

Hepatitis Delta Virus and GBV-C Infection in Two Neighboring Hepatitis B Virus and Hepatitis C Virus – Endemic Villages in Taiwan

Chang-Jung Chang¹, MD; Jui-Chin Chiang^{1,2,6}, MD;
Sheng-Nan Lu^{2,3,4,5}, MD, MPH, PhD; Jing-Houng Wang^{3,4}, MD

Background: Previous reports in Taiwan have shown that the hepatitis B virus (HBV)- and hepatitis C virus (HCV)-endemic areas are also endemic for hepatitis D virus (HDV), GBV-C and TT virus. This study aimed to elucidate the epidemiology of HDV and GBV-C infection in two neighboring HBV- and HCV-endemic villages, to deduce the epidemiological characteristics of multiple viral infections in communities.

Methods: A total of 74 adult residents of Wukwai (W) village and 95 adults residents of Haipu (H) village were studied. Laboratory tests for all subjects included alanine transaminase (ALT), hepatitis B surface antigen (HBsAg), anti-HCV, HCV RNA, genotype of HCV, GBV-C RNA, and anti-GBV-C E2. Anti-HDV was checked only in HBsAg-positive subjects.

Results: Subjects from W village were older than those from H village (61.7 ± 11.8 vs 56.6 ± 16.4 years, $p = 0.02$). The prevalence of ALT elevation (37.8% vs 15.8%, $p = 0.006$), anti-HCV (67.6% vs 34.7%, $p < 0.0001$), and GBV-C infection (39.2% vs 24.2%, $p = 0.054$), and the distribution of HCV genotype 1b (37.8% vs 70.4%, $p = 0.01$) were different in W and H villages, respectively. Among anti-HCV-positive subjects, HCV RNA-positive rates were 75.9% (63/83), and were higher for men (88.2%) than women (67.3%). Only one HBsAg-positive subject was positive for anti-HDV, and one anti-HCV-negative subject was positive for HCV RNA. In multivariate analyses, GBV-C infection correlated with HCV infection or HCV endemicity, and HCV RNA was the only determining factor in ALT elevation.

Conclusion: In HBV and HCV-endemic areas, GBV-C was more prevalent in areas with a higher prevalence of anti-HCV. Positive HCV-RNA, but not GBV-C infection, was associated with ALT elevation.

(*Chang Gung Med J* 2010;33:137-44)

Key words: hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus (HDV), GBV-C, genotype of HCV

From the ¹Departments of Family Medicine; ²Occupational Medicine; ³Division of Hepatogastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan; ⁴School of Medicine; ⁵Institute of Clinical Medical Science, College of Medicine, Chang Gung University Taoyuan, Taiwan; ⁶Graduate Institute of Environmental and Occupational Health, Medical College, National Cheng Kung University, Tainan, Taiwan.

Received: Feb. 18, 2009; Accepted: May 18, 2009

Correspondence to: Dr. Jing-Houng Wang, Division of Hepatogastroenterology, Department of Internal Medicine, Chang Gung Memorial Hospital – Kaohsiung Medical Center, 123, Dapi Rd., Niasong Township, Kaohsiung County 833, Taiwan (R.O.C.)
Tel.: 886-7-7317123 ext. 8301; Fax: 886-7-7322402; E-mail: jinghoung2001@yahoo.com.tw

Interaction among hepatotropic viruses, hepatitis B (HBV), C (HCV), D (HDV) GBV-C/ hepatitis G virus (HGV) and TT viruses has been well studied in patients with multiple viral infections.⁽¹⁾ Interaction among these viruses in areas endemic for multiple viruses is an important issue. GBV-C/HGV has proven to be a harmless hepatotropic virus and has the same transmission routes as HCV and other blood-borne viruses.⁽²⁾ In Taiwan, where HBV is endemic nationwide, several HCV-endemic areas have been reported.⁽³⁻⁷⁾ Iatrogenic infection via medical injection is thought to be the major cause of HCV transmission in these endemic areas because of poor sterilization technique and illegal medical service.⁽⁸⁻¹²⁾ According to prevalence studies, HCV was still spreading in some endemic areas in the 1990s.^(8,9) In other words, parenteral routes of transmission were still active in these areas at that time. Previous reports in Taiwan showed that HBV- and HCV-endemic areas are also endemic for HDV,⁽⁴⁾ GBV-C and the TT virus.^(13,14) We conducted this study of HDV and GBV-C infection in two neighboring HBV- and HCV-endemic villages to deduce the epidemiological characteristics of multiple viral infections in communities.

METHODS

Two neighboring HBV- and HCV-endemic areas, Wukai (W) village and Haipu (H) village in central Taiwan are reported. The prevalences of HBsAg and anti-HCV among residents aged ≥ 40 years in W village were 14.0% and 72.1%, and in H village, 17.0% and 38.3%, respectively.⁽⁶⁾ The study protocol was reviewed, including ethical considerations based on the Helsinki Declaration and was supported by the National Science Council, Republic of China and the Chang Gung Medical Research Program. All study subjects were tested voluntarily with consent.

Stored sera from a previous study⁽⁶⁾ were used for this study. All 95 serum samples from H village were tested. Based on a systematic non-stratified random sampling technique, 79 out of 159 subjects from W village were selected and 74 with enough sera for further testing were recruited. Besides the results of anti-HCV, hepatitis B surface antigen (HBsAg) and alanine transaminase (ALT) levels available from the previous study, HCV RNA, genotype of HCV, GBV-

C RNA and anti-E2 antibody of GBV-C (anti-GBV-C E2) were detected. Subjects who were positive for either GBV-C RNA or anti GBV-C E2 were defined as having GBV-C infection. All HBsAg-positive subjects were tested for anti-HDV.

ALT was measured by autoanalyzer (TBA-30FR, Toshiba, Japan). Both HBsAg and anti-HCV were detected by microparticle enzyme immunoassay (AxSYM, Abbott Laboratories, Chicago, IL, U.S.A.). A 3rd generation anti-HCV reagent was used. HCV RNA was detected by polymerase chain reaction (PCR) using a commercialized kit (AmplicorTM, Roche Diagnostics, Branchburg, NJ, U.S.A.). Genotypes of HCV were determined by a linear probe assay (Inno-LiPATM HCV II, Innogenetics, Zwigndrecht, Belgium). Anti-GBV-C E2 was also tested by enzyme immunoassay (Boehringer Mannheim, Roche Diagnostics, Branchburg, NJ, U.S.A.). GBV-C RNA was detected by nested reverse transcription (RT)-PCR using primers targeting the five prime untranslated region, as described previously.⁽¹⁵⁾ Anti-HDV was detected by radioimmunoassay (DiaSorin, Saluggia, Italy).

The chi-square test with or without Yate's correction was used to compare categorical variables between groups. Stepwise multiple logistic regression was employed to identify the independent variables of some categorical dependent variables. The alpha level was set at 0.05.

RESULTS

As shown in Table 1, the percentages of men and women were 42% and 58% in both villages. Subjects from W village were older than those from H village. (61.7 ± 11.8 vs 56.6 ± 16.4 years, $p = 0.02$). The positive rates of HBsAg were comparable in the 2 villages (12.2% vs 17.9%). Only one HBsAg-positive subject from H village was positive for anti-HDV. W village had a higher prevalence of anti-HCV than H village (67.6% vs 34.7%, $p < 0.0001$). Prevalence rates of HCV RNA among anti-HCV-positive subjects were not different between villages (74.0% vs 78.8%). An anti-HCV-negative subject was positive for HCV RNA in H village. However, there was a gender difference in HCV RNA positive rates (75.9%, 63/83) among anti-HCV positive subjects with an 88.2% rate (30/34) in men and a 67.3% rate (33/49) in women. In a multiple

Table 1. Data from Subjects from Two Villages in Central Taiwan

Items	Wukai (n = 74)		Haipu (n = 95)		p
	No of (+)	(%)	No of (+)	(%)	
Gender (M/F)	31/43	42%/58%	40/55	42%/58%	n.s.
Age range	27~79		21~86		
mean ± SD	61.7 ± 11.8		56.4 ± 16.5		0.02
HBsAg	9	12.2%	17	17.9%	n.s.
HCV or GBV-C	57	77.0%	47	49.5%	
anti-HCV	50	67.6%	33	34.7%	< 0.001
HCV-RNA	37	74.0%	26	78.8%	n.s.
GBV-C infection	29	39.2%	23	24.2%	0.054
GBV-C-RNA	12	41.4%	8	34.8%	n.s.
anti-GBV-C E2	20	69.0%	16	69.6%	n.s.
ALT (> 50 IU/L)	28	37.8%	15	15.8%	0.006

Abbreviations: n.s.: no significance; M: male; F: female; HBsAg: hepatitis B surface antigen; HCV: hepatitis C virus; ALT: alanine transaminase.

logistic model, village, sex, age (\leq or $>$ 60 years), HBsAg, anti-HCV, anti-GBV-C E2, GBV-C RNA, and GBV-C infection were candidates for independent factors of HCV RNA. Using stepwise analysis, only a positive anti-HCV (odds ratio [OR], 95% confidence interval [CI]: 391, 45.7~3340) and male sex (4.0, 1.2~13.2) were factors associated with HCV RNA (Table 2). The distribution of HCV genotypes 1b/2a/2b/unclassified were 14/18/2/3 in W village and 19/7/0/1 in H village, respectively. The genotype distributions were different between villages (genotype 1b vs non-1b, $p = 0.01$).

W village also had higher GBV-C infection levels than H village (39.2% vs 24.2%, $p = 0.054$). In 52 subjects with GBV-C infection, 16 (30.8%) were only positive for serum GBV-C RNA, 32 (61.5%) were only positive for anti-E2 antibodies and the other 4 (7.7%) had both GBV-C RNA and anti-E2. The case numbers in each category by village and HCV and GBV-C infection markers, are shown in Table 3. In multiple logistic models, village, sex, age (\leq or $>$ 60 years), HBsAg, anti-HCV and HCV RNA, were independent variables and each of GBV-C RNA, anti GBV-C E2 and GBV-C infection was a dependent variable. None of the above dependent

Table 2. Significant Factors Associated with HCV RNA by Multiple Logistic Regression

Variables	Comparison	OR	(95% CI)
anti-HCV	+ vs -	391	(45.7~3340)
Gender	male vs female	4.0	(1.2~ 13.2)

Abbreviations: OR: odds ratio; CI: confidence interval; HCV: hepatitis C virus.

Table 3. Case Number Distribution by Virus Marker and Village

HCV-RNA	Markers		Villages		Total
	GBV-C RNA	anti-GBV-C E2 antibody	Wukai	Haipu	
anti-HCV negative			n = 24	n = 62	N = 86
negative	negative	negative	17	48	65
negative	negative	positive	4	5	9
positive	negative	positive	0	1	1
negative	positive	positive	2	1	3
negative	positive	negative	1	7	8
anti-HCV positive			n = 13	n = 7	N = 20
negative	negative	negative	9	3	12
negative	negative	positive	3	4	7
negative	positive	positive	1	0	1
anti-HCV positive			n = 37	n = 26	N = 63
positive	negative	negative	19	21	40
positive	positive	negative	8	0	8
positive	negative	positive	10	5	15

Abbreviation: HCV: hepatitis C virus.

variables was associated with GBV-C RNA. Only anti-HCV was associated with anti-GBV-C E2 (OR, 95% CI: 2.15, 1.0~4.6). Only W village was associated with GBV-C infection (2.02, 1.04~3.9) (Table 4).

W village had also a higher percentage of subjects with elevated ALT levels (37.8% vs 15.8%, $p = 0.006$) than H village. Although anti-HCV, HCV

Table 4. Significant Factors Associated with GBV-C Markers by Multiple Logistic Regression

Dependent GBV-C markers	Significant factors	Comparison	OR	(95% CI)
GBV-C RNA	none			
Anti- GBV-C E2	anti-HCV	+ vs -	2.15	(1.0~4.6)
GBV-C infection	Village	Wukai vs Haipu	2.02	(1.04~3.9)

Abbreviations: OR: odds ration; CI: Confidence Interval.

RNA, HCV Genotype 1b, and W village were all associated with ALT elevation in univariate analyses, HCV RNA was identified as the only determining factor of ALT elevation in multivariate analysis.

DISCUSSION

Multiple hepatitis virus infections have been well studied in hospital-based studies. Liaw's observations of triple infections with HBV, HCV and HDV concluded that newcomers suppress existent viruses.⁽¹⁾ In Taiwan, most patients with chronic hepatitis B contracted HBV infection by vertical transmission or early exposure.⁽¹⁶⁾ HCV, the newcomer, is always dominant. Taiwan is an HBV-endemic country with a prevalence of 15~20% in the population born before mass HBV vaccination.⁽¹⁷⁾ All areas which are HCV-endemic are also endemic for HBV. These HCV-endemic areas should have active transmission routes for blood-borne diseases now or in the past. HCV, not HBV, is the newcomer in these endemic areas. Iatrogenic infection is one of the major routes.⁽⁸⁻¹²⁾ In decades ago, medical injection for symptoms control of common disease such as common cold, low back pain, and osteoarthritis were common and were one part of culture in Taiwan. Iatrogenic infection is thought to be the major cause of transmission of blood-borne viral infections because of poor sterilization technique and illegal medical service.⁽⁸⁻¹²⁾ Once the routes of transmission exist, other blood-borne viruses might also spread through these same routes. The issue of multiple blood-borne viral infections in HBV- and HCV-endemic communities has been investigated.

In Masago, an HCV-endemic area in southern Taiwan, (age and sex adjusted rate of anti-HCV

prevalence: 58.1%), the prevalence of GBV-C infection (40%) was higher than that in the blood donors tested (10%) in that study. The only associated factor of GBV-C infection was HCV infection. Thirty-one of 200 Masago residents (17.0%) were positive for serum GBV-C/HGV RNA and 51 (25.5%) were positive for anti-E2 antibodies. Six (3.0%) had both serum GBV-C RNA and anti-E2.⁽¹³⁾ These findings are similar to those in this study.

An HCV-RNA-positive state indicates "infectious" and an anti-HCV-positive state indicates "previously infected" in subjects with chronic HCV infection. However, the meaning of GBV-C markers is not as clear as HCV markers. The percentage of patients recovering from and duration to spontaneous recovery in both GBV-C infection and anti-GBV-C E2 seroreversion after virus clearance are unknown. The only thing known definitely is that subjects either positive to GBV-C RNA or anti-GBV-C E2 have been infected by HBV-C. Sixteen of our 52 subjects with GBV-C infection (30.8%) were only positive for serum GBV-C RNA, 32 (61.5%) were only positive for anti-E2 antibodies and the other 4 (7.7%) had both GBV-C RNA and anti-E2. The distributions of GBV-C infection were GBV-C RNA-positive in 37.4% (34/91) and anti-E2-positive in 56.0% (51/91) with 6.6% (6/91) positive for both in a published community study.⁽¹³⁾ This was similar to our results.

We did not identify the associated factors of GBV-C viremia. Subjects infected by HCV seem to have had a high chance of acquiring GBV-C infection. Residents of high HCV-endemic Wukai had a high chance of acquiring GBV-C infection. As there were only 20 subjects who were GBV-C-RNA-positive, 36 who were anti-GBV-C E2 positive, and 50 with GBV-C infection (n = 50), the sample size of GBV-C RNA-positive subjects might have been too small to identify associated factors using the present analysis. Subjects with HCV infection and residents living in HCV-endemic areas had a higher chance of contracting GBV-C infection.

Another hepatotropic virus, TT virus, was also studied in the Masago community. The conclusions were the same as for those for the GBV-C virus.⁽¹⁴⁾ Another township, Tzukuan, which is also endemic for HBV (age- and sex- adjusted rate of HBsAg among adults > 45 years: 12.8%), HCV (anti-HCV 41.6%) and HDV (anti-HD 15.3% among HBV car-

riers), had an HDV RNA-positive rate of only 12.7%. The associated factors of HDV infection were higher in the HCV-endemic part of the township as was HCV infection. The only factor for ALT elevation was also HCV RNA.⁽¹²⁾ The role of HDV in Tzukuan was the same as for GBV-C and TTV in Masago.

In this study, the study villages were not endemic for HDV. Similar to consistent results in studies of different hepatotropic viruses in different HBV- and HCV-endemic areas, we found that HCV was always dominant in multiple viral infections. HCV has higher rates of viremia and plays an important role in ALT elevation and liver inflammation. The infection rates of the other blood-borne viruses were associated with anti-HCV infection at the individual level and high HCV-endemic areas at the environmental level. This finding implies that subjects with risk for HCV infection or subjects living in high HCV-endemic areas have a higher chance of getting infected with other blood-borne viruses. However, the pathogens also play an important role. Despite active transmission routes, the prevalence of anti-HDV was quite low in the study villages. Not every HBV- and HCV-endemic area was endemic for all kinds of blood-borne viruses. This finding can perhaps explain the result of variant prevalences of HCV in Taiwan among people with similar attitudes toward medical injections and other percutaneous exposure influences. The infection markers of blood-borne viruses might be used as indicators of parenteral transmission routes in the community. Fortunately, recent studies have shown evidence of a decreasing incidence of acute HCV infection,⁽¹⁸⁾ and prevalence of anti-HCV in the new generation.⁽¹⁹⁾ This may imply that the use of parenteral transmission routes is decreasing in Taiwan.

Mongolia has also been reported as an area with high prevalence of HBV, HCV and HDV. HDV plays a significant role in hepatocellular carcinoma (HCC). The authors deduced that HCV was characterized by earlier epidemic expansion, whereas HDV spread with an approximately 50-year lag.⁽²⁰⁾ Although HDV was predominant, it was compatible with the previously mentioned stronger newcomer theory.

The rate of viremia among anti-HCV-positive residents in this study was 75.9%. The results are compatible with another community study in south-

ern Taiwan (74.5%).⁽²¹⁾ In community studies, prevalence rates of anti-HCV among women were always equal to or slightly higher than that of men.⁽²⁻⁶⁾ However, men had a higher risk of developing HCV-related HCC than women.⁽²²⁾ In this study, women had a lower rate of HCV viremia among anti-HCV-positive subjects. This finding has also been reported in a Japanese community study.⁽²³⁾ Women might have a higher probability of recovering from HCV infection. This finding might be a good explanation why women with chronic HCV infection have a lower risk of developing HCC than men.

In this study, we performed an HCV RNA test in both anti-HCV-positive and anti-HCV-negative subjects. Consistent with results of duplicate anti-HCV and HCV RNA tests, we found a subject who was anti-HCV-negative and HCV RNA positive. The prevalence was 1.1% (1/86; 95% CI: 0~3.4%) in this study in an area with high HCV prevalence. Although anti-HCV-negative subjects could still be HCV RNA-positive, this finding might be rare, especially in areas with low HCV prevalence.

The major genotypes of HCV in Taiwan are 1b and 2a. However, there are geographic variations.⁽²⁴⁻²⁶⁾ In a study in three townships in Taiwan, the proportions of genotype 1b ranged from 22.4% to 76.9%, while that for genotype 2a ranged from 3.6% to 63.5%.⁽²⁴⁾ In this study, there were also different distributions of HCV genotypes between the two neighboring villages. The proportions of genotype 1b/2a were 38%/49% in W village and 70%/26% in H village. Different initial sources of endemicity resulted in different genotypical distributions.

Comparing results from this study with those of previous studies in HBV- and HCV- endemic areas that were also endemic for the HDV,⁽⁴⁾ GBV-C,⁽¹³⁾ and TT viruses,⁽¹⁴⁾ we identified epidemiological characteristics of this kind of community. In HBV- and HCV-endemic areas, GBV-C is more prevalent in areas with a higher prevalence of anti-HCV. Positive HCV-RNA, but not GBV-C infection, is associated with ALT elevation.

Acknowledgements

This study was supported by grants from the National Science Council, Republic of China (NSC-86-2314-B-037-050) and the Chang Gung Medical Research Program (CMRP 763) to Dr. Sheng-Nan Lu. Dr. Chang-Jung Chang and Dr. Jui-Chin Chiang

contributed equally to this study.

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在 B 型及 C 型肝炎盛行地區之 D 型肝炎及 GB 病毒-C 的感染

張倡榮¹ 江瑞錦^{1,2,6} 盧勝男^{2,3,4,5} 王景弘^{3,4}

背景： 之前的台灣本土研究報告中指出在 B 型肝炎及 C 型肝炎盛行地區，同時也會合併 D 型肝炎、GB 病毒-C (GBV-C)，或 TT 病毒感染盛行。本研究的目的是在於釐清兩個鄰近在 B 及 C 型肝炎盛行地區之 D 型肝炎與 GBV-C 之流行病學，以推論社區多重病毒感染的流行病學特徵。

方法： 本研究共收案了 74 名五塊 (W) 村及 95 名海埔 (H) 村的居民，檢驗項目包括 ALT、HBsAg、anti-HCV、HCV RNA、genotype of HCV、GBV-C RNA 和 anti-GBV-C E2。HBsAg 陽性的個案再加驗 anti-HDV。

結果： 來自 W 村的研究對象較 H 村的年長 (61.7 ± 11.8 VS 56.6 ± 16.4 歲, $p = 0.02$)。在 W 及 H 兩個村有明顯差異的項目有：ALT 異常率分別為 37.8% 及 15.8% ($p = 0.006$)，anti-HCV 陽性率分別為 67.6% 及 34.7% ($p < 0.0001$)，HCV 基因型 1b 的比例分別為 37.8% 及 70.4% ($p = 0.01$)，GBV-C 感染率為 39.2% 及 24.2% ($p = 0.054$)。在 anti-HCV 陽性個案中其 HCV RNA 陽性率為 75.9% (63/83)，男性較女性 HCV RNA 陽性率較高，分別為 88.2% 及 67.3%。只有一位 HBsAg 陽性個案其 anti-HDV 為陽性，有一位 anti-HCV 陰性個案其 HCV RNA 為陽性。多變項分析顯示 GBV-C 感染與 C 型肝炎感染及居住在較盛行的地區有關，而 ALT 異常的唯一決定因子是 HCV RNA。

結論： 在 B 及 C 型肝炎盛行地區，C 型肝炎較盛行地區 GBV-C 也較盛行。HCV RNA 是 ALT 異常的主因。

(長庚醫誌 2010;33:137-44)

關鍵詞： B 型肝炎，C 型肝炎，D 型肝炎，GB 病毒-C，C 型肝炎基因型

長庚醫療財團法人高雄長庚紀念醫院 ¹家庭醫學科，²職業醫學科，³胃腸肝膽科系；長庚大學 醫學院 ⁴醫學系，⁵臨床醫學研究所；⁶國立成功大學 醫學院 環境及職業衛生研究所

受文日期：民國98年2月18日；接受刊載：民國98年5月18日

通訊作者：王景弘醫師，長庚醫療財團法人高雄長庚紀念醫院 胃腸肝膽科系。高雄縣833鳥松鄉大埤路123號。

Tel.: (07)7317123轉8301; Fax: (07)7322402; E-mail: jinghoung2001@yahoo.com.tw