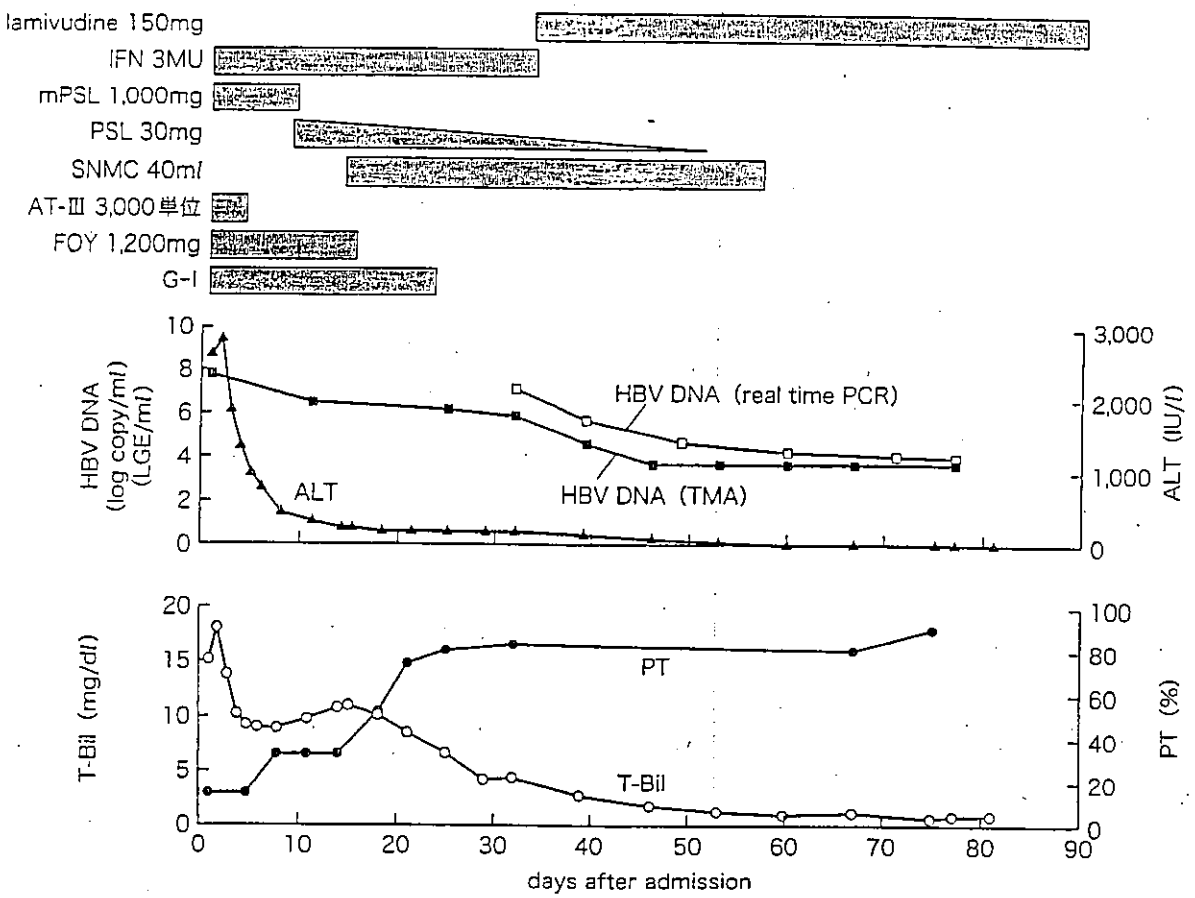

Fig. 2. 症例の臨床経過(27 歳，男性)

mPSL：methylprednisolone，PSL：prednisolone，SNMC：強力ネオミノファーゲン C，FOY：gabexate mesilate，G-I：グルカゴン-インスリン

されていたが，放置．1999 年 12 月 17 日に全身倦怠感，悪心，心窩部痛が出現し，近医で感冒，胃腸炎として加療を受けていたが，2000 年 1 月 4 日に黄疸に気づき，6 日に某院に急性肝炎の診断で入院した．しかし，翌日に PT の低下(27%)を認め，急性肝炎重症型として当科紹介入院となる．当科入院時，意識は清明．HBV キャリアの重症化例としてステロイドパルス療法，IFN，抗凝固療法などを行い，PT の上昇と肝機能の改善を認めた．HBV DNA 量は入院後減少傾向を認めていたが，肝炎の再燃防止を目的に lamivudine(エピビル 150 mg)の使用を行った．その後，HBV DNA 量は順調に減少し，肝機能も正常化し 3 月 29 日退院した．現在，lamivudine を継続投与し地元の病院での経過観察を行っているが，肝機能は正常であり耐性株の出現をみることなく推移している．

おわりに

B 型肝炎の重症化例または劇症化例に対する抗ウイルス療法として lamivudine がもっとも期待されているが，劇症化の阻止を確実に図るためには重症化する以前に投与を開始する必要があると考えられる．しかし，本剤の長期使用によって耐性株の出現をみることを念頭に置き，使用の際にはその適応か否かを慎重に検討することが重要と思われる．

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INFORMATION

第15回 日本末梢神経学会学術集会

日　時　2004年8月27日(金)，28日(土)
会　場　つくば国際会議場　エポカルつくば
(〒305-0032 つくば市竹園2-20-3　Tel 029-861-0001)
会　長　落合直之
内　容
1．シンポジウム：「末梢神経・脊髄再生へのアプローチの最前線」
2．特別講演：「交感神経活動と痛み—神経損傷モデルの教えたもの」
3．産業医学講座：「振動障害の末梢神経機能評価法について」
4．モーニングレクチャー：「CRPSの診断基準をめぐる混乱」
5．ランチョンレクチャー：「脊髄神経の投射路形成」
6．イブニングレクチャー：「末梢神経外科におけるCAT活性測定の有用性」
「末梢神経の病理—神経生検から糖尿病や虚血の病理まで」
7．一般演題(公募)：末梢神経のみならず，脊髄，筋疾患の演題も広く募集します．

一般演題募集要項
一次締め切り：2004年3月31日
演題名，所属，氏名を下記アドレスまでご送信下さい，抄録作成要項を送信します．
二次締め切り(抄録原稿締め切り)：2004年4月30日
送付先アドレス：seikei@md.tsukuba.ac.jp
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事務局　〒305-8575 つくば市天王台1-1-1
筑波大学臨床医学系整形外科　西浦康正，金岡恒治
Tel 029-853-3219　Fax 029-853-3162
E-mail：seikei@md.tsukuba.ac.jp

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Journal of Gastroenterology

Epidemiological and clinical study of sporadic acute hepatitis E caused by indigenous strains of hepatitis E virus in Japan compared with acute hepatitis A

Shigehiko Sainokami[1], Koichi Abe[1], Ichiro Kumagai[1], Akio Miyasaka[1], Ryujin Endo[1], Yasuhiro Takikawa[1], Kazuyuki Suzuki[1], Hitoshi Mizuo[2], Yoshiki Sugai[3], Yoshihiro Akahane[4], Yoichi Koizumi[5], Yoshiaki Yajima[6], and Hiroaki Okamoto[7]

[1]First Department of Internal Medicine, Iwate Medical University, Morioka, Japan
[2]Department of Internal Medicine, Kin-ikyo Chuo Hospital, Sapporo, Japan
[3]Department of Internal Medicine, Iwaki Kyoritsu General Hospital, Iwaki, Japan
[4]First Department of Internal Medicine, Faculty of Medicine, Yamanashi University, Yamanashi, Japan
[5]Department of Medicine, Shinonoi General Hospital, Nagano, Japan
[6]Department of Gastroenterology, Sendai City Hospital, Miyagi, Japan
[7]Division of Virology, Department of Infection and Immunity, Jichi Medical School, Tochigi, Japan

Editorial on page 702

Background. We compared acute hepatitis E (AH-E) and acute hepatitis A (AH-A) to investigate the epidemiology, clinical features, and prognosis of AH-E caused by an indigenous hepatitis E virus (HEV) in Japan. ***Methods.*** We enrolled 58 patients diagnosed with AH-A or AH-E (32 men and 26 women; age, 20–72 years) from December 1997 to October 2002. Phylogenetic analysis of the partial 412-nucleotide sequence of open reading frame (ORF) 2 was performed in patients with AH-E. ***Results.*** Regarding the geographic distribution of the HEV genotype, genotype III was principally distributed in Honshu Island, and genotype IV in Hokkaido Island ($P = 0.0034$). The phylogenetic analysis of the ORF2 region revealed that there were significant geographic differences in the distribution of the HEV strains in Japan, with some strains being widespread and some, localized. In comparison with AH-A patients, those with AH-E were older (56.1 ± 10.6 vs 45.9 ± 10.8 years; $P = 0.0017$). The proportion of males among patients with AH-E was significantly higher ($P = 0.0001$). Pyrexia was often observed in AH-A, and malaise in AH-E. Laboratory data indicate that AH-E induces a weak immunological reaction, whereas jaundice appears earlier in AH-E than in AH-A. One patient with AH-E died of acute hepatic failure, but none of those with AH-A died during the study period. ***Conclusions.*** Our results suggest that there are geographical differences between HEV strains in Japan, and that AH-E is more common in males and older patients than AH-A. Laboratory data indicate a weak immunological reaction and early appearance of jaundice in AH-E.

Key words: acute hepatitis E, epidemiology, hepatitis A, phylogenetic analysis

Introduction

The hepatitis E virus (HEV) is a small, non-enveloped, icosahedral, positive-sense, single-strand RNA virus. HEV is responsible for the majority of cases of what was previously called enterically transmitted non-A, non-B hepatitis. Hepatitis E is endemic in many subtropical and tropical areas. In these areas, hepatitis E occurs both epidemically and sporadically. Hepatitis E is a self-limiting disease of varying severity, presenting as acute, icteric hepatitis, with clinical and morphological findings similar to those of hepatitis A. Recent studies have found immunoglobulin G (IgG) to HEV (anti-HEV IgG) in several wild and domestic animal species native to developing and industrialized countries.[1] Molecular evidence for natural HEV infection in swine has been reported for HEV-endemic and -nonendemic countries worldwide.[2–8] Novel HEV strains from nonendemic areas were detected in patients in the United States, Taiwan, Greece, Italy, Spain, Austria, and Argentina.[4,5,9–11] Now, it is thought that HEV may be more widespread than previously thought.

In Japan, HEV infection rarely occurs, and most, if any, cases of hepatitis E observed thus far have been regarded as imported cases of hepatitis.[12,13] However, the seroprevalence of anti-HEV IgG in healthy individuals in Japan was reported to range from 1.9% to 14.1%, depending on the geographic area.[14] In addition,

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Reprint requests to: S. Sainokami
Present address: Mizusawa City Hospital, 3-1 Ootemachi, Mizusawa 023-0808, Japan

an indigenous HEV strain of genotype III (strain JRA1) has been isolated from a Japanese patient with acute hepatitis who had never been abroad,[15] and a swine HEV strain (strain swJ570) with the highest degree of similarity to the JRA1 isolate among the known HEV isolates has been isolated from domesticated pigs in Japan, although their entire genomes shared only 89% identity.[16] A recent study revealed that polyphyletic HEV strains of genotypes III and IV cocirculate in Japan and contribute to the development of sporadic acute hepatitis of non-ABC etiology, with higher prevalences in males, in those over 40 years of age, and in patients living in the northern part of Japan.[17] However, there are few cases of sporadic hepatitis E in nonendemic countries, including Japan, compared with endemic countries, where outbreaks of hepatitis E may often occur. Therefore, the clinical features of hepatitis E caused by indigenous HEV strains in Japan have not been sufficiently studied as compared with those in endemic countries. In the present study, we investigated the epidemiology, clinical features, and prognosis of acute hepatitis E (AH-E) in Japan compared with hepatitis A (AH-A), which shares similar transmission routes and clinical manifestations with AH-E.

Patients and methods

Patients

A total of 58 patients (32 men and 26 women; age, 20–72 years) diagnosed with AH-A or AH-E from December 1997 to October 2002 were enrolled in the present study. We retrospectively investigated patients with hepatitis E that occurred in Japan during this 5-year period, and we asked each hospital that had the patients to join the co-operative study. The patients with AH-E were treated at six city or university hospitals in Sapporo (Hokkaido Island), and in Iwate, Miyagi, Fukushima, Yamanashi, and Nagano in mainland Honshu, Japan. In all these patients the hepatitis E was non-imported. Patients with AH-A were all admitted to the university hospitals of Iwate Medical University. These patients were from the same general geographic region as the hospital at which they were treated. They were all negative for hepatitis B surface antigen (HBsAg), anti-hepatitis B virus (HBV) core immunoglobulin M (IgM), and anti-hepatitis C virus (anti-HCV). The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the Ethics Committee of each institution, and informed consent was obtained from each patient. Serum samples were obtained and stored at −20°C or below until assay.

Forty-one patients (16 men, 25 women; age, 20–26 years) with serum anti-hepatitis A virus (HAV) IgM (HAVAB-M; Abbott Laboratories, North Chicago, IL, USA) were diagnosed with AH-A. Seventeen patients (16 men, 1 woman; age, 42–72 years) were diagnosed with AH-E, based on positivity for IgM class antibodies to HEV (anti-HEV IgM), determined by serological study, as well as showing HEV RNA detected by reverse transcription-polymerase chain reaction (RT-PCR).

Epidemiological study and laboratory examinations

All patients enrolled in the study had their detailed history taken, including general data such as age, sex, time of onset of illness, travel history before onset of illness, history of blood transfusion, alcohol intake, medicine use, and disease complication. As the incubation periods of AH-A and AH-E are approximately 2 to 8 weeks and 2 to 10 weeks, respectively, travel abroad within 3 months before the onset of illness was regarded as having a travel history. In laboratory examinations, white blood cells, atypical lymphocytes (%), total bilirubin (T. Bil), thymol turbidity test (TTT) value, zinc sulfate turbidity test (ZTT) value, alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyl-transpeptidase (γ-GTP), alkaline phosphatase (ALP), and IgM were measured, using a sequential multiautoanalyzer at each hospital.

Detection of anti-HEV IgM

Anti-HEV IgM was measured using purified recombinant HEV open reading frame (ORF) 2 protein, according to a procedure described by Mizuo et al.[17] Briefly, wells of microplates were coated with purified virus-like particles of HEV expressed by a recombinant baculovirus. Fifty microliters of each sample was added to each well at a dilution of 1:100 in saline containing 40% calf serum. The microplates were incubated at room temperature for 1 h with gentle agitation and were then washed five times with washing buffer. Fifty microliters of phosphate-buffered saline containing 25% fetal bovine serum and peroxidase-conjugated mouse monoclonal anti-human IgM was added to each well. The microplates were incubated at room temperature for 1 h with gentle agitation and then washed five times with washing buffer. Fifty microliters of tetramethylbenzidine (TMB) soluble reagent as substrate was added to each well. The plate was incubated at room temperature for 10 min in the dark, and then 50 μl of TMB stop buffer was added to each well. The optical density (OD) of each sample was read at 450 nm. Test samples with ODs equal to or greater than the cutoff value were considered positive for anti-HEV IgM.

Detection of HEV RNA and sequence analysis of PCR products

Serum HEV RNA was detected by nested RT-PCR analysis as previously reported.[17] Briefly, total RNA was extracted from the serum sample with guanididium thiocyanate and phenol-chloroform, using TRIZOL LS reagent (Invitrogen, Groningen, The Netherlands). The RNA preparation was reverse-transcribed with SuperScript II RNase H$^-$ reverse transcriptase (Invitrogen) and was then subjected to nested PCR with ORF2-specific primers. The size of the amplification product of the first-round PCR was 506 base pairs (bp), and that of the second-round PCR was 458 bp.

The amplification products were electrophoresed on a 1.5% (wt/vol) NuSieve 3:1 agarose gel (FMC BioProducts, Rockland, ME, USA) stained with ethidium bromide, and photographed under UV light. The RT-PCR was performed in duplicate, and reproducibility was confirmed. The amplification products were directly sequenced on both strands. Sequence analysis was performed as previously reported.[17] A phylogenetic tree was constructed by the neighbor-joining method, based on the partial nucleotide sequence of the open reading frame (ORF) 2 region (412 nucleotides [nt]).[18] Bootstrap values were determined on 1000 resamplings of data sets.[19] The geographic origins and the GenBank accession numbers of the nucleotide sequences of the HEV strains used in the phylogenetic analysis were as follows: JRA1 (Japan, AP003430), HE-JF2 (Japan, AB079763), HE-JO-1982 (Japan, AB088418), swJ681 (Japan, AB073912), swJ570 (Japan, AB073912), US1 (United States, AF060668), HE-JI3 (Japan, AB080579), JKN-Sap (Japan, AB074918), JMY-Haw (Japan, AB074920), HE-JA10 (Japan, AB089824), US2 (United States, AF060669), swJ791 (Japan, AB073911), HE-JF1 (Japan, AB079762), JAK-Sai (Japan, AB074915), JKK-Sap (Japan, AB074917), HE-JI4 (Japan, AB080575), HE-JF3 (Japan, AB079764), T1 (China, AJ272108), C1 (China, D11092), C2 (China, L25547), C3 (China, M94177), C4 (China, D11093), C5 (China, L08816), P1 (Pakistan, M80581), P2 (Pakistan, AF185822), I1 (India, X98292), I2 (India, X99441), I3 (India, AF076239), I4 (India, AF459438), B1 (Myanmar, M73218), B2 (Myanmar, D10330), Ne1 (Nepal, AF051830), and MEX-14 (Mexico, M74506).

Statistical analysis

We used χ^2 analysis, Fisher's exact test, Student's *t*-test, and Mann-Whitney's *U*-test where appropriate in this study. All significant data were two-tailed, and a *P* value of less than 0.05 was considered significant.

Results

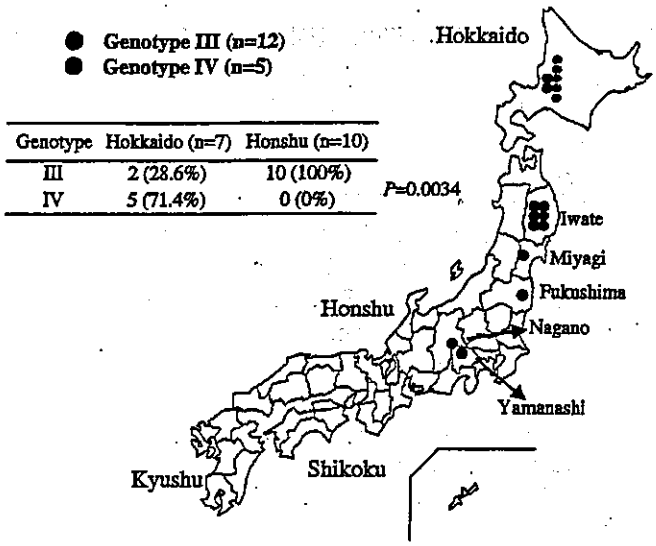
Geographic distribution of HEV according to HEV genotype in patients with AH-E, and phylogenetic analysis of the partial 412-nt sequence of the ORF2 region

Ten HEV isolates, from patients 1, 2, 3, 4, 8, 9, 10, 11, 15, and 16, have already been reported by Mizuo et al.,[17]

Table 1. Profiles of 17 patients with AH-E

Patient no.	Age (years)	Sex	Onset	Location	HEV genotype	Name of HEV isolate
1	55	M	Dec., 1997	Hokkaido	IV	HE-JA1[a]
2	71	M	Aug., 1998	Hokkaido	IV	HE-JA2[a]
3	42	M	Oct., 1998	Hokkaido	IV	HE-JA3[a]
4	44	M	Jan., 2000	Hokkaido	III	HE-JA4[a]
5	46	M	May, 2001	Hokkaido	IV	HE-JA13
6	72	M	Aug., 2002	Hokkaido	III	HE-JA16
7	64	M	Sep., 2002	Hokkaido	IV	HE-JF4
8	48	M	Aug., 1998	Iwate	III	HE-JA5[a]
9	47	F	May, 1999	Iwate	III	HE-JA6[a]
10	72	M	Mar., 2001	Iwate	III	HE-JA7[a]
11	56	M	Jul., 2001	Iwate	III	HE-JA8[a]
12	62	M	Sep., 2002	Iwate	III	HE-JA21
13	71	M	Oct., 2002	Iwate	III	HE-JA22
14	54	M	Jun., 2002	Miyagi	III	HEV-Sendai[b]
15	45	M	Jan., 2001	Fukushima	III	HE-JA9[a]
16	50	M	Nov., 2001	Yamanashi	III	HE-JA11[a]
17	55	M	Jul., 2002	Nagano	III	HE-JA23

AH-E, acute hepatitis E; HEV, hepatitis E virus
[a]These isolates have been reported previously by Mizuo et al.[17]
[b]This isolate has been reported by Yajima et al.[20]



Genotype	Hokkaido (n=7)	Honshu (n=10)
III	2 (28.6%)	10 (100%)
IV	5 (71.4%)	0 (0%)

P=0.0034

Fig. 1. Geographic distribution of patients with acute hepatitis E (AH-E) in Japan according to hepatitis E virus (HEV) genotype

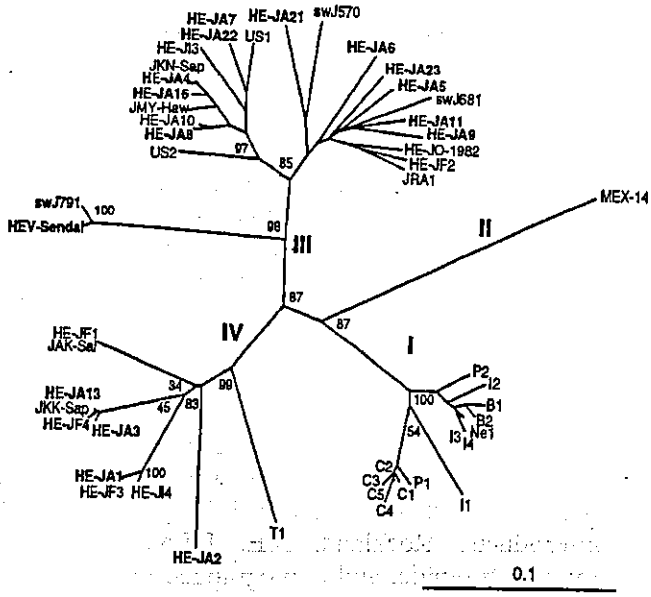


Fig. 2. Phylogenetic tree constructed by the neighbor-joining method, based on the partial nucleotide (nt) sequence of the open reading frame (ORF) 2 region (412 nt) of 50 human and swine isolates. In addition to 26 reported human and swine HEV isolates of genotypes I to IV whose entire or nearly entire sequences are known, seven reported isolates of genotype III or IV whose partial sequences of 412, 421, or 436 nt have been determined were included for comparison. They were deposited under accession nos. AB073910–AB073912, AB074915, AB074917, AB074918, AB074920, AB079762–AB079764, AB080575, AB080759, AB088418, AB089824, AF051830, AF060668, AF060669, AF076239, AF185822, AF459438, AJ272108, AP003430, D10330, D11092, D11093, L08816, L25547, M73218, M74506, M80581, M94177, X98292, and X99441. The 17 HEV isolates from this study are indicated in *boldface*. Bootstrap values are indicated for the major nodes as a percentage of the data obtained from 1000 resamplings

and an HEV isolate from patient 14 has been reported by Yajima et al.[20] HEV isolates from 5 patients were classified as genotype IV and those from 12 patients were classified as genotype III (Table 1).

According to the geographic distribution of HEV genotype (Fig. 1), the HEV isolates from ten patients in mainland Honshu (six in Iwate and one each in Miyagi, Fukushima, Nagano, and Yamanashi) were all classified as genotype III. However, of seven HEV isolates in Hokkaido, only two (28.6%) were classified as genotype III, and the others were classified as genotype IV. There was a significant geographic difference in the HEV genotype between Honshu Island and Hokkaido Island (P = 0.0034).

Phylogenetic analysis of the partial 412-nt sequence of the ORF2 region revealed that polyphyletic HEV strains of genotypes III and IV exist in Japan (Fig. 2). However, regardless of a different year of onset, nucleotide identity of the 412-nt sequence of the ORF2 region between HE-JA7 and HE-JA22 was 100%, and these two HEV strains were isolated from patients living in the same location in Iwate. Furthermore, these two isolates were found to be the most homologous to the human strain in the United States (US1).[8] For genotype IV, HE-JA3 from patient 3, HE-JF4 from patient 7, and HE-JA13 from patient 5, all of whom lived in Hokkaido, closely resembled JKK-Sap—isolated from a patient who also lived in Hokkaido—that has been reported previously.[21] On the other hand, HE-JA1, isolated from patient 1, who lived in Hokkaido, shared 100% nucleotide identity with the HE-JF3 isolate, which was isolated in 2002 from a patient who lived in Iwate, on Honshu Island.[22]

Comparison of clinical features between AH-A and AH-E

The month of onset of illness was investigated in patients with AH-A and those with AH-E (Fig. 3). AH-A onset in Japan showed a normal distribution from January to December, and AH-A occurred generally in winter and spring, particularly in March. However, the onset of disease was distributed almost equally over the year in patients with AH-E, and there was no particular season when AH-E occurred predominantly.

A comparison of clinical manifestations between AH-A and AH-E is shown in Table 2. As for the profile of patients, the mean age of AH-A patients was 45.9 years, whereas that of AH-E patients was 56.1 years. Patients with AH-E were significantly older at time of onset than those with AH-A (P = 0.0017). Moreover, the proportion of males among patients with AH-E was significantly higher than that among AH-A patients (P

= 0.0001). However, there were no significant differences between the groups in history of blood transfusion, medication, and disease complication.

According to clinical symptoms, pyrexia (>38°C) was present in 73.2% of patients with AH-A, but in only 41.2% of patients with AH-E, and the difference was significant ($P = 0.0210$). Malaise was noted in 65.9% of patients with AH-A, but in 100% of patients with AH-E, and the difference was significant ($P = 0.0055$). However, there were no significant differences between the groups in other symptoms, such as flu-like prodromes (including myalgia, arthalgia, or headache), nausea or vomiting, abdominal pain, pruritus, and diarrhea.

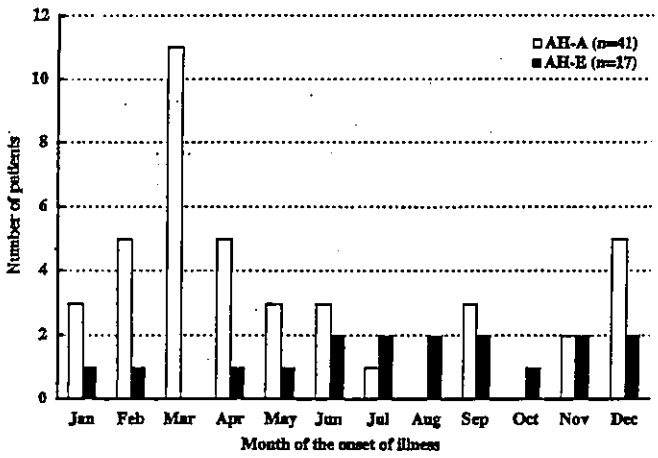


Fig. 3. Distribution of the onset of illness in patients with AH-A or AH-E in a year

As for physical findings, lymphadenopathy was observed in only 19.5% of patients with AH-A, whereas it was not observed in any patients with AH-E. However, there was no significant difference between the groups in lymphadenopathy, and there were no differences between the groups in other physical findings, such as jaundice, hepatomegaly, splenomegaly, exanthema, and edema.

Comparison of laboratory data between patients with AH-A and those with AH-E

We investigated laboratory data on admission, as well as investigating peak values, and we compared the mean values for the data between the study groups (Table 3). The percentage of atypical lymphocytes was higher in AH-A patients on admission (7.50% vs 2.07%; $P = 0.0288$). The T. Bil level was lower in AH-A patients on admission (4.27 vs 7.33 mg/dl; $P = 0.0032$), whereas the peak values were the same in the two groups. ZTT values were markedly higher in AH-A

Table 2. Patient demographics and clinical characteristics of AH-A and AH-E

Characteristics	AH-A ($n = 41$)	AH-E ($n = 17$)	P
Profile			
Age (years)			
Mean ± SD	45.9 ± 10.8	56.1 ± 10.6	0.0017
Sex			
Male/Female	16/25	16/1	0.0001
History of traveling abroad within 3 months before the onset of illness; no. (%)	0 (0)	0 (0)	0.9999<
History of blood transfusion within 3 months before the onset of illness; no. (%)	4 (9.8)	0 (0)	0.3100
History of alcohol intake (over 60 g ethanol daily); no. (%)	12 (29.3)	5 (29.4)	0.8562
Medication history; no. (%)	15 (36.6)	4 (23.5)	0.3349
Disease complication; no. (%)	17 (41.5)	7 (41.2)	0.9839
Symptoms; no. (%)			
Pyrexia (>38°C)	30 (73.2)	7 (41.2)	0.0210
Malaise	27 (65.9)	17 (100)	0.0055
Flu-like prodrome	17 (41.5)	10 (58.8)	0.2276
Nausea or vomiting	17 (41.5)	7 (41.2)	0.9839
Abdominal pain	9 (22.0)	2 (11.8)	0.4796
Pruritus	6 (14.6)	2 (11.8)	0.9999<
Diarrhea	1 (2.4)	0 (0)	0.9999<
Physical findings; no. (%)			
Jaundice	34 (82.9)	15 (88.2)	0.9999<
Hepatomegaly	10 (24.4)	4 (23.5)	0.9999<
Splenomegaly	8 (19.5)	3 (17.6)	0.9999<
Lymphadenopathy	8 (19.5)	0 (0)	0.0900
Exanthema	1 (2.4)	2 (11.8)	0.9999<
Edema	0 (0)	0 (0)	0.9999<

AH-A, acute hepatitis A; AH-E, acute hepatitis E

Table 3. Comparison of laboratory data on admission, and peak values, between AH-A and AH-E

Variable	Values on admission			Values at peak		
	AH-A (*n*)	AH-E (*n*)	*P*	AH-A (*n*)	AH-E (*n*)	*P*
White blood cells (per mm³)	5550 ± 2124 (41)	5402 ± 1615 (17)	0.7981	8620 ± 4088 (41)	9013 ± 8368 (17)	0.8104
Atypical lymphocytes (%)	7.50 ± 9.81 (41)	2.07 ± 2.40 (17)	0.0288	7.81 ± 9.56 (41)	3.28 ± 3.60 (17)	0.0643
Total bilirubin (mg/dl)	4.27 ± 1.71 (41)	7.33 ± 5.84 (17)	0.0032	8.88 ± 4.50 (41)	10.89 ± 8.31 (17)	0.2377
TTT (KU)	9.54 ± 4.19 (40)	11.58 ± 11.40 (15)	0.3319	15.79 ± 3.93 (40)	17.54 ± 14.83 (15)	0.4917
ZTT (KU)	15.86 ± 6.08 (41)	11.98 ± 6.94 (16)	0.0420	26.17 ± 8.50 (41)	14.24 ± 7.26 (16)	<0.0001
AST (IU/l)	3278 ± 4126 (41)	1689 ± 1667 (17)	0.1315	3384 ± 4117 (41)	1842 ± 1575 (17)	0.1410
ALT (IU/l)	3486 ± 2673 (41)	2204 ± 1417 (17)	0.0674	3775 ± 2682 (41)	2407 ± 1247 (17)	0.0496
γ-GTP (IU/l)	340 ± 210 (41)	363 ± 290 (17)	0.7350	400 ± 236 (41)	380 ± 294 (17)	0.7819
ALP (IU/l)	610 ± 208 (41)	659 ± 211 (17)	0.4117	730 ± 223 (41)	692 ± 194 (17)	0.5415
IgM (mg/dl)	422.1 ± 209.4 (39)	237.4 ± 129.4 (13)	0.0044	509.7 ± 204.1 (41)	237.6 ± 129.3 (13)	<0.0001

Plus-minus values are means ± SDs

AH-A, acute hepatitis A; AH-E, acute hepatitis E; TTT, thymol turbidity test; ZTT, zinc sulfate turbidity test; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl-transpeptidase; ALP, alkaline phosphatase; IgM, immunoglobulin M

patients, both on admission (15.86 vs 11.98 KU; $P = 0.042$) and at peak (26.17 vs 14.24 KU; $P > 0.0001$). The peak ALT level was higher in AH-A patients (3775 vs 2407 IU/l; $P = 0.0496$). The IgM titers were markedly higher in AH-A patients, both on admission (422.1 vs 237.4 mg/dl; $P = 0.0044$) and at peak (509.7 vs 237.6 mg/dl; $P = 0.0001$).

However, no significant differences between the groups were found in other laboratory variables; namely, the white cell count, and γ-GTP and ALP levels.

Prognosis of AH-A and AH-E

One patient with AH-E (patient 7), who lived in Hokkaido, died of acute hepatic failure during the study period, but none of the AH-A patients died during the study period (Table 4). In the 49 patients (34 with AH-A, 15 with AH-E) exhibiting jaundice, the period between the onset of illness and the decrease in the T. Bil level to less than 2.0 mg/dl was the same in both groups. In addition, there was no significant difference between the two groups in the period from the onset of illness to the decrease in the ALT level to less than 40 IU/l. In the patients with jaundice, the number of days from admission to the peak T. Bil level in the AH-E group was distributed as follows: 8 patients (53.3%) within 7 days; 5 (33.3%) from 8 to 14 days, and 2 (13.3%) at more than 15 days. In the AH-A group, the number of days from admission to the peak T. Bil, level was distributed as follows: 4 patients (11.8%) within 7 days, 20 (58.8%) from 8 to 14 days, and 10 (29.4%) at more than 15 days. Thus, the distribution of days from admission to the peak T. Bil level was significantly different between the two groups ($P = 0.0076$). It took a shorter time for the T. Bil level to reach the peak in AH-E than in AH-A.

Discussion

No outbreaks of AH-E have been reported in Japan, and the incidence of documented sporadic cases of AH-E seems to be very low. Thus, Japan has been thought to be a nonendemic area for HEV, and AH-E has been considered as an imported hepatitis from endemic countries.[12,13] However, recent studies have revealed the presence of an indigenous strain of HEV in Japan, which had caused sporadic non-A, non-B, non-C hepatitis, and might develop to fulminant hepatitis.[22] Domestic animals such as swine may play an important role as reservoirs of HEV in Japan, as they do in other industrialized countries,[16] and now, AH-E is considered as a potential zoonosis in industrialized countries because of a close genetic relationship between swine and human

Table 4. Comparison of prognostic characteristics between AH-A and AH-E

Characteristic	AH-A	AH-E	*P*
Mortality/Survival	0/41	1/16	0.2931
Period from the onset of illness to T. Bil <2.0 mg/dl (days)[a]			
No. of patients	34	15	
Median (range)	24.5 (12–55)	30 (11–95)	0.4036
Period from the onset of illness to ALT <40 IU/l (days)			
No. of patients	41	16[b]	
Median (range)	42 (16–66)	36 (18–95)	0.3421
Days from admission to the peak T. Bil level[a]			0.0076
≦7	4	8	
8–14	20	5	
15≦	10	2	

AH-A, acute hepatitis A; AH-E, acute hepatitis E, T. Bil; total bilirubin; ALT, alanine aminotransferase
[a]Excluding patients without jaundice on admission
[b]Excluding a patient who died of acute liver failure

HEV.[23] In the present study, we excluded patients with a history of traveling abroad within 3 months of onset of illness, to rule out imported AH-E, and we investigated AH-E caused by indigenous strains of HEV compared with AH-A. The clinical manifestations of AH-E in endemic areas are similar to those of AH-A. Both infections are transmitted by the fecal-oral route, and are related to poor hygiene and sanitation. Symptoms of AH-E and AH-A tend to be more severe in adults than in children.[24–26] However, a number of clinical and epidemiological differences between AH-E and AH-A have been revealed in recent studies. For example, HEV in endemic areas can cause severe fulminant hepatitis in pregnant women when the infection occurs during late pregnancy,[27] whereas exposure to HAV infection does not impose a high risk of fulminant hepatitis.[28,29] In a Japanese seroepidemiological study of anti-HEV IgG and anti-HAV in 1992 to 1993, the seroprevalence of anti-HAV was 65.3%–72.3%, but that of anti-HEV IgG was only 4.6%–6.7%.[30] Although the rate of positivity for anti-HAV increased with age in both males and females, the anti-HEV-positive rate tended to increase slightly with age in males, but not in females. Thus, HEV infection in Japan unlike HAV infection, was associated with male sex and older age.[30] Our data from the epidemiological study of acute hepatitis confirm that AH-E was more common in patients of older age and in men than AH-A in Japan. However, this result is different from that in endemic areas, where HEV infection was common in young adults age 15–40 years.[31–34]

In the present study, it was unclear when and why HEV infection occurred. However, among the patients who lived in Iwate, patients 8 and 9 were a retail meat dealer and a meat-processing trader, respectively. Patient 11 was a farmer working with pigs, and patient 12 had contact with pigs in his part-time job. In addition, patient 13 had raised young cattle, or cows for milk. The breeding of these domestic animals in farming families was principally undertaken by men over 40 years of age, whereas women and children rarely engaged in this work. These findings suggest that men are at a high risk for zoonotic HEV infection, particularly older men. Furthermore, of interest, is the finding that five HEV isolates; namely, HE-JA5, HE-JA6, HE-JA9, HE-JA11, and HE-JA23, were genetically close to the Japanese swine HEV isolate, swJ681, and an HEV isolate of HE-JA21 was also close to another Japanese swine HEV isolate, swJ570, based on the phylogenetic analysis of the ORF2 region.[16] In addition, it has been reported that the nucleotide identity of the ORF2 region (412 nt) between HEV-Sendai and Japanese swine HEV isolate of swJ791 was 98.3%.[20] These results suggest that the infection sources of indigenous HEV strains in Japan are closely associated with domestic animals such as pigs.

Most of the HEV outbreaks in endemic areas of tropical and subtropical countries have been observed during the rainy season.[26] However, in industrialized countries such as Japan, it has been unclear whether the HEV infection occurred in a particular season. HAV infection was observed in winter or spring in Japan; however, no particular season was associated with HEV infection in this study. Therefore, we have to take into consideration HEV infection in the diagnosis of acute sporadic hepatitis in any season.

In this study, there were significant geographic differences in HEV genotypes in Japan. It was considered that genotype III was widespread principally on Honshu Island, whereas genotype IV was localized on Hokkaido Island. From the phylogenetic analysis of the ORF2 region, HE-JA3, HE-JA4, and HE-JA13 isolates of genotype IV closely resembled JKK-Sap (isolated from a patient who lived in Hokkaido) that has been

reported previously.[21] In genotype III, the nucleotide identity between HE-JA7 and HE-JA22, which were isolated at different times of onset in the same location of Iwate, was 100%. On the other hand, in genotype IV, HE-JA1, isolated from patient 1, who live in Hokkaido, shared 100% nucleotide identity with the HE-JI4 isolate, which was isolated in 2000 from a patient who lived in Tochigi, in Honshu island.[35] These findings suggest that in Japan, indigenous or native strains of HEV may be circulating in certain localized areas, but that some strains of HEV may be widespread with both types of strains causing AH-E.

Many symptoms of AH-E appeared to be the same as those of AH-A, but pyrexia of more than 38°C was observed more frequently in AH-A, and malaise was more frequent in AH-E. The reason for the more frequent observation of malaise in AH-E was thought to be that it was closely related to the age at onset of illness, and patients with AH-E were older than those with AH-A. But, why is pyrexia observed more frequently in AH-A than in AH-E? In this study, there were no specific physical findings in AH-E. However, there could be findings of a significant difference in the incidence of lymphadenopathy between AH-E and AH-A, if we were to study a larger number of cases of AH-E. On the other hand, our results showed several laboratory findings specific for AH-E compared with AH-A. The percentage of atypical lymphocytes, the ZTT value, and the IgM titer on admission were higher in AH-A patients than in AH-E patients, and the peak ALT level, peak ZTT value, and peak IgM titer were higher in AH-A patients than in AH-E patients. However, the T. Bil level was higher in AH-E than in AH-A, and more than 50% of patients with AH-E had reached the peak within 1 week of admission. These laboratory findings indicate that AH-A induces a strong immunological reaction compared with AH-E, whereas jaundice appears earlier in AH-E than in AH-A. Therefore, pyrexia may appear more frequently in AH-A as the result of the strong immunological reaction.

Although one patient with AH-E died of acute liver failure during the study period, there was no significant difference in the recovery period, according to the clinical course of T. Bil and ALT levels, between the AH-A and AH-E patients. It has been reported that risk factors that contribute to mortality in AH-A were older age, comorbid condition, and an underlying chronic liver disease.[36–38] On the other hand, risk factors for AH-E have not been clarified, except for older age and pregnancy. In experimental infections of nonhuman primates, the clinical presentation of hepatitis E is dose-dependent.[39] Thus, the severity of infection is directly related to the infectivity titer of challenge virus, and consistent demonstration of hepatitis in experimentally infected nonhuman primates has required challenge doses of at least 1000 times greater than the minimum dose required for infection.[40,41] It is not known whether such a clinical-to-infectious-dose relationship exists for naturally infected humans, but it is considered that the severity of AH-E depends on the infective viral load, based on the observed lower immunoreactivity in AH-E than in AH-A.

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症例

発症時薬剤性肝障害との鑑別が困難であったC型急性肝炎の1例*

稲葉宏次　大内　健　阿部弘一
滝川康裕　鈴木一幸**

はじめに　急性ウイルス肝炎は感冒様症状で発症することが多く，消炎鎮痛薬などの感冒薬が投与されがちである．したがって肝機能障害が認められた時点でウイルス性か薬剤性かの鑑別を要することもしばしば経験される．

今回われわれは，発症時に薬剤性肝障害との鑑別が困難であったC型急性肝炎の1例を経験したので報告する．

症　例

症　例　66歳，女性

主　訴：皮膚掻痒感

既往歴：1997年，脳動脈瘤手術．2000年12月7日，大腸ポリペクトミー．

輸血歴：なし

現病歴：2000年12月下旬より感冒様症状を認め近医にて内服，点滴加療を受けた．2001年1月19日より掻痒を伴う発疹が出現し，1月25日近医を受診したところ，血液検査でT-Bil 2.8 mg/dl，AST 862 IU/l，ALT 907 IU/l，γ-GTP 617 IU/lと肝機能障害を認め，1月26日当科紹介，入院となった．

入院時現症：体温36.3°C．意識清明で眼球結膜に黄疸を認めた．皮疹は認めず．腹部は平坦・軟で，肝脾は触知せず．

第1回目入院時検査成績(Table 1)：胆道系酵素の著明な上昇を特徴とする肝機能障害を認めた．ウイルスマーカーでは，HCV抗体は低力価陽性，HCV-RNA(定量)は850 KIU/ml超と高ウイルス量を示した．他のウイルスマーカーや自己抗体は陰性であった．また，末梢血液では白血球数は正常で，好酸球の上昇も認めなかったが，感冒時に内服していた麻黄附子細辛湯が薬剤リンパ球刺激試験(DLST)でsensitivity index 181%と陽性を示した．

臨床経過①(Fig. 1)：血清学的にC型急性肝炎と診断したが，薬剤性肝障害の関与も否定できず，肝庇護薬の内服で経過をみたところ，退院4週間後の採血で肝機能の増悪を認め，同日2回目の入院となった．

第2回目入院時検査成績(Table 1)：血小板は$10.7\times10^4/\mu l$と低下し，トランスアミナーゼの著明な上昇を特徴とする肝機能障害を認めた．HCV抗体価はさらに上昇しており，ウイルス量は3 KIU/ml，血清型は1であった．

臨床経過②(Fig. 1)：再入院後，肝庇護薬の投与で速やかに肝機能は改善したがC型肝炎の慢性化が危倶されたため，インフォームド・コンセントのもとインターフェロン(IFN)療法を施行(IFN-α総投与量504 MU，24週間)したところ著効が得られた．

腹部超音波およびCT：初回入院時にて軽度の胆嚢の壁肥厚を認め，2回目入院時も同様の所見であった．肝，脾に異常所見は認めなかった．

腹腔鏡検査所見：発症より約2ヵ月後に腹腔鏡検査を施行した．肝には萎縮，腫大なく，辺縁は

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* A Case of Acute Hepatitis C with Typical Initial Symptoms of Drug Induced Hepatitis.
要旨は2002年2月16日の第172回日本消化器病学会東北支部例会において発表した．

** H. Inaba：岩手医科大学第一内科；K. Oouchi(科長)：岩手県立宮古病院消化器内科；K. Abe(講師)，Y. Takikawa(講師)，K. Suzuki(教授)：岩手医科大学第一内科．

Table 1. 入院時検査成績

血　算			Fbg(mg/dl)	228	
WBC(/μl)	5,500	4,040	FDP(μg/ml)	9.0	
RBC(×10⁴/μl)	402	386	ウイルスマーカー		
Hb(g/dl)	13.6	13.3	IgM-HA抗体	(−)	(−)
Plt(×10⁴/μl)	16.8	10.7	HBs抗原	(−)	(−)
Neut(%)	55.3	52.0	IgM-HBc抗体	(−)	(−)
Lym(%)	36.9	39.6	HCV抗体	(+)	(+)
Mono(%)	5.6	6.9	OD	0.529	2.579
Eos(%)	1.8	1.0	cut off値	0.362	0.656
Baso(%)	0.4	0.5	HCV-RNA(KIU/ml)	850超	3.0
生化学			HCV血清型		1
T-Bil(mg/dl)	3.21	2.32	EBV VCA IgM	(−)	
AST(IU/l)	521	1,451	EBV VCA IgG	×80	
ALT(IU/l)	728	1,817	EBNA	×20	
ALP(IU/l)	1,249	704	CMV IgM	(−)	
γ-GTP(IU/l)	616	217	CMV IgG	×160	
BUN(mg/dl)	12.6	15.2	免疫血清		
Cr(mg/dl)	0.6	0.7	CRP(mg/dl)	0.11	
Na(mEq/l)	144	141	IgG(mg/dl)	1,200	
K(mEq/l)	4.2	3.8	IgA(mg/dl)	160	
Cl(mEq/l)	110	105	IgM(mg/dl)	120	
TC(mg/dl)	180		ANA	(−)	
TG(mg/dl)	128		AMA	(−)	
TP(g/dl)	6.9		ヒアルロン酸(ng/ml)		98.7
Alb(g/dl)	4.27		Ⅳ型コラーゲン7S(ng/ml)		4.1
γ-gl(g/dl)	1.1		DLST		
凝　固			麻黄附子細辛湯	(+)	
PT(%)	85.2	85.2	TYK235	(−)	

左の数値は第1回目入院時(2001年1月26日)，右の数値は第2回目入院時(同年3月14日)の検査成績である．

鋭であり，表面には軽度の小陥凹が散在していた．赤色紋理は認めず，肝右葉外側に被膜の肥厚を認めた．

肝生検組織所見(Fig. 2)：門脈域の線維性拡大，小葉内にリンパ球，形質細胞を主体とした炎症性細胞浸潤，piecemeal necrosisを認め，新犬山分類でA2F2の所見であった．胆汁うっ滞の所見はみられなかった．

考　察

本症例は，HCV抗体の陽転化と抗体価の上昇およびHCV-RNAの検出よりC型急性肝炎と診断された．しかし，皮疹，皮膚掻痒などの臨床像および麻黄附子細辛湯がDLST陽性であることから薬剤アレルギー性肝炎の診断基準[1]にあてはめると確診例であり，発症時の肝機能障害の原因として薬剤性肝障害の関与も否定できなかった．近年，DLSTおよび本診断基準自体の問題点が指摘されている[2-4]が，本症例においては初回入院時は胆道系酵素優位の肝機能障害であり，2回目入院時はトランスアミナーゼ上昇が主体と病態が異なっていたことからも，C型急性肝炎に薬剤性肝障害が重なったと考えるのが妥当と思われた．

本症例ではIFN療法で著効が得られたが，一般にC型急性肝炎の慢性化率は70〜80%といわれており[5]，早期のIFN療法が有効とされている[6]．投与時期については，発症後3ヵ月を経過しても

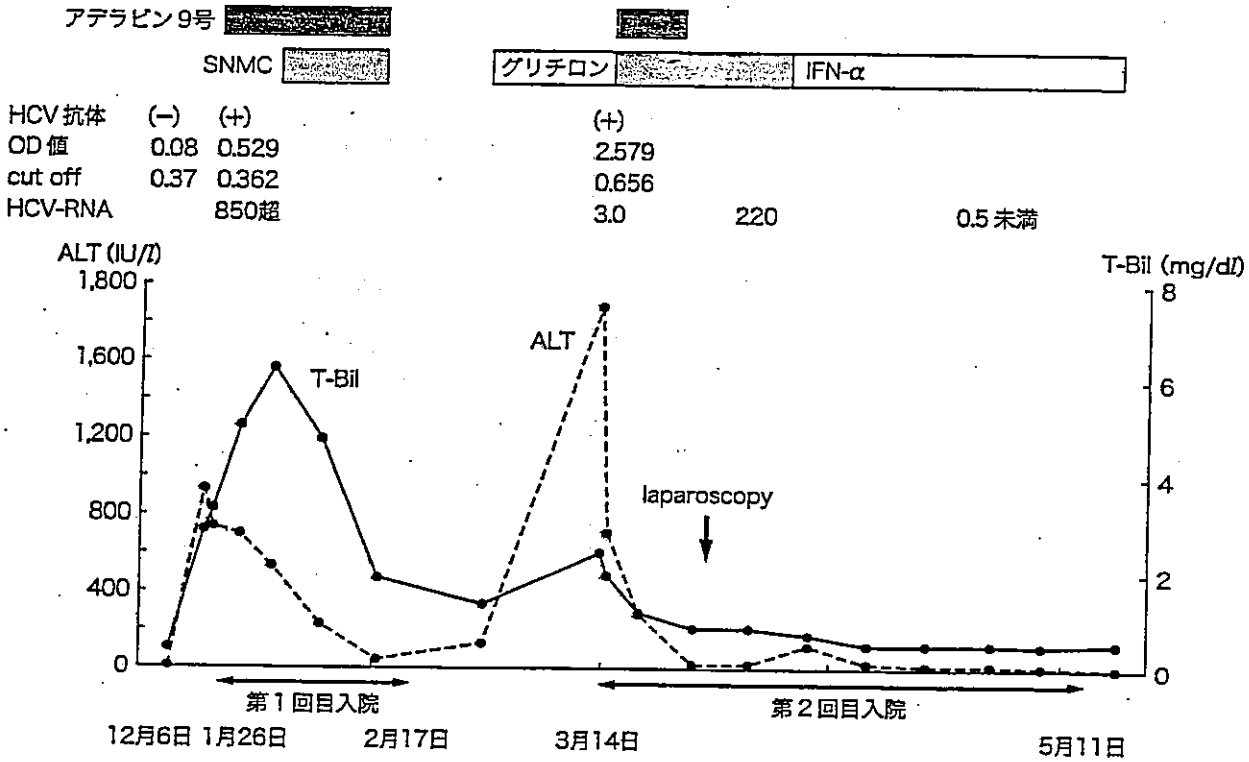

Fig. 1. 臨床経過

ALTが正常化せず，HCV-RNAが陽性である例に2年以内に治療することが望ましいとされている[7]．本症例のようにALTやウイルス量が多峰性に推移する際は高率に慢性化するといわれており[8]，早期に投与すべきと考えられる．さらに高齢者の急性肝炎は免疫応答の低下と再生力の低下のため遷延化ないし劇症化をきたしやすいといわれており[9]，IFN療法の適切な開始時期を逸しないように慎重な経過観察が必要と思われる．

なお，C型急性肝炎でも発疹がみられることもあり[10]，本症例に認められた皮疹がC型急性肝炎に伴うものであったか薬剤アレルギーによるものであったかは不明であった．

また，HCVの感染経路について検索したが，家族内感染は否定的であり，さらに内視鏡および処置具はガイドラインに基づいた洗浄，消毒[11]を施行しており，かつ同日に大腸内視鏡を受けた患者は全例HCV抗体陰性であったことから経内視鏡感染も否定的であり，不明であった．

おわりに　薬剤服用歴のある急性ウイルス肝炎では薬剤性肝障害の関与も念頭に置き，詳細な病歴聴取，他疾患の関与についての検索のほか，全身状態を観察したうえで，肝機能およびウイルスマーカーなどの定期的な経過観察が重要と考えられる．

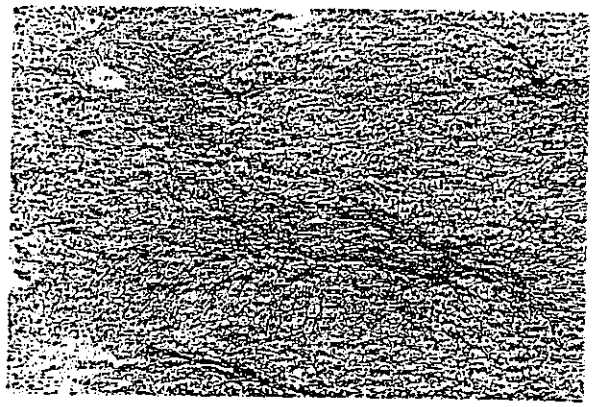

Fig. 2. 肝病理組織所見
門脈域の線維性拡大，小葉内に炎症性細胞浸潤，piecemeal necrosisを認める．

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原稿送付先

〒113-8410 東京都文京区本郷三丁目 42 番 6 号
㈱南江堂「内科」編集室

B型肝硬変症

B型肝硬変症に対する治療法の最新動向

Current status of treatment of HBV-related cirrhosis

池田健次

Key words：B型肝炎ウイルス，インターフェロン，肝硬変，ラミブジン

はじめに

e抗原陽性・HBV-DNA高値(一般的には血清で10^6copies/m*l*以上)であれば，トランスアミナーゼ変動が起こり，肝病変の進行が起こるため肝炎治療の対象となる．e抗原が陰性であっても，HBV-DNA高値・トランスアミナーゼ異常値であれば肝病変の進行が起こるため治療対象と考えるべきである．ALT正常値の症例は，e抗原陽性・陰性にかかわらず，直ちに治療を行う必要はない．

治療開始前には可能なら腹腔鏡や肝生検を行うことが望ましい．B型慢性肝炎が疑われた場合でも，血小板数が15万/mm^{3}未満の場合や，e抗原陽性であるのにHBs抗原が1：128(R-PHA法)以下の低い力価であるような場合には肝硬変である可能性が高いので，可能なら腹腔鏡＋肝生検を行うべきである．

e抗原陽性・HBV-DNA陽性の場合には，まずe抗原を陰性化させることを目標に治療が行われるが，肝硬変進行例や高齢者などではALT正常化を目指した抗ウイルス療法や肝庇護療法が行われることもある．e抗原が陰性の場合にはHBV-DNA陰性化(低下)もしくはALTの正常化を目標として治療される．

肝硬変に対する治療のうち，インターフェロン(IFN)治療に関しては，腹水や脳症の合併のない無症状の病理学的な診断例のみが対象であったが，ラミブジンに関しては非代償期の症例も治療対象の候補になってくることが注目すべき点である．

1. IFNのHBV-DNA，ALTに対する効果

HBs抗原陽性肝硬変症例に対するIFN治療は，保険診療がこれまでのところ困難であるが，e抗原またはHBV-DNA高値でトランスアミナーゼが変動している症例に対しては，ウイルス抑制を通じて肝炎状態に対する治療効果がみられる(図1)．

長期予後をみる観点で，10年以上のウイルスマーカーと生化学的所見が確認できたB型代償期肝硬変症例についてIFNの効果を検討した．1986-90年までの間にIFNの間欠投与を行った57例全例でのHBV-DNAとALTの臨床経過について検討した．IFNはIFN-αまたはIFN-βの300万-600万単位の週2回投与を行い，その使用期間の中央値は18カ月であった．

治療施行57例のうち，IFN投与中にHBV-DNAが5,000 copies/m*l*未満・ALT正常に低下し，その後もこれを維持したのは9例(15.8%)，IFN終了後にHBV-DNAが持続的に5,000 copies/m*l*未満かつALT正常化したのが16例(28.1%)であった．その他9例(15.8%)はIFN投与中はHBV-DNA 5,000 copies/m*l*かつALT正常

Kenji Ikeda: Department of Gastroenterology, Toranomon Hospital 虎の門病院消化器科

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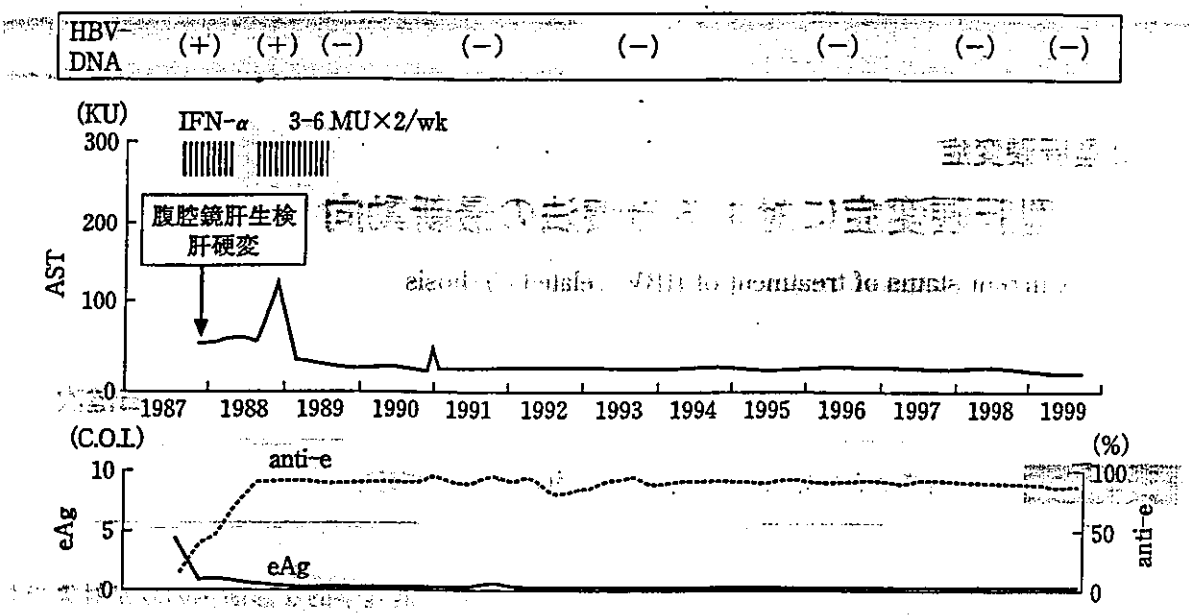

図1 長期間欠IFN投与を行った肝硬変症例
case S.K. 42y.o. male, cirrhosis, HBV+, HCV−

化した.

すなわち，長期経過でみると，57例中25例(43.9%)はやや長期の間欠IFN治療を行うことによりHBV-DNA 5,000 copies/ml未満かつALT正常を維持する'臨床的治癒'状態になった．更にIFN投与中のみ'臨床的治癒'状態が維持できたのはこれ以外に9例あり，IFNを持続して使用することを含めた治療効果は57例中34例(59.6%)に上った.

2. B型肝硬変に対するIFNの発癌抑制効果

ここでは，肝癌高危険群であるB型肝硬変に対して長期にIFNを投与して，治療が発癌率を抑制するかどうかの観点で，長期的効果を比較した[1].

対象は，1974-99年までの間に腹腔鏡肝生検で確定診断されたB型肝硬変351例で，IFN治療を行った105例(30.0%)とIFN治療を行わなかった246例との肝癌発癌率を比較した．IFN治療群では年齢の中央値は41歳で未治療群より3歳若年で，男性例の比率がやや高かった．また，治療群ではe抗原陽性率が65.6%で未治療群の46.0%より有意に高く，トランスアミナーゼ値も高値の傾向であった．IFN治療は1日300万-600万単位のIFN-αまたはβの投与を基本とし，週2回の間欠投与を6カ月もしくはそれ以上の期間行った．治療を行った94例での投与期間の中央値は10カ月であった．経過観察よりの脱落例は24例(6.8%)で，この症例も含めた経過観察期間の中央値は7.0年(最短0.1年，最長22.3年)であった.

観察期間の中央値7.0年の間に，IFN治療群・未治療群からはそれぞれ15例(14.3%)，58例(23.6%)の発癌例がみられた．IFN治療群・未治療群での3年累積発癌率はそれぞれ4.5%，13.3%，5年発癌率はそれぞれ，10.4%，19.8%，10年はそれぞれ20.3%，30.0%で，IFN治療群では有意に発癌率が低かった(log-rank test, p=0.038)(図2).

多変量解析では，B型肝硬変からの肝癌発癌に影響する因子は，①積算飲酒量(p=0.028)，②AFP値(p=0.011)，③ICG 15分値(p=0.029)，④IFN使用(ハザード比0.39，p=0.031)の4要因が独立要因であり，IFNの使用により発癌率が低下することが示された．すなわち，B型肝硬変からの発癌率を高める要因は，積算飲酒量が500 kg以上であること(これより少ない例と比べて3.27倍のハザード比)，AFP値が20 ng/ml以上(20 ng/ml未満に比し3.02倍のハザード

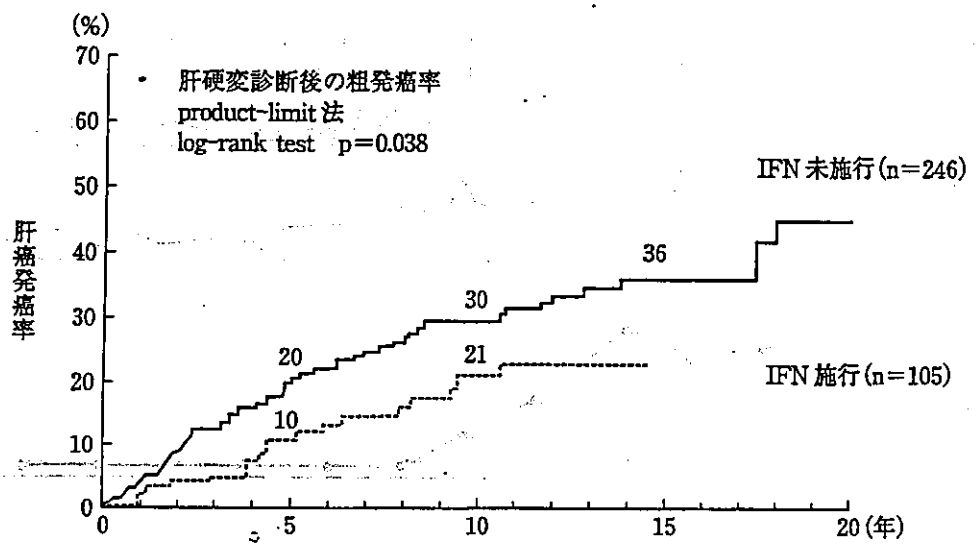

図2 IFN投与の有無によるB型肝硬変からの累積肝癌発癌率
1974-99年に診断したHBs抗原(+), HCV抗体(-)の肝硬変351例.

比), ICG 15分値が30%以上の例(30%未満の例に比し2.20倍のハザード比), IFN治療(ハザードが0.39に低下, p=0.031)であり, IFNがB型肝硬変からの発癌を抑制する結果であった.

3. B型肝硬変に対するラミブジン治療

ヌクレオチドアナログであるラミブジンは内服の抗ウイルス薬で, 副作用も少ないため, 慢性肝炎に対しては各国で広く使用されている. ALTが正常値の2倍以上の高値で経過する場合には, 本剤を使用する適応があるが, 肝臓専門医による投与が望ましい.

e抗原陰性例やe抗原陽性でもHBV-DNAが10^8 copies/ml以下であれば効果も良好であるが, e抗原陽性でHBV-DNAが10^8 copies/ml以上の場合には治療効果に限界があり, 6カ月目前後より耐性株の出現が高頻度であるため治療適応は慎重に判断するべきである. いずれの場合も1年以上の長期投与が原則である. HBV-DNAの血中濃度の低下に伴いALT低下・肝炎の安定化が得られ, 肝硬変病変の進行が抑制できる. 慢性肝炎症例に比し, ALTの正常化は緩徐にしか起こらず半年またはそれ以上の経過を必要とする場合もある(図3). IFNでは肝不全症状の増悪や血球減少など強い副作用が出現するため使用できないが, ラミブジンは腹水・脳症を伴う非代償期肝硬変に対して使用されることがあり[2-5], しばしば病態の著明な改善をもたらす.

耐性株の出現により, ALTの急上昇・HBV-DNA量増加がみられるが, ラミブジンの投与を急に中止することは危険で避けるべきである. 耐性株出現による肝炎急性増悪(breakthrough)に対しては, IFNのほか, 同様な抗ウイルス薬であるアデフォビル(adefovir)・エンテカビル(entecavir)が有効である.

ラミブジンがB型慢性肝炎に対して認可されて既に数年になるが, 肝硬変に対しての治療はまだ十分な環境が整っていない.

4. IFN治療の問題点とラミブジンとの使い分け

B型肝硬変治療におけるIFN治療の問題点としてあげられるのは; ①治療効果が十分でないこと, ②治療効果判定基準が統一されていないこと, ③治療効果を左右する宿主要因・ウイルス要因が少なくないこと, ④最も効果的な治療方法が未確立であること, ⑤副作用が強いこと, そして⑥ラミブジン治療との関係を含め, 真のIFN治療の適応症例が不明であることなどである.

IFNは抗ウイルス薬として以前より使用され

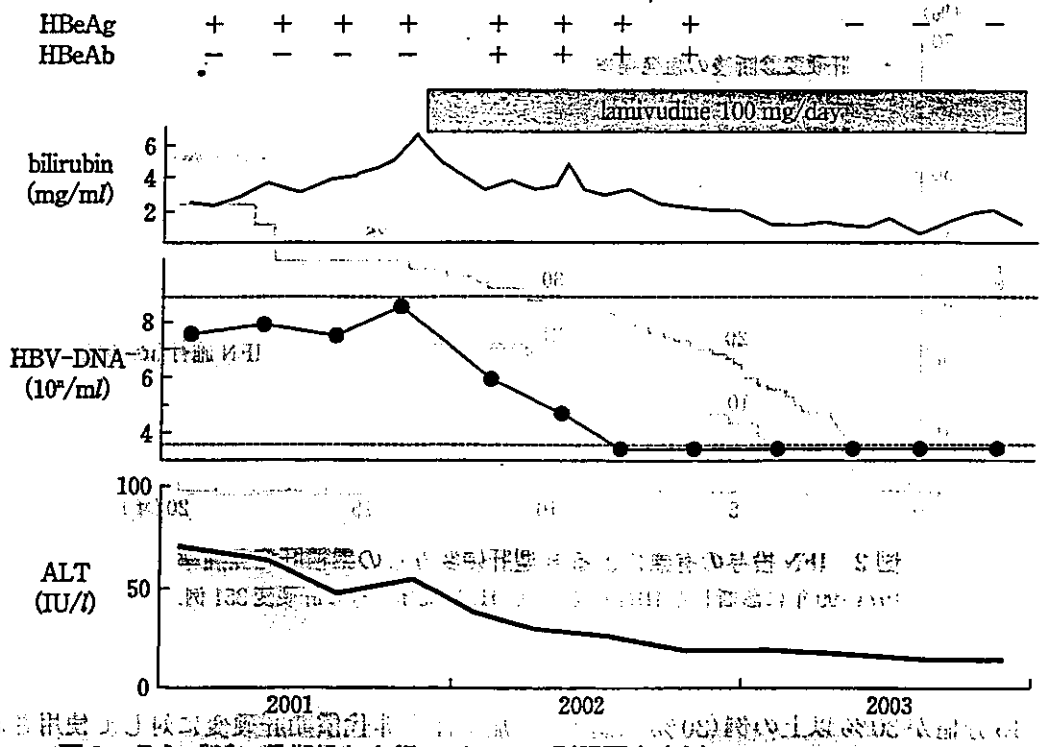

図3 ラミブジン長期投与を行っているB型肝硬変症例(44歳男性，HBeAg陽性)
ALT低下・ビリルビン低下・HBV-DNA低下などの治療効果は緩徐に現れている．

ており，ラミブジンと同様の治療目標で，同様の治療適応の薬剤である．ラミブジンとの使い分けは明確ではないが，IFNは注射剤であり，発熱・全身倦怠感・うつ病などの副作用もあるが，ラミブジンにみられるような耐性株の出現はない．両薬剤は，投与期間・薬剤費用・通院の手間・副作用出現などについて，患者への十分な説明・協議が必要である．IFN治療は，通常週2-3回の間欠長期投与で行われるが，治療開始初期には4週間程度の連日投与が行われることも多い．

5. B型肝硬変に対する肝移植

B型慢性肝炎からの急性増悪により劇症化した場合や肝硬変では肝移植が考慮される．B型肝硬変は最近まで移植後のgraft生着率，生存率が不良で，良い治療適応とはされず，禁忌と考えられることも多かった．特に，我が国では脳死肝移植のドナーが少なく，先天性胆道閉鎖症・非感染性肝硬変(原発性胆汁性肝硬変など)・代謝性疾患などの優先順位が高い事情があって，脳死肝移植は当面困難な状態にある．しかし，生体肝移植に関しては，移植前から抗ウイルス薬であるラミブジンを使用し[5,6]，これによりHBV-DNAを抑制することができれば，移植適応ありとする施設が一般的となっている．ラミブジンの内服で肝移植の成功率が向上するとの成績[3,5]，待ち時間を延長できたという報告[2]，更に移植そのものが不要になる症例が出現の報告[7]などがなされている．他の肝疾患とは異なり，移植後はHBグロブリンを定期的に注射するなどの処置を行って，HBs抗原が陽性にならないように維持する治療も必要となる．移植前後のラミブジン治療に関しては，今後のランダム化比較試験が待たれる．

劇症肝炎・肝硬変・肝癌合併例など，原疾患により生存率は異なるが，非ウイルス疾患より生存率はやや低い．

■文　献

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