SEROLOGICAL INVESTIGATIONS INTO SEQUELAE OF SCARLET FEVER WITH PARTICULAR REFERENCE TO RHEUMATIC FEVER

BY

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The question of detecting the changes in reactivity after streptococcal infections and before the first rheumatic attack is of great importance from the standpoint of rheumatology. This paper reports the results of our serological investigations after scarlet fever in a two-year follow-up of 31 children. Examinations, using nine laboratory tests, useful in rheumatology as indices of inflammation and immunobiological equilibrium, were carried out.

From the beginning of 1957 to the middle of 1959, 31 children with scarlet fever were treated for six days with penicillin and were followed up clinically and with laboratory tests. Sixteen of them were examined in the first 10 days of the disease, and tests were carried out later, after complications, in 15 cases.

Five children were 4 or 5 years old at the time they caught the disease, 23 were between 6 and 10 years, and three were between 11 and 13 years of age.

Three children were followed up for 10-12 months after the onset of the scarlet fever, two for 16-18 months, 12 for 20-24 months, and another 14 for 25-31 months.*

The disease took a comparatively mild course in all 31 children, but only four (13%) of them had neither complications nor intercurrent infections during the post-scarlet fever period. With the remaining 27 children (87%), the following complications were observed mainly during the first two months after the onset of the scarlet fever: tonsillitis acuta or tonsillopharyngitis chronica exacerbata in 20 cases (14 children underwent a tonsillectomy), arthralgias in eight cases (four having had arthralgias before scarlet fever), transient E.C.G. and clinical signs of myocardial involvement in three cases, lymphadenitis colli in five cases, otitis media in three cases and allergic manifestation$ in five cases (including a case with bronchial asthma).

The clinical and laboratory observations were carried out on each child at different intervals because of technical difficulties; the mean number of laboratory tests performed on each child was nine.

Methods

The laboratory tests were carried out using the following methods:

Erythrocyte sedimentation rate. The E.S.R. was determined by Westergren's method (1921, 1957), estimations up to 10 mm. in the first hour being accepted as normal.

C-reactive protein. This was determined by the method of Anderson and McCarty (1950), using C.R.P. anti-serum† and assessed as −, +, ++ or ++++, in accordance with the criteria suggested by Wuhrmann and Wunderly (1957).

Serum protein fractions. These were determined by paper electrophoresis following Flynn and De Mayo (1951), and total protein by Kingsley's method (1940). Normal figures for sera from 42 healthy children (Popov, Stanisheva and Kostova, in the press) are set out below:

<table>
<thead>
<tr>
<th>Serum Protein Fraction</th>
<th>Relative % ((\sigma = 1))</th>
<th>Serum (g./100 ml.) ((\sigma = 1))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumins ...</td>
<td>56.4 ± 3.1</td>
<td>3.93 ± 0.37</td>
</tr>
<tr>
<td>Globulins (a_1)</td>
<td>4.3 ± 0.8</td>
<td>0.30 ± 0.08</td>
</tr>
<tr>
<td>(a_2)</td>
<td>10.3 ± 1.1</td>
<td>0.72 ± 0.14</td>
</tr>
<tr>
<td>(\beta)</td>
<td>12.4 ± 1.5</td>
<td>0.87 ± 0.13</td>
</tr>
<tr>
<td>(\gamma)</td>
<td>16.6 ± 2.0</td>
<td>1.16 ± 0.17</td>
</tr>
</tbody>
</table>

Plasma fibrinogen levels. These were determined by the krehldalometric method; the normal range was 180-350 mg./100 ml. plasma and was in accordance with our own findings (Popov and Stanisheva, 1958).

Antistreptolysin reaction (A.S.O.). This was determined by the method described by Kalbak (1947).

* After the completion of the work another clinical and laboratory check was carried out and the term of observation was prolonged to three years.

† Manufactured by Schieffelin and Co., New York.
ARCHIVES OF DISEASE IN CHILDHOOD

Standard serum from the State Serum Institute, Copenhagen, was used. Though a titre of over 200 units was accepted as pathologically increased, we have previously shown (Popov and Bojadzieva, 1957) that serial estimations have a very much greater value than a single initial determination.

_Haemagglutination reaction._ Here the Waaler-Rose reaction was used as modified by Svartz and Schlossmann (1952) according to Dickgiesser and Harter (1953). A titre of over 16 units was accepted as increased.

_Coombs test_ was carried out (Coombs, Mourant and Race, 1945).

_Atypical anti-erythrocyte agglutinins:_ agglutinating and conglutinating (in 6% dextran solution) auto- and isoantibodies at +4°, +22° and +37° C.

_Tissue antibodies._ These were determined by the antihuman globulin consumption method of Steffen and Schindler (1955).

**Results**

The first clinical group of six children (Cases 1-6) was characterized by comparatively mild scarlet fever, but with various complications and intercurrent infections in the post-scarlet fever period. In this same group several complications were observed especially during the period within the third and sixth week after contracting the disease. During this period, as well as during the subsequent period, tonsillitis and tonsillo-pharyngitis occurred with frequent exacerbations. In two children (Cases 1 and 2) these inflammations lasted for more than a year and subsided after systematic penicillin treatment and tonsillectomy. With the second case the tonsillectomy resulted in a temporary turn for the worse, clinically (a severe pharyngitis) and in the laboratory findings. The combined antibiotic treatment and tonsillectomy with Cases 3 and 6 shortened the period of convalescence. Four of the children had shown allergic manifestations since early childhood, which were considerably aggravated after the scarlet fever. Case 6 had a relapse of scarlet fever seven months later. This 5-year-old child showed quite a number of allergic and septic complications (besides the usual children’s infectious diseases and an infectious mononucleosis). Parallel to the clinical developments the laboratory tests showed deviations from normal with a great number of peaks (Fig. 1). The tests for activity of the inflammation were positive in all children of this group as were the signs of streptococcal sensitization. Not one of the cases in the first group developed rheumatic fever during the observed period.

The second group consisted of 15 children (Cases 7-21). They also had mild scarlet fever. During the first three to five weeks temporary complications were observed, mainly persistent tonsillitis and tonsillo-pharyngitis, which necessitated penicillin treatment and tonsillectomy in seven children. During the following months the post-scarlet fever period was undisturbed, with only slight intercurrent ailments. The laboratory findings showed some deviation from the normal during the period of the complications, but the curves ran almost unchanged. No case of rheumatic fever was seen in this group of children.

The third group consisted of 10 children (Cases 22-31), considered as controls as they showed little symptomatology during the post-scarlet fever period and almost constantly normal laboratory findings (Fig. 2). Tonsillectomy was performed on three children. Here also no cases of rheumatic fever occurred.

During the time of the influenza epidemics (1957 and 1959) 21 children fell ill. The period of the disease passed mildly without complications. In 10 cases temporary changes were noted in some of the laboratory tests used.

The individual laboratory tests in this clinical material showed the following results:

**Erythrocyte Sedimentation Rates._** Constantly normal results were obtained in 12 children, while in 19 the E.S.R. was raised to a varying degree. The highest figure for the first hour was 52 mm. and more than 40 mm. in five children on isolated occasions. The raised E.S.R. was seen in connexion with complications of various kinds, e.g. severe tonsillo-pharyngitis, bronchopneumonia and mononucleosis. In two children (Cases 1 and 4) it was sustained for three months at a pathological level, and in another child (Case 2) up to a year.

The results indicate that the E.S.R. figures were highest during the first two months. In single estimations significant deviations were established up to the 12th month. During the following months, even with clinical signs of activity, the E.S.R. rarely surpassed the normal boundaries (the exceptions were in cases of mononucleosis and other severe complications).

**C-reactive Protein Test._** As a sensitive indicator of inflammation this test revealed interesting data during the different stages of the post-scarlet fever period. Negative results were obtained in only 11 cases. During the first 10 days the C.R.P. was positive in 10 of 16 cases investigated. The greatest number of positive results were seen during the period of the complications, i.e. the third to the sixth week. Up to the ninth month only in odd cases was the test positive, being usually + and rarely ++ (and linked with frequent exacerbations.
Fig. 1.—Summary of the laboratory tests on Cases 1-6.  
G = Influenza;  
T = Tonsillectomy.

Fig. 2.—Summary of the laboratory tests on Cases 22-31.  
G = Influenza;  
T = Tonsillectomy.
of an inflammation in the throat). At the end of the observed period a positive test occurred only in a few cases (in bronchopneumonia, mononucleosis and after tonsillectomy). After the ninth month even with clinical signs of active inflammation like tonsillo-pharyngitis the test remained negative. In cases with numerous complications (Cases 1-6), the estimation of C.R.P. during the time of activity showed a positive result repeatedly and the curve remained positive for a month or longer. A detailed analysis revealed that the test showed a positive result in active inflammation and then it quickly abated to become positive again with a new exacerbation. During the later stages of the post-scarlet fever period the test became scarcely positive even in an active inflammation.

**Serum Protein Fractions.** In 16 children the protein fractions were constantly normal, and in 15 children a moderate disproteinæmia was established. But even in Cases 1-6 the albumin levels rarely dropped below 45%, α₂ globulins did not surpass 6-6 relative % (0.52 g. %) and α₂ globulins reached maximal up to 15.8 relative % (1.31 g. %). The β globulins did not undergo significant changes. The most marked increase in the serum protein fraction levels occurred with the γ globulins, which increased early and remained high for a long time, reaching 26.5 relative % (1.85 g. %). From Fig. 1 it can be seen that the curves of the albumin/globulin ratio and of α and γ globulins show an irregular fluctuating course. These variations in the serum protein fractions correspond to the fluctuating course of the complications of infections of the mouth and throat as well as to the intercurrent infections. The variations of serum protein fraction levels indicated a fluctuation of α globulins chiefly during the first six weeks after the scarlet fever onset, being increased later only in odd cases with severe complications. The γ globulins were increased during the first 10 days and remained high for some months (in eight children up to five months and in some cases up to one year). During intercurrent infections and especially in influenza, changes took place only in γ globulins.

**Fibrinogen Levels.** In none of the cases was a plasma fibrinogen level over 600 mg. % recorded. In the plasma of six children a fibrinogen level of 400 to 600 mg. % was found: Case 1 on the fourth day of the disease, Case 2 on the third day after tonsillectomy, Case 4 on the tenth day of the scarlet fever, Case 5 on the 46th day, the period usually associated with complications, Case 12 on the 14th day and Case 19 on the 44th day in a severe tonsillo-pharyngitis.

**Antistreptolysin Reaction.** In 12 children the reaction was normal, and in 19 it was raised: being up to 400 units and up to 800 units in 10 and nine children respectively. Of nine children with raised A.S.O. five belonged to the group with numerous complications (chiefly of streptococcal type). The A.S.O. curve in this group remained at its high level for varying periods of time. In Case 4 a normal value was not established during 20 months. The greatest frequency of high titres was found between the third and the sixth week and in cases of persistent active inflammation of the throat. In the period after the second month the A.S.O. was raised only in a few cases.

**Haemagglutination Reaction.** During the post-scarlet fever period the test was positive in seven cases only after influenza.

**The Coombs Test.** The direct Coombs test was constantly negative; the indirect Coombs test was slightly positive in two cases after influenza and in a single case of infectious mononucleosis.

**Atypical Agglutinins.** These, with slightly or moderately raised titre, were found for a short time in four cases after influenza and in one case of infectious mononucleosis.

**Tissue Antibodies.** These were not found in the serum of any child.

The laboratory tests showed that symptoms of inflammatory and immunological type were found in 21 children, most clearly manifested in Cases 1 to 6. The laboratory changes in our 21 cases differed from those of the rheumatic attack (severe dysproteinæmia, hyperfibrinogenæmia and a raised A.S.O. titre) and were as those in infectious diseases, mainly with an increase of the γ globulins, slight and transient changes in the α globulins, normal or slightly raised fibrinogen levels, etc. There was no evidence of significant involvement of the connective tissue as in rheumatic fever. The immunological tests showed signs of streptococcal sensitization in 19 children, A.S.O. being slightly raised in 10 of them, and in the remaining nine children reaching 800 units. The raised level of the A.S.O. was likely to be caused both by the scarlet fever itself and by the different complications mainly of streptococcal origin. It is worth noticing that the A.S.O. in four children out of 21 who had had
influenza showed a non-specific raised titre of the
type of the anamnestic reaction.

There was a parallel between the clinical mani-
festations (mainly focal inflammations) and the
laboratory findings during the first six months, but
later changes in the immunobiological condition
were rarely found in the presence of clinical
symptoms.

In our series we had no experience with scarlet
fever patients who had not been treated with peni-
cillin.

Summary

Thirty-one children with scarlet fever treated with
penicillin were followed up for more than two years,
and laboratory tests (E.S.R., C.R.P., S.P.F.,
fibrinogen level, A.S.O., sensitized sheep cell
reaction, the Coombs test and reaction for tissue
antibodies) being carried out.

In 21 children immunobiological changes were
related to the numerous complications and inter-
current infections observed in the majority of
the cases during the first six months of the post-
scarlet fever period.

The clinical and cardiological check as well as
the laboratory tests showed no signs of rheumatic
fever.

There was no ground for considering that the
post-scarlet fever period was immunobiologically
identical with the acute phase of rheumatic fever,
nor with the period before the first rheumatic
attack.
Serological Investigations into Sequelae of Scarlet Fever with Particular Reference to Rheumatic Fever
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