

Endemic Typhus in Singapore – A Re-Emerging Infectious Disease?

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ABSTRACT

Singapore is a modern urban city and endemic typhus is thought to be a disease of the past. This may be due to lack of specific serological testing as indirect immunoperoxidase testing using specific rickettsial antigens (U.S. Army Medical Research Unit, Institute of Medical Research, Kuala Lumpur, Malaysia) has only recently become available. In the last fourteen months, twenty-one cases of endemic typhus were diagnosed in patients hospitalised for acute febrile illnesses at the National University Hospital. We conducted a case control study to define the clinical and laboratory features of endemic typhus in Singapore.

Method: Demographic, clinical and laboratory data were reviewed for cases and twenty-one age and sex matched controls who had negative serologic tests as part of a work-up for fever of unknown origin.

Results: Apart from a higher initial temperature (39°C vs 37.9°C (p<0.001)) and ALT (p=0.002), cases and controls had similar presentations of fever, myalgia, headache, cough, normal WBC and platelet counts. Singapore residents and migrant workers were represented in both groups (p=ns).

Conclusion: Endemic typhus remains an important cause of acute febrile illness in Singapore in both the local and migrant worker populations. The presentation is similar to other causes of acute febrile illnesses and the diagnosis will be missed unless it is specifically sought.

Keywords: endemic typhus, rickettsial disease, fever of unknown origin

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INTRODUCTION

Endemic (murine) typhus is a common cause of febrile illnesses in South East Asia⁽¹⁻⁶⁾. Caused by infection from *Rickettsial typhi*, endemic typhus is transmitted via peri-domestic rats and flea vectors. As Singapore is a modern urban city with a high standard

of public health, typhus was considered a disease of the past⁽⁷⁾. However with the introduction of specific rickettsial serology tests in 1998, the disease has been increasingly recognised as an important cause of febrile illnesses in Singapore. In a period of 14 months, 21 cases of endemic typhus were diagnosed in patients hospitalised for acute febrile illnesses at the National University Hospital. We conducted a case-control study to define the clinical and laboratory features of endemic typhus in Singapore.

PATIENT AND METHODS

Between January 1999 and February 2000, 21 cases of endemic typhus were diagnosed at the National University Hospital, Singapore. The National University Hospital is an urban 1,000-bed tertiary care hospital. A retrospective chart review of all confirmed cases of endemic typhus was conducted. Laboratory-confirmed cases were defined by a positive IgM serology on indirect immunoperoxidase testing using specific rickettsial antigens (U.S. Army Medical Research Unit, Institute of Medical Research, Kuala Lumpur, Malaysia) and a compatible clinical presentation. Demographic, clinical and laboratory data were reviewed for cases and 21 age and sex matched controls selected from among inpatients who had negative specific rickettsial serologic tests as part of a work-up for acute febrile illnesses. Data on presenting symptoms, initial physical findings and laboratory data were collected for all cases. Statistical analyses were performed using student t-test and Fisher's exact test for significance as appropriate.

RESULTS

Twenty-one cases of endemic typhus were diagnosed between January 1999 and February 2000. The demographic data and clinical features of both cases and controls are shown in Table I. The mean age of cases was 38 ± 14 years with men (n = 18) comprising the majority of cases. Singaporeans accounted for seven cases (33%), Bangladeshi nationals for seven (33%), Malaysians for three (14%) and Indonesians for three (14%); One patient was from the United

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Table 1. Features of Endemic Typhus in Singapore - compared with other acute febrile illnesses.

	Cases	Controls	P-value
Number	21	21	
Sex, M:F	18:3	18:3	1.0
Age, mean \pm SD	38.2 \pm 14.3	37.9 \pm 14.2	0.98
Nationality			
Singaporean	7	12	Singaporeans vs Non-Sing 0.21
Bangladeshi	7	2	Bangladesh vs Rest 0.13
Malaysian	3	0	
Others	4	7	
History of fever, %	90	76	0.41
Myalgia, %	43	19	0.10
Headache, %	29	24	1.0
Abdominal Pain, %	24	24	1.0
Cough, %	43	29	0.52
Initial Temperature, $^{\circ}$ C	39.0 \pm 1.0	37.9 \pm 1.2	0.002
Pulse/min	98.9 \pm 14.6	91.2 \pm 22.3	0.21
Mean Arterial Pressure, mmHg	86.8 \pm 14	91.0 \pm 15	0.36
Rash	2	2	1.0
Initial WBC, $\times 10^9$ /L	8.9 \pm 2.8	8.7 \pm 4.3	0.88
Initial ALC,	1.7 \pm 0.9	1.5 \pm 0.7	0.53
Haemoglobin, g/dL	13.5 \pm 1.7	13.2 \pm 2.0	0.70
Platelet Count, $\times 10^9$ /L	264 \pm 101	239 \pm 100	0.44
Creatinine, μ mol/L	83.1 \pm 13.8	84.6 \pm 16.2	0.76
Albumin, g/L	35.3 \pm 7.4	38.6 \pm 8.0	0.18
Glucose, mmol/L	5.3 \pm 1.9	6.8 \pm 3.3	0.09
ALT, u/L (N < 70)	86.3 \pm 77.1	45.5 \pm 27.7	0.03
AST, u/L (N < 50)	91.0 \pm 65.7	38.6 \pm 19.6	0.002

Kingdom. There was no seasonal or geographical clustering of cases. No patient had documented flea bites. Eighteen patients had been resident in Singapore for at least three months prior to admission with no recorded recent travel history. Two cases had visited Malaysia and one case had travelled to India just prior to admission. Nine of the cases (43%) had associated myalgia. A similar percentage had concomitant cough. Six cases (29%) had associated headache. Rash was not a prominent sign with both cases and controls having similar incidences (n = 2, 10%). The rashes seen in these cases were maculopapular in nature. One case had documented hepatomegaly with no splenomegaly. No other significant physical abnormalities were recorded for the remaining cases. Initial presenting mean arterial pressure was not significantly different between cases and controls (86.7 vs 91 mmHg, p = 0.35). All patients had documented fevers with the average temperature of

cases significantly higher than controls (39.0 $^{\circ}$ vs 37.9 $^{\circ}$, p<0.005). No difference in initial heart rates was seen in both groups. Presenting total white cell counts were not significantly elevated in either group (8.9 vs 8.7, p = 0.88) as with absolute lymphocyte counts (1.7 vs 1.5 cells $\times 10^9$ /L, p = 0.53). Anaemia was not a prominent feature amongst cases with average haemoglobin levels of 13.4 g/L (versus 13.2 g/L in controls, p = 0.70). Liver transaminases were significantly more elevated (ALT 86 vs 46, P = 0.03; AST 91 vs 39, P = 0.002) in cases than in controls.

DISCUSSION

Endemic typhus is a common cause of febrile illness in South East Asia^(1-6,8,9) especially in regions with inadequate vector and reservoir control^(4,5,10). Duffy et al reported that of Khmer refugees in shelters at the Thai-Cambodian border with unexplained fever, 70% had endemic typhus⁽⁵⁾. In Singapore, the disease

has previously been reported amongst migrant foreign construction workers whose temporary living quarters are often crowded, unhygienic and rodent infested⁽⁷⁾. The disease has not commonly been reported outside of this category. Although migrant foreign workers formed a large proportion of cases in this series (47%), local Singaporeans represented fully one-third of cases. This finding is surprising, given the high standard of living and public hygiene Singaporeans enjoy. However, it should be noted that the rodents and the vector fleas are unable to distinguish between foreign workers living in cramped containers and affluent Singaporeans living next door. Endemic typhus had been considered a disease of the past, but given these findings, could it represent a re-emerging disease or simply be a result of better diagnostic methods? We believe the latter to be more likely. Failure to diagnose this disease can be attributed to a number of complex considerations, the two most important of which being the non-specific presentation of the disease, as well continued dependence upon traditional Weil-Felix serologic testing. The diagnosis is also one that is considered less readily, given its perceived infrequency and its protean presentations as illustrated by our study.

In this study, our patients did not differ substantially in initial presentation from previous reports^(9,11,12). The frequency of symptoms in both cases and controls was not statistically different to allow differentiation of endemic typhus from other causes of acute febrile illnesses. The presentation of the disease is classically non-specific. The triad of fever, rash and headache has been often identified as a potential indicator of rickettsial infection and a diagnostic clue for endemic typhus^(11,13,14). However, headache was noted in only 29% of patients in this series and even fewer with a rash (10%). The most frequently reported findings in a series by Dumler et al from South Texas were fever (96%), severe headache (45%), chills (44%), myalgia (33%) and nausea (33%)⁽¹¹⁾. In a review of 137 cases of endemic typhus in Thailand, Silpapojakul reported abdominal pain in 15 patients (11%) with nausea and vomiting in 42 (31%)⁽⁹⁾. Cough was also noted in up to 35% of patients⁽¹¹⁾.

The rash of endemic typhus is not a frequent physical finding. In this study, two patients (10%) had documented maculopapular rash with rash being the initial presenting symptom for one case. Silpapojakul reported a rash in 20% of patients at presentation, predominantly maculopapular in appearance⁽⁹⁾. In two reviews of 80 and 200 endemic typhus patients in Texas, rash was noted in slightly over 18% at presentation and over 50% throughout the course of illness^(11,12). Petechiae are noted in

less than ten percent of cases⁽¹¹⁾. The distribution of the rash is predominantly truncal (88% of cases) although lesions involving the extremities are frequent⁽¹¹⁾. Furthermore, because the development of rash occurs later in the course of disease, its utility as a diagnostic clue is limited in early disease presentation.

The mean initial presenting temperature of cases in this series was significantly higher than controls (39.0° vs 37.9°, $p < 0.005$). Although very high fevers, $>40^{\circ}\text{C}$ are uncommon in adults, this feature adds little clinical discriminatory value as malaria and other infections are also associated with very high temperature. Hepatic enzyme elevations are the most common laboratory abnormality seen in patients with endemic typhus^(11,15,16). In this study, a mild to moderate transaminitis was noted in 15 of 21 cases (71%). Aspartate transaminase was significantly more elevated in cases than in controls (91 vs 38 units/L, $p < 0.05$). Alanine transaminase levels paralleled that of aspartate transaminase and were also significantly elevated compared to controls ($p < 0.05$). These findings are consistent with rickettsial-induced hepatitis as described by other authors⁽¹⁵⁾. Average haematological parameters between cases and controls did not differ to a large extent; Leukocyte counts, platelet and haemoglobin levels were not significantly different between groups. Although some patients may have a mild early leukopenia and mild leukocytosis in later stages, most patients have leukocytes within the normal range^(11,13) as was seen in this case series. Dumler et al in his report of patients with endemic typhus, noted hypoalbuminemia in 90% of patients. Although the average albumin level amongst our cases was lower than controls, it did not reach statistical significance.

The Weil-Felix test has long been the established diagnostic test for rickettsial disease in Singapore. However, it has been shown to be inaccurate in rickettsial disease serodiagnosis^(8,17). It yields false positive results with leptospirosis, malaria, *Proteus* infections and other febrile illnesses^(8,17). In addition, the *Proteus* OX-19 antibody used to diagnose endemic typhus is also raised in other rickettsial infections such as tick typhus, epidemic typhus and Rocky Mountain spotted fever. It has largely been supplanted by more sensitive serologic tests that utilise specific *R.typhi* antigens such as indirect fluorescent antibody, latex agglutination or solid-phase immunoassay^(16,17). Our institution recently introduced rickettsial specific indirect immunoperoxidase testing developed by the US Army Medical Research Unit in Malaysia as an adjunct to rickettsial disease diagnosis. This test has been shown to be both more sensitive and specific than the traditional Weil-Felix test^(18,19). All cases in this report were diagnosed by the former method.

With the availability of this more accurate test, we believe more cases of endemic typhus are being diagnosed in patients with undifferentiated acute febrile illnesses at our institution.

Exposure to known vectors of endemic typhus is necessary for inoculation of the etiologic agent *R.typhi*. The role of domestic rats and their fleas as vectors of endemic typhus is well documented. However, the history of exposure to fleas or implicated mammalian hosts of flea is often very low⁽¹¹⁻¹⁴⁾. Although no history of fleas bites was obtained in patients in this series, rat exposure either in the domestic or work environment was noted in a number of cases. This was seen in both local Singapore residents and foreign migrant workers. Living quarters for the latter are often crowded and rat-infested⁽⁷⁾. Local Singapore nationals reported rat exposure more commonly at the work place than in the peridomestic area. The importance of the cat flea, *Ctenocephalides felis*, has recently been recognised as a vector of a new rickettsial agent, *Rickettsia felis*. The latter is a significant cause of flea-borne typhus in some regions of Texas and southern California^(12,20,21). The role of the cat flea as a vector of disease has not been established in Singapore nor in South-East Asia.

Travel history was significant in only three cases in this series; their infection was most likely acquired during their foreign travel as their symptom onset was within days of their return. All cases were to countries within Asia where endemic typhus is prevalent^(20,22). The disease is found worldwide and is especially prevalent in temperate and subtropical seaboard regions where rat reservoirs and flea vectors are found^(20,22). It is a diagnosis that must be considered in tourists returning from endemic regions and presenting with a febrile illness^(23,24). However, the vast majority (18 of 21) of our patients acquired their infections in Singapore suggesting that a negative travel history certainly does not exclude the diagnosis.

Endemic typhus is a common and under-recognised zoonosis. Its diagnosis remains largely clinical. Because of its non-specific presentation, lack of distinguishing physical and laboratory finding, diagnosis is difficult in the absence of high clinical suspicion and appropriate diagnostic testing. The diagnosis will certainly be missed unless specifically looked for. As demonstrated by this series, endemic typhus remains an important cause of acute febrile illnesses in both locals and

foreign nationals of modern urban Singapore. Improved diagnostic methods have allowed for greater appreciation of the prevalence of this disease.

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