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# STUDY OF PLASMA LEVELS OF HIGHLY SENSITIVE C-REACTIVE PROTEIN IN CHILDREN WITH CHRONIC RHEUMATIC VALVE DISEASE

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## ABSTRACT

This study was done to estimate the levels of highly sensitive C-reactive protein (hs CRP) in patients with chronic quiescent rheumatic valvular disease as a marker for ongoing inflammatory process. It included 30 patients with chronic valvular rheumatic heart disease (CVRD). They were 11 males and 19 females. Their ages ranged from 6-17 years, they were taken as (group I) which further subdivided into group Ia included 7 patients with prosthetic valve and group Ib included 23 patients without prosthetic valve. Also 20 healthy children of age and sex matched to group I taken as control group (group II). All patients subjected to full medical history taken, full clinical diagnosis, plain X-ray, ECG and echocardiography to establish the diagnosis of (CVRD). hs CRP was done to all children. The mean level of hs CRP was  $3.3 \pm 1.4$  mg/l in group I and was  $1.79 \pm 1.88$  mg/l in group II and there was highly statistical significant difference between both groups. In our study the mean level of hs CRP in patients with prosthetic valves was  $2.33 \pm 0.42$  mg/l and was  $3.59 \pm 1.5$  mg/l in those without prosthetic valve and there was highly statistical significant difference between both groups. There was statistical significant positive correlation between hs CRP and duration of the disease, number of valves affected and number of recurrences of rheumatic fever.

In conclusion: hs CRP is a sensitive marker of low grade inflammation and it increased in chronic rheumatic heart disease. This may indicate that inflammatory process still persistent in the chronic phase of rheumatic fever and this may be responsible for progression of valvular lesions.

## INTRODUCTION

Rheumatic fever (RF) is still the most common cause of acquired heart disease in many developing countries as in Egypt, India and South America (Chandrashekhar and Narula, 2000). Rheumatic fever is generally classified as a connective tissue or collagen vascular disease. The rheumatic process is expressed as inflammatory reaction that involves multiple organs primarily the heart, the joints and the central nervous system (Stollerman, 1998 and Gerber, 2004).

The onset of RF in early childhood in Egyptian patients denotes the severity of the disease in this country. They become more subjected to rheumatic recurrences and more cardiac damage occurs, accordingly they are incapacitated in their early life (Kassem et al., 1995).

Chronic rheumatic valve disease (CRVD) is a late sequel of rheumatic fever, which appears approximately in 30% of RF patients (Chiu-Braga et al., 2005).

The precise pathogenic mechanisms of rheumatic fever and rheumatic heart disease have never been defined. C-reactive protein (CRP) is increased in patients with acute rheumatic fever but it is not known whether plasma levels increase in patients with (CRVD) or not

(Golbasi et al., 2002).

It becomes reactively detectable 6-12 hours after tissue injury or the onset of infection probably under the influence of humoral mediators such as leucocyte endogenous mediators and prostaglandin E (Baltz et al., 1985).

High sensitive methods have made it possible to measure and compare low CRP levels in the plasma. Prospective studies have shown that increased but comparatively low plasma CRP concentrations are associated with chronic heart disease (Tornval et al., 2003).

So the aim of this study was to determine highly sensitive C-reactive protein (hs RCP) levels in chronic quiescent rheumatic valvular disease as a marker for ongoing inflammatory process.

## SUBJECTS AND METHODS

This study was conducted on 30 children with chronic rheumatic valvular heart disease, they were attending to pediatric cardiology outpatient clinic of Benha University Hospital. They were 11 males and 19 females and their ages ranged from 6 to 17 years. They were further subdivided into two groups:

Group Ia included 7 patients with prosthetic valve and group Ib included 23 patients without prosthetic valve. Also 20 healthy children, they were 12 males and 8 females of age and sex matched to patients group were taken as control (group II).

#### **Exclusion Criteria**

Children with acute rheumatic fever, acute infection, inflammatory diseases, malignancy and trauma were excluded from the study.

All patients were subjected to the following:

- Full medical history taking and full clinical examination.

- Plain X-ray chest and heart.

- Electrocardiographic examination.

- Echo-Doppler study (complete 2-D, M-mode,

Doppler and colour Doppler mapping) were done using ATL 5000 equipped with 3.5 MHZ transducer.

- Laboratory investigations: These done to all children, they included routine ESR and CRP. Highly sensitive C-reactive protein (hs CRP) was determined using polystyrene particles coated with monoclonal antibodies to CRP. The intensity of the scattered light in the nephelometer depends on the CRP content of the sample. The method is standardized against the IFCC/BCR/CAP reference preparation (lot No. 91/0619 = CRM, 470 = RPPHS 91/0619 (Lot V) (Whicher et al., 1994).

#### **Statistical analysis:**

The collected data were tabulated and subjected to analysis using microsoft Excel version for the statistical package for social science (SPSS). All values were expressed as mean  $\pm$  SD, range, student's t test and correlations were done by regression analysis.

### **RESULTS**

The results of the present study are illustrated in tables (1-6):

### **DISCUSSION**

Rheumatic fever is an immunologically mediated multisystem inflammatory disease that follows episode of group A streptococcal pharyngitis (Kumar et al., 2003). Rheumatic fever is still the most common cause of acquired heart disease in many developing countries as in Egypt (El-Said et al., 1998).

The overall prevalence of rheumatic heart disease in Egypt was found to be 8/1000 school children (Zaher et al., 1999). Elevated level of CRP has been found in blood during all diseases associated with active inflammation or

tissue destruction (Kushner et al., 1990). hs CRP is considered an acute phase reactant, that is increased during an inflammatory process. It has been used as a marker of inflammation. It has become clear that an assay for hs CRP is much more sensitive than the routine assay for CRP as it can determine the low levels of CRP in what was considered the normal range (Dessein et al., 2004).

In this study CRP was positive in 10% only of patients with chronic rheumatic valvular heart disease (CRVD) group I and negative in 100% of control group. hs CRP mean level was  $3.3 \pm 1.4$  mg/l in group I and was  $1.79 \pm 1.88$  mg/l in group II and there was statistical significant difference between both groups. High levels of hs CRP in patients with CRVD indicate the persistence of inflammation in the chronic phase that is not detected by ordinary CRP assay. Dessein et al. (2004) found that high sensitivity CRP reveals inflammation that is not detectable with routine CRP assay and this is associated with disease activity in rheumatic fever. Davutoglu et al. (2005) suggested that the chronic phase of rheumatic valve disease is associated with serum inflammatory mediators as IL-6, IL-8, IL-2R and TNF  $\alpha$  which correlate strongly with the severity of valve involvement.

It was shown that myocarditis associated with acute rheumatic fever itself may remain active months after the clinical disease has entered a quiescent period (Narula et al., 1989).

Krassuski et al. (2003) stated that hs CRP was detected in 76% of patients with CRVD. Procedural success of percutaneous balloon mitral valve commissurotomy (PBMC) was 89% of patients with undetectable hs CRP as compared with only 67% in patients with detectable hs-CRP. They suggest that persistent inflammation may affect the results of (PBMC). Also the persistence of inflammation during quiescent phase of chronic rheumatic valve disease was suggested by Yamouchi et al. (2004). In our study the mean hs CRP level in 7 patients with prosthetic valve was  $2.33 \pm 0.42$  mg/l and was  $3.59 \pm 1.5$  mg/l in CRVD without prosthetic valve and there was statistical significant difference between both groups. This was in agreement with Golbasi et al. (2002) who found that levels of hs-CRP were significantly higher in patients with CRVD than in patients with prosthetic valve(s). They suggested that this may be due to attenuation of the antigenic stimulus after removal of the involved valves carrying antigenic similarity.

In our study the mean level of hs-CRP in patients

Table (1): Statistical distribution of clinical data among group I.

| Variable                                  | Percentage  |
|---|---|
| Sex                                       | Male: 33.34%<br>Female: 66.66%                              |
| 1 <sup>st</sup> attack                    | Carditis: 26.56%<br>Arthritis: 73.44%                       |
| Family history                            | + ve: 30%<br>- ve: 70%                                      |
| Long acting penicillin (LAP) intake every | 21 days: 64.23%<br>15 days: 35.77%                          |
| LAP regularity                            | Regular: 66.66%<br>Irregular: 33.34%                        |
| Number of valves affected                 | One valve: 56.66%<br>Two valves: 40%<br>Three valves: 3.34% |

Table (2): Laboratory parameters among group I.

| Variable      | Range                  | Mean $\pm$ SD   |
|---------------|------------------------|-----------------|
| hs CRP (mg/l) | 1.73-7.17              | 3.3 $\pm$ 1.4   |
| ESR (mm/hour) | 8-11                   | 8.96 $\pm$ 8.99 |
| Variable      | Percentage             |                 |
| CRP (mg/dl)   | + ve: 10%<br>- ve: 90% |                 |

NB: CRP above 6mg/dl is considered +ve.  
Below 6mg/dl is considered - ve.

Table (3): Statistical comparison of hs CRP mean values mg/l among the studied groups.

| Group I<br>(Mean ± SD) | Group 2<br>(Mean ± SD) | t     | p      |
|------------------------|------------------------|-------|--------|
| 3.3 ± 1.4              | 1.79 ± 1.88            | 0.001 | < 0.05 |

Table (4): Statistical comparison of hs CRP mg/l mean values in patients with and without regular LAP.

| Regular LAP<br>n = 16<br>(Mean ± SD) | Irregular LAP<br>n = 14<br>(Mean ± SD) | t    | p       |
|--------------------------------------|--|------|---------|
| 2.80 ± 0.7                           | 3.87 ± 1.8                             | 0.17 | < 0.03* |

Table (5): Statistical comparison of hs CRP mean values mg/ l among patients with prosthetic valve and those without prosthetic valve

| Without prosthetic valve<br>n = 23<br>(Mean ± SD) | With prosthetic valve<br>n = 7<br>(Mean ± SD) | t     | p       |
|---|---|-------|---------|
| 3.59 ± 1.5  | 2.33 ± 0.42                                   | 2.178 | < 0.05* |

\* Significant

Table (6): Correlation coefficient of serum hs CRP with duration of the disease, number of disease recurrences and number of valves affected.

| Variable                  | Hs CRP |          |
|---------------------------|--------|----------|
|                           | r      | p        |
| Duration of the disease   | 0.775  | < 0.01*  |
| Number of recurrences     | 0.948  | < 0.01*  |
| Number of valves affected | 0.486  | < 0.007* |

\* Significant

receiving regular long acting penicillin (LAP) was  $2.80 \pm 0.7$  mg/l and was  $3.87 \pm 1.8$  mg/l in patients receiving irregular LAP and there was statistical significant difference between both groups. This was in agreement with Golbasi et al. (2002) who stated that regular LAP decrease exposure to GABHS which leads to less exposure to inflammatory process. Also in this study there was a statistical significant positive correlation between hs-CRP levels and duration of the disease, number of valves affected and number of recurrences of rheumatic fever. These was in agreement with Davutoglu et al. (2005) and Chiu-Braga et al. (2005) who correlate levels of hs CRP and severity and number of valves affected.

In conclusion we found that hs CRP persistence in CRVD suggests an ongoing low grade inflammation that can't be detected by routine CRP assay. This persistent inflammation may be responsible for progression of valvular lesions. So we recommend that hs CRP must be measured to follow up patients with chronic rheumatic valve disease. Further researches should focus on whether extended duration of anti-inflammatory drugs intake might reduce progressing morbidity and mortality in patients with chronic rheumatic valvular disease.

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## دراسة لمستوى البروتين سى التفاعلي عالي الحساسية فى الأطفال المصابين بمرض

### صمامات القلب الروماتيزمية المزمنة

تعتبر الحمى الروماتيزمية من أهم أسباب أمراض القلب المكتسبة فى العديد من الدول النامية مثل مصر والهند وجنوب أمريكا . تحدث إصابة صمامات القلب الروماتيزمية فى ٣٠٪ من الأطفال المصابين بالحمى الروماتيزمية.

وقد وجد أن إصابة صمامات القلب فى مرضى الحمى الروماتيزمية ينتج من التهابات مستمرة حتى فى حالة كمون المرض ولذلك أجريت هذه الدراسة لإثبات أن إصابة الصمامات ينشأ من الالتهاب المستمر وذلك عن طريق قياس البروتين التفاعلي سى عالي الحساسية كمؤشر لهذا الالتهاب.

وقد أجريت هذه الدراسة على ٣٠ مريض مصاب بمرض صمامات القلب الروماتيزمية تم اختيارهم من الأطفال المترددين على وحدة قلب الأطفال فى مستشفى بنها الجامعي وكانت أعمارهم تتراوح بين ٦-١٧ عاما وكانوا عبارة عن ١١ ذكر و ١٩ أنثى.

كما تم أخذ ٢٠ طفل صحيحا من نفس الفئة العمرية ١٢ ذكر و ٨ إناث كمجموعة ضابطة. وقد خضع جميع المرضى الى أخذ التاريخ المرضى للحالة بالتفصيل وفحص إكلينيكي كامل، أشعة عادية على الصدر والقلب ، رسم قلب وأشعة بالموجات فوق الصوتية للقلب.

كما تم عمل تحاليل معملية اشتملت على سرعة ترسيب، بروتين سى التفاعلي والبروتين سى التفاعلي عالي الحساسية .

وقد أظهرت هذه الدراسة أن مستوى البروتين سى التفاعلي عالي الحساسية يزيد بقيم ذات دلالة إحصائية فى المرضى المصابين بصمامات القلب المزمنة عنه فى المجموعة الضابطة.

كما أظهرت هذه الدراسة أنه فى المرضى الذين أجريت لهم عملية تغيير صمامات فى القلب كان مستوى البروتين التفاعلي سى عالي الحساسية أقل من الأطفال الذين لم يخضعوا لعمليات تغيير صمامات القلب بقيم ذات دلالة إحصائية.

وقد وجد علاقة طردية وثيقة بين مستوى البروتين التفاعلي سى عالي الحساسية وبين عدد الصمامات المصابة وطول فترة المرضي وبين تكرار حدوث الحمى الروماتيزمية.

### الخلاصة:

فى حالات صمامات القلب الروماتيزمية المزمنة هناك التهابات مستمرة فى فترات سكون الحمى الروماتيزمية وهذا يمكن الاستدلال عليه بواسطة قياس مستوى البروتين سى التفاعلي عالي الحساسية .

### ولذلك نوصي :

١- بقياس البروتين سى التفاعلي عالي الحساسية فى جميع الأطفال المصابين بمرض صمامات القلب الروماتيزمية كدلالة على استمرار الالتهابات .

٢- كما نوصي بوضع تصور لمد فترة العلاج بالأدوية المضادة للالتهاب ومقارنة نسبة البروتين التفاعلي سى عالي الحساسية بين هؤلاء الأطفال والأطفال الذين يخضعون للعلاج بالمدد المحددة سابقا.



بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ

الحمد لله رب العالمين  
والصلاة والسلام على سيدنا محمد  
الذي بعث في طينتنا رسولا  
مباركا توفيقا لنا  
وهدى لنا صراطا مستقيما

السنة السادسة عشر العدد الخامس أكتوبر (تشرين الأول) ٢٠٠٥ م رمضان ١٤٢٦ هـ

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# مجلة الطفل العربي

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مجلة يصدرها إتحاد جمعيات طب الأطفال العربية  
رئيس التحرير أ.د. حسين كامل بهاء الدين