Clinical Manifestations, Laboratory Findings and Complications of Pediatric Scrub Typhus in Eastern Taiwan

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Background: Scrub typhus is a clinically important endemic disease in Taiwan. The aims of this study were to analyze the clinical manifestations, laboratory data and complications of pediatric scrub typhus in eastern Taiwan.

Patients and methods: We searched medical records for all patients with scrub typhus who were hospitalized between 1992 and 2002 at the Taitung branch of Mackay Memorial Hospital, Taiwan. Records of children under the age of 18 with a confirmed diagnosis were selected for retrospective review.

Results: During the study period, 145 patients fulfilled the diagnostic criteria for scrub typhus, of whom 106 (73%) were adults and 39 (27%) were children. The mean age of the children was 7.6±4.6 years. The most common clinical manifestations of pediatric scrub typhus were fever (n=39; 100%), cough (n=28; 72%), anorexia (72%), eschar (69%), chill (67%) and lymphadenopathy (64%). The most common complications were hepatic dysfunction (77%) and pneumonitis (54%). Three children (8%) required intensive care, but the overall survival rate was 97%. One child died with multi-organ failure within 8 hours after admission.

Conclusion: Scrub typhus should be considered in children with fever and hepatic dysfunction, particularly in those with a history of environmental exposure in an endemic area for scrub typhus. The presence of an eschar offers an important diagnostic clue, but not for all cases. Children with scrub typhus may develop serious complications and may even die if appropriate treatment is not given. Doxycycline is an effective antibiotic for pediatric scrub typhus in Taiwan.
1. Introduction

Scrub typhus is a zoonotic disease caused by *Orientia tsutsugamushi* (also called *Rickettsia tsutsugamushi*). It is transmitted by larval trombiculid mites to rodents, while humans are opportunistic hosts. Scrub typhus is widely distributed in the western Pacific area and Asia, from Japan and South Korea in the north, as far south as northern Australia, and to the west as far as Afghanistan and Pakistan. In Taiwan, the Taitung and Hualien counties are areas with the highest annual incidence of scrub typhus.

Scrub typhus was first reported in Taiwan by Hatori in 1915. An outbreak was documented in 1970 in eastern Taiwan and, since then, cases have been reported every year. Between 2002 and 2006, a total of 1742 cases of scrub typhus were reported in Taiwan, of which 142 (8.2%) were children. However, in other Asia-Pacific areas, approximately 25–50% of cases have occurred in children. Scrub typhus may cause mild symptoms, serious complications, or even death. Mortality may be as high as 35–60% if diagnosis or appropriate therapy is delayed.

2. Subjects and Methods

The Taitung Branch of Mackay Memorial Hospital serves people in southeast Taiwan, including those living on offshore islands. From January 1st 1992 to December 31st 2002, 402 patients were treated at our hospital for scrub typhus. Their medical records were reviewed to verify the diagnosis, which required at least one of the following criteria: (1) a four-fold rise in the indirect immunofluorescent antibody (IFA) test for *O. tsutsugamushi* measured in acute and convalescent paired sera (test material provided by National Institute of Preventive Medicine, Department of Health, Executive Yuan, Taiwan); (2) an IgM antibody titer against *O. tsutsugamushi* >1:80; or (3) a positive PCR test for *O. tsutsugamushi* (available since 2002). According to information in the records, 145 patients fulfilled the diagnostic criteria for scrub typhus. Data extracted from the records included clinical manifestations, laboratory data and complications. X-rays were also reviewed.

Descriptive statistics were used to analyze numerical data. Continuous data are expressed as mean±standard deviation unless otherwise specified.

3. Results

In the study period, 145 patients fulfilled the diagnostic criteria for scrub typhus, 106 (73%) were adults and 39 (27%) were children, of which 26 were boys and 13 were girls. Of the 39 children, 26 (66.7%), 11 (28.2%) and two (5.1%) patients were diagnosed based on a four-fold rise in the IFA test in paired sera, an IgM antibody titer >1:80, or a positive PCR test, respectively. The mean age of the children was 7.6±4.6 years (range, 1–18 years). Over half (22 of 39, 56%) lived in Taitung County, and 17 (44%) lived on Orchid Island. Most cases were diagnosed from March to December in a bimodal distribution, with a higher peak in May and a smaller one in November (Figure).

The mean duration of fever before hospitalization was 6.2±2.3 days. The six most common symptoms and signs of pediatric scrub typhus were fever, cough, anorexia, eschar, chills and lymphadenopathy (Table 1). Most patients had a normal hemoglobin level, and only about a third had abnormal white blood cell counts (leukocytosis or leucopenia), or thrombocytopenia. However, increased C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), were found in 95% and 88% of patients, respectively. Thirty children had abnormal liver enzyme levels. The median serum level of aspartate aminotransferase was 126.0 (range 44–3625) IU/L and that of alanine aminotransferase was 136.0 (range 37–2464) IU/L. Hypoalbuminemia was present in 41% of the children (mean serum albumin, 2.7±0.4 g/dL) (Table 2).

Thirty-eight of 39 (97%) children recovered during hospitalization, with evidence of recovery from fever at a mean of 1.5±1.1 days after starting the antibiotics. The complications of scrub typhus...
The two most common complications of scrub typhus were hepatic dysfunction and pneumonitis, which occurred in 77% and 54% patients, respectively. Pneumonitis was manifested as bilateral interstitial infiltrates on chest X-rays. Abdominal pain was present in 20 (51%) patients, with symptoms in six patients appearing as an acute abdomen. On abdominal ultrasound, they had findings suggestive of cholecystitis (double wall of gallbladder, hydrops of gallbladder) and hyperechogenicity of the liver parenchyma. Three children required intensive care (Table 4); two of whom had pneumonitis, pericardial effusion, severe hepatic dysfunction, and disseminated intravascular coagulation. The third patient died within 8 hours after admission with multiple organ failure (fulminant hepatic failure, respiratory distress syndrome, disseminated intravascular coagulation and septic shock).

### 4. Discussion

We found that the pediatric cases scrub typhus described here showed a range of disease severity. Most of the children recovered with either no or only mild complications. However, three had more serious diseases, and one died.

There is one possible explanation for the peaked distribution of cases, with most cases occurring in...
early summer, peaking in May, and then again in early winter, peaking in November. The primary vectors for *O. tsutsugamushi* are *Leptotrombidium deliense* (also called “chiggers” or “red bugs”). It seems likely that rodents are more commonly infested with the vectors during these seasons. Meanwhile, children, who are incidental hosts, have higher numbers of field trips and outdoor activities in those particular periods, increasing the risk of exposure.

Taitung and Hualien counties are the two most common areas for scrub typhus, with the highest annual prevalence in Taiwan. Interestingly, nearly half of the children in our series lived on Orchid Island. You et al. found a 96% seropositivity rate for scrub typhus in children older than 6 years of age on Orchid Island, indicating that this is a highly endemic area. We suggest that better vector control could reduce the incidence of the disease there.

Scrub typhus should be considered in all patients who have a fever of obscure cause and have been in an endemic area. Because many of the clinical manifestations such as fever, cough, anorexia and chill are non-specific, diagnosis is difficult to make. The key to diagnosing scrub typhus is finding a typical eschar, which is the result of the insect bite that transmits the pathogen; this is frequently accompanied by regional lymphadenopathy. We found an eschar in two-thirds of our patients after careful examination, often in the axillary and genital regions, and this finding is compatible with those reported by Sirisanthana et al. and Chanta and Chanta. Characteristically, an eschar is a non-painful ulcer covered by a centrally depressed dark scab and surrounded by a red areola. One child had an eschar on his neck without a dark scab because he had scratched it off.

The laboratory findings are also non-specific, and routine blood cultures are inadequate for isolating the organism. *O. tsutsugamushi* can only be grown on mouse or chick embryos or tissue culture. Markers of inflammation, including CRP and ESR, were elevated in the majority of our patients, and three-quarters of them had liver enzyme abnormalities, with or without hypoalbuminemia. These findings have been reported in earlier studies.

About half of our children had a mild cough and had evidence of interstitial pneumonitis in chest roentgenograms. The most frequently reported chest X-ray abnormalities in scrub typhus are diffuse, bilateral, reticulonodular opacities. Abdominal pain is not uncommon, and it may mimic an acute abdomen. Chen et al reported two patients with scrub typhus in whom an unnecessary laparotomy was performed. Thus, accurate diagnosis of scrub typhus may help to avoid unnecessary surgery.

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<th>Characteristics of three children with serious complications of scrub typhus</th>
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*Multiple organ failure: pericardial effusion, pneumonitis with pleural effusion, DIC and meningitis; **Multiple organ failure: fulminant hepatic failure, DIC, septic shock, myocarditis, pneumonitis, and ARDS; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DIC = disseminated intravascular coagulation.
an average of 1.5 days. When diagnosis is still uncertain, this rapid improvement might offer a clue to the actual cause.

Although hepatic dysfunction and pneumonitis were fairly common in our patients, most of the children recovered well. The severity of scrub typhus varies considerably, which might correlate with the virulence of the particular *O. tsutsugamushi* strain responsible for the infection. Furthermore, serious complications of scrub typhus normally involve multiple organs, including the liver, lungs, heart, brain or kidneys, are often pathologically associated with focal or diffuse vasculitis. Pneumonitis, thrombocytopenia and disseminated intravascular coagulopathy are serious complications of scrub typhus, and occurred in three of our patients. Based on the studies by Song and Tsay, patients with pneumonitis progressing to acute respiratory distress syndrome may be at increased risk of death. Therefore, appropriate antibiotic treatment with intensive respiratory care is essential for all patients with pneumonitis.

This study involved a relatively small retrospective series of patients, which might not be representative of the experience elsewhere in Taiwan. In addition, conventional treatment regimens for scrub typhus infection are based on clinical studies in adults. A 1-week regimen of oral doxycycline and new macrolide antibiotics is recommended only for mild or uncomplicated scrub typhus in children.

However, the optimal dose and duration of treatment for complicated scrub typhus and life-threatening cases have not been established for children. Thus, it is necessary to gather information on a larger numbers of patients to determine whether there are particular risk factors associated with more serious complications and to determine the optimal therapy for children with serious complications of scrub typhus.

5. Conclusion

Scrub typhus is a treatable disease that may develop serious complications and may even result in death if appropriate antibiotic therapy is not given. Therefore, it is important to promptly reach the correct diagnosis and initiate appropriate treatment. Physicians should maintain a high index of suspicion, especially in endemic areas for scrub typhus. A careful search for an eschar, while not helpful in all cases, is important in evaluating children with a fever, particularly those with hepatic dysfunction or pneumonitis without an obvious cause. Doxycycline is an effective antibiotic for children with scrub typhus in Taiwan.

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