Original Article

An Analysis of Epidemiological Characteristics and the Clinical Features of 394 Cases of Sporadic Acute Hepatitis E in Southwest China from 2008 to 2010

Hui Li¹, Xiao-Dong Yang¹, Yong-Rui Yang¹, Si-Yuan Gao¹, De-Ying Tian² and Quan Yuan³

Background and Aims Recently, epidemiology studies of hepatitis E in different areas are attracted more attention. Extensive studies of prevalent status and clinical manifestations could help us to broaden our knowledge, so as to excellently prevent and treat hepatitis E. The study analyzed the epidemiological characteristics and clinical features of 394 cases of sporadic acute hepatitis E (AHE) in Southwest of China from 2008 to 2010.

Methods The clinical data of 394 cases with sporadic AHE in Southwest of China from 2008 to 2010 were reviewed.

Results In the 394 cases with sporadic AHE, the ratio of male/female was 1.432 : 1, and the mean age was (31.53 ± 18.12) years. Totally, 94 (23.86%) patients aged under 18, 271 (68.78%) patients aged between 18 and 60, and 29 (7.36%) patients aged above 60. The incidence rate was significantly increased in summer ($P = 0.000$), especially in May (14.72%) and July (13.71%). In addition, the characteristics of occupation and ethnic group distribution were migrant laborers (106/394, 26.90%) and Han people (365/394, 92.64%). The length of stay, incidence of jaundice, the peak value of total bilirubin and alanine aminotransferase in male patients were all higher than those in female patients significantly ($P < 0.05$). The prolonged length of stay, decreased levels of ALT/ALB/CHE, increased levels of TBil, and increased incidence of jaundice and fatigue were associated with older age significantly ($P < 0.05$). The differences in peak values of total bilirubin (TBil), total bile acid (TBA), glutamyltransferase (GGT), cholinesterase (CHE) between AHE group and the groups of AHE accompanied respectively by chronic hepatitis B (CHB), acute alcoholic fatty liver (AFL), nonalcoholic fatty liver disease (NAFLD) were significant ($P < 0.05$). In addition, no significant difference was found in length of stay and biochemical indexes among anti-HEV-IgG positive group, anti-HEV-IgM positive group and anti-HEV-IgM/IgG both positive group ($P > 0.05$).

Conclusions Four epidemiological characteristics, including aged between 18 and 60, male, summer and migrant laborers, are found to be associated with acute hepatitis E. The prognosis of AHE in the majority of patients was favorable, but aged above 60 years and coexistence with CHB, AFL and NAFLD could be considered as the factors inducing the infaust prognosis.

Key words: Acute hepatitis E; Epidemiology; Clinical feature; Sporadic infection; Hepatitis E virus

¹Department of Liver Diseases, No. 3rd People's Hospital of Kunming, Kunming (650041), Yunnan Province, China. ²Department of Infectious Diseases, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan (430030), Hubei Province, China.

³National Institute of Diagnostics and Vaccine Development in Infectious Diseases, School of Life Science, Xiamen University, Xiamen (361005), Fujian Province, China

Correspondence: Department of Liver Diseases, No. 3rd People's Hospital of Kunming, Kunming (650041), Yunnan Province, China. Email: lihuidoc@126.com. Tel: +8615911645100

In 1980, hepatitis E was the last of the 5 recognized human hepatitis discovered; in 1990, the genome of hepatitis E virus (HEV) was cloned and serological detection was developed.¹ It proved to be an important cause of acute clinical hepatitis among adults throughout Asia, the Middle East and Africa.² Contributing to 10%-20% of acute hepatitis in sporadic cases, acute hepatitis E (AHE) is a fecal-oral transmitted disease caused by hepatitis E virus. Its clinical features are similar to hepatitis A, which is characterized by young adult-dominant, acute, self-limited and lower than 0.1% mortality.³ Even though, the mortality rate is over 20% in patients with severe complications or pregnant patients.^{2,4} Recently, epidemiology studies of hepatitis E in different areas caused more attention.^{5,6} Extensive studies of prevalent status and clinical manifestations could help us broaden our knowledge, so as to prevent and treat hepatitis E.

Totally, 394 sporadic AHE patients from the 3rd People's Hospital of Kunming (one of the largest infectious disease hospital in the Southwest of China), Southwest China, from 2008 to 2010 were enrolled. The epidemiological characteristics and clinical features of these cases were described.

PATIENTS AND METHODS

Patients

In a total, 394 patients were enrolled for this study based on the following inclusion criteria: hospitalization from January, 2008 to December, 2010 for clinical features suggestive of acute hepatitis, and infection by HEV as determined serologically. All patients originated from the Yunnan Province in Southwest China.

The diagnostic standards were obtained from the guideline of prevention and treatment for viral hepatitis of the Chinese Society of Infectious Diseases and Parasitology, and the Chinese Society of Hepatology of the Chinese Medical Association, which was established in Xian in September of 2000⁶: clinical features of acute hepatitis, serum anti-HEV IgM positive and (or) HEV nucleic acid positive.

Pathogenic detection and biochemical detection

Diagnostic kits targeting anti-hepatitis E virus (HEV) IgM/IgG were commercially supplied by the MP Biomedicals Company (Shanghai, China). HBV S antigen (HBsAg), anti-HBs, HBV e antigen (HBeAg), anti-HBe and anti-HBc were supplied by the Abbott Health Care Company (Shanghai, China).

Olympus AU400 automatic biochemical analyzer was applied to analyze serum biochemistry parameters, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBil), albumin (ALB), γ -glutamyltransferase (GGT), cholinesterase (CHE), total bile acid (TBA), and prothrombin activity (PTA).

Statistical analysis

All parameters were analyzed by SPSS 17.0. Quantitative variables were expressed as means $\pm$ SD and compared by the Student *t*-test between two groups. One-Way ANOVA was used to analyze the mean among groups. Grouped data shown in percentage (%) were analyzed by Chi-square test. *P* < 0.05 was recognized as statistical significance.

RESULTS

Epidemiological characteristics

Gender and age

Among the 394 sporadic cases, 232 were male, 162 were female, and the ratio of male to female was 1.432:1. Mean age was 31.53 ± 18.12 (2-84) years old, 94 (23.86%) were children under 18 years old, 271 (68.78%) were adult aged 18-60, 29 (7.36%) were elderly patients above 60 years old (Figure 1).

Onset seasons

Among the 394 patients, 107 (27.16%) fell in ill in spring (February to April), 140 (35.53%) in summer (May to July), 86 (21.83%) in autumn (August to October), and 61 (15.48%) in winter (November to January). Significant difference ($\chi^2 = 34.081$, *P* = 0.000) could be recognized that patients were more predisposed to hepatitis E in summer compared to other seasons, especially in May (58, 14.72%) and July (54, 13.71%) (Figure 2).

Figure 1. AHE patients of different gender and age.

Figure 2. AHE patients with different onset points.

Occupations

Grouped by occupations, among the 394 AHE patients, 106 were migrant laborers (26.90%), who was the highest composition, followed by agriculture workers (21.57%) and school students (18.53%) (Table 1).

Ethnic groups

Among the 394 AHE patients, 92.64% (365/394) were Han people, 7.36% (29/394) were minority nations, including 9 Yi people, 5 Hui people, 5 Bai people, 3 Dai people, 2 Miao people, 2 Naxi people, 1 Man people, 1 Buyi people and 1 Hani people (Table 2).

Clinical Features

Clinical symptoms

Classified by gender, age and underlying diseases among the 394 patients, fatigue, anorexia and

Table 1. Occupations of 394 sporadic AHE patients

Occupations	Number	Proportion (%)
Migrant laborers	106	26.90
Agriculture workers	85	21.57
School students	73	18.53
Manual labors	39	9.90
Business employees	34	8.63
Unemployed and semi-employed	33	8.38
Retired	8	2.03
Private-owned enterprise owners	6	1.52
Skilled labors	6	1.52
Civil servants	4	1.02
Total	394	100.00

jaundice were commonly considered as clinical features. Jaundice was extremely more often in male patients than female ($\chi^2 = 47.039$, $P = 0.000$).

Table 2. Ethic groups of 394 sporadic AHE patients

Ethic Groups	Numbers of Patients	Proportion (%)
Yi people	9	7.36
Hui people	5	
Bai people	5	
Dai people	3	
Miao people	2	
Naxi people	2	
Man people	1	
Buyi people	1	
Hani people	1	
Han people	365	92.64
Total	394	100.00

Fatigue and jaundice were common in patients elder than 60 years old ($\chi^2_{\text{fatigue}} = 77.911$, $P = 0.000$; $\chi^2_{\text{jaundice}} = 15.045$, $P = 0.001$). Among patients with different underlying diseases, the difference in their clinical features was not significant (Table 3).

Biochemistry tests and in-hospital days of different gender

Among the 394 AHE patients, the period of hospital stay, TBil and ALT of male patients were significantly longer and higher than female patients ($P < 0.05$), however, other biochemical detection was proved with no statistical significance ($P > 0.05$) (Table 4).

Biochemistry detection and hospital stay among different age groups

Grouped by age, the main presentations of patients under 18 years old were elevated ALT level (ALT > 1 200 U/L), slight to medium elevation of total serum bilirubin (TBil < 100 $\mu\text{mol/L}$) and short hospital stay (25 days on average). In contrast, markedly ascending of total serum bilirubin (TBil > 171 $\mu\text{mol/L}$), lower ALT level (ALT < 1 000 U/L), poor synthesize function such as low ALB and CHE level, long

Table 3. Clinical symptoms in 394 sporadic AHE patients

Groups	n	Fatigue	Anorexia	Jaundice	Abdominal distention	Nausea	Vomit
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Grouped by gender							
Male	232	183 (78.9)	158 (68.1)	222 (95.7)*	74 (31.9)	48 (20.7)	14 (6.0)
Female	162	123 (75.9)	112 (69.1)	115 (71.0)	47 (29.0)	27 (16.7)	9 (5.6)
Grouped by age							
< 18 years old	94	42 (44.7)	67 (71.3)	69 (73.4)	24 (25.5)	17 (18.1)	8 (8.5)
18 - 60 years old	271	237 (87.5)	182 (67.2)	241 (88.9)	87 (32.1)	53 (19.6)	13 (4.8)
> 60 years old	29	27 (93.1)*	21 (72.4)	27 (93.1)*	10 (34.5)	5 (17.2)	2 (6.9)
Grouped by diseases							
AHE	274	213 (77.7)	194 (70.8)	243 (88.7)	75 (27.4)	49 (17.9)	12 (4.4)
Super-infection							
with chronic hepatitis B	87	68 (78.2)	60 (69.0)	77 (88.5)	25 (28.7)	21 (24.1)	6 (6.9)
With AFL	10	8 (80.0)	7 (70.0)	9 (90.0)	3 (30.0)	2 (20.0)	1 (10.0)
With NAFLD	8	6 (75.0)	5 (62.5)	7 (87.5)	2 (25.0)	1 (12.5)	1 (12.5)

Notes: AFL, alcoholic fatty liver; NAFLD, non-alcoholic fatty liver disease. * $P < 0.01$.

Table 4. Biochemical detection and hospital stay between different genders

Groups	n	Hospital stay (d)	TBil peak value ($\mu\text{mol/L}$)	ALT peak value (U/L)	AST peak value (U/L)
Male	232	34.6 $\pm$ 33.4.6 ^a	216.7 $\pm$ 198.1 ^b	1181.2 $\pm$ 1152.1 ^a	579.1 $\pm$ 715.7
Female	162	27.2 $\pm$ 19.3	133.0 $\pm$ 104.3	894.7 $\pm$ 1003.3	526.8 $\pm$ 761.3

Groups	n	GGT peak value (U/L)	ALB valley value (g/L)	CHE valley value (U/L)	PTA value value (%)
Male	232	239.9 $\pm$ 233.2	38.2 $\pm$ 5.9	5314.4 $\pm$ 2151.3	86.1 $\pm$ 38.4
Female	162	224.4 $\pm$ 202.7	40.8 $\pm$ 31.6	5361.9 $\pm$ 1740.9	91.0 $\pm$ 34.5

Notes: ^a $P < 0.05$; ^b $P < 0.01$

Table 5. Biochemical detection and hospital stay among different aged groups

Groups (years old)	n	Hospital stay	TBil peak value	ALT peak value	AST peak value
		(d)	($\mu\text{mol/L}$)	(U/L)	(U/L)
< 18	94	23.7 $\pm$ 11.6	86.5 $\pm$ 53.9	1265.1 $\pm$ 853.2	508.4 $\pm$ 605.6
18 - 60	271	32.6 $\pm$ 15.9 ^a	196.2 $\pm$ 109.6 ^a	1001.5 $\pm$ 1179.3	567.8 $\pm$ 761.96
> 60	29	49.3 $\pm$ 43.3 ^{bd}	254.0 $\pm$ 131.6 ^{bc}	845.9 $\pm$ 943.2 ^{bc}	536.2 $\pm$ 678.66

Groups (years old)	n	GGT peak value	ALB valley value	CHE valley value	PTA valley value
		(U/L)	(g/L)	(U/L)	(%)
< 18	94	212.7 $\pm$ 162.6	39.6 $\pm$ 3.7	5776.2 $\pm$ 1923.7	93.3 $\pm$ 35.6
18-60	271	240.3 $\pm$ 241.1	39.6 $\pm$ 24.8	5305.6 $\pm$ 2005.3	87.2 $\pm$ 36.8
> 60	29	230.9 $\pm$ 189.3	33.2 $\pm$ 8.6 ^{bd}	4361.5 $\pm$ 1722.1 ^{bd}	82.5 $\pm$ 27.9

Notes: Compared with <18 years old group, ^a $P < 0.05$, ^b $P < 0.01$; Compared with 18 - 60 years old group, ^c $P < 0.05$, ^d $P < 0.01$.

Table 6. Biochemical detection and hospital stay among patients with different underlying diseases

Groups with different underlying diseases	n	Hospital stay	TBil peak value	ALT peak value	TBA peak value
			($\mu\text{mol/L}$)	(U/L)	(U/L)
AHE only	289	33.5 $\pm$ 28.7	174.2 $\pm$ 89.2	1066.8 $\pm$ 1106.7	206.5 $\pm$ 307.8
Super infection with CHB	87	36.2 $\pm$ 13.0	278.7 $\pm$ 149.2 ^a	1171.9 $\pm$ 1033.9	126.7 $\pm$ 118.1
With AFL	10	35.8 $\pm$ 13.4	262.8 $\pm$ 111.8 ^a	911.9 $\pm$ 1105.9	398.7 $\pm$ 973.3 ^a
With NAFLD	8	36.5 $\pm$ 6.9	248.4 $\pm$ 86.2 ^a	1007.1 $\pm$ 425.7	115.1 $\pm$ 147.6 ^a

Groups with different underlying diseases	n	GGT peak value	ALB valley value	CHE valley value	PTA Valley Value
		(U/L)	(g/L)	(U/L)	(%)
AHE only	289	248.3 $\pm$ 227.9	37.6 $\pm$ 22.9	5448.6 $\pm$ 1978.2	90.4 $\pm$ 34.5
Super infection with CHB	87	168.2 $\pm$ 173.2 ^a	37.4 $\pm$ 5.8	4413.8 $\pm$ 1972.1 ^a	83.2 $\pm$ 35.4
With AFL	10	356.9 $\pm$ 278.7 ^a	36.1 $\pm$ 6.8	4265.5 $\pm$ 2257.9 ^a	82.1 $\pm$ 38.0
With NAFLD	8	335.9 $\pm$ 295.4 ^a	37.3 $\pm$ 3.0	4689.7 $\pm$ 1768.2 ^a	85.9 $\pm$ 26.6

Notes: ^a $P < 0.05$, compared with AHE only group

Table 7. Biochemical detection and hospital stay among different anti-HEV antibody types

Groups with different antibody types	n	Hospital stay	TBil peak value	ALT peak value	TBA peak value
		(d)	($\mu\text{mol/L}$)	(U/L)	(U/L)
Anti-HEV-IgM (+) only	159	36.8 $\pm$ 10.6	187.8 $\pm$ 80.6	1107.0 $\pm$ 1144.5	212.9 $\pm$ 280.6
Anti-HEV-IgG (+) only	58	35.2 $\pm$ 53.7	168.3 $\pm$ 90.3	993.1 $\pm$ 736.1	193.2 $\pm$ 436.5
Anti-HEV-IgM (+) and anti-HEV-IgG (+)	72	35.0 $\pm$ 28.3	189.6 $\pm$ 118.2	1110.9 $\pm$ 1117.4	205.3 $\pm$ 208.8

Groups with different antibody types	n	GGT peak value	ALB valley value	CHE valley value	PTA valley value
		(U/L)	(g/L)	(U/L)	(%)
Anti-HEV-IgM (+) only	159	251.9 $\pm$ 238.6	38.3 $\pm$ 29.0	5433.7 $\pm$ 1910.5	85.3 $\pm$ 36.1
Anti-HEV-IgG (+) only	58	234.6 $\pm$ 219.6	39.0 $\pm$ 7.8	5629.9 $\pm$ 2279.4	90.2 $\pm$ 39.4
Anti-HEV-IgM (+) and anti-HEV-IgG (+)	72	241.8 $\pm$ 208.5	39.1 $\pm$ 6.5	5459.0 $\pm$ 1846.4	87.7 $\pm$ 35.0

hospital stay (50 days on average) were recognized as the main clinical features of elder patients aged over 60 years. Biochemical detection of patients aged 18-60 years were in the medium among the 3 groups. In

summary, prolonged hospital stay, descending ALT, ALB, CHE level, rising TBil level were obviously observed in elder patients than young adults, which was statistically significant ($P < 0.05$). Nevertheless,

there were significant differences in AST, GGT, PTA among different aged groups ($P > 0.05$) (Table 5).

Biochemical detection and hospital stay among patients with different underlying diseases

Among the 394 patients, 289 were AHE (excluding HAV, HBV, HCV, CMV, EBV infection, AFL, NAFLD, drug-induced liver injury, autoimmune liver disease, congenital metabolic liver disease); 87 were with chronic hepatitis B (CHB); 10 were with alcoholic fatty liver (AFL); 8 were with non-alcoholic fatty liver disease (NAFLD). Compared with patients who were super-infected with CHB, with AFL and NAFLD, patients with only AHE, showed significant differences in TBil, TBA, GGT and CHE ($P < 0.05$). There were no differences in ALT, ALB, PTA and in-hospital days ($P > 0.05$) (Table 6).

Biochemical detection and hospital stay among different Anti-HEV antibody types

Patients manifested as acute hepatitis, who had only AHE, were grouped by different anti-HEV antibody, which implied that there were no significant differences in TBil, ALT, hospital stay, TBA, GGT, ALB, CHE and PTA ($P > 0.05$) among different antibody groups (Table 7).

DISCUSSION

Hepatitis E has been prevalent in developing countries such as India, Burma, Somalia and Mexico since 1950. Major outbreaks even occurred in Xinjiang, Jilin, Liaoning Provinces and Inner Mongolia, China, which led to high mortality rate.⁷ Yet, elevated infection rate has been reported in developed countries such as USA and Japan recently.⁸ Moreover, new researches even reported that hepatitis E might progress to chronic infection in immune compromised patients, elder patients and patients who underwent organ transplantation^{9,10} In short, as a public health problem in China, hepatitis E now has been considered to be one of the most indispensable health hazards.

According to our study, firstly, young adults aged 31.53 ± 18.12 years constitute the major group of patients. Different sporadic HEV infection mainly affected middle-aged and elder people,¹¹ children

contribute to 23.86% of all AHE patients in our study. The possible reason might be poor sanitation and living conditions in rural areas in Southwest China. Secondly, the incidence ratio of male to female was 1.432:1, different from previously reported data,¹²⁻¹⁴ which was probably attributed to livestock kept predominantly by women in some areas of Southwest China and AHE is a zoonotic disease. Thirdly, as a waterborne disease, although AHE is sporadic all year round in Southwest China, with the highest incidence in May and July, which could be the consequence of rich rainfall in summer. In addition, poor food hygiene and poor living conditions led migrant rural workers to the highest constituent ratio of patients; low incomes, medical insurance deficiency and inadequate understanding towards disease led agriculture workers to second large component of AHE patients and frequently eating outside may be the reason why student were huge group following the two above. Taking ethnic groups into consideration, Han people constitute the largest patient ratio, which was the consequence of largest population of Han people in Southwest China.

Among the 394 patients, although 85.5% patients underwent acute icteric hepatitis, indicating severe necrosis, intrahepatic cholestasis of hepatocytes, resulting in long course of disease, fulminant inflammation, brisk jaundice and complicated clinical features, most patients progressed with good prognosis. Also it could be concluded that male had severer inflammation, more jaundice and longer hospital stay than female; children had mild manifestations, which could be described as elevated ALT, slight to medium elevation of total bilirubin and short hospital stay. Elder patients had ascending jaundice; severer symptoms and prolonged hospital stay. Elder patients over 60 years had decreasing ALT level and raising jaundice level, which contributed to longer hospital stay (twice of children). Decreased hepatocyte number, low metabolic enzymes activity, dysfunction of excretion, synthesizes and detoxication, disability of cell compensation might be possible explanation to the above phenomenon.¹⁵ In addition, elder patients experienced severe inflammation and necrosis, with low regeneration and repair ability,

which brought about harsh disease and prolonged disease course. Patients suffered from worse disease, often with rising TBil, TBA and GGT level, decreasing CHE level and even appeared as subacute liver failure especially when they were super infected with CHB, or with AFL and NAFLD. In conclusion, elder than 60 years, super infected with CHB, with AFL and NAFLD might directly play an important role in AHE prognosis. Age and super infection could both be considered as the independent prognosis predictors. Therefore, elder patients with hepatitis E and super infections should be under careful surveillance, therapeutic strategies to hepatitis such as artificial liver support system and liver transplantation should be strictly taken into consideration.

So far, there are no standardized diagnosis detection of AHE worldwide. In China, serum detection of AHE is commonly applied, including ELISA assay of anti-HEV IgG and anti-HEV IgM, with the latter considered to be a sign of acute infection. In our study, there were no statistical differences among 289 pure AHE patients (HAV, HBV, HCV, CMV, EBV infection, AFL, NAFLD, drug-induced liver injury, autoimmune liver disease, congenital metabolic liver disease excluded), 159 anti-HEV IgM positive patients, 58 anti-HEV IgG positive patients and 72 anti-HEV IgM positive/anti-HEV IgG positive patients in biochemical detection and hospital stay. Hence, it could be concluded that only serum anti-HEV-IgG positive could be the marker of AHE if other underlying hepatitis and other virus infections are excluded in acute hepatitis patients. However, universally acceptable detection of standardized diagnosis is still urgently needed.

CONFLICTS OF INTEREST

None.

FINANCIAL SUPPORT

The project described was supported by the Major Program of National High Technology Research and Development of China (No.2006AA02A209).

AUTHOR'S CONTRIBUTIONS

Dr. Hui Li designed and participated in the coordination of the study and helped to draft the manuscript. Dr. Ya-Ling Wang and Quan Yuan carried out pathogenic detection and biochemical detection. Dr. Yong-Rui Yang and Si-Yuan Gao performed the statistical analysis. Xiao-Dong Yang and Xiao-Lin Li participated in samples collecting. Prof. De-Ying Tian participated in the design of the study. All authors approved the final manuscript.

REFERENCES

1. Reyes GR, Purdy MA, Kim JP, Luk KC, Young LM, Fry KE, et al. Isolation of a cDNA from the virus responsible for enterically transmitted non-A, non-B hepatitis. *Science* 1990;247:1335-1339.
2. Purcell RH, Emerson SU. Hepatitis E: an emerging awareness of an old disease. *J Hepatol* 2008;48:494-503.
3. Geng YS, Wang YC. Advances in immunology of hepatitis E virus infection. *World Chin J Digestol* 2010;18(9):897-901.
4. Boutrouille A, Bakkali-Kassimi L, Crucière C, Pavio N. Prevalence of anti-hepatitis E virus antibodies in French blood donors. *J Clin Microbiol* 2007;45(6):2009-2010.
5. Dong C, Dai X, Shao JS, Hu K, Meng JH. Identification of genetic diversity of hepatitis E virus (HEV) and determination of the seroprevalence of HEV in eastern China. *Arch Virol* 2007;152(4):739-746.
6. Protocol of prevention and treatment in viral hepatitis. *Chin J Hepatol (Chin)* 2000;8:324-333.
7. Buti M, Domínguez A, Plans P, Jardi R, Schaper M, Espuñes J, et al. Community-based seroepidemiological survey of hepatitis E virus infection in Catalonia, Spain. *Clin Vaccine Immunol* 2006;13(12):1328-1332.
8. Fukuda S, Ishikawa M, Ochiai N, Suzuki Y, Sunaga J, Shinohara N, et al. Unchanged high prevalence of antibodies to hepatitis E virus (HEV) and HEV RNA among blood donors with an elevated alanine aminotransferase level in Japan during 1991-2006. *Arch Virol* 2007;152(9):1623-1635.
9. Aggarwal R. Hepatitis E: does it cause chronic hepatitis? *Hepatology* 2008;48(4):1328-1330.
10. Kamar N, Selves J, Mansuy JM, Ouezzani L, Péron JM, Guitard J, et al. Hepatitis E virus and chronic hepatitis in organ-transplant recipient. *N Engl J Med* 2008;358:811-817.
11. Sainokami S, Abe K, Kumagai I, Miyasaka A, Endo R, Takikawa Y. Epidemiological and clinical study of sporadic acute hepatitis E caused by indigenous strains of hepatitis E virus in Japan compared with acute hepatitis A. *J Gastroenterol* 2004;39:640-648.
12. Takeda H, Matsubayashi K, Sakata H, Sato S, Kato T, Hino S,

- et al. A nationwide survey for prevalence of hepatitis E virus antibody in qualified blood donors in Japan. *Vox Sang* 2010; 99:307-313.
13. Labrique AB, Zaman K, Hossain Z, Saha P, Yunus M, Hossain A, et al. Population seroprevalence of hepatitis E virus antibodies in rural Bangladesh. *Am J Trop Med Hyg* 2009; 81:875-881.
14. Cheng PN, Wang RH, Wu IC, Wu JC, Tseng KC, Young KC, et al. Seroprevalence of hepatitis E virus infection among institutionalized psychiatric patients in Taiwan. *J Clin Virol* 2007;38:44-48.
15. Lu WM. The characteristics in elderly hepatitis E patients. *Chin J Gastroenterol Hepatol* 2007;16:65-68.