COMPARATIVE SEROLOGIC CHARACTERISTICS OF RHEUMATIC FEVER AND RHEUMATOID ARTHRITIS

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UDC 616-002.77+616.72-002-022.6]-078.73

Rheumatic fever and rheumatoid arthritis are included at the present time in the group of the collagen diseases on the basis of their common clinical manifestations and the similarity of their pathomorphological signs. Many investigators consider that a factor of considerable importance in the onset and development of these diseases in the formation of foci of chronic infection, which may be regarded as a trigger mechanism for the immunological changes, the sensitization, and the development of the clinical manifestations [1, 5]. The hemolytic streptococcus is the main etiological factor concerned in the formation of the chronic foci preceding the development of rheumatic fever. From recent investigation V. I. Ioffe [2] concludes that rheumatic fever may be regarded as a "chronic streptococcal infection with recurrent exacerbations." There is no general agreement regarding the etiology of rheumatoid arthritis. Some investigators believe that rheumatic fever and rheumatoid arthritis are both variants of streptococcal infectious–allergic diseases, while others consider that rheumatoid arthritis has a multiple etiology.

The object of the present investigation was to evaluate the importance of the streptococcus in the onset and development of rheumatoid arthritis. The methods used in this study were those previouly adopted for the study of the serological characteristics of rheumatic fever [4, 6, 7].

EXPERIMENTAL METHOD

Streptococcal antigen was detected by the complement fixation reaction at a low temperature with 1, 1.5, and 2 doses of complement. The test sera were used in a dilution of 1:5 and the high-titer streptococcal antiserum in a dilution of 1:15. The control tests were carried out with a heterologous (paratyphoid) rabbit antiserum. The reaction was assessed by the scheme devised for describing the results of the complement fixation reaction: ++++ complete inhibition of hemolysis with two doses of complement; +++ incomplete inhibition of hemolysis with two doses of complement; ++ complete inhibition of hemolysis with 1.5 doses of complement; and + complete inhibition of hemolysis with 1 dose, and incomplete with 1.5 doses of complement; if hemolysis took place with all doses or inhibition with one dose, the reaction was taken as negative.

The response reaction to the streptococcal antigens was assessed from the titer of antibodies against polysaccharide streptococcal antigen in the patients' blood, also determined by the complement fixation reaction in the cold. The polysaccharide antigen used was prepared from a virulent culture of Streptococcus haemolyticus of serological type I and group A. The antigen was used in the experiment in a dilutions of 1:20, and the test sera in dilutions of 1:20 or 1:80.

Antistreptolysis O was determined by A. P. Konikov's method [3].

C-reactive protein was determined by the complement fixation reaction in the same way as the antigen. The test sera were diluted 1:5 and the C-reactive antiserum 1:50.

Rheumatoid factor was determined by the Svartz–Schlossmann method [9], with slight modifications introduced by the authors. The test sera were inactivated at 56° for 30 min, absorbed with sheep's erythrocytes for 40 min in a refrigerator, and then a series of half-and-half dilutions was made from 1:4 to 1:1024. The experiment was carried out on organic glass plates. Each dilution of serum, in a volume of 0.2 ml, was mixed with 0.2 ml of sensitized sheep's erythrocytes. Sensitization was carried out as follows. A mixture of equal volumes of a 3% suspension of sheep's erythrocytes and hemolytic serum in a subthreshold agglutinating dose was kept for 30 min at room temperature. To verify the completion of absorption,

Department of Microbiology and Clinic for Internal Diseases, Leningrad San.-Gig. Medical Institute
(Presented by Active Member of the Academy of Medical Sciences D. A. Biryukov). Translated from Byulleten' Éksperimenta'noi Biologii i Meditsiny, Vol. 63, No. 3, pp. 89-92, March, 1967. Original article submitted May 3, 1965.

TABLE 1. Content of Streptococcal Antigen in Blood of Patients with Rheumatic Fever and Rheumatoid Arthritis

Clinical diagnosis	Number of investigations	Intensity of reactions		
		–	+	++ and over
Rheumatic fever	19	10	2	7
Rheumatoid arthritis	33	22	8	3
Bacterial endocarditis	3	2	1	–
Chronic tonsillitis	7	5	–	2

the test serum in a dilution of 1:4 was mixed with unsensitized erythrocytes, and a suspension of sensitized and unsensitized erythrocytes was tested mixed with physiological saline. The results were read after the samples had been kept at room temperature for 3-5 h, and again, 24 h later, after shaking.

The presence of autoantibodies against heart tissue was tested for in some patients by means of Steffen's reaction [8].

EXPERIMENTAL RESULTS

Altogether 72 patients were investiaged, including 33 with rheumatoid arthritis, 19 with rheumatic fever, 4 with subacute bacterial endocarditis, 8 with tonsillogenic lesions of the myocardium, and 8 with diseases of nonstreptococcal etiology. Blood for investigation was taken at intervals of 2-3 weeks, and on the average twice or three times from each patients.

The results of determination of streptococcal antigen in the patients' blood are given in Table 1.

In previous test conducted by one of the authors (A. M. S.) on 136 adult patients with rheumatic fever, it was found [4] that the percentage of positive reactions to streptococcal antigen was 54, including 42% of cases with a strongly positive result. Similar proportions were found in the present investigation: among the 19 patients with rheumatic fever antigen was found in 9, and in 7 of them the reaction was strongly positive. Hence, without enlarging the group of patients with rheumatic fever, it was possible to draw a comparison with the group with rheumatoid arthritis, among the 33 patients of which streptococcal antigen was found only in 11, while a strongly positive reaction was given only by 3. Among the 10 patients with nonrheumatic streptococcal diseases, antigen was found in the blood of three, but strongly positive reactions were given by only two patients, suffering from chronic tonsillitis.

Streptococcal antigen, characterizing the size of the focus of (streptococcal) infection, was thus found in the blood of the patients with rheumatic fever significantly more frequently than in the patients with rheumatoid arthritis, and the intensity of the reactions was greater.

Meanwhile C-reactive protein, a nonspecific index of the acuteness of an inflammatory or destructive process, was found equally often in rheumatic fever (in 17 of 19 patients tested) and in rheumatoid artritis (in 29 of 33). This shows that, given the same severity of the pathological process, the etiological importance of the hemolytic streptococcus in these diseases in different. The detection of C-reactive protein in the patients' blood without information regarding the content of streptococcal antigen cannot be used in the diagnosis of rheumatic fever for estimating the activity of the rheumatic process.

The results of determination of the titers of antibodies against polysaccharide streptococcal antigen (APA) and antistreptolysin O (ASL-O) are given in Table 2. Increased titers of streptococcal antibodies, demonstrating the participation of streptococci in the development of the diseases, were found much more frequently in rheumatic fever than in rheumatoid arthritis. In the 19 patients with rheumatic fever, for instance, titers of ASL-O higher than 400 units/ml were found in 5 cases, and in 3 of these the titers were above 600 units/ml. Among the 33 patients with rheumatoid arthritis, increased ALS-O titers were found in only 4, and a titer over 600 units/ml in only 1 case. Among the 12 patients with nonrheumatic streptococcal diseases, increased ALS-O titers were found in only 4. The response reaction to polysaccharide antigen likewise was more marked in the patients with rheumatic fever and other streptococcal diseases than in those with rheumatoid arthritis. Consequently, the corresponding antigenic stimulus (the focus of streptococcal infection) is weaker in rheumatoid arthritis and less important to the development of the underlying disease process than in rheumatic fever.

TABLE 2. Content of Antistreptolysin O and Antigodies against Polysaccharide Streptococcal Antigen in the Blood of Patients with Rheumatic Fever and Rheumatoid Arthritis

Clinical diagnosis	ASL-O				APA			
	number of patients investigated	titer (in units/ml)			number of patients investigated	intensity of reactions		
		under 400	401–600	over 600		–	+	+ + and over
Rheumatic fever	19	14	2	3	19	5	7	7
Rheumatoid arthritis	32	27	4	1	33	16	11	6
Bacterial endocarditis	4	3	1	—	4	1	—	3
Chronic tonsillitis	8	5	2	1	8	2	5	1

Positive results of the tests for rheumatoid factor were obtained in only one patient with rheumatic fever of the 19 investigated, in 1 patient with chronic tonsillitis, and in 1 patient with a nonstreptococcal disease. Of the 33 patients with rheumatoid arthritis, rheumatoid factor was found in only 19. The frequency of discovery of this factor in the blood of persons after an attack of rheumatoid arthritis is known to vary within wide limits—from 35% according to some observations [11] to 100% according to others [9]. Tests for the detection of rheumatoid factor are evidently of some value, but they are not completely reliable as a basis for the differential diagnosis.

Autoantibodies against heart issue were found by Steffen's reaction twice as frequently in patients with rheumatic fever. A positive Steffen's reaction was obtained in 6 patients with rheumatoid arthritis and in 1 patient with chronic tonsillitis with no disease of the valves, and also in 1 patient with an allergic reaction to typhoid vaccine. These observations did not give the impression of the strict specificity of Steffen's test in rheumatic heart disease.

From the results of all these serological investigations of patients with rheumatic fever and rheumatic fever and rheumatoid arthritis it can be concluded that streptococcal infection is not equally important in the development of these diseases. Evidently different etiological and pathogenic factors must be sought in patients with rheumatoid arthritis.

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