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• CLINICAL RESEARCH •

Serum hepatic enzyme manifestations in patients with severe acute respiratory syndrome: Retrospective analysis

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Abstract

AIM: To evaluate the hepatic function in patients with severe acute respiratory syndrome (SARS) and possible causes of hepatic disorder in these patients.

METHODS: One hundred and eighty-two patients with SARS were employed in a retrospective study that investigated hepatic dysfunction. Liver alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactic dehydrogenase (LDH) were analyzed in these patients. Patients with different hospital treatments were further investigated.

RESULTS: Of the 182 patients, 128(70.3%) had abnormal ALT activity, 57(31.3%) had abnormal AST activity and 87 (47.8%) had abnormal LDH activity. The peak of elevated hepatic enzyme activities occurred between the sixth day and the tenth day after the first day of reported fever. Of the 182 patients, 160(87.9%) had been treated with antibiotics, 137(75.2%) with Ribavirin, and 115(63.2%) with methylpredisolone. There was no statistically significant correlation between the duration of Ribavirin treatement and hepatic dysfunction.

CONCLUSION: Abnormal liver functions were common in patients with SARS and could be associated with virus replication in the liver.

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INTRODUCTION

Severe acute respiratory syndrome (SARS) or so-called atypical pneumonia with unknown etiology started to appear in Guangdong Province, China in November 2002 and quickly spread to other parts of China and around the world[1,2-4]. A novel coronaviruses has been identified as the etiological agent of the syndrome[5-8]. Most coronaviruses may cause either a respiratory or an enteric change. During the outbreak of SARS, abnormal hepatic enzyme activity was reported in patients of Toronto area, Canada[9]. The present study summarized the hepatic enzyme activities in patients with SARS who were treated at the China-Japan Friendship Hospital, Beijing, which started to receive patients with SARS in mid-March 2003, and was designated as one of the three hospitals in Beijing to treat patients with SARS in April 2003.

MATERIALS AND METHODS

Patients

Our study included all patients who received a diagnosis of SARS with no pre-existing live diseases and were treated at the China-Japan Friendship Hospital between March 10 and May 31, 2003, and excluded such patients with a history of liver disorders. According to the criteria for SARS that have been established by the Ministry of Health, China-Clinical Diagnostic Criteria for Severe Acute Respiratory Syndrome[10], our case definition was a fever (temperature >38 ℃), a chest radiograph of the thorax showing evidence of consolidation with or without respiratory symptoms and a history of close contact with a person to whom SARS had been diagnosed. The diagnosis was confirmed by an indirect immunofluorescence assay with fetal rhesus kidney cells that were infected with coronavirus and fixed in acetone to detect a serological response to the virus[3] or by a positive viral culture. Patients in the study included 103 male and 79 female with age ranging from 11 to 86. The age distribution is shown in Table 1.

Table 1 Age distribution of the patient

Age range (yr)	Case number (*n*)	%
Under 20	18	9.89
21-30	45	24.73
31-40	35	19.23
41-50	29	15.93
51-60	18	9.89
Above 60	37	20.33

Laboratory examination

Hepatic functions included alanine aminopeptidase (ALT), aspartate aminotransferase (AST) and lactic dehydrogenase (LDH). We studied these variables from the first day of admission to May 31, 2003. The normal values of these enzymes were 0-40 U/L for ALT, 0-42 U/L for AST and 100-250 U/L for LDH.

Data collection

We retrospectively analyzed data from 3 aspects. First, total incidence rate of abnormal liver enzyme activities were analyzed from 182 patients with SARS. Second, the time course of abnormal liver enzyme activities was dissected in 57 patients because these patients were admitted to China-Japan Friendship Hospital from beginning of the illness. The other large proportion of patients with SARS was transferred to China-Japan Friendship Hospital after the hospital was designated

specifically to treat patients with SARS on April 28, 2003. Third, analysis of ribavirin treatment for patients with SARS was performed in 84 cases, as well as their abnormal liver enzyme activities after ribavirin treatment.

Statistical analysis

We used univariate analysis to compare patients with normal and abnormal serum hepatic enzyme activities, and an unpaired Student' s *t* test, χ^2 test, or Fisher' s exact test, as appropriate. We then performed multiple logistic regression analysis with stepwise analysis to identify independent predictors of the abnormality[3]. A *P* value of less than 0.05 was considered to indicate statistical significance. All probabilities are two tailed. Statistical analysis software StatView 5.0 for Macintosh OS was employed and data were reported as mean±SD unless otherwise indicated.

RESULTS

Between March 10, and May 31, 2003, more than 100 of patients with SARS were admitted to the China-Japan Friendship Hospital; especially on May 8 a large number of patients with SARS were transferred to our hospital at severe stage and some patients were at convalescent stage. Serum samples were collected immediately after the patients were admitted to the hospital. The study included 103 male and 79 female patients from all ethnic background. The mean age was 40.42 years (range 15-78 years).

Incidence rate of abnormal liver enzyme activities in 182 patients

Transiently elevated ALT was observed in 128 (70.3%) patients with SARS. Of the 182 patients with SARS, 57 (31.3%) had elevated AST while 87 (47.8%) had abnormal LDH as indicated in Table 2.

Table 2 Incidence rate of abnormal-liver-function outcomes

	ALT	AST	LDH
Total cases (*n*)	182	182	139
Abnormal cases (*n*)	128	57	87
Ratio (%)	70.3	31.3	62.6

Time course of abnormal liver enzyme activities

The time course of abnormal liver enzyme activities was obtained from 57 patients with SARS who were admitted to our hospital at the beginning of illness. The earliest day of abnormal liver enzyme activities was the first day of illness. The peak of abnormal liver enzyme activities was between the sixth and the tenth d of illness. Liver function started to recover 15 d after onset. However, for some patients, abnormal liver enzyme activities could last for almost a month (Figure 1).

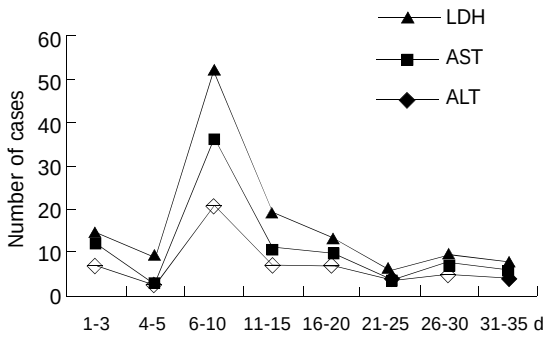

Figure 1 Abnormal-liver-function outcomes at different days.

Comparison of liver enzyme activities before and after hospital treatment

To explore whether hospital treatment could lead to abnormal liver enzyme activities in patients with SARS, we analyzed data of all patients who had normal or abnormal liver enzyme activities before and after hospital treatment. The deadline for entering analysis was June 15, 2003. Patients with hospital treatment less than 15 d were excluded from the study. As shown in Table 3, statistically significant difference was observed in AST and LDH ($P<0.01$) while no significant difference was obtained in ALT.

Table 3 Abnormal-liver-function outcomes before treatment *vs* after treatment

Cases (*n*)	ALT		AST		LDH	
	Before	After	Before	After	Before	After
Total	182	166	182	164	122	105
Normal	93	85	133	145	46	81
Abnormal	89	81	49	19	76	24

Hospital treatment in 182 patients with SARS

Most patients with SARS in our hospital received empirical treatment with antibiotics or ribavirin 400-500 mg, twice daily, or intravenous methylprednisolone at high dosage. As listed in Table 4, of the 182 patients with SARS, 160(87.9%) received antibiotics, 137(75.2%) received ribavirin and 115 (63.2%) received methylprednisolone. Since Ribavirin is a drug that inhibits viral replication, it has been widely used in patients with SARS after it was confirmed that coronavirus is etiological factor of SARS. We further analyzed the duration of Ribavirin treatment and its relation to abnormal liver enzyme activities in patients with SARS.

Table 4 Therapeutic drugs in 182 SARS patients

	Antibiotics	Ribavirin	Methylpredisolone
Cases (*n*)	160	137	115
Rate of usage (%)	87.9	75.2	63.2

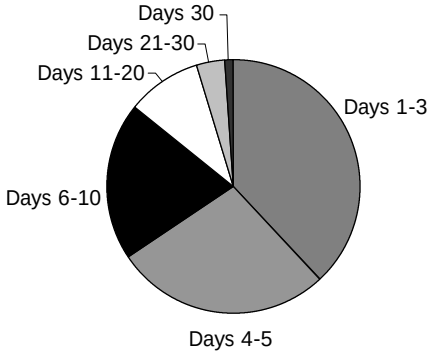

Figure 2 The distribution of of ribavirin treatment in 84 SARS patients.

Distribution of ribavirin treatment in 84 patients with SARS

Although 137 patients with SARS were recorded of ribavirin treatment, only 84 patients were employed for analysis of ribavirin treatment. The reason for choosing these patients was that these patients had detailed record of receiving ribavirin in our hospital and the other 53 patients had already received ribavirin treatment before admitting to our hospital. As shown in Figure 2, 32(38.1%) patients with SARS received ribavirin treatment at d 1 to 3 after diagnosis of SARS, 23(27.4%) patients received ribavirin treatment at d 4 to 5, 17(20.2%)

patients received ribavirin treatment at days 6 to 10. A total of 55(65.5%) patients with SARS received ribavirin treatment within 5 d of the illness while a total of 72(85.7%) patients received ribavirin treatment within 10 d of the illness.

Correlation of ribavirin treatment and abnormal liver enzyme activities

Correlation of ribavirin treatment and abnormal liver enzyme activities was analyzed in 84 patients with SARS. The duration of ribavirin treatment was different among these patients. Twenty-six (29.8%) patients with SARS received ribavirin treatment for 1 to 7 d, 32(35.7%) patients for 8 to 14 d, 20(22.6%) patients for 15 to 21 d and 10(11.9%) patients for more than 22 d. However, as shown in Table 5, there was small increase in liver enzyme activities in patients with longer Ribavirin treatment, but it did not reach statistically significant.

Table 5 The distribution of ribavirin treatment in 84 SARS patients

Treatment	Days 1-3	Days 4-5	Days 6-10	Days 11-20	Days 21-30	Days 30
Cases number	32	23	17	8	3	1
%	38.1%	27.4%	20.2%	9.5%	3.6%	1.2%

DISCUSSION

Abnormal serum liver enzyme activities have been reported by different hospitals with inconsistent incident rates. It was reported that there were 44.7% patients with SARS having abnormal liver enzyme activities in Guangzhou Southern Hospital[11], And 53.3% was reported in the First Hospital of Beijing University[12]. Moreover, 40% patients with SARS having abnormal liver enzyme activities were reported in hospitals around great Toronto area[9]. In our study, we have found that 70% patients with SARS suffered from abnormal liver enzyme activities. The higher percentage of liver damage in our patients might be related to the fact that large number of patients with severe illness were transferred to our hospital.

The difference between these reports may also be associated with different treatment strategies between these areas, especially in the use of ribavirin. Ribavirin (1-b-D- ribofuranosyl- 1,2,4-triazole), a broad spectrum antiviral nucleoside, is one of the first antiviral drugs ever discovered. It was first approved in the United States in an aerosol form for the treatment of a severe lung infection in infants[13]. Recently, it has been employed as an anti-HIV treatment[14-17] and in combination with interferon for the treatment of hepatitis A, B, and C[18-21]. Compared with hospitals around great Toronto area (88%), the usage of ribavirin in our hospital (75%) was less. However there were a larger proportion of patients (70%) with abnormal liver enzyme activities in our hospital than that (40%) in hospital around Toronto area. This indicated that ribavirin could not be a contributing factor for abnormal liver enzyme activities observed in patients with SARS. Although there was an increased trend of elevated liver enzyme activities with duration of ribavirin treatment, there was no statistic significant correlation between abnormal liver enzyme activities and duration of ribavirin treatment.

Abnormal liver enzyme activities could also be caused by coronavirus induced liver damage. Although liver biopsy was not feasible in these patients, pathological evaluation of the fatal cases revealed that hepatocytes underwent fatty degeneration, cloudy swelling, focal hemorrhage, apoptosis and dot necrosis, Kupffer cell proliferation, portal infiltration of lymphocytes and dispersive eosinophilic body in the liver[22, 23]. There was an enlargement of the liver in 23 patients with SARS in our study observed by B-ultrasonic examination (data reported in another study). Because of difficulty in clinical practice, it was not documented whether pathological impairments of liver function and structure were present in the early stage of the disease. However, we have used herbal medicines and liver protective drugs in these patients. These treatments did not alter the outcome of abnormal liver enzyme activities. Therefore, it is unlikely that hospital treatment contributes to the outcome of abnormal liver enzyme activities in patients with SARS.

Our conclusions are that abnormal liver enzyme activities are common in patients with SARS and coronaviruses that cause severe acute respiratory syndrome might affect the liver and induce liver damage in the course of infection.

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