RESEARCH PAPER

Rickettsial Diseases in Central India: Proposed Clinical Scoring System for Early Detection of Spotted Fever

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Objectives: To report a series of cases of rickettsial infections from central India and to develop a clinical scoring system for its early detection.

Design: Retrospective review of children hospitalized during one year period with fever without a source, and presence of one or more of the clinical features suggestive of rickettsial infection. Diagnosis of rickettsial disease was made by classical clinical features and detection of IgM antibody by ELISA. A clinical scoring system was developed to diagnose spotted fever group by using classical clinical and laboratory findings.

Results: 161 patients were admitted and met the inclusion criteria, 75 (45.6%) were diagnosed with rickettsial diseases. 52 (69.3%) had spotted fever group and 23 (30.7%) scrub typhus. The mortality rate with rickettsial diseases was 9%. By using proposed clinical scoring system, a score of 14 has sensitivity and specificity of 96.15% and 98.84%, respectively in making a diagnosis of spotted fever group.

Conclusion: Rickettsial diseases are common in the central part of India and should be included in the differential diagnosis of patients with fever of undetermined source. The proposed scoring system can be used for early detection, treatment and prevention of mortality and morbidity from spotted fever group.

Key words: *Clinical scoring system, Diagnosis, India, Rickettsiae, Spotted fever, Scrub typhus.*

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Rickettsial diseases have been reported from various parts of India [1-5]. However, no study has been done in central India to investigate the existence of rickettsial disease in this region. Physicians, including pediatricians, usually do not include rickettsial infection in their differential diagnosis. Factors predisposing to rickettsial infections are prevalent in this part of the country.

The greatest challenge to the clinician is the diagnostic dilemma posed by these infections early in their clinical course when antibiotic therapy is most effective [6,7]. Only the Weil-Felix test is easily available for diagnosis in India but most of the western literature has advised against performing this test for diagnosis of rickettsial infections [7,8]. Other serological tests are based on detecting antibodies, and aid in diagnosis only 5-7 days after the onset of the disease and are not helpful in the early initiation of therapy in a suspected case. Immunofluorescence assay (IFA), the gold standard diagnostic test for rickettsial infections, is not available in India, is expensive, and can take more than a week to get the results. As no single laboratory finding is specific for early diagnosis, treatment needs to be started on clinical suspicion. We are reporting a series of cases of rickettsial infections, recently diagnosed in our practice with a dramatic response to appropriate antibiotics. Given the urgent need for a clinical diagnostic tool, we herein propose a clinical scoring system for early detection of spotted fever group.

METHODS

We conducted a retrospective review of children admitted at our center in Central India between January 2009 and December 2009.

Inclusion criteria: Age <20 years; hospitalized with fever without a source; presence of one or more of the following clinical features: rash, edema, hepatospenomegaly, lymphadenopathy, eschar, and tick bite or tick exposure.

Exclusion criteria: The cause of fever known at the time of admission; and patients treated on an outpatient basis.

The Institutional Review Committee at Cooper University Hospital, Camden, USA, approved the study. One hundred and sixty one patients qualified for the review. The clinical and laboratory data were collected from the patient's medical records. The ELISA for spotted fever IgM antibody (Panbio, Brisbane, Australia) and scrub typhus IgM antibody (InBios International, Seattle, USA) were performed on 146 patients. Weil-Felix test (Tulip Diagnostics Pvt Ltd. Goa, India) was done in 157 cases and a titer of 1:80 or more was considered as a positive test. IFA IgM for spotted fever group (Focus Tech Inc, Cypress, CA), was performed on 10 patients diagnosed with rickettsial disease by clinical features and positive ELISA for IgM antibody and a titer of 1:64 or more was considered as a positive test. The serological tests were performed more than 7 days after the onset of the disease. The suspected cases were treated with doxycycline (dose 5 mg/kg/day for 7-10 days) and response to treatment and days to defervescence were recorded. In seriously ill patients, doxycycline was given via Ryle's tube. The diagnosis of rickettsial disease was made by the detection of IgM antibody by ELISA, exclusion of other diseases, and prompt response to the treatment. Rural area was defined as a village with a population of less than 10,000. Tick exposure was said to occur when ticks were seen on the clothes of the child or inside the house, or history of playing in an area where ticks are seen.

The patients were categorized into rickettsial infection group and no rickettsial infection group. The baseline demographics, risk factors, clinical and laboratory characteristics were compared between the two groups.

Clinical scoring system: A clinical scoring system viz. Rathi Goodman Aghai (RGA) Clinical scoring system was developed using classical clinical and laboratory findings seen in spotted fever group (SFG). A score of 0-3 was given for each clinical or laboratory finding based on their association with SFG. This scoring system was applied on each patient in SFG and no rickettsial infection group. The total scores were compared between the two groups. Receiver operating characteristics (ROC) curve analysis was performed to determine the cut off level of total score for the diagnosis of SFG. The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), likelihood ratio of positive test (LR+) and likelihood ratio of negative test (LR-) were calculated using the total score from each patient.

Statistical analyses were performed using Sigma Stat 3.1 for Windows statistical package (Systat Software, Inc; Point Richmond, CA). ROC curve analysis was performed using MedCalc (Broekstraat, Belgium) statistical software The comparisons between groups were performed using Student's *t*-test and Mann-Whitney Rank Sum test for continuous data and χ^2 or Fisher's exact test for categorical data. The difference was considered significant for $P<0.05$.

RESULTS

A total of 161 admitted patients met the inclusion criteria. Seventy five patients (45.6%) were diagnosed with rickettsial diseases while 86 patients had other diagnoses. Of the 75 patients with rickettsial infections, 52 (69.3%) had spotted fever group (SFG) and 23 (30.7%) scrub typhus (ST). No case of typhus fever was seen in our series. ELISA for IgM antibody against spotted fever was positive in 47 out of 52 patients (90%) with SFG. Five patients who were included in the SFG group with negative IgM antibody for spotted fever had strong clinical features of rickettsial infection, other diagnoses were excluded and responded promptly to doxycycline. IFA was performed in 10 patients with SFG who were positive for IgM antibody against

spotted fever by ELISA. Each of them had positive IgM by IFA. ELISA for IgM antibody against scrub typhus was positive in 21 out of 23 patients (91%) with ST. Two patients included in the ST group with negative IgM antibody had strong clinical features of scrub typhus (one was positive for Weil-Felix), other diagnoses were excluded and responded promptly to doxycycline.

Clinical features in the two groups are described in ***Table* I**. Anorexia, irritability, myalgia and headache were present in the majority of patients with rickettsial diseases. There was no significant difference in the number of cases with rash in the two groups. However, the rash was more purpuric, palpable purpuric, ecchymotic or necrotic in patients with rickettsial diseases. The laboratory findings between the two groups are compared in ***Table* II**. The Weil-Felix test was positive only in 49% of the patients with rickettsial diseases (sensitivity 49%, specificity 96%). ELISA for IgM antibody had a sensitivity and specificity of 91% and 100%, respectively for making a diagnosis of rickettsial infection.

The clinical and laboratory characteristics were also compared between the patients with SFG and ST. The patients with SFG were younger, more likely to have rash but the duration of the fever and rash was shorter (***Table* III**). Anasarca, eschar and lymphadenopathy were more common in patients with ST. There was no significant difference in the laboratory findings in the two groups.

Abnormal neurological finding (28%) was the most common complication of rickettsial diseases

TABLE I DEMOGRAPHICS AND BASELINE CLINICAL CHARACTERISTICS OF PATIENTS WITH AND WITHOUT RICKETTSIAL INFECTIONS

	Rickettsiae (*n*=75)	No Rickettsiae (*n*=86)	*P* value
Age (y)*	5 (2m-20y)	4 (7m-15y)	0.3
Sex (M:F)	52:23	51:35	0.3
Rural (%)	60 (80)	26 (30)	<0.001
Pets (%)	29 (39)	16 (19)	0.008
Tick exposure (%)	60 (80)	17 (20)	<0.001
Tick bite (%)	21 (28)	0 (0)	<0.001
Duration of fever (d)*	10 (5-22)	7 (3-25)	<0.001
Rash (%)	62 (83)	72 (84)	0.97
Duration of rash (d)*	7 (2-20)	2 (1-11)	<0.001
Onset of rash after fever (d)*	3 (2-6)	4 (1-14)	<0.001
Purpura, or rash (%)	53 (62)	3 (4)	<0.001
#Conjunctival congestion (%)	39 (52)	11 (13)	<0.001
Pedal edema (%)	69 (92)	18 (21)	<0.001
Anasarca (%)	21 (28)	9 (10)	0.008
Eschar (%)	5 (7)	0 (0)	0.048
Rash on palms and soles (%)	44 (59)	15 (17)	<0.001
Hepatomegaly (%)	74 (99)	40 (46)	<0.001
Lymphadenopathy(%)	31 (41)	17 (20)	0.005
Died (%)	7 (9)	7 (8)	1.0

**median (range), #Non exudative.*

TABLE II LABORATORY FINDINGS IN CHILDREN WITH AND WITHOUT RICKETTSIAL INFECTIONS

	Rickettssial Infection		*P* value
	Present (*n*=75) No (%)	Absent (*n*=86) No (%)	
TLC ($X10^3$/cumm)*	9.8 (1.8-38.0)	4.3 (2.1-43.6)	0.007
Hemoglobin (g/dL)*	8.8 (4.2-12.2)	11.1 (2.3-14.8)	<0.001
Hemoglobin ≤9 g/dL (%)	53 (71)	19 (22)	<0.001
Platelets ($X\ 10^3$/cumm)*	103 (12-599)	141(12-754)	0.01
Platelets ≤150,000/cumm	51 (68)	42 (49)	0.02
CRP (mg/L)*	55 (6-169)	10 (3-138)	<0.001
CRP ≥50 mg/L	42 (56)	17 (20)	<0.001
Serum albumin g/dL*	3 (1.8-4.4)	3.9 (2-5)	<0.001
Albumin <3 g/dL	38 (51)	21 (24)	0.001
Urine albumin ≤2+	30 (40)	3 (3)	<0.001
SGPT ≥100 (U/L)	49 (65)	21 (24)	<0.001
Na ≤130 (meq/L)	48 (64)	14 (16)	<0.001
Positive Weil Felix test	37 (49)	3 (3.4)	<0.001
Positive ELISA IgM antibody	68 (91)	0* (0)	<0.001

** Median (range); Performed on 71 patients; CRP- C reactive protein; TLC- Total leucocyte count; SGPT- Serum glutamic pyruvic transaminase*

TABLE III DEMOGRAPHIC AND BASELINE CLINICAL CHARACTERISTICS OF CHILDREN WITH SPOTTED FEVER GROUP (SFG) AND SCRUB TYPHUS (ST)

	SFG (*n*=52) No. (%)	ST (*n*=23) No. (%)	*P* value
Age *	4 (2m-16y)	8 (8 m-20y)	0.009
Sex (M:F)	33:19	19:4	0.2
Rural (%)	43 (81)	17 (74)	0.5
Pets (%)	19 (36)	10 (43)	0.8
Tick exposure (%)	43 (81)	17 (74)	0.5
Tick bite (%)	14 (27)	7 (30)	0.9
Duration of fever (d)*	9 (5-20)	13 (7-22)	<0.001
Rash(%)	51 (98)	10 (43)	<0.001
Duration of rash (d)*	7 (2-17)	16 (6-20)	<0.001
Onset of rash after fever (d)*	3 (2-6)	3 (2-3)	0.6
#Conjunctival congestion (%)	27 (52)	12 (52)	0.9
Pedal edema (%)	49 (94)	20 (87)	0.8
Anasarca (%)	4 (8)	17 (74)	<0.001
Eschar (%)	0 (0)	5 (22)	0.002
Hepatomegaly (%)	52 (100)	22 (97)	1.0
Lymphadenopathy (%)	13 (25)	18 (78)	<0.001
Died (%)	4 (8)	3 (13)	0.7

#*Non exudative; *Median* (*range*).

(encephalopathy 15%, meningitis 5%, meningo-encephalitis 5%, encephalitis 3%). Pnuemonia (21%), gangrene (11%), renal failure (7%) and shock, myocarditis, gastrointestinal hemorrhage, DIC, ARDS (5% each) were other complications reported in our patients. Two patients (3%) had hemophagocytic syndrome. The median age of defervescence was 2 days (range 1-5 days). The mortality rate with rickettsial diseases was 9%. All 4 patients who developed ARDS and two patients who had hemophagocytic syndrome died. One more patient who died of rickettsial disease had encephalitis.

A clinical scoring system utilizing clinical and laboratory characteristics seen more frequently with SFG was developed and tested. As described in ***Table* IV**, a score of 0-3 was given for each clinical or laboratory finding. The RGA scoring system has a total score of 35 (25 clinical and 10 laboratory findings). The median score in the SFG was 22 (range, 10-30), compared to 6.5 (range, 1-16) in the no rickettsial group ($P<0.001$). On ROC curve analysis the cut-off score with the highest accuracy was found to be 14, with a sensitivity and specificity of 96.15% and 98.84%, and a PPV and NPV of 98.0% and 97.7%, respectively. With a cut-off score of 14, the likelihood ratio of positive test (LR+) and likelihood ratio of negative test (LR-) were 82.7 and 0.04, respectively. Fifty out of 52 patients (96%) in spotted fever group had a score of 14 or more compared to only 1 out of 86 (1%) with no rickettsial infection ($P<0.001$). A score of 17 had 100% specificity (sensitivity 86.5%) and a score of 9 had 100% sensitivity (specificity 81.4%).

TABLE IV SCORING SYSTEM TO DIAGNOSE SPOTTED FEVER GROUP (TOTAL SCORE = 35)

Clinical features	Score	Laboratory	Score
Rural	1	Hemoglobin ≤9 g/dL(%)	1
Pets	1	Platelets <150,000 (cells/L)	1
Tick exposure	2	CRP ≥50 (mg/dL)	2
Tick bite	3	Serum albumin <3 g/dL	1
Conjunctival congestion (Non exudative)	2	Urine albumin ≥2+	1
		SGPT ≥100 (U/L)	2
		Na ≤130 (mEg/L)	2
Maculopapular rash	1		
Purpura	2		
Palpable purpura/ ecchymosis/ necrotic rash	3		
Rash appearing 48-96 h after fever	2		
Pedal edema	2		
Rash on palms and soles	3		
Hepatomegaly	2		
Lymphadenopathy	1		
Total	25		10

DISCUSSION

While rickettsial diseases are reported from various parts of India [1-5], this is the first study showing its existence in central India.

However, the reported cases underestimate the burden of rickettsial diseases in India due to the lack

WHAT IS ALREADY KNOWN?

- Rickettsial diseases are reported from various parts of India. Definitive treatment should be instituted on the basis of clinical and epidemiological clues as early as possible.

WHAT THIS STUDY ADDS?

- Rickettsial diseases are common in the Central India.
- When applied to the patients presenting with fever of unknown source, a clinical score of 14 or more on the proposed scoring system has very high sensitivity and specificity for the diagnosis of spotted fever group of rickettsial diseases.

of both community based studies and availability of specific laboratory tests [9]. We are reporting a large series of cases that were diagnosed during a short period of time from Akola and adjoining districts from Maharashtra in Central India. We found that 45.6% of children hospitalized with fever of undetermined sources had rickettsial diseases. Rickettsial infection in our series is prevalent across all age groups and the youngest child was only 2 months old. Majority of our cases were seen during the months of June to October. SFG was more common than ST and no case of typhus fever was identified. Kamasaru, *et al*. [10] reported higher incidence of ST in Tamil Nadu, whereas SFG was more common in a case series reported by Kulkarni, *et al*. [4] from the Western part of India [5,14]. More recently, a single case of scrub typhus was reported from Mumbai [5].

The common clinical features of rickettsial infections in this series were similar to those reported earlier [1-5]. We, however, could identify specific clinical and laboratory characteristics to develop a scoring system to differentiate SFG from non-rickettsial infections in patients presenting with fever of undetermined source. The clinical scoring system was tested on each patient from both the groups. When applied to the patients presenting with fever of unknown source, a clinical score of 14 or more on proposed RGA scoring system has sensitivity and specificity similar to the detection of specific IgM antibody by ELISA. The clinical scoring system may help physicians in early diagnosis, prompt treatment and prevention of complications and death from this dreaded disease. Another important clinical tool in differentiating rickettsial infections from non rickettsial infections is the response to treatment with doxycycline. 73 out of 75 patients with rickettsial infections in our series had prompt defervescence with doxycycline in a median time of 2 days.

Several investigators have expressed that rickettsial infections are under-reported in India [4, 10]. Although, no case has been reported from the Central India (Vidharba, Madhya Pradesh and Chattisgarh), factors predisposing to rickettsial infections are prevalent in this part of the country. Since no case has been documented, pediatricians usually do not include rickettsial infections in their differential diagnosis. It is not obvious whether rickettsial infections were endemic or re-emerging in Central India. Awareness of the existence of rickettsial infection will also prevent excessive investigations in patients with fevers of unknown sources and lower the economic burden to families and society.

We recognize several limitations of the current report. This is a retrospective review from a single center reporting data from patients who were hospitalized with fever of undetermined source and other clinical features commonly seen with rickettsial infections. The sample size for developing the scoring system is also small. A larger study, at multiple centers, involving hospitalized as well as patients in an ambulatory set up is required to find true prevalence of rickettsial infection in Central India. The proposed clinical scoring system needs to be validated using a larger sample size at multiple sites.

Despite these limitations, we conclude that rickettsial diseases are common in the Central India and should be included in the differential diagnosis

of patients with fever of undetermined source. The RGA scoring system can be used for early detection, treatment and prevention of mortality and morbidity from SFG.

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REFERENCES

1. Mahajan SK, Kashyap R, Kanga A, Sharma V, Prasher BS, Pal LS. Relevance of Weil-Felix test in diagnosis of Scrub Typhus in India. J Assoc Phys India. 2006;54:619-21.
2. Mathai E, Lloyd G, Cherian T, Abraham OC, Cherian AM. Serological evidence of continued presence of human Rickettsiosis in southern India. Ann Trop Med Parasitol. 2001;95:395-8.
3. Sundhindra BK, Vijaykumar S, Kutti AK. Rickettsial spotted fevers in Kerala. Natl Med J India. 2004;17:51-2.
4. Kulkarni A, Vaidya S, Kulkarni P, Bidri, LH Padwal S. Rickettsial disease-an experience. Pediatr Infect Dis. 2009;1:118-24.
5. Shah V, Vaidya V, Bang V, Shah I. Spotted fever in a child in Mumbai, India. J Vector Borne Dis. 2009;4:310-2.
6. Chapman AS, Bakken JS, Folk SM, Paddock CD, Bloch KC, Krusell A, *et al*. Diagnosis and management of tickborne rickettsial diseases. MMWR Recomm Rep. 2006;55:1-27.
7. Rathi N, Rathi A. Rickettsial infections: Indian perspective. Indian Pediatr. 2010;47:157-64.
8. Siberry GK, Dumler JS. Rickettsial infections. *In*: Kliegman RM, Behrman RE, Jenson HB, Stanton BF, editors. Nelson Textbook of Pediatrics, 18th ed. Pennsylvania: Saunders. 2007; p. 1289-301.
9. Chugh TD. Emerging and reemerging bacterial diseases in India. J Biosci. 2008;33:549-55.
10. Kamarasu K, Malathi M, Rajagopal V, Subramani K, Jagadeeshramasamy D, Mathai E. Serological evidence for wide distribution of spotted fevers & typhus fever in Tamil Nadu. Indian J Med Res. 2007;126:128-30.