SHORT REPORT: ABNORMAL LIVER FUNCTION IN SCRUB TYPHUS

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Abstract. Scrub typhus is one kind of rickettsial disease and may cause fever, cough, and skin rashes in infected humans. Regarding liver involvement, it was uncommon to be reported in previous medical literature from Western countries. This study observes the relationship between scrub typhus and liver function. From January 1998 to August 2003 in Kaohsiung Chang Gung Memorial Hospital in Taiwan, we observed 30 patients with scrub typhus, and 29 of them had liver function abnormality. In these patients, we found 89.3% with elevated aspartate aminotransferase (AST) levels, 91.7% with elevated alanine aminotransferase (ALT) levels, 84.2% with elevated alkaline phosphatase (ALP) levels, and 38.5% with elevated total bilirubin levels. In our study, there is a close relationship between scrub typhus and impaired liver function tests. Therefore, if patients are found with fever of unknown origin and abnormal liver function, we should take scrub typhus into consideration.

Scrub typhus is a zoonotic disease that is caused by Orientia tsutsugamushi (formerly called Rickettsia tsutsugamushi) and is accidentally transmitted to humans by the bite of larval-stage trombiculid mites (chiggers). It prevails in eastern and southern Asia, northern Australia, and on the islands of the western Pacific region, including Taiwan. Clinical manifestations include fever, headache, skin rash, lymphadenopathy, and gastrointestinal symptoms. Also, eschar is a characteristic skin lesion and is the site of chigger feeding. Severe complications include prominent encephalitis, interstitial pneumonia, acute renal failure, and acute respiratory distress. Regarding liver involvement, it is uncommonly mentioned in the Western literature. “No consistent liver enzyme abnormality” is even shown in Western medical textbooks. In the Asian studies, it is uncommon to focus on a relationship between scrub typhus and abnormal liver function.

To investigate the incidence of abnormal liver function in scrub typhus, we observed 37 patients with diagnosis of scrub typhus in Kaohsiung Chang Gung Memorial Hospital from January 1998 to August 2003. The diagnosis of scrub typhus was from patients’ blood samples based on the evidence by the method of polymerase chain reaction (PCR) or the serology of indirect microimmunoﬂuorescent antibody (IFA) for Orientia tsutsugamushi from the Center for Disease Control in Taiwan. Diagnostic IFA must meet the following criteria: the total antibody titer for Karp, Kato, and Gilliam strains of O. tsutsugamushi must have a fourfold or greater rise in paired serum samples or antibody titer for IgM ≥ 1:80.8,9 For analyzing the relationship between scrub typhus and liver function, the patients with previously known hepatitis were excluded. Therefore, four patients with hepatitis B virus infection (none with hepatitis A or C infection), two with chronic alcoholism, and one with previous abnormal liver biochemical test (severe fatty liver) were excluded. A total of 30 patients (13 females and 17 males) were enrolled for the retrospective study, including 5 patients (16.7%) proved by PCR and 25 patients (83.3%) proved by serology.

Due to localized distribution, most of these patients were from southern and eastern Taiwan including some of the surrounding islands. The main symptoms and signs were fever (100%), chills (37%), headache (30%), and skin rash (40%). Eschars (67%) were found in 20 patients. All except two patients received antirickettsial antibiotic treatment including doxycycline,10,11 oxytetracycline,12 chloramphenicol,12 or clarithromycin. Three patients had severe complications including two with acute respiratory distress and one with consciousness change. Concerning the prognosis of these patients: 29 had complete recovery, and 1 old patient died of sepsis and circulatory collapse due to delayed diagnosis and treatment.

Regarding hepatitis-like manifestations, six patients had jaundice. Liver biochemical tests were taken within the initial days after visiting the emergency department. We found that abnormal liver biochemical data were revealed in all examined patients (29 patients). The data showed elevated aspartate aminotransferase/AST (median: 148 U/L, interquartile range: 73 to 175 U/L), alanine aminotransferase (ALT; 120 U/L, 83–206 U/L), alkaline phosphatase (ALP; 168 U/L, 117–201 U/L), total bilirubin (0.9 mg/dL, 0.5–1.2 mg/dL), albumin (2.7 g/dL, 1.9–3.0 g/dL), and prothrombin time (10.75 seconds, 10.25–11.20 seconds). Only one patient did not have any of the above examinations (Table 1). Of 16 patients receiving abdominal ultrasonography, 9 had acute hepatitis-like imaging including minimal ascites, mild splenomegaly, and edematous gall bladder wall, and 2 had right-side pleural effusion. Only six patients took follow-up serial liver function profiles later; hepatic dysfunction improved in all of them and were normalized in 3 patients with the cure of scrub typhus infection.

Liver involvement was rarely mentioned in Western medical literature. But in our retrospective study, 25 of 28 (89.3%) patients who received AST examination had abnormal AST levels. Also, the abnormal rate was 91.7% (22 of 24) in ALT levels, 84.2% (16 of 19) in ALP levels, 38.5% (5 of 13) in total bilirubin levels, and 38.3% (5 of 6) in albumin levels. None received liver biopsy or surgery, but obviously scrub typhus infection did lead to liver function impairment. Certainly, the frequent liver dysfunction rates seen in these patients may be related in part to a selection bias whereby particularly severe
patients are being referred to our tertiary care medical center. These findings were consistent with a previous report from Yang and others. From these patients in our study, we found acute hepatitis-like changes, and abnormal liver biochemical tests improved with the treatment of scrub typhus infection.

For the research about liver histopathologic changes in scrub typhus patients, there have been few case reports so far and they showed bi- or triple nucleated changes and fat deposition in swollen hepatocytes and small lymphocyte aggregation in sinusoids or with granulomatous changes. One patient received liver biopsy for viewing under electron microscope and showed rod-shaped organisms within the hepatocytes and sinusoids with variable degree of cytoplasmic organelle damage. Because there are not enough cases or convincing histopathologic documentation of liver damage, it will be necessary to work in prospective studies to clarify the relationship between scrub typhus and hepatitis in the future.

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