IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 6 Ver. VIII (June. 2016), PP 52-57
www.iosrjournals.org

Prognostic Value of C - reactive protein in Pediatric Tubercular Patients on ATT

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Abstract
Objective: *To determinechange in CRP levels inpediatric tubercular patients on ATT so as to prognosticate them.*
Method:*CRP level of different types of Tubercular patients (200 cases) on ATT were compared with 60 healthy controls .The selection of Tubercular patients was based on Kenneth jone's criteria .CRP level were recorded at admission , at 1 month, at 3 – 6 months of therapy .There mean and standard deviation and Significance of the results were determined statistically .*
Result: *In study group CRP was positive in 97 % of cases .Highest serum CRP was observed in TBM and Miliary tuberculosis (37.5 ± 13.61 µg /ml and 28.0 ± 2.82 µg /ml) which denotes the activity of disease .The mean initial serum CRP in Pulmonary ,TBM , Miliary and Abdominal tuberculosis were 12.15 ± 4.89 µg /ml , 37.5 ± 13.61 µg /ml , 28.0 ± 2.82 µg /ml and 23.33 ± 2.49 µg /ml respectively , after 1 month of treatment 9.27 ± 1.13 µg /ml , 14.04 ± 3.36 µg /ml , 12.67 ± 1.15 µg /ml and 10.67 ± 4.16 µg /ml respectively and after 3—6 months of treatment 6 ± 1.12 µg /ml in all four types of tuberculosis . This decline in CRP level correlates with clinical improvement .*
Conclusion: *It is concluded that serial serum CRP levels are useful in monitoring the course of antituberculartherapy irrespective of types of tuberculosis . It provides anearly indication of response to treatment. The persistence or insignificant decline of CRP with treatment may tell us about inadequate treatment or development of resistance and thus help us to re-evaluate the patient condition. Thus serum CRP levels have led to better insight in the understanding of disease severity which plays an important role in clinical outcome of disease.*
Keywords*: ATT,CRP, Kenneth jones criteria, Prognosis, Tuberculosis*

I. Introduction

CRP is an annular pentamericdiscoid shape protein found in blood plasma and synthesized in liver. The discovery of C-reactive protein was reported in 1930 by Tillett and Francis The CRP gene is located on chromosome 1q21-q23. It is a member of small pentraxins family. It has 224 amino acids, has a monomer molecular mass of 25106 Da. Tuberculosis is still a major health hazard in children in India . The annual risk of infection is about 2-5 % . On the basis of clinical , haematological , x-ray and biopsy finding, Kenneth Jone devised a scoring system in 1990 for diagnosing active tuberculosis. The system is very useful in arriving at an exact diagnosis of active tuberculosis, which can form basis of treatment. CRP is a very sensitive marker for the acute phase response but cannot be used as specific diagnostic tool because of its non-specificity . Nevertheless measurement of CRP in a patient's serum can provide useful information to clinician , as it is used as a marker of inflammation . CRP has been advocated as a replacement for the ESR as a general screening test for illness. On serial estimation of CRP in children with tuberculosis , the level falls significantly and thus correlates with clinical improvement and so its gives a clue to response of antitubercularthерapy .

Different studies indicate CRP level rises with the onset of infection and return to normal level when the inflammatory reaction subsides . It appears to be a suitable indicator of activity of disease and if its level do not fall within 3-6 months of therapy, the patient should be reviewed to rule out progressive tuberculosis or failure of treatment. The CRP response is not affected by commonly used anti - inflammatory or immunosuppressive drugs including steroids unless these affect the activity of underlying disease .Further CRP evaluation by semiquantitative , latex agglutination technique is quite rapid , giving result in 15 -20 minutes , reliable and cheap. The test can be done in small laboratory and even in rural areas lacking in recent technology.

II. Materials And Methods

The present work was carried out in Department of Pediatrics over a period from 2010 – 2012 in Darbhanga medical college, Darbhanga, INDIA. Cases are selected from the children attendingthe indoor and outdoor services in department of paediatrics ..The selection of patient was based on Kenneth Jone's criteria for the diagnosis of tuberculosis .

In study group, we included four types of tuberculosis viz. pulmonary (140) , TBM (48) , Miliary (6) and abdominal tuberculosis (6) . Other types of tuberculosis like tuberculouslymphadenopathy , tuberculosis of the bones and joints , cutaneous tuberculosis , genito - urinary tuberculosis , tuberculouspericarditis etc .were*excluded* from this study.At the same time , 60 healthy children were also studied and subjected to same investigations as study sample . This control group formed the basis for the comparison of the results obtained in the study sample .

Kenneth Jone'sCriteria

I. Score +3

1. Demonstrable bacilli – recovery of AFB from sputum, gastric lavage, laryngeal swab etc .Tuberculous granuloma – choroid tubercle on fundoscopy and granulomatous lesion in liver biopsy and lymph node biopsy mainly .
2. Positive Mantoux test – induration exceeding 10 mm.

II. Score +2

1. Suggestive x-ray chest – lymphadenitis with or without parenchymal lesion .
2. Suggestive physical finding – pleurisy , skin lesion , osteomyelitis , pott's spine , ascities .
3. Doubtful Mantoux test – Induration of 5-9 mm .
4. Recent Mantoux Conversion from negative to positive .
5. Contact with sputum positive patient – A definite history of contact with an open case of tuberculosis .

III. Score +1

1. Non – specific changes in x – ray chest – Hilar prominence ,bizarre shadow .
2. Compatible physical finding .
3. History of contact – contact with relative , servant , or neighbour suffering from tuberculosis.
4. Non – specific granuloma .
5. Age under 3 years .

IV. Score -1

BCG Vaccination during the preceding 2 years .

Interpretation of Results .

1 to 2 points –Tuberculosis unlikely
3 to 4 points --Tuberculosis possible
5 to 6 points –Tuberculosis probable
7 or above – Tuberculosis unquestionable.

A maximum of 24 points can be gathered with this scoring system.

CRP was estimated in serum by RAPITEX (R) CRP a latex agglutination kit manufactured by HOESHST pharmaceuticals ltd .It is a semiquantitative method utilizing serial dilutions of the test sample .Assay range is 6 – 500 µg/ml.

III. Results

The study was conducted on 200 cases and 60 controls based on Kenneth Jone's criteria scoring with following results.In study group , there were 108 males(36%) and 92 females (33%) children(M:F ratio was 1.2 :1). 60 controls also had almost similar pattern of age distribution (M:F ratio was 1 : 1) . Pulmonary tuberculosis comprised 70 % of the total patient followed by tuberculous meningitis (24 %) .Apparently there was no sex predilection for pulmonary tuberculosis however male preponderance (70.83 %) was observed among children suffering from meningitis(table 1) .(62%) patients presented within 3 months of illness and 23 % presented within 3 – 6 months duration after the start of illness . Among TBM (91.66%) , duration of illness was < 3 months as compared to pulmonary tuberculosis where only 55.85% came with less than 3 months of illness (table 2) Fever was the Most Commonsymptoms (94 %) in all form of tuberculosis , loss of weight (45%) and cough (36%) . Among the meningitis cases , altered sensorium (70.83%) , abnormal movements (70.83 %) and neurological deficit (50 %) were the other common presenting symptoms .Out of 200 cases ,

194 cases (97 %) were CRP positive. Among 140 cases of pulmonary tuberculosis , 134 cases (95.71 %) were CRP positive . The CRP was positive in 100 % cases of TBM , Miliary and abdominal tuberculosis . CRP was negative in all the cases of control group .The highest Mean CRP value was recorded in TBM (37.5 ± 13.61) and lowest in pulmonary tuberculosis (12.15 ± 4.89) . The difference between them was highly significant (P<0.001) on statistical analysis .Further analysis revealed that the variation in serum CRP levels was not significant among other types of Tuberculosis (table 3).Statistical analysis of the sample shows the initial serum CRP levels were significantly higher ($P < 0.001$) than the CRP levels at second visit (after 1 month of therapy). The third estimation in the study group after 3 months of treatment also reveals a significant decline ($P < 0.001$) in CRP when compared with the mean value of second estimation done after 1 month of treatment (table 4). During acute stage of illness the serum CRP level was the highest and there after falls proportionately with increasing duration of the illness . This decline in the mean serum CRP levels is found to be statistically insignificant (P>0.05) in all the group except between the group with less than 1 month and 3 – 6 months (table 5). Statistical analysis of the sample shows that initial serum CRP levelsin both pulmonary TB and TBM were significantly higher ($P < 0.05$) than the CRP levels at second visit (after 1 month of therapy) . The third estimation done after 3 – 6 month of therapy also revealed that there was significant decline ($P < 0.05$) in CRP level when compared with the mean value of second estimation done after 1 month of treatment.Statistical analysisin initial serum CRP level in both Miliary and Abdominal TB were significantly higher ($P < 0.001$) than the CRP level at second visit (after 1 month of therapy) . The third estimation done after 3 – 6 month of therapy also revealed that there was significant decline ($P < 0.001$) in CRP level when compared to with the mean value of second estimation done after 1 month of treatment(table 6) .

Tables

Table 1: Distribution of Study subject as per types of Tuberculosis

S . N o	Types of Tuberculosis	Total No. of cases	M a l e		F e m a l e	
			N o .	%	N o .	%
1 .	P u l m o n a r y	1 4 0	6 8	4 8 . 5 6	7 2	5 1 . 4 2
2 .	T . B . M	4 8	3 4	7 0 . 8 3	1 4	2 9 . 1 6
3 .	M i l i a r y	6	4	6 6 . 6 6	2	3 3 . 3 3
4 .	A b d o m i n a l	6	2	3 3 . 3 3	4	6 6 . 6 6
T o t a l		2 0 0	1 0 8		9 2	

Table 2: Distribution of cases according to duration of illness

Sl. No.	Duration of illness	Pulmonary n = 140	T . B . M n = 48	Miliary n = 6	Abdominal n = 6	T o t a l
1 .	0-1 ,mon	3 2 (22.85%)	2 2 (45.83%)	0	0	5 4
2 .	1-3 ,mon	4 2 (30%)	2 2 (45.83%)	4 (66.66%)	2 (33.33%)	7 0
3 .	3-6 ,mon	3 6 (25.71%)	4 (8.33%)	2 (33.33%)	4 (66.66%)	4 6
4 .	6mo -1yr	3 0 (21.42%)	0	0	0	3 0
T o t a l		1 4 0	4 8	6	6	2 0 0

Table 3: Correlation of CRPwith types of tuberculosis .

Sl. No.	Types of Tuberculosis	No. of Patients	Mean CRP level(µg/ml)
1 .	T B M	4 8	3 7 . 5 ± 1 3 . 6 1
2 .	P u l m o n a r y	1 4 0	1 2 . 1 5 ± 4 . 8 9
3 .	M i l i a r y	6	2 8 . 0 0 ± 2 . 8 2
4 .	A b d o m i n a l	6	2 3 . 3 3 ± 2 . 4 9

On application of ANOVA P value <0.001

Table 4: Serum CRP level in study cases at First, Second and Third visit

		M E A N S E R U M C R P L E V E L (µ g / m l)	
STUDY CASES	Initial Value(a) n = 200	**1 mon. after therapy(b) n = 200**	**3 – 6 mon after therapy (c) n = 88**
Mean ± S.D	18.68 ± 13.65	0 7 . 2 4 ± 6 . 0 4	6 . 1 ± 1 . 9
Range	6 - 6 2	6 - 2 0	0 ± 6
P v a l u e		< 0 . 0 0 1	< 0 . 0 0 1

P valuecalculated in relation to initial value

TABLE 5: Correlation of CRP with duration of illness

S.L. No.	Duration of illness	No. of Patients	Serum CRP in µg/ml Mean ± S.D
1.	0 -1 month	5 4	23.15 ± 17.13
2.	1 -3months	7 0	21.2 ± 14.65
3.	3 -6 months	4 6	13.74 ± 6.55
4.	6 mon- 1 year	3 0	12.33 ± 6.94

On application ofANOVA P value= <0.001

Table 6: Serial estimation of CRP at First, Second and Third visit in Different Types of Tuberculosis .

Types of Tuberculosis	Serum CRP Level (µg/ml) Mean ± S.D		
	Initial Value (a)	**1 mon. after therapy (b)**	**3 – 6 mon after therapy(c)**
Pulmonary	N = 140	N = 140	N = 134
	11.63 ± 4.89	9.27 ± 1.13	6.1 ± 1.7
P value		***< 0.001***	***< 0.001***
T.B.M	n = 48	n = 48	n = 48
	37.5 ± 13.91	14.04 ± 3.36	7.4 ± 2.5
P value		***<0.001***	***< 0.001***
Miliary Tuberculosis	n = 6	n = 6	n = 6
	28.00 ± 2.82	12.67 ± 0.94	6.5 ± 2.1
P value		***<0.001***	***< 0.001***
Abdominal Tuberculosis	n = 6	n = 6	n = 6
	23.33 ± 2.49	10.67 ± 3.4	6.9 ± 2.3
P value		***< 0.001***	***< 0.001***

IV. Discussion

Since the problem of tuberculosis has been uniformly present all over India , it is imperative to find a suitable marker for monitoring the antitubercular chemotherapy . The present work was conducted to assess the level of c-reactive protein as prognostic indicator of tuberculosis. A large number of methods are available for the estimation of CRP in the serum and such specialised investigations are not available at all centres .In the present work serum CRP concentration of 6 microgram per ml or more is considered as positive. Ali et al (1988) used similar criteria for evaluation. Most of the serious complications (TBM and Miliary tuberculosis) occurs within two years of infection . It is due to hematogenous dissemination of primary complex and occurred due to various precipitating factors that caused T- Lymphocyte deficiency and compromised immune status like measles, whooping cough, chronic diarrhea and severe malnutrition.However , male preponderance was observed among children suffering from meningitis. Taneja and ghai (1955),Khatua (1961) ,Udani et al (1973) , Bohr et al(1983) Satya Gupta and Kamlesh Chopra (1985) also reported similar observations . The explanation given by Taneja and Ghai is that males are brought more commonly for the treatment as they were given more attention by their parent .Further analysis of table 2 revealed that among children suffering from TBM (91.66 %) and milliary tuberculosis (66.66 %) duration of illness was less than 3 months as compared with pulmonary tuberculosis where only 52.85 % of cases came with less than 3 months of duration of illness . Udani P.M(1983) ,Seth V. (1988) , Chopra K . (1988) and DasturD .K (1974) also observed similar findings .On average all patients with tuberculosis were found to be anemic . Total leucocyte count and ESR both were elevated maximally in miliary tuberculosis and TBM. The elevation of white cell count is due to significant increase in neutrophil and monocytes .Grang et al (1984) found significant association between the extent of disease and ESR and white cell count , both being higher in more extensive disease . They were of the opinion that the best indicators of the extent of disease apart from radiology , appeared to be the ESR and leucocyte count . ThePresent finding of significant positive CRP test in 97 % of the patient with pulmonary tuberculosis closely resembles that of Haghighi(1966) . He reported that every patient suffering from acute pulmonary tuberculosis was CRP positive . Shetlar et al (1955) similarly obtained positive reaction in 23 out of 24 patients (94 %) with active tuberculosis . Mescolini and stroniell (1957) found that 88 % of patients with exudative disease and 40 % with productive disease were CRP positive . Pero S GolubiCi C.T (1991) similarly found high percentage (99 %) of CRP positive in active tuberculosis .On the contrary , Lofstrom (1942) found CRP to be positive in 17 out of 23 (74 %) patients with active tuberculosis . Similarly findings of lower percentage (50 % , 3 out of 7 patients) of CRP positive in early active tuberculosis and 25 % (3 out of 12 patients) of positive CRP in patient with post primary tuberculosis . Roantree and Rantz (1955) observed 3 out of 7 patients (50 %) of active tuberculosis were CRP positive . Carcassi et al (1957) observed 3 out of 12 patients (25 %) of post primary tuberculosis were CRP positive . Immanuel et al (1990) similarly

obtained a lower percentage (68 %) of CRP positive in active tuberculosis .Serum CRP was negative in 100 % cases of control group . Anderson and Mc Carty (1950) observed similar result . They said that the CRP is not found in normal healthy person therefore any positive reaction should be considered abnormal . Pero S GolubiCi C.T. (1991) similarly found negative CRP test in healthy control.Table3.shows that serum CRP level varies with the types of tuberculosis. The highest level was recorded in TBM (37.5 ± 13.61 µg/ml), followed by miliary tuberculosis (28.0 ± 2.82 µg/ml) , abdominal tuberculosis (23.33 ± 2.49 µg/ml) and lowest value in pulmonary tuberculosis (12.15 ± 4.89 µg /ml) . The difference in the value between the TBM and pulmonary tuberculosis was highly significant ($P < 0.001$) on statistical analysis . Further analysis revealed that the variation in serum CRP level was not significant among other types of tuberculosis. Bajaj G . et al (1989) observed similar result of CRP in pulmonary (18.52 µg /ml) , milliary (26.06 µg /ml) , TBM (30.89 µg /ml) and abdominal tuberculosis (24.72 µg /ml) .Lin M.S. et al (1990) observed higher value of serum CRP in miliary tuberculosis (81.1 ± 24.9 µg /ml) , in exudative fibrotic tuberculosis (18.62 ± 11.34 µg/ml) and in tuberculous cavity (16.66 ± 10.18 µg /ml). In Table 4. From serial estimation of CRP it was observed that with antituberculous treatment CRP levels decreased , and on 1 month recording , the fall was highly significant ($P < 0.001$) as compared to initial recording **Table 5**. Recording after 3—6 months , also showed significant difference with 1 month recording ($P < 0.001$) . The fall in CRP correlates with clinical response and clinical improvement was noted in all those cases where CRP became negative . It is concluded that CRP can serve as a sensitive indicator of activity of disease and the return to normal value of initially elevated CRP level may indicates a good therapeutic response . Shetlar (1956) , Zitrin (1960) also observed similar result and said that the CRP level in TBM and miliary tuberculosis are higher because it closely correlate with activity and severity of disease and resultant tissue damages. From Table6 . Afterserial estimations it was observed that with therapy CRP decreased in all four types of tuberculosis . On first month recording , fall was significant in pulmonary tuberculosis ($P <0.001$) and highly significant in abdominal tuberculosis ($P <0.001$) as compared to initial value at the time of admission .On estimation of serum CRP after 3—6 month of therapy , fall in level in serum CRP was significant in pulmonary tuberculosis ($P <0.05$) , significant in TBM ($P< 0.05$) , highly significant in Miliary Tuberculosis ($P < 0.001$) and highly significant in Abdominal tuberculosis ($P < 0.001$) as compared to initial value of serum CRP. The above observations confirm the utility of C-reactive protein as a laboratory tool in following the course of antitubercular chemotherapy . Zitrin C.M. (1959) , Bajaj G et al (1989) , Lin M.S et al (1990) , Scott G.M. (1990) , Immanuel C . et al (1990) and Suzuki K. et al (1992) also gave similar views regarding prognostic implications of the test .They said that a positive CRP test indicates the presence of activity of disease and conversion from positive to negative CRP test appears to be a good prognostic sign . They also said that by serial estimation of CRP one can monitor the effectiveness of antitubercular chemotherapy and provides an early indication of response to treatment .

V. Conclusion

The above observation suggests that the CRP is good prognostic indicator and can be used to monitor the antitubercular chemotherapy response .A detailed survey of literature was made and discussed .The material and methods were presented in details , data obtained were presented in forms of tables and the statistical analysis was done when ever needed .Thus serial measurements of serum CRP levels are useful in monitoring the course of antitubercular chemotherapy irrespective of types of tuberculosis . It provides an early indication of response to treatment . The persistence or insignificant decline of CRP with treatment may tell us about inadequate treatment or development of resistance and thus help us to re-evaluate the patient condition and manage accordingly .

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