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A case series of spotted fever rickettsiosis with neurological manifestations in Sri Lanka

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SUMMARY

Background: Spotted fever group (SFG) rickettsial infections are increasingly detected in Sri Lanka. We describe 17 patients with SFG who developed neurological manifestations.
Methods: The cases were studied prospectively from 2008 at the Teaching Hospital, Peradeniya. An immunofluorescent antibody assay (IFA) was used to confirm the diagnosis.
Results: All had an IFA IgG titer ranging from 1/64 to 1/4096 and a positive IFA IgM titer against *Rickettsia conorii* antigen; in 10 (59%) cases the IgG titers were ≥1/256 (definitive cases). The median age of the patients was 62 years (range 26–82 years); 10 were male and seven female. The median duration of fever was 12 days (range 4–35 days). Neurological manifestations on admission were drowsiness or confusion in 14 (82%) and a semi-comatose state in three (18%). Rigidity of the limbs occurred in 14 (82%), bradykinesia and resting tremors in 12 (71%), which persisted after defervescence, neck stiffness in seven (42%), weakness of the limbs in five (29%), deafness in two (12%), and stupor in three (18%). Electroencephalograms in three (18%) showed generalized slow waves. Cerebrospinal fluid examination showed a cellular reaction, predominantly lymphocytes, in three cases. Two patients died (fatality rate 12%).
Conclusion: We have documented for the first time the neurological features of SFG rickettsioses in the Central Province, Sri Lanka. These were predominantly extrapyramidal features in patients of older age.

1. Introduction

The first recorded reference to rickettsial infections in Sri Lanka dates back to 1937–1945. Hospital-based studies carried out in 2001 and 2008 described the predominant prevalence of spotted fever group rickettsiae (SFG) in the hilly Central Province of Sri Lanka, and *Orientia tsutsugamushi* (scrub typhus) in the Western Province, the low country wet zone of Sri Lanka.[1–3] The emergence of SFG rickettsial infections in the Central Province was discovered among patients with clinically presumed rickettsial infections by immunofluorescent antibody assay (IFA) against *Rickettsia conorii* antigen. In the same region, IFA reactivity was found against *Rickettsia helvetica*, *Rickettsia japonica*, *Rickettsia slovaca*, *Rickettsia asiatica*, *Rickettsia heilongjiangensis*, and *Rickettsia felis* YH and TT118 antigens.[4] However, the rickettsial species that cause spotted fever in the region remain unknown. Rickettsial pathogens primarily infect endothelial cells causing disseminated vasculitis, which may subsequently lead to multiple-organ involvement.[5,6]

Involvement of the nervous system has been described in patients with scrub typhus in Sri Lanka.[7] Common clinical manifestations among SFG rickettsioses in the hilly Central Province include vasculitic skin rashes and arthritis, but clinical manifestations are sometimes obscure. However, since 2008 we have detected diverse neurological manifestations among spotted fever patients. The objective of this study was to summarize these manifestations in 17 such patients.

2. Methods

Data collected prospectively on patients admitted to the Teaching Hospital, Peradeniya since 2008 and who were later confirmed to have rickettsioses by IFA were analyzed, including history, clinical features, co-morbidities, laboratory investigations, and the presence of animal and insect bites. Those patients with an altered level of consciousness or those with other neurological manifestations such as unsteady gait, tremors, or focal neurological

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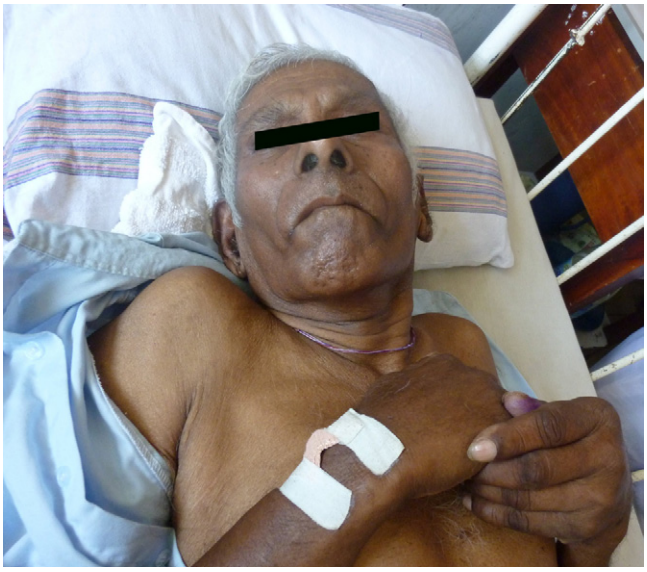

Figure 1. An elderly patient in a confused state with extrapyramidal rigidity.

signs were identified as neuro-rickettsial cases. The initial clinical diagnosis of rickettsial infection was made based on three criteria: fever of more than 5 days, presence of a maculopapular rash, particularly involving palms and soles, and defervescence with anti-rickettsial antibiotics.[2] Blood samples for serology were obtained between day 8 and day 12 of the illness, and the IFA was carried out only on acute serum samples.

IFA assays were carried out to detect IgG and IgM antibody titers against prototype strains of *O. tsutsugamushi* (serotype Karp), *Rickettsia typhi* (Wilmington), and *R. conorii* (Malish) antigens. Antibodies were detected using fluorescein-conjugated goat anti-human IgG (γ-chain) or IgM (μ-chain) (KPL, Inc., Gaithersburg, MD, USA). The serum samples were screened at 1/32 dilution, and positive samples were titered to the endpoint using two-fold dilutions. Based on the published literature, an IFA IgG titer of 1/256 or more was considered positive for a definite diagnosis of SFG in this study.[8,9]

This study forms part of the rickettsial studies that are currently being carried out, for which ethical approval was obtained from the Ethics Committee, Faculty of Medicine, Peradeniya University, Sri Lanka.

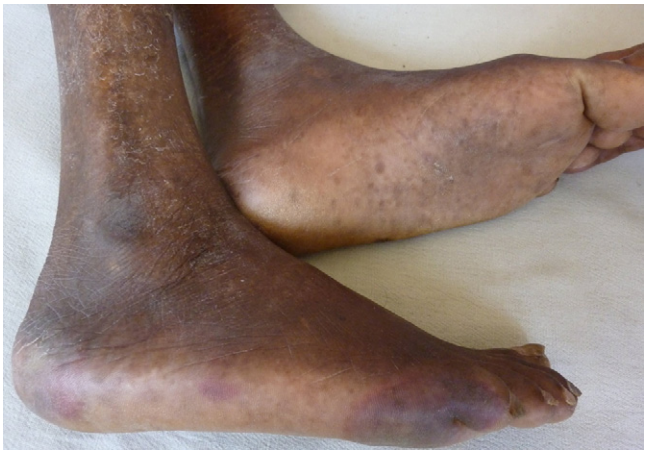

Figure 2. Vasculitic skin rash and area of necrosis on the feet of the patient in Figure 1.

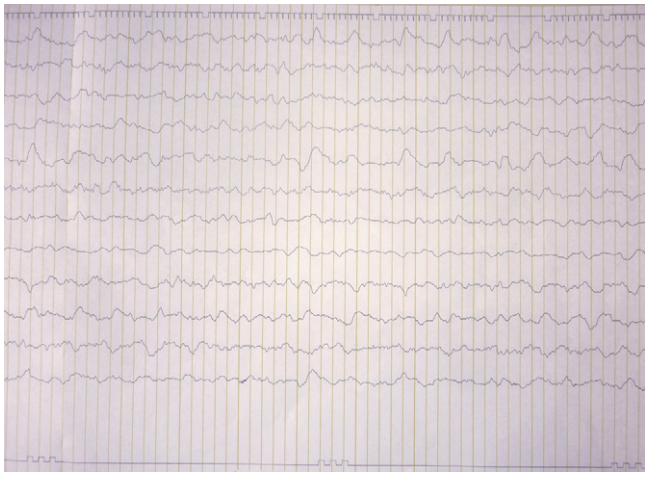

Figure 3. EEG of a patient showing a generalized slow wave pattern.

3. Results

A total of 134 patients fulfilled the clinical and serological diagnosis of rickettsial infection during the study period. Of these, we identified 17 patients who had neuro-rickettsioses. They had a positive IgM titer of 1/16 and positive IgG titers ranging from 1/64 to 1/4096 against *R. conorii* antigen. Ten patients (59%) had IgG titers ≥1/256 (definitive cases), whilst seven patients (41%) had titers <1/256 (presumed cases). All were non-reactive to *R. typhi* and *O. tsutsugamushi* antigens.

The median patient age was 62 years (range 26–82 years); 10 were male and seven female. The median duration of fever was 12 days (range 4–35 days). Out of the neurological manifestations, 14 (82%) were either drowsy or confused and three (18%) were in a semi-comatose state on admission. Fourteen patients (82%) had rigidity of the limbs, 12 (71%) had bradykinesia and resting tremors (which persisted even after defervescence), seven (42%) had neck stiffness, five (29%) had weakness of the limbs (a 33-year-old male patient developed flaccid quadriparesis and recovered), two (12%) had deafness, and three (18%) had stupor (Figure 1). Other manifestations were headache in 16 (94%), skin rash (Figure 2) in 17 (100%), fern leaf skin necrosis in seven (41%), conjunctival injection in 11 (65%), arthritis in seven (41%), and icterus in six (35%). Electroencephalograms (EEG) were done in four patients (24%), and three (18%) had generalized irregular slow waves suggestive of encephalitis (Figure 3). Of the seven cerebrospinal fluid (CSF) examinations, three had a cellular reaction in the form of pleocytosis.

Clinical and laboratory details are presented in Tables 1 and 2, according to the serology cut-off value of 1/256 (patients with titer ≥1/256 and patients with titer <1/256). Mean liver enzyme levels were high, and most patients had leukocytosis. The definitive cases had a mean platelet count of 97×10^9/l (range $4–194 \times 10^9$/l). The clinical details of the definitive cases are shown in Table 3. Two patients died (death rate 12%), but they had IgG titers <1/256. The remaining patients made a slow recovery with treatments such as doxycycline, chloramphenicol, and steroids.

4. Discussion

Obscure neurological manifestations such as altered level of consciousness, extrapyramidal manifestations, tremor, rigidity, and dyskinesia were observed in a series of patients with SFG rickettsial infections, predominantly affecting those of older age. In

Table 1
Clinical features of patients based on IFA titer levels

Parameter	Titer ≥1/256 (*n* = 10)	Titer <1/256 (*n* = 7)
Age (years), median (range)	63 (33–79)	60 (26–82)
Gender, *n* (%)		
Male	5 (50)	5 (71)
Female	5 (50)	2 (29)
Clinical features, *n* (%)		
Fever	10 (100)	7 (100)
Headache	9 (90)	7 (100)
Myalgia	10 (100)	6 (86)
Vomiting	5 (50)	5 (71)
Cough	5 (50)	3 (43)
Icterus	3 (30)	3 (43)
Conjunctival injection	6 (60)	5 (71)
Skin rash	10 (100)	7 (100)
Necrotic rash	4 (40)	3 (43)
Arthritis	5 (50)	2 (29)
Diarrhea	3 (30)	1 (14)
Hepatomegaly	3 (30)	1 (14)
CNS clinical features, *n* (%)		
Drowsy	1 (10)	2 (29)
Confusion	7 (70)	4 (57)
Semi-comatose	2 (20)	1 (14)
Hallucinations	1 (10)	0
Extrapyramidal rigidity	9 (90)	5 (71)
Tremors (Parkinsonism)	8 (80)	4 (57)
Stupor	1 (10)	2 (29)
Neck stiffness	5 (50)	2 (29)
Motor weakness of the limbs	2 (20)	3 (43)
Tinnitus	1 (10)	1 (14)
Deafness	1 (10)	1 (14)

IFA, immunofluorescent antibody assay; CNS, central nervous system.

most of the patients cure was possible by administration of anti-rickettsial antibiotics.

We used *R. conorii* antigen to diagnose SFG in these patients, as it has been used in previous studies in Sri Lanka.[2,3] This was based on the knowledge of the existence of wide cross-reaction between SFG rickettsiae, even though the exact local rickettsial pathogens of SFG remain unknown. According to the published literature on SFG, neurological manifestations in Rocky Mountain spotted fever caused by *Rickettsia rickettsii* are not uncommon. There is a report of neurological manifestations in a series of dogs infected by *R. rickettsii*.[10] However, neurological manifestations of Mediterranean spotted fever are limited to case reports, and common neurological problems in these cases have been alterations of the level of consciousness, headache, and CSF abnormalities such as pleocytosis and increased protein levels suggestive of meningoencephalitis.[11–13] Some have reported ataxia and dysarthria. Similarly, a case of meningitis has been reported due to Japanese spotted fever.[14] In comparison, some patients in the current series had EEG changes compatible with encephalitis, whilst others had CSF changes. Computed tomography (CT) scans were done in only three patients, and one of these showed a cerebral infarction. However, the majority of patients had extrapyramidal manifestations along with an altered level of consciousness. Although magnetic resonance imaging (MRI) scans of the brain would have been more informative, none of the patients underwent an MRI scan of the brain due to limited availability.

In addition to neurological manifestations, all patients had a skin rash of varying severity and some patients developed a fern

Table 2
Clinical features and investigations of patients based on IFA titer levels

Parameter	Titer ≥1/256 (*n* = 10)	Titer <1/256 (*n* = 7)
Total duration of fever, days	12 (4–27)	17 (7–35)
Fever duration on admission, days	6 (3–12)	11 (3–30)
Radial pulse, per min	89 (72–100)	95 (78–120)
Systolic blood pressure, mmHg	116 (90–150)	126 (100–160)
Diastolic blood pressure, mmHg	76 (60–90)	78 (60–90)
ALT, U/l	82 (31–146)	85 (35–256)
AST, U/l	123 (53–222)	169 (18–520)
WBC, cells × 10^9/l	16 (5–34)	11 (3–34)
Platelets, cells × 10^9/l	97 (4–194)	120 (59–266)

IFA, immunofluorescent antibody assay; ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell count.

Table 3
Clinical details of definitive cases

Case No.	Age (years), gender	*R. conorii* IgG titer	Skin necrosis	Neurological examination	Details and outcome
1	62, F	1/2048	Pos	Drowsy, mask-like face, rigidity, tremors of hands and bradykinesia	Arthritis, cough, icterus, thrombocytopenia; poor response to chloramphenicol; recovered with doxycycline
2	62, F	1/4096	Neg	Confused, neck rigidity, rigidity, tremors of hands and bradykinesia	Generalized skin rash, mild thrombocytopenia, high liver enzymes, normal CSF, EEG – slow waves suggestive of encephalitis; recovered with chloramphenicol/doxycycline
3	66, M	1/4096	Neg	Confused, rigidity, tremors of hands and bradykinesia, tinnitus, deafness	Generalized skin rash, arthritis, thrombocytopenia, high liver enzymes, normal CSF, EEG – slow waves suggestive of encephalitis; recovered with chloramphenicol/penicillin
4	60, F	1/2048	Pos	Confused, neck stiffness, rigidity, tremors of hands	Rash on the legs and feet, arthritis, CSF – high proteins, 100×10^6 cells/l (80% neutrophils); treated with doxycycline/penicillin/cefotaxime; recovered
5	63, F	1/2048	Pos	Semi-comatose, neck stiffness, rigidity and tremors, reduced power of limb muscles	Skin rash on the limbs, abdominal pain, icterus, mild thrombocytopenia, EMG – normal, CSF – 10×10^6 cells/l (60% neutrophils); treated with chloramphenicol and ceftriaxone; recovered
6	33, M	1/4096	Pos	Semiconscious, neck rigidity, flaccid motor weakness of limbs suggestive of Guillain–Barré syndrome	Skin rash, developed hepatic failure, icteric myocarditis, respiratory failure and required assisted ventilation, EEG – normal, EMG – motor axonal polyneuropathy; treated with many antibiotics including chloramphenicol and doxycycline; complete recovery
7	65, M	1/256	Pos	Confused, rigidity, tremors of hands and bradykinesia, weak right arm	Skin rash, thrombocytopenia, CT brain – left cortical infarction; recovered with chloramphenicol
8	72, M	1/2048	Neg	Confused, abnormal behavior, rigidity and tremors in the hands	Skin rash over feet, hands, and chest, mild thrombocytopenia, CSF – 5×10^6 cells/l, high proteins; treated as meningoencephalitis; recovered
9	79, F	1/512	Neg	Confused, mask-like face, rigidity, tremors of hands and bradykinesia	Skin rash on feet, normal blood counts; recovered with chloramphenicol/doxycycline
10	55, M	1/1024	Neg	Confused, neck stiffness, photophobia	Generalized skin rash, facial puffiness and leg swelling, arthritis, EEG – slow waves suggestive of encephalitis; recovered with chloramphenicol/doxycycline

F, female; M, male; Pos, positive; Neg, negative; CSF, cerebrospinal fluid; EEG, electroencephalogram; EMG, electromyogram; CT, computed tomography.

leaf necrotic skin rash. The development of arthritis, conjunctival injection, and icterus were detected in some patients. Thrombocytopenia and leukocytosis were common hematological findings and some patients had raised liver enzymes. Similar manifestations have been reported in the published cases of spotted fever with neurological manifestations.[11–14] This evidence suggests that involvement of the nervous system in spotted fever is not an isolated event and it may occur with the other clinical manifestations of rickettsiosis. Susceptibility to cerebral involvement in spotted fever was not clear in this study, however most of our patients were over the middle age.

Pathologically, direct infection or toxins should be the reason for inflammatory lesions in the vascular endothelium. A necropsy study in 1974 found both gray matter and white matter necrosis, and another study involving two cases of South African tick bite fever found foci of vasculitis in the brain with mononuclear leukocyte cell infiltration in the blood vessel wall and perivascular space.[15–17] However, further studies are needed to determine the pathogen and host factors that are responsible for nervous system involvement.

During the last two decades many novel rickettsial agents have been isolated and characterized. The emergence or reemergence of rickettsial infection are occurring in many regions of the world, thus clinicians should be vigilant to detect novel clinical manifestations. With this report, we draw attention to the importance of neurological manifestations in spotted fever group rickettsioses. These presentations may be infrequent, but awareness is essential as early treatment is important to save lives. Thus, a strong clinical suspicion and the establishment of rickettsial disease diagnostic facilities in endemic areas are the key determinants in achieving this final goal.

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Conflict of interest: The authors declare that they have no competing interests.

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