

IMMUNOLOGIC FACTORS IN ACUTE RHEUMATIC FEVER COMPARED TO RHEUMATIC HEART DISEASE

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ABSTRACT

Background/Objective: To clarify the state of different immunologic factors in patients with acute rheumatic fever (ARF) and rheumatic heart disease (RHD) compared to healthy individuals.

Patients and Methods: Patients with ARF (#21), patients with RHD six months after the onset of ARF (#19), and healthy children from the same age group with normal physical examination and no history of pharyngitis during the previous month as the control group (#20) were studied. All patients were evaluated and followed for the presence and the severity of carditis, heart failure, and valvular involvement with echocardiography. Antistreptolysin-O (ASO) titer, erythrocyte sedimentation rate (ESR), serum complements C3 and C4, immunoglobins IgA, IgM, and IgG, IgM Rheumatoid Factor (RF), IgM and IgG anti-cardiolipin antibody (ACLA), and IgM and IgG anti-M group A streptococcal protein (AMP) were compared.

Results: There was a significant difference for IgG and IgM.ACLA between groups ($p=0.005$ and $p=0.0001$, respectively). These results were shown to reflect the difference between patients with ARF and the other two groups. There was a significant difference for IgG AMP between ARF and RHD groups ($p=0.05$). There was a significant difference for IgM RF between ARF and RHD groups ($p=0.05$). There was a significant difference for serum IgG between groups ($p=0.0005$). This was shown to reflect a significant difference between patients with ARF and the two other groups. Serum IgG was significantly lower in patients with, than in patients without, aortic valve involvement ($p=0.039$). Similarly, Serum IgG was significantly lower in patients with pericardial effusion ($p=0.013$).

Conclusion: There are significant differences for IgG and IgM ACLA and IgG AMP and serum IgG levels and IgM RF between ARF patients and the other two groups. Whether IgG has a "protective effect" in patients with ARF preventing them from developing pericardial effusion, aortic valve involvement, or other complications is a notable question that must be answered.

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Key Words • Rheumatic fever, acute • rheumatic heart disease • immunologic factors, humoral

Introduction

After more than a century of research on rheumatic fever, ambiguities remain as to its precise pathogenesis except that it is triggered

by a group A β -hemolytic streptococcal pharyngitis in susceptible individuals.¹ This is more challenging when one considers that the disease is still a major problem worldwide particularly in developing countries.^{2,3}

Although all authorities accept the role of immunologic, and especially humoral factors,⁴ there is no consensus on their exact role and changes of these immunologic parameters.⁸

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Table 1: Humoral immunologic factors in 21 patients with acute rheumatic fever (ARF), 19 patients with rheumatic heart disease (RHD) lasting more than six months, and 20 healthy children from the same age group as the control group.

Immunologic Factor	Patients with ARF		Patients with RHD		Control group	
	Range	Mean \pm SD*	Range	Mean \pm SD	Range	Mean \pm SD
ACLA [†] IgG	0.182-0.627	0.333 \pm 0.114	0.073-0.357	0.213 \pm 0.07	0.102-0.557	0.192 \pm 0.102
ACLA IgM	0.077-0.406	0.275 \pm 0.079	0.045-0.55	0.161 \pm 0.111	0.054-0.309	0.162 \pm 0.085
AMP [‡] IgG	0.410-1.239	0.99 \pm 0.222	0.106-1.184	0.797 \pm 0.313	0.264-1.126	0.845 \pm 0.259
AMP IgM	0.33-1.038	0.625 \pm 0.215	0.246-1.131	0.529 \pm 0.196	0.124-0.993	0.563 \pm 0.245
RF [‡] IgM	0.105-1.173	0.33 \pm 0.239	0.075-0.511	0.179 \pm 0.122	0.048-0.721	0.203 \pm 0.161
IgG	8.6-32	26.5 \pm 6.65	1.6-32	18.8 \pm 10.39	3-25.4	14 \pm 6.98
IgM	0.8-4	2.44 \pm 1.08	0.6-4	1.95 \pm 1.1	1-3.8	2.29 \pm 0.88
IgA	0.4-6.2	3.31 \pm 1.51	1.2-6.2	3.24 \pm 1.56	0.6-6	2.9 \pm 1.67
C3	0.99-2.18	1.5 \pm 0.34	0.63-1.9	1.28 \pm 0.35	0.47-1.9	1.34 \pm 0.42
C4	0.04-0.68	0.4 \pm 0.18	0.12-0.78	0.38 \pm 0.16	0.19-6.1	0.69 \pm 1.28
ASO ^{**}	200-1600	647.6 \pm 446.8	-	-	-	-
ESR ^{**}	21-135	71.5 \pm 32.3	-	-	-	-

Standard Deviation, [†]Anti-Cardiolipin Antibody, [‡]Anti-M group A streptococcal protein, [‡]Rheumatoid factor, ^{**}Antistreptolysin-O titer, ^{**}Erythrocyte sedimentation rate

This study intends to investigate the state of humoral immunologic factors involved in patients with acute rheumatic fever (ARF) and rheumatic heart disease (RHD).

Materials and Methods

The following groups were enrolled in the study: 1- Patients developing ARF for the first time (#16) or in the acute phase of recurrent ARF (#5). Using modified Jones inclusion criteria. 2-Patients with RHD developing more than six months after the onset of ARF (#19). The latter group was receiving monthly benzathin penicillin. 3- Healthy children from the same age group with normal physical examination and no history of pharyngitis during the previous month serving as the control group (#20).

Informed written consent was obtained from all subjects or their parents prior to enrollment in the study.

All patients were evaluated and followed for the presence and severity of carditis, heart

failure, and valvular involvement by echocardiography. Peripheral blood sampling was undertaken before starting any medications. Antistreptolysin-O (ASO) titer, erythrocyte sedimentation rate (ESR), serum complements C3 and C4, IgA, IgM, IgG immunoglobulins, IgM rheumatoid factor (RF), IgM and IgG anti-cardiolipin antibody (ACLA), and IgM and IgG anti-M group A streptococcal protein (AMP) were measured. The same data were obtained for the control group.

IgM RF, IgM and IgG ACLA, and IgM and IgG AMP were measured using enzyme linked immunosorbant assay (ELISA). Serum complements C3 and C4 and immunoglobulins were measured using single radial immunodiffusion (SRID).

Rabbit anti-human IgG peroxidase conjugate and rabbit anti-human IgA peroxidase conjugate from DAKO, Denmark; human IgG from Pasteur-Merieux, France, and anti-human IgG peroxidase conjugate and anti-human IgM peroxidase conjugate from Calbiochem, USA.

Data were analyzed using Student's *t*-test, one-way ANOVA, TUKEY, and LSD statistical tests.

Results

The mean \pm standard deviation (SD) for age in patients with ARF was 9.3 ± 3.4 years. This was 11.2 ± 3.8 and 12.1 ± 3.1 for patients with RHD and healthy children, respectively. There was no significant age difference between the three groups ($p > 0.05$, one-way ANOVA).

The immunologic parameters in the three groups are summarized in Table 1. One-way ANOVA showed that there is a significant difference for IgG ACLA between the two studied groups ($p = 0.005$). This illustrates the difference between patients with ARF and the other two groups using TUKEY test. There was also a significant difference for IgM ACLA between groups using one-way ANOVA ($p = 0.0001$). This also reflects the difference between patients with ARF and the two other groups.

There was no significant difference for IgG AMP between groups using one-way ANOVA and TUKEY tests. However, there was a significant difference for IgG AMP between ARF and RHD groups using LSD test ($p = 0.05$). There was no significant difference for IgM AMP between groups using one-way ANOVA, TUKEY, or LSD tests.

There was no significant difference for IgM RF between groups using one-way ANOVA and TUKEY tests. However, there was a significant difference in IgM RF between ARF and RHD groups using LSD test ($p = 0.05$).

In contrast to TUKEY's test, one-way ANOVA showed that there is a significant difference for serum IgG between groups ($p = 0.0005$).

No significant difference in serum IgM, IgA, C₃, and C₄ was found between groups using one-way ANOVA test.

Patients with ARF were divided into two groups according to the presence or absence of heart failure. We found no significant difference between these two groups in terms of the immunologic parameters. Grouping patients with ARF according to the degree of mitral valve involvement, recurrence of ARF, and improvement on successive echocardiograms had similar results with no significant difference between the two groups for the immunologic parameters.

In grouping patients with ARF according to the presence of aortic valve involvement, there was no significant difference in immunologic parameters between the groups except for serum IgG that had a mean \pm SD of 24.18 ± 7.36 in patients with and 30.25 ± 2.72 in patients without aortic valve involvement ($p = 0.039$). Grouping patients with ARF according to the presence of pericardial effusion had similar results with no significant difference between the two groups for the immunologic parameters except for serum IgG that had a mean \pm SD of 25.8 ± 6.95 in patients with and 30.67 ± 1.16 in patients without pericardial effusion ($p = 0.013$).

Discussion

This study shows that both IgG and IgM ACLA in patients with ARF is significantly higher than patients with RHD. This is in accord with previous studies showing the relation between ACLA and ARF.⁹ In contrast to those studies,¹⁰ our data did not show any correlation between ACLA and complications of ARF such as heart failure, pericardial effusion, mitral and aortic valve involvement. This study also failed to detect a statistically significant difference in ACLA between patients with first episode of, and patients with recurrent, ARF. However, this finding may be a result of the small number of patients with recurrent ARF enrolled in this study and must be evaluated in larger studies.

There was no significant difference for IgG and IgM AMP between groups. Although there was a significant difference for IgG AMP between ARF and RHD groups using LSD test ($p=0.05$), this difference was very small as this test detects small differences. This finding is in contrast to the significant difference for AMP between patients with ARF, streptococcal pharyngitis and control reported by Mori and co-workers.¹¹ Our findings show no relation between AMP and complications of ARF such as heart failure, pericardial effusion, mitral and aortic valve involvement. To the best of our knowledge, there is no previous research investigating this relation and the findings of this study must await confirmation by future studies.

Our study shows that RF and other immunologic parameters such as serum IgM, IgA, C₃, C₄, and ASO titer are not different between patients with ARF, RHD, and the control group. Nor are they related to complications of ARF such as heart failure, pericardial effusion, mitral and aortic valve involvement.

Our findings reveal that serum IgG in patients with ARF is significantly higher than patients with RHD and the control group, a finding which is in accord with previous studies.¹² Although not related to carditis, serum IgG is significantly lower in patients with ARF and pericardial effusion. It is also significantly lower in patients with ARF and aortic valve involvement. Unfortunately, there are no previous reports on this issue. The reproducibility of these findings as well as the question whether or not IgG has a "protective effect" in patients with ARF preventing them from developing pericardial effusion, aortic valve involvement, or other complications are

noteworthy and require further study.

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