



ANTISTREPTOLYSIN O TITER AND C-REACTIVE PROTEIN LEVELS IN PEDIATRIC PATIENTS OF ACUTE RHEUMATIC FEVER.

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INTRODUCTION

Acute Rheumatic fever (ARF), an inflammatory disease, is a sequela of *Streptococcus pyogenes*. A infection. It typically manifests two to three weeks after group A streptococcal (GAS) throat infection.^{1,2} The common symptoms include fever, multiple joint pains and reflexive muscle movements; in very rare cases non-itchy rash, and erythema marginatum can occur. Carditis and Arthralgia accounts for the most common manifestations of ARF accounting for 30-80% and 35-66% of cases, respectively.^{3,4} Rheumatic carditis is the most disabling complication of ARF accounting for spectrum of manifestations ranging from myocarditis, to pericarditis and

ABSTRACT... Objectives: To determine serum levels of antistreptolysin O titre (ASOT) and C-reactive protein (CRP) and their association with clinical manifestations of Acute rheumatic fever (ARF). **Study Design:** Descriptive study. **Setting:** Department of Diagnostic Immunology and Serology, Children's Hospital and Institute of Child Health, Lahore. **Period:** Jan 2015 to Jan 2016. **Material & Methods:** Fifty clinically confirmed patients of ARF were included in this descriptive study. The samples were taken from Children hospital and Institute of Child Health Lahore after written informed consent. The sampling technique was convenient sampling. **Results:** Out of 50 enrolled patients, males were 32(64%) and females 18(36%). Only 5(10%) patients had normal ASOT levels, 20(40%) patients were with borderline ASOT, and 25(50%) patients had titres above 200 IU/ml. There was no significant association of ASOT with gender, age and arthralgia with p-value = 0.060, 0.875 and 0.473, respectively. However, a significant association was found in ASOT with carditis and C-reactive protein (p-value = 0.028 and 0.014, respectively). Only 3 (6%) patients had CRP levels below 6mg/l, whereas 43 (86%) patients were with CRP levels above 6. Only 4(8%) patients had borderline value of CRP titer. There was no significant association between C-reactive protein with gender, age and arthralgia (p-value = 0.148, 0.184 and 0.574, respectively). Moreover, there was a significant association between C-reactive protein with carditis and AOST (p-value = 0.020 and 0.014, respectively). **Conclusion:** ASOT and CRP are important laboratory parameters reflecting undergoing infection (mainly caused by *Streptococcus pyogenes* A) and inflammation in patients of ARF. Rising levels of ASOT and CRP in ARF patients might be used as an indicator of involvement of heart tissues and therefore can be used to monitor transition of rheumatic carditis into rheumatic heart disease.

Key words: Acute Renal Failure, Antistreptolysin O Titer, C-reactive Protein.

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valvular involvement (endocardium). Transition from rheumatic carditis to rheumatic heart disease (RHD) which manifests as chronic valvular lesions is usually seen following one or more episodes of ARF. Susceptibility to RHD is thought to be due to genetic factors that are influenced by environmental factors, such as crowding and poverty.⁵

Arthritis is generally the earliest symptom of ARF, usually presenting within 2-3 weeks of throat infection. Arthralgia is more prominent than typical signs of joint inflammation and usually involves several joints (poly-arthralgia). Being considered a common manifestation of many

rheumatologic disorders, arthralgia is highly nonspecific. Nevertheless, poly-arthralgia after exclusion of other causes must be considered.⁶

Longo *et al.* highlighted the impact of socioeconomic status on the development of RHD with a prevalence of 22.2 per 1000 in children from slums versus a prevalence of 4 per 1000 in children going to city schools.⁷ The exact involvement of genetic predisposition is unclear in autoimmune diseases. However, few genetic factors have been found to be associated with increase susceptibility to autoimmune reactions in RHD. MHC class II present on lymphocytes and antigen presenting cells are the main component of RHD associated susceptibility, especially the DR and DQ alleles on human chromosome 6. RHD is also associated with TNF- α present on human chromosome 6.⁸

The diagnosis of rheumatic fever (RF) was first made by Jones criteria. The standard Jones criteria was modified in 1944 by T. Duckett Jones.⁹ Later on, it has been periodically revised by the American Heart Association in collaboration with other groups.¹⁰ According to latest revised Jones criteria, the diagnosis of RF is confirmed with a presence of two of the major criteria, or one major criterion plus two minor criteria along with evidence of streptococcal infection that is characterized by elevated/increased anti streptolysin O titer (ASOT).¹¹ Chorea and indolent carditis are exceptions in diagnosis of RF as they themselves can indicate rheumatic fever.¹²

Tests that can give an evidence of Streptococcal infection include culture, rapid tests and antistreptolysin O titre (ASOT). The serum levels of ASO titre are significant in pointing towards recent infection or an earlier exposure in a hypersensitive person with persistently high antibody levels. In this regard, serum levels of greater than 160-200 units are considered very high and support a diagnosis of streptococcal infection.¹³ C-reactive protein (CRP) is a non-specific acute phase protein present in the blood and discovered by Tillett in 1930. The levels of CRP rise in response to inflammation and infections.¹⁴ CRP elevates significantly in acute

rheumatic carditis and chronic rheumatic heart disease patients.¹⁵ The purpose of the study was to evaluate increased levels of ASOT and CRP in children of ARF and its association with clinical manifestations such as carditis and arthralgia.

MATERIAL & METHODS

This descriptive study was conducted in the Department of Diagnostic Immunology and Serology, Childrens Hospital and Institute of Child Health, Lahore after getting approval from the Ethical Review Committee and Advance studies and Research Board of Children Hospital Lahore. The sampling technique was convenient sampling. The diagnosed fifty ARF patients with age ranging from 5-15 years were included in this study. An informed written consent was obtained from his/her guardian. Pediatric patients who fulfilled the Jones criteria were included in the study group while the patients with other autoimmune disease and malignancy were excluded. The clinical manifestation such as carditis diagnosed on echocardiography and arthritis were recorded on the basis of clinical history. Demographic data and clinical manifestation were recorded for every patient. Using the kit Human Tex ASOT, Wiesbaden, Germany, the ASOT >200IU/ml was taken as positive and according to kit Human Tex CRP Wiesbaden, Germany the CRP >6mg/l was taken as positive.

The data was entered and analyzed using SPSS 25.0 (Chicago, USA). For quantitative variables, mean \pm standard deviation (SD) was calculated such as age. For qualitative variables, frequencies and percentages were calculated. Chi-square test was applied to observe association between qualitative variables. A p-value of ≤ 0.05 was considered as statistically significant.

RESULTS

Out of 50 ARF patient, 32(64%) were males and 18(36%) were female, making a male to female ratio of 2:1. The mean age of male and female participants was 10.03 ± 2.43 years and 10.33 ± 1.57 years, respectively. Out of these patients, 33 (66%) patients fell in the age group 5-10 years while 17(34%) patients belonged to 10-15 years age group. A total number of 44(88%)

ARF patients developed carditis whereas 6(12%) patients did not show any signs of carditis. Similarly, 44(88%) had arthralgia and 6(12%) did not have any joint related symptoms. Considering >200 IU/ml as positive, 200 IU/ml as borderline and <200 IU/ml as normal for ASO titres in the studied population, only 5(10%) patients had normal ASOT levels, 20(40%) patients had borderline ASOT and 25(50%) patients had titres above 200 IU/ml. The CRP levels of >6mg/l was considered as high, 6mg/l as borderline and <6mg/l as normal titers of CRP; only 3 (6%) patients had normal, 4(8%) had borderline and 43 (86%) patients had high CRP levels.

On comparison of ASOT levels with clinical symptoms of RHD i.e. carditis and arthralgia, there was a significant association observed between ASO titres and carditis (p-value = 0.028) whereas no statistically significant link was found between ASOT and arthralgia (p-value = 0.473) (Table-I).

Furthermore, in our study, CRP levels were compared with the same clinical symptoms of

carditis and arthralgia. There was significant association found between CRP with carditis (p-value 0.020) but no significant association was found in between CRP and arthralgia with p-value 0.574 (Table-II). In this study, ASOT and CRP levels were measured and there was a significant association in between these two parameter with p-value as shown in Table-III.

DISCUSSION

Acute rheumatic fever (ARF) is characterized by an immune response to Group A streptococcus (GAS) pyogenes bacterial infection.¹ Carditis and arthralgia are two important manifestations of ARF, and are also included in the Jones diagnostic criteria. If untreated or sub-treated carditis can transform into rheumatic heart disease (RHD) that is characterized by permanent damage to the valves of the heart.¹

Early diagnosis of RF is vital to inhibit progression of disease towards its complications. Diagnosis of AFR is based on both clinical as well as laboratory criterion. Important laboratory parameters include ASOT, CRP and ESR.

ASOT	Carditis		Arthralgia	
	Yes	No	Yes	No
Normal (<200)	2(4.5%)	2(33.3%)	4(9.3%)	1(14.3%)
Borderline (200)	18(40.9%)	3(50%)	16(37.2%)	4(57.1%)
High (>200)	24(54.5)	1(16.7%)	23(53.5%)	2(28.6%)
p-value	0.028		0.473	

Table-I. Comparison of ASOT with carditis and arthralgia

CRP	Carditis		Arthralgia	
	Yes	No	Yes	No
Normal (<6)	2(4.5%)	1(16.7%)	3(6.8%)	0(0%)
Borderline (6)	2(4.5%)	2(33.3%)	4(9.1%)	0(0%)
High (>6)	40(90.9%)	3(50%)	37(84.1%)	6(100%)
p-value	0.020		0.574	

Table-II. Comparison of C-reactive protein (CRP) with carditis and arthralgia

	CRP			P-Value
	Normal (<6)	Borderline (6)	High (>6)	
Normal (<200)	0(0%)	1(25%)	25(58.1%)	0.014
Borderline (200)	2(66.7%)	1(25%)	16(37.2%)	
High (>200)	1(33.3%)	2(50%)	2(4.7%)	

Table-III. Comparison of CRP with ASOT

ASOT points towards infection caused by *Streptococcus Pyogenes* group A (GAS); CRP and ESR are non-specific markers of inflammation. In the current study, we enrolled the pediatric patients of AFR and measured serum levels of ASOT and CRP. These patients were further divided into four groups on the basis of presence or absence of two important clinical symptoms i.e. carditis and arthralgia. ASOT and CRP levels were compared in these groups in order to establish an association to see if these laboratory markers and their levels correlate with these two serious disease manifestations.

Most of the patients exhibited high ASOT levels in this study. Similar observations were made by Kotby *et al* with significantly high ASOT in ARF (mean 1334.9).¹⁶ In this study, we observed a significant association between ASOT levels and carditis with 24 (54.54%) patients expressing high ASO titres as compared to only 2 patient expressing normal ASOT. In the current study, ASOT showed no significant association with arthralgia. This study was partially in agreement with Roodpeyma *et al*. who also failed to establish any link between ASOT and severity of any clinical manifestation including number of valves involved.¹⁷

When CRP levels were studied in our study group suffering from carditis, a significant association was established between patients suffering from carditis and CRP levels. This indicates that CRP in spite of being non-specific marker gives an insight for undergoing cardiac inflammation. Our findings were in agreement with a study by Habeeb *et al*. who measured the levels of hsCRP in acute rheumatic carditis and patients with chronic rheumatic heart disease and compared them with control group. CRP levels were significantly elevated in patients suffering from acute carditis and also correlated with the degree of valvular involvement.¹⁵ In a similar study carried out in 2006, Chiu-Braga *et al*. measured the levels of CRP in patients with RHD and reported a significantly elevated hs-CRP levels in these patients compared with controls.¹⁸ Golbasi *et al*. evaluated levels of CRP in patients with chronic rheumatic valve disease, prosthetic valve disease

and healthy subjects and reported significantly higher levels of hs-CRP in patients with chronic rheumatic heart disease than in patients with prosthetic valve(s) and healthy subjects.¹⁹

In the present study, CRP levels showed a non-significant association with arthralgia. Similar findings were reported by Roodpeyma *et al*. who found no significant association between clinical manifestations and laboratory parameter.¹⁷ One plausible explanation is absence of underlying inflammation in the involved joint, making polyarthralgia more of a non-specific symptom and not correlating with Inflammatory markers.

To conclude, ASOT and CRP are important laboratory parameters reflecting undergoing infection (caused by *Streptococcus pyogenes* A) and inflammation in patients of ARF. Both ASOT and CRP levels correlate significantly with carditis while arthralgia is not related to both laboratory parameters in children suffering from ARF. Rising levels of ASOT and CRP in ARF patients might be used as an indicator of involvement of heart tissues and therefore can be used to monitor transition of rheumatic carditis into rheumatic heart disease.



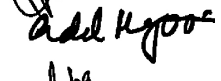
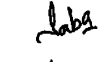
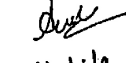
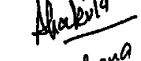
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5	Anum Wasim	Drafting and manuscript.	
6	Shakila Akram	Drafting and manuscript.	
7	Farhana Shehzad	Data analysis, Study design, drafting & review.	