Fulminant and Subfulminant Hepatitis in Japan — Etiological Considerations

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To determine the relative frequency of various hepatitis viruses as the cause of acute hepatic failure and the natural history in relation to the etiologic agents in Japan, a collaborative survey was carried out from 1983 to 1987. The criteria for inclusion were acute hepatitis patients who developed i) hepatic encephalopathy of grade II or more within two months after the onset of hepatic symptoms, ii) plasma prothrombin levels less than 40%, or iii) massive or submassive necrosis of the liver on biopsy or at necropsy. Patients with previous chronic or alcoholic liver disease were excluded, but asymptomatic hepatitis B virus (HBV) carriers were included.

Active members of the Japanese Gastroenterological Society in 278 institutions participated by filling in a questionnaire designed to obtain information about patients with fulminant hepatic failure. Completed questionnaires of 507 patients were received. Of these 38 patients had drug-induced hepatitis and 17 had developed acute hepatic failure following halothane anesthesia. The remaining 452 patients (89.2%) were presumed to have a viral etiology. Of these 412, in 236 patients the available serological data for HAV and HBV were deemed adequate (HCV serological data were not available at the time of study).

Survival rate and length of pre-encephalopathy period

None of the 24 patients with a pre-encephalopathy period (PEP) (from onset of hepatic symptoms) of less than 3 days lived, but nearly 40% of those with a PEP of 5-6 days lived. The survival rate for all patients with a PEP of less than 11 days was 29.4%, which was significantly higher (p < 0.001) than the corresponding figure of 14.8% for those who developed encephalopathy more than 11 days after the onset of symptoms. Based on these results, comparison was made for various factors between those with a PEP of 10 days or less (acute form) and those with a PEP of more than 10 days (subacute form).

Types of virus

HBsAg was positive in 35.6% of 447 patients. The 236 patients with complete viral serology data consisted of 18 with hepatitis A (HA) (IgM anti-HAV positive), 112 with hepatitis B (HB) (high IgM anti-HBc positive) and 106 with non-A, non-B hepatitis (HNAHB) (negative for IgM anti-HAV and IgM anti-HBc). The average PEP was 8 (3-29) days in the HAV group, 7 (1-60) days in HBV, and 19 (2-60) days in the HNAHB group. HNAHB showed significantly longer PEP compared with the other two groups (p < 0.05). While none of the HA cases were associated with blood transfusion, 24.1% of HB and 13.2% of HNAHB patients had history of transfusion. The overall survival rate was 61.1% in HA, 36.6% in HB, and 18.9% in HNAHB, indicating the poorest prognosis in HNAHB patients.

Acute and subacute forms

Among 234 patients in whom PEP was accurately determined, the survival rate was 40.0% in those with acute form (n = 120) and 20.2% among those with the subacute form (n = 114) (p < 0.001). The mean age was 40.4 and 47.6 years respectively (p < 0.01). The acute form comprised 83.3% of HA patients, 70.0% of HB and 26.4% of HNAHB patients. Thus, 73.6% or the large majority of HNAHB patients belonged to the subacute group (for further analysis, see below). Among the HNAHB group, which consisted of 28 patients of the acute form and 78 of the subacute form, certain differences were noted in the laboratory data between the two forms (Table 1). The

Table 1: Comparison of clinical features among acute NAB and subacute NAB fulminant hepatitis (1983-87) in Japan (With permission from Blackwell Scientific Publications).

<table>
<thead>
<tr>
<th>Pre-encephalopathy period</th>
<th>≤10 days (n = 20)</th>
<th>&gt;10 days (n = 78)</th>
</tr>
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<tbody>
<tr>
<td>Survival (%)</td>
<td>39.3</td>
<td>11.5</td>
</tr>
<tr>
<td>Anti-HBs positive (%)</td>
<td>48.1</td>
<td>22.4</td>
</tr>
<tr>
<td>MEL</td>
<td>13.5</td>
<td>27.5</td>
</tr>
<tr>
<td>AST</td>
<td>86.9</td>
<td>32.6</td>
</tr>
<tr>
<td>ALT</td>
<td>1080</td>
<td>359</td>
</tr>
<tr>
<td>Bilirubin (μmol/L)</td>
<td>13.5</td>
<td>23.3</td>
</tr>
<tr>
<td>Prothrombin (%)</td>
<td>20.3</td>
<td>25.8</td>
</tr>
<tr>
<td>History of blood transfusion (%)</td>
<td>17.4</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Laboratory data at the time when encephalopathy developed.
average leukocyte count was 12,300/μL, ALT 1,080 U/L, and total bilirubin 13.5 mg/dL in the acute form as compared to corresponding figures of 9,5000/μL (p < 0.05), 35 U/L (p < 0.001) and 23.3 mg/dL (p < 0.01) for the subacute form.

Fulminant and subfulminant failure and etiology

Several workers proposed different cut-off periods to distinguish between fulminant and subfulminant hepatic failure using different terms. Banhamou et al. suggested 2 weeks from onset of jaundice, and Redeker et al. suggested an interval of 8 weeks from onset. They further subdivided their cases of early onset hepatic failure into hyperacute, acute and subacute hepatic failure; serological data were not taken into account in these classifications. We compared our classification with those of Redeker and Banhamou with reference to our own data (Table 2). The results showed that while our subacute cases were mostly due to HNANB (73.6%), in the other two studies, 70% of the fulminant cases were due to HNANB. We presume that the subacute type of hepatic failure caused by viral hepatitis is mainly due to HCV (HANB), and for that reason, our classification may be more practical and realistic from a virological point of view. When Redeker's classification was applied to our patients, only 1 of our HAV and 9 of 104 (8.7%) of our HBV patients were of subacute type.

The relationship between our subacute form, fulminant hepatitis and late onset hepatic failure (LOHF) proposed by Williams has to be defined. The subacute form by our definition seems to have features of both acute fulminant hepatic failure and LOHF, and may be regarded as an intermediate form. Patients who develop hepatic encephalopathy within 24 weeks may represent a continuous spectrum in terms of acuteness of illness, with acute fulminant failure on one end and LOHF on the other; the former is characterized by acute onset of encephalopathy, and the latter by late onset of encephalopathy and relatively early development of ascites, with no clearly separable point in time. For practical purposes, the spectrum may be divided into three: fulminant, subfulminant and late-onset hepatic failure. Subfulminant and late onset hepatic failure carry a graver prognosis because they are mostly due to HNANB.

The National Group for the Study of Fulminant Hepatic Failure in Japan is still continuing to study this problem. Late onset hepatic failure cases were also included in the survey after 1985. Patients who developed hepatic failure signs between 8 weeks and 6 months from the onset of disease were further divided into LOHF (Gimson's definition), in which grade II coma set in before ascites, and subacute hepatitis (SAH) in which ascites developed first and remained grade I or less. The latter more or less corresponds to the original definition given by Tandon in India. Thus, there were 22 LOHF and 27 SAH cases compiled during the period from 1985 to 1989 (Table 3). There were several distinct differences between LOHF and SAH: (i) mortality was 100% in the former whereas 88.9% of the latter survived, (ii) there were no drug induced cases in LOHF, and (iii) ALT was lower in LOHF. It seems that LOHF and SAH are less common as compared to fulminant hepatic failure in Japan and clearly SAH is far more common in India. Hepatitis E as a cause needs further investigation in the Indian cases.

One imminent problem at the moment is whether HCV is the main cause of subacute form of fulminant hepatitis and LOHF. Although several reports from Japan have suggested an etiologic role of HCV, data from Paris and London do not support such a notion (Banhamou J-P and Williams R, personal communication). At the Chiba University Hospital, none of the 500 post-trans-
fusion HNANB cases was fulminant, suggesting the incidence of HCV induced fulminant hepatitis to be less than 0.2% if we presume that all HNANB cases were C hepatitis (Omata M, personal communication).

Conclusion

In Japan, the main etiology of fulminant and subfulminant hepatic failure is viral in Japan. HAV does not cause subfulminant or subacute form of fulminant hepatitis, which is mainly caused by HNANB. Whether HCV is the major type of HNANB causing severe hepatitis remains to be determined.

References