

Epidemiological, Clinical and Laboratory Characteristics of 19 Serologically Confirmed Rickettsial Disease in Singapore

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ABSTRACT

Aim: To identify epidemiological, clinical and laboratory features of serologically-proven typhus in the local setting.

Method & Results: Retrospective study looking at rickettsial serologies done over a six-month period and collection of the epidemiological, clinical, laboratory and treatment response data from the case notes of the patients with an ordered rickettsial serology. Twenty of the 35 cases had a positive serology. Of these 20 patients, 18 were already clinically diagnosed as having murine typhus. All except one were males and all were migrant workers. Majority of the patients were construction workers staying in containers where rats abound. The most consistent clinical features were high fever (100%) for a median period of seven days, headache (94%) and cough (47%). The white cell count was usually normal (74%) but thrombocytopenia was common (68%). Transaminitis was also common (90%) with the AST component higher than the ALT in half of the cases. Response to doxycycline therapy was rapid and most (88%) were afebrile by 72 hours.

Conclusion: Typhus (notably murine type) can be confidently diagnosed from consistent clinical features supported by epidemiological and laboratory clues. Early recognition with the prompt treatment response will result in shorter hospital stay with decreased cost. Serological testing may only prove useful in difficult situations when the clinical diagnosis is less clear.

Keywords: rickettsial, typhus, murine, scrub

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INTRODUCTION

Rickettsial diseases are an important but often under-recognised cause of febrile illness locally. Of the wide range of rickettsial diseases, typhus disease is the most commonly recognised entity in South East Asia. Several reports from Thailand described the common occurrence of the disease including a report identifying

both scrub and murine typhus as a significant cause of obscure fever in 320 children⁽¹⁾. Although murine typhus is endemic in South East Asia, it is known to occur worldwide. In Europe, authors in Spain reported murine typhus to be the cause in 6.7% of 926 cases of fever of intermediate duration⁽²⁾.

In Singapore, six cases of murine typhus occurring within a period of three months were reported by Loh KC et al in 1996⁽³⁾. The high incidence rate among migrant workers was described. Their study underscored the importance of recognising this not infrequent and readily treatable febrile illness locally.

The objective of our study was to identify epidemiological, clinical and laboratory features of typhus disease in the local setting, using indirect immunoperoxidase (IIP) as the gold standard for diagnosis. Based on our findings, we will also suggest a pragmatic approach to the management of cases of suspected typhus disease.

METHODS

Selection of cases

This is a retrospective study looking at patients for which rickettsial serology was performed at the Communicable Diseases Centre in Singapore for a period of six months from Jan 1999 to June 1999. All subjects had a blood specimen sent for rickettsial serology by indirect immunoperoxidase technique (IIP). This was used as the confirmatory laboratory test for clinically suspected typhus disease. Epidemiological information and clinical parameters of those confirmed with typhus disease by a positive result for IIP were analysed.

Data collection

A total of 35 patients with an ordered rickettsial serology were identified. Epidemiological and demographic data on sex, age, country of origin, type of accommodation, occupation and history of exposure to rats were recorded. Clinical parameters included presence and duration of fever, headache, cough and a visible rash. Laboratory tests including full blood count and liver function tests and other

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serological tests such as Weil Felix (WF) serology, Dengue serology and Rickettsial serology (using IIP) were recorded. Treatment response was measured in terms of hours taken for patients to become afebrile after starting oral doxycycline.

Laboratory test - indirect immunoperoxidase

In this study, diagnosis of typhus disease was based on a positive indirect immunoperoxidase (IIP) test. The IIP kits were supplied by the US Army Research Unit, Institute of Medical Research, Kuala Lumpur, Malaysia. The control sera provided with the kits were run in each batch of tests performed and expected values were obtained. The methodology was according to the instructions given by the manufacturer. A modification of the method described by Suto⁽⁴⁾ has been incorporated into this slide based indirect immunoperoxidase technique. Antigens used were prepared from *Rickettsia tsutsugamushi*, as well as the species that cause tick typhus and murine typhus. These are the species that have been described as being endemic in neighbouring Malaysia⁽⁵⁾. In accordance with the manufacturers' instructions, results were considered to indicate recent infection when either (a) IgM was detected; (b) a single IgG titre equal to or more than 400; or (c) when there was a four fold rise in titre over 10 - 14 days. The known sensitivity for this test is about 95%.

RESULTS

A total of 35 patients with a rickettsial serology were identified from Jan 1999 to June 1999.

Of the 35 patients, typhus disease was the primary clinical diagnosis in 23 cases, of which only five were not serologically confirmed by a positive IIP test. Twenty of the 35 patients have a positive serology (including the 18 cases where the primary clinical diagnosis was typhus). IgM was positive (with or without IgG >400) in 18 cases, and IgG 2400 without a positive IgM in two cases. One patient who had concomitant positive Dengue IgM serology was excluded from further analysis.

Analysis on these 19 patients with serologically-proven typhus was carried out. Of these, 13 were serologically positive for murine typhus, three were positive for scrub typhus, and three were serologically positive for both scrub and murine typhus. The clinical diagnosis of the other 15 cases with negative IIP included five cases clinically diagnosed as having typhus disease. Another five were diagnosed as dengue fever, four of which were serologically confirmed. The last five cases were diagnosed variously as rubella, viral fever, sepsis of unknown origin, fever for investigation and pyrexia of unknown origin.

Table I. Epidemiological characteristics of serologically confirmed cases of typhus.

	Stay in containers	Work in construction	Exposed to rats
* Valid cases	15	19	17
All cases	93% (14)	95% (18)	88% (15)

* Cases with missing records excluded from analysis.

Table II. Laboratory features (n=19).

Full Blood Count	Range	Median			
White cells ($\times 10^9/L$)	2.6 – 10.5	5.9	<4.0 15.8% (3)	4.0 – 10.0 73.7% (14)	>10.0 10.5% (2)
Polymorphs (%)	30 – 80	63	<40 10.5% (2)	40 – 70 78.9% (15)	>70 10.5% (2)
Platelets ($\times 10^9/L$)	85 – 480	114	<100 36.8% (7)	101 – 140 31.6% (6)	>140 31.6% (6)
Liver panel	Range	Median	Normal	Borderline	>3x ULN
ALT (U/L)	22 – 329	97	7 – 36 10.5% (2)	37 – 107 57.9% (11)	≥ 108 31.6% (6)
AST (U/L)	30 – 222	88	15 – 32 15.8% (3)	33 – 95 47.4% (9)	≥ 96 36.8% (7)
				Yes	No
AST > ALT				52.6% (10)	47.4% (9)

Table III. Response to doxycycline (n=17).

	Within 24 hrs	>24 – 48 hrs	>48 – 72 hrs	>72 hrs
Frequency % (n=17)	17.6% (3)	52.9% (9)	17.6% (3)	11.8% (2)
Cumulative %	17.6%	70.6%	88.2%	100%

Epidemiological and demographic characteristics

There was a male predominance with only one female in our series of 19 cases. All were non-Singaporeans and most (68%) came from India. Their age ranged from 21 to 45 years with a mean of about 30 years.

It is noteworthy that the characteristic epidemiology is that of a construction worker staying in a container, with a history of exposure to rats. Of the 19 serologically positive cases of rickettsial disease, only one was not a construction worker (he worked as a carpenter). While the information about accommodation and exposure to rats was less complete, amongst the valid cases, only one did not stay in a container and only two denied exposure to rats. Information on flea bites was not routinely recorded in case sheets.

Signs and symptoms

Fever was a consistent feature (100%) with a median duration of seven days at presentation, and ranged

from two to 17 days. The maximum temperature recorded ranged from 37.2 to 40.2°C, with a mean of 39.1°C. Other common symptoms included headache (94.4%) and cough (46.7%). A visible rash was recorded in only 11.8%. No eschar characteristic of scrub typhus was recorded in any of the cases.

Laboratory features

The leukocyte counts and granulocyte proportion were usually normal (73.7% and 78.9% respectively). Leukopenia and mild leucocytosis were seen in 15.8% and 10.5% respectively. Thrombocytopenia with platelet counts below $140,000 \times 10^9/L$ was noted in 13 (68%) patients. Elevation of transaminases was noted in 17 (90%) subjects (Table II). The AST was higher than ALT in 52.6% (Table II).

Results of WF were available in 18 subjects. Of these, only 50% were positive for WF. Interestingly, none was positive to OX-K, which is used as a surrogate marker for diagnosing scrub typhus. The two serologically diagnosed cases of scrub typhus were instead positive for OX-19, which is the surrogate marker for murine typhus. Only one positive WF serology was not positive for typhus disease by IIP.

Response to treatment

Seventeen out of the 19 subjects were started on a therapeutic trial of doxycycline (100 mg bd for one week). Resolution of fever on the initiation of doxycycline was rapid, and frequently occurred between 24 to 48 hours (52.9%). Fifteen of the 17 valid cases (88%) had resolution of fever by 72 hours (Table III). The remaining two cases also achieved fever lysis by discharge, but the fever lasted for six days in one case. Two of the serologically positive subjects did not receive doxycycline during their admission. One case had doxycycline given prior to admission. The other case was misdiagnosed as pyelonephritis.

Five cases diagnosed clinically to have typhus were not confirmed serologically. Amongst the five, the diagnoses were supported by a positive WF serology to OX19 in one case. Rapid lysis of fever (within 48 hours) upon initiation of doxycycline was also seen in four of the five cases.

DISCUSSION

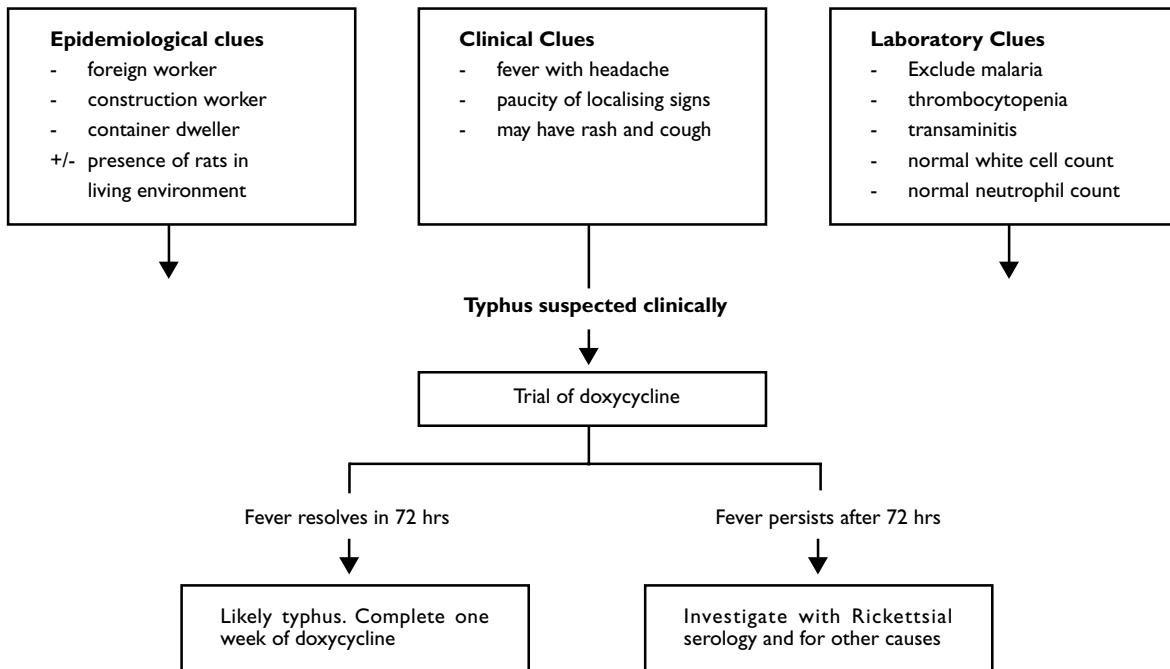
Our study shows that typhus (both murine and scrub) is endemic in Singapore. They are not rare as we recorded a total of at least 19 serologically proven cases over a six-month period. Moreover, as the sensitivity of IIP and WF is not absolute, four of the five non-serologically proven cases could very well be murine typhus from the consistent clinical features and

response to empirical doxycycline. In addition, we also showed that the disease could be reliably diagnosed based on epidemiological, clinical, laboratory features and response to doxycycline. In 18 out of the 20 serologically proven cases, murine typhus was the primary clinical diagnosis. In contrast, of the 12 cases for which murine typhus was a differential diagnosis, serology was only positive in one of these cases.

The epidemiologic importance of typhus disease as a cause of febrile illness in this region has been highlighted in several papers from Thailand⁽¹⁾ and neighbouring Malaysia^(5,6). However, in spite of the last article published by our CDC in 1996⁽³⁾, the disease remains largely an under-recognised cause of febrile illnesses locally. This infection is routinely reported to the Ministry of Environment (notifiable under "others") by our staff and vector (rat) control is often carried out at the worksites where the infection originated (Goh KT personal communication). Important epidemiological features were recognised in this study. Firstly, all 19 serologically confirmed cases in this series were foreign workers. However, it must be noted that this disease is not exclusive to foreign workers as the authors have diagnosed cases of murine or scrub typhus in Singaporeans with occupational or recreational epidemiological risks. Secondly, 90% of our patients worked in the construction industry and stayed in containers. Lastly, almost all had noticed the presence of rats in their living environment. Flea bites are rarely reported as the bites are usually not apparent.

The classical triad of typhus disease that has been described is fever, headache and a rash. Other common symptoms that have been reported are generalised body aches, cough and gastrointestinal complaints^(2,7,8). Fever was the most consistent feature in this cohort and approximately 70% of them had fever for more than five days at presentation. Headache was the second most common symptom and was reported in close to 95% of the cases. But rash was only noted in 11.8% of subjects. This finding concurs with Dumler et al who noted that the classical triad served limited usefulness in early diagnosis because only a low percentage had a rash on admission⁽⁷⁾. It should also be noted that in our study, the rash might not be apparent as majority of the cases have a dark complexion. Important laboratory clues of typhus disease were a normal total white and differential granulocyte proportion, as well as thrombocytopenia and the presence of mild transaminitis. Noteworthy was the fact that AST was higher than ALT in about half of the cases, indicating muscle involvement in addition to the effects of the disease on the liver.

Fig. 1 Pragmatic approach to diagnosing rickettsial disease.



The clinical features and laboratory findings of typhus in Singapore as described above therefore mimic dengue fever, which is a much more common infection here. Therefore, physicians should be wary of typhus in cases of suspected dengue virus infection when the fever becomes persistent. A Mexican study reported that IgM antibodies to rickettsiae were found in 40% of 50 patients clinically diagnosed to have dengue fever but who had no dengue antibodies⁽⁹⁾. In the local context, there is a high possibility that typhus is also commonly misdiagnosed initially as dengue fever because of the overlapping clinical features of fever, headache and a rash, together with the common occurrence of thrombocytopenia which is seen in close to 70% of our patients with typhus.

Clinical suspicion of typhus disease can now be confirmed by slide based indirect immunoperoxidase (IIP) technique, which has superseded the Weil Felix (WF). IIP has been verified by Kelly D. J. et al⁽¹⁰⁾ for scrub typhus. It has sensitivity in excess of 95% for both IgG (at a dilution of 400) and IgM. For the IgG test for *R. typhi*, there can be false positives with *Proteus* and Rheumatoid factor positive sera, but notably there are no reported cross-reactivity with dengue virus, typhoid and malaria, which are the common differential diagnoses. There is known serological cross-reactivity^(10,11) between rickettsial species, however, which may explain why some of our cases were positive for both murine and scrub typhus. In addition, there are epidemiological grounds for believing that the cases positive for scrub typhus by IIP

in our series may actually reflect cases of murine typhus. Scrub typhus is caused by infection with *Rickettsia tsutsugamushi* that shares an antigen with *Proteus* OX-K. The organism is transmitted by the bite of larval trombiculid mites and is characterised by the presence of eschar and regional lymphadenitis. It is the authors' experience that scrub typhus is much less common than murine typhus in Singapore; and in those cases, eschar is often observed.

However, as treatment for these two diseases are similar, the failure of IIP to distinguish the two does not significantly negate its usefulness. But while the IIP is sensitive and specific for typhus disease, it is hampered by the complexity of the test and its cost. A control sera is used every time the test is run, and for practical reasons, the test is only done in batches in low demand areas like Singapore, resulting in a late report from the laboratory. For these reasons and the fact that typhus could be reliably diagnosed clinically as shown in this study, the authors do not advocate routine serological testing when the clinical diagnosis is clear.

Weil Felix (WF) test, on the other hand, which has been in use for a long time, is known to lack both sensitivity and specificity in diagnosing typhus disease. This study confirms the finding of earlier studies on the disappointing sensitivity of WF serology^(2,12).

Once diagnosed, however, typhus is eminently treatable. Tetracycline remains the treatment of choice⁽¹³⁾. Silpapojakul et al in Thailand reported that 79% of their cases were afebrile 48 hours after starting treatment with doxycycline, compared with only 29%

of the untreated group⁽⁸⁾. In concurrence with their findings, fever in our subjects resolved quickly with treatment, hence, a therapeutic trial of doxycycline may serve as a quick and effective diagnostic tool in clinically suspected typhus disease. At 72 hours after starting appropriate therapy, close to 90% of our cases had resolution of fever.

We therefore believe a therapeutic trial of doxycycline to be a safe and accurate diagnostic tool. Definitive diagnosis may not be reached as sensitivity of the IIP test is not perfect (verified at about 95%) and some cases may have presented earlier than seroconversion (paired serology was not done in our particular study for practical reasons). We note that, of the five cases of clinically diagnosed typhus with negative IIP, four cases showed quick resolution of fever with doxycycline. They may indeed have been cases of typhus disease.

Taking into consideration all of the factors discussed above, the authors would like to propose a pragmatic approach towards patients suspected of typhus disease (Fig. 1). Doxycycline should be offered to patients suspected of typhus disease after considering the appropriate epidemiology, clinical presentation and supportive basic laboratory markers. If the fever persists into 72 hours of doxycycline treatment, this atypical feature would indicate the need of further work-up for causes of pyrexia, including a rickettsial serology. One major advantage of this approach is cost effectiveness. A therapeutic course of doxycycline costs less than S\$1 as compared to S\$30 per rickettsial serology test using IIP. In addition, such an approach cuts short the clinical course of the disease, which while usually benign, has been known to result in serious complications. These include hepatic⁽¹⁴⁾ and renal^(2,7,8,15) failure, aseptic meningitis and encephalitis^(7,16), and pneumonitis with respiratory failure^(2,7). Mortality has been documented in other series^(2,7,8,14,16). All our 20 serologically confirmed cases, however, were discharged without any complications. Aside from the potential mortality and morbidity, rapid treatment of this disease also returns patients to work earlier.

While our study demonstrated the essential epidemiology and clinical features of typhus disease, it was hampered by several factors. Firstly, there has actually been no gold standard established for diagnosing murine typhus, which consists the bulk of our cases. While the IIP method used here has been verified for scrub typhus⁽¹³⁾, we know of no publications on its sensitivity and specificity in murine typhus. Moreover, cases diagnosed as typhus clinically but with a negative serology should have had a paired serology done to increase our diagnostic sensitivity.

As it was a retrospective study, data on epidemiological and clinical features in some cases were incomplete. We were also unable to ascertain if there were any case clusterings in our study as the addresses in the case records may not represent the construction sites that these patients reside in. There were also no pre-established clinical criteria to determine which patients should have a rickettsial serology performed. It would be useful to compare serologically proven cases of typhus against other febrile illnesses with overlapping clinical features. However, in this study, the serologically negative cases were too diverse to allow any meaningful analysis.

A prospective study on febrile illnesses presenting to our centre is underway. Some of the unanswered questions in this study may be addressed. There is also a possibility that the dot-ELISA test may supersede indirect immunoperoxidase and the Weil Felix tests as the diagnostic tool of choice for quick and accurate serological confirmation of typhus disease^(6,17).

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