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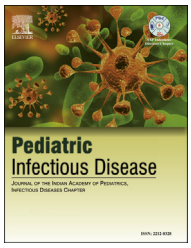

Review Article

Rickettsial diseases in Indian context

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ABSTRACT

Rickettsial diseases are one of the most covert re-emerging infections of the present times. Rickettsial diseases are extraordinarily difficult to diagnose due to low index of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic tests but are extraordinarily easy and inexpensive to treat if diagnosed early. Suspecting Rickettsial diseases in nonspecific febrile illnesses on the basis of clinical, laboratory and epidemiological clues is the key to prevent high morbidity and mortality associated with undiagnosed or late diagnosed cases. Their early diagnosis also reduces financial strain on patients of fever without source (FWS) and pyrexia of unknown origin (PUO) by reducing load of extensive investigations and multiple empiric therapies. This review is aimed at practicing pediatricians to increase awareness of these diseases in India contributing to improvement in public health.

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1. Introduction

Rickettsial infections are unique in various aspects. They occur across all countries and are reported from almost all parts of India. Rickettsial infection in the past has taken more lives than all the wars combined together.[1] As no single laboratory finding is specific for early diagnosis, treatment needs to be started empirically on clinical and epidemiological suspicion. In view of low index of suspicion, nonspecific signs and symptoms, and absence of widely available sensitive and specific diagnostic test, these infections are extremely difficult to diagnose but treatment is easy, affordable and often successful with dramatic response to antimicrobials.[2] Physicians, including pediatricians, usually do not include Rickettsial infection in their differential diagnosis[3] and hence antimicrobials effective for Rickettsial disease are usually not included in empirical therapy of nonspecific febrile illnesses.

2. Epidemiological considerations

The National Centre for Disease Control (NCDC, formerly National Institute of Communicable Disease) has played an important role in providing serological evidence of Rickettsial diseases in India in various States like Jammu & Kashmir, Himachal Pradesh, Uttarakhand, Haryana, Rajasthan, Assam, West Bengal, Maharastra, Tamil Nadu, Kerala, Sikkim, and Manipur in the last decade.[3–9] These reported cases are an underestimate as there are no community based studies and there is a lack of availability of confirmatory laboratory tests. Mittal et al[10] stated that in the entomological study poorly

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maintained kitchen garden and long grass attracted rodent population. At many places vector mites were collected from the rodents caught from active rodent burrows in kitchen gardens. Presence of vector mite above the critical limit indicates that during monsoon season these areas may act as potential sites for the transmission of Rickettsial diseases. Animal sheds near houses in rural areas, pet and stray dogs, cattles and long uncut grass are other factors favoring vectors.

3. Pathophysiology

Rickettsial diseases are caused by organisms belonging to family Rickettsiaceae, which phylogenetically falls between bacteria and viruses. Rickettsiae are small, nonflagellate, gram negative pleomorphic cocco-bacilli adapted to obligate intracellular parasitism and transmitted by arthropod vectors like lice, fleas, ticks and mites.[2] After entering human host, target cells for these organisms are vascular endothelium and reticuloendothelial cells explaining thereby the basic pathophysiological mechanism of vasculitis seen in these infections. Due to their obligate intracellular nature, these organisms cannot be cultured in routine media and their isolation would obviously need tissue culture media or laboratory animals. These organisms are classified into four groups i.e. scrub typhus (*Orientia tsutsugamushi*), spotted fever (*Rickettsia rickettsii*, *Rickettsia akari*, *Rickettsia conorii*), typhus group (*Rickettsia prowazekii*, *Rickettsia typhi*) and miscellaneous like *Ehrlichia*, *Anaplasma*, *Rickettsia slovaca*. Of these *R. conorii* and *O. tsutsugamushi* are the commonest organisms causing Rickettsial diseases in India. Vasculitis is responsible for skin rash, microvascular leakage, edema, tissue hypoperfusion and end-organ ischemic injury. Formation of thrombi can lead to tissue infarction and hemorrhagic necrosis. Inflammation and vascular leakage leads to interstitial pneumonitis, noncardiogenic pulmonary edema, cerebral edema and meningoencephalitis. Infection of endothelial cells also induce procoagulant activity that promote coagulation factor consumption, platelet adhesion and leukocyte emigration and may result in clinical syndrome similar to disseminated intravascular coagulation.

4. Clinical aspects

Incubation period is usually 2–21 days. Early diagnosis of these infections from clinical features is a difficult task due to nonspecificity of early symptoms and signs, often resembling benign viral illness, symptomatology varying from mild to severe, low index of suspicion, absence of rash in initial 2–3 days and rash as a clinical feature of Rickettsia being neither sensitive nor specific. Various clinical features of Rickettsial diseases are:

1. **Fever**: Abrupt onset, high-grade fever associated with headache and myalgia is the most common feature.
2. **Rash**: Though rash is considered as hallmark of Rickettsial disease, it is neither seen at presentation nor in all the patients,[11] thus it is said that spotted fevers could be spotless too! Rash appears after 2–3 days of fever and is evolving in untreated patients i. e. macular to maculopapular to purpuric to palpable purpuric to hemorrhagic or ecchymotic (Fig. 1) to frank gangrene (Fig. 2). Presence of rash on palms and soles, considered so typical of Rickettsial disease, can be seen in other diseases like infective endocarditis, syphilis, meningococcemia, enteroviral diseases and adverse drug reactions. Rash often spreads centripetally from wrists and ankles.

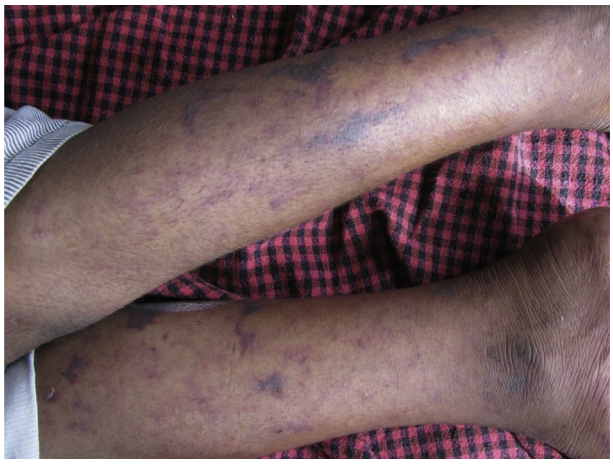

Fig. 1 – Ecchymotic rash on legs in spotted fever Rickettsiosis.

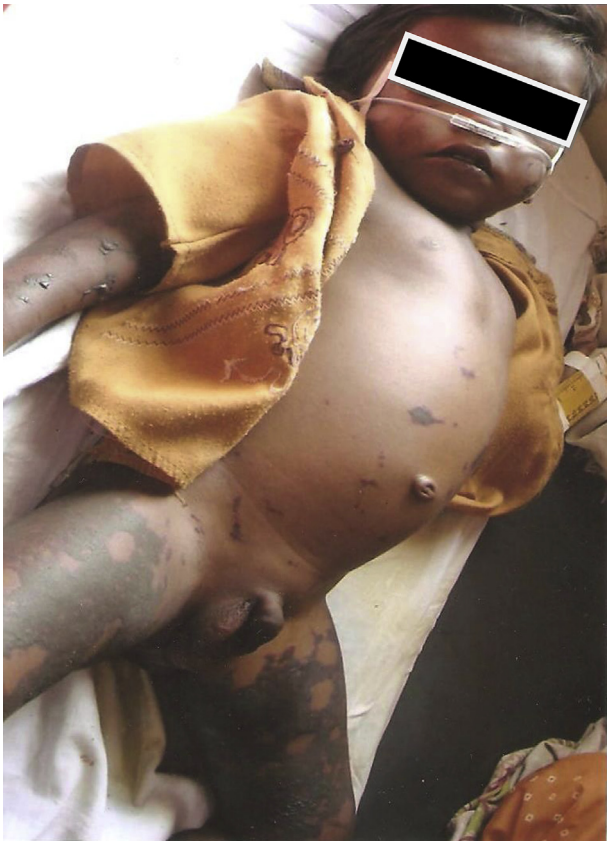

Fig. 2 – Gangrenous patches in a patient of spotted fever Rickettsioses.

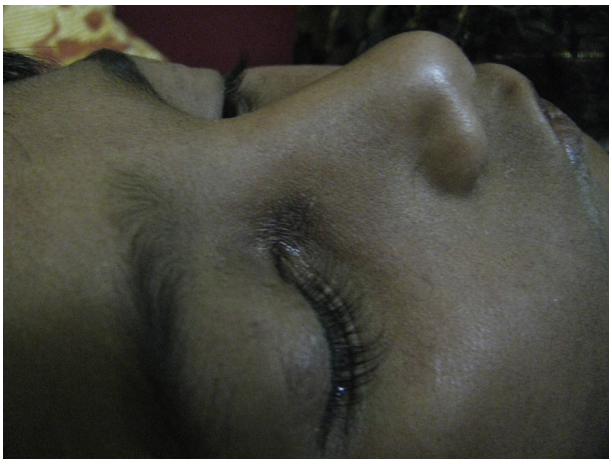

Fig. 3 – Eschar near medial canthus in a patient of scrub typhus.

3. **Eschar**: A painless necrotic area covered with black crust looking like a cigarette burn (Fig. 3) seen at the site of attachment of vector is called eschar. It evolves from papule, has erythematous ring and usually associated with enlarged regional lymph nodes. Recently it has been shown that patient's eschars can be used for detection and genetic characterization of *Orientia tsutsugamushi* during the convalescent phase.[12] Immunohistochemical staining of skin biopsy specimens, particularly that of eschars, is sensitive and specific, and this technique can be reliable for confirming the diagnosis of scrub typhus.[13]
4. **Systemic features**: Nonspecific gastrointestinal, respiratory and neurological features are often noted. Hepatosplenomegaly and generalized lymphadenopathy is sometimes seen in patients of scrub typhus. Pain and tenderness of calf muscles is also seen in some patients.
5. **Edema**: Periorbital, edema of dorsum of hand or foot or generalized edema and polyserositis is sometimes seen.
6. **Complications**: Various complications seen in Rickettsial illness are neurological (encephalopathy 15%, meningitis 5%, meningoencephalitis 5%, encephalitis 3%), pneumonia (21%), gangrene (11%), renal failure (7%), shock, myocarditis, gastrointestinal hemorrhage, DIC, ARDS (5% each) and hemophagocytic syndrome (3%).[3]

5. Investigations

No laboratory parameter is specific for it's early diagnosis but laboratory clues suggestive of Rickettsial diseases are normal to low leukocyte count with marked left shift, thrombocytopenia, hyponatremia and mildly elevated hepatic transaminases. Leukocytosis is seen as the duration of untreated disease increases. Various serological tests (Microimmunofluorescence, immunoperoxidase assay, latex agglutination, indirect hemagglutination, enzyme-linked immunosorbent assay, dot blot immunoassay and Weil–Felix test) for diagnosis are positive usually after 5–7 days and hence play no role for early initiation of specific therapy. In spite of all the drawbacks of low sensitivity (but reasonably high specificity at cut-off of 1 in 320 or four fold rising titer) associated with it, the Weil–Felix test still serves as a useful and cheapest available tool for the laboratory diagnosis of Rickettsial diseases in India.[12] In a study from Delhi,[10] healthy blood donors were screened by Weil-Felix test and 667 (95.2%) showed titer of 1:20 or less in OX2, OX19 and OXK antigens. Twenty-one (3.0%) samples showed titer of 1:40 and 12 (1.7%) showed tire of 1:80 or more in one or more Weil–Felix antigens. Hence, cut-off titer can be taken as 1:80 for Delhi population and results in FUO cases be interpreted accordingly. Almost 100% correlation was obtained in OXK 1:160 titer or more and ELISA test in this study. IgM ELISA is available at some centers and has better sensitivity and specificity. IFA (Immunofluorescence assay), a gold standard for diagnosis, is not available in India.

RGA (Rathi, Goodman, Aghai) scoring system (Table 1) using clinical, laboratory and epidemiological features can serve a useful tool for the diagnosis[3] of spotted fever group. 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

Table 1 – RGA scoring system to diagnose spotted fever Rickettsioses (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

97.7%, respectively. 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.

6. Differential diagnoses

Diagnosis of Rickettsial infection must be suspected in compatible clinical situations (like FWS, PUO, fever with rash, fever with edema, dengue like illness) associated with history of vector exposure (like tick bite, tick removal from body, visualization of tick on child's clothing, playing in areas where ticks are often seen, contact with tick infested dog) along with suggestive laboratory features (normal to low leukocyte count with marked left shift, thrombocytopenia, hyponatremia and mildly elevated hepatic transaminases). Such cases should be started on specific antimicrobial agent and blood sample be collected for serology. Prompt defervescence with appropriate antibiotic clinches the diagnosis. Rickettsial diseases can be easily confused with a variety of viral (measles, enteroviral exanthems, dengue, infectious mononucleosis), protozoal (malaria), bacterial (meningococcemia, typhoid, leptospirosis, toxic shock syndrome, scarlet fever) and collagen vascular (Kawasaki disease, other vasculitis) diseases, and adverse drug reactions.[2] Presence of fever beyond 5–6 days, evolving nature of rash, anemia rather than polycythemia differentiates Rickettsial infection from dengue as fever, rash, edema, capillary leak, hepatomegaly and thrombocytopenia are seen in both.

7. Management

Early institution of anti Rickettsial antimicrobials is the key to prevent high morbidity and mortality associated with untreated disease. Various antibiotics effective in Rickettsial diseases are Doxycycline, Rifampin, Chloramphenicol, macrolides and fluoroquinolones. Doxycycline is the drug of choice. It is used in the dose of 5 mg/kg/day in two divided doses for children below 45 kg and 100 mg twice a day for those above 45 kg. Total duration of therapy is 3 days after defervescence or minimum of 5–7 days. Use of tetracycline to treat children below 8 years is no longer a subject of controversy. It has been observed that cosmetically perceptible staining of teeth require six or more multiple day courses of therapy. Because Rickettsial diseases can be life threatening and limited courses with tetracycline class antibiotics do not pose a substantial risk for tooth staining, the American Academy of Pediatrics committee on infectious diseases revised it's recommendations in 1997 and has identified doxycycline as the drug of choice for treating presumed or confirmed cases in children of any age.[14] Clinicians should monitor the progress of patients in the light of reports of drug resistance. Rifampicin is seen to be more effective than doxycycline in areas where scrub typhus appears to respond poorly to standard anti Rickettsial drugs.[15] Clarithromycin can be considered a valid alternative to tetracycline and chloramphenicol, especially for children less than 8 years of age. Sulfonamides are contraindicated, as they are known to stimulate growth of Rickettsia. Good supportive therapy is needed in critically ill patients as iatrogenic cerebral and pulmonary edema is easily precipitated due to preexisting microvascular leakage. Judicious use of corticosteroids is advocated by some in meningoencephalitis. Supportive care is also needed for hypovolemia, coagulopathy, seizures and intercurrent infections.[2]

8. Prevention

The following is a summary of salient features of prevention:

- Avoid tick bites, by avoiding tick infested areas, which is key to the prevention of Rickettsial diseases.
- Limit exposure to tick habitats, including grassy and wooded areas.
- Avoid contact with vector reservoirs like dogs, cattle, sheep, goats and rodents.[16]
- Inspect the body carefully for ticks after being in a tick habitat.
- Remove attached ticks immediately by grasping with tweezers close to skin and pulling gently with steady pressure
- Antibiotic prophylaxis after tick bite is not beneficial.

Conflicts of interest

All authors have none to declare.

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