Clinical Features of Fulminant Hepatitis in Nagasaki Prefecture, Japan

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Abstract

Objective Fulminant hepatitis is a rare but fatal disease. In the present study, we examined the changes in etiology and prognosis of fulminant hepatitis in Nagasaki Prefecture, Japan between 1980 to 1999.

Methods Eighty-one patients with fulminant hepatitis admitted to our hospitals from 1980 to 1999 were examined with respect to the etiology and prognosis.

Results Fulminant hepatitis was due to hepatitis A virus in 2 (12%) cases, hepatitis B virus in 18 (22%) cases, unknown etiology in 50 (62%) cases, and drug-induced in 11(14%) cases. The number of cases in the first half of the study (1980–1989) was 47 and that of the latter half (1990–1999) was 34 cases. The incidence of fulminant hepatitis type B also decreased from 14 cases (30%) to 4 cases (12%) during these periods. The overall survival rate of fulminant hepatitis was 32%; it was equal in fulminant hepatitis type B, fulminant hepatitis of unknown etiology and fulminant drug-induced hepatitis. The survival rate of fulminant hepatitis type A was 100%, though only two cases were identified. Retrospectively, the survival rate in patients with a pre-encephalopathy period of ≤ 10 days and aged ≤ 39 years was significantly higher than in patients ≥ 40 years of age ($p < 0.01$). There was no difference between the two age groups when pre-encephalopathy period was ≥ 11 days.

Conclusions The incidence of fulminant hepatitis especially that of fulminant hepatitis type B in Nagasaki Prefecture has decreased in recent years. The survival rate is significantly higher in younger patients with a short pre-encephalopathy period.

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Key words: etiology, survival rate

Introduction

Fulminant hepatitis is characterized by a rapidly fatal clinical course due to massive necrosis of the liver and encephalopathy. Even though viral hepatitis and drug-induced liver injury account for most cases of this rare form of hepatitis (1), we often experience difficulties in etiological diagnosis of fulminant hepatitis because of the rapid course. Recent studies have described new hepatitis viruses, such as GB virus C/hepatitis G virus (GBV-C/HGV) (2, 3) and TT virus (TTV) (4) but these viruses have not been reported to cause fulminant hepatitis (5, 6).

Nagasaki Prefecture is endemic for hepatitis B virus (HBV) infection (7). The mortality rate due to liver disease in this area is high compared to other areas of Japan (8). Recent studies have shown a decrease in the HBV carrier rate in Nagasaki Prefecture as well as in Japan and that the major form of liver diseases is from hepatitis C virus (HCV) infection (7, 9, 10). Though HBV infection is the major cause of fulminant hepatitis in Japan (11), the etiology and prognosis of fulminant hepatitis in this area have not been reported previously.

Various clinical trials on the treatment of fulminant hepatitis, such as plasma exchange or glucagon-insulin therapy, have been conducted because of its fatal course, but a marked improvement of prognosis has not been observed until now. Recently, a few centers in Japan have begun using liver transplantation. It is hoped that this treatment results in the improvement of prognosis in patients with fulminant hepatitis. In the present study, we investigated the changes in etiology and survival rates in patients with fulminant hepatitis admitted to our hospitals in the past 20 years.

Methods

Eighty-one patients with fulminant hepatitis were admitted

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to our regional hospitals between July 1980 and June 1999. There was no history of blood transfusion or liver diseases in these patients. Clinical features and results of pertinent laboratory tests are summarized in Table 1. The criteria used for the diagnosis of fulminant hepatitis were based on those described by Trey et al (12) and included: i) development of stage II to IV hepatic encephalopathy within 8 weeks of the onset of illness; ii) prothrombin time <40%; and iii) no past history of liver disease.

The diagnosis of fulminant hepatitis type A was based on the presence of IgM anti-hepatitis A virus antibody (IgM anti-HAV). Diagnosis of fulminant hepatitis type B was established by the presence of IgM anti-hepatitis B virus core antibody (IgM anti-HBc) or hepatitis B surface antigen (HBsAg). Fulminant hepatitis unknown etiology was established when IgM anti-HAV, IgM anti-HBc and HBsAg were negative and no obvious cause of drug was noted. Diagnosis of drug-induced fulminant hepatitis was established when an obvious cause of drug was identified. IgM anti-HAV was assayed in 72 patients and antibody to HCV (anti-HCV) was assayed by second or third generation radioimmunoassay in 30 patients. Tests for these virus markers were performed in all patients at the time of admission.

Fifty-one percent of patients were treated with plasma ex-

change and 54% received glucagon-insulin therapy. Fifty-one percent of patients were treated by corticosteroids and only one case was treated by liver transplantation. Statistical analysis was performed using the Student t-test and chi-square test. Differences between groups were considered statistically significant when $p < 0.05$.

Results

Clinical background and etiology of fulminant hepatitis

Of 81 patients, 2 (2%) patients were classified as fulminant hepatitis type A, 18 (22%) patients as fulminant hepatitis type B, 50 (62%) patients as fulminant hepatitis of unknown etiology and 11 (14%) patients as fulminant drug-induced hepatitis. The cause of fulminant drug-induced hepatitis was antituberculous drugs in 4 cases, halothane in 2 cases, 5-fluorouracil in 2 cases, amoxicillin in 1 case, acetaminophen in 1 case and mercazole in 1 case. Anti-HCV was positive for 1 case though the relationship between fulminant hepatitis and HCV infection is not known. The sex ratio and pre-encephalopathy period were not different between the four groups. The mean age of patients with fulminant drug-induced hepatitis was significantly higher than those with fulminant hepatitis type B ($p < 0.001$) and fulminant hepatitis of unknown etiology ($p < 0.05$) (Table 2).

To examine changes in the etiology of fulminant hepatitis across the period of the study, we divided our patients into those diagnosed between 1980 to 1989 and the second group diagnosed between 1990 and 1999 (Table 3). The numbers of fulminant hepatitis in the second period (34 cases) was less than in the first period (47 cases). The sex ratio, mean age, pre-encephalopathy period and survival rate were similar between these two groups (Table 3). Figure 1 shows the sequential percent changes in the etiology of fulminant hepatitis. The frequency of fulminant hepatitis type B in the second period (4 cases, 12%) was less than in the first period (14 cases, 30%). The frequency of patients with fulminant hepatitis of unknown etiology in the second period (22 case, 65%) was also lower than in the first period (28 cases, 60%), though these percents were similar between these periods. In contrast, the frequency of fulminant drug-induced hepatitis was equal between these periods.

Table 1. Clinical Background of Patients with Fulminant Hepatitis

n	81
M/F	30/51
Age (years) (range)	47 (12–90)
Survival rate (%)	32
AST (IU/l) (range)	1,320 (42–7,500)
ALT (IU/l) (range)	1,328 (26–8,200)
TB (mg/dl) (range)	17.4 (0.5–41.5)
PT (%) (range)	22.8 (0–39)

n: number, M/F: males/females, IU/l: international unit/liter, AST: aspartate aminotransferase, ALT: alanine aminotransferase, TB: total bilirubin, PT: prothrombin time.

Table 2. Etiology of Fulminant Hepatitis

Etiology	n	M/F	Age*	Pre-encephalopathy period (days)	Survival rate (%)
HAV	2	2/0	44	9.5 (6–13)	100
HBV	18	7/11	39.1±16.3†	9.9 (1–30)	28
Unknown etiology	50	5/6	46.7±20.8‡	14.5 (1–47)	30
Drug	11	16/34	63.1±14.9	13.4 (1–43)	36

n: number, M/F: males/females. HAV and HBV denotes hepatitis A virus and hepatitis B virus, respectively. *Data are expressed as mean ± SD. † $p < 0.001$ compared to the drug-induced group. ‡ $p < 0.05$ compared to the drug-induced group.

Table 3. Clinical Background of Patients with Fulminant Hepatitis According to the Year of Hospitalization

	1980–1989	1990–1999
n	47	34
M/F	17/30	13/21
Age*	47.0±19.6	47.5±20.8
Pre-encephalopathy period (days) (range)	21 (1–47)	14 (1–43)
Survival rate (%)	30	36

n: number, M/F: males/females. *Data are expressed as mean±SD.

Figure 1. Changes in the etiology of fulminant hepatitis during the period of 1980 to 1999. □: hepatitis A virus, ▨: hepatitis B virus, ▩: unknown etiology, ■: drug-induced.

Survival rate in patients with fulminant hepatitis

Of 81 patients with fulminant hepatitis, 26 (32%) survived. The survival rates in patients with fulminant hepatitis type B, fulminant hepatitis of unknown etiology and fulminant drug-induced hepatitis were similar (Table 2). Though the fulminant hepatitis type A group consisted of only two cases, both survived. No gender difference was detected in the survival rate. In patients whose pre-encephalopathy period was ≤10 days, survival rate in ≤39-year-old patients was significantly higher than that in patients those ≥40 years of age ($p<0.05$). This difference was not seen in patients whose pre-encephalopathy period was ≥11 days (Table 4).

Discussion

In this study, 18 (22%) patients had fulminant hepatitis type B. A previous Japanese report by Takahashi and Shimizu (11) showed that among 236 patients with fulminant hepatitis throughout Japan, 48% were diagnosed with fulminant hepatitis type B. The overall incidence of fulminant hepatitis type B in our study was slightly lower compared with the above-mentioned report. More importantly, however, the incidence of ful-

Table 4. Survival Rate in Patients with Fulminant Hepatitis According to the Duration of Pre-encephalopathy Period

Age (years)	Pre-encephalopathy period			
	≤10 days		≥11 days	
	n	Survival (%)	n	Survival (%)
≤39	20	12 (60)*	8	2 (25)
≥40	24	4 (17)	29	8 (28)

* $p<0.05$.

minant hepatitis type B in our study decreased from 30% in 1980–1989 to only 12% in 1990–1999. The first half of this study (1980–1989) was almost the same period as that reported by Takahashi and Shimizu (11). A recent report from the Ministry of Health and Welfare in Japan also showed a higher incidence of fulminant hepatitis type B in 1989–1997 compared with our data, however, it had decreased during the observation period (13). The reduction in the number of patients with fulminant hepatitis type B seems to be associated with a reduction of the number of HBV carriers. Several investigators have recently reported patients with HBV-related liver diseases who were negative for serum HBV markers (14, 15). Using polymerase chain reaction (PCR), we have also shown the presence of HBV genome in the serum of more than half of the patients with fulminant hepatitis in Nagasaki Prefecture, though some of these patients were negative for HBsAg or IgM anti-HBc (16). Interestingly, many patients with fulminant hepatitis type B showed a rapid clearance of HBsAg and early appearance of antibody to HBsAg. This reason probably explains the frequent presentation of seronegative patients with fulminant hepatitis type B. Thus, it is likely that the number of patients with fulminant hepatitis type B would have been higher in the present study if PCR for HBV genome was performed. The number of patients with fulminant hepatitis type B as well as patients with all types of fulminant hepatitis has been diminishing in recent years. A high incidence of fulminant hepatitis type B has also been observed in Greece (17), India and France (18). In contrast, acetaminophen overdose is the leading cause of fulminant hepatitis in the United Kingdom (19) and United States (18).

In the present study, 50 (62%) of 81 patients were found to have fulminant hepatitis of unknown etiology. The frequency of fulminant hepatitis of unknown etiology also decreased in the second half of our study. HAV and HBV are the major causative viruses of fulminant hepatitis in Japan. The importance of delta virus or hepatitis E virus as a cause of fulminant hepatitis has also been demonstrated (1), however, the incidence of these forms of viral hepatitis in Japan is low (20, 21) and there are no reports of patients with fulminant hepatitis caused by these viruses in Japan. Furthermore, newly identified GBV-C/HGV and TTV have not been reported to cause fulminant hepatitis (5, 6). Unfortunately, the relationship between fulminant

hepatitis and GBV-C/HGV or TTV in this study was not clear because PCR for these viruses was not performed. Further efforts should be directed to find new viruses of fulminant hepatitis of unknown etiology.

The survival rates in patients with fulminant hepatitis type B, fulminant hepatitis of unknown etiology and fulminant drug-induced hepatitis were equal in our study (range, 28–36%). Similar results were also reported by Takahashi and Shimizu (11). We also showed that the survival rate in the first half was equal to that in the latter half of the study. Liver transplantation is the most effective method for the treatment of fulminant hepatitis in other countries (22). It clearly improves the prognosis of patients with fulminant hepatitis (22). However in Japan, liver transplantation begun only recently and to date only a small number of patients have undergone such treatment. The present cases included only one patient treated by liver transplantation. In this study, the survival rate of patients younger than 39 years of age was significantly higher than those over 40 years of age. This difference was only seen in patients whose pre-encephalopathy period was ≤ 10 days. The reason for this difference is not clear at this stage as the etiologies and other factors in these groups were similar.

In conclusion, the incidence of fulminant hepatitis, especially that of fulminant hepatitis type B in Nagasaki Prefecture, has decreased in recent years. However, the survival rate has not improved in the past 20 years though various types of treatments have been tried.

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