

Studies on Acute Rheumatic Fever in the Adult

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The cases of acute rheumatic fever admitted to the Department of Internal Medicine of Toho University Hospital, were 42 patients in the period 1958 to 1960. The ratios of these patients to the total admitted patients in each year, were 2% respectively.

Considering an adult as 20 years old or over, such cases were found to be about half in number.

Furthermore, in this clinic, the incidence of rheumatic fever was much higher than that of other classical collagen diseases, with the exception of rheumatoid arthritis. Thus this disease seemed to have a great importance among collagen diseases in the field of internal medicine. Consequently, studies were made on several clinical and laboratory findings of adult rheumatic fever from the angle of collagen diseases. The rheumatic fever studied in this paper was limited to systemic non-suppurative inflammatory disease of protean manifestations, and fulfilled the Jones' modified criteria¹⁾.

The Comparison of Rheumatic Fever to Other Collagen Diseases

In the so-called collagen diseases²⁾, all elements of connective tissue are said to be involved. Since fibrinoid degeneration was frequently found at the involved vascular walls in collagen diseases, histological changes of vascular walls in various organs of 8 autopsy cases with rheumatic fever were observed.

Abnormal changes of arterial walls and perivascular connective tissue were found in the heart and lung, particularly the former, but unlike systemic lupus erythematosus and polyarteritis, no abnormal change was found in the spleen, kidney and liver. In 3 cases found with Aschoff bodies, subendothelial bloody infiltration,

perivasculitis and perivascular fibrosis were found. Furthermore, the histological findings of subcutaneous nodules showed the typical fibrinoid degeneration.

Clinically, however, the vast majority of rheumatic fever is an acute and self-limited disease¹, while other collagen diseases are chronic and progressive. The high titer of ASL-O in rheumatic fever seemed to prove its close relationship to streptococcal infection², but such a condition was not seen in other collagen diseases.

Blood ascorbic acid content³ was in the normal range in patients with rheumatic fever, but was low in rheumatoid arthritis during the active period. Urinary excretion ratio of ascorbic acid after intravenous administration of 100 mg. of ascorbic acid⁴ was remarkably low in both diseases. These results suggested the shortage of vitamin C in the body in rheumatoid arthritis, and an added requirement of vitamin C in rheumatic fever. Furthermore, the blood concentration of vitamin C had a positive correlation with serum mucoprotein (MP) level in rheumatic fever, but on the other hand, it had a negative tendency in rheumatoid arthritis. Accordingly, the changes of vitamin C metabolism were different between the both diseases.

In the acute phase with fever, serum iron level was decreased in rheumatic fever, rheumatoid arthritis and other classical collagen diseases; however, serum copper content was increased in rheumatic fever and rheumatoid arthritis but was normal in other collagen diseases¹. Thus the magnitude of serum iron and copper in rheumatic fever was more similar to that of infectious diseases than classical collagen diseases. Therefore, urinary 2, 5-Dihydroxyphenylpyruvic acid (2, 5-DHPPA)⁵ was measured in various diseases.

In the urine of cases with rheumatic fever, the white blueish fluorescent, ellipsoid spot similar to 2, 5-DHPPA, was blurred. FeCl₃ reaction of this spot showed the colour of blueish purple. Gibbs' reagent gave a fresh blue of the positive reaction, but one part was not corresponded exactly with this spot but appeared in neighbouring areas. Since these colour-producing reactions suggested that urine fluorescent substance in rheumatic fever different from synthetic 2, 5-DHPPA lactone, urine extracts were developed by one-dimensional chromatography of 7 kinds of solvent systems. In spite of these

many solvent systems, observing the Rf value, the character of fluorescence under ultra-violet light and the colour reactions, the fluorescent reducing substance could not be identified as 2, 5-DHPPA. Furthermore, by the two-dimensional chromatography, employing n-propanol and NH_4OH followed by the butanol system, the fluorescent substance was divided into two spots. Developed by the streak method, it was proved that the fluorescent spot was composed of three different fluorescent substances. The ultra-violet absorption curve of the substance of Rf 0.85 among this composition was apparently different from that of 2, 5-DHPPA.

As a result, a similar substance to 2, 5-DHPPA could be demonstrated but was unable to be identified exactly.

However, this fluorescent reducing substance was found in 8 of 9 patients with rheumatic fever, in 5 of 10 cases of rheumatoid arthritis, in all 3 cases of systemic lupus erythematosus and in one case of progressive systemic sclerosis. On the contrary, in normal individuals and in cases with infectious diseases and malignant tumors, in which clinical symptoms resembled those of collagen diseases, such a substance was not found (Table 1).

Thus, also from the point of this biochemical view, rheumatic fever was not an infectious disease but may be included in the category of collagen diseases.

Recently, a few references⁷⁾ have reported that although, in the early stage, several symptoms seemed to be confirmed as rheumatic

Table 1. The number of cases found with urine fluorescent reducing substance.

Diseases	Total cases	Cases found	%
Rheumatic Fever	9	8	88
Rheumatoid Arthritis	10	5	50
Systemic Lupus Erythematosus	3	3	
Progressive Systemic Sclerosis	1	1	
Infectious Diseases	8	0	0
Malignant Tumor	2	0	
Normal Individual	4	0	0

fever or rheumatoid arthritis, at some later time lose the features exclusive of these maladies and present evidence of unmistakable systemic lupus erythematosus, polyarteritis, dermatomyositis or scleroderma. Thus, the relationship of the rarer collagen diseases to rheumatic fever is the important problem.

In all cases of rheumatic fever observed in this study for 3 years, LE cell test, Wassermann reaction and Coombs' test were negative, but in a few cases, positive CCF, TTT and RA-test were found. These positive findings were found to continue for a long time in spite of treatment in other collagen diseases, but transient in rheumatic fever.

In cases which showed positive LE cell test, initial symptoms were observed and analyzed based on major symptoms of Jones' modified criteria. In one case, a suspicious presence of active carditis because of congestive heart failure, was observed. But in this case, since the symptom of polyarthrititis and the elevation of ASL-O were not found, the diagnosis of rheumatic fever was denied.

Comment: From the histological changes and urine fluorescent reducing substance, rheumatic fever was similar to other collagen diseases. From the behavior of ascorbic acid metabolism and the magnitude of serum iron and copper content, rheumatic fever was differentiated from other collagen diseases.

The Clinical Characteristics of Adult Rheumatic Fever⁸⁾

At the onset, the sudden occurrence of joint symptoms appeared in 78%. Arthralgia was found in 57% of the younger group between the ages of 14 and 19 years, but in 80% of the adult group. Arthritis was also found in adult group more frequently than in younger group. On the other hand, the skin symptoms were found in only a few cases of adult group. Subcutaneous nodules and chorea were not found at all in adult group.

One of most important problems in rheumatic fever is active carditis. The criteria of diagnosis of carditis was difficult, particularly, in adult rheumatic fever⁸⁾, because it was presumed that there were many recurrent cases despite no previous history. Thus retrospective studies on cardiac symptoms were made.

The cases with systolic heart murmur of grade 3 or more at apex or diastolic murmur at admission, were found in 80% of younger group and in 88% of adult group. Among these cases, the disappearance of significant heart murmur after treatment was found in 12% of the former and in 25% of the latter. Although it was thought that the disappearance of heart murmur was influenced by the mode of treatment and the stage of beginning of treatment, it was assumed that the initial attack was found even in adult rheumatic fever, and such carditis was not so severe compared to that of younger group.

The various abnormal findings of E. C. G. at admission were observed. There was a tendency that the findings of PR prolongation, QT prolongation and sinus tachycardia were observed more frequently in younger group, while the findings of low voltage, extrasystole, atrial fibrillation and atrioventricular heart block were more frequent in adult group. These abnormal findings, particularly, the finding of conduction defects were found to be very unstable for a short period.

In this study, the change of PR interval was observed, although the change could not be detected as vagal effects. This change was found in 69% in younger group and in 42% in adult group.

Since the heart size were frequently experienced to become smaller due to anti-inflammatory drugs, the roentgenological heart figures were investigated. In a few cases, transverse diameter, longitudinal diameter, transverse thickness of the left ventricle and breadth diameter were changed in a parallel rate. Consequently, the transverse diameter was used as the indicator of heart size. In normal individual and slight pulmonary tuberculosis from 18 to 40 years old, the differences of transverse diameter ranged from +0.6 to -0.5 cm. In a few cases of pulmonary tuberculosis in which many chest X-rays were examined for 1 to 3 years, the differences between the maximum and the minimum was found to be 0.8 cm. in. only one case, and 0.6 cm. or under in other cases. The difference of transverse diameter between systole and diastole was said to be 0.6 to 0.7 cm. In this study, since the roentgen kymography was not used, 1.0 cm. or more was decided as a significant difference. In only a few cases with rheumatic fever, its difference

showed 0.7 to 0.9 cm. but in most cases, it showed 1.0 cm. or more.

In many cases with rheumatic fever of both groups, the transverse diameters were greater than that of control group. The shortening two months after beginning of treatment, showed 1.0 cm. or over in both groups. But before treatment, in some cases, the transverse diameter became greater by 1.0 cm. or more, for a relatively short period. This significant change of 1.0 cm. or more, was found in 69% of younger group and in 67% of adult group.

Congestive heart failure associated with polyarthrititis was found in 25% of younger group and in 17% of adult group.

Pericarditis was found in 25% of the former and in 16% of the latter.

Viewing the relationship of these abnormal findings, it was found that in the cases with significant change of transverse diameter, other abnormal findings coexisted. Thus, it was assumed that the significant change of diameter demonstrated the active carditis. Judging conclusively from these changes of abnormal findings, it was said that active carditis was found in 82% of younger group and in 67% of adult group. Accordingly, it was emphasized that active carditis was found, by no means, in low incidence even in adult rheumatic fever.

In B. S. R., leucocyte counts, serum MP level, CRP and protein fractions, no difference was found between both groups.

The number of cases which showed 250 units or over of ASL-O titer, was the same in both groups.

Comment: Compared to younger group, as the clinically characteristic feature of adult rheumatic fever, high incidence of joint symptoms, low incidence of skin symptoms and carditis and furthermore no case of subcutaneous nodules and chorea were shown. However, active carditis could not be said to be rare.

A Few Problems of Diagnosis

The diagnosis of rheumatic fever was dependent upon clinical symptoms; however, typical migratory polyarthrititis was not found so frequently and it was also difficult to determine whether or not active carditis was present unless the clinical course was observed.

In 70% of rheumatic fever, ASL-O titer showed 500 units or more; however, in other various diseases, such high titer was rarely found. Thus, measurement of ASL-O titer was the important examination to help the diagnosis, but it did not have an absolute value.

Urine fluorescent reducing substance, as mentioned previously, was valuable to differentiate rheumatic fever from other diseases exclusive of collagen diseases. However, in the urine obtained after aspirin administration, two fluorescent spots which showed Rf values of 0.95 and 0.85 respectively, were developed. By the Rf values in various solvent system and various colour-producing reactions, the former was identified as salicylic acid. This salicylic acid spot disappeared within 24 hours in both normal individuals and rheumatic fever patients. The latter had remained much longer than 24 hours; furthermore, this spot was similar to 2,5-DHPPA in respect of Rf value and the character of fluorescence. It was interesting that in rheumatic fever, this spot had been found to remain for a longer time than in the normal individual. This spot was apparently differentiated from 2,5-DHPPA by colour producing reactions and Rf values by other solvent systems, and was identical to salicyluric acid of Armstrong's data.

The yellow fluorescent spot of Rf 0.66 by Nishimura's method⁵⁾ was not free homogentisic acid, but divided into two spots by two-dimensional chromatography. As shown in Fig. 1, this spot was always and most definitely found in rheumatic fever, but scarcely found in the normal individual.

Furthermore, when the urine was developed by 3% NH_4Cl , a spot was found at Rf 0.28. This spot was also typical of rheumatic fever and was influenced by aspirin. Immediately after one dose of aspirin administration, the intensity of this fluorescence was decreased but gradually returned to the original condition (Fig. 2).

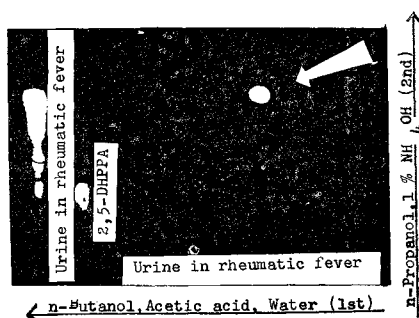


Fig. 1. Urine fluorescent reducing substance (two-dimensional chromatography).

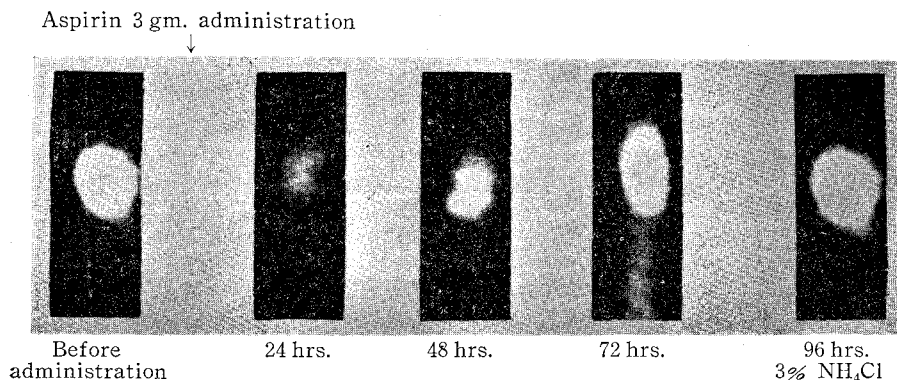
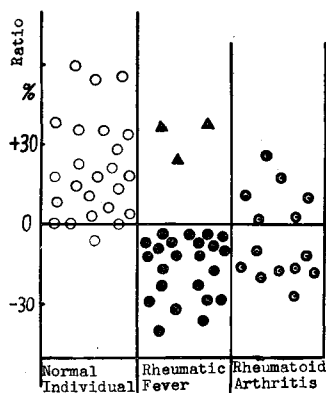


Fig. 2. The change of urine fluorescent reducing substance (Rf 0.28) after aspirin administration in rheumatic fever.

In the early stage, it is frequently difficult to differentiate it from other collagen diseases. Thus the response to aspirin was observed. The effect of 3 or 6 gm. of aspirin on fever was not different between rheumatic fever and rheumatoid arthritis. However the effect on arthralgia was dramatic in only rheumatic fever, and disappeared within 5 days⁹⁾. Accordingly, the aspirin response was a valuable test to differentiate it from other collagen diseases.

Chondroitin Sulfate Tolerance Test⁹⁾

The MP level in active rheumatic fever was decreased 48 hours



▲ 90 days or more from the onset to the performance of the test

Fig. 3. Chondroitin sulfate tolerance test.

after an intravenous injection of 2 c.c. of 3% chondroitin sulfate solution. This phenomenon was not found in all healthy individuals. In 3 cases in which this test was performed after 90 days or more from the onset, contradictory evidence was found (Fig. 3). However, in these cases, this test showed abnormal reaction immediately after prednisolone treatment.

Fifteen to 20 mg./kg. of allylamine hydrochloride¹⁰⁾ in Michaelis solution was injected into normal

rabbits 4 times every other day. In these rabbits, histological findings of angitis was not found, but in 1/3 of the cases, serum MP level was found to be increased. In these cases, the behaviour of this test was the same as active rheumatic fever and the results of normal rabbits were the same as normal individuals. Unfortunately, the mechanism of this test is, at present, obscure. But the reliance of this test was proved by the above mentioned animal experiments.

Next, it was examined whether or not this tolerance test had any significant value during hormone treatment, since the MP level was gradually decreased with the suppression of the inflammatory process particularly when large doses of steroid hormone were used. When the decrease of MP level was observed, it is necessary to determine whether it is due to the influence of chondroitin sulfate or due to the anti-inflammatory potency of hormone.

During the prednisolone (60 mg.) treatment, the MP level was measured twice at 48 hours intervals, and the second MP level was compared with the first.

Immediately following the second removal of blood for MP level determination, 2 cc. of 3% chondroitin sulfate solution was intravenously injected, while continuing the prednisolone dose. Forty-eight hours after the injection of this solution, the MP level was measured again, and was compared with the second.

The MP level was not decreased by the administration of prednisolone for at least 48 hours in most cases. However, when chondroitin sulfate solution was injected, marked decrease of MP level was found in all cases.

From these results, this test could be performed during anti-inflammatory treatment. Even in the cases in which steroid hormone was withdrawn after the return to normal of this test, the deterioration of laboratory, clinical or both findings, was observed in 13 of 19 cases.

These deteriorations occurred 2 to 7 days after withdrawal of steroid hormone, and spontaneously disappeared, or responded to the small dose of hormone for a short period of 1 to 3 days.

However, in the cases in which steroid hormone was withdrawn before the return to normal of this test, in spite of the return to normal or disappearance of acute phase reactants, the reappearance

of abnormal laboratory and clinical symptoms occurred immediately after cessation of treatment. These deteriorations continued for a long time, and did not respond to small doses for a short time.

Particularly, the changes of transverse diameter of the heart after the cessation of treatment were not found to be increased in the former group at all except one case which was suggested to be a recurrent one, but were found to be increased about 1.0 cm. during the short period, in all 4 cases of the latter group. Thus it should be said that the deteriorations found in the former group were rebound²¹⁾, and those found in the latter were relapse.

Comment: Although the mechanisms of chondroitin sulfate tolerance test is unknown, it was emphasized that this test was postulated as the indicator of cessation of anti-inflammatory drugs.

Effect of Steroid Hormone and Aspirin on Rheumatic Fever

The effect of the following drugs were^{3),9),11)~21)} compared: 60mg. and 30 mg. of prednisolone and 6 gm. and 3 gm. of aspirin.

Effect on the toxic symptoms:

There was a tendency that 60 mg. of hormone was able to bring about more rapid control of toxic symptoms of fever and arthralgia than the other groups. However, on the whole, marked difference of the effect on toxic symptoms was not found in all groups.

Effect on the acute phase reactants:

The effect of 60 mg. of hormone on acute phase reactants of serum MP, CRP, and protein fractions, was definitely superior to that of the other 3 groups. However, the effect of 6 gm. of aspirin was not different from 30 mg. of prednisolone, while the 3 gm. of aspirin was the least effective.

Effect on the cardiac symptoms:

Only in cases receiving continuous penicillin prophylactic therapy, the effect on cardiac symptoms were judged from the disappearance of significant heart murmur and the significant change of the transverse diameter. In 60 mg. of prednisolone group, 6 cases with disappearance of significant heart murmur were found, and in 6 gm. of aspirin group, only one such case was found, but in the other groups, no case was found. Compared to the change of trans-

verse diameter 10 weeks after the beginning of the treatment, in 77% of 60 mg. prednisolone group, its shortening of 1.0 cm. or more was found, but its significant elongation was found in no case. In 60% of 30 mg. prednisolone group, significant shortening was found, while in aspirin group, only 25% was found. Furthermore, it should be mentioned that in the latter two groups, its elongation of 1.0 cm. or more was found in about 20%.

Side effects:

The frequency of side effects in cases of 60 mg. of prednisolone was less than that of 6 gm. of aspirin. These symptoms disappeared after the cessation of steroid hormone. Severe side effects, which necessitated the cessation of hormone, were not found.

The effects on the course of rheumatic fever:

It was assumed that the return to normal of chondroitin sulfate tolerance test showed the recovery of the inflammatory process. If this hypothesis may be adopted, the period from the onset to the return to normal of this test might be indicated as the inflammatory process of rheumatic fever.

Judging from the whole length of the inflammatory process used in this test, this process was shortened in some cases of 60 mg. of prednisolone. Among these shortened cases, the significant heart murmur disappeared in 3 cases.

Summary

1) Rheumatic fever showed the characteristics of collagen diseases. But in reality when compared with other collagen diseases, it showed independent traits.

2) Even in adult rheumatic fever, the first attack was found. In such cases, sequel heart damage may be prevented when large doses of steroid hormone were administered in the early stage and continued until the return to normal of chondroitin sulfate tolerance test.

3) Therefore, it was assumed that this disease should be differentiated from other similar diseases in which a different mode of treatment was necessary. For this purpose, a few results were reported.

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