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THE USE OF STANDARD SEROLOGICAL TESTS FOR SYPHILIS IN SCREENING FOR AUTO-IMMUNE CONNECTIVE TISSUE DISEASE

Chronic Biological False-Positive Reactions and Anticomplementary Activity

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Abstract. Screening of 6737 consecutive dermatological inpatients for syphilis with two flocculation and two complement-fixation tests brought to light 31 patients (0.5%) with chronic biological false-positive (CBFP) reactions for syphilis and 24 patients (0.4%) whose serum was repeatedly anticomplementaty (AC). Four patients had both immunological aberrations. During a follow-up period of 3—5 years, 13 of the CBFP reactors and 6 of the AC reactors developed definite or "probable" SLE. Three CBFP reactors had rheumatoid arthritis and 1 had purpura. Purpura was found in 3 AC reactors and 3 others had necrotizing vasculitis. Lymphosarcoma was found in 1 AC reactor and chronic lymphatic leukaemia in another. Myeloma was found in 1 AC reactor and in 1 CBFP reactor. It was concluded that the use of complement-fixation tests in screening for syphilis provides the clinician with a valuable clue to the presence of both connective tissue disease of SLE type, dysglobulinaemic vascular diseases and malignant lymphomas and myelomas.

Chronic biological false-positive reactions in the standard tests for syphilis (STS) have generally been regarded as a clue to auto-immune connective tissue diseases, especially to systemic lupus erythematosus (SLE) (5, 6, 7, 10, 13, 16). In addition, another phenomenon also detectable with STS, namely the anticomplementary (AC) serum activity, has proved to be an indicator not only of myeloma and liver disease associated with hypergammaglobulinaemia (cf. 19) but also of auto-immune connective tissue diseases (1, 8, 11). So far no comparative study on the prevalence and significance of CBFP reactions and AC reactions has been performed.

In the present study of a dermatological series the incidence of CBFP and AC reactions, as well as their connection with connective tissue disease, especially of SLE type, will be evaluated within a dermatological series of inpatients. Special attention is paid to the finding of antinuclear factors, cold agglutinins, cryoglobulins, rheumatoid factors and hypergammaglobulinaemia in the sera of the CBFP and AC reactors.

MATERIAL AND METHODS

The series comprised 6737 consecutive dermatological inpatients hospitalized in 1964–1966 (9). On admission the sera of all patients had been screened for syphilis with two flocculation tests (VDRL slide and Kahn) and with two complement-fixation tests (Kolmer and semi-quantitative Reiter protein complement-fixation (RPCF)). The tests were performed at the Department of Serology and Bacteriology, University of Helsinki (cf. 4,17). Patients with persistently positive results in STS (≥ 6 months) and negative results in the *Treponema pallidum* immobilization and fluorescent treponemal antibody-absorption tests and without clinical or anamnestic evidence of syphilis were classified as CBFP reactors. Patients with repeatedly anticomplementary results in the Kolmer and/or RPCF tests were classified as AC reactors. This excluded 28 patients who had AC reactivity in only one serum sample.

All CBFP and AC reactors were evaluated for the clinical score for SLE (14). In addition, the sera of all patients were screened for antinuclear factors (3), cold agglutinins (2), cryoglobulins and rheumatoid factors (15) and for hypergammaglobulinaemia with paper electrophoresis using Spinco Analytrol equipment.

A follow-up study of 47 of the 51 CBFP and AC reactors who were still alive has been performed in 1969, using the same clinical and serological examinations as described above.

RESULTS

CBFP reactors. The series was found to include 31 CBFP reactors, accounting for 0,5% of the 6 737 patients. The age and sex distributions of the patients are presented in Table I.

The clinical diagnoses of the 31 CBFP reactors at the beginning of the follow-up study are

Table I. *Age and sex distribution of the CBFP and AC reactors*

Age (in years)	CBFP reactors			AC reactors		
	♀	♂	Total	♀	♂	Total
0–10	0	0	0	0	0	0
11–20	4	0	4	2	0	2
21–30	2 [a]	1	3	2	1	3
31–40	5	0	5	1	1	2
41–50	4	2	6	1	1	2
51–60	2	3	5	3	2	5
61–70	4	3	7	4	2	6
71–	1	0	1	3	1	4
Total	22	9	31	16	8	24

[a] SLE in 6 cases.

presented in Table II. There were 5 patients with a clinical score high enough for the diagnosis of definite SLE, while 2 patients were classed as "probable" SLE. Five patients had rheumatoid arthritis in addition to some dermatosis, and 4 had sarcoidosis, while discoid lupus erythematosus and hypergammaglobulinaemic purpura were each present in 1 patient. Thirteen of the CBFP reactors were placed in the group of miscellaneous diseases, having dermatoses not usually classified as connective tissue diseases. Three of them had atopic dermatitis and 4 psoriasis, 2 of them with the psoriatic type of arthritis.

During the follow-up study 1 patient was diagnosed as definite SLE and 5 additional patients as "probable" SLE. Of these patients, 2 were originally diagnosed as having rheumatoid arthritis and 1 as sarcoidosis, while 3 patients were placed in the group, miscellaneous diseases. In addition, 1 case of myeloma was diagnosed during the follow-up period. The final distribution of the clinical diagnoses of the CBFP reactors is shown in Table III.

There was a comparatively high incidence of antinuclear factors, rheumatoid factors and cryoglobulins among the CBFP reactors, while hypergammaglobulinaemia ($\geqslant$ 2,0 g/100 ml) was found in only a few cases and cold agglutinins were not detected in a single case (Table IV). As many as 24 of the 31 CBFP reactors had at least one of the globulin aberrations mentioned. That was the case in 6 of the 9 patients with miscellaneous diseases, 3 of whom had antinuclear factors, 2 rheumatoid factors, 1 hypergammaglobulinaemia and 1 other cryoglobulinaemia.

AC reactors. At the beginning of the follow-up study definite SLE had been diagnosed in 4 of the 24 AC reactors (Table II). One of the patients with purpura had hypergammaglobulinaemia and another had cryoglobulinaemia, while in the third case the nature of the purpura was unknown. This 20-year-old woman had antinuclear factors in her serum. Three women had necrotizing vasculitis. They all had hypergammaglobulinaemia and 1, in addition, cryoglobulins in her serum. Malignant lymphoma was found in 2 cases. One of them had been hospitalized because of chronic lymphatic leukaemia with leukaemids and 1 because of lymphosarcoma.

During the follow-up study, 2 patients developed "probable" SLE, while 1 patient was found to have myeloma (Table III). The 9 remaining AC-reactors had some dermatosis. One of the 2 patients with psoriasis was a man of 61 with psoriatic arthritis and the other was a woman of 39 who was suspected to have temporal arteritis. She had cardiac infarction at the age of 34 and recurrent severe headaches, and her left temporal artery was not palpable. Histopathologically, however, the diagnosis could not be verified al-

Table II. *Clinical diagnoses of the 31 CBFP reactors and 24 AC reactors before the follow-up study*

	CBFP reactors	AC reactors	Total in the series of 6737 inpatients
Definite or probable[a] systemic lupus erythematosus	7	4	37
Discoid lupus erythematosus	1	—	61
Necrotizing vasculitis	—	3	26
Purpura	1	3	44
Rheumatoid arthritis	5	—	52
Sarcoidosis	4	—	281[b]
Malignant lymphoma and myelosis[c]	—	2	23
Miscellaneous dermatoses[d]	13	12	6213
Total	31	24	6737

[a] These groups each included 1 patient with both CBFP and AC reactions.
[b] 189 verified cases.
[c] This group included 2 cases of myeloma, 5 cases of mycosis fungoides, 6 cases of leukaemia and 4 cases of both lymphosarcoma and lymphoma.
[d] This group included 2 patients with both CBFP and AC reactions.

though there was some thickening and fibrosis of the arterial wall. A man of 63 with varicose leg ulcer had been treated for secondary syphilis 40 years before. A man of 21 with atopic dermatitis had hypergammaglobulinaemia and his mother had definite SLE. Further, a woman of 19 suffered from recurrent polyarthritis with hypergammaglobulinaemia and cryoglobulinaemia. The sixth of the nine AC reactors was a woman of 67 with erythrodermia and hypergammaglobulinaemia and has been suspected of having incipient myeloma. The 3 remaining patients had some kind of eczema. One of them was a woman of 78 with hypergammaglobulinaemia, 1 a male alcoholic of 55 with chronic liver disease, and the third a man of 54 with untreated latent syphilis. Only 2 of the 24 AC reactors did not show any other abnormal serological finding (Table III). One of them was the woman with leukaemia and the other was the man with eczema and latent syphilis. More than one-half of the patients had hypergammaglobulinaemia and about one-third had either antinuclear factors, rheumatoid factors or cryoglobulins in the serum. None exhibited an elevated cold agglutinin titre. Four patients displayed both a CBFP reaction and an AC reaction. One of them had "probable" SLE, 1 atopic dermatitis, 1 psoriatic arthritis and the fourth patient had purpura. Three of them had hypergammaglobulinaemia and the patient with psoriatic arthritis who had normal serum gammaglobulins had antinuclear factors.

Table III. *Clinical diagnoses of the 31 CBFP and 24 AC reactors after the follow-up study*

	CBFP reactors	AC reactors
Definite or probable systemic lupus erythematosus	13	6
Discoid lupus erythematosus	1	—
Necrotizing vasculitis	—	3
Purpura	1	3
Rheumatoid arthritis	3	—
Sarcoidosis	3	—
Malignant lymphoma and myelosis	1	3
Miscellaneous dermatoses	9	9
Total	31	24

Table IV. *Serological findings in 31 CBFP and AC reactors*

	CBFP reactors	AC reactors
Antinuclear factors	12	8
Cold agglutinins	0	0
Cryoglobulins	9	7
Rheumatoid factors	8	9
Hypergammaglobulinaemia (≥2.0 g/100 ml)	6	15
At least one positive finding	24	22

DISCUSSION

The CBFP reaction has been the object of comprehensive investigations during the last two decades. Even if the CBFP phenomenon occurs in only 10–25 % of the recently reported series of SLE patients (5, 6, 12, 18) the extensive use of serological tests for syphilis has made them a worthwhile screening method for auto-immune connective tissue diseases. The value of the complement-fixation tests for syphilis in screening for connective tissue diseases is further stressed by the finding that even an anticomplementary reaction may serve as a clue to an auto-immune disorder (11).

The present study emphasizes that both the CBFP phenomenon and the AC phenomenon are of value in this respect. There were only a few patients who exhibited both reactions, which suggests that the nature of the globulin aberrations detected by these two systems is different. Of these two aberrations, the CBFP phenomenon seems to have somewhat more value as a suggestive indicator of SLE, especially as a harbinger or an early sign of this disease in young women (16). Furthermore, in four of the AC reactors ten had or later developed definite or probable SLE. In addition, there was quite a high incidence of purpura and of necrotizing vasculitis among the AC reactors, diseases which were both infrequently associated with the CBFP phenomenon. When the malignant disorders showing AC reactions are also taken into consideration, it may be concluded that a repeatedly anticomplementary reaction in routine complement-fixation tests for syphilis is at least as significant a finding as a CBFP reaction. The use of complement-fixation tests in screening for syphilis provides the clinician with a valuable clue not only to auto-immune connective tissue diseases but also to dysglobulinaemic vascular diseases and to malignant lymphomas and myelomas.

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