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VIROLOGY

# A high seroprevalence of human herpesvirus type 8 already present in patients with chronic hepatitis before the development of cirrhosis

JEN-PI TSAI[1,2,3], KUO-CHIH TSENG[1,2], MING-NAN LIN[2,4], CHENG-CHUAN SU[2,5,6]

*[1]Department of Internal Medicine, Buddhist Dalin Tzu Chi Hospital, Chiayi County, Taiwan; [2]School of Medicine, Tzu Chi University, Hualien, Taiwan; [3]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan; [4]Department of Family Medicine, Buddhist Dalin Tzu Chi Hospital, Chiayi County, Taiwan; [5]Department of Clinical Pathology, Buddhist Dalin Tzu Chi Hospital, Chiayi County, Taiwan; [6]Department of Anatomic Pathology, Buddhist Dalin Tzu Chi Hospital, Chiayi County, Taiwan*

**Summary**

A high seroprevalence of human herpesvirus type 8 (HHV-8) in mild cirrhotics is significantly associated with hepatitis activity. Cirrhosis is always derived from chronic hepatitis. We aimed to evaluate the prevalence of HHV-8 infection in patients with chronic hepatitis. Blood samples collected from 129 patients with chronic hepatitis and 129 age- and sex-matched healthy controls were analysed for monocyte and platelet counts, hepatitis B surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV), HHV-8 antibody and DNA, and alanine aminotransferase (ALT). Mean monocyte and platelet counts were significantly higher and lower in patients than in healthy controls ($p = 0.02$ and $< 0.0001$, respectively). Seropositive rate for HHV-8 antibodies was significantly greater in patients (32.6%) than in controls (20.9%, $p = 0.04$), particularly in patients with HCV infection, or higher plasma ALT levels, or both ($p = 0.004$, 0.01, and 0.0009, respectively). Antibody titres for HHV-8 in patients also exceeded those in controls ($p = 0.02$). The mean age of HHV-8 seropositive patients (60.3 years) was significantly older than that of seronegatives (52.3 years) ($p = 0.0007$). Patients aged 55 or older had higher seropositive rate and titres for HHV-8 antibodies than those younger ($p = 0.005$ and 0.007, respectively). A significantly high HHV-8 seroprevalence is already present in patients with chronic hepatitis before the development of cirrhosis, particularly in patients with HCV infection and/or higher plasma ALT levels. Advancing age seems to play an important role in HHV-8 seroprevalence in patients with chronic hepatitis.

*Key words:* ALT; HBV; HCV; alcohol; HHV-8.

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## INTRODUCTION

To date, human herpesvirus type 8 (HHV-8) DNA has been found consistently in all types of Kaposi's sarcoma (KS).[1–4] KS occasionally develops in human immunodeficiency virus (HIV) non-infected patients with variable immunological abnormalities subsequent to corticosteroid, cytotoxic, or immunosuppressive therapy.[3,5–11]

Impaired immunity and a higher incidence of lymphoproliferative disorders and other malignancies have been documented, and are associated with spontaneous bacterial peritonitis in cirrhotics.[12–14] In our earlier studies, Child–Pugh class B or C cirrhotics were found to have a significantly higher prevalence of HHV-8 infection compared with healthy controls, particularly those with severe cirrhosis, hepatitis B virus (HBV) infection, and alcoholism.[15,16] Antibody titres in seropositive cirrhotics also significantly exceeded those measured in healthy controls. Our recent study further showed that hepatitis activity and old age are two risk factors for HHV-8 infection in Child–Pugh class A cirrhotics.[17] It is known that liver cirrhosis is always derived from chronic hepatitis. To date, the prevalence of HHV-8 infection in patients with chronic hepatitis remains unknown. It is unclear whether a high prevalence of HHV-8 infection in cirrhotics is already present in the stage of chronic hepatitis. This study aimed to investigate the statuses of HHV-8 antibodies, HHV-8 DNA, and HHV-8 viral load in patients with chronic hepatitis and to compare them to those measured in healthy control subjects.

## MATERIALS AND METHODS

### Healthy controls and study group

After obtaining informed consent from all subjects, plasma samples were collected from 129 patients with chronic hepatitis and 129 age- and sex-matched healthy controls. The healthy controls were selected from persons admitted in Buddhist Dalin Tzu Chi Hospital undergoing routine health examinations during the same period as the patients with chronic hepatitis, and were free of cirrhosis, malignancies, or other major diseases.

Chronic hepatitis was diagnosed if plasma alanine aminotransferase (ALT) levels were at least 1.5 times the upper limit of the normal range at the time of specimen collection and the ALT needed to be raised on at least two separate occasions over 6 months. Patients were included if there was no use of illicit drugs for at least one year and the absence of liver cirrhosis was demonstrated by ultrasonography. Patients were excluded if other liver disease or any other major diseases, such as diabetes mellitus, chronic renal failure, and malignancy, were diagnosed. Chronic hepatitis patients with positive plasma hepatitis B virus surface antigen (HBsAg) for > 6 months, who were negative for anti-hepatitis C virus (anti-HCV) and had no other causes of chronic liver

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disease, were considered to be HBV-related. Patients with positive plasma anti-HCV for > 6 months, who were negative for HBsAg and had no other causes of chronic liver disease, were considered to have HCV-related hepatitis. Subjects with alcohol-related hepatitis were defined as those who had consumed at least 80 g of alcohol daily for at least the past year, were negative for HBsAg and anti-HCV, and had no other causes of chronic liver disease. All subjects were HIV negative.

This study protocol was approved by the institutional review board of the Buddhist Dalin Tzu Chi Hospital (B09704029).

#### Immunofluorescence assay (IFA) for detection of HHV-8 antibody

A commercially available IFA kit (Advanced Biotechnologies Inc., USA) was used to detect HHV-8 IgG antibodies against the lytic antigens in the plasma samples according to the manufacturer's instructions. Samples that displayed fluorescence at a dilution of 1:40 were considered positive. Subjects displaying a positive result with IFA were considered to be HHV-8 seropositive. Maximum HHV-8 antibody dilutions were determined by an endpoint IFA.

#### Chemiluminescence immunoassay for HBsAg and anti-HCV and anti-HIV antibodies

Plasma samples were assayed for HBsAg and anti-HCV, anti-HIV-1, and anti-HIV-2 antibodies using the Vitros HBsAg, anti-HCV, and anti-HIV 1+2 reagent packs, respectively, with appropriate controls and calibrators (Ortho-Clinical Diagnostics, UK), and Vitros ECi immunodiagnostic system (Ortho-Clinical Diagnostics, USA) according to the manufacturer's instructions.

#### Assay for ALT

Plasma samples were assayed for ALT with the ALT Liquid Reagent using appropriate controls and calibrators (Roche Diagnostics, Germany) and the Roche Integra 800 system (Roche Diagnostics) according to the manufacturer's instructions.

#### DNA extraction and amplification of HHV-8 DNA

HHV-8 DNA was extracted and amplified exactly as reported previously.[16]

#### Statistical analyses

A $\chi^2$ test was used to assess the significance of between-group differences in categorical variables. Differences in means of continuous variables between two groups of patients were analysed by the *t*-test. The comparison of anti-HHV-8 titres in plasma between healthy controls and patients with active chronic hepatitis was analysed by the Mann–Whitney test. Statistical significance was set at a $p$ value < 0.05. Statistical analyses were performed using SPSS V. 12.0 for Windows (SPSS, USA).

## RESULTS

### HHV-8 antibody and DNA

The seropositive rate and titres for HHV-8 antibodies in both the healthy controls and the hepatitis patients are shown in Table 1. Both the rate and titres were significantly higher in patients with chronic hepatitis than in the healthy controls. One male patient was positive for HBsAg, HHV-8 antibody (1:640), and HHV-8 DNA (85 copies/μL). None of the HHV-8 seropositive individuals had received intravenous gamma globulins. Seropositivity was not associated with clinical manifestations of HHV-8 infection, such as KS, primary effusion lymphoma, or multicentric Castleman disease.

### Analysis of HHV-8 positive samples

Patients seropositive for HHV-8 were significantly older than seronegative patients (60.3 ± 12.5 vs 52.3 ± 12.2, $p = 0.0007$; *t*-test). In patients with chronic hepatitis, the seropositive rate for HHV-8 antibodies in males (32.9%, 25/76) was similar to that in females (32.1%, 17/53, $p = 0.92$; $\chi^2$). The mean ages of the male and female healthy controls who were seropositive for HHV-8 were 57.8 ± 11.3 years and 59.3 ± 9.1 years, respectively ($p = 0.73$; *t*-test). The mean age of the seropositive male patients (58.5 ± 13.1 years) was not significantly different from that of seropositive females (62.9 ± 11.3 years, $p = 0.26$; *t*-test).

### HHV-8 status, aetiology, and ALT levels

As described in Table 2, the prevalence of HHV-8 antibodies was significantly higher in patients with HCV infection ($p = 0.004$), or higher plasma ALT levels ($p = 0.01$), or both ($p = 0.0009$) than in healthy controls.

### HHV-8 status in various subgroups of patients with chronic hepatitis

Table 3 demonstrates that patients aged 55 or older had higher seropositive rate and titres for HHV-8 antibodies than those younger ($p = 0.005$ and 0.007; $\chi^2$ and Mann–Whitney, respectively). The difference in seropositive rates and titres

**Table 1** Baseline characteristics of 129 patients with chronic hepatitis and 129 age- and sex-matched healthy control subjects

| | Healthy controls | Chronic hepatitis | *p* |
|---|---|---|---|
| Age (mean ± SD) | 54.9 ± 12.8 | 54.9 ± 12.8 | |
| IFA-positive[a] | 20.9% (27/129) | 32.6% (42/129) | 0.04[b] |
| Age of IFA-positive[a] (mean ± SD) | 58.3 ± 10.4 | 60.3 ± 12.5 | 0.50[c] |
| Anti-HHV-8 titres | | | 0.02[d] |
| 1:40 | 18 | 21 | |
| 1:80 | 8 | 11 | |
| 1:160 | 1 | 3 | |
| 1:320 | 0 | 5 | |
| 1:640 | 0 | 2 | |
| Rate of high titres[e] | 0.8% (1/129) | 7.8% (10/129) | 0.006[b] |

Data are expressed as mean ± standard deviation.
HHV-8, human herpesvirus type 8; IFA, immunofluorescence assay; SD, standard deviation.
[a] Positive results of immunofluorescence assay.
[b] $\chi^2$ test.
[c] *t*-test.
[d] Mann–Whitney test.
[e] HHV-8 antibody titres ≥ 1:160.

**Table 2** Effect of dilution and positive rates for HHV-8 antibodies in plasma in patients with chronic hepatitis

| | IFA titres | | | | | IFA-positive[a] | $p$[b] |
|---|---|---|---|---|---|---|---|
| | 1:40 | 1:80 | 1:160 | 1:320 | 1:640 | | |
| HBV-related[c] ($n$ = 39) | 6 | 2 | 0 | 2 | 1 | 11/39 (28.2%) | 0.34 |
| HCV-related[d] ($n$ = 64) | 14 | 6 | 2 | 3 | 1 | 26/64 (40.6%) | 0.004 |
| Alcohol-related[e] ($n$ = 23) | 3 | 2 | 1 | 1 | 0 | 7/23 (30.4%) | 0.31 |
| HBV & HCV co-related ($n$ = 3) | 1 | 0 | 0 | 1 | 0 | 2/3 (66.7%) | 0.06 |
| Unknown aetiologies ($n$ = 8) | 0 | 1 | 0 | 0 | 0 | 1/8 (12.5%) | 0.57 |
| 1.5×[f] < ALT ≤ 3×[g] ($n$ = 101) | 13 | 8 | 2 | 5 | 2 | 30/101 (29.7%) | 0.13 |
| ALT > 3×[g] ($n$ = 30) | 9 | 3 | 1 | 0 | 0 | 13/30 (43.3%) | 0.01 |
| HCV-related[d] and ALT > 3×[g] ($n$ = 15) | 7 | 2 | 0 | 0 | 0 | 9/15 (60.0%) | 0.0009 |

ALT, alanine aminotransferase HHV-8, HBV, hepatitis B virus; HCV, hepatitis C virus; human herpesvirus type 8; IFA, immunofluorescence assay.
[a] Positive results of IFA.
[b] vs control subjects, 20.9% (27/129); $\chi^2$ test.
[c] Including HBV-related only ($n$ = 35), HBV and alcohol co-related ($n$ = 1), and HBV and HCV co-related ($n$ = 3).
[d] Including HCV-related only ($n$ = 60), HCV and alcohol co-related ($n$ = 1), and HBV and HCV co-related ($n$ = 3).
[e] Including alcohol-related only ($n$ = 21), HBV and alcohol co-related ($n$ = 1), and HCV and alcohol co-related ($n$ = 1).
[f] Plasma ALT levels 1.5 times the upper limit of the normal range.
[g] Plasma ALT levels at least 3 times the upper limit of the normal range.

for HHV-8 antibodies between patients with and without HCV infection showed borderline significance ($p$ = 0.05 and 0.08; $\chi^2$ and Mann–Whitney, respectively).

## DISCUSSION

Patients with chronic hepatitis B or C tend to have late, transient, or narrowly focused T-cell responses.[18–21] Chronic viral hepatitis is characterised by an inefficient T-cell response unable to completely clear virus from the liver, which consequently sustains continuous cycles of low-level cell destruction. Over long periods of time, recurrent immune-mediated liver damage contributes to the development of cirrhosis.[22] In our recent study concerning Child–Pugh class A cirrhotics, the seropositive rate and titres for HHV-8 antibodies in patients with HCV infection markedly exceeded those in patients without HCV infection ($p$ = 0.007 and 0.0008, respectively).[17] In the present study, the seropositive rate and titres for HHV-8 antibodies were greater in patients with HCV infection compared to those without a concurrent HCV infection ($p$ = 0.05 and 0.08, respectively). The relationship between HHV-8 and HCV is certainly worthy of further research.

Our recent study about Child–Pugh A cirrhotics also showed that the positive rate for HHV-8 antibodies was significantly higher in patients with hepatitis activity (22/30, 73.3%) than in those without (24/64, 37.5%, $p$ = 0.003). Hepatitis activity was also an independent risk factor for HHV-8 seropositivity ($p$ = 0.005) in these mild cirrhotics.[17] Similarly, the study presented herein demonstrated that the seropositive rate for HHV-8 antibodies was significantly greater in patients with chronic hepatitis (42/129, 32.6%) than in healthy controls (27/129, 20.9%, $p$ = 0.04), particularly in individuals with higher plasma ALT levels (12/28, 42.9%, $p$ = 0.01) and in those with both HCV infection and higher plasma ALT levels (9/15, 60%, $p$ = 0.0009). HHV-8 antibody titres in patients with chronic hepatitis were also significantly higher than titres measured in healthy control subjects ($p$ = 0.02). HHV-8 antibodies might be associated with hepatocellular injury. However, this needs further investigation.

In a study concerning HHV-8 seroprevalence in patients with end-stage renal disease we found that the less sensitive enzyme-linked immunosorbent assay (ELISA) or specifying the IFA antibody to higher titres allowed differentiation of risk factors for HHV-8 infection.[23] In that study one of the two healthy controls with the highest IFA antibody titre (1:160) was positive by ELISA. If the cut-off point of the HHV-8 antibody titre in the present study was set at 1:160, patients with chronic hepatitis still had a significantly higher HHV-8 seropositive rate than controls ($p$ = 0.006, Table 1).

The prevalence of HHV-8 antibodies was somewhat less in the patients with chronic hepatitis (42/129, 32.6%) in the present study compared to the Child–Pugh A cirrhotics without hepatitis activity (24/64, 37.5%) in our recent study ($p$ = 0.50; $\chi^2$).[17] This finding suggests that most of the HHV-8 infection in cirrhosis patients was already present during the chronic hepatitis stage of disease. The seropositive rate for HHV-8 antibodies was also significantly less in the patients with chronic hepatitis (42/129, 32.6%) in the present study than in the Child–Pugh A cirrhotics with hepatitis activity (22/30, 73.3%) included in our previous study ($p$ < 0.0001; $\chi^2$).[17] As such, it is possible that both inflammation and cirrhosis may play roles in the seroprevalence of HHV-8. They might be associated with a decrease in immunity. However, this needs further exploration.

KS has been found mainly in elderly persons and an age-related slightly increased risk for classic KS was identified among individuals originating from Asia and Africa.[24,25] Child–Pugh class A cirrhotics seropositive for HHV-8 antibodies were significantly older than those seronegative ($p$ = 0.02).[17] Besides, old age (≥55 years old) was an independent risk factor for HHV-8 seropositivity ($p$ = 0.04) in mild cirrhotics.[17] Similarly, in the present study, the seropositive patients with chronic hepatitis were also older than seronegatives ($p$ = 0.0007). Thus, old age seems to play an important role in HHV-8 infection in patients with mild cirrhosis and/or chronic hepatitis.

HHV-8 DNA was rarely detected in plasma, serum, or buffy coat samples from individuals without KS.[25–27] In the

**Table 3** Comparisons of mean age and maximal titres and positivity of plasma HHV-8 antibodies among various subgroups of patients with chronic hepatitis

| Serum dilution | Age, years Mean ± SD | $p$[a] | IFA maximal titres | | | | | | $p$[b] | IFA+[c] | $p$[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Negative | 1:40 | 1:80 | 1:160 | 1:320 | 1:640 | | | |
| Age ≥ 55 years | | | | | | | | | | | |
| Yes | 64.9 ± 6.5 | < 0.0001 | 39 | 15 | 9 | 2 | 3 | 1 | 0.007 | 30/69 (43.5%) | 0.005 |
| No | 43.4 ± 7.5 | | 48 | 6 | 2 | 1 | 2 | 1 | | 12/60 (20%) | |
| HBV-related[e] | | | | | | | | | | | |
| Yes | 46.4 ± 12.4 | < 0.0001 | 28 | 6 | 2 | 0 | 2 | 1 | 0.50 | 11/39 (28.2%) | 0.49 |
| No | 58.6 ± 11.2 | | 59 | 15 | 9 | 3 | 3 | 1 | | 31/90 (34.4%) | |
| HCV-related[f] | | | | | | | | | | | |
| Yes | 60.1 ± 9.7 | < 0.0001 | 38 | 14 | 6 | 2 | 3 | 1 | 0.08 | 26/64 (40.6%) | 0.05 |
| No | 49.8 ± 13.5 | | 49 | 7 | 5 | 1 | 2 | 1 | | 16/65 (24.6%) | |
| Alcohol-related[g] | | | | | | | | | | | |
| Yes | 54.4 ± 13.3 | 0.81 | 16 | 3 | 2 | 1 | 1 | 0 | 0.87 | 7/23 (30.4%) | 0.81 |
| No | 55.1 ± 12.8 | | 71 | 18 | 9 | 2 | 4 | 2 | | 35/106 (33.0%) | |
| ALT ≥ 3×[h] | | | | | | | | | | | |
| Yes | 54.0 ± 13.1 | 0.64 | 17 | 9 | 3 | 1 | 0 | 0 | 0.34 | 13/30 (43.3%) | 0.15 |
| No | 55.2 ± 12.8 | | 70 | 12 | 8 | 2 | 5 | 2 | | 29/99 (29.3%) | |
| IFA+[c] | | | | | | | | | | | |
| Yes | 60.3 ± 12.5 | 0.0007 | 0 | 21 | 11 | 3 | 5 | 2 | | 42/42 (100%) | |
| No | 52.3 ± 12.2 | | 87 | | | | | | | 0/87 (0%) | |

HBV, hepatitis B virus; HCV, hepatitis C virus; HHV-8, human herpesvirus type 8; IFA, immunofluorescence assay; SD, standard deviation.
[a] *t*-test.
[b] Mann–Whitney test.
[c] Positive results of immunofluorescence assay.
[d] $\chi^2$ test.
[e] Including HBV-related only ($n$ = 35), HBV and alcohol co-related ($n$ = 1), and HBV and HCV co-related ($n$ = 3).
[f] Including HCV-related only ($n$ = 60), HCV and alcohol co-related ($n$ = 1), and HBV and HCV co-related ($n$ = 3).
[g] Including alcohol-related only ($n$ = 21), HBV and alcohol co-related ($n$ = 1), and HCV and alcohol co-related ($n$ = 1).
[h] Plasma alanine aminotransferase (ALT) levels 3 times the upper limit of the normal range.

present study, one male patient was positive for HBsAg, HHV-8 antibody, and HHV-8 DNA. However, in this study we could only detect 5–10 copies/μL of HHV-8 DNA. The question of whether other patients have HHV-8 DNA at levels less than 5–10 copies/μL will be resolved only if the detection sensitivity can be increased.

In the present study no patients with chronic hepatitis received biopsies to prove the presence of HHV-8 DNA in their liver tissues. The role of HHV-8 infection in hepatitis needs to be clarified. Although this is the first comprehensive study concerning HHV-8 infection and patients with chronic hepatitis, it was the third limitation of our study that the subjects were recruited from a single community hospital and the number of cases was relatively small. Hence, the results were not representative of the overall status in Taiwan or in the world elsewhere. The fourth limitation was that a group with HBV or HCV infection but without chronic hepatitis was not included in the present study. In the near future we will investigate the status of HHV-8 in HBV or HCV carriers, and the association of co-infection of HHV-8 and hepatitis virus with active hepatitis and progression to cirrhosis.

In conclusion, patients with chronic hepatitis have higher seropositive rate and titres for HHV-8 antibodies than healthy controls. The results presented herein suggest that a significantly high seroprevalence of HHV-8 is already present in the chronic hepatitis stage of disease before cirrhosis, particularly in patients with HCV infection, or higher plasma ALT levels, or both. This seroprevalence is significantly associated with old age. Advancing age seems to play an important role in the seroprevalence of HHV-8 in patients with chronic hepatitis.

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**Address for correspondence:** Dr C. C. Su, Department of Clinical Pathology, Buddhist Dalin Tzu Chi Hospital, 2, Minsheng Road, Dalin Town, Chiayi County, 622, Taiwan. E-mail: sucpo@yahoo.com.tw

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