

Rickettsial infection in children- clinical profile and response to treatment

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Abstract

Background: Rickettsial infections are re-emerging and are becoming more prevalent throughout the world. From India, they are reported from Maharashtra, Tamil nadu, Karnataka, Kerala, Jammu and Kashmir, Uttaranchal, Himachal Pradesh, Rajasthan, Assam and West Bengal. Hence the study was taken to study the clinical profile of rickettsial infection. **Materials and Methods:** A prospective observational study on 48 children was conducted at department of pediatrics, Govt. Medical College, Kozhikode from January 2014 to May 2015. Children below 12 years of age with compatible clinical presentations of rickettsial infection. **Results:** Fever is the predominant symptom in most of the cases. Most of the children (47.9%) presented during the second week of fever. Eight children (16.7%) presented after 2 weeks of fever. Fever was less than 1 week in 17 patients (35.4%). Rash was present in 21 children (43.7%). In those children with rash, the rash appeared between the first and fourth day of fever in 12 children (57.1%). In 2 children rash appeared along with fever. Doxycycline was given to 47 cases at a dose of 5mg/kg/day and 46 cases (97.8%) responded to it. The most common complication in children with rickettsial infection was hepatitis. It was present in 21 children(43.7%). The second common complication was thrombocytopenia in 18 cases (37.5%). **Conclusion:** Rickettsial infection is commonly seen in the school going age group. Absence of a rash does not rule out the possibility of rickettsial infection and when it occurs, the involvement of palms and soles is not invariable. A large proportion of children develop complications including thrombocytopenia, acute kidney injury, hepatitis, meningoencephalitis and hemophagocytic lymphohistiocytosis among which hepatitis is the most common. Doxycycline is effective in the treatment of rickettsial infection.

Keywords: Rickettsial infection, Fever, Rash, Hepatitis, Doxycycline.

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INTRODUCTION

Rickettsial infection or rickettsiosis is a zoonotic acute febrile illness caused by small gram negative, pleomorphic cocco-bacilli which is an obligate intracellular parasite. It is transmitted by arthropod vectors like lice, fleas, ticks and mites, in which the organisms are found in the alimentary

canal.¹ Rickettsial infections are grossly under-diagnosed in India because of their non-specific clinical presentation, a limited awareness about the disease, a low index of suspicion among clinicians, and a lack of availability of diagnostic facilities. Failure of timely diagnosis causes significant morbidity and mortality. With timely diagnosis, treatment is easy, affordable and often very successful with dramatic response to antimicrobials. There is a paucity of studies regarding the incidence and clinical profile of scrub typhus in children from India and majority of the published studies are retrospective studies. Rickettsial infections are re-emerging and are becoming more prevalent throughout the world. From India, they are reported from Maharashtra, Tamil Nadu, Karnataka, Kerala, Jammu and Kashmir, Uttaranchal, Himachal Pradesh, Rajasthan, Assam and West Bengal. ²⁻⁶ Hence the study was taken to study the clinical profile of rickettsial infection.

MATERIAL AND METHODS

A prospective observational study on 48 children was conducted at department of pediatrics, Govt. Medical College, Kozhikode from January 2014 to May 2015. Children below 12 years of age with compatible clinical presentations of rickettsial infection like fever without a source, fever of unknown origin, fever with rash (rash which is petechial or maculopapular involving palms and soles, having centripetal spread), fever with eschar, meningoencephalitis or aseptic meningitis, acute renal insufficiency with eschar and Weil-felix test positive (a titre of 160 or more for OX-K and 160 or more for others or a rise in titre in serial samples) were included. Children less than one month of age and for whom an alternate diagnosis has been made were excluded. Clinical data, including the duration of the fever, associated symptoms, vital signs and the general and systemic examination findings were recorded. Patients were treated with oral doxycycline (5mg/kg/day BD) for five days or at least three days after defervescence. Data collected were entered into Microsoft excel and analysis was done with SPSS software.

OBSERVATIONS

48 children with rickettsial infection were included in the study after screening 298 children with clinical

presentation compatible with rickettsial infection. Majority of the children (47.9%), i.e.23 out of 48 belonged to the age group between 9-12 years. Out of the 48 children included under the study, 28 (58%) were males. Boys are engaged in outdoor activities more than the girls and hence are more susceptible to the disease. Rickettsial infection is a disease with seasonal variation. In the current study most of the cases were reported during the cooler months from October to February. This shows that transmission of the disease is more during these periods of the year. There is another peak at the beginning of rainy season. Most of the children diagnosed to have rickettsial infection were from Kozhikode. We expected maximum cases from the hilly areas of Wayanad. But there were less than expected case from Wayanad may be because doctors from the peripheral hospitals are treating the cases of fever with common antibiotics like azithromycin without knowing that they are rickettsial infection. Rickettsial infection responds well to the common antibiotics used in periphery like azithromycin. As per the state protocol in areas outbreaks of Leptospirosis cases were established, all fever cases are to be treated with doxycycline especially during epidemic season. Due to easy access to medical college, the children with fever from Kozhikode are being referred to medical college more.

RESULTS AND DISCUSSION

Table 1: Table showing comparison of gender distribution (%)

Gender	Present study	M Kumar <i>et al.</i> ⁷	Kumar N Bhat <i>et al.</i> ⁸	Nigwekar <i>et al.</i> ⁹	Tanveer <i>et al.</i> ¹⁰	Huang CT <i>et al.</i> ¹¹
n=	48	35	66	50	30	28
Male	58	57	59	54	43	60.7
Female	42	43	41	46	57	39.3

Seasonal Variation

Rickettsial infection is a disease with seasonal variation. In our study maximum number of rickettsial infection occurred during the period of October to February. This is in consistent with the study by Tanveer *et al.* ¹⁰. The scrub typhus cases were clustered during the period of October to February which is similar to the study by M Kumar *et al.* ⁷.

Table 2: Comparison of symptoms with other studies (%)

Symptoms	Present study			M	Kumar	Garuda	Tanveer	Nigwekar	Huang	N Murali
	All cases	Scrub typhus	Tick typhus	kumar <i>et al.</i> ⁷	Bhat <i>et al.</i> ⁸	Rama <i>et al.</i> ¹²	<i>et al.</i> ¹⁰	<i>et al.</i> ⁹	CT <i>et al.</i> ¹¹	<i>et al.</i> ¹³
n=	48	34	14	35	66	25	30	50	28	12
Fever	100	100	100	100	100	100	100	100	100	100
Rash	43.8	38.2	50	20	20	40	83.3	100	35.7	100
Headache	33.3	35.3	28.5	11	18	36	16.7	-	39.2	-
Myalgia	47.9	40.8	21.4	26	4	52	-	10	-	-
Arthralgia	12.5	14.7	7.1	-	-	-	-	-	-	-
Cough	35.4	32.4	42.8	51	35	56	-	-	50	-
Breathlessness	4.2	2.9	2.1	37	29	36	-	-	-	-
Vomiting	12.5	15.6	7.1	49	37	40	36.7	-	28.6	-
Loose stools	10.4	11.7	7.1	11	6	12	10	-	-	-
Oliguria	12.5	11.4	14.4	43	29	8	-	-	-	-
Altered sensorium	18.8	14.7	28.5	23	23	4	-	12.6	-	25
Seizures	8.3	5.9	14.2	11	20	4	-	36	-	16.6

Table 3: Comparison of physical signs in various studies (%)

Physical signs	Present study			M	Kumar	Garuda	Tanveer	Jain <i>et al.</i>	Huang
	All cases	Scrub typhus	Tick typhus	kumar <i>et al.</i> ⁷	Bhat <i>et al.</i> ⁸	Rama <i>et al.</i> ¹²	<i>et al.</i> ¹⁰	¹⁴	CT <i>et al.</i> ¹¹
n=	48	34	14	35	66	25	30	19	28
Hypotension	10.4	8.8	14.2	34	36	32	-	10.5	-
Pallor	27.1	32.3	14.2	-	62	-	-	-	-
Lymphadenopathy	68.8	79.4	44.1	37	38	28	3.3	42.1	42.9
Eschar	8.3	8.8	7.1	11	20	32	6.6	47.3	50
Hepatomegaly	45.8	47.1	42.8	91	82	72	46.7	26.3	35.7
Splenomegaly	20.8	23.5	14.2	60	59	56	23.3	26.3	17.9
Meningeal signs	10.4	5.8	21.3	-	18	-	-	-	10.7

Laboratory Parameters

In the present study Weil-Felix test was positive in 45 children out of the 48 children included under the study satisfying the inclusion criteria. In 31 children OX-K for scrub typhus was positive. In 14 cases OX-2 for Indian tick typhus was positive. Weil-Felix test was negative in 3 cases of scrub typhus. A titre of 160 or more or a fourfold rise in titre with paired sera were taken as a positive test for scrub typhus and 320 or more or four fold rise in titre for Indian tick typhus. . IgM ELISA for scrub typhus was done in all the positive Weil-felix cases and also in those cases with a Weil-Felix test titre of 80. IgM ELISA for scrub typhus was positive in 26 of the total 48 children under the study. The negative IgM ELISA in 5 cases with positive Weil-felix test is because in those cases, the serum for test was taken within 7 days of onset of illness which can cause false negative IgM ELISA. Indirect immunofluorescence assay (IFA) for scrub typhus was done in all the Weil-felix positive cases and also in those cases with a Weil-Felix test titre of 80. IFA was positive in 20 cases of scrub typhus. Indirect immunofluorescence antibody (IFA) test is more sensitive, and results are available in a couple of hours; however, the test is more expensive and requires considerable training .It is highly subjective, in that the relative reactivity or brightness of the fluorescing organisms requires observation by a consistent, well-trained eye. The test is more sensitive and faster but costly and antigenic variation is common. The assay rely on cultured *O. tsutsugamushi* antigen preparations, and procedures for the production and preparation of antigen can vary greatly among different laboratories, leading to inconsistencies in interpretation of results.¹⁵

Table 4: Comparison of laboratory parameters in various studies (%)

Laboratory parameter	Present study			M	Kumar	Garuda	Tanveer et	Jain	Huang
	All cases	Scrub typhus	Tick typhus	kumar <i>et al.</i> ⁷	Bhat <i>et al.</i> ⁸	Rama <i>et al.</i> ¹²	<i>et al.</i> ¹⁰	<i>et al.</i> ¹⁴	CT <i>et al.</i> ¹¹
n=	48	34	14	35	66	25	30	19	28
Low platelet	37.5	41.2	28.5	61	53	-	23.3	68.4	50
WBC- normal	50	44.1	64.3	-	-	-	73.4	-	-
- elevated	41.7	50	21.9	37	-	-	26.6	47.3	39.3
- low	8.3	5.9	14.3	-	-	-	-	-	-
Elevated ESR	64.6	35.4	71.1	-	-	-	-	-	-
Elevated SGPT	43.8	52.9	21.4	-	13.6	48	-	54.2	54.2
Hypoalbuminemia	25	20.6	35.7	54	-	32	20	47.3	47.3
Hyponatremia	47.9	50	42.9	-	-	4	-	-	-
Elevated serum creatinine	22.9	26.5	14.3	20	16.7	8	-	-	-

Table 5: Comparison of complications in various studies (%)

Complications	Present study			M	Kumar	Garuda	Jain <i>et al.</i>	Huang
	All cases	Scrub typhus	Tick typhus	kumar <i>et al.</i> ⁷	Bhat <i>et al.</i> ⁸	Rama <i>et al.</i> ¹²	¹⁴	CT <i>et al.</i> ¹¹
n=	48	34	14	35	66	25	19	28
Thrombocytopenia	37.5	41.1	28.5	31	53	56	68.4	50
AKI	22.9	26.4	14.2	20	16.7	8	-	-
Shock	6.2	8.8	-	-	25.8	-	-	-
Meningoencephalitis	16.6	14.7	21.4	-	30.3	8	10.5	-
Hepatitis.	43.7	52.9	31	31	-	31	-	88.9

Treatment and its outcome

Doxycycline was given to 47 cases at a dose of 5mg/kg/day and 46 cases responded to it. In seriously ill patients, doxycycline was given via Ryle's tube. One case of scrub typhus didn't respond to doxycycline, which was then given iv chloramphenicol and azithromycin after that, for which she didn't respond. She responded to Rifampicin. One child with probable Indian tick typhus who presented as meningoencephalitis was given rifampicin (along with other anti-tubercular drugs) initially suspecting TB meningitis and later the Weil-Felix result came as OX-2 positive with rising titre on repeat test; after the repeat test, all other drugs except rifampicin were stopped and the child responded to the treatment and was discharged. One child developed hemophagocytic lympho histiocytosis who was treated with methylprednisolone along with doxycycline. In those children with nutritional anaemia, deworming done and treated with oral iron at a dose of 3mg/kg/day. Dietary advice was also given for nutritional anaemia. Most of the children responded to treatment with doxycycline within 48 hours of initiating treatment for rickettsial infection. 20.8% of the children responded to treatment within 24 hours. 54.1% of the children responded after 24 hours, but within 48 hours. 12.5% of the cases showed response to treatment after 48 hours, but within 72 hours. 10.4% of the children took another 24 hours more for defervescence; those children presented late and they had complications like shock and meningoencephalitis. Severely ill patients with multiple organ dysfunction and in whom treatment was initiated late can take longer time to respond.¹ One child with multidrug resistant scrub typhus who didn't respond to doxycycline or azithromycin or IV Chloramphenicol responded later on to rifampicin. That child showed defervescence on day 7 of treatment when the child was finally started on rifampicin. In the study by Huang CT *et al.*¹¹, most of the children responded to treatment within 3 days of starting treatment. They used doxycycline, minocycline and tetracycline in various patients. In the study by M Kumar *et al.*⁷, 90% of the children responded within 48 hours of doxycycline therapy. In a case report of multidrug resistant scrub typhus by Watt *Get al.*¹⁶ from Western Thailand, the patient responded to Rifampicin. In 2014 Sung-Hoon Lee¹⁷ reported a case of doxycycline-resistant tsutsugamushi meningoencephalitis in a 63-year-old man in Korea who responded to treatment with Azithromycin. 10 cases of doxycycline resistant scrub typhus were reported in a study of Scrub typhus in adults by Balasubramanian P *et al.*¹⁸ in a tertiary care centre in Kerala.

CONCLUSION

Rickettsial infection is commonly seen in the school going age group. Absence of a rash does not rule out the

possibility of rickettsial infection and when it occurs, the involvement of palms and soles is not invariable. Myalgia is a frequent symptom in children with rickettsial infection. Respiratory symptoms are not unusual and the most common is cough. Gastrointestinal symptoms like vomiting and loose stools are often seen in children with rickettsial infection. A large proportion of children develop complications including thrombocytopenia, acute kidney injury, hepatitis, meningoencephalitis and hemophagocytic lymphohistiocytosis among which hepatitis is the most common. Doxycycline is effective in the treatment of rickettsial infection. Clinical response to doxycycline often gives a clue to the diagnosis before serological test results are available. Weil-Felix test is useful and correlates well with IgM ELISA positivity in scrub typhus.

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