

Acute fulminant myocarditis in scrub typhus

REKWAN SITTIWANGKUL, YUPADA PONGPROT, SUCHAYA SILVILIARAT,
PENINNAH OBERDORFER*, PODJANEE JITTAMALA* &
VIRAT SIRISANTHANA*

Cardiology Unit and *Infectious Diseases Unit, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

(Accepted February 2008)

Abstract Scrub typhus is a zoonotic disease caused by *Orientia tsutsugamushi* in which humans are accidental hosts. It is a febrile illness which is confined to rural Asia and the Western Pacific islands. Severe complications are very rare. We report four cases of acute fulminant myocarditis in children with scrub typhus. This complication led to severe cardiogenic shock and death in two of them. We believe this is the first report of fulminant myocarditis complicating scrub typhus in children.

Introduction

Scrub typhus is a common zoonotic disease of rural Asia and the Western Pacific islands.¹ The causative agent, *Orientia tsutsugamushi*, is transmitted by the larvae of trombiculid mites (chiggers). In Thailand, scrub typhus is considered one of the most common causes of obscure fever in children.^{2–4} Eschar is found in 7–75% and complications usually develop after the 1st week of illness. Common complications include pneumonitis and meningo-encephalitis. Other uncommon fatal complications include acute respiratory distress syndrome, septic shock and acute renal failure.^{1–4} Cardiac involvement is not common and is usually not serious. Minor electrocardiogram (ECG) abnormalities such as non-specific ST segment, T-wave changes and

premature ventricular contractions have been reported in adults.^{5,6} There are few reports of myocarditis caused by scrub typhus in the English literature.^{7–9} Scrub typhus myocarditis is usually not life-threatening and, as far as we are aware, has not been described in children. We therefore report four children with acute fulminant myocarditis caused by scrub typhus who presented with fever and cardiogenic shock.

Subjects and Methods

This study was conducted at Chiang Mai University Hospital. The medical records of all children (age <15 years) with scrub typhus between October 2005 and September 2007 were reviewed and four cases of myocarditis were identified. The diagnosis of scrub typhus was confirmed either by a single indirect immunofluorescent antibody (IFA) titre against *O. tsutsugamushi* of >1/400 or a fourfold or greater rise in IFA titre to at least 1/200.¹⁰ The IFA test for antibodies against *O. tsutsugamushi* was performed using standard methods at

Reprint requests to: Dr Rekwang Sittiwangkul, Department of Pediatrics, Faculty of Medicine, Chiang Mai University, Chiang Mai, 50200, Thailand. Email: rsittiwa@mail.med.cmu.ac.th; fax: +66 53 946461.

Chiang Mai University Hospital.^{10,11} The antigens used were pooled Karp, Kato and Gilliam strains of mouse fibroblast cells (L 929)-propagated *O. tsutsugamushi* prepared at the Department of Medical Sciences of the Ministry of Public Health. The fluorescein conjugates used were rabbit anti-human Igs G and M (Dakopatts, Glostrup, Denmark, codes F 202 and F 203). Serum samples were tested at dilutions of 1/50, 1/100, 1/200, 1/400, 1/800 and 1/1600.¹²

Evaluation of cardiac status included chest radiograph, ECG and echocardiogram. Biochemical cardiac markers including creatine kinase-MB, cardiac troponin T and N-terminal pro-brain natriuretic peptide (NT-proBNP) were tested using standard methods previously described.¹³ Acute fulminant myocarditis was defined as (i) severe haemodynamic compromise requiring a vasopressor (≥ 5 $\mu\text{g}/\text{kg}/\text{min}$ of dopamine or dobutamine) or intra-aortic balloon pumping, and (ii) left ventricular dysfunction by echocardiography without a history of previous cardiomyopathy.¹⁴

Results

Of the nine serologically confirmed cases of scrub typhus, four had acute fulminant myocarditis. The demographics, clinical characteristics and outcome are shown in Table 1. All were referred to the hospital's cardiac intensive care unit. Two children had eschars. Signs and symptoms of myocarditis occurred on days 7–9 of fever. All had a fulminant course of myocarditis, demonstrated by severe hypotension, and required multiple vasopressor drugs or aggressive mechanical cardiac support. They received intravenous anti-rickettsial antibiotic (chloramphenicol) on days 7, 7, 7 and 10 of fever, respectively. Two children who developed hypotensive episodes died before scrub typhus was diagnosed (cases 1 and 4). One child (case 4) also had disseminated intravascular clotting and severe liver involvement.

The diagnosis of scrub typhus was made by a fourfold or greater rise in IFA titre against *O. tsutsugamushi* in two children who survived. The other two, who died within a few days of collecting the first blood sample, had a single IFA titre of $>1/400$ against *O. tsutsugamushi*. Blood cultures of all the children were negative and serological tests for dengue infection and leptospirosis showed no evidence of either.

Despite aggressive cardiac support and appropriate antibiotic treatment, two patients died. The cause of death was severe left ventricular dysfunction resulting in irreversible cardiogenic shock and refractory ventricular tachycardia. Autopsies were not performed. The two children who survived received anti-rickettsial antibiotic therapy for 2 weeks in total.

The reason why only nine cases of scrub typhus were seen during the study period is because Chiang Mai University Hospital is a tertiary referral hospital. Most cases of scrub typhus are treated in community or provincial hospitals and only cases with severe complications are referred to our hospital.

Discussion

We have described four cases of acute fulminant myocarditis in children with scrub typhus. All presented in the October and November of 2005 and 2006, the months of peak incidence of scrub typhus in this area.² All were referred from hospitals in the wide catchment area of our university hospital. Three children received anti-rickettsial antibiotics after they developed hypotensive episodes and after the suspected diagnosis of scrub typhus had been made. The delay in specific rickettsial treatment might have increased the severity of myocarditis which caused the death of two children. The finding of eschar in two cases was similar to the findings in case series studies in northern Thailand where 68–75% of cases had eschar.^{2–4} Thrombocytopenia occurred in only 27% in one case series study²

TABLE 1. Demographic, clinical characteristics and outcome.

	Case 1	Case 2	Case 3	Case 4
Month/year of admission	October 2005	October 2005	November 2005	November 2006
Age (yr), gender	12, F	14, M	11, F	10, M
Days of illness at a myocarditis episode	7	8	8	9
Other signs/symptoms	Cough, dyspnoea	Headache, drowsiness	Headache, abdominal pain	Jaundice, hepatomegaly
Eschar lesion(s)	A few	One	None	None
Haematological parameters				
Haematocrit (%)	32.8	25.7	40	18
WBC (/mm ³)	3900	8300	8980	12,900
Platelet count (/mm ³)	25,000	47,000	39,300	55,000
<i>O. tsutsugamushi</i> IFA titre				
Blood sample 1 (days of fever)	IgM 1:800, IgG 1:1600 (7)	IgM 1:800, IgG 1:200 (7)	IgM 1:200, IgG 1:400 (8)	IgM > 1:400 (10)
Blood sample 2 (days of fever)	-	IgM 1:1600, IgG 1:3200 (14)	IgM 1:400, IgG 1:1600 (14)	-
Cardiac parameters				
Chest radiograph	CTR 60%, mild venous congestion	CTR 65%, bilateral pulmonary infiltration, pleural effusion	CTR 45%	CTR 60%, venous congestion
Electrocardiogram	Low voltage, ST-T changes, wide QRS, PVCs, ventricular tachycardia	Low voltage, ST changes, PVCs	ST-T changes, prolonged PR	Low voltage, ST-T changes, ventricular tachycardia
Echocardiogram	Mild LA & LV dilation, EF 45%	Mild LA & LV dilation, EF 26%	EF 37%	Mild LA & LV dilation EF 36%, pericardial effusion 42.3
Creatinine kinase-MB (normal 0.63–5 U/L)	6.9	37	21	0.065
Cardiac troponin-T (normal <0.01 ng/ml)	0.05	<0.01	0.036	>35,000
NT-proBNP (normal 5–391 pg/ml)	2972	4465	1350	
Treatment				
Anti-rickettsial antibiotic(s), no. of days illness at receiving	IV chloramphenicol, 7	Oral doxycycline, 5 IV chloramphenicol, 7	IV chloramphenicol, 7	IV chloramphenicol, 10

TABLE 1. *Continued.*

	Case 1	Case 2	Case 3	Case 4
Other supportive treatment	Dopamine, dobutamine, epinephrine, amiodarone prednisolone, on ventilator	Dopamine, dobutamine methylprednisolone, IVIG 2 g/kg, intra-aortic balloon pump, on ventilator	Dopamine, dobutamine methylprednisolone	Dopamine, dobutamine, milrinone, amiodarone, methylprednisolone, on ventilator
Outcome	Dead: day 10, ventricular tachycardia, shock	Alive: EF recovered by 1 wk	Alive: EF recovered by 1 wk	Dead: day 13, ventricular tachycardia, shock

CTR, cardiothoracic ratio (normal <50%); EF, ejection fraction of left ventricle (normal $\geq 50\%$); IV, intravenous; PVC, premature ventricular contractions.

compared with all in this report. This might be because of the degree of severity of acute fulminant myocarditis in three and myocarditis with disseminated intravascular coagulation in one.

Although myocarditis can be a clinical manifestation of scrub typhus, it has rarely been reported. Some children with scrub typhus might have undetected mild myocarditis. The only case of scrub typhus myocarditis confirmed by endomyocardial biopsy was reported in 1991 in a Japanese adult in whom heart failure occurred 3 months after an acute febrile illness.⁷ It was much less severe and might have been improved by an oral inotropic agent. So far, there has been no report in MEDLINE of acute fulminant myocarditis caused by scrub typhus in children.²⁻⁴

Early diagnosis of myocardial complications is crucial. Until our patients developed hypotension, we found no physical warning signs that helped make an early diagnosis of myocarditis. The investigation that might have helped was the ECG which was abnormal prior to hypotension in all cases. However, the ECG abnormalities were non-specific and can be found in one-fourth of scrub typhus patients with no cardiac symptoms.⁵ Cardiac biomarkers (creatinine kinase-MB and cardiac troponin-T) are non-invasive and highly specific for myocarditis.^{15,16} If available, both biomarkers can be useful in predicting fulminant myocarditis. The elevated NT-proBNP level found in all patients is non-specific but is a useful tool in assessing the degree of acute left ventricular dysfunction.¹³

The outcome of scrub typhus myocarditis depends on adequate haemodynamic support and the early administration of appropriate antibiotics. The mortality rate of acute fulminant myocarditis in our study was high (2/4 cases) but cardiac recovery was excellent in the two who survived.

Although the gold standard for diagnosing myocarditis is myocardial biopsy, to perform the biopsy in patients who are severely haemodynamically compromised is

invasive and insensitive.¹⁶ The clinical manifestations and the abnormal cardiac parameters (chest radiograph, ECG, echocardiogram and cardiac biomarkers) in our patients were strong evidence for the diagnosis of fulminant myocarditis.

These four cases of acute fulminant myocarditis in children with scrub typhus presented with obscure fever. Hypotension as a sign of myocarditis developed in the 2nd week of illness. Clinicians should be aware of this serious cardiac manifestation of scrub typhus, especially in patients living in or returning from areas endemic for scrub typhus. Vital sign monitoring, chest radiographs and early ECG monitoring should be done in suspected cases. Cardiac biomarkers might help to confirm damage to the myocardium. Echocardiogram is a useful tool in measuring the severity of myocarditis. Prompt recognition and appropriate antibiotic treatment are essential to prevent death.

References

- 1 Silpapojakul K. Scrub typhus in the Western Pacific region. *Ann Acad Med Singapore* 1997; **26**:794-800.
- 2 Sirisanthana V, Puthanakit T, Sirisanthana T. Epidemiologic, clinical and laboratory features of scrub typhus in thirty Thai children. *Pediatr Infect Dis J* 2003; **22**:341-5.
- 3 Silpapojakul K, Varachit B, Silpapojakul K. Pediatric scrub typhus in Thailand: a study of 73 confirmed cases. *Trans R Soc Trop Med Hyg* 2004; **98**:354-9.
- 4 Chanta C, Chanta S. Clinical study of 20 children with scrub typhus at Chiang Rai regional hospital. *J Med Assoc Thai* 2005; **88**:1867-72.
- 5 Fang RCY, Dennis DT, Lee JB. Electrocardiographic changes in scrub typhus patients. *Southeast Asian J Trop Med Public Health* 1977; **8**:503-9.
- 6 Watt G, Kantipong P, Jirajarus K. Acute scrub typhus in Northern Thailand: EKG changes. *Southeast Asian J Trop Med Public Health* 2002; **33**:312-13.
- 7 Yotsukura M, Aoki N, Fukuzumi N, Ishikawa K. Review of a case of *Tsutsugamushi* disease showing myocarditis and confirmation of rickettsia by endomyocardial biopsy. *Jpn Circ J* 1991; **55**:149-53.
- 8 Ben RJ, Feng NH, Ku CS. Meningoencephalitis, myocarditis and DIC in a patient with scrub typhus. *J Microbiol Immunol Infect* 1999; **32**:57-62.

- 9 Chawalparit O, Suttinont C, Niwattayakul K, et al. Scrub typhus: chest radiographic and clinical findings in 130 Thai patients. *J Med Assoc Thai* 2006; **89**:600–7.
- 10 Robinson DM, Brown GW, Gan E, Huxsoll DL. Adaptation of a microimmunofluorescent test to the study of human *Rickettsia tsutsugamushi* antibody. *Am J Trop Med Hyg* 1976; **25**:900–5.
- 11 Elisberg BL, Bozeman FM. The rickettsiae. In: Edwin HL, Nathalie JS, eds. *Diagnostic Procedures for Viral, Rickettsial and Chlamydial Infection*, 5th edn. Washington, DC: American Public Health Association, 1979; 1061–108.
- 12 Chenchittikul M. Rickettsial infection. In: Warachit P, Poonwan N, Saengkijporn S, eds. *Handbook of Laboratory Diagnosis*. Bangkok: Department of Medical Sciences, Ministry of Public Health, 1998; 247–56.
- 13 Fried I, Bar-Oz B, Perles Z, et al. N-terminal pro-B-type natriuretic peptide levels in acute versus chronic left ventricular dysfunction. *J Pediatr* 2006; **149**:28–31.
- 14 Lieberman EB, Hutchins GM, Herskowitz A, Rose NR, Baughman KL. Clinicopathologic description of myocarditis. *J Am Coll Cardiol* 1991; **18**:1617–26.
- 15 Lauer B, Niederau C, Kuhl U, et al. Cardiac troponin T in patients with clinically suspected myocarditis. *J Am Coll Cardiol* 1997; **30**:1354–9.
- 16 Magnani JW, Dec WD. Myocarditis: current trends in diagnosis and treatment. *Circulation* 2006; **113**:876–90.