serum HCV RNA levels at 4 weeks compared to those with a <3 $\log_{10}$ decrease in serum HCV RNA levels ($P < 0.0001$). When a 3 $\log_{10}$ decrease in serum HCV RNA levels was defined as the cut-off point, 56.5% of patients were considered to have a ≥3 $\log_{10}$ decrease in serum HCV RNA levels. The sensitivity, specificity, positive predictive value, and negative predictive value for a sustained virologic response were 86.8, 75.2, 78.6, and 84.4%, respectively.

Among the 65 patients who had the TG/GG genotype, no patient achieved a rapid virologic response at 4 weeks after initiating therapy. The decrease in serum HCV RNA levels at 4 weeks after starting therapy ranged from 0.11 $\log_{10}$ to 4.75 $\log_{10}$ (mean, 1.66 $\log_{10}$). The reduction in serum HCV RNA levels at 4 weeks after starting the therapy were smaller in patients with the TG/GG genotype than those with the TT genotype (1.66 ± 1.02 $\log_{10}$ in patients with the TG/GG genotype vs. 3.12 ± 1.37 $\log_{10}$ in patients with TT genotype excluding RVR, $P < 0.0001$). The reduction in serum HCV RNA levels was ≥3 $\log_{10}$ in five patients (7.7%), <3 $\log_{10}$ and ≥2 $\log_{10}$ in 10 patients (15.4%), <2 $\log_{10}$ and ≥1 $\log_{10}$ in 27 patients (41.5%), and <1 $\log_{10}$ in 23 patients (35.4%). Figure 1B shows the rates of a sustained virologic response according to the reduction in HCV RNA levels at 4 weeks after starting therapy in patients with the TG/GG genotype. There were no differences in the rate of a sustained virologic response based on the reduction in HCV RNA levels at 4 weeks after starting therapy; the rate of a sustained virologic response remained at 20% approximately regardless of the reduction in HCV RNA levels in 42 patients with a ≥1 $\log_{10}$ reduction in serum HCV RNA levels.

Association Between an Early Virologic Response at 12 Weeks and Treatment Outcome Based on Genetic Polymorphisms Near the *IL28B* Gene

Figure 2 shows the rate of patients with the TT genotype or TG/GG genotype for rs8099917 who achieved a complete early virologic response, a partial early virologic response, and those who did not achieve early virologic response at 12 weeks after starting therapy based on the reduction in serum HCV RNA level at 4 weeks after initiating therapy. Nearly 75% of patients with the TT genotype whose HCV RNA levels were reduced by ≥3 $\log_{10}$ at 4 weeks after starting the therapy achieved a complete early virologic response. In contrast, 80% of patients with the TG/GG genotype whose HCV RNA levels were reduced by ≥3 $\log_{10}$ at 4 weeks after starting the therapy showed a partial early virologic response. The majority of patients with the TT or TG/GG genotypes achieved a partial early virologic response when their reduction in HCV RNA levels was <3 $\log_{10}$ and ≥2 $\log_{10}$ or <2 $\log_{10}$ and ≥1 $\log_{10}$.

Figure 3 shows the rates of a sustained virologic response according to the type of early virologic response in patients with the TT genotype (Fig. 3A) and TG/GG genotype (Fig. 3B). Among patients with the TT genotype, the rate of sustained virologic response was significantly higher in patients with a complete early virologic response than in those with a partial early virologic response ($P < 0.0001$). In contrast, there was no difference in the rate of a sustained virologic response between patients with a complete early virologic response and those with a partial early virologic response ($P = 0.8917$) among patients with

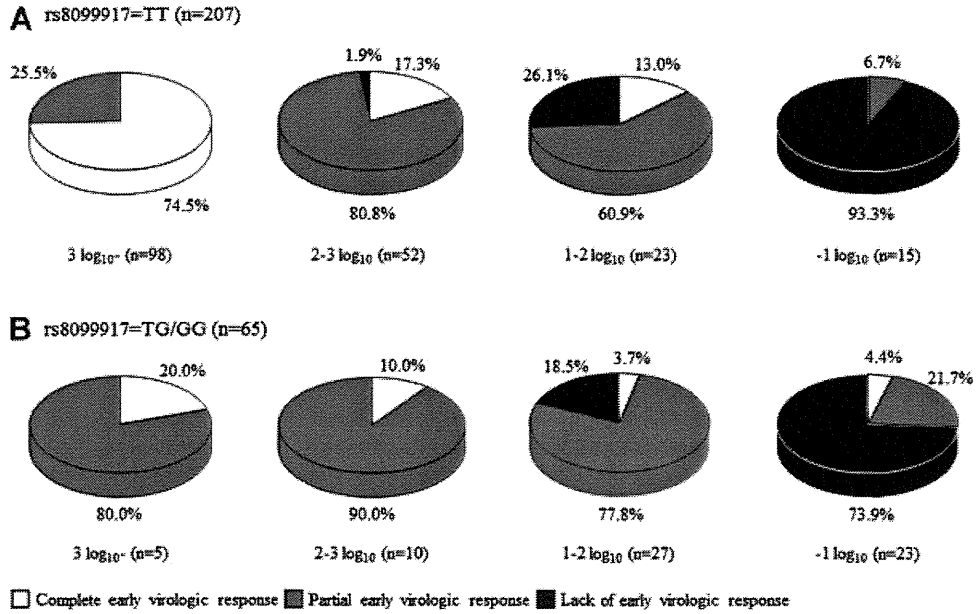

Fig. 2. The association between the virologic responses at 12 weeks after starting therapy and the reduction in serum HCV RNA levels at 4 weeks after starting therapy. **A**: Patients with the TT genotype for rs8099917, (**B**) patients with the TG/GG genotype for rs8099917.

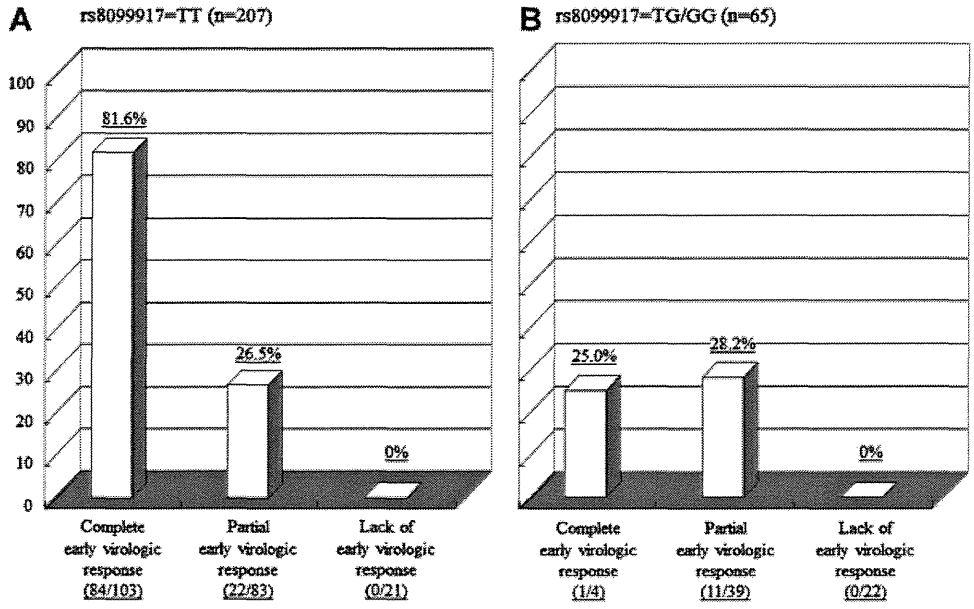

Fig. 3. The rate of sustained virologic responses based on the type of early virologic response. **A**: Patients with the TT genotype for rs8099917, (**B**) patients with the TG/GG genotype for rs8099917.

the TG/GG genotype. None of the patients with the TT genotype or TG/GG genotype who yielded a lack of an early virologic response reached a sustained virologic response.

Univariate and Multivariate Analyses for Factors Associated With a Sustained Virologic Response to Peginterferon and Ribavirin Combination Therapy in Patients With the TT and the TG/GG Genotype for the rs8099917

Univariate and multivariate analyses were conducted for factors associated with a sustained virologic response based on different genetic polymorphisms near the *IL28B* gene. In patients with the TT genotype, the factors that were associated with a sustained virologic response included serum alkaline phosphatase levels, serum albumin, platelet counts, hepatitis activity grade, liver fibrosis grade, reduction in HCV RNA levels at 4 weeks after starting therapy, and a complete early virologic response based on a univariate analysis (Table IIIA). In a multivariate analysis, the serum albumin levels, reduction in HCV RNA levels 4 weeks after starting therapy, and a complete early virologic response were independent factors that were significantly associated with a sustained virologic response (Table IIIB). A reduction in HCV RNA levels 4 weeks after starting therapy was the strongest factor that affected a sustained virologic response. In patients with the TG/GG genotype, the factors that were associated with a sustained virologic response included patient age, platelet counts, and pretreatment HCV RNA levels based on a univariate analysis (Table IIIA). A reduction in the HCV RNA levels at 4 weeks after starting therapy was not associated with a sustained virologic response. In a multivariate analysis, patient age and pretreatment HCV RNA levels were independent factors that were significantly associated with a sustained virologic response (Table IIIC).

Characteristics of Patients who Achieved a Sustained Virologic Response to the Combination Therapy Despite the Unfavorable TG/GG Genotype Near the *IL28B* Gene

Table IV shows the characteristics of 12 patients who achieved a sustained virologic response despite having the unfavorable TG/GG genotype for rs8099917 near the *IL28B* gene. All but one patient was under 60 years old and had liver fibrosis not more than grade 2 (one patient did not undergo a liver biopsy). Except for one patient, the reduction in the serum HCV RNA levels at 4 weeks after starting therapy was less than 3 $\log_{10}$ and all but one patient showed a partial early virologic response at 12 weeks after starting the therapy. In all 11 patients with a partial early virologic response, the serum HCV RNA was undetectable up to 24 weeks after starting the therapy. All but one patient extended the treatment duration from 48 to 72 weeks (two patients discontinued therapy at 60 weeks during the extended treatment period). When the characteristics of patients who achieved a sustained virologic response were compared between those with the unfavorable TG/GG genotype and those with the favorable TT genotype, patients with the TG/GG genotype were younger (41.8 ± 14.4 years vs. 55.1 ± 10.4 years, $P = 0.0023$) and had lower pretreatment HCV RNA levels (5.91 ± 0.44 $\log_{10}$ IU/ml vs. 6.21 ± 1.05 $\log_{10}$ IU/ml, $P = 0.0199$).

TABLE III. Univariate and Multivariate Analyses for Factors Associated With a Sustained Virologic Response to Peginterferon and Ribavirin Combination Therapy in Patients With the TT and the TG/GG Genotype for the rs8099917

(A) Univariate analyses	*P*-value	
	Patients with TT genotype of rs8099917 (n = 207)	Patients with TG/GG genotype of rs8099917 (n = 65)
Age (years)	0.0505	0.0007
Sex (female/male)	0.1830	0.2296
Body weight (kg)	0.6891	0.2456
Alanine aminotransferase (IU/L)	0.7988	0.4032
Aspartate aminotransferase (IU/L)	0.5021	0.1705
Gamma-glutamyl transpeptidase (IU)	0.6340	0.6648
Alkaline phosphatase (IU/L)	0.0315	0.0599
Albumin (g/dl)	0.0002	0.6594
Total bilirubin (mg/dl)	0.2929	0.7130
White blood cell count (/μl)	0.2508	0.5549
Hemoglobin (g/dl)	0.0847	0.2289
Platelet count ($\times 10^3$/μl)	0.0454	0.0411
Liver histology-activity (A0–1/A2–3)	0.0445	0.1117
Liver histology-fibrosis (F0–1/F2–3)	0.0002	0.2283
Pretreatment HCV RNA concentration (≥ 6.5 $\log_{10}$ vs. <6.5 $\log_{10}$)	0.5279	0.0379
Reduction in the peginterferon dose	0.4316	0.5563
Reduction in the ribavirin dose	0.1823	0.4272
Reduction in HCV RNA levels at 4 weeks after starting the therapy (≥ 3 $\log_{10}$ vs. < 3 $\log_{10}$)	<0.0001	0.9265
Early virologic response (complete vs. partial)	<0.0001	0.9777
Early virologic response (partial vs. non)	0.8632	0.0686

(B) Multivariate analyses: Patients with TT genotype of rs8099917	*P*-value	Odds ratio (95% confidence interval)
Alkaline phosphatase (IU/L)	0.2617	
Albumin (g/dl)	0.0365	28.287 (1.4107–755.41)
Platelet count ($\times 10^3$/μl)	0.2599	
Liver histology-activity (A0–1/A2–3)	0.6678	
Liver histology-fibrosis (F0–1/F2–3)	0.2307	
Reduction in HCV RNA levels at 4 weeks after starting the therapy (≥ 3 $\log_{10}$ vs. <3 $\log_{10}$)	<0.0001	16.029 (6.8593–40.406)
Early virologic response (complete vs. partial)	0.0224	0.3685 (0.1557–0.8749)

(C) Multivariate analyses: Patients with TG/GG genotype of rs8099917	*P*-value	Odds ratio (95% confidence interval)
Age (years)	0.0022	0.0034 (0.0000–0.0840)
Platelet count ($\times 10^3$/μl)	0.3344	
Pretreatment HCV RNA concentration (≥ 6.5 $\log_{10}$ vs. <6.5 $\log_{10}$)	0.0304	0.0548 (0.0020–0.4950)

HCV, hepatitis C virus.

DISCUSSION

Several previous studies reported that patients who achieved a rapid virologic response, in which serum HCV RNA become undetectable at 4 weeks after starting therapy, had a high likelihood of achieving a sustained virologic response [Martinez-Bauer et al., 2006; Poordad et al., 2008; de Segadas-Soares et al., 2009; Martinot-Peignoux et al., 2009]. In addition, several recent studies reported the predictive value of the degree of reduction in serum HCV RNA levels at 4 weeks after starting therapy [Yu et al., 2007; Huang et al., 2010; Toyoda et al., 2011]. Therefore, the viral dynamics of HCV at 4 as well as 12 weeks after starting therapy is important for response-guided therapy.

Genetic polymorphisms near the *IL28B* gene have emerged as the strongest predictive factor of a sustained virologic response in patients infected with HCV genotype 1 [Hayes et al., 2011; Kurosaki et al., 2011]. In addition, Thompson et al. [2010 reported that genetic polymorphisms near the *IL28B* gene were associated strongly with early viral dynamics during PEG-IFN and ribavirin combination therapy. These findings raised an important issue of whether response-guided therapy, based on the reduction in serum HCV RNA levels at 4 or 12 weeks after starting

TABLE IV. Patients who Achieved a Sustained Virologic Response Despite the TG/GG Genotype for the rs8099917

	Age (years)	Sex	Liver histology	Pretreatment HCV RNA level (log_{10} IU/ml)	HCV RNA reduction at 4 weeks	Response at 12 weeks	HCV RNA became undetectable (weeks)	Treatment duration (weeks)
1.	31	Female	A1/F1	6.13	2.19	partial EVR	20	48
2.	55	Male	A1/F1	5.80	1.77	partial EVR	16	72
3.	57	Female	A1/F1	5.58	3.01	partial EVR	16	72
4.	57	Female	A1/F1	6.21	1.81	partial EVR	20	72
5.	62	Male	N.D.	6.23	1.13	partial EVR	24	72
6.	21	Male	A1/F2	6.04	1.83	partial EVR	24	72
7.	42	Male	A1/F1	6.27	0.57	partial EVR	24	72
8.	29	Female	A1/F2	5.83	1.83	partial EVR	20	60
9.	52	Male	A1/F0	5.91	2.12	complete EVR	12	48
10.	40	Male	A2/F1	5.84	1.34	partial EVR	20	72
11.	27	Male	N.D.	5.63	0.42	partial EVR	24	72
12.	28	Male	A1/F0	6.59	0.76	partial EVR	20	60

N.D., not done; HCV, hepatitis C virus; EVR, early virologic response.

therapy, retains a predictive value when considering genetic polymorphisms near the *IL28B* gene.

In the present study, the predictive value of the decrease in serum HCV RNA levels was evaluated at 4 and 12 weeks after starting therapy in Japanese patients infected with HCV genotype 1b based on genetic polymorphisms near the *IL28B* gene. Consistent with previous reports, patients with the TG/GG genotype for rs8099917 had a smaller reduction in serum HCV RNA levels at 4 weeks after starting treatment ($P < 0.0001$), which indicates an unfavorable response to the combination therapy. Patients with the TT genotype for rs8099917, which is associated with a favorable response to the combination therapy, exhibited a significant difference in the rate of a sustained virologic response based on the reduction in serum HCV RNA levels at 4 weeks after initiating the therapy. Patients with a rapid virologic response or with a ≥ 3 log_{10} reduction in HCV RNA levels had a higher likelihood of achieving a sustained virologic response.

In contrast, these factors did not have any predictive value in patients with the TG/GG genotype. Only 18.5% of patients achieved a sustained virologic response (12 of 65 patients), and it was difficult to identify these patients based on the reduction in HCV RNA levels at 4 weeks or the type of an early virologic response at 12 weeks after starting therapy. Patients who achieved a sustained virologic response, despite the TG/GG genotype for rs8099917, were identified among those with a <2 log_{10} and ≥ 1 log_{10} or even <1 log_{10} reduction in HCV RNA levels at 4 weeks after starting therapy. Interestingly and paradoxically, the possibility of a sustained virologic response can be expected in patients with a <1 log_{10} reduction in HCV RNA levels at 4 weeks after starting therapy only when they have the unfavorable TG/GG genotype.

In the evaluation at 12 weeks after starting therapy, patients with the TT genotype who achieved a complete early virologic response had a higher rate of a sustained virologic response significantly than patients who achieved a partial early virologic response, whereas this difference was not found in patients with the TG/GG genotype. No patients who failed to achieve an early virologic response achieved a sustained virologic response regardless of the genetic polymorphisms near the *IL28B* gene. Thus, the lack of an early virologic response retained a strong predictive value for the failure of achieving a sustained virologic response. This result supports the recommendation in the AASLD guidelines, in which treatment may be discontinued in patients without an early virologic response at 12 weeks of treatment.

The characteristics of patients who achieved a sustained virologic response despite the unfavorable TG/GG genotype were younger in age and lower pretreatment HCV RNA levels. Most patients with the TG/GG genotype who achieved a sustained virologic response showed a partial early virologic response and extended the treatment duration. It was difficult to identify these patients according to viral dynamics at 4 or 12 weeks after starting therapy.

There are several limitations in this study. Some patients with a slow virologic response did not have their treatment period extended from 48 to 72 weeks. This is because the effectiveness of a 72-week combination therapy regimen in patients with HCV genotype 1 with a slow virologic response [Berg et al., 2006; Pearlman et al., 2007] had not been established in Japan in the earlier part of this study. This fact might have influenced the treatment outcome especially in patients with the unfavorable TG/GG genotype. Another limitation is a smaller sample size of patients with the TG/GG genotype in comparison to that of patients with the TT genotype. This sample size could have caused the lack of statistical significance in the rate of a sustained virologic response according to the reduction in HCV RNA levels at 4 weeks after starting therapy or according to the type of an early virologic response in patients with the TG/GG genotype. In addition, the data were based on Japanese patients infected with HCV genotype 1b. Therefore, these results should be confirmed in other ethnicities and patients infected with HCV genotype 1a.

In conclusion, among patients infected with HCV genotype 1b with the TT genotype for rs8099917, a rapid virologic response or a ≥ 3 $\log_{10}$ reduction in HCV RNA levels at 4 weeks after starting therapy, or a complete early virologic response indicate strongly that these patients will achieve a sustained virologic response as a final outcome for PEG-IFN and ribavirin combination therapy. Early viral dynamics retain the predictive value in this patient subpopulation. A reduction in HCV RNA levels at 4 weeks after starting therapy or the type of an early virologic response does not predict the likelihood that patients with the TG/GG genotype will achieve a sustained virologic response. In contrast, the lack of an early virologic response retains a strong predictive value for the failure to achieve a sustained virologic response regardless of *IL28B* polymorphisms, which remains useful as a factor to stop therapy.

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HEPATOLOGY

Clinical impact of HFE mutations in Japanese patients with chronic hepatitis C

Yoji Ishizu, Yoshiaki Katano, Takashi Honda, Kazuhiko Hayashi, Masatoshi Ishigami, Akihiro Itoh, Yoshiki Hirooka, Isao Nakano and Hidemi Goto

Department of Gastroenterology, Nagoya University Graduate School of Medicine, Nagoya, Japan

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Correspondence
Yoshiaki Katano, Department of Gastroenterology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. Email: ykatano@med.nagoya-u.ac.jp

Abbreviations
CHC, chronic hepatitis C; HCV, hepatitis C virus; HH, hereditary hemochromatosis; IFN, interferon; IL28B, interleukin 28B; PCR, polymerase chain reaction; PEG-IFN, pegylated-interferon-alpha 2b; RBV, ribavirin; SNP, single-nucleotide polymorphism; SVR, sustained virological response.

Abstract

Background and Aim: HFE mutations, a common cause of hereditary hemochromatosis (HH), are reportedly associated with hepatic iron overload, severe liver fibrosis, and good response to interferon treatment in European patients with chronic hepatitis C (CHC). HH shows ethnicity-based differences and little is known about the effects of HH mutations on CHC in the Japanese. Thus, the aim of this study was to clarify the clinical influence of HFE mutations in Japanese CHC patients.

Methods: In a total of 251 patients with CHC, we analyzed the frequencies of H63D and S65C mutations in the HFE gene, and the influence of these mutations on clinical parameters and response to pegylated-interferon-alpha 2b (PEG-IFN) plus ribavirin therapy.

Results: Fourteen patients (5.6%) carried the H63D mutation; all were heterozygotes. No S65C mutations were found. Only hemoglobin levels in the H63D heterozygotes were higher than in wild-type patients. Eleven of 14 H63D heterozygotes achieved sustained virological response (SVR). On univariate analysis, factors associated with SVR were interleukin 28B (IL28B) polymorphism, age, hepatitis C virus (HCV) genotype, HCV viral load, white blood cell count, stage of fibrosis and H63D mutation. All patients with both TT genotype in IL28B (rs8099917) and H63D mutation in HFE ($n = 10$) achieved SVR.

Conclusions: The H63D mutation has little impact on the clinical characteristics of CHC, but is related to favorable response to PEG-IFN plus ribavirin therapy, particularly in patients with the TT allele in IL28B.

Introduction

Hepatitis C virus (HCV) infection is a significant global health problem, affecting 170 million individuals worldwide. HCV infection causes chronic hepatitis that can develop into cirrhosis and hepatocellular carcinoma. Elevated hepatic iron concentration has often been found in patients with chronic hepatitis C (CHC),[1] and this excess iron increases oxidative stress, which can accelerate the progression of fibrosis[2] and may promote hepatic carcinogenesis.[3] Moreover, hepatic iron accumulation is thought to lower the response rate to interferon (IFN)-based therapy in patients with CHC.[4–8]

HFE mutations are the major gene variations in hereditary hemochromatosis (HH),[9] which is a common autosomal recessive disorder associated with iron overload in Caucasians.[10] Therefore, there has been much interest in the roles of HFE mutations in patients with HCV infection. Several studies have been performed in order to assess the correlations among HFE mutations, hepatic iron overload and disease progression in CHC. However, the effects of HFE mutations on hepatic iron concentration and disease severity remain controversial.[11–18] On the other hand, the presence of HFE mutations was reported to be associated with good response to IFN therapy.[11,19] As the prevalence of HFE mutations is lower in Asian populations than in Caucasian populations,[20] most studies on HFE mutations have been conducted in Western countries, with only one small study being conducted in an Asian country.[21] Clarifying the effects of these mutations on iron loading and clinical features in Asian patients may help to further understand the role of HFE mutations in HCV-infected patients.

The aim of this study was to examine the influence of HFE gene variants on iron overload and clinical characteristics, and to investigate whether HFE mutations affect response to pegylated-interferon-alpha 2b (PEG-IFN) plus ribavirin (RBV) therapy in Japanese CHC patients.

Methods

Patients. A total of 251 Japanese patients infected with HCV and being treated at Nagoya University Hospital were enrolled in this retrospective study. Patients included 143 men and 108 women with a mean age of 53.8 ± 12.3 years. Exclusion criteria

were as follows: hepatitis B surface antigenemia; human immunodeficiency virus infection; chronic alcohol abuse; autoimmune liver disease; and history of phlebotomy. Degree of inflammatory activity and stage of fibrosis were assessed according to the histological scoring system of METAVIR[22] by pathologists who were blinded to clinical data. Hepatic iron storage was graded with Perls' Prussian blue stain on a scale of 0–4 as follows: grade 0, iron granules absent or barely discernible × 400; grade 1, barely discernible × 250 or easily discernible × 400; grade 2, discrete granules resolved × 100; grade 3, discrete granules resolved × 25; grade 4, massive visible × 10, or naked eye.[23] Patients received subcutaneous injections of PEG-IFN (1.5 μg/kg) once per week plus oral RBV (600 mg for < 60 kg, 800 mg for 60–80 kg, 1000 mg for > 80 kg) daily, in accordance with Japanese guidelines.[24] Sustained virological response (SVR) was defined as undetectable HCV RNA at 24 weeks after withdrawal of treatment. The other patients were considered to have non-SVR. This study was approved by the Nagoya University Hospital ethics committee, and was conducted in accordance with the principles of the 1975 Declaration of Helsinki. Written informed consent was obtained from all patients.

Genomic analysis. Genomic DNA was isolated from peripheral blood leukocytes by standard procedures. HFE mutations at position 63 (histidine to aspartic acid, H63D) and at position 65 (serine to cysteine, S65C) were determined by the polymerase chain reaction (PCR)-restriction fragment length polymorphism method with *Bcl*-I (for H63D) and *Hinf*-I (for S65C), as described previously.[11] Detection of the rs8099917 single-nucleotide polymorphism (SNP) in interleukin 28B (IL28B) was also performed by real-time PCR using custom-designed primers and probes (Taqman SNP Genotyping Assays; Applied Biosystems, Foster, CA, USA). IL28B SNP rs8099917 was amplified and the results were analyzed by real-time PCR in a thermal cycler (7300 Real-time PCR System; Applied Biosystems).

Statistical analysis. Quantitative variables were compared by the Mann–Whitney *U*-test, and are expressed as median values with interquartile range. The distribution of qualitative variables was compared by the χ^2-test or Fisher's exact test, as appropriate. Multiple logistic regression analysis was performed in order to determine the factors contributing to SVR. *P*-values less than 0.05 were considered to be statistically significant and $0.1 > P \geqq 0.05$ were referred to as marginally significant. Statistical analyses were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Influence of H63D mutation on clinical characteristics. Of the 251 patients with CHC, 14 carried the H63D mutation (5.6%); all were heterozygous. Patient characteristics according to the presence of H63D mutation are shown in Table 1. No significant differences in clinical, laboratory, or histological data were observed between H63D heterozygotes and wild-type patients, except that hemoglobin levels were higher in H63D heterozygous patients. There was no correlation between the presence of H63D mutation and genotype of IL28B. Histological evaluation of hepatic iron deposition using Perls' Prussian blue method in nine H63D heterozygous patients demonstrated low levels of iron staining in the liver: six had grade 0, two had grade 1, and one had grade 2 positive staining.

Influence of H63D mutation on response to PEG-IFN plus RBV therapy in patients with CHC. Of the 251 patients who received PEG-IFN plus RBV therapy, 116 (46.2%) achieved SVR. Univariate analysis identified seven factors that influenced SVR: younger age ($P = 0.003$); genotype 2 ($P < 0.001$); lower viral load (< 1000 KIU/mL) ($P < 0.001$); higher white blood cell count ($P = 0.039$); lower stage of fibrosis ($P = 0.002$); genotype TT of IL28B rs8099917 ($P < 0.001$); and presence of H63D heterozygosity ($P = 0.012$)

Table 1 Comparison of characteristics according to the presence of the H63D mutation

	H63D heterozygotes ($n = 14$)	Wild type ($n = 237$)	*P*-value
Sex (male/female)	11/3	132/105	0.093
Age (years)	53 (44–56.8)	56 (47–63)	0.148
Body mass index (kg/m^2)	21.6 (19.6–24.4)	22.1 (20.3–24.4)	0.282
Alanine aminotransferase (IU/L)	35 (28.2–50.1)	38 (28–68)	0.520
Aspartate aminotransferase (IU/L)	53.5 (26.5–103.3)	46 (29–80)	0.748
Gamma-glutamyl transpeptidase (IU/L)	49 (25–62)	32.0 (21.0–62.3)	0.327
Total bilirubin (mg/dL)	1.00 (0.78–1.03)	0.8 (0.6–1.0)	0.247
Albumin (g/dL)	4.1 (4.0–4.3)	4.1 (3.8–4.3)	0.292
Serum ferritin (ng/mL)	110 (82–143)	89 (40–180)	0.580
White blood cell counts (/mm^3)	4550 (3950–4950)	4600 (3900–5400)	0.652
Hemoglobin (g/dL)	14.7 (13.5–15.8)	13.7 (13.0–14.8)	0.040
Platelet counts (/mm^3)	177 000 (135 000–158 000)	164 000 (132 000–203 000)	0.468
HCV genotype (1/2)	12/2	181/56	0.326
Viral load (KIU/mL) (< 1000/ 1000)	5/9	56/181	0.334
Stage of inflammatory activity (0/1/2/3)	0/6/5/0	4/96/82/4	0.592
Stage of fibrosis (0/1/2/3/4)	0/7/4/0/0	28/74/50/26/7	0.381
IL28B rs8099917 genotype (TT/TG or GG)	10/4	175/62	0.538

Data is expressed as median values and (interquartile range).
HCV, hepatitis C virus; IL28B, interleukin 28B.

Table 2 Characteristics of SVR and non-SVR in patients with chronic hepatitis C

	SVR ($n = 116$)	non-SVR ($n = 135$)	*P*-value
Sex (male/female)	69/47	74/61	0.456
Age (years)	54 (43.3–60)	58 (49–64.5)	0.003
Body mass index (kg/m^2)	22.0 (20.4–23.8)	22.3 (20.5–24.9)	0.140
Alanine aminotransferase (IU/L)	34 (26–63)	39.5 (29.3–69.8)	0.094
Aspartate aminotransferase (IU/L)	46 (26–94)	46 (29.3–77)	0.896
Gamma-glutamyl transpeptidase (IU/L)	31 (21–53)	34 (21.8–64.5)	0.248
Total bilirubin (mg/dL)	0.80 (0.60–1.00)	0.8 (0.6–1.0)	0.736
Albumin (g/dL)	4.1 (3.8–4.3)	4.0 (3.8–4.2)	0.109
Serum ferritin (ng/mL)	95.5 (40–178)	86.4 (44.3–161.5)	0.661
White blood cell counts (/mm^3)	4800 (4000–5800)	4550 (3900–5200)	0.039
Hemoglobin (g/dL)	14.0 (13.0–15.0)	13.7 (13.0–14.6)	0.136
Platelet counts (/mm^3)	167 000 (137 000–206 000)	160 000 (131 000–199 000)	0.499
HCV genotype (1/2)	76/40	117/18	< 0.001
Viral load (KIU/mL) (< 1000/≥ 1000)	42/74	18/117	< 0.001
Stage of inflammatory activity (0/1/2/3)	1/49/38/1	3/53/49/3	0.344
Stage of fibrosis (0/1/2/3/4)	13/45/21/6/1	15/36/33/20/6	0.002
H63D mutation (present/absent)	11/105	3/132	0.012
IL28B rs8099917 genotype (TT/TG or GG)	101/15	82/53	< 0.001

Data are presented as median values and (interquartile range).
HCV, hepatitis C virus; IL28B, interleukin 28B; SVR, sustained virological response.

Table 3 Factors associated with SVR in patients with chronic hepatitis C by multivariate analysis

Factor	Category	OR (95%CI)	*P*-value
IL28B rs8099917	Genotype TT	7.089 (2.961–16.976)	< 0.001
Age (years)	Younger age (each 1 year decrease)	1.062 (1.030–1.094)	< 0.001
HCV genotype	Genotype 2	2.978 (1.357–6.535)	0.001
Viral load (KIU/mL)	< 1000	4.631 (1.937–11.073)	0.007
H63D mutation	Present	5.281 (0.994–28.072)	0.051

Variables that achieved statistical significance ($P < 0.05$) or marginal significance ($P < 0.10$) on multivariate logistic regression analysis are shown.
CI, confidence interval; HCV, hepatitis C virus; IL28B, interleukin 28B; OR, odds ratio; SVR, sustained virological response.

(Table 2). On multivariate analysis, IL28B genotype (TT; $P < 0.001$), age (each 1-year decrease; $P < 0.001$), HCV genotype (2; $P = 0.001$), viral load (< 1000 KIU/mL; $P = 0.007$) and H63D mutation (heterozygosity; $P = 0.051$) were significant or marginal independent predictors of SVR (Table 3). In our study population, the SVR rate among patients with genotype TT in IL28B was 55.8% and that for genotypes TG and GG was 21.7%. In the analysis of IL28B SNP, H63D mutation was considered to improve prediction of SVR, as among 14 patients carrying the H63D mutation, the 10 patients with genotype TT in IL28B all achieved SVR. The characteristics of the patients are shown in Table 4.

Table 4 Characteristics of patients with both H63D mutation in HFE and genotype TT in IL28B (rs8099917)

Patient	Sex	Age (years)	HCV genotype	Viral load (KIU/mL)
1	Male	52	1	106
2	Male	57	2	342
3	Male	44	1	2080
4	Male	50	1	4950
5	Female	55	1	3220
6	Male	25	1	5100
7	Male	70	1	100
8	Female	28	2	2650
9	Male	66	1	2900
10	Female	57	1	250

HCV, hepatitis C virus; IL28B, interleukin 28B.

Discussion

The clinical penetrance of the HFE gene mutation is low. A large cohort study reported that, even in male carriers of the homozygous C282Y mutation, which is the most common genotype resulting in HH, only 28% of the subjects showed the clinical expression of iron overload, and in female patients, only 1% developed iron overload-related symptoms, possibly due to iron loss caused by menstruation.[25] With regard to the H63D mutation, its effect on body iron stores was much milder than the C282Y mutation and, particularly in heterozygotes, iron overload was scarcely observed.[20,26,27] However, in patients with chronic HCV infection, which is often associated with hepatic iron deposition, it was unclear whether HFE mutations were associated with iron

overload.[11–18] These conflicting results may have been due to genetic and environmental factors that affect iron accumulation. The Hemochromatosis and Iron Overload Screening (HEIRS) Study group indicated the importance of considering the effects of ethnic differences on serum iron markers.[28] In this study, H63D heterozygotes with CHC did not show any differences in laboratory data, except for hemoglobin levels, as compared with wild-type patients (Table 1). In Korea, Won *et al.* showed no correlation between serum ferritin levels and the H63D heterozygous state; however, the number of subjects was small.[21] This study also confirmed the lack of correlation between the presence of H63D heterozygosity and serum ferritin levels in Asia. Histological examination of liver iron stores substantiated the notion that H63D heterozygosity had no influence on hepatic iron deposition. We did not analyze the C282Y mutation because of its very low prevalence in Asian countries, including Japan, as reported previously.[10,20,29–33] On the other hand, we assessed the frequency of the S65C mutation, as no reports on this mutation have been published in Japan. However, in line with other studies from Asia,[31–33] none of the present subjects carried the S65C mutation.

The effects of H63D heterozygosity on fibrosis progression in patients with chronic HCV infection also remain unclear.[11,12,14–18] Although we did not find a correlation between the H63D mutation and fibrosis stage, some reports have suggested that the H63D heterozygote state would accelerate progression of fibrosis.[16–18] In these studies, the H63D heterozygotes showed increased hepatic iron deposition. Iron-related oxidative stress can increase hepatic inflammation and promote fibrosis,[2] and the authors of these studies suggested that progression of hepatic fibrosis was due to hepatic iron overload. Our study showed no evidence of excess iron deposition, which explains why H63D heterozygotes showed no correlation with fibrosis stage.

This study demonstrated that H63D heterozygotes with CHC show a good response to PEG-IFN plus RBV therapy. The positive effect of H63D mutation on IFN responsiveness in patients with CHC was reported in 2004.[19] The Hepatitis C Anti-Viral Long-Term Treatment to Prevent Cirrhosis (HALT-C) trial, a large and well-designed study, showed the same results in advanced CHC patients who received PEG-IFN plus RBV therapy.[11] Hepatic iron overload was shown to be associated with lower response rates to interferon therapy[4–8] and recent meta-analysis confirmed the beneficial effects of phlebotomy on response to interferon therapy.[34] Whereas H63D mutation is a potential cause of hepatic iron overload, a better treatment response was observed in H63D mutation carriers. The present study does not confirm the effects of H63D mutation on iron overload, but supports the positive effect of this mutation on IFN responsiveness. The precise mechanism of this effect remains unclear. The immunologic functions of HFE mutations were thought to play an important role.[11,19] The HFE gene is closely linked to the human leukocyte antigen-A3 locus, and some immunological differences, such as decreased cell-surface expression of major histocompatibility complex class I[35] and elevated monocyte chemoattractant protein-1 levels,[36] have been reported in HFE mutation carriers, as compared with wild-type patients. Further studies on the association between HFE mutations and immunologic functions in CHC patients are necessary in order to clarify these issues.

Factors associated with SVR have been widely studied, and several factors, including HCV genotype, viral load, mutations in HCV core and NS5A region, sex, liver fibrosis, ethnicity and age, have been suggested to play important roles in IFN responsiveness. Recently, three genome-wide association studies validated the correlation between SVR and SNP near the IL28B gene.[37–39] A minor allele in this genetic variation strongly predicts the failure of PEG-IFN plus RBV therapy; the SVR rate for our patients with this minor IL28B allele was 21.7%, and the positive predictive value of the major IL28B allele for SVR was 55.8%. Thus, another factor was considered to be necessary for improving SVR prediction.

Our study suggests that the H63D mutation is correlated with the outcome of IFN treatment, and combining IL28B SNP and H63D mutation may improve the predictive value for SVR. All patients with both H63D mutation and the major allele (genotype TT) of IL28B (rs8099917) achieved SVR. Although the frequency of H63D mutations is low in the Japanese population, it is much higher in North American and European populations; this correlation may therefore be more useful as a predictive factor for SVR in Western regions.

In conclusion, 5.6% of patients with CHC in Japan carry the H63D mutation in the HFE gene, and the S65C mutation was not detected. The H63D mutation had no influence on hepatic iron overload, but the presence of this mutation was associated with a good response to PEG-IFN plus RBV therapy.

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C型肝炎ウイルス（HCV）による感染

田中純子　広島大学大学院　医歯薬学総合研究科　疫学・疾病制御学
小山富子　岩手県予防医学協会　医療技術部
相崎英樹　国立感染症研究所　ウイルス二部

1. はじめに

ウイルス性肝炎の病因ウイルスの1つであるC型肝炎ウイルス（HCV）は，1989年に米国のHoughtonらによりHCV遺伝子の一部がクローニング[1]された比較的新しいウイルスである．1990年代は，急速に世界中でその測定系の開発と普及が推進されたことにより，さまざまな集団における肝炎ウイルス検査や調査等が広く行われ，徐々にC型肝炎ウイルス感染の状況が明らかになってきた．1992年以前，すなわち，C型肝炎ウイルス関連抗体検査(HCV抗体検査)が輸血用血液のスクリーニングとして普及・導入され始める以前には，世界中の輸血後肝炎の主な原因はC型肝炎ウイルスであったことをWHO(World Health Organization）は報告[2]している．また，HCVキャリア率は平均で3.0%，世界中のHCVキャリア数は1.3億人から1.7億人であると推計している．

本稿では，わが国におけるC型肝炎ウイルスによる感染状況(prevalence)を示すとともに，新規感染率（incidence）を垂直感染（母子感染）および水平感染に分けて成績を示す．

2. C型肝炎ウイルス（HCV）について

ウイルス性肝炎は，経口感染による伝染性肝炎と血液を介して感染する血清肝炎に大きく二分できる．経口感染による伝染性肝炎の病因ウイルスには，A型肝炎ウイルス（HAV：ピコルナウイルス科ヘパトウイルス属RNAウイルス）とE型肝炎ウイルス（HEV：ヘペウイルス科ヘペウイルス属RNAウイルス）があり，感染したヒトの糞便中に検出され，これに汚染された飲料水・食物を摂取することによって感染する．一方，血清肝炎の病因ウイルスには，B型肝炎ウイルス（HBV：ヘパドナウイルス科オルソヘパドナウイルス属DNAウイルス），C型肝炎ウイルス（HCV：フラビウイルス科ヘパシウイルス属RNAウイルス），D型肝炎ウイルス（HDV：サテライトウイルス科）があり，感染したヒトの血液中や微量な血液が混じった体液に検出されるが，これらの血液や体液がヒトの血液に入ることによって感染が起こる．D型肝炎ウイルス（HDV）はHBVをヘルパーウイルスとして増殖する特殊なウイルス（不完全ウイルス defective virus）でありHDV単独での感染はなく，日本では稀である．

C型肝炎ウイルス（HCV）は，直径55～57nmの球形をしたRNA型ウイルスである．ウイルス粒子は二重構造をしており，ウイルスの遺伝子（RNA）とこれを包んでいるヌクレオカプシド（コア粒子），そして，これを被う

Prevalence of hepatitis C virus infection and incidence of vertical and horizontal hepatitis C virus infection in Japan
Junko TANAKA, Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical Sciences, Hiroshima University
Tomiko KOYAMA, Division of Medical Technology, Iwateken Yobouigakukyoukai Inc. (Iwate Association of Preventive Medicine)
Hideki AIZAKI, Department of Virology II, National Institute of Infectious Diseases (NIID)
別刷請求先：田中純子　〒734-8551　広島市南区霞1-2-3　広島大学大学院医歯薬学総合研究科
Tel：082-257-5161　Fax：082-257-5164　E-mail：jun-tanaka@hiroshima-u.ac.jp

外殻（エンベロープ）から成り立っている．

C型肝炎ウイルスの抗体，すなわちHCV抗体とは，HCVのコア粒子に対する抗体（HCVコア抗体），エンベロープに対する抗体（E2/NS-1抗体），HCVが細胞の中で増殖する過程で必要とされるタンパク（非構造タンパク）に対する抗体（NS抗体：C100-3抗体，C-33c抗体，NS5抗体など）のすべてを含む総称となっている．

HCV抗体陽性者には，HCVに持続感染している例とウイルスがすでに排除された感染既往例とが混在している．1992年から献血時のスクリーニング検査に用いられていたHCV抗体測定系（凝集法，HCV PHA法，又はHCV PA法）では，この方法により陽性と判定された場合，その約70％がHCV RNA陽性（C型肝炎ウイルス持続感染者：HCVキャリア）であることが過去に行った基礎的調査により明らかになっている（なお，2008年5月末より日赤血液センターではHCV抗体測定はCLEA法により行われている）．

3. 肝癌による死亡の推移とその成因

人口動態統計[3]資料から得た肝癌による死亡の推移を図1に，またそのうちC型肝炎ウイルス（HCV）の持続感染に起因する死亡の割合について，人口動態統計資料と日本肝癌研究会による調査成績[4]を元に試算したものを図2に示す．

まず，悪性新生物「肝」(肝および肝内胆管の悪性新生物，人口動態統計，2009年）による死亡は，肺癌，胃癌に次いで，第3位と上位を維持し，死亡実数は32,725人（26.0/人口10万人対）と前年2008年（33,665人，26.7/人口10万人対）と比べやや死亡数は微減したが依然として3万人を超えている（図1）．

肝癌による死亡は，1950年代初めから1970年代半ばまでは人口10万人あたり10人前後（死亡実数は1万人以下）であったが，増加を始め2002年にピーク（人口10万人対27.5）を示した後，漸く横ばいとなっている．男性は，女性の肝癌による死亡の約2倍を示す高値（男性35.3，女性17.2/人口10万人対）であり，2002年以後には若干の減少傾向が認められるが，女性では現在に至るまで微増を続けている．

図2は，人口10万人あたりの肝細胞癌による死亡の推移とその病因別にみた内訳を試算したものである．

1975年以後，肝細胞癌による死亡数は増加しているが，HBVの持続感染に起因すると考えられる死亡の割合は人口10万人対5前後の一定値を示し増減がないまま推移している．すなわち，1970年代から2000年にかけて肝細胞がんによる死亡の増加は非A非B型によるものであっ

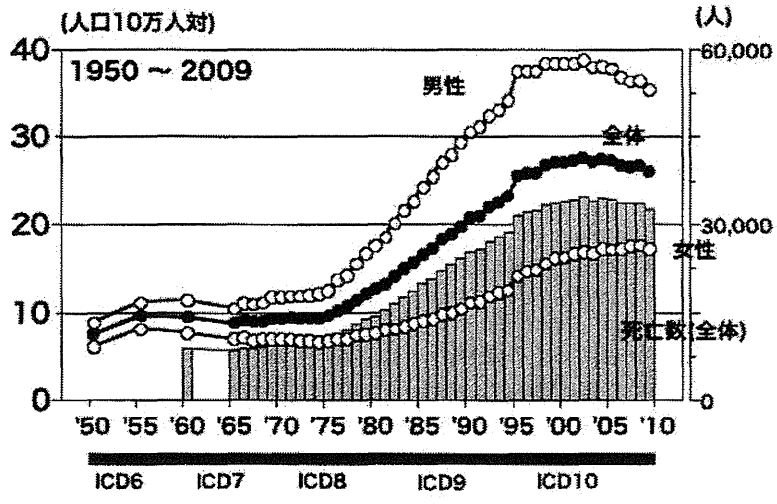

図1 わが国における肝がんによる死亡の推移

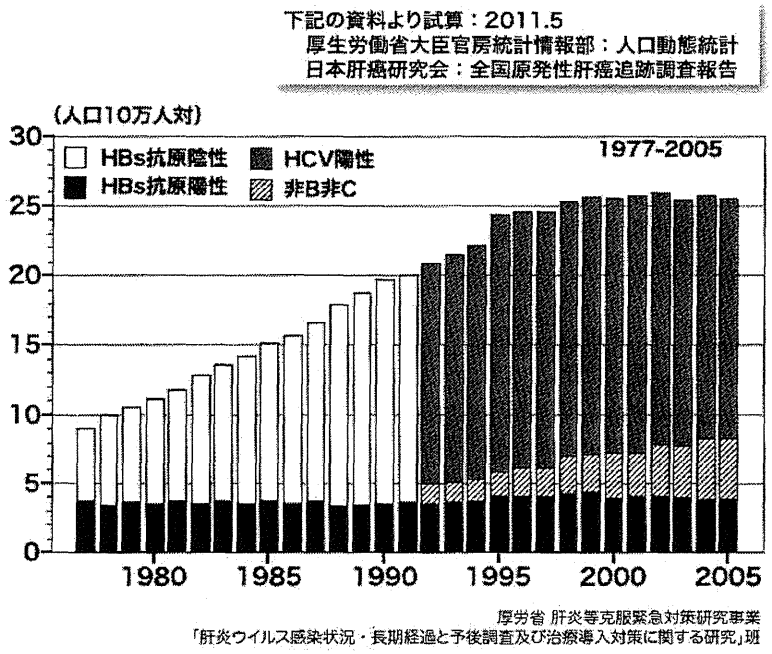

図２　病因別にみた肝がんによる死亡数の経年的推移

たことがわかる．1992年以降，HCV 感染の診断が可能となると図２のようにそのうちの約90％がHCV の持続感染に起因するものであったことが見て取れる．一方，2000年以降，非Ｂ非Ｃ型に由来する肝細胞癌による死亡割合が増加傾向にあることが明らかとなり，その原因や動向について NASH(Non-alcoholic steatohepatitis) との関連性が示唆されている．しかし，わが国の肝細胞がんによる死亡の約７割はHCV の持続感染に起因するものであり，肝癌対策を構築する上でも，HCV 持続感染者（HCV キャリア）の規模の把握や HCV 感染予防対策が重要と考えられる．

4．HCV キャリア率の把握（Prevalence）

4-1．一般集団における HCV キャリア率

HCV 持続感染者（HCV キャリア）の規模の把握を試みるために，2000年以後に得られた大規模集団，すなわち初回供血者集団と節目検診受診者集団から一般集団における年齢階級別にみた HCV キャリア率（prevalence）を算出し示す．

日本赤十字血液センターの献血時のスクリーニング検査は，輸血用血液の安全性確保のために行われるものであり，全国一律の基準，同一の試薬を用いて精度を維持し判定されている．また，2002年から５ヶ年計画で実施に移された節目・節目外検診は，老人保健法の住民検診に組み込まれた形で，公的補助により肝炎ウイルス検査（Ｃ型肝炎ウイルス検査，Ｂ型肝炎ウイルス検査）が行われたものであり，全国統一の検査手順に従って判定されたものである．

いずれも，自身が肝炎ウイルスに感染していることがわかっている場合は，献血や検診の対象者にはならないと考えられることから，この２つの集団から得られた HCV キャリア率は，感染を知らずにいる感染者の割合を示している．

また，初回供血者集団はその約85％が40歳未満の年齢であり，また，節目検診受診対象者は40歳以上の年齢層であることから，40歳未満の年齢層における HCV キャリア率については初回供血者集団の資料を，40歳以上の年齢層における HCV キャリア率は節目検診受診者集団の資料を用いた．

すなわち，2001年から2006年の全供血者のうち「初回供血者」3,748,422人の資料を抽出し，20～39歳（2005年時点の年齢換算）のHCV抗体陽性率に70%を乗じた値をHCVキャリア率とした．また，厚生労働省「肝炎ウイルス検診」の「節目検診受診者」6,204,968人の成績を用いて40～74歳のHCVキャリア率を算出した(図3)[5]．

全国8地域別，5歳刻みの年齢階級別HCVキャリア率を図3に示す．HCVキャリア率は，8地域ともに高年齢層において高い値を示し，20歳代以下の若年層では0.2%以下の極めて低い値を示す傾向が認められている．また，肝発がん年齢と考えられる60歳以上の高年齢集団のHCVキャリア率は，関東以西の地域，すなわち北陸東海(1.9%)，近畿(2.1%)，中国(1.7%)，四国（2.0%）の地域では，北海道（1.1%）や東北地域（0.9%）と比較して高い値を示していることがわかる．

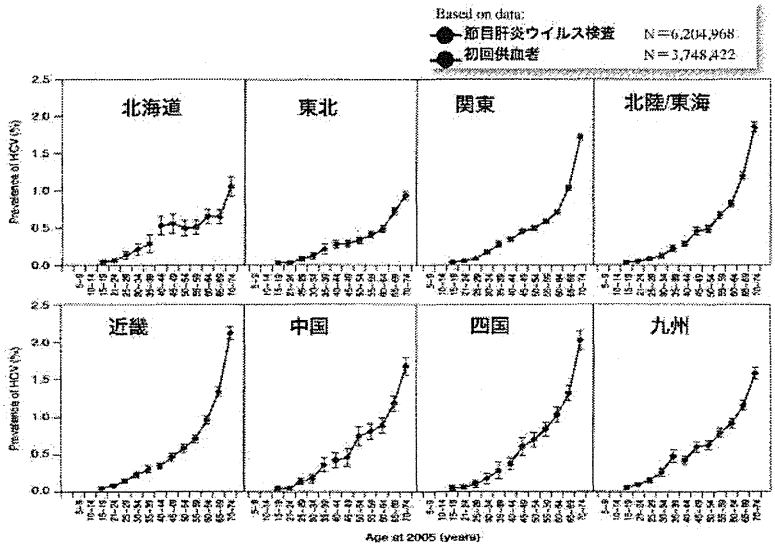

図3　地域別年齢階級別にみたHCVキャリア率

表1　出生年別にみた小学生でのHCV感染率

岩手県予防医学協会

出生年	対象数	HCV抗体陽性数(%)		小計
1978	2,429	4	(0.16)	
1979	4,180	4	(0.10)	HCV抗体陽性数
1980	3,538	6	(0.17)	24/26,996(0.09)
1981	2,512	3	(0.12)	
1982	1,591	1	(0.06)	HCV RNA陽性数
1983	1,088	0	(0.00)	Not Done
1984	5,991	4	(0.07)	
1985	5,667	2	(0.04)	
1986	6,775	2	(0.03)	HCV抗体陽性数
1987	6,505	6	(0.09)	26/32,049(0.08)
1988	6,310	10	(0.16)	
1989	6,436	5	(0.08)	HCV RNA陽性数
1990	6,023	3	(0.06)	7/32,049(0.02)
合計	59,045	50	(0.08)	

4-2. 児童における HCV キャリア率

岩手県予防医学協会がとりまとめた小学校入学時の調査成績を表１に示す．HCV 抗体陽性率は，いずれの出生年においても0.1%あるいは0.1%以下の極めて低い値を示していることがわかる．ただし，節目検診の成績からみた HCV キャリア率を都道府県別にみると，岩手県は全国でも低率の県にあたることから，岩手県の調査成績がそのまま全国の児にあてはまるとはいえない．しかし，20歳以下の年齢層における HCV キャリア率は前項で示したように全国いずれの地域においても低いことから，他の地域における児童の HCV キャリア率も同様に低い値であることが推察される．

なお，HBV 母子感染防止事業は1986年以後に出生したすべての児を対象に全国規模で実施されているが，HCV 抗体陽性率 /HCV キャリア率に関しては1986年を境にした前後の２つの期間に出生した児の集団間の差は認められていない．

5. HCV 感染のリスク（Incidence）

感染の広がりを示す prevalence については，地域別あるいは年齢別の HCV キャリア率あるいは HCV 抗体陽性率からその概要を示した．次に，感染のリスクを示す incidence について，これまでの疫学的調査結果をもとに，水平感染と母子感染の項を分けて示す．

5-1. 水平感染について

水平感染による HCV 新規発生について前向き調査を行った成績を表２に示す．

供血者集団を対象とした調査では，広島県赤十字血液センターにおける1994年６月から2004年４月までの供血者418,269人（総献血本数1,409,465本）を対象として前向きに観察し[6]，新たな感染の有無について解析を行ったところ，期間内に複数回献血をした218,797人（861,842人年）のうち新たな HCV 感染が確認されたのは16例であり，人年法による解析で HCV 新規発生率は10万人年あたり1.86人（95% CI：1.06～3.01人 /10万人年）と示された．この成績は，同様の調査を1992年から３年間の観察期間で行った結果（1.8/10万人年，95% CI:0.4～5.2人 /10万人年）とほぼ同じ値であった[7]．一方，女性の HCV 新規発生率は2.77人 /10万人年（95% CI：1.38～4.95人 /10万人年）と，統計学的な有意差は認められなかったが，男性（1.08人 /10万人年（0.35～2.51人 /10万人年））

表２　HCV 感染の新規発生率　1988～2004

	対象者	新規感染	観察人年	新規感染率　95% CI Incidence Rate
●供血者【広島】				
1992～1995	114,266	3	168,479	1.8/10万人年 0.4～5.2
1994～2004	218,797	16	861,842	1.9/10万人年 1.1～3.0
●供血者【大阪】				
1992～1997	448,020	59 ※抗体陽転	1,095,668	5.4/10万人年 4.1～7.0
●定期健康診断受診者【広島】				
1992～1995	3,079	0	5,786	0/10万人年 0～0.6
●障害者・老人福祉施設入所者【静岡】				
1988～1992	678	0	2,712	0/10万人年 0～1.3
●血液透析施設【広島】				
1999～2003	2,744	16	4,893	3.3/1000人年 1.7～4.9

のHCVキャリア妊婦から生まれた87児のうち，6ヶ月時点で感染が確認されたのは2例（2.3%）であった．2例の母親の出産時のHCV RNA量は1.0×10^7 Eq /ml(bDNA)，2.3×10^7 Eq /ml(bDNA)と高く，genotypeは母子共にそれぞれ2a，1bであり，児は24ヶ月，12ヶ月時点でHCV RNAが検出され感染が確認されている．

一方，HCV母子感染率の頻度に関する他の調査成績から報告された値は，調査地域や対象妊婦の背景因子の相異などにより2～10%と幅が大きい[12,13]．また，感染が確認された児の同胞すべてが感染成立したとはいえず，分娩方法や児の免疫能，出産時の母体のHCV RNA量などが関与していることが示唆されている．諸外国における調査報告からは，母親がHIV-HCV重複感染の場合のHCV母子感染率は高いことが明らかとなっているが，HCV単独感染の場合の母子感染率は低いことから，わが国では公的補助によるHCVの母子感染予防措置は行われていない．

6. 感染症法によるC型急性肝炎の発生状況について（相崎）

わが国では1999年4月に施行された感染症法により，急性のウイルス性肝炎を診断した医師は全例保健所へ届け出ることが必要になった．C型急性肝炎は，5類感染症に分類されており，届け出に基づいた集計解析は国立感染症研究所において行われている．

1999年4月から2009年12月までに届け出されたC型急性肝炎723例について[14]まとめたものを紹介する．1999年以来，急性C型肝炎と診断され報告された年別の患者数は，1999年136症例，2000年119症例，2001年65症例と2001年までは減少傾向が認められたが，それ以降2009年まで年間約30～70症例でほぼ横ばいに転じており，男女別に相異は認められていない．年齢階級別にみた報告数の分布では，30代前半及び50代後半の2つのピークが認められるが，14歳以下の小児または90歳以上の高齢者の報告は極めて少ない．男女別にみると，30代前半及び50代後半にみられる報告数のピークは女性で認められており，背景に感染の要因が潜在していることが推察される．都道府県別にみると，大都市部である大阪（125例），東京都（55例）等の報告数が多い一方，報告数がゼロの都道府県もありC型急性肝炎発生率には地域差が認められるが，報告義務の履行状況が地域ごとに異なる可能性もあり，発生数（率）の評価には注意が必要である．

2006年4月以降に報告されたC型急性肝炎167例について，感染の「原因不明」が全体の62%を占め，HCV感染原因は特定しにくいことが示されている．そのほかの感染原因として報告されたのは，針等刺入（22%），性的接触（11%）であった．また，報告総数は少ないが全体の22%を占める「針等刺入」の内訳では，針刺事故など医療行為に伴う感染以外に，ピアス，刺青，カミソリの共用，覚醒剤など，と報告されている．

医師の届け出義務の周知を広く徹底すると共に，得られる情報を適切に予防対策や啓蒙活動に取り入れることが求められている．

7. おわりに

わが国の社会生活全般における水平感染の発生要因が急速に消滅し，新規感染が低下した結果，若い世代におけるHCV抗体陽性率/HCVキャリア率は低い値を示すに至っている．わが国では「肝炎対策基本法」(2009年12月）を基盤として，すでに感染しているキャリアへの対策，具体的には，肝炎ウイルス検査の推進，肝疾患診療ネットワークの構築，新規治療法の開発等が積極的に進められている．

さまざまな機会で肝炎ウイルス検査が行われることにより感染を知る機会が増えたことで，感染を知らないままでいるHCVキャリア数は2005年時点，約81万人と推計し[15]，2000年時の推計値と比較して減少したと示した．一方で，感染していることを知ったがさまざまな理由から医療機関への受診をしないままでいるHCVキャリアや医療機関への継続受診に至っていないHCVキャリアが増加していることが問題点として指摘されている[16]．

世界的にみても肝炎対策先進国であるわが国は，これまでの感染防止策を継続しつつ，肝炎肝がん対策の新たな局面を迎えていると考えら

れる．

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医学の歩み

和文タイトル：HCV 感染と代謝異常（脂質・エネルギー）

英文タイトル：HCV and metabolism disorders

著者名：相崎英樹

欧文著者名：HIDEKI AIZAKI

所属名：国立感染症研究所ウイルス第二部

１．はじめに

C 型肝炎ウイルス(HCV)感染が慢性肝炎、肝硬変、肝細胞癌の原因となるだけでなく、インスリン抵抗性や脂肪肝などの糖質や脂質の代謝異常も引き起こしていることが明らかになってきている。抗ウイルス療法によりウイルスを駆除すると脂肪化が改善すること、遺伝子型３型のウイルスで脂肪化が顕著なことなどから、これらの代謝異常はウイルス感染による炎症よりも、ウイルスそのものの宿主細胞への直接作用が深く関わっているものと考えられている。本稿では、代謝物質の網羅的解析結果（メタボロミクス）を踏まえて、特に HCV 感染が宿主代謝に与える影響について述べたい。

２．HCV 感染が宿主脂質代謝に与える影響

これまで細胞の働きを理解しようとするとき、DNA 配列の網羅的解析（ゲノ

ミクス）や蛋白質の網羅的解析（プロテオミクス）が行われてきた。しかしながら、実際の細胞内ではホメオスタシスによりゲノムレベルでの変動が表現型に一致しないことも多い。その点で、代謝産物は表現型に最も近いため、表現型での変化が観察しやすいという特徴があり、メタボロミクスが注目されている。Roe らは、J6/JFH ウイルスを Huh-7.5 細胞に感染させ３日後にメタボローム解析を行ったところ、アミノ酸合成、RNA 核酸合成、ペントースリン酸経路の亢進を認めた(1)。脂質代謝に関しては、HCV 感染に伴い、グリセロリン脂質、スフィンゴ脂質、コレステロール、脂肪酸などが増加していた。グリセロリン脂質、スフィンゴ脂質、コレステロールはいずれも生体膜の主要脂質成分として知られており、生活環の多くのステップで細胞の小胞体，ゴルジ体，細胞膜といった生体膜脂質を利用している HCV にとって好都合な状況となっていると考えられる。特に、スフィンゴ脂質、コレステロールは脂質ラフトの構成成分であることから、HCV の感染、複製、粒子形成にも役立っているものと考えられる(2, 3)。　HCV による肝細胞の脂肪化の機序は HCV コア遺伝子トランスジェニックマウスを用いた研究などで明らかになっている(4)。HCV コア蛋白は脂質合成系の転写因子 sterol regulatory element binding protein-1 の増加を介して、脂肪酸合成酵素の活性を上げて、脂肪酸合成を亢進させている。一方、ミトコンドリアに局在化したコア蛋白は脂肪酸のベータ酸化を抑制し、脂肪酸の消費を低下させている。また、microsomal triglyceride transfer protein を低下させるため、超低比重リポ蛋白分泌を抑制し、細胞外への脂肪酸の放出を抑制している。さらに、HCV が誘発するインスリン抵抗性による高インスリン血