

# Hepatic Dysfunction in Pediatric Scrub Typhus: Role of Liver Function Test in Diagnosis and Marker of Disease Severity

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**Objective:** Determine the frequency of abnormalities of liver function test in children with scrub typhus and its relation with severity of disease.

**Material and Method:** Fifty-four children diagnosed with scrub typhus at Chiang Rai Regional Hospital from January 2004 to December 2005 were studied. The diagnosis of scrub typhus in the present study was based on a single indirect immunofluorescent antibody (IFA) titer against *O. tsutsugamushi* of  $\geq 1:400$  or a four fold or greater rise in IFA titer to at least 1:200. Liver function tests (LFT) were done on the first few days of admission in all patients. Abnormalities of LFT were focused on serum AST, ALT, albumin and total bilirubin level. All of the patients were divided into two groups based on the presence or absence of complications.

**Results:** Fifty-two patients (96.3%) had abnormal LFT. Evaluation of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were detected in 52 (96.3%) and 36 (66.7%) cases, respectively. Hypoalbuminemia and hyperbilirubinemia were detected in 23 (42.6%) and 4 (7.4%) cases, respectively. The higher level of AST, ALT, and lower level of serum albumin correlated significantly with the severity of scrub typhus in children.

**Conclusion:** Hepatic dysfunction is common in children with scrub typhus. Elevation of AST level may be used as a screening test for diagnosis of scrub typhus in areas where rapid diagnostic test is not commercially available. Increased AST, ALT, and hypoalbuminemia related with severity of disease.

**Keywords:** Hepatic dysfunction, Liver function test, Pediatric scrub typhus

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Scrub typhus is a common infectious disease in Southeast Asia including Thailand, especially in the northern part<sup>(1-3)</sup>. It is a systemic disease caused by *Orientia tsutsugamushi* during the bite of a chigger. The basic pathophysiological changes of scrub typhus are focal or disseminated multiorgan vasculitis such as lung, brain, etc due to inflammatory lesions from infiltrating leukocytes and destruction of the endothelial cells lining small blood vessels<sup>(4,5)</sup>. Liver is one of the organs involved by this organism. Previous studies in adult patients with scrub typhus have shown that hepatic dysfunction is common and represents the

severity of the disease<sup>(4,6-8)</sup>. However, hepatic involvement in children with scrub typhus has not previously been reported in the medical literature. The present study aimed to assess abnormalities of liver function test in children diagnosed with scrub typhus and its relation with severity of disease.

## Material and Method

The present prospective study was conducted at the pediatric inpatient department of Chiang Rai Regional Hospital from January 2004 to December 2005. All hospitalized children age  $\leq 15$  years who presented with fever for more than 5 days and without obvious causes were tested for antibody against *O. tsutsugamushi*. The diagnosis of scrub typhus in the present

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study was based on the presence of a single indirect immunofluorescent antibody (IFA) titer against *O. tsutsugamushi* of  $\geq 1:400$  or 4 fold or greater rise in antibody titer to at least 1:200<sup>(9)</sup>. Children with the diagnosis of scrub typhus were enrolled and followed prospectively by the same physician. The present study was approved by the Institutional Review Board of Chiang Rai Regional Hospital.

Complete blood count (CBC) and peripheral blood smear for malarial parasite, urinalysis, liver function tests (LFT), Widal, Weil-Felix test and chest x-ray (CXR) were done on the first few days of admission in all patients. Other laboratory tests such as BUN and creatinine, liver ultrasonography, CK, CK-MB, hemoculture, PT, PTT, Leptospira antibody and lumbar puncture were done in some patients when clinically indicated. After admission, all patients were treated with chloramphenicol 100 mg/kg/day intravenously and switched to oral when clinically improved. Empirical antibiotics were added in some patients when clinically indicated. Liver function test (LFT) was repeated periodically if abnormal on day 3, day 7 after treatment with antibiotic or 1-3 weeks after discharge from hospital until normal.

Liver function test (LFT) included serum albumin, total bilirubin (TB), alanine aminotransaminase (ALT), aspartate transaminase (AST). The alkaline phosphatase was not evaluated due to its wide variation in serum levels of activity in children. The normal values of AST, ALT and total bilirubin were 0-35 IU/L, 0-45 IU/L and 0-1.5 mg%, respectively. Elevation of AST and ALT were defined as serum level  $\geq 1.25$  fold of upper normal limit. Hypoalbuminemia was defined as serum albumin  $< 3$  gm%. Complications of scrub typhus in the present study were defined as those who presented with systemic and organ manifestations<sup>(2,10)</sup>. They included hypotension, pneumonitis, jaundice, renal insufficiency and meningitis. The patients were divided into two groups based on the presence or absence of complications. The data were analyzed using SPSS version 11.5. Descriptive data were analyzed by mean, range, percentage and standard deviation. The different between complications and LFT parameters was analyzed by using Student's *t*-test. Statistical significance was set at  $p < 0.01$ .

## Results

Fifty-four patients with IFA confirmed scrub typhus were studied, 32 were boys and 22 were girls with the mean age of 6.6 years. LFT on initial admission are shown in Table 1.

Abnormalities of liver function tests were seen in 93.6% (52/54) of patients. The most common abnormal parameter was AST which was seen in 96.3% (52/54). Abnormalities in ALT, albumin and total bilirubin were seen in 81.5% (44/54), 42.6% (23/54) and 7.4% (4/54), respectively. Of 33 patients with abnormal LFT and complete follow-up after treatment, 12/33 (37%) had liver function test profile returning to normal level within one week, the other 21/33 (63%) in two to four weeks. Complications were seen in 31 cases (58%). They included pneumonitis 24 (44%), shock 6 (13%), meningitis 2 (4%), jaundice 2 (4%) and renal insufficiency 1 (2%).

The association between disease severity and LFT parameters are shown in Table 2.

Level of AST and ALT were significantly higher and albumin was significantly lower among patients with complications ( $p < 0.01$ ) and AST level was higher than ALT. Level of TB was not significantly different between the two groups.

## Discussion

Most children with scrub typhus have a high fever with non-specific clinical symptoms and signs such as anorexia, abdominal pain, cough or hepatomegaly that are frequently misdiagnosed by general physicians especially when eschar is not present. The commercial available Weil-Felix test is poor, lacking sensitivity and specificity. The confirmatory gold standard tests e.g., indirect immunofluorescent antibody (IFA), indirect immunoperoxidase test (IIP) are limited to a small number of reference centers. The present study shows that most children with scrub typhus

**Table 1.** Liver function test in 54 children with scrub typhus

Parameters	mean $\pm$ SD (range)	Numbers of patient with abnormality (%)
AST (IU/L)	152.98 $\pm$ 112.17 (29-727)	52 (96.3)
ALT (IU/L)	78.52 $\pm$ 46.71 (21-287)	36 (66.7)
Albumin (g/dL)	2.79 $\pm$ 0.69 (0.2-4.1)	23 (42.6)
TB (mg/dL)	0.81 $\pm$ 0.77 (0-4.6)	4 (7.4)

AST = aspartate aminotransferase

ALT = alanine aminotransferase

TB = total bilirubin

**Table 2.** Liver function tests in scrub typhus patients with and without complication

Parameters (mean $\pm$ SD)	Without complication (n = 23)	With complication (n = 31)	p-value
AST (IU/L)	92.7 $\pm$ 44.6	197.7 $\pm$ 126.2	<0.001*
ALT (IU/L)	57.5 $\pm$ 31.7	94.1 $\pm$ 50.2	<0.003*
Albumin (g/dL)	3.24 $\pm$ 0.75	2.46 $\pm$ 0.41	<0.001*
TB (mg/dL)	0.61 $\pm$ 0.32	0.96 $\pm$ 0.96	NS

\* p < 0.01 using Student's *t*-test

AST = aspartate aminotransferase, ALT = alanine aminotransferase, TB = total bilirubin, NS = Not significant

have abnormal liver function test result especially elevation of plasma AST level which has a high sensitivity of 96.3%, similar to previous studies in adults<sup>(8,11)</sup>. It may be used as an indicator for screening test and diagnosis of scrub typhus in endemic areas with limited rapid laboratory test. However, this application must be used cautiously in tropical areas with other endemic diseases such as DHF, typhoid fever, malaria and leptospirosis that may cause hepatocellular injury and elevated AST levels<sup>(12)</sup>. The present study also demonstrated that elevated AST level was higher than ALT and correlated significantly with severity of disease. This may be due to the fact that increased AST is caused by other organ injury in addition to the liver.

Histopathological study of liver taken before treatment in patients with scrub typhus showed reactive hepatitis and rickettsial organisms could be identified within the hepatocytes and sinusoids under light microscopy<sup>(13)</sup>. This may explain that hepatic involvement with elevated transaminase enzymes caused by direct invasion of the organism, resulting in hepatocellular damage. Hypoalbuminemia is another LFT parameter that changes in patients with scrub typhus, which presents about 40% in the present study and is associated with severity of the disease. Plasma leakage due to diffuse vasculitis and increased vascular permeability may cause low serum albumin and is a transient process supported by the reason that the level of plasma albumin returned to normal level within one to four weeks after appropriate antibiotic treatment in the present study.

In conclusion, the present study demonstrates that abnormalities of liver function test are common in children with scrub typhus. Increased AST level may help as a clue for diagnosis of scrub typhus in endemic areas where rapid laboratory tests are not available. The severity of disease is associated with elevated AST, ALT and hypoalbuminemia.

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## ภาวะตับทำงานผิดปกติในผู้ป่วยเด็ก สครับ ทัยพัส: บทบาทของการตรวจหน้าที่ตับในการวินิจฉัยและบอกความรุนแรงของโรค

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**วัตถุประสงค์:** ศึกษาความถี่ของภาวะผิดปกติในการตรวจหน้าที่ตับในผู้ป่วยเด็ก สครับ ทัยพัส และความสัมพันธ์กับความรุนแรงของโรค

**วัสดุและวิธีการ:** ทำการศึกษาในผู้ป่วยเด็ก 54 คนที่ได้รับการวินิจฉัยเป็นโรค สครับ ทัยพัส ที่โรงพยาบาลศูนย์เชียงใหม่ประชาชนนคราห์ ตั้งแต่เดือนมกราคม พ.ศ 2547 ถึงเดือนธันวาคม พ.ศ 2548 การวินิจฉัยโรคสครับ ทัยพัส อาศัยการตรวจน้ำเหลือง indirect immunofluorescent antibody (IFA) โดยมีค่าไตเตอร์  $\geq 1:400$  ในการส่งตรวจครั้งเดียวหรือมีการเพิ่มขึ้น 4 เท่า หรือเพิ่มขึ้น 1:200 จากการส่งตรวจ 2 ครั้ง การตรวจหน้าที่ตับจะทำในผู้ป่วยทุกรายหลังรับไว้รักษาในโรงพยาบาล ความผิดปกติของตับจะเน้นการตรวจหาค่า AST, ALT, albumin และ total bilirubin ผู้ป่วยทั้งหมดจะได้รับการแบ่งเป็น 2 กลุ่มตามการมีหรือไม่มีภาวะแทรกซ้อน

**ผลการศึกษา:** ผู้ป่วย 52 ราย (96.3%) มีความผิดปกติของการตรวจหน้าที่ตับ พบมีการเพิ่มมากขึ้นของค่า AST และ ALT ในผู้ป่วย 52 (96.3%) และ 36 (66.7%) ราย ตามลำดับ พบมีภาวะ hypoalbuminemia และ hyperbilirubinemia ในผู้ป่วย 23 (42.6%) และ 4 (7.4%) ราย ตามลำดับ ระดับเอนไซม์ AST และ ALT ที่สูงขึ้น และระดับอัลบูมินในเลือดที่ต่ำมีความเกี่ยวข้องอย่างมีนัยสำคัญกับความรุนแรงของโรค

**สรุป:** ภาวะตับทำงานผิดปกติพบได้บ่อยในผู้ป่วยเด็ก สครับ ทัยพัส การเพิ่มขึ้นของระดับเอนไซม์ AST อาจช่วยในการตรวจเพื่อวินิจฉัยโรคสครับ ทัยพัส ในพื้นที่ไม่สามารถส่งเลือดตรวจเพื่อการวินิจฉัยอย่างรวดเร็วได้ การเพิ่มขึ้นของระดับเอนไซม์ AST, ALT และระดับอัลบูมินในเลือดที่ต่ำสัมพันธ์กับความรุนแรงของโรค

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