ANTICARDIOLIPIN ANTIBODIES (acL) IN ACUTE RHEUMATIC FEVER

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Gazi Medical Journal 2000; 11: 103-106

ABSTRACT

Background : *Acute rheumatic fever (ARF) is a multisystemic autoimmune inflammatory disease. Anticardiolipin antibodies (acL) are found in different clinical situations such as autoimmune disease, infections, myocardial infarction, thrombocytopenia etc. This study was planned to detect the incidence of two major immunoglobulin (IgM and IgG) classes of acL in rheumatic patients.* ***Method and Results:*** *Twenty-four rheumatic patients, 10 uncomplicated streptococcal tonsillitis and 10 normal controls were screened for acL by ELISA technique. acL IgM was detected in 41.0% of patients with active carditis on first admission (17.22±9.73 units), 33.3% on the second and sixth weeks (9.93±7.41 units) and 66.6% in total. The difference between the first and the sixth weeks were significant. acL IgM plus IgG positivity was 75% in patients with rheumatic carditis. acL IgM was detected in 58.3% of patients with rheumatic arthritis. C3,C4,ANA and VDRL tests were negative in all groups. Control groups showed 10% acL positivity that was significantly lower than the rheumatic patients.* ***Conclusion :*** *The results of this study showed that both major Ig classes of acL have been detected in ARF patients. However, IgM acL is more frequent and appears to correlate best with clinical disease activity. IgG acL occurs more frequently in SLE and thrombosis cases and was not frequent in ARF. Characterization of the acL isotype and the follow up of their evolution are useful in the diagnosis, follow up and therapy of the disease. Their pathogenic potential in different autoimmune diseases seem different according to their isotype and antigen specificity.*

Key Words: *Rheumatic Fever, Anticardiolipin Antibody, Carditis.*

INTRODUCTION

Acute rheumatic fever (ARF) is still an important disease in developing countries, as well as developed countries, as it has resurfaced in recent years. It is estimated that there are 15-20 million new cases of ARF in the world each year (1). Studies concerning its pathogenesis still continue. Some studies about anticardiolipin antibodies (acL) in ARF are present in recent literature. Reyes et al. (2) found 16% acL positivity in rheumatic patients while Narin et al. (3) did not find significant elevation of acL in ARF patients. However Figueroa et al. (4) have reported 67 % IgG acL positivity in rheumatic patients. These conflicting results cannot be explained on the basis of methodological

differences, but could easily be a result of the large variation in the natural course of the disease. Therefore we decided to study the incidence of two major immunoglobulin (IgM and IgG) class of acL in different forms of rheumatic fever, follow up their evaluation and correlate the results with disease activity, clinical manifestations, and discuss the significance of their pathogenesis.

PATIENTS and METHODS

Patients

This study was carried out in two groups: First; 12 ARF patients between 6-15 years of age with carditis, second; 12 ARF patients of the same age with pure arthritis. The diagnosis of ARF was confirmed by clinical findings and laboratory examinations according to the modified Jones criteria (5). Eight of the carditis patients were treated with prednisolone (2mg/kg/day), and four carditis and all arthritis cases were treated with acetylsalicylic acid (100mg/kg/day). None of the patients had any signs or symptoms of systemic lupus erythematosus (SLE).

The controls consisted of two age-matched groups:

First ; 10 normal healthy children without any infection or disease.

Second; 10 children with upper respiratory tract infection (URTI) and positive throat culture for group A beta hemolytic streptococcus (GABHS) .

Methods

Blood samples for the following tests were taken from the patients and controls, prior to medication on first admission and also on the second and the sixth weeks of the disease. Blood samples from the control groups were taken only on admission.

Erythrocyte sedimentation rate (ESR) by Westergreen method , C-reactive protein by latex particle technique, antistreptolysine-O by latex particle technique, VDRL by flocculation technique with cromatest kit M 170 (Linear Chemicals, Spain), antinuclear antibody (ANA) by indirect fluorescent method, C3 and C4 by nephelometry method and anticardiolipin antibodies (acL) by ELISA technique with Imulyse-TC acL kit (Biopool International, Ventura, USA) were applied (6). GPL and MPL units (units corresponding to the binding activity of 1mg/ml of purified anticardiolipin antibody) were used for the IgG and IgM acL respectively .

The cut of levels of positivity for IgG acL and IgM acL were 23 GPL and 11 MPL respectively (7).

The chi-square test was used for the statistical analysis, and the relationship of acL to acute phase reactants was analyzed by Pearson's correlation test.

RESULTS

The IgM acL and the IgG acL positivities of the groups are shown in Table 1 . We selected new cases for positivity of acL in each period. Total acL positivity in ARF was 75 % ; 66.6% of carditis and 58.3 % cases of arthritis showed positive test results.

The IgM acL (MPL) and IgG acL values of the groups are shown in Table 2. There were significant differences between the first (17.22±9.73 units) and sixth week (9.93±6.07

Table 1: IgM acL and IgG acL positivity of the groups (%).

Group		IgM acL	IgG acL
Carditis:			
	1st week	41.0	0.0
	2nd week	33.3	0.0
	6th.week	33.3	8.3
	Total	66.6	8.3
Arthritis:			
	1st.week	33.3	25.0
	2nd.week	25.0	8.3
	6th.week	25.0	0.0
	Total	58.3	33.3
URTI		0.0	10.0
Normal controls		20.0	10.0

Table 2 : IgM acL (MPL units) and IgG acL (GPL units) values: mean±SD.

Group		Minimum	Maximum	Mean	SD	Range	Variance
Carditis							
1st week	IgM	6.84	37.67	17.22	9.73	30.83	94.76
	IgG	4.34	21.31	13.93	5.97	16.97	35.59
2nd week	IgM	5.42	27.08	11.94	7.41	21.66	55.03
	IgG	2.56	10.84	6.69	2.71	8.28	7.37
6th week	IgM	4.47	25.44	9.93	6.07	20.97	36.89
	IgG	5.26	25.34	12.73	6.14	20.08	37.65
Arthritis							
1st week	IgM	5.80	28.05	12.16	6.99	22.25	48.90
	IgG	6.29	29.26	13.73	6.45	22.97	41.64
2nd week	IgM	4.15	34.68	10.66	8.91	30.53	79.42
	IgG	3.91	32.48	12.61	8.49	28.57	72.18
6th week	IgM	1.79	26.89	9.09	7.69	25.10	59.13
	IgG	1.27	18.49	9.52	5.05	17.22	25.50
URTI	IgM	3.06	10.36	5.59	2.70	7.30	7.31
	IgG	2.43	44.72	14.82	3.85	42.29	148.55
Normal Controls	IgM	2.48	15.28	6.78	4.29	12.80	18.38
	IgG	1.64	29.09	8.92	7.93	27.45	62.83

units) IgM acL levels of carditis group ($p<0.05$).

The IgM acL levels were higher in ARF patients than URTI and normal controls ($p<0.05$). There was no significant difference between IgG acL levels of ARF and control groups.

ANA and antiDNA, VDRL, C3 and C4 levels were within normal limits in all groups.

ASO, CRP ve ESR values were significantly high in ARF group ($p<0.05$), but there was no significant difference between arthritis and carditis groups. There was no correlation between these values and acL measurements.

DISCUSSION

Anticardiolipin antibodies are formed in different clinical situations such as autoimmune diseases, infections, drug exposure, myocardial infarction, thrombocytopenia and malignancy. Their three subclasses; namely IgG, IgM and IgA were studied extensively in disease states (8, 9). IgM acL was demonstrated in children with infectious diseases as a transient phenomenon (8), but it did not show an association with any of the thrombotic clinical complications (10). IgG acL occurs more frequently in SLE and thrombosis cases. Both of the major classes have been detected in SLE cases, but IgG acL appears to correlate best with the clinical activity. In a group of patients with valvular heart disease (MI and AI), lupus anticoagulant and stroke were identified by Chartash et al. in 1986 (11). Also Asherson et al. documented two mitral insufficiency (MI) cases in their patients with chorea and acL (12). Figueroa et al. (4) reported 67% IgG acL positivity in rheumatic carditis cases which is even higher than the SLE cases reported by Hugnes (13) as 40%-60% and JRA cases reported as 7.9% to 53% (14). In our study both IgG acL and IgM acL levels were moderately high in ARF. IgM acL was found more frequently in active carditis. Its total frequency was 75% in ARF (66.6% in active carditis, 58.3% in acute arthritis cases). This result correlates well with Figueroa's cases who found it to be 67% in carditis cases. The difference is in the type of the immunoglobulins and positivity in ARF patients with arthritis (4). Reyes found 16% IgG acL positivity in rheumatic heart disease cases which was not in conflict with our results (2). We found 8.3% IgG acL positivity in inactive heart disease. Narin et al. did not find significant elevation of acL in any of their rheumatic cases (3). We think that the differences arise from the stage and the clinical form of the disease and, possibly from the medication used. We tried to follow the patients during the active state and take the blood samples every 2-3 weeks; so that we could be able to detect the time when acL becomes positive. The natural course of IgM acL in ARF cases showed high level on admission, and a decline beginning on the second week and reaching normal control levels at the sixth week. Only two cases did not show any decrease in the sixth week, but they reached the

normal level at the 8th week. This course correlated well with the clinical and laboratory findings of activity as with ESR and CRP. Treatment with salicylates and steroids did not show significant differences in the course of the acL levels in patients with active carditis. However the arthritis cases that were treated with salicylates only displayed a more rapid decline than carditis cases. Although the number of cases were not sufficient to draw a clear conclusion, the IgM acL levels were higher in severe carditis with congestive heart failure than mild or moderate carditis cases. It seems possible that acL may play a role in the severity of carditis by its effect on the endothelial tissues. However IgM acL or IgG acL positive cases did not have any thrombosis or bleeding symptoms. This result does not support the reports indicating high frequency of thrombotic events in acL positive patients (8). However, it is in favor of the reports that IgM acL developed in infectious diseases and their concentrations progressively decrease when the inducing cause stops (12). acL may play the role of a mediator of tissue injury in rheumatic fever. Its appearance at the beginning of the disease and decline through the second week supports this idea. acL may have a different pathogenic potential in different autoimmune disorders (15). This may be related to its potential cross reactivity with several tissue phospholipids in different diseases.

In conclusion, whether acL plays a crucial role in the pathogenesis of ARF yet needs to be elucidated. However it can be helpful in the diagnosis of activity as a nonspecific test like acute phase reactants.

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