported correlation[a]	Number of patients	Follow-up study[b]	Year of publication
Nydegger et al. [23]	+	4	+	1974
Tron and Bach [24]	–	30	–	1977
Frank et al. [25]	+	14	±	1979
Abrass et al. [26]	–	48	±	1980
Imman et al. [27]	–	33	–	1980
Boyd et al. [28]	–	11	+	1983

[a] Positive correlation between disease activity versus the serologic parameter; – negative correlation
[b] Data were sampled in a serial manner; ± data were mostly sampled at a single point in disease course, prospectively; – data were sampled at one point of the disease, retrospectively

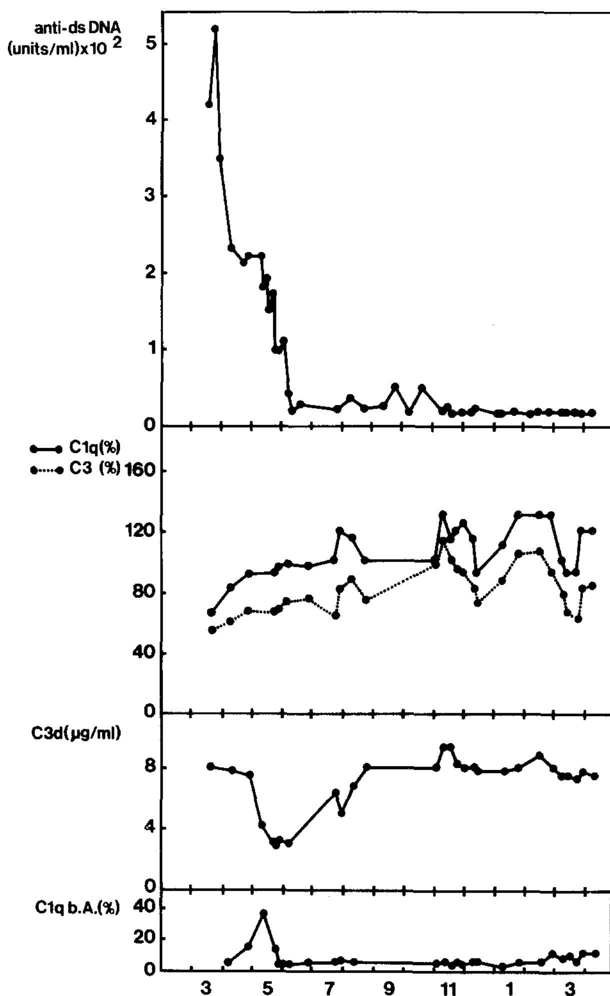

Fig. 3. The profiles of the serologic parameters (anti-dsDNA, C_{1q}, C_3, C_{3d}, and $C_{1q}bA$) in Patient 9, a woman born in 1947. In 1978 she was admitted to the hospital for the first time with a serious exacerbation of her disease (skin involvement, neurologic symptoms (polyneuropathy, psychosis), and hematologic abnormalities). After starting with high doses of prednisolone the symptoms subsided. The study started just before she was readmitted to the hospital with pericarditis (May 1979), and treatment was started with 40 mg prednisolone. After this period she had periods of skin rashes and polyarthralgia. Other signs were not observed

tions between disease manifestations and the presence of CIC were reported. However, in those studies which used the same assay conflicting results were also obtained (Table 5). By comparing the reports difficulties arise in the interpretation of results; these difficulties are not only caused by the different assays used but also by (a) the different groups of patients (most studies focused on patients with severe disease manifestations (nephritis)), (b) the different definitions of disease activity, (c) the retrospective character of the studies, and (d) the results are mostly based on correlations of disease activity with the presence of CIC at one point in the disease course.

In this study a graded scale of disease activity was used; by this method each serum sample can be defined by a corresponding grade of disease activity. An advantage of this method is also that a change in disease activity could directly be related to the serologic parameters (course) and vice versa. Considering that most of the biologic effects of immune complexes are mediated through the activation of the complement system, in this study the relationship between C_3 breakdown products (C_{3d}) and CIC with lupus disease activity was evaluated. All possible relationships between the different parameters were investigated. No correlation between the disease activity and $C_{1q}bA$ and/or C_{3d} next to the complement profile (C_{1q} and C_3) could be detected. Also no relationship between C_{3d} and $C_{1q}bA$ could be found.

An excellent correlation (inverse relationship) between C_{3d} and C_3 levels has been claimed, and it was stated that the level of C_{3d} indicates the degree of C_3 activation [29]. That presumption could not be confirmed in this study nor in our previous study [30] concerning the relationship between the metabolisms of C_3 versus the presence of C_3 breakdown products in the circulation. Also it was proved that the C_3 serum level was no indication of the degree of complement activation. The fact that no correlation could be found between the C_{3d} level and serum C_3 levels (as shown in this prospective study), and the inability to find a correlation with the C_3 turnover and the C_{3d} levels, proved that in our SLE patients C_{3d} determination as a parameter for complement activation is of very limited value.

Changes in disease activity were only observed in two patients, however, no clear or understandable reflection was seen in the levels of C_{3d} and C_{1q}bA. During this prospective study the other patients had a stable course with mainly skin involvement or discomfort in their joints. However a positive C_{1q}bA and/or C_{3d} was frequently detected. As demonstrated in Fig. 1 a persistent high level of CIC could be found without the existence of serious disease activity. In Fig. 3 an increase of the CIC was detected at the end of the disease course in this period, however, no change in disease activity was noted. Despite the small number of patients one could say that irrespective of the disease activity both serologic parameters could be either positive or negative (Table 3). Taking sera together no evidence was obtained that detection of CIC would indicate increased C_3 breakdown products, or decreased levels of complement (C_{1q} and C_3).

As described earlier the level of anti-dsDNA cannot be used as a parameter for disease activity [18, 31] as used by others [32]. In correlating the level with both serologic parameters the only striking finding was that in those patients with low anti-dsDNA levels more elevated C_{3d} levels were detected. These findings are therefore in contrast with those of Davis et al. [32]. In that study the assumption was made that levels of anti-dsDNA could be used as a parameter of disease activity. Our results demonstrated that in SLE patients who clearly are in an inactive stage of their disease, C_3 breakdown products (C_{3d}) and/or CIC (C_{1q}bA) can be frequently found. No evidence was obtained that patients in whom the serologic parameters were positive had more complaints (disease activity score). No correlations were found between changes of disease activity with the levels or profiles of the serologic parameters.

Each of the currently available methods for immune complex detection is limited by its ability to measure only one of the immunochemical properties of immune complexes. By using the C_{1q}bA only those immune complexes are measured that bind C_{1q} and are precipitated in polyethylene glycol. The only conclusion that can be made in this study is that in SLE the immune complexes measured by the C_{1q}bA presumably play no part in the pathogenesis of the disease symptoms as noted in our patients. It is suggested that in SLE a defective immune complex handling exists, so that levels of CIC may vary widely irrespective of the disease activity. A further complicating factor in evaluating the interpretation of CIC is that certain types of disease activity may not involve CIC, because just in situ complex formation can be responsible for signs of disease activity.

A drawback of our study is still the limited number of investigated patients, and also that only two patients with an active disease state were observed. Both influence our conclusion that the immune complexes measured by the C_{1q} binding assay play no part in the pathogenesis of the disease symptoms and that C_{3d} gives no indication of the degree of complement activation. This is mainly based on our complement turnover studies published earlier [30]. By extending the number of patients and the duration of the follow-up period, it may be shown that only the changes of both parameters in an individual patient correlate with the disease course. Presumably this correlation is lost when all patients are taken together.

Despite the small number of investigated patients in this study, our results showed that both parameters at one point in the disease course cannot be used as indices for disease activity, as well as the level of anti-dsDNA antibodies [31]. This conclusion is in agreement with the many conclusions in the literature on this subject (Table 5). Considering these factors in this study no evidence of the possible pathogenic significance of C_{1q} binding immune complexes was obtained; second the detection of C_{3d} which was frequently positive in our patients was not correlated to the presence of CIC.

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