

## ANTICOMPLEMENTARY REACTIONS AND THEIR RELATION TO SOME AUTO-IMMUNE PHENOMENA IN SYPHILITIC INFECTION

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A serum which inhibits hemolysis in an antigen-free mixture of serum and complement is not suited for complement-fixation tests. As has been earlier established, such anticomplementary (AC) activity in serum is often associated with hypergammaglobulinemia and rheumatoid factor activity (2, 4, 10) and also with cryoglobulinemia (6). According to several authors (1, 3, 7) AC-reactions are frequent in syphilitic sera. On the other hand syphilitics also frequently exhibit globulin aberrations such as rheumatoid factor activity and cryoglobulinemia (8).

In the present study the incidence of AC-reactions in the different stages of syphilis and their association with hypergammaglobulinemia, rheumatoid factor activity and cryoglobulinemia will be evaluated.

### Material and Methods

The study material included 1399 patients with clinical and/or serological evidence of syphilis, admitted between 1960 and 1967 to the wards of the Department of Dermato-Venereology, University Central Hospital, Helsinki. For the different stages of syphilis the following principal criteria were used (Table 1):

*Active primary syphilis:* All 147 patients had darkfield-positive primary lesions.

*Active secondary syphilis:* The 85 patients had typical clinical signs of secondary

syphilis and 65 of them had darkfield-positive lesions.

*Treated primary or secondary syphilis:* This group included 159 patients who had been treated by a venereologist for either primary or secondary syphilis at least 10 years before the present study.

*Latent syphilis:* The 235 patients had anamnestic and/or epidemiological evidence of syphilis but no signs of clinical activity of the disease.

*Serological syphilis:* The 289 patients had no clinical evidence of syphilis. The diagnosis was based on reactive TPI and/or FTA-ABS tests.

*Benign tertiary syphilis:* The 35 patients had before treatment typical cutaneous findings of tertiary syphilis, which responded well to treatment.

*Neurosyphilis:* The group included 230 patients of which 132 had positive Wassermann tests in the cerebrospinal fluid (5) as the only evidence of neurosyphilis (asymptomatic neurosyphilis). On the basis of neurological and/or mental findings 41 of the remaining patients could be classified as having meningovascular neurosyphilis, 37 tabes and 20 dementia paralytica.

*Cardiovascular syphilis:* The 28 patients had clinical and/or roentgenological evidence of cardiovascular syphilis in addition to a reactive TPI or FTA-ABS test. Patients with signs of both neurosyphilis and cardiovascular syphilis were included in the group of neurosyphilis.

Table 1. Sex, age and status of treatment of the patients

Stage of syphilis	Total	Females	Males	Age in years							Treated
				—19	20—29	30—39	40—49	50—59	60—69	70—	
Active primary	147	12	135	26	86	23	8	4	0	0	0
Active secondary	85	35	50	18	40	15	10	1	1	0	0
Treated primary or secondary	159	75	84	0	0	17	50	41	38	13	159
Latent	235	177	58	8	23	34	79	64	23	4	199
Serological	289	183	106	2	19	50	62	75	57	24	187
Benign tertiary	35	20	15	0	0	2	8	7	14	4	20
Neurosyphilis	230	139	91	0	5	25	75	68	41	16	195
Cardiovascular	28	10	18	0	0	0	4	6	13	5	25
Congenital	191	138	53	59	48	53	22	5	3	1	165
Total	1399	789	610	113	221	219	318	271	190	67	950

Table 2. Incidence of anticomplementary reactions in different stages of syphilis

Stage of syphilis	Total number of patients	Anticomplementary reaction in serum	Per cent
Untreated primary	147	0	—
Untreated secondary	85	1	1.2
Treated primary or secondary	159	16	10.1
Latent	235	18	7.7
Serological	289	26	9.0
Benign tertiary	35	4	11.4
Neurosyphilis	230	12	5.2
Cardiovascular	28	1	3.6
Congenital	191	7	3.7
Total	1399	85	6.1

*Congenital syphilis:* This group included 191 patients. The diagnosis was based on stigmata of congenital syphilis (5) or syphilis of the mother and/or congenital syphilis of siblings if the patient had been found seropositive before the age of 16.

All patients in the study material, except a few cases with untreated primary syphilis, had or had at some time been found to have reactive lipoidal tests.

The complement-fixation tests for syphilis used were the Kolmer and the semi-quantitative Reiter protein complement-fixation tests (5). In both tests a 2 exact unit of complement was used. The Waaler-Rose and Latex tests as well as the turbidimetric screening for cryoglobulins were performed as described by Mustakallio *et al.* (8). The amount of gammaglobulins was estimated by paper electrophoresis.

## Results

Altogether 3218 serum samples from 1399 patients were tested with the two complement-fixation tests. AC-reactions were found in 126 of them (3.9 per cent). Eighty-five of the 1399 patients (6.1 per cent) were found to have AC-activity in at least one serum sample (Table 2). In 22 cases AC-activity was found in more than one sample (Table 3). Fifty-one females (6.5 per cent) and 34 males (5.6 per cent) had AC-active sera. When correlating the AC-activity with the age of the patients it was found that the incidence was highest in the age group 50—59 years and lowest among those who were 19 years or younger (Table 4). AC-reactions were most frequently found in the group of benign tertiary syphilis and did not occur at all in patients with untreated primary syphilis

Table 3. Frequency of anticomplementary reactions

Number of occurrences	Number of patients
1	63*
2	12
3	5
4	2
5	2
6	1

\* In 21 of the 63 cases only one serum sample was tested.

(Table 2). In the group of neurosyphilis the over-all incidence of AC-reactions was 5.2 per cent. AC-reactions did not occur in any of the 20 cases with dementia paralytica, but were found in 12.2 per cent of the patients with meningovascular neurosyphilis, in 5.4 per cent of the tabetic patients and in 4.5 per cent of the patients with asymptomatic neurosyphilis. Twenty-one of the 449 patients (4.7 per cent) who had not received any antisyphilitic treatment and 64 of the 950 treated patients (6.7 per cent) had AC-activity in the serum. However, when the 232 cases with untreated primary or secondary syphilis were excluded it was found that as many as 9.7 per cent of the remaining untreated patients had AC-active sera.

Rheumatoid factor activity was investigated with both the Waaler-Rose and the latex-fixation test in 642 cases. In 88 cases (13.7 per cent) a positive reaction was noted in one or both tests. AC-activity was found in 18 of the sera with rheumatoid factor activity (20.5 per cent) and in 22 of the sera showing no rheumatoid factor activity (3.9 per cent). Paper electrophoresis was performed on sera of 525 patients, of which 35 (6.7 per cent) had a total amount of gammaglobulins  $\geq 2.0$  g per 100 ml. Nine of the latter patients (25.7 per cent) and 20 of the 490 patients with a lower amount of gammaglobulins (4.1 per cent) were found to have AC-reactions in serum. The turbidimetric screening for cryoglobulins was carried out in 512 cases and cryoglobulins were found in 80 of them

Table 4. Frequency of anticomplementary reactions in different age groups

Age in years	Number of patients	Anti-complementary reactive	Per cent
-19	113	1	0.9
20-29	221	7	3.2
30-39	219	6	2.7
40-49	318	22	6.9
50-59	271	28	10.3
60-69	190	15	7.9
70-	67	6	9.0

(15.6 per cent). Twelve of the cryoglobulinemic (15.0 per cent) and 17 of the non-cryoglobulinemic sera (3.9 per cent) were found AC. The sera of 485 patients were screened for all three globulin aberrations and at least one of them was found in the sera of 129 patients (26.6 per cent). AC-reactions were found in the sera of 21 of the latter patients (16.2 per cent) but in the sera of only seven of the 356 patients without any of the three globulin aberrations (2.0 per cent) (Table 5).

#### Discussion

The 6.1 per cent incidence of AC-reactions in the study material is significantly higher than the 0.8 per cent incidence in the dermatological patient series studied with the same complement-fixation tests by Lassus and Mustakallio (6). Furthermore, Berndt and Hippus (1) found that AC-reactions occur significantly more often in patients with syphilis than in patients with neurological and psychiatric diseases.

In the present material the female patients appeared to have a somewhat higher incidence of AC-reactions than the male patients (cf. 9). The difference was due to the fact that almost all the patients with untreated primary syphilis, in which there was not a single case with AC-activity, were males. The young patients who mostly had either primary, secondary or congenital syphilis showed also a low incidence of AC-reactions. This contrasts the material studied by Lighter (7), in which the ma-

Table 5. Association between anticomplementary activity, and rheumatoid factor activity, hypergammaglobulinemia and cryoglobulinemia

	No. screened	No. positive	AC/positive	Per cent	AC/negative	Per cent
Rheumatoid factor	642	88	18/88	20.5	22/554	4.0
Hypergammaglobulinemia ( $\geq 2.0$ g/100 ml)	525	35	9/35	25.7	20/490	4.1
Cryoglobulins	512	80	12/80	15.0	17/432	3.9
All three globulin aberrations	485	129 <sup>1</sup>	21/129	16.3	7/356	2.0

<sup>1</sup> Means that at least one of the three globulin aberrations had been found.

majority of syphilitic patients with AC-reactions had congenital syphilis. However, the majority of patients with congenital syphilis in the present series of patients had received antisyphilitic treatment in the early years of their lives.

It is of special interest to note that a high incidence of AC-reactions was found in old treated primary or secondary syphilis, while the incidence was very low in early infectious syphilis. Most of the former patients had been treated with metal chemotherapy 20–30 years before the present study and the majority of them had later received antibiotics. Liver damage caused by the heavy metals (9) might have been the cause of the AC-reactivity in some of these cases. On the other hand an altered immunological status in patients with old treated syphilis, possibly induced by a continuous stimulus of surviving treponemes with formation of pathological globulins, could also explain the high incidence of AC-reactivity in this group.

A quarter of the screened 485 syphilitic patients exhibited at least one of the three globulin aberrations, hypergammaglobulinemia, rheumatoid factor activity and cryoglobulinemia. The AC-reactivity correlated significantly with the finding of these pathological globulins (6). It is therefore concluded that AC-activity in syphilitic sera often indicates an auto-immune phenomenon. The high incidence of AC-reactions in syphilitic patients stresses the importance of syphilis as a potential cause of auto-immune disorders. Moreover, it is of interest that a high incidence of AC-

activity has been found also in other chronic infectious diseases such as lymphogranuloma inguinale (10), malaria and tuberculosis (3).

#### SUMMARY

Anticomplementary reactions were found in 126 (3.9 per cent) of 3218 samples taken from 1399 patients with syphilis when tested with the Kolmer and Reiter protein complement-fixation tests. The anticomplementary reaction was found in serum from 85 of the patients (6.1 per cent). The incidence was higher in older patients and in patients with advanced syphilitic infection. There was no significant difference between females and males. The anticomplementary activity correlated significantly with the occurrence of hypergammaglobulinemia, rheumatoid factor activity and cryoglobulinemia in serum.

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