CLINICAL PROFILE OF RICKETTSIAL INFECTION IN VIJAYAPUR, NORTH KARNATAKA- A RETROSPECTIVE STUDY

Satish Talikoti[1], Nijora Deka[2]

[1]Assistant Professor, Department of General Medicine, Al-Ameen Medical College and Hospital, Vijayapur, Karnataka.
[2]Associate Professor, Department of General Medicine, Al-Ameen Medical College and Hospital, Vijayapur, Karnataka.

ABSTRACT

BACKGROUND

We wanted to analyse the clinical profile of Rickettsial cases with an emphasis on epidemiology, clinical features, diagnosis and management issues of these infections, in a major tertiary referral medical college hospital in Vijayapur.

METHODS

We have summarized the data from 113 hospitalized patients who were laboratory confirmed for Rickettsial infection at Al Ameen Hospital, Vijaypur. Patients were treated as per recommendations of Tick-Borne Rickettsial Diseases Working Group of Centre for Disease Control (CDC), Atlanta, for management of Rickettsial infections.

RESULTS

312 cases from June 2017 to December 2018 were studied retrospectively for patient's demography, clinical presentation, treatment and outcome. Patients with history of fever of 2-4 weeks and positive Weil-Felix test, a negative malaria, chikungunya and dengue serology were diagnosed as probable rickettsial disease positive. Four patients had skin rashes. 3 persons had eschar at presentation. Number of males affected was marginally higher in number. 44 cases belonged to the rural areas surrounding Vijayapur city. No deaths were recorded.

CONCLUSIONS

Rickettsial fever is not a common diagnosis for fever because of nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests. Failure of timely diagnosis leads to significant morbidity and mortality. Some patients with rickettsial diseases might initially receive an alternative diagnosis, and be empirically treated with antibiotics inactive against rickettsia. However, treatment for this disease is easy, affordable and often successful with good response if diagnosed with a higher index of suspicion than is being warranted at the present juncture.

KEYWORDS

Rickettsia, Weil Felix Test, Empirical Treatment.

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BACKGROUND

Rickettsiae are a heterogeneous group of small, obligate intracellular, gram-negative coccobacilli and short bacilli, most of which are transmitted by a tick, mite, flea, or louse vector. Except in the case of louse-borne typhus, humans are incidental hosts.[1] Clinical infections with rickettsiae can be classified according to: (1) the taxonomy and diverse microbial characteristics of the agents, which belong to seven genera (Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia, Candidatus-Neoehrlichia, and Coxiella) (2) epidemiology or (3) clinical manifestation.

In an analysis of cases in South India, majority of cases are from Karnataka (50%), Andhra Pradesh (32.3%) and Tamil Nadu (17.7%).[2,3,4,5] At presentation during the first 3 days of illness, only 3% of patients exhibit the classic triad of fever, rash, and history of tick exposure. However, many illnesses considered in the differential diagnosis also can be associated with a rash, including rubeola, rubella, meningococcaemia, disseminated gonococcal infection, secondary syphilis, toxic shock syndrome, drug hypersensitivity, idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, Kawasaki syndrome, and immune complex Our aim was the analysis of the clinical profile of rickettsial cases during an outbreak in a major tertiary referral medical college hospital in Vijayapur. A high degree of clinical suspicion with minimal or delayed access to advanced laboratory parameters is important in a resource-poor setting. We aimed to highlight the clinical features that can increase the identification of rickettsial infections and help distinguish it from other febrile illnesses so prompt treatment can be instituted. Doxycycline is the empirical drug of choice for most of these infections. Azithromycin is the drug of choice in pregnant women as doxycycline is contraindicated.

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Corresponding Author:
Dr. Nijora Deka,
Associate Professor,
Department of General Medicine,
Al-Ameen Medical College and Hospital,
Vijayapur- 586101, Karnataka, India.
E-mail: drnijora@gmail.com
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METHODS

A total of 312 cases presented with fever to Al Ameen Hospital from June 2017 to December 2018 and 224 patients were hospitalized. Of these, 113 hospitalized patients were included in the study after they were laboratory-confirmed to be Weil -Felix positive. The study is done at the Al Ameen Hospital, Vijayapur.

Clinical history, physical examination, haematological, biochemical and microbiological investigations were recorded. This study was approved by the ethics committee.

Inclusion Criteria

All patients above 18 years with fever and found to be Weil-Felix positive and negative for other protozoal/viral infections were included in this study.

Exclusion Criteria

Cases who have undergone treatment before giving a blood sample.

Statistical Methodology

Quantitative data are presented as the average mean estimate. The categorical variables are reported as frequencies and percentages. Descriptive statistics for the study population characteristics and laboratory findings were performed with Microsoft Excel and SPSS Inc. version 17.

RESULTS

Age		32.9 yrs. ± (4.2) yrs.
Sex a. Male b. Female		 73 (65%) 51 (45%)
	Fever	99 (88%)
	Headache	6 (5%)
R	Rash	50 (44%)
E	Eschars	50 (44%)
	Multiple eschars	2 (2%)
	Myalgia	77 (68%)
	Nausea and/or vomiting	62 (55%)
	Abdominal Pain	25 (22%)
	Petechial Rash	41 (36%)
	lymphadenopathy	0
	Conjunctivitis	29 (26%)
	Diarrhoea	2 (2%)
	Oedema	14 (12%)
	Jaundice	5 (4%)
	Hepatomegaly	1 (1%)
	Cough	88 (78%)
	Dyspnoea	52 (46%)
	Seizures	0
	Ataxia	0
	Coma	0
	Shock and/ or Hypotension	18 (16%)
	Arrhythmia	0
	Pneumonitis	14 (12%)
	Meningismus	0
	Myocarditis	12 (11%)
Number of deaths		0
Days of hospitalization		11 days

Table 1. Clinical Features N=113

	N= 113	%
OX2	1: 160	80
OX K	1: 160	80
OX 19	1: 320	67

Table 2. Serology (Weil-Felix Test) Results

		N = 113
	Haemoglobin < 11 g/dl	74(65.1%)
	Leukopenia < 3700 cells/cumm	25(22%)
	Thrombocytopenia < 150000/ microlitre	24(21%)
H	Hyponatremia	63(56%)
	ALT(5-40 U/L)	44(39 ~ 55.0)
	AST(5-40 U/L)	68(56 ~ 75.5)
	Raised Serum Cr > 1.1 mg/dl in women > 1.3 mg/dl in men	14(12%)

Table 3. Laboratory Values

Out of the total of 312 cases presenting with fever to Al Ameen Hospital from June 2017 to December 2018, 224 patients were hospitalized. Of these, 113 had rickettsial disease. No deaths were recorded during hospital stay. The mean age of the patients was 32.9 ± 4.2 years. Younger age group have a higher incidence in our study, but older age groups could probably be at higher risk for more severe disease. Typical clinical symptoms included fever, headache, cough, myalgia, rash, petechiae and eschar (Table 1). Inoculation eschar (tâche noire) was noticed only by 5 patients. The rest were a result of general physical examination by the physician. Rash was evident in 14% of patients on the first day of illness and rose to 44% after 5 days. 36% had petechial rashes that did not disappear upon compression. None required respiratory support / ventilation. Cardiac involvement manifested as myocarditis in 6% Photophobia, with considerable conjunctival injection and eye pain was seen in 22% Laboratory evidence suggested the prevalence of anaemia (haemoglobin <11.0 g/dl) as 65.1% and abnormal liver function in 68.0% of the patients. Thrombocytopenia and leukocytosis were seen in 47.6% and 44.7% of the cases, respectively. Hyponatremia was seen in 56% of the cases.

The Weil-Felix test was positive in 80% of the patients with rickettsial diseases (sensitivity 88.7%, specificity 43.9%, positive predictive value 70.5% and negative predictive value 72%). Imaging studies in the form of Chest X-ray, USG abdomen did not yield significant results. MRI brain was not done because we did not have CNS manifestations in our patients. ECG was normal in all cases.

DISCUSSION

In their study on Rickettsial disease outbreaks in India: A review by Dasari Vishal, Kaur Prabhdeep, Murhekar, Manoj V most of the cases occurred among the middle and older aged individuals[6] which was not a finding in our study. Younger age group have a higher incidence in our study.

In our study, rickettsial infection presented with varied clinical features. The conventionally associated features of rash and eschar were present in very few patients in our study. This is similar to the findings from recent studies from Northern and Southern India.[7] Dasari V et al searched the

published literature about rickettsial diseases outbreaks in India between the years 2000 and 2011. The common clinical manifestations included fever (100% in all outbreaks), chills and rigors (71-88% in two outbreaks), headache (25%-100%, in five outbreaks), myalgia (10-52% in five outbreaks), cough (10-44% in five outbreaks) and lymphadenopathy (13%-45% in seven outbreaks).

Rash is a variable manifestation, appearing on day 6 or later in 20% of cases and not appearing at all in 9-16% of cases. It is possible that patients could be unaware or ignore the presence of an eschar, and a detailed physical examination needs to be done to look for the eschar.[8] Mediterranean Spotted Fever (Boutonneuse Fever), African Tick-Bite Fever, And Other Tick-Borne Spotted Fevers inoculation eschar (tâche noire) appears before the onset of fever at the site of the tick bite. Rash was more commonly associated with spotted fever (56.5%) and becomes apparent after 3–5 days of the onset of symptoms.[8,9] More severe vascular damage results in frank haemorrhage at the center of the maculopapular rash, producing a petechia that does not disappear upon compression. Rocky Mountain spotted fever has more severe vascular damage results in frank haemorrhage at the center of the maculo-papule, producing a petechial that does not disappear upon compression. Manjunath Hulmani, et al have studied the Tick Typhus Presenting as Purpura Fulminans in their study.[10] Eschar was observed in most (10/11) of the outbreaks.[6] In our study, Inoculation eschar (tâche noire) appeared before the onset of fever at the site of the tick bite. Meningoencephalitis was a complication (24%) in our study population and was more common in spotted fever patients (44%), though previous studies have reported a lower level of CNS involvement; from South India of 18.8%[3] and 9.5%[4] and North India of 14.3%.[5] Endemic murine typhus infection of the pulmonary microcirculation leads to non-cardiogenic pulmonary oedema; 12% of patients have severe respiratory disease, and 8% require mechanical ventilation. Pneumonitis developed in 12% of cases in this study. Cardiac involvement manifests as dysrhythmia in 7–16% of cases. In severe respiratory disease, 8% require mechanical ventilation as per studies. Photophobia, with considerable conjunctival injection and eye pain, is common epidemic (louse-borne) typhus. Life-threatening complications occur most often in the elderly and include renal failure, adult respiratory distress syndrome, a toxic shock–like syndrome, pneumonia, and a DIC- or sepsis-like syndrome. We did not have patients with these manifestations. None had to undergo mechanical ventilation. Variable clinical manifestations could be due to differences in the infecting strains that result in a high level of antigenic variation. Case fatality can be as high as 30-45%.[2] We observed no mortality among our study. As per studies, Anaemia develops in 30% of cases and is severe enough to require transfusions in 11%. Blood is detected in the stool or vomitus of 10% of patients, and death has followed massive upper-gastrointestinal haemorrhage. Total leucocyte count, during early course of the disease, is normal to low normal with marked shift to left. Later in the course of the disease, it shows leukocytosis in 30% of cases.[11] Low platelet counts are present in about 60% cases. Erythrocyte sedimentation rate is usually high. Thrombocytopenia, hyponatremia and normal to low leucocyte count are certain clues to early diagnosis. Scrub typhus were more likely to have thrombocytopenia, while those with spotted fever patients were more likely to manifest leucocytosis.[7] In our study, prevalence of anaemia was 65.1% and abnormal liver function in 68.0% of the patients. Thrombocytopenia and leukocytosis were seen in 47.6% and 44.7% of the cases, Hyponatremia and hypoalbuminemia, reflecting increased vascular permeability, are sometimes helpful in differentiating rickettsial infections from other acute infections. Hyponatremia was seen in 56% of the patients in our study. Hepatic transaminase values are frequently elevated. Blood urea can be elevated due to prerenal mechanisms. Available published literature under -estimates actual scenario of the disease in the country mainly due to its under- reporting. Most of the outbreaks reviewed are confirmed by the Weil-Felix test. Unfortunately, the laboratory tests that are more specific and sensitive than the commonly used Weil-Felix test are too expensive and are available in very few laboratories in India. In spite of all its drawbacks, Weil-Felix test still serves as a useful and cheap diagnostic tool for laboratory diagnosis of rickettsial disease.[7] Either four-fold rise in agglutinin titer in paired sera or single titer of more than 1:320 is considered diagnostic for infection with these febrile agents. The use of this test is accepted in conditions where definitive investigations are not available.[12] Isaac, et al. Have demonstrated that the sensitivity of Weil-Felix was 30% at a breakpoint titer of 1:80, but the specificity and positive predictive value were 100%. Though this test is a retro-confirmatory test, done to confirm the presence of the infection two weeks after the onset of the disease rather than to diagnose it in its early stages, it documented the presence of the disease in several areas.[13] Hence Weil-Felix test is still not entirely obsolete but has to be interpreted in the correct clinical context.[14] The specific gold standard test for rickettsial infection is the micro immuno-fluorescence test, namely immune-fluorescence assay (IFA).[15] However, this test is not widely available. Other confirmatory tests such as the indirect immunoperoxidase (IP) test, ELISA, and the isolation of the organisms in animals or cell culture are also not available in most of the settings in India. The limitation of this study is the small sample size restricted to admitted cases. The wider variety cases who did not undergo hospitalization were not included in this study.

CONCLUSION

Establishing the etiologic diagnosis of rickettsioses is very difficult during the acute stage of illness. Heightened clinical suspicion is based on epidemiological data, history of exposure to vectors or reservoir animals, travel to endemic locations, clinical manifestations (sometimes including rash or eschar), and characteristic laboratory findings (including thrombocytopenia, normal or low white blood cell (WBC) counts, elevated hepatic enzyme levels, and hyponatremia). Such suspicion should prompt empirical treatment. If a viral

infection is suspected during rickettsial season in an endemic area, it should always be kept in mind that rickettsia can mimic viral infection early in the course; if the illness worsens over the next couple of days after initial presentation, the patient should return for re-evaluation.

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