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Original Article

Five-year analysis of rickettsial fevers in children in South India: Clinical manifestations and complications

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Abstract

Introduction: Rickettsial infections are re-emerging in the Indian subcontinent, especially among children. Understanding geographical and clinical epidemiology will facilitate early diagnosis and management.

Methodology: Children aged <18yrs hospitalized with clinically-diagnosed rickettsial fever were reviewed retrospectively. Frequency distributions and odds ratios were calculated from tabulated data.

Results: Among 262 children hospitalized between January 2008-December 2012, median age was five years, and 61% were male children. Hospitalized cases increased steadily every year, with the highest burden (74%) occurring between September and January each year. Mean duration of fever was 11.5 days. Rash was present in 54.2% (142/262) of children, with 37.0% involving palms and soles. Prevalence of malnutrition was high (45% of children were underweight and 28% had stunting). Retinal vasculitis was seen in 13.7% (36/262), and the risk appeared higher in females. Severe complications were seen in 29% (purpura fulminans, 7.6%; meningitis and meningoencephalitis, 28%; septic shock, 1.9%; acute respiratory distress syndrome, 1.1%). Complications were more likely to occur in anemic children. Positive Weil-Felix test results (titers ≥1:160) were seen in 70% of cases. Elevated OX-K titers suggestive of scrub typhus were seen in 80% (147/184). Patients were treated with chloramphenicol (32%) or doxycycline (68%). Overall mortality among hospitalised children was 1.9%.

Conclusions: This five-year analysis from southern India shows a high burden and increasing trend of rickettsial infections among children. The occurrence of retinal vasculitis and a high rate of severe complications draw attention to the need for early diagnosis and management of these infections.

Key words: rickettsial infections; children; India.

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Introduction

Rickettsial infections are distributed throughout the world and are re-emerging in the Indian subcontinent, especially among children. Rickettsial disease has been reported from various parts of India, such as Tamil Nadu, Karnataka, Kerala, Maharashtra, and some parts of northern India [1-9]. The infection has established itself as an endemic disease in Southeast Asia including Thailand, China, and Taiwan [10-12]. Multiple factors contribute to the gross under-diagnosis of rickettsial infections; these include the relatively non-specific disease presentation, low index of suspicion, and lack of awareness about its re-emergence [3,11-13].

The lack of proper clinical diagnostic techniques in low-income settings such as India further contributes to a delay in starting treatment. This is mainly due to the fact that the only test available is the Weil-Felix test, which does not lead to a definitive diagnosis. The immunofluorescence assay (IFA) is the gold standard for diagnosis, but it is not available in India [3]. These diagnostic deficiencies result in physicians relying on clinical suspicion alone to begin treatment, and point to a need for the development of newer, cost-effective diagnostic assays.

Methodology

A retrospective medical chart review was performed within St. John's Hospital, a tertiary-care setting in Bangalore. Hospitalized children younger than 18 years of age admitted between January 2008 and December 2012 with a clinical diagnosis of rickettsial fever were included in the review. The clinical diagnosis was made on the basis of fever lasting for more than five days and features suggestive of rickettsial fevers. Demographic data, clinical features, laboratory parameters, hospital course, and

complications were recorded. Weil-Felix test results that had titers of 1:80 or more were considered to be highly suggestive of rickettsial infection. Treatment response was measured as the number of hours taken for patients to become afebrile after starting specific anti-rickettsial antimicrobial agents. Children with laboratory-confirmed cases such as leptospirosis, dengue fever, malaria, typhoid fever, pneumonia, and urinary tract infection were excluded from the study. Statistical analyses were performed using SPSS version 16.0 (SPSS, Chicago, USA). Frequency distributions of geographic epidemiology and clinical features were analyzed. Trend analysis using the non-parametric Kruskal-Wallis test for significance was used to study changes in epidemiology over time. Chi-square test and t test were used to test for associations of clinical variables and laboratory values. All p values were two-sided, and a value of < 0.05 was considered as significant.

Ethical clearance for retrospective review of medical records was obtained from the institutional ethical review board, St. John's Medical College, Bangalore.

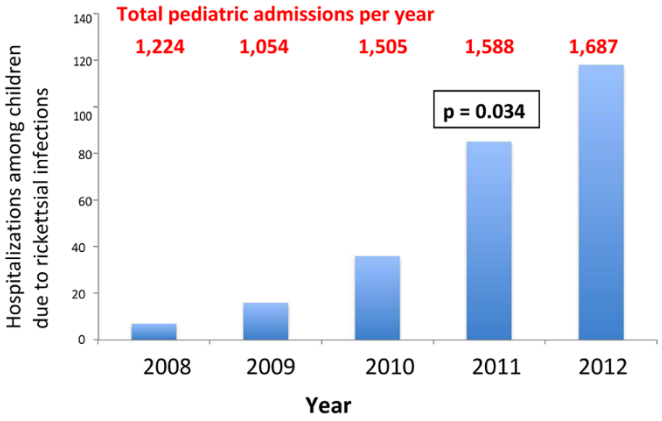
Results

A total of 262 children were diagnosed as having rickettsial infection over the five-year study period. Ages ranged from 2 months to 17 years (median age 5 years, interquartile range [IQR] 3, 8), and 159 (61%) of the children were males. The overall number of cases increased each year during the five-year study period (Figure 1). Patients hailed from Bangalore (19%) and other districts of Karnataka (30%), Andhra Pradesh (41%), and Tamil Nadu (10%), which are the neighboring southern states of India. The highest burden of cases (74%) occurred during the post-monsoon and cooler months of September to January each year (Figure 2).

All patients had fever at presentation of illness. The list of clinical features and their prevalence is presented in Table 1. Rash was present in 54.2% of children and was mostly macular-papular in nature. This rash extended to the palms and soles in 37.0% children. The characteristic eschar was seen only in 5.7% (15/262) of the cases. Retinal vasculitis was seen in 13.7% (36/262), and this risk appeared to be higher in female children (odds ratio 2.3; $p = 0.02$). Abnormal cerebrospinal fluid analysis (proteins > 40 mg/dL, cells > 7 cells/mm^3) suggestive of aseptic meningitis was seen in 24% patients.

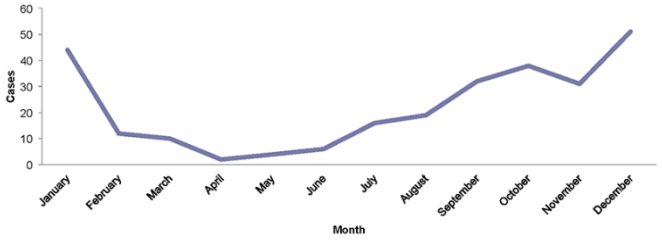
Positive Weil-Felix results (titers ≥ 1:80) were seen in 70% of cases. High OX-K titer suggestive of scrub typhus was observed in 80% (147/184). Children were treated with chloramphenicol or doxycycline. Rapid defervescence (within 48 hours) upon initiation of doxycycline was seen in 89% (145/163) of cases.

Figure 1. The 2008-2012 trend in rickettsial infection-related hospitalizations.



This figure was generated by plotting the total number of rickettsial infections for every month during all the years studied. A significant increase in the number of rickettsial infection-related hospitalizations over the past five years is seen ($p = 0.034$).

Figure 2. Seasonal variation of rickettsial infections among hospitalized children.



This figure was generated by plotting the incidence of rickettsial infection for every month on a line diagram. This was done for each year. Following this, an average was taken of all the years to generate a single line.

Increased severity of illness and complications were seen in 76 (29.0%) children. The prevalence of complications was 30.9% (81/262). Complications of rickettsial diseases included predominantly neurological abnormalities (28%) (meningo-encephalitis and meningitis). Other complications included pneumonia (6.1%), purpura fulminans (7.6%), retinal vasculitis (13.7%), acute respiratory distress syndrome (ARDS) (1.1%), shock (1.9%), and renal failure (0.4%). Among all hospitalized children, 37 (14.1%) required intensive care. Five children died of complications, resulting in a mortality of 1.9% among children hospitalized with clinical rickettsial fever. Four of the five children who died had severe complications.

Table 1. Clinical features of rickettsial fevers in children

	Clinical features	Prevalence (%) (n = 262)
Symptoms	Rash on palms and soles	97 (37.0)
	Upper respiratory features	53 (20.2)
	Altered sensorium	64 (24.4)
	Seizures	50 (19.1)
	Arthralgia	10 (3.8)
Signs	Periorbital edema	100 (38.2)
	Hepatomegaly	228 (87.0)
	Splenomegaly	131 (50.0)
	Lymphadenopathy	57 (21.8)
	Eschar	15 (5.7)
	Retinal vasculitis	36 (13.7)
Investigations	Anemia (Hb < 11 g/dL)	180 (68.7)
	Elevated liver enzymes (AST, ALT > 2 ULN)	93 (35.5)
	Hyponatremia (Na < 130 Meq/L)	30 (11.5)

AST: aspartate aminotransferase; ALT: alanine transaminase; ULN: upper limit of normal; CSF: cerebrospinal fluid; Hb: hemoglobin

Discussion

We found an increasing trend of rickettsial infection prevalence among hospitalized children in our setting over a five-year period. Rickettsial diseases have been reported from the various parts of India and are showing a trend of re-emergence [1-9]. More than 75% of our cases occurred during the fourth and fifth year of our five-year analysis. Other studies from India also corroborate this trend of re-emergence, highlighting the need for clinical suspicion and knowledge of disease trends.

In our study, most patients were from the rural areas Karnataka, Andhra Pradesh, and Tamil Nadu. This finding is similar to those of other studies, where the rural population appears to be more susceptible to rickettsial infections [19,20]. The seasonal determinants of rickettsial infection depend on the climate, temperature, and degree of rainfall in that region [18]. These factors in turn determine the trombiculid mite breeding activities. Most cases of rickettsial infection are seen after the monsoon season in India as the hatching of eggs into larvae (chiggers) is favored by the increased humidity that occurs after the heavy rains between June and August. The larva is the only stage that can transmit the disease to humans and other vertebrates, since the other life stages (nymph and adult) do not feed on vertebrate animals. Earlier reports from India indicate similar period of disease occurrence [1,8]. Knowing the seasonality may help in advocating policies for early prevention.

Clinical features of rickettsial diseases are mostly nonspecific and likely to be misdiagnosed for other causes of acute febrile illnesses. The median age of presentation and increased predilection for males was similar to that found in other studies in India and South Asia [1-12]. The relatively long duration of fever, which in our study was eight days, should increase the clinical suspicion of rickettsial fever. Rash was only observed in about half of the cases we encountered, while this ranged from 14%–83% in other studies [8,9,12]. There is a wide range in the occurrence of clinical features in literature. Kumar *et al*. reported that 60% of cases had splenomegaly [7]. However, Huang *et al*. reported that splenomegaly occurred in only 18% of cases, which is lower than that seen in our study and other studies across the Indian subcontinent [1,9,11]. South Indian studies reported a high incidence of hepatomegaly similar to that seen in our study [4,7]. The prevalence of eschar was lower than that found in other studies carried out in South India [1,9]. Neurological features such as altered sensorium and seizures were similar to those found in other studies across Asia [10-12]. Lymphadenopathy was prevalent in 22% of cases, although this is a non-specific feature, and may be often seen in the etiologies of other common infections. It is noteworthy that the prevalence of retinal vasculitis in our patient population was significantly higher than previously reported. It can be expected that patients with central nervous system involvement probably have a more severe form of the disease and will have a poorer response to treatment. Retinal vasculitis is a relatively serious complication and may be asymptomatic in the early stages. The visual prognosis is usually favorable, with lesions usually resolving by six months after recovery from the acute illness. The increased prevalence of females with vasculitis cannot be explained and is a potential area for further research.

The presence of numerous diverse species of *Rickettsia* renders specific serologic testing laborious

and expensive. Weil-Felix is a simple and low-cost test, albeit somewhat non-specific, and can guide the clinician in initiating appropriate treatment. However, the low sensitivity of Weil-Felix is a problem. Mittal *et al*. suggest that the Weil-Felix test could be used successfully as an initial screening test [6]. Isaac *et al*. observed only 30% sensitivity at a titer of 1:80, but the specificity and positive predictive value were both 100% [17]. A good correlation of Weil-Felix test and detection of immunoglobulin M antibodies by an indirect IFA was observed [18]. The IFA has favorable sensitivity and specificity for diagnosing rickettsial infections, and can be used as a good screening test [13]. Rathi *et al*. recommend a sensitive and specific scoring system for making a provisional clinical diagnosis of spotted fever, particularly in the Indian context [14]. However, a confirmatory laboratory diagnosis is also often necessary. Lijuan *et al*. found that the gold standard IFA is not a practical means of establishing a diagnosis, particularly in rural areas [12]. They recommend a rapid diagnostic test using immunoglobulin M and immunoglobulin G titers. This rapid test is especially useful during the acute phase of illness and has 100% specificity.

Rickettsial infections show prompt response to antimicrobial therapy. Doxycycline remains the choice antibiotic, but chloramphenicol is sometimes used in many endemic areas [8]. Therapy should be continued until the patient has been afebrile for at least 24 hours or a minimum of seven days [4]. In our report, patients treated with doxycycline or chloramphenicol early during the course of disease were more likely to recover without complications. Anemia appeared to be a significant risk factor for the development of severe disease with complications. It remains to be determined if the anemia occurred due to the disease itself or if anemia preceded the disease. There are reports of hemophagocytosis occurring in rickettsial infection, thought studies also show anemia as a significant, independent risk factor for the occurrence of complications [15-16]. Timely diagnosis is critical, as mortality can be as high as 30%–35% in untreated cases [9]. Overall mortality was low in our study, although almost a third of the children had severe complications. Timely recognition and treatment along with widespread and immediate use of preventive measures are required to control the infection.

There are some limitations in this study. Only hospitalized patients were included, and the prevalence of rickettsial infections in the community was not well assessed. The retrospective nature of the study precluded the availability of complete data in the categories of clinical features and laboratory test results. The diagnosis of rickettsial disease was based on clinical features and was not confirmed by gold standard tests such as IFA, PCR, or culture.

Conclusions

Our five-year study highlights the re-emerging nature and rising trends of this predominantly pediatric infection with a propensity for life-threatening complications, and questions our complacency in having non-specific diagnostic methods. The Weil-Felix assay may be used as an initial screening test, but cannot be relied upon as the sole method in laboratory diagnosis due to its poor sensitivity. Early diagnosis with specific, feasible, and low-cost assays will go a long way in instituting early management and reducing the morbidity and mortality of rickettsial infections in children.

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