A Comparative Study of Hepatitis Caused by Scrub Typhus and Viral Hepatitis A in South Korea

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Abstract. We compared clinical features and laboratory findings of 104 patients with hepatitis A and 197 patients with scrub typhus. Nausea, vomiting, abdominal pain, hepatomegaly, and jaundice were common in patient with hepatitis A, and fever and headache were significantly more common in patients with scrub typhus. At presentation, an alanine aminotransferase (ALT) level ≥ 500 U/L was observed in 1% of scrub typhus patients and in 87.5% of hepatitis A patients ($P < 0.001$). A bilirubin level ≥ 1.3 mg/dL was observed in 16.8% of scrub typhus patients and 90.4% of hepatitis A patients. The ALT:lactate dehydrogenase ratio was ≤ 5 in 97.4% of the patients with scrub typhus and > 5 in 95.2% of those with hepatitis A ($P < 0.001$). Fever, headache, rash, and eschar are findings that indicate scrub typhus. An ALT level ≥ 500 U/L (adjusted odds ratio = 0.011) a bilirubin level ≥ 1.3 (adjusted odds ratio = 0.024), an ALT:lactate dehydrogenase ratio > 5 , and hepatomegaly are indications of viral hepatitis A.

INTRODUCTION

Scrub typhus is an infectious disease caused by *Orientia tsutsugamushi*, which is transmitted by the bites of chigger mites. In recent studies conducted in Taiwan, levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were found to be increased in 97% of patients with scrub typhus.^{1,2} In clinical practice, it is somewhat difficult to differentiate scrub typhus hepatitis from acute viral hepatitis on the basis of their clinical features. Scrub typhus is prevalent in countries in Asia such as Thailand, South Korea, and Japan, and hepatitis A occurs worldwide.

Because hepatitis A spreads via the fecal–oral route and is more prevalent in low socioeconomic areas such as Southeast Asia, it is also a concern in Southeast Asia where scrub typhus is more prevalent.³ Acute hepatitis A can manifest atypical symptoms such as fever, chills, myalgia, evanescent rash, arthritis, cervical lymphadenopathy and sometimes fever $\geq 38^{\circ}\text{C}$, which may result in a misdiagnosis of acute febrile disease other than viral hepatitis A. As a result, unnecessary tests are performed and the frequent use of antibiotics may result in substantial medical costs.⁴

Previously, hepatitis A mostly occurred during childhood in South Korea, formerly an area highly endemic area for hepatitis A. However, with recent improvements in quality of life, inapparent infections have tended to decrease, whereas apparent infections have tended to increase. The number of patients with hepatitis A in South Korea was 105 in 2000, 355 in 2004, and 2,233 in 2007.^{5,6} In South Korea, the number of patients with scrub typhus was 1,758 in 2000, 4,698 in 2004, and 6,022 person in 2007, which indicated that the prevalence of scrub typhus has increased abruptly.

Scrub typhus is an acute febrile disease that is frequently associated with fever, chills, and myalgia and can be easily diagnosed by its typical eschars. However, this disease could be difficult to diagnose when the patient has dark skin, for example in Thailand. Patients frequently are not aware of eschars because those associated with mite bites are usually

not accompanied by pain or itching.⁷ It is usually difficult to diagnose scrub typhus in the early stage in the absence of a rash or eschar. In developing or third-world countries where polymerase chain reaction (PCR) and indirect immunofluorescent antibody assays are unavailable, clinical diagnosis of scrub typhus tends to be delayed. Thus, proper treatment is also delayed, and this leads to poor outcomes and increased medical costs.

Therefore, this study was conducted to identify easily-available markers from clinical and routine laboratory findings that are useful in differentiating hepatitis A from scrub typhus.

MATERIALS AND METHODS

Patients. This study was a retrospective analysis of the medical records of 104 patients who were given a diagnosis of acute hepatitis A during January 2005–August 2008 at Chosun University Hospital in South Korea and of 197 patients with confirmed scrub typhus (72 patients diagnosed by PCR alone, 17 patients diagnosed by serologic tests alone, and 108 patients diagnosed by both methods).^{8,9} Clinical history, examination results, and results of laboratory investigations were recorded on a previously validated proform from hospitalization until discharge.

Methods. Acute hepatitis A was diagnosed when patients were positive for IgM against hepatitis A virus. Scrub typhus was diagnosed when either a ≥ 4 -fold increase in IgM or IgG titer measured by indirect immunofluorescent assay was observed in the acute phase and convalescent phase, or a PCR result was positive. We used a nested PCR with a buffy coat to enhance the detection rate. The nested PCR was based on specific primers derived from the 56-kD major outer membrane protein antigen of *O. tsutsugamushi*.¹⁰ Patients with concurrent hepatitis B or C were excluded from the study by identification of hepatitis B surface antigen, IgM against the hepatitis B core antigen and antibody against hepatitis C virus.

We compared clinical and biochemical data for the hepatitis A and scrub typhus groups at presentation, including medical history, results of physical examination, and measures of leukocytes, platelets, hemoglobin, albumin, protein, AST, ALT, γ -glutamyl transpeptidase (γ -GGT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), prothrombin time, and

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creatinine phosphokinase. Results are expressed as number (%) or mean $\pm$ SD.

Categorical variables such as age, sex, and fever were analyzed by using the Pearson χ^2 test, and continuous variables (laboratory values such as leukocyte and platelet counts) were analyzed by using the unpaired *t*-test. Using multiple logistic regression analyses, we investigated the associations between signs, major liver enzyme levels, and type of hepatitis (scrub typhus and hepatitis A). The odds ratios for hepatitis caused by scrub typhus according to major signs (jaundice, fever, and hepatomegaly) were calculated after adjustment for age, sex, and disease history. Additionally, the odds ratios for hepatitis caused by scrub typhus according to major liver enzymes (ALT, bilirubin, and ALT) were calculated after adjustment for age, sex, and major signs. A *P* value < 0.05 was considered statistically significant. All statistical analyses were performed by using SPSS Windows version 16.0 (SPSS, Inc., Chicago, IL).

RESULTS

Epidemiologic and clinical characteristics. The mean $\pm$ SD age of the patients was 27 ± 7.5 years in the hepatitis A group and 62.2 ± 14.7 years in the scrub typhus group (*P* < 0.001). Age ≥ 40 years had a sensitivity of 95% and a specificity of 91% (area under the curve [AUC] = 0.961, 95% confidence interval [CI] = 0.937–0.985) for scrub typhus (Figure 1A). There were 69 males (69 of 104, 66.4%) in the hepatitis A group and 69 males (69 of 197, 35%) in the scrub typhus group (*P* < 0.001).

Regarding clinical characteristics, frequencies of fever, headache, eschar, and rash were much higher in the scrub typhus

TABLE 1

Frequency of characteristics in patients with acute hepatitis A and scrub typhus, South Korea*

Characteristic	Acute hepatitis A (n = 104)	Scrub typhus (n = 197)	P
Male sex	69 (66.4)	69 (35.0)	< 0.001
Age, years	27.4 ± 7.5	62.2 ± 14.7	< 0.001
Disease history†	2 (1.9)	42 (21.3)	< 0.001
Hepatomegaly	31 (29.8)	5 (2.5)	< 0.001
Fever	33 (31.7)	152 (77.6)	< 0.001
Headache	22 (21.2)	153 (77.7)	< 0.001
Nausea	69 (66.3)	72 (36.5)	< 0.001
Vomiting	46 (44.2)	29 (14.7)	< 0.001
Myalgia	70 (67.3)	143 (72.6)	0.338
Abdominal pain	31 (29.8)	36 (18.3)	0.022
Jaundice	63 (60.6)	7 (3.6)	< 0.001
Diarrhea	6 (5.8)	9 (4.6)	0.302
Eschar	0 (0.0)	191 (97.0)	< 0.001
Rash	0 (0.0)	174 (88.3)	< 0.001

*Values are no. (%) or mean $\pm$ SD.

†Hypertension, diabetes mellitus, and chronic kidney disease.

group than in the hepatitis A group (Table 1). Conversely, nausea, vomiting, abdominal pain, hepatomegaly, and jaundice were considerably more frequent in the hepatitis A group (Table 1). Multiple logistic analysis factors such as age, male sex, disease history, jaundice, fever, and hepatomegaly identified jaundice (adjusted odds ratio [AOR] = 0.048, 95% CI = 0.008–0.271) as an independent factor of viral hepatitis and fever (AOR = 10.044, 95% CI = 2.686–37.556) and old age (AOR = 1.199, 95% CI = 1.133–1.268) as an independent predictive factor of scrub typhus (Table 2).

Laboratory findings. Routine blood tests showed that the mean $\pm$ SD number of leukocytes was $5,582 \pm 2,574/\text{mm}^3$ in the hepatitis A group and $8,017 \pm 3,804/\text{mm}^3$ in the scrub typhus

FIGURE 1. Receiver-operator characteristic curves and optimal cutoff points for differential diagnosis of scrub typhus and hepatitis A, South Korea. **A**, Age; **B**, aspartate aminotransferase; **C**, alanine aminotransferase.

TABLE 2

Odds ratios for hepatitis caused by scrub typhus according to signs, South Korea*

Characteristic	AOR (95% CI)
Age	1.199 (1.133–1.268)
Male sex	0.613 (0.181–2.077)
Disease history	0.490 (0.045–5.344)
Jaundice	0.048 (0.008–0.271)
Fever	10.044 (2.686–37.556)
Hepatomegaly	0.133 (0.017–1.061)

*AOR = adjusted odds ratio; CI = confidence interval. Values in **bold** are statistically significant.

group ($P < 0.001$). The hemoglobin level was 12.6 ± 1.7 g/dL in the scrub typhus group and 14.5 ± 1.6 g/dL in the hepatitis A group ($P < 0.001$). The number of platelets was $145 \pm 70 \times 10^3/\text{mm}^3$ in the scrub typhus group and $176 \pm 90 \times 10^3/\text{mm}^3$ in the hepatitis A group ($P = 0.003$) (Table 3).

Biochemical tests showed that serum AST, ALT, bilirubin, albumin, and LDH levels were significantly higher in the hepatitis A group than in the scrub typhus group (Table 3). In liver function tests at presentation, an ALT level ≥ 40 U/L was observed in 102 (98.1%) patients in the hepatitis A group and in 147 (74.6%) patients in the scrub typhus group. An AST level ≥ 40 U/L was observed in 177 (89.8%) of patients in the hepatitis A group and in 177 (89.8%) of patients in the scrub typhus group. However, at presentation, an AST level ≥ 500 U/L was observed in only 2 (1%) patients in the scrub typhus group compared with 76 (73.1%) of patients in the hepatitis A group (76 patients) ($P < 0.001$). An AST level ≥ 500 U/L had a sensitivity of 73.1% and a specificity of 99% (AUC = 0.935, 95% CI = 89.8–97.2) for hepatitis A (Figure 1B). Similarly, an ALT level ≥ 500 U/L was found in only 2 (1%) patients in the scrub typhus group but in 91 (87.5%) patients in the hepatitis A group. An ALT level ≥ 500 U/L had a sensitivity of 87.5% and a specificity of 99% (AUC = 0.966, 95% CI = 93.9–99.3) for

hepatitis A (Figure 1C). An ALP level ≥ 130 U/L was detected in 53 (27.2%) of patients in the scrub typhus group and in 53 (51.0%) of patients in the hepatitis A group ($P < 0.001$).

The ALT:LDH ratio, in which both enzymes are expressed in multiples of the upper limit of the reference range, was ≤ 5 in 187 (97.4%) patients in the scrub typhus group and > 5 in 60 (95.2%) patients in the hepatitis A group ($P < 0.001$) (Table 3). An ALT:LDH ratio > 5 had a positive predictive value of 93.7% (95% CI = 84.7–98.2) and a negative predictive value of 98.4% (95% CI = 95.5–99.7) for hepatitis A at a cutoff value of 5. The C-reactive protein (CRP) level was 1.07 ± 0.87 mg/dL in the hepatitis A group and 9.09 ± 7.37 mg/dL in the scrub typhus group ($P < 0.001$) (Table 3). The CRP level was ≤ 3 in 95.2% of the patients in the hepatitis A group and > 3 in 85.4% of those in the scrub typhus group. At a cutoff value of 3 mg/dL, a CRP level < 3 mg/dL had a positive predictive value of 70.4% (95% CI = 61.2–78.6) and a negative predictive value of 98.8% (95% CI = 95.5–99.8) for hepatitis A. Multiple logistic analysis including ALP, bilirubin, and ALT identified a bilirubin level ≥ 1.3 mg/dL (AOR = 0.024, 95% CI = 0.004–0.163) and an ALT level ≥ 500 U/L (AOR = 0.011, 95% CI = 0.001–0.246) as independent predictive factors for viral hepatitis (Table 4).

DISCUSSION

Definitive diagnoses of acute hepatitis A and scrub typhus can be established by serologic tests for hepatitis A IgM and indirect immunofluorescent antibody assays or PCR for *O. tsutsugamushi*. However in developing or third-world countries in the Far East or Southeast Asia, the aforementioned tests are often unavailable. Therefore, this study was conducted to identify easily available markers from clinical and routine laboratory findings that are useful in differentiating hepatitis A from scrub typhus.

TABLE 3
Hematologic and biochemical profiles in acute hepatitis A and scrub typhus patients, South Korea*

Characteristic	Acute hepatitis A (n = 104)	Scrub typhus (n = 197)	P
Major liver enzymes			
ALP (U/L)	141 $\pm$ 71 (33–703)	126 $\pm$ 104 (38–583)	0.166
< 129	51 (49.0)	142 (72.8)	< 0.001
≥ 130	53 (51.0)	53 (27.2)	
Bilirubin (mg/dL)	5.12 $\pm$ 3.26 (0–20)	1.00 $\pm$ 1.01 (0–7)	< 0.001
< 1.2	10 (9.6)	164 (83.3)	< 0.001
≥ 1.3	94 (90.4)	33 (16.8)	
ALT (U/L)	2,618 $\pm$ 2,203 (16–10,097)	96 $\pm$ 121 (12–1,221)	< 0.001
< 39	2 (1.9)	50 (25.4)	< 0.001
40–499	11 (10.6)	145 (73.6)	
≥ 500	91 (87.5)	2 (1.0)	
Other laboratory findings			
Leukocytes (μL)	5,582 $\pm$ 2,574 (1,070–17,180)	8,017 $\pm$ 3,804 (1,850–20,000)	< 0.001
Platelets (μL)	176 $\pm$ 90 $\times 10^3$ (21–550 $\times 10^3$)	145 $\pm$ 70 $\times 10^3$ (17–585 $\times 10^3$)	0.003
Hemoglobin (g/dL)	14.5 $\pm$ 1.6 (10.6–18.7)	12.6 $\pm$ 1.7 (7.0–17.6)	< 0.001
CPK (U/L)	184 $\pm$ 517 (0–3,818)	241 $\pm$ 561 (9–6,114)	0.464
LDH (U/L)	2,024 $\pm$ 2,679 (189–18,100)	884 $\pm$ 339 (290–3,510)	< 0.001
CRP (mg/dL)	1.07 $\pm$ 0.87 (0–4)	9.09 $\pm$ 7.37 (0–78)	< 0.001
ESR (mm/hr)	16 $\pm$ 17 (2–85)	20 $\pm$ 17 (2–86)	0.087
γ -GGT (U/L)	309 $\pm$ 192 (9–1,022)	129 $\pm$ 159 (15–1,141)	< 0.001
AST (U/L)	2,486 $\pm$ 3,176 (42–10,875)	112 $\pm$ 122 (17–1,164)	< 0.001
ALT:LDH	36.88 $\pm$ 63.22 (6–487)	1.60 $\pm$ 1.84 (2–20.9)	< 0.001
Albumin (g/dL)	3.96 $\pm$ 0.38 (2.80–4.90)	3.63 $\pm$ 0.57 (2.10–4.99)	< 0.001
Protein (g/dL)	6.77 $\pm$ 0.67 (5.3–8.2)	6.51 $\pm$ 0.82 (3.2–8.6)	0.004
Creatinine (mg/dL)	1.0 $\pm$ 0.7 (0.6–6.8)	1.2 $\pm$ 0.7 (0.4–5.1)	0.03

*Values are no. (%) or mean $\pm$ SD. ALP = alkaline phosphatase; ALT = alanine aminotransferase; CPK = creatine phosphokinase; LDH = lactate dehydrogenase; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; γ -GGT = γ -glutamyl transpeptidase; AST = aspartate aminotransferase.

TABLE 4

Odds ratios for hepatitis caused by scrub typhus according to major liver enzyme levels, South Korea*

Enzyme	AOR†	95% CI
ALP (U/L)	1.002‡	0.995–1.009
< 129	1.00	
≥ 130	0.463§	0.113–1.903
Bilirubin (mg/dL)	0.455‡	0.282–0.735
< 1.2	1.00	
≥ 1.3	0.024§	0.004–0.163
ALT (U/L)	0.997‡	0.994–0.999
< 39	1.00	
40–499	0.874§	0.071–10.728
≥ 500	0.011§	0.001–0.246

*AOR = adjusted odds ratio; CI = confidence interval; ALP = alkaline phosphatase; ALT = alanine aminotransferase. Values in **bold** are statistically significant.

†Adjusted for age, sex, jaundice, fever, and hepatomegaly.

‡Odds ratios for continuous variables.

§Odds ratios for discontinuous variables.

Among clinical findings, eschar and rash were identified in 97% and 88.3% of the patients in the scrub typhus group, respectively, whereas they were observed in none of the patients in the hepatitis A group. These findings suggest that that these two clinical findings might be helpful in identifying scrub typhus and hepatitis A. However, there was no eschar and skin rash in hepatitis A population, and we believed it was unreasonable to include these variables in the analysis because odd ratios could not be obtained. Thus, we excluded these variables in final multivariate logistic regression.

Silpajakul and others reported that eschars were observed in 7% of dark-skinned children in Thailand.¹¹ In contrast, eschars are observed frequently in yellow-skinned children in Japan.¹² In children in Thailand, eschars are relatively difficult to detect because of darker skin, and when the eschars are atypical at the early stage they are easily overlooked. In countries in Southeast Asia such as Thailand, where scrub typhus and hepatitis A are endemic, differentiation between scrub typhus and hepatitis A is difficult in cases where eschars or rashes do not occur. Therefore, we attempted to identify markers from laboratory findings that would distinguish scrub typhus from hepatitis A.

At presentation, an AST level ≥ 40 U/L was observed in 98.1% of the patients in the hepatitis A group and 89.8% of those in the scrub typhus group. An ALT level ≥ 40 U/L was observed in 98.1% of the patients in the hepatitis A group and in 74.6% of those in the scrub typhus group. However, an ALT level ≥ 500 U/L was observed in only 1% (2 patients) of the patients in the scrub typhus group (1 patient had an ALT level $\geq 1,000$ U/L) compared with 87.5% of the patients in the hepatitis A group. Moreover, 80 (76.9%) patients in the hepatitis A group had an ALT level $\geq 1,000$ U/L. A bilirubin level ≥ 1.3 mg/dL was found in 90.4% of patients with hepatitis A and in 33% of patients with scrub hepatitis. Multiple logistic analysis confirmed ALT ≥ 500 U/L and bilirubin ≥ 1.3 mg/dL as independent predictive factors for hepatitis A. We believe that these findings will be useful in differentiating scrub typhus from hepatitis A.

It is thought that *O. tsutsugamushi* infection causes direct cytopathic injury to Kupffer cells and hepatocytes and sinusoidal endothelial cell vasculitis, resulting in increases in serum levels of AST, ALT, and γ -GGT. Conversely, in hepatitis A, liver injury is secondary to the host immune response.^{13,14} Hepatitis A virus multiplies in the cytoplasm of hepatocytes and causes non-cytopathic infections, but it leads to hepato-

cellular damage and destruction of infected hepatocytes by HLA-restricted, HAV-specific CD8+ T lymphocytes and natural killer cells.

We found that degeneration, necrosis, and apoptosis of hepatocytes are significantly more severe in patients with viral hepatitis than in those with scrub typhus, which explains the marked increase in serum AST and ALT in patients with hepatitis A. In addition, hepatic cholestasis, seen as hepatic bile plugs or brown hepatocyte pigmentation, which are more common findings in patients with hepatitis A, leads to increases in levels of γ -GGT, alkaline phosphatase, and bilirubin¹⁵. Thus, major hepatocellular necrosis and hepatic cholestasis did not develop in patients with scrub typhus but could develop in patients with hepatitis A. These are important differentiation points for scrub typhus and hepatitis A.

We confirmed that ALT levels ≥ 500 mg/dL and bilirubin levels ≥ 1.3 mg/dL are independent predictive factor of viral hepatitis. El-Newihi and others reported that the ALT:LDH ratio was < 4 in 27 patients with *Salmonella* hepatitis and ≥ 5 in 27 patients with viral hepatitis.¹⁶ Those investigators demonstrated on the basis of this result that the ALT:LDH ratio is the best discriminator between *Salmonella* hepatitis and viral hepatitis. In our study, the ALT:LDH ratio was ≤ 4 in 183 (95.3%) patients in the scrub typhus group and ≥ 5 in 60 (95.2%) patients in the hepatitis A group. An ALT:LDH ratio of 5 showed a positive predictive value of 93.7% (95% CI = 84.7–98.2) and a negative predictive value of 98.4% (95% CI = 95.5–99.7) for hepatitis A, which suggests that the ALT:ADH ratio would be useful in differentiating scrub typhus from hepatitis A. Furthermore, an increase in the ALT:LDH ratio in patients with increase liver enzyme levels can discriminate acute viral hepatitis from other forms of hepatitis, including *Salmonella* hepatitis, scrub typhus hepatitis, toxic hepatitis, and ischemic hepatitis.¹⁷

C-reactive protein is a plasma protein that is produced in the liver in response to acute and chronic stimuli, including infections, burns, surgery, major trauma, and various inflammatory conditions.¹⁸ This protein has been shown not to be useful in differentiating viral infections from bacterial infections.¹⁸ However, in our study, a CRP level ≤ 3 mg/dL was observed in 95.2% of patients in the hepatitis A group, and had a negative predictive value of 98.8% for hepatitis A, which indicates that a CRP level ≥ 3 mg/dL could be helpful in ruling out hepatitis A.

In conclusion, the results of this study suggest that several clinical and laboratory findings may be useful for differentiating scrub typhus hepatitis from hepatitis A. Clinical findings including an older age, fever, headache, rash, eschar are indicative of scrub typhus hepatitis. As for laboratory findings, an ALT level > 500 U/L, a bilirubin level ≥ 1.3 mg/dL, and an ALT:LDH ratio > 5 indicate hepatitis A. Therefore, major hepatocellular necrosis and hepatic cholestasis did not develop in patients with scrub typhus but could develop in patients with hepatitis A. These features are important differentiation points for scrub typhus and hepatitis A.

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