SEQUENTIAL CHANGES OF SERUM AMINOTRANSFERASE LEVELS IN PATIENTS WITH SEVERE ACUTE RESPIRATORY SYNDROME

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Abstract. Severe acute respiratory syndrome (SARS) is a newly emerging infectious disease. To describe the hepatic injury caused by this disease, we report the sequential changes of serum transaminase in probable SARS patients during a hospital outbreak in southern Taiwan. From April to June, 2003, 52 probable SARS patients were hospitalized. Serial serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were retrospectively analyzed and hepatitis B surface antigen (HBsAg) was also evaluated to correlate with the progression of this disease. Fifty-three percent of the patients had abnormal liver function during hospitalization. More than 70% of abnormal transaminase levels were mildly elevated. Most elevated levels were noted during the second week after onset of fever. Neither transaminase elevation nor HBsAg was related to the prognosis of SARS, and only advanced age was an independent predictor of poor outcome. Our study suggested that coronavirus causing SARS might induce liver damage.

INTRODUCTION

Severe acute respiratory syndrome (SARS) is an emerging infectious disease that first manifested in humans in China in November 2002, and has subsequently spread worldwide. At present, it has affected more than 33 countries and regions all over the world, infected 8,089 people, and killed 774 patients by September 26, 2003.¹

A new virus, the SARS-associated coronavirus, has been identified as the causal agent.^{2–5} Most coronaviruses cause either respiratory or enteric disease, and may be transmitted by the fecal-oral route. The clinical, radiologic, and other laboratory findings at the initial presentation regarding SARS have been previously described.^{2,6–10}

Mildly elevated aminotransferase levels (indicating liver damage) or liver dysfunction at the later stages of disease were noted in some patients with SARS,^{2,6,7,10} and chronic infection with hepatitis B virus was reported to be an important independent risk factor of severity in SARS.¹¹ However, sequential changes in serum aminotransferase levels are still unclear. There was an outbreak of SARS in southern Taiwan between April and June 2003. Herein we describe the sequential changes in serum aminotransferase levels and retrospectively analyze the correlation between abnormal serum aminotransferase levels, hepatitis B surface antigen (HBsAg) carrier status, and the progression of SARS.

MATERIALS AND METHODS

Between April 25 and June 5, 2003 we identified 52 probable SARS patients whose symptoms met the Centers for Disease Control and Prevention (CDC) (Atlanta, GA) definition of March 17, 2003 in our medical center in southern Taiwan. All cases were diagnosed clinically by a Committee for SARS Diagnosis in this hospital, based on the patients' clinical symptoms and the ruling out of common bacterial and viral pathogens that cause pneumonia. On the basis of the criteria for SARS that had been established by the CDC, our case definition was fever (temperature $>38^{\circ}\text{C}$), a chest radiograph (a plain radiograph of the thorax) showing evidence of consolidation with or without respiratory symptoms (e.g.,

cough or shortness of breath), and a history of exposure to an index patient suspected to have SARS or direct contact with a person who became ill after exposure to an index patient.¹² Aspartate aminotransferase (AST, upper limit of normal [ULN] = 37 units/L), alanine aminotransferase (ALT, ULN = 40 units/L), and creatine kinase (CPK, ULN = 130 units/L) levels were checked within two days after the onset of fever in 52 patients and sequentially assessed and analyzed during hospitalization. Day 1 was defined as the day of onset of fever. The clinical end point was the need for care in an intensive care unit, death, or both. We used univariate analysis to compare patients who reached the end point and those who did not, and also analyzed clinical and laboratory variances between patients with normal ALT levels and abnormal ALT levels by an unpaired Student's *t*-test, or chi-square test, as appropriate. A *P* value < 0.05 was considered to indicate statistical significance. Serial AST and ALT data were available for 48 cases. Four patients were excluded because two patients had no data on serum aminotransferase levels and two patients had extremely abnormal serum aminotransferase levels due to shock and hypoxemia. Results of testing for HBsAg were available for only 38 patients. All of these patients received the medical protocol therapy, i.e., patients received broad spectrum antibiotics and a combination of ribavirin and prednisolone as an empirical treatment. Intravenous methylprednisolone at high dosages was used in patients with respiratory distress or progressive consolidations as detected in their chest radiograph.¹³ A pulse oximeter reading was obtained if the patient had dyspnea. Eight patients carriers of were hepatitis B virus, including one with cirrhosis, but no alcoholism was noted in these patients.

RESULTS

Fifty-two patients (20 men and 32 women) with a mean $\pm$ SD age of 45 ± 20 years old (range = 21–84) were included in this retrospective study. There were 16 medical care workers, 14 relatives of hospitalized patients, and 22 patients. Forty-two patients might have been exposed to an index patient or ward in our hospital. The other 10 patients were transferred from other hospitals. The incidence of abnormal

AST and ALT levels in patients with SARS was 53%. The distribution of serum aminotransferase levels is shown in Figure 1. Most patients showed mild elevation of these levels. Seventy percent of the abnormal AST levels and 77% of the abnormal ALT levels were mildly elevated (1–2.5 times the ULN, 41–100 units/L). Only 3.8% of the patients had ALT levels greater than 200 units/L (five times the ULN). Based on the available data, the sequential changes in median serum aminotransferase levels are shown in Figure 2. Slightly elevated AST and ALT levels occurred during the second week after the onset of fever. There was no correlation between serum aminotransferase levels and muscle damage (CPK levels). There was no significant difference in the percentage of abnormal AST and ALT levels in patients who died or needed intensive care and in those who did not. Advanced age was an independent predictor of adverse outcomes. Eight patients were positive for HBsAg among 38 cases with available results. Only one patient with liver cirrhosis progressed to respiratory failure, and other seven patients had a self-limited course of SARS and did not suffer progression to respiratory failure. Twenty-one patients received intensive care and intubation during hospitalization. All patients who required intensive care also required intubation. There were no significant differences in age, sex, severity of SARS and hepatitis B virus carrier status between patients with normal ALT and abnormal ALT levels (Table 1). Only two patients received abdominal ultrasonography. One had only mild parenchyma liver disease and the other had liver cirrhosis. Sixteen patients died and the mortality was 30.7%. No autopsies were performed. Forty-six provided nasopharyngeal swabs for a reverse transcriptase–polymerase chain reaction (RT-PCR) and 19 patients provided rectal swabs. The positive rates of the RT-PCR of pharyngeal and rectal swabs were 26% and 5%, respectively. Convalescent serum antibody to SARS coronavirus was not available because some patients died and some surviving patients refused further examination.

DISCUSSION

Elevation of serum aminotransferase levels is believed to be the result of leakage from damaged cells and thus reflects hepatocyte injury. The levels of these enzymes are elevated in many forms of liver disease, especially those associated with significant hepatocyte necrosis, such as acute viral hepatitis and chemical or ischemic injury.¹⁴ The results of our study

FIGURE 1. Percentage of serum transaminase levels in patients with severe acute respiratory syndrome. AST = aspartate aminotransferase; ALT = alanine aminotransferase.

FIGURE 2. Sequential changes of serum median aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels in patients with severe acute respiratory syndrome. CPK = creatine kinase.

show that 53% of the patients with SARS had mildly elevated levels of serum aminotransferases. There was no alcoholism in these patients. Abnormal data for two patients with evidence of severe hypoxemia or shock were excluded from this study. A major side effect of ribavirin is reversible hemolytic anemia,¹⁵ but no evidence that hepatic damage could be induced by ribavirin or steroids has ever been reported. These medications (including ribavirin and steroids) were not likely to be related to the hepatic damage seen in our study. Thus, it is suggested that SARS might be involved in liver damage without a relationship to medicinal or ischemic injury.

In our study, during hospitalization some patients presented with mildly elevated aminotransferase levels at the second week after the onset of SARS. Peiris and others reported that the clinical progression of SARS was divided into a triphasic pattern.¹¹ They also hypothesized that lung damage at the second week may be related to immunopathologic damage as a result of an overly exuberant host response, rather than uncontrolled viral replication.¹¹ Although we did not perform liver biopsies on these patients, some investigators found that pathologic evaluation of the fatal SARS cases showed that hepatocytes underwent fatty degeneration, cloudy swelling, apoptosis, and dot necrosis, with Kupffer cell proliferation and portal lymphocyte infiltrations.^{16,17} Suckling mice inoculated with SARS-infected samples also demonstrated hepatocytic lesions, including vacuolar and hydropic degenerations, focal cellular condensation, and necrosis, and no coronavirus-like particles were found in the hepatocytes.¹⁸ According to our study and the earlier description, we suspect that the mechanism of liver injury by SARS coronavirus may be related to immunopathologic damage.

Chronic infection with hepatitis B virus was reported to be an important independent risk factor in the severity of SARS,¹¹ but in our study we could not find any relationship between SARS and infection with hepatitis B virus. Because only eight patients had chronic infection hepatitis B virus in our study, the power to show effect of hepatitis B virus infection on the progression of SARS was small. Of the hepatitis B virus carriers in our study, only one, the patient with cirrhosis,

TABLE 1

Univariate analysis of clinical and laboratory variables associated with abnormal alanine aminotransferase (ALT) levels

	ALT		P
	Normal	Abnormal	
Mean $\pm$ SD age (years)	48 $\pm$ 19	44 $\pm$ 17	0.378
Male/female	6/14	13/15	0.370
Hepatitis B carrier	1/12 (8.3%)	7/23 (30%)	0.216
Intensive care	10/20 (50%)	7/28 (25%)	0.125

progressed to respiratory failure. In our study, there was no significant correlation in age, sex, infection with hepatitis B virus, or poor progression between SARS patients with abnormal liver function, and no evidence of medication injury. Thus, the abnormal liver function may be due to a SARS-induced systemic inflammatory reaction. Duan and others¹⁹ reported elevated levels of ALT and (or) AST in 37.7% of 154 patients (43% were mildly elevated and 56.9% were moderately elevated); 75% of the ALT levels normalized within two weeks; levels of six types of interleukin and TNF- α were higher during the first week of hospitalization than those during the fourth week and in control groups; and the levels of some factors, such as interleukin-1 β (IL-1 β), IL-6, and IL-10, in patients with elevated levels of ALT were higher than those in patients with normal ALT levels. Duan and others also suggested that there may be a systemic inflammatory response in most SARS patients at an early stage, and liver damage is only a partial sign of this. In our study, elevated ALT levels in 53% of the patients (77% of the abnormal ALT levels were mildly elevated and only 3.8% were greater than five times the ULN) normalized in 63% of the patients within two weeks. Further study is needed to determine the hypothesis of the mechanism of liver injury.

In conclusion, SARS may be associated with a mild elevation of aminotransferase levels, and the SARS coronavirus may induce liver damage. In our study, we found that serum aminotransferase levels were only mildly elevated and developed at approximately the second week after the onset of fever in most patients with SARS. This suggests that these results might be due to the immune response induced by the SARS coronavirus rather than the cytotoxic effect of the virus. Based on our study, there was no correlation between hepatitis B virus infection and the progression of SARS. Further large-scale, longitudinal studies are needed to clarify these findings.

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