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A TERTIARY CARE CENTER INVESTIGATION OF THE CLINICAL CHARACTERISTICS OF PATIENTS WITH RICKETTSIAL FEVER

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Conflicts of Interest: Nil

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BACKGROUND:

Rickettsial diseases are a group of Febrile illnesses caused by obligate intracellular gram-negative coccobacilli and transmitted to man by arthropod vectors., often underdiagnosed due to poor awareness. Rickettsia is obligate intracellular proteobacteria spread by eukaryotic vectors like ticks, mites, fleas, and lice. Rickettsial infections are generally incapacitating and difficult to diagnose; Case fatality rates up to 45 percent are seen in cases with multiple organ dysfunction. The disease continues to be underdiagnosed and treated. The objective of this study was to study the clinicopathological profile and outcome of children admitted with rickettsial fever. To study the correlation between the Rathi-Goodman-Aghai score and the Weil-Felix test. To study the response of rickettsial fever to Doxycycline.

AIM: The aim of this study was to study the clinicopathological profile and outcome of children admitted with rickettsial fever.

MATERIAL AND METHOD:

This study is a prospective observational study conducted in the Department of General Medicine. Involving patients admitted between 2 months to 18 years of age with a diagnosis of Rickettsial fever. They were followed up and diagnosed to have a rickettsial fever by Weil-Felix titer of more than 1 in 160. In possible cases, a paired serology was done to further validate the diagnosis of rickettsial infection. The clinical course of the illness and complications of infection were recorded. WHO classification of anemia, 1989 was used for the classification of anemia. Clinical data and investigations were collected and analyzed. The response to doxycycline was recorded in terms of clinical improvement within 2 days. Under the rule and regulation of the institutional ethical committee, signed informed consent was taken from every study subject. Informed written consent was taken from the patients or their guardians willing to participate in the study.

RESULTS:

The total number of rickettsial cases admitted during the study period was forty. The most common age group observed was 1-5 years accounting for 30%. The youngest affected patient was a 2-month-old. Males (50%) were the most commonly affected group in our study. 65% of the patients hailed from a rural background. Fever was the most common symptom present in all the cases enrolled in the study followed by a rash in 23(57%) cases. Eschar though a characteristic feature of rickettsial infection was found in only 3(10%) of the cases. Clinical examination revealed hepatomegaly in 36(91.8%) cases, followed by lymphadenopathy in 11(28.6%) cases, and splenomegaly in 9(22.4%) cases. The response to Doxycycline showed 29(78%) cases improved within 48 hours of the start of treatment.

CONCLUSION:

Any child with undifferentiated fever >5 days, hailing from a rural background; strong suspicion of rickettsial fever to be made. Rathi-Goldman-Aghai score and Weil-Felix test combined together aid

in early diagnosis. Early initiation of treatment prevents complications and results in rapid recovery of the patient, hence reducing morbidity and mortality. The outcome isn't satisfactory in patients for whom delayed initiation of treatment is done. Rickettsial fever poses a significant challenge to any physician, especially in the early course because of its varied clinical presentation.

KEYWORDS: Rathi-Goodman-Aghai score, Response to doxycycline, Rickettsial fever.

Introduction

Rickettsial diseases, caused by a variety of obligate intracellular, Gram-negative bacteria from the genus Rickettsia, belonging to the Alpha-proteobacteria, are considered some of the most covert emerging and re-emerging diseases and are being increasingly recognized.[1,2] The infection has established itself as an endemic disease in Southeast Asia including Thailand, China, and Taiwan. [3-4] Rickettsial disease has been reported from various parts of India, such as Tamil Nadu, Karnataka, Kerala, Maharashtra, and some parts of northern India.[1,2] The Rickettsiae are a heterogenous group of small obligatory intracellular, gram-negative coccobacilli and short bacilli, most of which are transmitted by a tick, mite, flea, or louse vector. Clinical infections with rickettsia were earlier classified according to the taxonomy and diverse microbial characteristics of the agents, into six genera Rickettsia, Orientia, Ehrlichia, Anaplasma, Neorickettsia, and Coxiella.[5] But the past decade has witnessed a resurgence in the incidence of rickettsial infection.[6]

Among the major groups of rickettsioses, commonly reported diseases in India are scrub typhus, murine flea-borne typhus, Indian tick typhus, and Q fever.[7] Rickettsial infections are generally incapacitating and difficult to diagnose; untreated cases have case fatality rates as high as 30-45 percent.[8]

In most clinical scenarios the presentation of rickettsial infection does not fit into a particular pattern. The clinical presentation of rickettsial infection is wide and varied. Severity varies from subclinical illness to severe illness with multiple organ system involvement, which can be serious enough to be fatal unless diagnosed early and treated.[9] Untreated cases have case fatality rates as high as 30-45% with multiple organ dysfunction, if not promptly diagnosed and appropriately treated. Even though the specific gold standard tests for diagnosing rickettsial infections are the immunofluorescence antibody (IFA) and the indirect immunoperoxidase (IP) test, these are expensive and not easily available in India.[10]

The family of Rickettsia is named after HOWARD TAYLOR Ricketts who discovered Spotted fever and died during his studies in 1909.[11,12] Rickettsial are a group of motile, gram-negative, non-spore-forming, highly pleomorphic bacteria present as coccobacilli, or thread-like intracellular obligate parasites., divided epidemiologically into 4 groups.[13,14] 1. Spotted fever group, Indian tick typhus 2. Typhus fever group 3. Scrub Typhus 4. Miscellaneous.

Spread by Arthropod vectors, lice, fleas, ticks, and mites the most frequent presenting symptoms include, high-grade fever, headache, rashes, myalgia, anorexia, nausea, vomiting, diarrhea, abdominal pain., and complicated cases may have multi-organ involvement - encephalopathy, pulmonary edema, acute renal failure, vascular collapse, myocarditis, hepatic failure.[15,16] Rickettsial Diseases are dangerous among children, due to atypical presentations and complications, as increasing trends in India since last many years.[15,16]

Single titers of 1:160 or more are diagnostic of rickettsial as is a fourfold rise in titer.[17,18]During the interpretation of the Weil-Felix test, OX 19 is significantly and predominantly positive in epidemic typhus, Brill Zinser disease, Murine typhus, and rocky mountain spotted fever. Rickettsial infection is grossly underdiagnosed in India due to its nonspecific clinical presentation, limited awareness and low index of suspicion among clinicians, and lack of specific diagnostic facilities. The objective of this study was to study the clinical profile and various complications of rickettsial diseases in patients admitted to a tertiary care hospital so

that the documentation of various clinical presentations will help in early diagnosis and treatment, prevention of life-threatening complications, and reduction in morbidity and mortality.

MATERIAL AND METHODS

This study is a prospective observational study conducted in the Department of General Medicine. Involving patients admitted between 2 months to 18 years of age with a diagnosis of Rickettsial fever. They were followed up and diagnosed to have a rickettsial fever by Weil-Felix titer of more than 1 in 160. In possible cases, a paired serology was done to further validate the diagnosis of rickettsial infection. The clinical course of the illness and complications of infection were recorded. WHO classification of anemia, 1989 was used for the classification of anemia. Clinical data and investigations were collected and analyzed. The response to doxycycline was recorded in terms of clinical improvement within 2 days. Under the rule and regulation of the institutional ethical committee, signed informed consent was taken from every study subject. Informed written consent was taken from the patients or their guardians willing to participate in the study.

Inclusion criteria

- ✓ Eligible patients 2 months to18yrs of age who had undifferentiated fever >5days
- ✓ Compatible clinical scenario
- ✓ Suggestive epidemiological features.

Exclusion criteria

- ✓ Cause of fever known at the time of admission.
- ✓ Patients diagnosed with other causes of fever, during the course in the hospital.
- ✓ Children treated elsewhere prior to admission.
- ✓ Patient treated on an outpatient basis or details not available.
- ✓ Fever and Rashes with Dengue Positive, Leptospirosis, Brucella infections

Baseline Data of age, sex, local residing area, exposure to animals, Socioeconomic status, date of admission, days onset of first symptom fever/ rash, distribution of the rash, and associated other systemic comorbidities, were recorded, and done CBC of all patients, Weil Felix test to identify the type of species.

The procedure of the Weil Felix test

The Weil-Felix test is based on the detection of antibodies to various cross-reacting Proteus antigens with Rickettsia (Proteus vulgaris OX2 with spotted fever Rickettsia, P. vulgaris OX19 with typhus group Rickettsia and Proteus mirabilis OXK with O.Tsutsugamushi). The Weil-Felix test was performed on all the serum samples collected at the time of presentation at the hospital (acute sample) Done by Slide test method using PROGEN- Proteus antigen suspensions for the Weil Felix test. [Manufactured by TULIP DIAGNOSTICS (P) LTD, Verna Goa.] packed with 3 separate containers of 5ml of Reagents of OX-K [scrub typhus], OK-19 [epidemic typhus] and OX-2 [scrub typhus]. A clean white background reaction circle glass slide is taken, place one drop of Positive control, physiological saline, and patient serum is to be tested in each circle of the slide, then put 1 drop of appropriate PROGEN antigen to each circle, mix with separate mixture sticks wait for 1 minute, and see the level of agglutinins in serum circle, positive agglutinins indicates the presence of Rickettsial antibodies in the patient serum, Agglutination titer of 1:80 or more was considered significant for Rickettsial infection.

Probable rickettsial fever cases were treated with Doxycycline (4.4mg/kg day in two divided doses) for 3 days after the subsidence of fever or a total of 7 days in uncomplicated cases and up to 10 days in severe or complicated cases. Doxycycline was administered through the intravenous route or nasogastric tube or orally according to their clinical status. The response to treatment was recorded in terms of defervescence within 48 of starting therapy.

STATISTICAL ANALYSIS

Data were entered into a Microsoft Excel data sheet and analyzed using SPSS 22 version software. Categorical data was represented in the form of frequencies and proportions. Continuous data were represented as mean and standard deviation. The chi-square test or Fischer's exact test (for 2x2 tables only) was used as a test of significance for qualitative data. An Independent t-test was used as a test of significance to identify the mean difference between two quantitative variables.

RESULT: -

The total number of rickettsial cases admitted during the study period was forty. The most

common age group observed was 1-5 years accounting for 30%. The youngest affected patient was a 2-month-old. Males (50%) were the most commonly affected group in our study. 65% of the patients hailed from a rural background.

Table 1: Symptoms and clinical findings in the study population.

Parameter	Frequency	Percentage
Symptoms		
Fever	40	100%
Maculopapular rash	23	57.1%
Headache	14	34.7%
Altered sensorium	13	32.7%
Convulsions	11	26.5%
Difficulty in breathing	11	26.5%
Abdominal distension	9	24.5%
Eschar	3	10.2%
Gangrene	2	6.1%
Clinical examination		
Hepatomegaly	36	91.8%
Edema	18	51%
Lymphadenopathy	11	28.6%
Splenomegaly	9	22.4%

Fever was the most common symptom present in all the cases enrolled in the study followed by a rash in 23(57%) cases. Eschar though a characteristic feature of rickettsial infection was found in only 3(10%) of the cases. Clinical examination revealed hepatomegaly in 36(91.8%) cases, followed by lymphadenopathy in 11(28.6%) cases, and splenomegaly in 9(22.4%) cases.

Table 2: Laboratory findings.

Laboratory derangements	Frequency	Percentage
Thrombocytopenia	36	91.8%
Hypoalbuminemia	35	89.8%
Hyponatremia	34	87.7%
Anemia	16	51.1%
Leukocytosis	11	34.6%
Weil-Felix test		
Scrub typhus (OX-K)	23	67%
Spotted fever (OX-19, OX-2)	7	21%
Other typhus	3	12%

Investigations done on our study subjects showed that out of the 40 cases, 36(91.8%) had thrombocytopenia. Hypoalbuminemia was seen 35(89.8%) cases and hyponatremia was seen in 34(87.7%). Anemia was seen in 16(51.1%) of the cases. The response to Doxycycline showed 29(78%) cases improved within 48 hours of the start of treatment. Out of the remaining 10 cases, 5 cases showed a delayed response, and the remaining 5 cases showed no response due to late presentation and for whom treatment was started after 2 weeks of illness.

DISCUSSION

Rickettsial infections have a global distribution and are reported from almost all parts of India. Rickettsial diseases vary in severity from self-limited mild illnesses to fulminating life-threatening infections. [10] In the scenario of over-whelming bacterial and viral infections and parasitic infestations, Rickettsial diseases continue to be underdiagnosed.[19] All over the country the proportion of rickettsial fever in cohorts analyzing febrile illness is found to have increased significantly over the past two

decades. It is believed that the increasing use of these antibiotics for the treatment of febrile illnesses in the community during recent times may be contributing to the unmasking of rickettsial fever as rickettsia are inherently resistant to them.[20] **Murali et al,2001**[21](100%) and **Kumar et al,2012**[22](20%). Though a characteristic feature of eschar was found only in 10% of the patients presenting with rickettsial fever, which was the same in other studies. 22 Hepatomegaly was seen in 91.8% of cases which was consistent with other studies. 6,12,13 Lymphadenopathy was found in 28.6% of the cases and splenomegaly was found in 22.4% of the cases which was less common as compared to the study conducted by **Reddy et al.2013**.[23]

Varghese et al 2006[24] observed thrombocytopenia in 62.5 % of the patients and **Subbalaxmi et al2014**[25] in 30.2%. If a combination of tests i.e elevated transaminases, thrombocytopenia, and leukocytosis is used, the specificity and positive predictive value are about 80%. Respiratory system involvement was present in approximately 1/3rd of the patients (cough – 29.3%, dyspnoea – 23.2%) in the present study.

Hypoalbuminemia is commonly observed in rickettsial cases even if the disease has been of short duration. Hypoalbuminemia was seen in 78.8% of the present study. Although the pathogenetic mechanisms for hypoalbuminemia in patients with scrub typhus have not yet been elucidated, it is postulated that vasculitis, the main pathology of scrub typhus, increases vascular permeability, and thus plasma protein is leaked from the blood vessels which subsequently causes hypoalbuminemia.[26] **Min et al1996**[27] demonstrated that patients with scrub typhus showed intestinal protein loss by measuring the concentrations of α-1-antitrypsin in the stool and that 11 of 14 patients with scrub typhus revealed intestinal albumin loss by 99m Tc-human serum albumin (HSA) abdominal scintigraphy. The presumed mechanism for intestinal albumin loss is the increase in permeability due to vasculitis of the capillaries and arterioles.

Response to doxycycline was measured in terms of time for defervescence. 78% of the patients responded to doxycycline within 48 hours of starting the treatment. 10.2% of the cases showed a delayed response. No response was seen in patients who presented late, for whom treatment was started after 2 weeks of illness. Complications were seen in patients presenting after 1 week of illness and were present in 59% of the cases. Most commonly seen was meningoencephalitis in 18% of cases which was comparable to studies. [7,21] Supportive treatments in the form of ventilatory support were required in 26% of cases and 2% required peritoneal dialysis. Unlike studies done by **Thomas et al2016**[7], **Murali et al2001**[21] and **Kumar et al 2012**[22] authors observed a higher mortality rate of 10.2% due to late presentation and hence delay in starting appropriate therapy. [7,21,22]. As the delay in treatment may lead to complications and higher mortality, empiric treatment with doxycycline or macrolides may be given in cases where scrub typhus is suspected and facilities for diagnosis are not available. Rickettsial fever is known to produce serious complications and has a mortality rate of 7-30%. In our study, only one patient died in ICU with multi-organ dysfunction syndrome. Deaths are attributable to late presentation, delayed diagnosis, and drug resistance.[28] This can be vastly prevented by increased awareness among physicians, early institution of appropriate antibiotics & increased availability of serological tests for diagnosis. The limitation of this study was to the Diagnosis of rickettsia was made clinically for enrolling in the study and a confirmatory test was not conducted.

CONCLUSION:

Any child with undifferentiated fever >5 days, hailing from a rural background; strong suspicion of rickettsial fever to be made. Rathi-Goldman-Aghai score and Weil-Felix test combined together aid in early diagnosis. Early initiation of treatment prevents complications and results in rapid recovery of the patient, hence reducing morbidity and mortality. The outcome isn't satisfactory in patients for whom delayed initiation of treatment is done. Rickettsial fever poses a significant challenge to any physician, especially in the early course because of its varied clinical presentation. Thus it becomes important to have a high degree of clinical suspicion based on clinical cues to diagnose early, if not rickettsial fever can cause considerable morbidity, mortality, and financial liability to the patient. Early diagnosis and

treatment with Doxycycline can reduce hospital stays and costs. The use of Empirical treatment may be considered to reduce the morbidity and mortality observed with the disease.

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