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Original Research Article

Serum Highly Sensitive C-Reactive Protein in Asthma and its Ability in Predicting Asthma Severity and Control

Giriraj Prasad Meena[1], Nani Kumari Dhaker[2], Ashok M.[3]

[1]SS Pediatrics, SRM Govt. Dist. Hospital, Baran, Rajasthan, India
[2]Resident Pediatrics, SRM Govt. Dist. Hospital, Baran, Rajasthan, India
[3]Resident Pediatrics, SRM Govt. Dist. Hospital, Baran, Rajasthan, India

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Corresponding Author: Dr. Giriraj Prasad Meena
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Abstract:

Background: Asthma is a globally significant non-communicable disease with a high morbidity and mortality in both children and adults. Approximately 300 million people have asthma worldwide and by 2025 a further 100 million may be affected.

Methods: Present study entitled "Serum hs –CRP in Asthma and its ability in predicting asthma control" with the objectives to evaluate hs-CRP level in serum of asthmatic children and the relation of hs-CRP with pulmonary function test (spirometry).

Results: 98.1% cases with poorly control asthma had abnormal hs-CRP while only 47.1% cases in well controlled asthma had abnormal hs-CRP. This was found to highly significant ($p<0.001$). When abnormal hs-CRP is used as a test of poor control of asthma it has a sensitivity of 98%, Specificity of 52%, Positive Predictive Value of 92.6% and Negative Predictive Value of 81%.

Conclusion: Serum hs-CRP was evaluated in cases of childhood asthma. Majority of cases with frequent acute exacerbations and poor control had significantly elevated levels of hs-CRP. The mean hs-CRP was significantly greater in these cases. hs-CRP can be used as an affordable, easily available, bedside test for assessing asthma control.

Keywords: hs-CRP, Asthma, Acute exacerbations

Introduction

Asthma is a globally significant non-communicable disease with a high morbidity and mortality in both children and adults [1]. Approximately 300 million people have asthma worldwide and by 2025 a further 100 million may be affected [2].

Asthma is characterized by airway hyper-responsiveness and chronic inflammation in which various cells, cytokines and mediators play a role [1]. It has been shown that levels of acute phase proteins (such as plasma fibrinogen and serum amyloid A) are positively associated with asthma [2]. It has also been demonstrated that increased levels of amyloid A are present in patients with asymptomatic asthma [3] indicating systemic inflammation in asthma.

CRP is one of the most characteristic markers of the inflammatory process. The monitoring of CRP levels is a good diagnostic tool and is very useful for the assessment of early inflammation and treatment monitoring [3].

It is well known that CRP increases during infection and autoimmune disorders [4]. In recent years, there have been some reports concerning the measurement of serum levels of hs-CRP as a useful tool for detecting systemic inflammation in asthma [5,6]. Several studies have indicated a positive co-relationship has been reported between raised CRP levels and current asthma [7,8], respiratory impairment, and bronchial hyper-responsiveness [9].

The use of high sensitivity assays for CRP determination (hs-CRP) has made the assessment of low-grade systemic inflammation possible in several disorders, such as cardiovascular disease and diabetes mellitus [10].

There has been increasing interest in measuring hs-CRP in the assessment of control and treatment monitoring of asthma [11].

Material and Methods

Study Design: Hospital based observational study.

Study Population: All children (4-15 years) in routine OPD and indoor patient fulfilling the inclusion criteria.

Sample Size: Approximately 150 patients out of which 120 asthmatic children were finally selected as 10 were diabetic, 8 were having sinusitis,5 was having rhinitis and 8 didn't give consent.

Sampling Method: Convenience sampling.

Inclusion Criteria: Children aged 4 to 15 years with asthma defined as per GINA guidelines (cough, shortness of breath, wheeze and chest tightness) (4)

Exclusion Criteria: Children with other associated inflammatory conditions such as pulmonary infections, bronchiectasis, connective tissue diseases, vasculitis, coexistent acute or chronic localized or systemic infection or inflammatory conditions at respiratory or musculoskeletal, gastrointestinal, urinary tract as well as patients with malignancies and history of inflammatory disease as well as those who didn't give consent.

Data Collection: A total of 150 asthmatic children were screened but 30 were excluded as 10 were diabetic, 8 were having sinusitis, 5 were having rhinitis and 8 didn't give consent. After applying inclusion and exclusion criteria 120 children were enrolled and their serum hs-crp and ACT (Asthma control test questionnaire) were done at admission. Pre and Post bronchodilatory FEV1, FEV1/FVC, FEF25 (-75% measured using spirometry and Pre and Post bronchodilatory PEFR was measured using Breath-o-meter.

For Diagnosis

- Serum hs-crp levels were measured by immunoturbidimetric test by MISPA analyser (using Beckman Coulter test kit)
- Pulmonary function test (spirometry) was done using PONY FX advanced desktop spirometer.
- Asthma control test (ACT) questionnaire (see Annexure-1) and Pulmonary score index (see Annexure-2)
- Also, comprehensive history taking, physical examination and lab investigations were carried out.

Data Analysis: To collect required information from eligible patients, a pre-structured pretested proforma was used. Data analysis was done using SPSS with the help of tables and figures.

A value of hs-crp more than or equal to 3mg/l was considered abnormal.

Observations

Table 1: Distribution of cases according to age and gender

Age Group (Years)	Gender				Total		p-value
	Female		Male				
	No.	%	No.	%	No.	%	
≤5	13	26.0	23	32.9	36	30.0	>0.05
6-10	29	58.0	30	42.9	59	49.2	>0.05
11-15	8	16.0	17	24.3	25	20.8	>0.05
Total	50		70		120		
χ^2	2.779						
p	0.249						

In present study out of total 120 cases, 50 were female and 70 were male. Out of total 50 females, 29(maximum) had their age between 6-12 years followed by 13 cases had their age group ≤5 years and 8 females had their age group 13-15 years. Out of total 70 males, 30, 23 and 17 cases had their age group 6-12, ≤5 years and 13-15 years respectively (p>0.05).

Table 2: Frequency of exacerbation in relation to number of cases with abnormal hs-CRP

Frequency	hs-CRP Group				Total
	Normal		Abnormal		
	No.	%	No.	%	No.
≤1	7	63.6	18	16.5	25
2	3	27.3	48	44.0	51
≥3	1	9.1	43	39.5	44
Total	11		109		120
χ^2	13.8219				
p	<0.001				

In present study, out of total 120 cases, 11 cases had normal hs-CRP while 109 cases had abnormal hs-CRP. Out of total 109 cases with abnormal hs-CRP 48(44%), 43(39.5%) and 18(16.5%) cases had 2, ≥3 and ≤1 exacerbation per year respectively and this difference was found statistically highly significant (p<0.001).

Table 3: Mean hs-CRP according to Frequency of exacerbation

Frequency	Mean hs-CRP	SD
1	31.12	26.59
2	47.68	33.10
≥3	75.07	39.92
f	14.452	
p	<0.001	

Highest mean hs-CRP level (75.07) was observed in cases who had ≥3 acute exacerbation per year followed by 47.68 and 31.12 in cases having 2 and 1 exacerbation per year respectively. The difference was highly significant (p<0.001).

Table 4: PSI Score in relation to number of cases with abnormal hs-CRP

PSI Score	hs-CRP				Total
	Normal		Abnormal		
	No.	%	No.	%	No.
<4	8	72.7	10	9.2	18
≥4	3	27.3	99	90.8	102
Total	11		109		120
χ^2	31.652				
p	<0.001				

All cases were divided in two groups according to their PSI score i.e. <4 and ≥4. 90.8% cases with abnormal hs-CRP had ≥4 PSI score while 72.7% cases with normal hs-CRP had PSI score <4. This difference was found statistically highly significant (p<0.001).

Table 5: Mean hs-CRP according to PSI Score

PSI Score	Mean hs-CRP	SD
<4	10.43	12.44
≥4	62.01	36.10
t	5.982	
p	<0.001	

Mean hs-CRP of cases with PSI score <4 was 10.43±12.44 while mean hs-CRP in cases who had their PSI score ≥4 was 62.01±36.10 and this difference was found statistically highly significant (p<0.001).

Table 6: Relation between pulmonary function test and hs-CRP

hs-CRP	FEV_1		FVC		FEV_1/FVC		$FEF_{25-75\%}$		PEFR	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Normal	1.14	0.19	1.18	0.19	97.03	4.62	2.47	0.93	494.00	623.58
Abnormal	1.01	0.13	1.06	0.15	95.14	4.44	1.55	0.60	131.84	38.16
t	2.964		2.196		1.273		4.291		5.646	
p	0.004		0.030		0.206		<0.001		<0.001	

In cases with abnormal hs-CRP, mean FEV_1 was 1.01±0.13, mean FVC was 1.06±0.15, mean FEV_1/FVC was 95.14±4.44, mean $FEF_{25-75\%}$ was 1.55±0.60 ad mean PEFR was 131.84±38.16. In cases having normal hs-CRP, the mean FEV_1 was 1.14±0.19, mean FVC was 1.18±0.19, mean FEV_1/FVC was 97.03±4.62, mean $FEF_{25-75\%}$ was 2.47±0.93 and mean PEFR was 494.00±623.58.

On applying student 't' test, the difference was found statistically significant in FEV_1, FVC (p<0.05), highly significant in $FEF_{25-75\%}$ and PEFR (p<0.001) and insignificant in FEV_1/FVC (p>0.05).

Table 7: Asthma control test score in relation to number of cases with abnormal hs-CRP

Asthma Control Test Score	hs-CRP Group				Total
	Normal		Abnormal		
	No.	%	No.	%	
≤19	2	18.2	101	92.7	103
>19	9	81.8	8	7.3	17
Total	11		109		120
χ^2	45.58				
p	<0.001				

All cases were grouped according to their ACT score i.e. ≤19 and >19. 92.7% cases having abnormal hs-CRP values had ACT score ≤19 while 81.8% cases with normal hs-CRP had ACT score >19 and this difference was found statistically highly significant (p<0.001).

Table 8: Mean hs-CRP according to Asthma control test

Asthma Control Test	Mean hs-CRP	SD
≤19	62.13	35.53
>19	6.63	8.82
t	6.389	
p	<0.001	

Mean hs-CRP of cases with asthma control test score ≤19 was 62.13±35.53 while mean hs-CRP in cases who had their asthma control test score >19 was 6.63±8.82 and this difference was found statistically highly significant (p<0.001).

Table 9: hs-CRP as a test for predicting asthma control

hs-CRP	Asthma Control				Total
	Well Controlled		Poorly Controlled		
	No.	%	No.	%	
Normal	9	52.9	2	1.9	11
Abnormal	8	47.1	101	98.1	109
Total	17		103		120
χ^2	45.580				
p	<0.001				

98.1% cases with poorly control asthma had abnormal hs-CRP while only 47.1% cases in well controlled asthma had abnormal hs-CRP. This was found to highly significant (p<0.001).

When abnormal hs-CRP is used as a test of poor control of asthma it has a sensitivity of 98%, Specificity of 52%, Positive Predictive Value of 92.6% and Negative Predictive Value of 81%.

Table 10: Sensitivity and specificity of various tests for poor control of asthma

Parameters	Sensitivity	Specificity
Abnormal hs-CRP (≥3mg/l)	98.00%	52.00%
Abnormal PSI (≥4)	90.80%	72.00%
Abnormal ACT (≤19)	92.60%	18.18%
Abnormal PFT	74.31%	36.36%

Sensitivity was found to be highest with hs-CRP (98%) as compared to other tests used for poor control of asthma.

Discussion

Asthma is a chronic airway disorder characterized by airway hyper-responsiveness and a common problem encountered in children. Prompt diagnosis is important in guiding asthma treatment and control by the appropriate therapy. Diagnosis is helpful in reducing the burden of mortality and morbidity contributed by the disease. The already established tests are either too cumbersome to perform or give subjective results and also cost is an issue. Spirometry, one of the most prevalent tests tells the lung function only on the day of testing as asthma is a dynamic condition. Also, it is very difficult to perform it on paediatric population. There is a need for an easy to perform, bedside and cost-effective test which can be applied uniformly on paediatric population and can help us in guiding therapy required and in changing therapy according to the level of control of the disease. Lately, role of biomarkers has taken a central stage in the quest.

Levels of various acute phase reactants such as plasma fibrinogen and serum amyloid A have been found to positively correlate with asthma. Keeping this in mind our study has focused on the role of simple bedside tests like hs-CRP which indirectly indicate the degree of airway inflammation and can be used to assess the asthma control and treatment response. Our study evaluated relation of hs-CRP level in serum of asthmatics and its association with pulmonary function test abnormality (spirometry), asthma control test and PSI score.

80.2% cases were found to have ≥2 exacerbations of acute asthma per year. Highly significant relationship was observed between hs-CRP and number of acute exacerbations. Majority of cases (63.6%) having ≤1 exacerbation per year had normal hs-CRP level while 83.5% cases with abnormal hs-CRP level had 2,3 or more exacerbations per year. The mean hs-CRP level was raised parallel to the number of exacerbations per year. It was 31.12+-26.59 mg/l,47.68+-33.10 mg/l and 75.07+-39.92 mg/l in cases with 1,2 or ≥3 acute exacerbations per year respectively. Jain et al [12] observed "exacerbation-prone phenotype" in asthmatic patients who suffered from more frequent and life-threatening exacerbations as compared to other asthmatics, which might be the result of improper adherence techniques and incorrect techniques of inhaler use causing poor control of symptoms. Miller et al [13] concluded that subjects with exacerbations in past were more prone to develop future exacerbations. Kupczyk et al [14] characterized asthma with a subtype-frequent exacerbators with FeNO >45 p.p.b. and history of smoking who were more prone to exacerbations.

85% cases had a PSI score of ≥4. A large majority of cases (90.8%) with high PSI score (≥4) had abnormal hs-CRP (≥3mg/l) values and also had higher mean values of hs-CRP i.e.62.01±36.10 mg/l while 72.7% cases with PSI score <4 had normal hs-CRP values.This group also had lower mean values of hs-CRP level (10.43±12.44 mg/l). PSI or pulmonary score index for emergency room assessment (of children with acute asthma includes respiratory rate, wheezing and accessory muscle involvement with 0-3 defined as mild,4-6 defined as moderate and >6(6-9) defined as severe grade of asthma. Smith et al [15] compared pulmonary score with peak expiratory flow rate (PEFR) enrolling children between 5-17 years of age. PEFR (best of 3 attempts) and pulmonary score before and after albuterol (bronchodilator) inhalation were recorded. They concluded pulmonary score as a substitute for estimating airway obstruction in children having difficulty in performing PEFR. Hsu et al [16] on 65 subjects between 1-12 years of age also concluded that pulmonary index score correlated well with National Asthma Council Guidelines (NACG) and cab be used as a practical assessment tool for childhood asthma.

Majority of cases in our study (70.8%) had ACT score of ≤19.92.7% cases in our study with ACT ≤19 had abnormal hs-CRP values and also had higher mean values of hs-CRP (62.13±35.53 mg/l) while 81.8% cases with ACT>19 had normal hs-CRP values. These cases had low mean values of hs-CRP (6.63±8.82 mg/l). ACT or asthma control test is used for defining control of asthma with <20 defined as uncontrolled asthma and ≥20 as controlled asthma. Monadi et al [17] in their study compared serum hs-CRP in subjects with controlled and uncontrolled asthma. They defined severity of asthma on basis of ACT or asthma control test, ≥20 was defined as controlled asthma and <20 as uncontrolled asthma,120 patients and 115 controls were enrolled and they found that median serum hs-CRP values were higher in uncontrolled group as compared to the controlled group. Similarly, Kilic et al [18] found that when asthmatic cases were divided into two groups according to ACTs; the levels of hs-CRP in the groups of ACT<20 (uncontrolled groups) were significantly higher than the groups of ACT≥20 (controlled groups) (p=0.02). On contrary Sigari and Ghasri [19] found no significant differences were found in hs-CRP levels in patients with different levels of asthma control based on ACT.

Pulmonary function test (PFT) is a non-invasive test to check the reversibility of air flow and impairment of lung functions. The test measures lung volume, capacity, rate of flow and gas exchange done by using desktop spirometer.

In our study 73.3% cases were found to have abnormal pulmonary function test. Normal hs –CRP group had higher mean values of FEV_1 (1.14±0.19), FVC (1.18±0.19), FEV_1/FVC (97.03±4.62) $FEF_{25-75\%}$ (2.47±0.93) and PEFR (494.00±623.58) whereas abnormal hs-CRP group (≥3mg/l) had lower mean values of FEV1 (1.01±0.13), FVC (1.06±0.15), FEV_1/FVC (95.14±4.44), $FEF_{25-75\%}$ (1.55±0.60) and PEFR was 131.84±38.16. The difference was found statistically significant in FEV_1, FVC ($p<0.05$), highly significant in $FEF_{25-75\%}$ and PEFR ($p<0.001$) and insignificant in FEV_1/FVC ($p>0.05$). Ko et al [20] in 2015 enrolled a total of 276 asthmatic children with median age of 7.5 years and conducted PFT and hs-CRP on the same day and compared spirometric values in hs-CRP positive (≥3mg/l) and negative group(<3mg/l). Significant correlation was found between FEF25-75% and hs-CRP. Sahoo et al [21] evaluated serum hs-CRP, spirometry with reversibility testing, serum Ig-E and skin test for allergy in 200 asthmatic and 50 non-asthmatic control subjects, while Allam et al [22] in 2009 in 50 asthmatic patients (26 steroid inhaled and 24 steroids naïve) found negative correlation between hs-CRP and pulmonary function tests. On contrary

study done by Razi et al [23] found that among asthmatic patients, PSI and mean hs-CRP levels were not correlated with indices of pulmonary function tests (forced expiratory volume in one second, forced vital capacity and forced mid-expiratory flow.

Conclusion

Serum hs-CRP was evaluated in cases of childhood asthma. Majority of cases with frequent acute exacerbations and poor control had significantly elevated levels of hs-CRP. The mean hs-CRP was significantly greater in these cases. hs-CRP can be used as an affordable, easily available, bedside test for assessing asthma control.

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