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Research Article

Hepatic histological comparison between Acute Self-limiting Hepatitis A and Hepatitis E

Abstract

Background: Histological findings of the liver in acute liver injury are basically affected by degree of liver damage. However, the differences in liver histology between acute self-limiting hepatitis A (AH-A) and hepatitis E (AH-E) have not yet been clarified. This study aimed to clarify the differences in histological findings of the liver between AH-A and AH-E.

Methods: Fourteen patients with AH-A and 11 patients with AH-E matched with the period between the onset of AH and the performance of liver biopsy and with the degree of liver function impairment were studied. The activity grade and fibrosis stage were evaluated using the METAVIR scoring system and the semiquantitative scores using 9 items from histological findings: interface hepatitis, portal lymphocytes, portal neutrophils, lobular necrosis, lobular inflammation, steatosis, ballooning, Mallory bodies, and cholestasis.

Results: The patients with AH-E were significantly older and had a higher proportion of males than the patients with AH-A. Although liver function test values and prothrombin time on admission significantly differed between AH-A and AH-E, these values on the day of liver biopsy were not significantly different between AH-A and AH-E. Among the histological scores studied, lobular necrosis score was significantly higher in AH-A than in AH-E. Alcohol abuse did not affect the histological differences between AH-A and AH-E. Among the AH-E patients, activity grade, lobular necrosis, and lobular inflammation scores were significantly high in patients showing positive drug-induced lymphocyte stimulation tests.

Conclusions: The lobular necrosis score among the histological findings of the liver was significantly higher in AH-A than in AH-E. Aging and immunoreaction against drugs might contribute to the histological changes in AH-E.

Background

Both hepatitis A virus (HAV) and hepatitis E virus (HEV) are well known as enteric transmission hepatitis viruses [1-6]. Acute hepatitis due to HAV (AH-A) and HEV (AH-E) infections usually occurs in young people, both sporadically and epidemically, in developing countries. On the other hand, AH-A and AH-E in industrialized countries including the USA, European countries and Japan are often seen even in older people, because the positive rate of serum anti-HAV immunoglobulin (Ig) G has decreased in older people; additionally, the positive rate of serum anti-HEV IgG has become extremely low in all age groups [7-11]. AH patients with HAV and HEV infection often progress to acute liver failure (ALF) [12-15]. In particular, sex, age, genotype and the existence of pregnancy in AH-E, and nucleotide variations in the 5' non-translated region of HAV RNA in AH-A have been closely associated with the progression of ALF, respectively [3,4,8-15].

Worldwide, the serological diagnoses of HAV and HEV infection are already being confirmed based on the tests of anti-HAV IgM and anti-HEV IgM and/or anti-HEV IgA. Furthermore, while HAV has six genotypes (I-VI), of which genotypes I, II and III are found in humans, HEV has four genotypes [1-8]. The prevalence of specific genotypes of HAV and HEV are different among the various areas of the world. In Japan, genotype I of HAV, and genotypes 3 and 4 of HEV are the major genotypes, respectively. Additionally, HEV genotypes 3 and 4 have been known as zoonotic and autochthonous viruses [4,8,12,15-24]. Our previous recent reports have shown that, on Honshu Island, including Iwate Prefecture and excluding Hokkaido Island, the majority of sporadic cases of AH have shown genotype IA in AH-A, and genotype 3 in AH-E [12,25-

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27]. Furthermore, peak values of liver function tests showed significant differences in the AH-E patients with genotype 3 or genotype 4. The AH-E patients with genotype 4 had high peak alanine aminotransferase (ALT) and lower prothrombin time activity (PT) compared to the patients with genotype 3, suggesting that the HEV genotype is one of the important risk factor associate with the disease severity [12,26,27].

When the clinical symptoms and laboratory data have been compared between AH-A and AH-E patients, the prevalence of clinical symptoms such as high fever (≥38°C) and peak values of liver function tests representing serum transaminases (ALT and aspartate aminotransferase (AST)) and total bilirubin (T-Bil)) have been significantly higher in AH-A patients than in AH-E patients, while the peak values of serum gamma-transpeptidase (γGTP) and alkaline phosphatase (ALP) have been higher in AH-E patients than in AH-A patients. Additionally, the majority of patients with AH-E have been male, and the mean age has been >50 years except in imported cases [25-27]. These findings suggest that the immunological reaction in the liver may be different between AH-A and AH-E.

In typical AH patients with HAV or HEV infection, except for patients who progress to ALF or acute on chronic liver failure (AOC), histological findings of the liver such as focal necrosis, infiltration of lymphocytes and plasma cells into the portal area, and cholestasis are generally seen [13,28-32]. These pathological changes may be affected by the following factors: 1) degree of liver damage; 2) duration from disease onset to observation of liver histology; and 3) area of the liver biopsy that is performed. However, the differences in liver histology between self-limiting AH-A and AH-E have not yet been clarified.

The aims of the present study were to compare the histological findings between self-limiting AH-A and AH-E and to clarify whether histological changes of the liver could explain the differences in liver function test results between AH-A and AH-E.

Materials and Methods

Subjects

We experienced a total of 103 patients with AH-A or AH-E (68 in AH-A and 35 in AH-E) from 1998 to 2014. AH-A and AH-E were diagnosed by the patient's past history, course of the present illness, routine biochemical examinations including liver function tests and serological viral markers, and imaging tests such as abdominal sonography and computed tomography and/or liver histology. Among these 103 patients, those having ALF with hepatic encephalopathy or liver cirrhosis (LC) and AOC determined by clinical definitions, liver biopsy and/or autopsy were excluded [33-36]. To precisely evaluate the histological differences between AH-A and AH-E, it is fundamentally important to match the period from the onset day of hepatitis to the liver biopsy with the degree of liver function. Therefore, we excluded two AH-E cases showing a long period (152 or 146 days) until liver biopsy. Finally, 14 patients with AH-A and 11 patients with AH-E who underwent liver biopsy were recruited into the present study (Tables 1,2). Serum viral markers of hepatitis B virus, hepatitis C virus, Epstein-Barr virus, and cytomegalovirus were negative in all patients with AH-A and AH-E on admission.

HAV and HEV infections were diagnosed by positivity for anti-HAV IgM and anti-HEV IgA or IgM in serum, respectively. When serum anti-HAV IgM and anti-HEV IgA or IgM were positive, HAV-RNA and HEV-RNA were examined by nested reverse transcription polymerase chain reaction (RT-PCR) as previously reported [1-4,8]. Additionally, genotype and subgenotype of HAV and HEV were also examined using

Table 1: Profiles of Patients with Acute Hepatitis A.

Case No.	Age (y)	Sex (M/F)	HAV genotype/ subgenotype	T.Bil (mg/dl) peak/at biopsy+	ALT (IU/L) peak/at biopsy+	PT (%) min/at biopsy+	Alcohol (>40 g/day)	Death	DLST	Biopsy (day)++
A1	47	M	n.t	11.3/1.0	9640/18	23/81	Yes	No	n.t	77
A2	45	F	IA	7.9/0.8	5160/28	17/76	No	No	n.t	41
A3	43	M	IA	7.2/0.9	4394/47	46/72	No	No	n.t	37
A4	52	M	IA	17.4/1.5	9120/37	23/100	Yes	No	n.t	47
A5	24	F	IA	13.4/2.2	4846/41	47/93	No	No	n.t	41
A6	41	M	IA	11.4/1.3	4926/53	42/64	No	No	negative	44
A7	46	F	IA	7.9/1.1	380/241	65/74	No	No	n.t	48
A8	54	M	IA	9.8/1.4	3695/89	65/100	No	No	n.t	24
A9	49	M	IA	9.1/1.3	7949/44	11/89	No	No	n.t	50
A10	47	M	IA	11.2/1.0	2515/154	68/68	Yes	No	negative	79
A11	47	F	IA	4.7/0.7	4698/41	27/78	No	No	n.t	42
A12	41	F	IA	7.5/1.0	1180/44	100/100	No	No	n.t	31
A13	28	M	IA	10.4/1.6	7540/39	36/60	No	No	n.t	27
A14	69	F	IA	9.8/2.8	8150/148	59/100	No	No	n.t	34

+ Peak or minimum value during administration period and value at the day of biopsy.

++ Days from onset of the disease to liver biopsy. M: male, F: female, HAV, hepatitis A virus; T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PT: prothrombin time activity, DLST: drug-induced lymphocyte stimulation test, n.t, no test.

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previously reported methods [12,16]. Alcohol intake (ethanol, g/day) was calculated from the questionnaire administered to each patient and divided into two categories: over 40 g/day and under 40 g/day. Among the 20 (12 with AH-A and 8 with AH-E) patients who had a history of receiving any drugs before and after the early stage of disease onset, 7 (2 with AH-A and 5 with AH-E) underwent the drug-induced lymphocyte stimulation test (DLST) (namely, the lymphocyte transforming test) [37-39]. DLST was measured by a clinical laboratory (SRL Institute, Tokyo, Japan). For specimen collection, approximately 10 ml of peripheral blood with EDTA were obtained from the cubital vein in each patient, after which the blood sample was immediately transferred into an ice box, carried to the laboratory, and measured within 48 hours.

Histological examination

Liver biopsy was performed after obtaining written informed consent from each patient. In all cases, tissue samples were obtained by percutaneous liver biopsy under abdominal sonography and immediately fixed with 10% neutral formalin and embedded with paraffin. The samples were serially sectioned and stained with hematoxylin, periodic acid-Schiff with and without amylase digestion (PAS, d-PAS), Masson's trichrome, and Perls' Prussian blue stains. Evaluation of histological criteria was made by two pathologists (co-authors, Tatemichi Y and Masuda T). Because the standard histological criteria for AH were not confirmed, we evaluated the grade of activity and the stage of fibrosis using the French METAVIR scoring system (A0, no activity; A1, mild activity; A2, moderate activity; A3, severe activity; and F0, no portal fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with few septa; F3, portal fibrosis with many septa but no cirrhosis) [40,41]. Additionally, interface hepatitis, portal lymphocytes, portal neutrophils, lobular necrosis, lobular inflammation, steatosis, ballooning, Mallory bodies, and cholestasis were scored semiquantitatively, as shown in table 3. The calculated mean score by two observers was used as the value in each patient.

Ethics

Liver biopsy was performed after obtaining written informed consent from each patient. The study was conducted according to the ethical guidelines of the 1975 Declaration of Helsinki.

Table 2: Profiles of Patients with Acute Hepatitis E.

Case No.	Age (y)	Sex (M/F)	HEV Genotype$	T.Bil (mg/dl) peak/at biopsy+	ALT (IU/L) peak/at biopsy+	PT (%) min/at biopsy+	Alcohol (>40 g/day)	Death	DLST	Biopsy (day)++
E1	46	M	3jp	4.1/0.8	2824/22	74/80	No	No	n.t.	41
E2	72	M	3us	20.0/4.4	947/28	98/100	Yes	No	n.t.	37
E 3	73	M	3us	1.6/0.6	672/21	73/78	No	No	n.t	26
E 4	65	M	3jp	30.4/11.0	1483/972	82/79	No	Yes*	positive	72
E 5	68	M	3jp	25.9/2.3	2875/58	51/94	Yes	No	negative	75
E 6	61	M	3jp	32.4/3.9	409/39	100/100	No	No	n.t	68
E 7	70	M	3us	1.7/0.7	1821/60	100/100	No	No	negative	23
E 8	51	M	3jp	23.8/11.6	1356/53	100/90	No	No	positive	71
E 9	18	F	3jp	4.5/0.7	1820/26	41/100	No	No	n.t	22
E 10	61	M	3jp	17.5/3.7	3541/46	33/100	No	No	positive	24
E 11	71	M	3jp	13.0/2.8	3086/104	45/84	No	No	n.t	21

$Genotype 3 was further divided into two groups (3jp and 3us) in the present study: 3jp stands for Japan-type and 3us stands for US- type

+ Peak or minimum value during administration period and value at the day of biopsy.

++ Days from onset of the disease to liver biopsy. M: male, F: female; T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PT: prothrombin time activity, DLST: drug-induced lymphocyte stimulation test, n.t, no test.

*The causes of death in patient E4 were gastrointestinal bleeding and disseminated intravascular coagulation induced by hypersensitive syndrome and cytomegalovirus infection

Table 3: Histological Findings Scored Semiquantitatively.

Score	0	1	2	3
Interface hepatitis*1	<5%	5%≤33%	33%≤66%	>66%
Portal lymphocytes	none	a few	some	frequent
Portal neutrophils	none	a few	some	frequent
Lobular necrosis	none	focal	zonal	massive
Lobular inflammation	none	a few	some	frequent
Steatosis*2	<5%	5%≤33%	33%≤66%	>66%
Ballooning	none	a few	some	frequent
Mallory bodies	none	1/HPF	2-5/HPF	>5/HPF
Cholestasis	none	a few	some	frequent

*1: Percentage of portal tract perimeter displaying interface hepatitis; *2: Percentage of lobule area displaying hepatocytes with steatosis; HPF: high power fields.

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Statistical analysis

Results were expressed as mean ± standard deviation (SD), unless otherwise specified. We performed statistical analysis using the unpaired Student's *t*-test and/or Mann-Whitney's U-test, as appropriate. All significant data were two-tailed, and a P value of less than 0.05 was considered to be significant.

Results

Differences in clinical background and laboratory data between AH-A and AH-E patients

There was no significant difference in the number of days until liver biopsy between the patients with AH-A and AH-E. The mean age of the AH-E patients was significantly higher than that of the AH-A patients, and the proportion of males among the AH-E patients was also significantly higher than in the AH-A patients. There was no significant difference in the amount of alcohol intake (>40 g/day) between the patients with AH-A and AH-E (3 cases, 21.4% in AH-A; and 2 cases, 20% in AH-E, respectively). The clinical disease forms of AH were divided into two groups: self-limiting AH and acute severe hepatitis without encephalopathy (ASH) based on the criteria for these diseases in Japan [24, 28-31]. The prevalence of these two forms was not significantly different between the AH-A and AH-E patients (Table 4).

While the maximum values of serum AST and ALT were significantly higher in AH-A, the maximum values of serum T-Bil in AH-A and AH-E were similar. The minimum values of prothrombin time activity (PT) were significantly lower in AH-A. The maximum values of serum γGTP and ALP in AH-E were higher than those in AH-A, but not significant. The values of these liver function tests on the day of liver biopsy were not significantly different between AH-A and AH-E.

Among the 7 patients who underwent DLST (Table 5), DLST was positive in 3 with AH-E (3/5, 60%), but in none with AH-A (0/2, 0%). Thus, we divided the AH-E patients into two groups: group I were the patients who were DLST-positive; group II were the patients who were both DLST-negative and who did not receive DLST. The values of these liver function tests on the day of liver biopsy were not significantly different between the two groups (data not shown).

Differences in liver histology between AH-A and AH-E patients

The scores of each histological item except lobular necrosis were not significantly different between AH-A and AH-E (Table 6). Mallory bodies were not seen in either AH-A or AH-E. Furthermore, there was no significant difference between AH-A and AH-E for history of alcohol abuse (data not shown). The relationship between the genotypes of HAV and HEV with respect to histological findings could not be evaluated, because the genotypes of HAV were all IA, and those of HEV were all 3 (3jp in 8, 3us in 3).

In AH-E patients who were DLST-positive (group I), the scores of three items—activity grade, lobular necrosis, and lobular inflammation—were significantly higher than in group II. The steatosis score in group II was significantly higher than in group I (Table 7). The degree of eosinophilic leukocyte infiltration showed no significant difference between the two groups (data not shown).

Table 4: Differences in Clinical and Laboratory Data between AH-A and AH-E Patients.

Parameters	AH-A (n=14)	AH-E (n=11)	P value
Sex (male/female)	8/6	10/1	0.061
Age (years)	45 ± 10	56 ± 16	0.013
AH/ASH+	9/5	8/3	0.669
Days until liver biopsy	44 ± 16	44 ± 23	0.924
Maximum or minimum values of liver function tests on acute phase$			
T. Bil (mg/dl)	9.9 ± 3.0	16 ± 12	0.125
AST (IU/ml)	6064 ± 4582	1749 ± 941	0.004
ALT (IU/ml)	5296 ± 2861	1894 ± 1050	0.001
PT (%)	45 ± 25	74 ± 28	0.013
γGTP (IU/l)	444 ± 247	547 ± 657	0.591
ALP (IU/l)	718 ± 245	1553 ± 1585	0.101
Values of liver function tests on the day liver biopsy performed			
T. Bil (mg/dl)	1.3 ± 0.6	3.9 ± 4.0	0.059
AST (IU/ml)	46 ± 34	426 ± 1281	0.348
ALT (IU/ml)	73 ± 64	131 ± 280	0.459
PT (%)	83 ± 14	91 ± 10	0.091
γGTP (IU/l)	101 ± 74	146 ± 103	0.216
ALP (IU/l)	306 ± 92	550 ± 456	0.061

+AH: acute hepatitis, ASH: acute severe hepatitis without hepatic encephalopathy. AH-A: acute hepatitis A, AH-E: acute hepatitis E.
$ T-Bil: total bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, PT: prothrombin time activity, γGTP: gamma glutamyltranspeptidase, ALP: alkaline phosphatase. Values are expressed as the mean ± standard deviation.

Discussion

Generally, cases of classical and self-limiting AH with HAV and HEV infection display focal necrosis, infiltration of lymphocytes and plasma cells into the portal area, and cholestasis, except in cases that progress to ALF showing submassive or massive necrosis of the hepatocytes [3-6]. These histological findings may be closely affected by the degree of liver injury. Peron et al. reported that severe intralobular necrosis, polymorph inflammation and acute cholangitis might have been the characteristic pathological signs of AH-E in 11 cases in France [30]. However, in that paper, 5 patients with history of alcohol abuse (>40 g/day) were involved and 5 patients except one patient without alcohol abuse were revealed to have liver cirrhosis. Moreover, the period from onset of illness until liver biopsy and genotype of HEV were not shown [30]. Malcolm et al. also published a report on the histology of acute autochthonous hepatitis E virus infection, in which 4 AH-E patients ranging in age from 19 to 82 years showed portal tracts expanded by severe mixed polymorph and lymphocytic inflammatory infiltration, with a geographical distribution of polymorphs at the interface and lymphocytes

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Table 5: Summary of AH-A and AH-E Patients Who Underwent DLST.

Case No.	Name and type of medication+	Numbers of medications tested in the DLST	Results
A6	Etizolam, Sulpiride, Tizanidine hydrochloride, Hydroxyzine, Misoprostol, Lomefloxacin hydrochloride, Tiquizium bromide, and Clostridium butyricum	4 (Etizolam, Sulpiride, Tizanidine hydrochloride, Hydroxyzine)	Negative
A10	Ursodeoxycholic acid, Sodium gualenate hydrate-L-glutamine, and teprenone	3 (Ursodeoxycholic acid, Sodium gualenate hydrate-L-glutamine, and Teprenone)	Negative
E4	Commercial drugs for common cold (Sin-jikinin®), Digestive system (Otaisan®), and Liver protection (Heparize®)	3 ((Sin-jikinin®, Otaisan®, and Heparize®)	Positive (Sin-jikininn®)
E5	Antibiotics (Cefcapene pivoxil hydrochloride hydrate), Tiaramide hydrochloride, Oxatomide, Domperidone, and Cimetidine	5 (Cefcapene pivoxil hydrochloride hydrate), Tiaramide hydrochloride, Oxatomide, Domperidone, and Cimetidine	Negative
E7	Commercial drugs for common cold (Shin-jikinin® and Fujiminhi®)	2 (Shin-jikinin® and Fujiminhi®)	Negative
E8	Chinese herbal medicine (Kosanchya®), and commercial supplements (Taishimandara® and Touchi®)	3 (Kosanchya®), Taishimandara® and Touchi®)	Positive (Kosanchya®)
E10	Rosuvastatin calcium, Famotidine, Pioglitazone hydrochloride, Metformin hydrochloride, Glimepiride, and Sitagliptin phosphate hydrate	6 (Rosuvastatin calcium, Famotidine, Pioglitazone hydrochloride, Metformin hydrochloride, Glimepiride, and Sitagliptin phosphate hydrate)	Positive except Pioglitazone hydrochloride

+ Drugs were used before and after early stage of disease onset.
A6 and A10; AH-A patients, E4, E5, E7, E8, and E10; AH-E (Detailed information in each case is shown in Table 1 and Table 2.)

Table 6: Difference in Each Liver Histology Parameter between AH-A and AH-E Patients.

Parameter	AH-A (n=14)	AH-E (n=11)	P value
Activity*	1.4 ± 0.5	1.1 ± 0.9	0.372
Fibrosis*	0.36 ± 0.5	0.4 ±0.5	0.975
Interface hepatitis**	0	0.2 ± 0.4	0.167
Portal lymphocytes**	1.1 ± 0.3	0.9 ±0.3	0.167
Lobular necrosis**	1.4 ± 0.5	0.9 ± 0.7	0.043
Lobular inflammation**	1.0	0.9 ± 0.7	0.676
Steatosis**	0.6 ± 0.6	0.4 ± 0.5	0.245
Ballooning**	0.3 ± 0.5	0.2 ± 0.4	0.565
Cholestasis**	0	0.4 ± 0.5	0.082

AH-A: acute hepatitis A, AH-E: acute hepatitis E.
*METAVIR score, ** semi-quantitative score. Values are expressed as the mean ± standard deviation.

Table 7: Difference in Each Parameter of Liver Histology in AH-E Patients Based on the Result of DLST.

Parameter	Group I (n=3)	Group II (n=8)	P value
Activity*	2.0 ± 1.0	0.8 ± 0.7	0.042
Fibrosis*	0.7 ± 0.6	0.3 ± 0.5	0.241
Interface hepatitis**	0.3 ± 0.6	0.1 ± 0.4	0.476
Portal lymphocytes**	1.0	0.9 ± 0.4	0.586
Lobular necrosis**	1.7 ± 0.6	0.6 ± 0.5	0.018
Lobular inflammation**	1.7 ± 0.6	0.6 ± 0.5	0.018
Steatosis**	0	0.5 ± 0.5	0.033
Ballooning**	0	0.4 ± 0.5	0.080
Cholestasis**	0	0.4 ± 0.5	0.080

AH-E: acute hepatitis E. DLST: drug-induced lymphocyte stimulation test
Group I: DLST-positive cases, Group II: DSLT-negative cases and cases in which DLST was not performed
*METAVIR score, ** semi-quantitative score. Values are expressed as the mean ± standard deviation.

centrally. Additionally, moderate to severe interface hepatitis and cholangitis were present. Among the 4 cases, 1 patient recovered and received liver transplantation and another patient died within 24 h of admission. However, the time periods in these patients from onset of illness until observation of liver histology were not shown in the report [31]. In another study, Drebber et al. examined HEV RNA of the liver tissues using RT-PCR with specific primers from patients having acute hepatitis of clinically unexplained origin, and compared the hepatitis activity index score and the number of infiltrating inflammatory cells between HEV biopsies and matched non-HEV biopsies [32]. These investigators reported that the portal inflammation score was high and that cholestasis and cholangitis were predominant in the HEV group; in contrast, infiltration of eosinophilic leukocytes was more predominant in the non-HEV group.

The aim of the present study was to clarify the differences in histological findings of the liver between AH-A and AH-E. As shown in the Results section, when the degree of liver injury and the duration until liver biopsy were almost matched, the lobular necrosis score was initially found to be significantly higher in AH-A compared to AH-E. This result might support the finding that the peak values of ALT, AST were significantly higher in AH-A patients than in AH-E patients. Furthermore, we expected that the cholestasis score, which indirectly indicates the presence of increased biliary tract enzymes, might be higher in AH-E than in AH-A, because the peak values of serum γGTP and ALP have been found to be higher in AH-E patients than in AH-A patients [25-27]. However, the cholestasis score did not show a significant difference between AH-A and AH-E.

In the present study, we also examined the influence on histological changes of the liver due to drugs that were administrated before and after the early stage of disease onset. Because anti-HEV IgM, anti-HEV IgA and/or HEV RNA for the identification of HEV infection could not be routinely examined

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before 2012 in Japan, AH patients with HEV infection were considered to be "non-B, non-C", except for patients whose stored blood samples were later tested for the presence of HEV RNA. Interestingly, DLST was positive in 3 (60%) of 5 patients with AH-E (Tables 2,5). In particular, patient E10 showed all 5 drugs to be positive for DLST and exhibited severe liver dysfunction on admission. As shown table 7, activity grade, lobular necrosis and inflammation scores were significantly higher in group I (DLST-positive cases), while the steatosis score was significantly higher in group II (DLST-negative and not examined case). However, because all patients with AH-E in the present study did not undergo examination for DLST, it is not clear whether these histological findings are characteristic changes in AH-E patients who are DLST-positive. Further histological study of the liver is necessary to clarify the influence of allergic drugs in AH-E.

It has been considered that diagnosis of drug-induced liver injury (DILI) is very difficult [38, 39, 42-48], because the challenge test to identify the causative DILI cannot be ethically performed in clinical practice. Although DLST has been considered one of the modalities for diagnosis of DILI in Japan, this test has not yet been confirmed because the positive rate of DLST has been lower than 50% in patients with DILI [38, 39]. Additionally, it is difficult to completely exclude DILI, even if all the patients receive DLST, because the sensitivity of DLST in detecting DILI itself is often insufficient. Furthermore, in patients who have received herbal medicine, the DLST often shows a false-positive result [45]. Davern et al. reported that HEV infection contributes to a small but important proportion of cases of acute DILI [42]. Although we previously reported an AH-E patient with multidrug hypersensitivity [49], we could not confirm whether the 3 DLST-positive patients with AH-E (case E4, 8 and 10 in table 5) had both AH (-due to HEV infection) and DILI, or whether their DLST-positive status was a fortuitous result, as none of the patients were examined for DLST.

Concerning the immunoreaction among hepatitis virus infections, the cytochrome P450 2E1 (CYP2E1) gene polymorphism has been strongly associated with the anti-HAV response. CYP2E1 is also the principal P450 polymorphism responsible for the metabolism of ethanol and many low molecular weight toxins including acetaminophen [50,51]. The CYP2E1 gene polymorphism has been found to be closely associated with the level of serum transaminases and survival in murine acetaminophen-induced liver injury [50]. Deka et al. reported a significant association between the CYP2E1 gene polymorphism and liver damage in AH-A in Indian patients [51]. Furthermore, AH-A has shown a high concentration of serum cytokines such as tumor necrosis factor α, and a difference in immunoreaction between AH-A and AH-E [52]. In the future, it is necessary to clarify three problems: first, the reason why HEV infection may be relatively connected with drug allergy compared to HAV infection; second, the difference in immunoreaction involving cytokine profiles between HAV and HEV infection; and finally, pathological characteristics of cases that overlapped with HAV or HEV infection and DILI [53,54].

Conclusions

Physical condition (sex and age) and genotypes of both HAV and HEV have been closely associated with the severity of liver dysfunction and the disease progression in AH-A and AH-E patients. However, when the period from onset day of hepatitis to the performance of liver biopsy and the degree of liver dysfunction matched between self-limiting AH-A and AH-E patients, the lobular necrosis score among histological findings in the liver was significantly higher in AH-A than AH-E. In addition, aging and immunoreaction against drugs might contribute to the histological changes in the liver in AH-E patients. Further hepatic histological study is necessary to clarify the differences between AH-A and AH-E from the viewpoint of association with immunoreaction against drugs.

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