Original Article

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High-sensitivity C-reactive Protein? Is It Significant in Tuberculous Spondylitis

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Abstract

Introduction: Spinal tuberculosis (TB) is a common entity in Asian subcontinent, occurring in the first three decades of life. TB of spine most commonly affects the dorsolumbar spine region followed by cervical spine. Early diagnosis and treatment are necessary to avoid long-term disability. Elevated erythrocyte sedimentation rate (ESR) and positive mantoux test provide supportive evidence for the diagnosis of TB but are not specific. Imaging of spine is the most important preliminary tool to make the diagnosis of TB spondylitis. Acid-fast bacilli smear and culture are not positive in all the cases. In this study, we have assessed the role of high-sensitivity C-reactive protein (hs-CRP) in the diagnosis of TB spondylitis and in monitoring the clinical response to treatment.

Materials and Methods: This is a prospective study carried out in the Department of neurosurgery, Government General Hospital, Vijayawada, from July 2015 to February 2016. Patients with imageological features suggestive of TB of the spine were evaluated clinically, and blood samples were taken for measurement of hs-CRP. All these patients were evaluated clinically and radiologically and were correlated with inflammatory marker at the follow-up of for 3 months and 6 months.

Results: A total of 56 patients were included in the study and control group. hs-CRP was raised in 70.96% and 32% of patients in study group and control group with statistically significant $P = 0.004$. Patients with elevated hs-CRP had a worser visual analogue scale score and neurological status (ASIA grade < C and NURICK grade > 2) as compared to patients with normal hs-CRP, but this correlation did not reach the level statistical significance.

Conclusion: Elevated hs-CRP is a useful marker to supplement the diagnosis of TB of spine and monitoring the patients for the response to treatment. Elevated hs-CRP strongly correlates with vertebral body collapse and presence of soft tissue component in TB of spine. Larger clinical studies are required to validate this results of ours in endemic regions.

Key words: High-sensitivity C-reactive protein, Tuberculosis, Spine

INTRODUCTION

TB spondylitis was first described in 1776 by Percival Pott.[1] It accounts for 2-3% of total cases of tuberculosis (TB).[2] It has become a major health hazard after HIV has emerged in the western world.[3] TB Infection can vary from an acute presentation over several days to a more prolonged, chronic course over a period of weeks or months, with a latent period of 1-week to 3-year.[4] It can be devastating because of its ability to cause bone destruction, deformity, and permanent neurological deficits.[1] Early diagnosis and treatment are necessary to avoid long-term disability. Elevated erythrocyte sedimentation rate (ESR) and positive mantoux test provide supportive evidence for the diagnosis of TB but are not specific. Various imaging modalities such as X-ray, computed tomography (CT) scan, and magnetic resonance imaging (MRI) scan of spine help in diagnosis of TB and in defining the extent of TB. Acid-fast bacillus (AFB) smear and culture are gold standard methods for confirmation of diagnosis but it is not conclusive in all the cases.[5] In this study, we have tried to assess and define the role of high-sensitivity C-reactive protein (hs-CRP), in the diagnosis of TB spondylitis and in monitoring the clinical response to treatment.

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MATERIALS AND METHODS

Study Population

This is a prospective study carried out in the Department of neurosurgery, Government General Hospital, Vijayawada,

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from July 2015 to March 2016. Patients presenting with a backache with or without neurological deficits were evaluated with MRI spine (plain and contrast images). Patients with imageological features suggestive of TB of spine were included in the study group. Patients with proven neoplastic disorders or degenerative conditions of spine were included in the control group. Patients on anti-TB therapy for more than 1 month, spinal infection in HIV positive patients, patients with focal or systemic infections other than spine for past 1 month and patients with autoimmune disease were excluded in this study.

A total of 31 patients were included in the study group, and 25 patients were included in the control group respectively. All the patients were evaluated clinically and imageologically and measurement of inflammatory markers *viz*. ESR, hs-CRP before starting treatment was performed. Patients requiring decompression or stabilization of spine were operated upon and biopsy was taken intraoperatively. Postoperatively they were started upon anti-TB chemotherapy as per WHO protocol.[5] The rest of patients not requiring surgery were started on anti-TB treatment. All these patients were evaluated clinically and hs-CRP levels were repeated at 3 months and 6 months follow-up. Pre-treatment imageological and clinical findings were correlated with serum hs-CRP. Post-treatment clinical response to anti-TB chemotherapy was correlated with post-treatment levels of serum hs-CRP. Serum inflammatory levels were assessed in the control group once before starting treatment and correlated with clinical findings.

Clinical Evaluation

At presentation all the patients in study and control group were examined clinically and severity of pain was assessed by visual analogue score (VAS), with a score of 0 for patients with no pain and 10 for patients who are bed ridden due to severe pain. Neurological deficits were graded using American Spinal Injury Association Impairment Scale (ASIA) and NURICK grading system. VAS, ASIA, and NURICK grading systems are described in Appendices A-C, respectively.

Imageological Evaluation

All the patients in the study and control group were evaluated with plain radiographs CT spine and MRI spine with contrast. Patients with classical imageological evidence of end plate changes, paradiscal vertebral involvement, intensity changes in the vertebral body (VB) with or without epidural or prevertebral or paraspinal soft tissue component were susupected to be having TB and were included in the study group. Patients without the evidence of above changes and with imageology showing evidence of degenerative changes or neoplasms were included in the control group. A number of vertebral bodies involved, presence or absence of soft tissue shadow, the collapse of VB, presence or absence of spinal deformity were correlated with the level of inflammatory markers in serum and serum results were analyzed.

Inflammatory Marker - hs-CRP

Inflammation is a stereotyped biological response of tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. In this study we are assessing the level of inflammatory marker (hs-CRP) is evaluated in the blood.

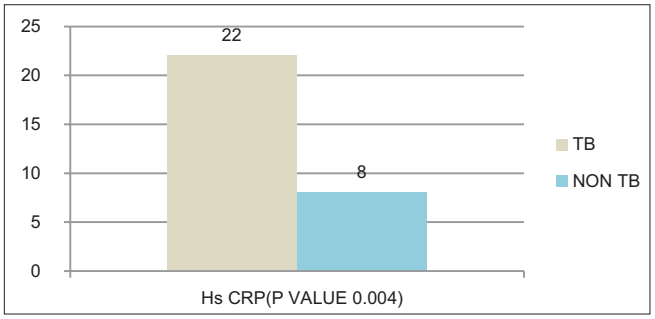
Statistical Analysis

MINITAB version 16 was used for analysis of the data and Microsoft word and Excel have been used to generate Graphs 1-3 and Tables 1-3, etc. Continuous variables are presented as mean and categorical variables are presented in number (%). Statistical significance has been arrived using Chi-square test. A $P < 0.005$ has been considered statistically significant.

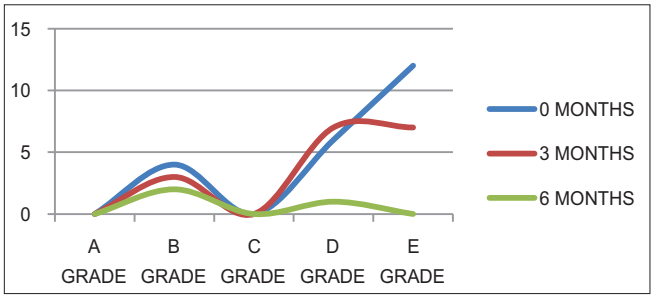
RESULTS

Patient Characteristics

A total of 31 patients were included in the study group, and 25 patients were included in the control group. The study group had patients ranging from 10 years to 70 years with a mean of 34 years. About 17 patients were males and 14 were females. In the control group, the patients had age ranging from 18 years to 80 years with a mean age of 50 years. Around 14 patients were males and 11 were females.



Graph 1: Correlation of high-sensitivity C-reactive protein in tuberculosis (TB) and non-TB spine patients



Graph 2: Correlation of elevated high-sensitivity C-reactive protein patients with neurological status (American Spinal Injury Association grade)

Clinical Characteristics

All patients presented with back pain or neck pain. The VAS score ranged from 2 to 8 with a mean score of 4.51 and mean duration of 4.5 months. About 19 patients had ASIA Grade E, 7 had Grade D, 5 had Grade B. Exactly 16 patients had NURICK Grade 0, 6 had Grade I, 6 had Grade II, 1 had Grade III and two had Grade IV myelopathy.

Imageological Characteristics

The spinal deformity was seen in 6 (19.35%) patients. One VB was involved in 8 (25.80%), two vertebral bodies in 18 (58.06%), three vertebral bodies in 3 (9.67%), four or more vertebral bodies were involved in 2 (6.45%) patients. Soft tissue involvement was seen in 21 (67.74%) of patients. VB collapse was seen in 11 (35.48 %) of patients (Figures 1-3).

Table 1: Correlation of elevated hs-CRP with clinic imageological findings (statistical significant)

Clinical and image Findings	hs-CRP		*P* value
	Raised	Not raised	
NURICK grade			0.170
<2	19	9	
≥2	3	0	
ASIA grade			0.329
≤C	4	1	
>C	18	8	
No of VB			0.170
≤2	17	9	
>2	5	0	
Deformity of Spine			0.398
Present	5	1	
Absent	17	8	
Collapse of VB			0.002
Present	11	0	
Absent	11	9	
Soft tissue			0.004
Present	18	3	
Absent	4	6	

hs-CRP: High-sensitivity C-reactive protein, VB: Vertebral body, ASIA: American Spinal Injury Association

Table 2: Correlation of severity of pain with level hs-CRP

Months	VAS	hs-CRP (mg/l)
0 months (*n*=31)	4.51	20.84
3 months (*n*=30)	2.13	8.38
6 months (*n*=25)	0.8	3.64

VAS: Visual analogue scale

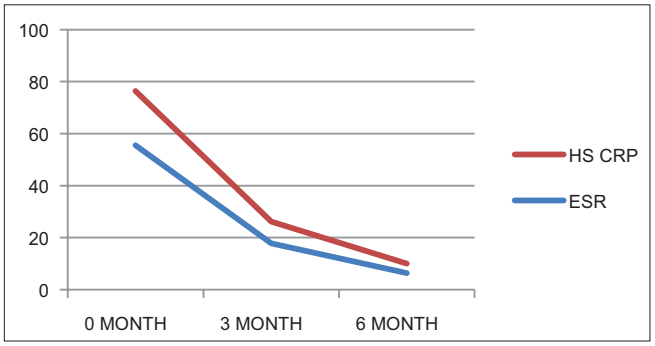
Table 3: Correlation of NURICK grade (myelopathy/ radiculopathy) with level of hs-CRP

Months	NURICK grade	hs-CRP
0 months (*n*=31)	0.64	20.84
3 months (*n*=30)	0.48	8.38
6 months (*n*=25)	0.32	3.64

hs-CRP: High-sensitivity C-reactive protein

hs-CRP in TB and Non TB Patients

hs-CRP was raised in 70.96% of patients in study group and 32% of patients in control group. The difference was statistically significant with a $P = 0.004$. Serum ferritin was raised in 14.81% of patients in study group and 8.69% of



Graph 3: Regression of erythrocyte sedimentation rate and high-sensitivity C-reactive protein levels during the course of antithrombotic trialists

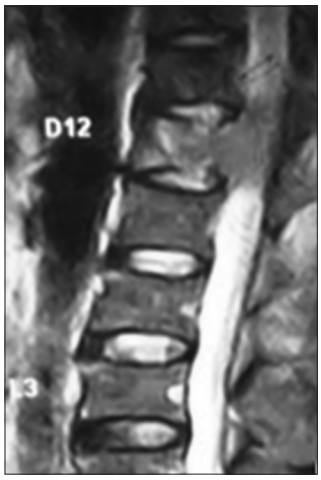


Figure 1: Tuberculosis spine (T2W sagittal image) shows end plate distruction and epidural soft tissue

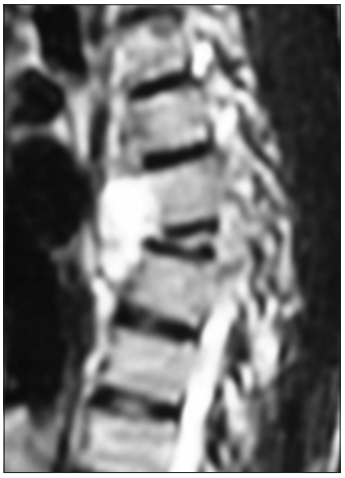


Figure 2: Tuberculosis spine (T2W sagittal image) shows collapsed vertebral body and pre vertebral soft tissue

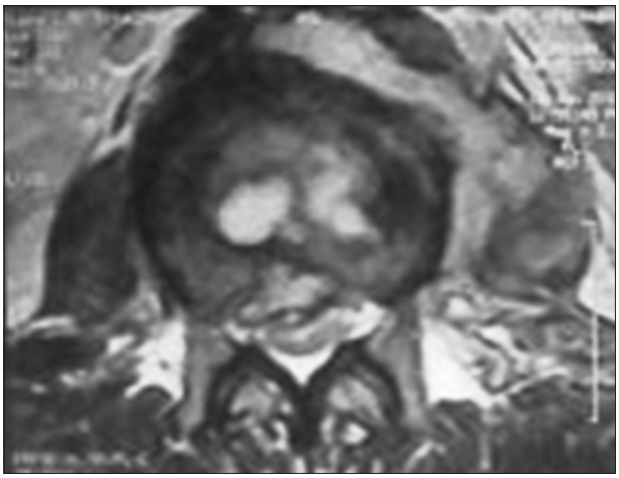


Figure 3: Tuberculosis spine (T2W axial image) shows epidural and paraspinal soft tissue

patients in control group. The difference was statistically insignificant with a $P = 0.555$. ESR was raised in 80.64% of patients in study group and 8% of patients in control group. The difference was statistically significant with a $P = 0.003$. Thus raised hs-CRP and ESR provided supportive evidence for the diagnosis of TB.

All the patients in study group with elevated hs-CRP except one had VAS score > 4. All the patients in study group with elevated serum ferritin had VAS score > 4. The level of hs-CRP correlate with the severity of pain. In follow-up as VAS score improved with treatment, the levels of hs-CRP is decreased and at 6 months, hs-CRP reached the baseline level of 5 mg/dl in all except three. In the remaining three, hs-CRP showed a decreasing trend. Similarly, as shown in Table 1, patients with elevated hs-CRP had a worser neurological status (ASIA Grade < C and NURICK Grade > 2) compared to patients with normal hs-CRP. But this correlation didn't reach the level statistical significance.

DISCUSSION

Spinal TB is common in the first three decades of life,[2] affecting mostly young adults in poor socio economi stiata. TB of spine most commonly affects the dorso-lumbar spine region followed by cervical spine. Spinal TB is a slowly progressive disease and diagnostic delay is of major concern. A number of neoplastic, degenerative and bony tumors like metastasis, osteoblastoma, aneurysmal bone cyst mimic TB spine. TB responds well to anti TB therapy and biopsy with a demonstration of AFB smear or growth of TB bacilli colonies on culture media is gold standard. A biopsy is not always possible in early stages of disease. As imaging is not specific and biopsy is not always possible,[6] other methods for diagnosis of spinal TB are always required especially in endemic regions. In this study, we have assessed the role of hs-CRP in diagnosis of TB spine.

When biopsy confirmation of TB is not available, elevated levels of serum inflammatory markers may provide collaborative evidence for diagnosis of TB spine. C-reactive protein was the first acute-phase protein to be described and is an extremely sensitive systemic marker of inflammation and tissue damage.[7] Weng *et al.*[8] suggested spinal TB to be included in the differential diagnosis of chronic back pain in elderly patients with elevated ESR. Similarly, Spinal TB should also be included in the differential diagnosis of chronic back pain in patients with elevated hs-CRP.[9]

In our study, hs-CRP was raised in 70.96% of patients with study group and 32% of patients in the control group. The difference was statistically significant ($P = 0.004$). Thus elevated hs-CRP provided a good collaborative evidence for diagnosis of TB spine in our patient. According to Shanly *et al.*,[10] described less common variant of TB of spine, which is limited to a single VB may lead to VB collapse and development of vertebra plane. According to our study, patients with collapse of VB and raised hs-CRP have a high probability of harboring a TB of spine.

Sturmer *et al.* found the concentration of hs-CRP to be directly proportional to the severity of inflammation and pain. In our study group, most of the patients with raised hs-CRP had deformity of spine, extensive soft tissue component, VB collapse and extensive VB involvement (> two VB's). They also had a poorer VAS score (VAS score > 4), poorer neurological status (NURICK Grade > 2, ASIA Grade < C) at presentation. Severity of pain (VAS score), neurological status (ASIA grade, NURICK grade), spinal deformity and number of vertebral bodies involved had a correlation with raised hs-CRP, but correlation was not statistically significant. Soft tissue involvement and the presence of VB collapse correlated with hs-CRP levels, and the correlation was statistically significant (Table 1).

hs-CRP is a nonspecific biochemical marker of inflammation and its concentration in blood is useful for monitoring the response of inflammation to treatment.[11] According to Mahadev *et al.*, most of patients who responded to treatment demonstrated a decrease in their CRP value by at least 50%.[12] In our study group, at 3 and 6 months follow-up, improved clinical status (VAS score and neurological status) was associated with fall in hs-CRP levels. At the end of 3 months follow-up, all patients showed reduction in hs-CRP values, which continued to do so till the end of 6 months. In all patients except three in the study group, the hs CRP levels reached baseline value

of 5 mg/l by 6 months and the remaining three patients also showed a diminishing trend. The average reduction in hs CRP was approximately by 50% at the end of 3 months and another 50% by next for 6 months. There was a proportionate reduction in the CRP levels with treatment.

In our study hs-CRP levels, the values declined with decreasing VAS score. However, Sturmer *et al*., found higher levels of hs-CRP in patients with higher pain levels.[13] In their observation neither in acute back ache nor chronic back ache, there was correlation of hs-CRP levels in clinical course of disease in the 6-month period. This is contrary to our findings. Wang *et al*.,[14] achieved excellent results with ultra-short course of anti-TB chemotherapy course (4.5 months) in conjunction with partial excision of pathologic vertebrae and clinical improvement was associated with decreased ESR, CRP levels. Similarly, in our study, hs-CRP levels decreased in response to chemotherapy (Table 2). At 3 and 6 months of chemotherapy with or without surgical intervention and correlated well with improvement of neurological status (ASIA and NURICK grade - Graph 2 and Table 3). Hence, hs-CRP levels were found useful to monitor the respone to treatment. According to Pawar *et al.,*[15] resistance to 1st line TB drug should be considered in the absence of clinical and imageological improvement. Similarly, resistance to TB drug should be considered in the absence of declining trend in hs-CRP levels.

ESR is widely used for monitoring clinical progress in patients with TB.[12] It is cheap, easy to perform and does not require expensive equipment. Ring *et al.* have found 94% of patients with TB spine in their series was elevated ESR at presentation.[7] ESR rarely exceeded 55 mm/h in TB of spine.[5] hs-CRP is less sensitive and specific 70.96% and 68%) compared to ESR (80% and 76%) for diagnosis of TB spine. However, hs-CRP responds more rapidly to treatment compared to ESR as shown in Graph 3. Based on study of Syed Ather Enam *et al*., when compared with CRP, ESR may provide clinicians more useful information in evaluating the treatment response of spinal TB.[7] Our study also strongly proposed that the serial monitoring of hs-CRP could be considered as valuable index, to assess the progression or regression of the disease to the treatment (Graph 3).

CONCLUSION

We can conclude from above findings that the hs-CRP is a useful marker to supplement the diagnosis of the TB of spine. The hs-CRP is significantly elevated in those patients with the presence soft tissue component and collapse of VB. The serial measurements of serum values of hs-CRP were useful in assessing the treatment response of the patient.

Limitation of Study

The study population was small and the role of this hs-CRP in the diagnosis of TB of spine in the presence of simultaneous infection elsewhere in the body is not studied. The TB was suspected on the basis of imageology. Only 50% patients had biopsy confirmation of TB.

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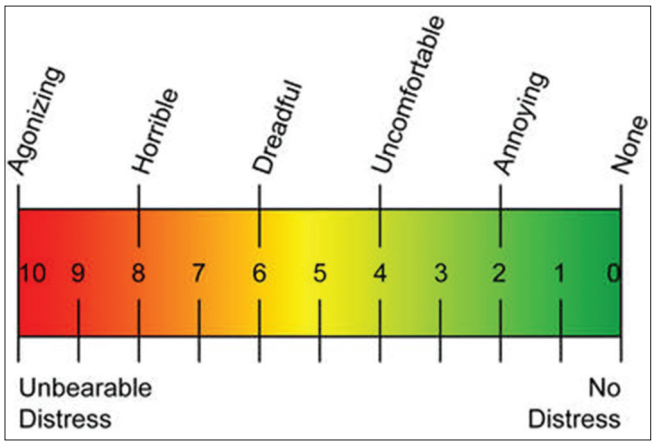
APPENDICES



Appendice A: Visual analogue scale

Appendice B: ASIA impairment scale

Grade A	Complete lack of motor and sensory function below the level of injury (including the anal area)
Grade B	Some sensation below the level of the injury (including anal sensation)
Grade C	Some muscle movement is spared below the level of injury, but 50% of the muscles below the level of injury cannot move against gravity
Grade D	Most (more than 50%) of the muscles that are spared below the level of injury are strong enough to move against gravity
Grade E	Normal neurological status (no sensory or motor or autonomic disturbances

Appendice C: NURICK scale

Grade 0	Signs or symptoms of root involvement but without evidence of spinal cord disease
Grade1	Signs of spinal cord disease but no difficulty in walking
Grade 2	Slight difficulty in walking which does not prevent full-time employment
Grade 3	Difficulty in walking which prevented full time employment or the ability to do all housework, but which was not so severe as to require someone else's help to walk
Grade 4	Aable to walk only with someone else's help or with the aid of a frame
Grade 5	Chairbound or bedridden