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Rickettsial infections and their clinical presentations in the Western Province of Sri Lanka: a hospital-based study☆

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Summary
Background: Rickettsial infections are re-emerging. A study of the geographical distribution of rickettsial infections, their clinical manifestations, and their complications would facilitate early diagnosis.
Methods: Thirty-one selected patients from the Western Province of Sri Lanka were studied for rickettsial species, clinical manifestations, and complications.
Results: Of 31 patients with possible rickettsioses, 29 (94%) fell into the categories of confirmed, presumptive, or exposed cases of acute rickettsial infections (scrub typhus was diagnosed in 19 (66%), spotted fever group in eight (28%)). Early acute infection or past exposure was suggested in two (7%) cases; cross-reactivity of antigens or past exposure to one or more species was suggested in nine (31%). Seventeen out of 19 (89%) patients with scrub typhus had eschars. Nine out of 29 (32%) patients had a discrete erythematous papular rash: seven caused by spotted fever group, two by scrub typhus. Severe complications were pneumonitis in eight (28%), myocarditis in five (17%), deafness in four (14%), and tinnitus in two (7%). The mean duration of illness before onset of complications was 12.0 (SD 1.4) days. All patients except one made a good clinical recovery with doxycycline or a combination of doxycycline and chloramphenicol.
Conclusions: In a region representing the low country wet zone of Sri Lanka, the main rickettsial agent seems to be *Orientia tsutsugamushi*. Delay in diagnosis may result in complications. All species responded well to current treatment.

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Introduction

In the Asia Pacific region rickettsial infections most frequently include endemic (murine) typhus, scrub typhus, and several spotted fever group rickettsioses.[1–3] The incidence of different rickettsial infections depends on the presence of specific vectors and their hosts. Scrub typhus is associated with trombiculid mites and their rodent hosts. Spotted fever group rickettsiae are transmitted by hard ticks, mites, or fleas, and the hosts are rodents, dogs, and wild animals.[3,4] Although some rickettsial infections such as scrub typhus and spotted fevers are considered to be more rural in their distribution, urbanization per se has not contributed to the decline of these infections.[4]

Recent reports from Southeast Asia suggest the re-emergence of rickettsial infections.[5–7] In Sri Lanka, we have experienced several outbreaks of suspected rickettsial infections over the past few years.[8–10] These outbreaks have been in addition to year-round sporadic cases (RP, personal experience). Many of the sporadic cases have been from urban or semi-urban areas.

In both clinical practice and epidemiological surveys, the main difficulty in the diagnosis and management of rickettsial infections is the lack of facilities for definitive diagnosis. The most available test, the Weil–Felix test, is now considered obsolete, but better diagnostic techniques, such as indirect fluorescent antibody (IFA) assays, are only available at reference centers.[4,11] The clinical diagnosis, and therefore reporting of rickettsial infections, is based mainly on clinical features, such as the presence of eschars or characteristic rashes. Although clinical manifestations of rickettsial infections are well documented,[3] recent studies from Asian countries have reported complications such as gastrointestinal manifestations, tinnitus, and hepatitis syndromes.[10,12,13] Awareness of the different clinical presentations of these infections may assist early diagnosis, especially in areas where no diagnostic facilities are available.

Infections with *Orientia tsutsugamushi*, *Rickettsia typhi*, and spotted fever group rickettsiae have been documented in a recent hospital-based study in the hilly Central Province of Sri Lanka.[9] However, the distribution of rickettsial infections in the low lying areas of the country is not well documented,[10] other than a serological survey done in 1976 in Colombo, which reported a low prevalence (<6%) of exposure.[14]

The objective of this study was to identify the different etiologic agents and their clinical characteristics in patients suspected of having rickettsial infections, presenting to a tertiary hospital in the Western Province, which represents the low country wet zone of Sri Lanka.

Methods

During the 12-month period from November 2002 to October 2003, a prospective study was done on patients who were admitted to the Professorial Medical Unit, Colombo North Teaching Hospital, Ragama, Sri Lanka, with fever of more than five days duration and a clinical suspicion of rickettsial infection. The case definition included patients with high intermittent fever and having at least five out of the following eight clinical features present: headache, myalgia, regional lymphadenopathy, generalized lymphadenopathy, hepatomegaly, splenomegaly, presence of an eschar, or presence of a maculopapular rash. Demographic details of each patient (those resident in municipal and urban-council administrative areas were considered urban, and those resident in the outskirts of these administrative areas were considered semi-urban), the clinical course of the illness, and complications of infection were recorded.

Basic hematological and biochemical tests and relevant imaging were carried out. More specific tests were done when indicated, especially when there were complications such as myocarditis and encephalitis. The confirmatory tests to identify the causative agent were performed on 2 ml of serum collected at presentation (acute sample) and after two weeks of treatment (convalescent sample). These serum samples were stored at −20 °C until they were analyzed at the Viral and Rickettsial Zoonoses Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA. IFA assays were carried out using rickettsial antigens grown in vitro: *Rickettsia conorii* (Malish), *Rickettsia typhi* (Wilmington), and *Orientia tsutsugamushi* (Karp). Antibodies were detected using fluorescein-conjugated goat anti-human $IgG_{(\gamma)}$ or $IgM_{(\mu)}$ (KPL, Inc., Gaithersburg, MD, USA). Sera were screened at 1/32, and positive samples were titered to the endpoint using a two-fold dilution series. Patients with antibody titers (either IgM or IgG) showing a four-fold rise or decline between acute and convalescent samples were considered confirmed cases. Patients with single high IgM or IgG titers of >1:256, clinical symptoms compatible with acute illness, and rapid defervescence with doxycycline were considered presumptive cases. Patients with acute antibody titers of only 1:128 were considered to possibly have had past exposure to rickettsial infections. Patients who were confirmed or considered presumptive cases for one rickettsial infection, and who had antibody titers of 1:128 or more for a second rickettsial infection were considered to either have serologic cross-reactivity or past exposure to a second rickettsial species. (Our cut-off values for IFA titers were chosen to minimize the possibility of serologic cross-reaction and were higher than the titers selected in previous publications.[9])

Results

A total of 31 patients (22 female, mean age 52 years (SD 5.6)) fulfilled our case definitions and were further investigated. Paired blood samples were obtained at least two weeks apart from 11 (35%) patients. All patients presented as sporadic cases and were living an average of 10 km (range 4–25 km) from the hospital. Of these patients, 19 (61%) were living in urban areas and 12 (39%) were living in semi-urban areas. They were living in houses with cement floors and either tile or asbestos sheet roofing. All of them claimed that there were rats in the vicinity, and all patients had engaged in some activity in the garden surrounding their house. None of them had visited scrub jungle areas, slept on the floor or bare ground, or visited areas outside their hometown during the preceding three months.

Results of serological analyses are shown in Table 1. Out of the 31 patients, 29 (94%) were either confirmed, presumptive, or exposed cases of acute rickettsial infections. Of the 29 cases, acute scrub typhus infection was diagnosed in 19 (66%) patients, and out of them, six (32%) were confirmed

Table 1 Acute and convalescent IFA serum titers using *Orientia tsutsugamushi*, *Rickettsia conorii*, and *Rickettsia typhi* antigens

Patient	Case	*O. tsutsugamushi* (Karp) IgM IFA titer		*O. tsutsugamushi* (Karp) IgG IFA titer		*R. conorii* IgM IFA titer		*R. conorii* IgG IFA titer		*R. typhi* IgG IFA titer	
		Acute	Convalescent	Acute	Convalescent	Acute	Convalescent	Acute	Convalescent	Acute	Convalescent
1	P	8192		4096		ND		<32		32	
2	P	16384		128		ND		32		<32	
3	C	2048	256	256	8192	ND	ND	<32	<32	<32	<32
4	P	16384	8192	32768	32768	ND	ND	64	<32	<32	<32
5	P	<16		16		2048		256		<32	
6	P	4096		512		ND		32		<32	
7	C	4096	1024	2048	512	<32	32	<32	128	<32	128
8	C	<16	<16	<16	32	2048	256	512	2048	32	128
9	P	<16		32		1024		8192		<32	
10		<16		<16		ND		<32		<32	
11	C	<16	<16	128	<16	4096	256	4096	256	32	<32
12	C	1024	512	2048	8192	ND	ND	<32	<32	<32	<32
13	C	2048	128	2048	64	ND	ND	<32	<32	<32	<32
14	P	8192		2048		<32		<32		<32	
15	P	4096		2048		ND		128		<32	
16	P	256		128		ND		128		<32	
17	C	<16	<16	<16	<16	256	2048	256	8192	<32	<32
18	C	2048	2048	512	128	32	32	128	128	<32	<32
19	P	<16		<16		1024		1024		<32	
20	C	<16	<16	<16	<16	16384	256	32768	1024	128	<32
21		<16		<16		ND		<32		<32	
22	C	4096	16384	2048	8192	ND	ND	256	512	<32	<32
23	E	<16		<16		ND		128		<32	
24	P	8192	Died	4096		ND		64		<32	
25	E	32		128		ND		128		<32	
26	P	16384		4096		32		32		<32	
27	P	32768		16384		ND		128		<32	
28	P	1024		512		ND		<32		<32	
29	P	1024		256		32		256		<32	
30	P	256		1024		ND		<32		<32	
31	P	32		<16		512		<32		<32	

C = confirmed case; P = presumptive case; E = past exposure; ND = not done. Indirect fluorescent antibody (IFA) titer required for case diagnosis $\geq$1:256.

cases and 13 (68%) were presumptive cases. Acute spotted fever group rickettsial infections were diagnosed in eight (28%), and of these, four (50%) were confirmed cases and four (50%) were presumptive cases. Early acute rickettsial infection or past exposure to one or more species was suggested in two (7%; cases 23 and 25), and cross-reactivity of antigens or past exposure to one or more species was suggested in nine (31%; cases 7, 11, 15, 16, 18, 20, 22, 27, and 29). One patient (case 10) who was included by our case definition but who was negative for rickettsial infections by serology was later diagnosed with systemic lupus erythematosus. One patient (case 21) had fever and an eschar but was negative for rickettsial infections by serology.

The most striking feature among the uncomplicated cases was that the patients did not feel very ill when afebrile. However, the bouts of fever were associated with chills, severe headache, and body aches. Patients without a rash seem to have had more frequent, high grade, intermittent fever than those with a rash. Nine out of 29 patients (32%) had a discrete erythematous papular rash mainly distributed over the extremities, involving palms and soles; seven were caused by spotted fever group *Rickettsia spp* and two by *O. tsutsugamushi*. The rashes were most prominent at the time when the patients were febrile. There were no hemorrhages or tissue necrosis associated with the rashes. However, rashes were often accompanied by a patch of redness in the lateral limbus of each eye, which again was more prominent when the patient was febrile.

Complications seen in patients diagnosed with rickettsial infections are shown in Table 2. The mean duration of illness at the time of admission in patients who developed complications was 12.0 days (SD 1.4) compared to 9.2 days (SD 3.5) for those who had no complications ($p < 0.05$). Myocarditis, seen in five patients (cases 4, 12, 20, 22, and 24), was characterized by transient arrhythmia (atrial fibrillation in cases 4 and 24), low blood pressure, and a transient reduction in ejection fraction. One patient (case 22) demonstrated apical hypokinesia on echocardiography, which subsequently disappeared. Patients with pneumonitis (cases 4, 6, 12, 13, 15, 18, 22, and 24) had a dry cough associated with coarse crepitations. There was no reduction in capillary oxygen saturation except in the two seriously ill patients (cases 12 and 24), who had minimum O_2 saturations of 94 and 92 KPa, respectively. Of those with hearing impairment, three (cases 6, 12, and 13) had bilateral high tone deafness, which progressed to complete deafness in less than 24 hours; clinical recovery with treatment was dramatic, and objective improvement was proportionate to the initial degree of deafness. Features of encephalitis (cases 4, 12, 22, and 24) included high frequency coarse tremors of extremities associated with abnormal lateral head movements and rapid oscillations of the eyes in all directions. The latter manifestations were seen in the more severe cases (cases 12 and 24).

With one exception, all patients had complete symptomatic recovery within 48 hours of commencement of treatment with oral doxycycline. Two patients who had severe myocarditis, encephalitis, and pneumonitis were treated with intravenous chloramphenicol in addition to doxycycline (cases 12 and 24). One patient (case 24) died despite this treatment.

Discussion

During the study period, of the 31 patients who had clinical features compatible with our case definition, there were 10 serologically confirmed cases, 17 presumed cases, and two persons who were considered previously exposed to rickettsiae. All cases were sporadic presentations. Of these 29 patients, 19 had acute scrub typhus caused by *O. tsutsugamushi* and eight had spotted fever group rickettsial infections. Among patients with scrub typhus, there was evidence of past exposure to spotted fever group rickettsiae in two patients, and serologic cross-reactivity or past exposure to two or more rickettsial species was seen in eight other cases, although only one spotted fever group case exhibited seroreactivity to *O. tsutsugamushi*. Further study is needed to determine if the patients diagnosed with spotted fever group rickettsiosis were exposed to *R. conorii* or to other species of *Rickettsia* such as *Rickettsia africae*. Surprisingly, low (>1:128) antibody titers for *R. typhi* were detected in only three cases, and in two of them were possibly due to the well-known serologic cross-reactivity of typhus and spotted fever rickettsiae.

We admit that the number of cases studied is small, and patients who were selected for the study had a presumptive clinical diagnosis of rickettsial infection. However, our results suggest that in urban and semi-urban areas of the Western Province, which represent the low country wet zone of Sri Lanka, scrub typhus is more common than spotted fever group rickettsioses. The reverse pattern of prevalence was demonstrated in the study conducted in the hilly Central Province of Sri Lanka.[9] Rodents and dogs, which can be

Table 2 Summary of complications seen in patients diagnosed with rickettsial infections

Patient	Duration of fever at admission (days)	Eschar	Hearing	Pneumonitis	Myocarditis	Encephalitis
4	13	Yes	Normal	Yes	Yes	Yes
6	11	Yes	Deaf	Yes	No	No
12	12	Yes	Deaf	Yes	Yes	Yes
13	10	Yes	Deaf	Yes	No	No
15	13	Yes	Tinnitus	Yes	No	No
18	12	Yes	Tinnitus	Yes	No	No
20	11	No	Normal	No	Yes	No
22	12	Yes	Normal	Yes	Yes	Yes
24	14	No	Deaf	Yes	Yes	Yes

reservoirs for *O. tsutsugamushi* and spotted-fever group rickettsiae, respectively, are ubiquitous, irrespective of the geography in Sri Lanka. Therefore, our findings suggest that the distribution or prevalence of different vector and reservoir species may be different in the hill country compared to the low country. Our results also suggest an urban or semi-urban distribution of the infected vectors exists. Further studies are needed to clarify the ecological factors for vector selectivity and the precise rickettsial etiology of spotted fever infections in Sri Lanka.

Out of the 19 patients who were diagnosed with scrub typhus, 17 (89%) had eschars on the body. This observation is compatible with the literature.[1] The reason for this high figure could be due to our case definition or due to our careful search for an eschar. The common sites for the eschar were the axillae and the groin. None of the spotted fever group patients had eschars. Nine patients, all of whom were diagnosed with scrub typhus, had one or more complications, such as deafness, myocarditis, pneumonitis, or encephalitis. Our findings suggest that delays in seeking medical care and in the initiation of appropriate therapy give rise to these serious complications.

Although most of our patients had clinical features suggestive of rickettsial infections that are well documented in the literature, their diagnosis was usually missed at first contact. This might be because rickettsial infections are not commonly considered in the differential diagnosis of short duration fever in Sri Lanka (RP, personal experience). The lack of awareness of the re-emergence of rickettsial diseases might be the underlying reason.[4] At the time of their presentation to us, all of our patients had received one or more antibiotics at first contact. However, none of these antibiotics were anti-rickettsial agents.

All patients except one had a good clinical recovery after treatment with either doxycycline or a combination of doxycycline and chloramphenicol. One patient died; the possible reasons for death could be the severity of the illness, delayed diagnosis, or non-response to treatment due to drug resistance. Drug-resistant rickettsial strains have been reported in Asia.[15]

In conclusion, the most prevalent rickettsial species causing infection in patients presenting at a tertiary care hospital in the Western Province, which represents the low country wet zone of Sri Lanka, was *O. tsutsugamushi*. Rickettsial infection seems to be re-emerging and should be considered in the differential diagnosis of fevers of short duration in Sri Lanka. Delay in diagnosis may result in serious complications. Tetracycline and chloramphenicol are effective treatments.

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