

Acute viral hepatitis in Hong Kong: a study of recent incidences

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Acute hepatitis patients admitted to a referral centre from January 1995 through December 1995 were studied to determine the seroprevalence of the hepatitis viruses and related risk factors. Of the 434 patients with acute viral hepatitis, the episodes due to hepatitis A, B, C, D, and non-A, non-B, non-C, (non-ABC) were 214 (49.3%), 163 (37.6%), 7 (1.6%), 0 (0%), and 50 (11.5%), respectively. Acute hepatitis A and non-ABC hepatitis commonly occur in late spring and early summer and are probably related to the intake of shellfish and travel to endemic areas. Approximately 60% of cases of symptomatic hepatitis B infection were acute exacerbations of chronic infection. Sexual exposure was the single most important risk factor for acute hepatitis B infection. The rarity of acute hepatitis C and D might be related to the low rate of intravenous drug use in our locality. Hepatitis E virus probably contributed significantly to the cases of non-ABC hepatitis. Further studies are needed to establish the importance of various causative agents of acute hepatitis in Hong Kong.

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Introduction

Acute viral hepatitis is a serious health problem in many countries. In Hong Kong, the incidence rate is 1.1 per 10 000 total population, and is the third most common notifiable infectious disease, after tuberculosis and food poisoning.¹ There are at least five known types of hepatitis, namely A, B, C, D, and E. The outcome of the disease depends on the type of viral infection involved. The diagnosis of some cases can only be made with recently developed serological assays. With the introduction of hepatitis vaccines and improved sanitation and social hygiene conditions in Hong Kong, the incidence of acute viral hepatitis is expected to decrease. However, outbreaks of acute hepatitis still occur² and may be related to the city's proximity to mainland China, where hepatitis A and E are endemic.^{3,4}

The purpose of this epidemiological survey was to establish the incidence of various types of acute

hepatitis and to define the relevant risk factors.

Patients and methods

From January 1995 through December 1995, 444 patients aged 15 years and older with acute hepatitis were admitted to the Infectious Disease Service of the Princess Margaret Hospital, a referral centre for acute viral hepatitis patients. The diagnosis was made based on a suggestive history, the presence of typical symptoms and signs of acute hepatitis, and an increase in serum aminotransferase levels in excess of five times the normal upper limit. Patients with a history of alcohol abuse, drug-induced hepatitis, autoimmune hepatitis, or metabolic causes of hepatitis were excluded.

A record was taken of the sex, age, history of drug injection, blood product transfusions, drinking habits, seafood consumption within six weeks of the onset of symptoms, drug intake, recent travel history, history of close contact with hepatitis patients, and any family history of hepatitis for each patient. Sexual orientation was assessed by direct questioning about the patient's marital status, number of sexual partners, length of any stable sexual relationship, hepatitis carrier state of sexual partners, and sexual contact with prostitutes. Intercourse with a fixed partner was classified as a stable relationship, whereas those who

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had sex with prostitutes were categorised as promiscuous. Blood tests included liver function test, complete blood picture, reticulocyte count, renal function test, prothrombin time, partial thromboplastin time, and viral serological markers. Liver function tests were checked twice weekly when the patients were hospitalised and one month after onset, and then one to three times monthly, until the results returned to normal.

A diagnosis of hepatitis A was confirmed by the presence of anti-hepatitis A virus IgM (anti-HAV IgM) by enzyme-linked immunosorbent assays (Vidas, bioMérieux Vitek Inc., Lyon, France). Acute hepatitis B was diagnosed by the presence of anti-hepatitis B core IgM (anti-HBc IgM) in enzyme immunoassay (Corzyme-M, Abbott Laboratories, Chicago, Ill, US) and/or radioimmunoassay (Corab, Abbott Laboratories, Chicago, Ill, US) together with a positive hepatitis B surface antigen (HBsAg) result in a reversed passive haemagglutination and/or radioimmunoassay (Ausria II, Abbott Laboratories, Chicago, Ill, US). An acute episode of chronic hepatitis B infection was diagnosed by a known history of positive hepatitis B status or the presence of isolated HBsAg and negative anti-HBc IgM with the exclusion of hepatitis D superinfection or co-infection (i.e. negative anti-hepatitis D antibody [Abbott Laboratories, Chicago, Ill, US]) by enzyme immunoassay. In the absence of serological evidence of acute hepatitis A and B, anti-hepatitis C antibody (anti-HCV) was checked by a second generation enzyme immunoassay (EIA, Ortho Diagnostic Systems, Ravitan, NJ, US), immediately and six months later. Patients with clinical features of acute hepatitis and anti-HCV seropositivity, either on presentation or six months after initial symptoms, were considered to have acute hepatitis C, although cases of acute-on-chronic hepatitis C could also be included. The diagnosis of non-A, non-B, non-C (non-ABC) hepatitis was made by the exclusion of the above three viral types.

Results

During the study period, 444 patients with acute hepatitis were admitted to the Infectious Disease Unit. Ten patients were excluded from the study for the following reasons: six had alcohol-induced hepatitis; two had autoimmune hepatitis; one had a fluconazole-induced hepatitis; and one patient had Wilson's disease.

Incidence

The incidences of the different types of acute viral hepatitis are shown in Table 1. Viral hepatitis A was the most common cause of acute hepatitis, followed

Table 1. Hepatitis virus type distribution found in patients with acute hepatitis who were treated at the Princess Margaret Hospital from January 1995 through December 1995

Type	No. of patients (%)
A	214 (49.3)
B	163 (37.6)
C	7 (1.6)
D	0
Non-ABC	50 (11.5)

by hepatitis B. Of the 163 patients with hepatitis B, 67 patients (41%) had acute hepatitis B, while 96 patients (59%) had acute-on-chronic hepatitis B, according to our definition. No hepatitis D co-infection or superinfection with hepatitis B was diagnosed in this survey. Cases of acute hepatitis C were uncommon but a mixture of both acute and acute-on-chronic cases of hepatitis C could have been present. The differentiation was difficult since the incubation period was largely unknown and the HCV RNA assay was not available. Non-ABC hepatitis accounted for 12% of all cases of acute viral hepatitis seen during the study period.

Sex ratio

The sex ratios for various types of acute viral hepatitis are shown in Table 2. Acute viral hepatitis occurred more commonly in males than females with the ratio ranging from 5.3:1 in hepatitis B to 1.6:1 in hepatitis A and non-ABC hepatitis. Among male patients, the incidences of acute hepatitis A and hepatitis B were similar.

Age

The age distributions for patients with the four hepatitis types are shown in Figure 1. Acute hepatitis A was the most common between the ages of 20 to 29 years, with none being seen in patients older than 50 years. The incidences of acute hepatitis B and acute-on-

Table 2. Sex distribution of acute hepatitis patients treated at the Princess Margaret Hospital from January 1995 through December 1995

Type	Male	Female	Ratio (M:F)
A	132	82	1.6:1
B	137	26	5.3:1
C	5	2	2.5:1
D	0	0	na
Non-ABC	31	19	1.6:1
Total	305	129	2.4:1

na not applicable

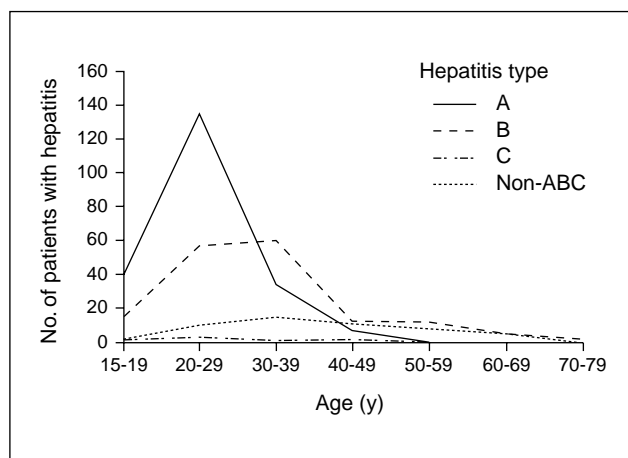


Fig 1. Age distribution plot for patients with acute hepatitis

chronic hepatitis B peaked at the ages of 20 to 29 years and 30 to 39 years, respectively (Fig 2). Furthermore, the incidence of acute hepatitis B decreased markedly from the age of 40 onwards. On the other hand, the incidence of acute-on-chronic hepatitis B increased rapidly after adolescence and outnumbered that of acute hepatitis B from the 30 to 39 year age group onwards. The age groups of patients with non-ABC hepatitis showed a wide spread and there was a higher proportion of non-ABC hepatitis cases than hepatitis A cases after the age of 40 years.

Seasonal distribution

The seasonal distribution of various types of acute hepatitis is shown in Figure 3. Acute hepatitis A and non-ABC hepatitis show seasonal predominance in late spring and early summer. In non-ABC hepatitis patients, disease onset coincided with a recent history of eating shellfish or travel to endemic areas. There was no seasonal predominance for hepatitis B and C.

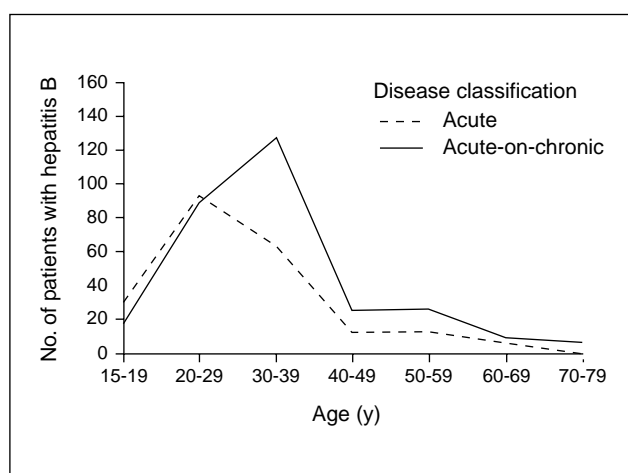


Fig 2. Age distribution plot for patients with hepatitis B

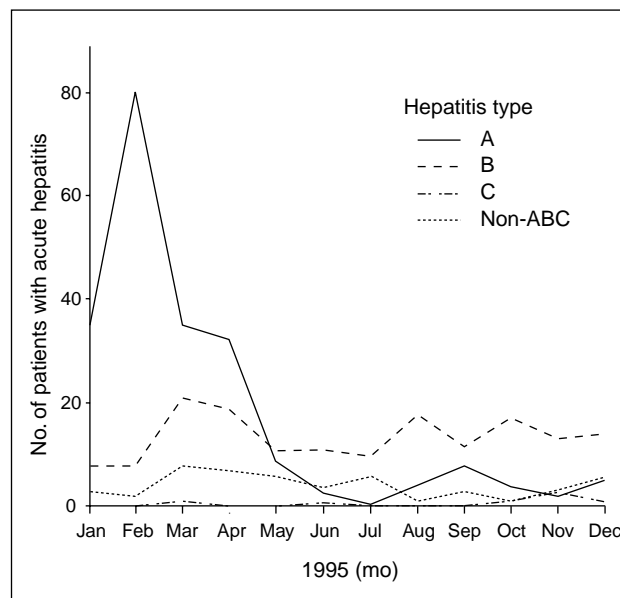


Fig 3. Seasonal distribution of acute hepatitis cases

Risk factors

Most patients with acute hepatitis A had a recent history of intake of shellfish (57%) or had travelled to endemic areas such as southern China and Thailand (14%), or to both (7%). No patient had a history of contact with an individual with jaundice.

The risk factors for hepatitis B infection are shown in Table 3. Patients with acute hepatitis B had a higher rate of sexual contact with known carriers than did those with acute-on-chronic hepatitis B and the difference was statistically significant. Of the 19 acute hepatitis B patients with sexual exposure, five had stable relationships with known HBV carrier partners; the exposure time ranged from three months to two years. Patients with acute-on-chronic hepatitis B had a higher rate of positive family history of hepatitis B than the acute hepatitis B group, but the difference was not significant (χ^2 test, $P=0.09$). Other risk factors known to cause hepatitis B infection were not common.

The diagnosis of hepatitis C in the acute phase is difficult. Only seven patients with acute hepatitis C or acute-on-chronic hepatitis C were identified: two were intravenous drug users, one had a history of blood transfusion two months before illness began, and one had had sexual exposure to prostitutes one month prior to the onset of symptoms. Seroconversion from anti-HCV(-) status on presentation to anti-HCV(+) status at six months occurred in the patient who had been transfused and in one intravenous drug user. No patient had a previous

Table 3. Known risk factors for contracting hepatitis B infection and associated cases with acute or acute-on-chronic hepatitis B treated at the Princess Margaret Hospital from January 1995 through December 1995

Risk factor	No. of patients with acute hepatitis B (%) n = 67 [HBsAg(+), anti-HBc IgM(+)]	No. of patients with acute-on-chronic hepatitis B (%) n = 96 [HBsAg(+), anti-HBc IgM(-)]	P value
Sexual exposure*	19 (28.3)	7 (7.3)	P<0.005
Family history of hepatitis B	6 (9.0)	19 (20.8)	ns
Previous episode of acute hepatitis	0	35 (36.5)	ns
Intravenous drug abuser	1 (1.5)	0	ns
Acupuncture/tattooing	2 (3.0)	1 (1.0)	
Unknown	39 (58.2)	34 (35.4)	

*Sexual exposure recent history of sexual intercourse with prostitutes or partners who are known hepatitis B carriers
ns not significant

history of hepatitis and all biochemical abnormalities subsided within six months.

There were 50 patients with non-ABC hepatitis. Hepatitis E is known to be an important cause of non-ABC hepatitis. Transmission is via the faecal-oral route and the disease is endemic in southern China. Half of these patients had risk factors: 14 (28%) had recently eaten shellfish; nine (18%) had travelled to endemic areas; and three patients (6%) had both risk factors. Fifteen (75%) of 20 patients with possible faecal-oral infection were detected in late spring and early summer (March to May). Other risk factors for non-ABC hepatitis included sexual exposure (five patients), history of blood transfusion (one patient), tattooing (one patient), and a previous history of hepatitis (two patients).

Discussion

With improvements in sanitation, the incidence of acute hepatitis A had reached a plateau in Hong Kong. However, it increased gradually again from 1989 onwards and an outbreak occurred in 1992.² The incidence then decreased progressively from 4357 cases in 1992 to 666 cases in 1995.¹ This phenomenon can be explained by improved public hygiene and socioeconomic conditions leading to decreased transmission of the hepatitis A virus before 1989. Decreased herd immunity in the population was thought to predispose to the outbreak that occurred in 1992. With more people lacking immunity to the hepatitis A virus and the increasing movement of people to and from hepatitis A endemic areas such as local residents travelling to Southeast Asia and immigrants coming from mainland China, acute hepatitis A virus attacks may become a potentially

serious health problem in our community. Chin et al⁵ reported that the prevalence of anti-HAV antibody was only 17.1% for those younger than 20 years during the period 1987 to 1989 while it was 44.8% during 1978 to 1979. To prevent further epidemics in Hong Kong, hepatitis A vaccine, which has recently become available, is considered useful, particularly in the young adult population in which clinical illness is more common. A government-sponsored educational campaign about the need for dietary hygiene and the avoidance of consumption of raw or undercooked shellfish should be implemented. A local study has shown that the hepatitis A virus is commonly isolated in shellfish in Hong Kong (30% of oysters, 14% of mussels, and 6% of clams).⁶

Hepatitis B virus infection is endemic in Hong Kong and the prevalence of HBsAg carriers is 9.5% in the general population.⁷ Unlike countries that have a low prevalence of hepatitis B where the presence of HBsAg can be used as a diagnostic criterion for acute hepatitis B, positive anti-HBc IgM assay must also be documented in Hong Kong to diagnose acute hepatitis B. Firstly, anti-HBc IgM may be detected in the absence of HBsAg in a case of acute hepatitis B in the core window period.⁸ Secondly, the presence of HBsAg can only indicate the presence of hepatitis B virus infection, but does not indicate whether the infection is acute or chronic. However, studies show that anti-HBc IgM persists in chronic hepatitis B patients in association with disease activity.⁴⁻¹³ Recently, antibody to the woodchuck hepatitis virus (anti-HBcW) was identified as a useful marker in distinguishing between acute and chronic hepatitis B infection.¹⁰ High titres of anti-HBcW were detected in patients with

chronic infection while little or no anti-HBcW was present in those with acute infection. There was virtually no overlap in anti-HBcW titres for acute and chronic hepatitis B infection. Worldwide assessment of this assay is necessary before it can be applied clinically.

We used the Corzyme-M assay, which has a relatively high cut-off antibody level (250 units/mL). In previous studies, using a similar method, only 0% to 3% of chronic hepatitis B patients showed positive results.^{11,12} Six patients with a positive family history of hepatitis B were diagnosed as having acute hepatitis with positive HBsAg results and anti-HBc IgM. It is possible that these patients had contracted hepatitis B virus infection at birth or during childhood and were having an acute exacerbation of the disease. The differentiation of acute hepatitis B from symptomatic chronic hepatitis B infection is important for prognosis. The risk of chronicity is usually less than 5% in acute hepatitis B.¹³

Sexual contact with HBsAg carriers or prostitutes is probably the most common means of acquiring acute hepatitis B infection. The peak age was within the third decade when most people become sexually active. Our results are consistent with the results obtained by Yeoh¹⁴ in which there was an increase in the prevalence of serological markers of hepatitis B in young adults aged 21 to 30 years. While mass vaccination against hepatitis B virus for the newborn has been operational since 1986, the vaccination should be strongly advised for children born before 1986 who have no hepatitis B serological markers.

The role of hepatitis C virus infection in acute non-A, non-B hepatitis varies greatly between countries. The prevalence of anti-HCV may be up to 60% to 70% of acute non-A, non-B hepatitis in Japan¹⁵ and western countries¹⁶⁻¹⁸ while it contributes up to 30% to 50% in some African countries.¹⁹ The prevalence seems to be lower, however, in Chinese populations, Wu et al²⁰ reported that the seroprevalence of anti-HCV antibody in patients with acute hepatitis was 4% in Lanzhou, western China. Our results also demonstrated a low seroprevalence (1.6% of acute hepatitis and 12.3% of acute non-A, non-B hepatitis). However, the incidence may have been underestimated in our study because anti-HCV antibody was checked only if serological markers for acute hepatitis A and B were negative. For the same reason, cases of co-infection or superinfection of hepatitis B and C could also have been missed. Furthermore, in some patients, both the first and second generation tests might fail to detect anti-HCV

antibody unless the HCV RNA has first been amplified with the polymerase chain reaction (PCR), but this phenomenon is not common.¹⁷ Another Hong Kong study²¹ in which anti-HCV and serum HCV RNA in all acute hepatitis patients were checked, also showed that the seroprevalence of acute hepatitis C was 1.4%. No hepatitis D infection was detected in Hong Kong patients with acute hepatitis,²¹ which is probably related to the low rate of intravenous drug use in the population.

Hepatitis E virus infection is not uncommon in Chinese people. The seroprevalence in a healthy population ranges from 10.7% in Taiwan²² to 18.2% in southern China.⁴ Lok et al²³ reported that 16.1% of healthy Chinese in Hong Kong were positive for anti-HEV IgG and hepatitis E accounted for one third of the non-ABC hepatitis in that study. Although anti-HEV assay was not available for this study, hepatitis E virus was probably the cause in some patients with non-ABC hepatitis who had either of the two known risk factors. Preliminary results of a prospective study on hepatitis E infection performed at our centre showed that one third (10/30) of patients with acute non-ABC hepatitis tested from February 1996 to April 1996 had positive anti-HEV IgM by the new and as yet unestablished EIA test (Abbott Laboratories, Chicago, Ill, US). Since the mode of transmission of hepatitis E virus infection is similar to that of hepatitis A virus infection and most people are unlikely to have immunity to the hepatitis E virus, the potential risk of outbreaks cannot be ignored.

Recently, scientists have cloned the hepatitis G virus, which may account for at least a minority of non-A to E hepatitis. This virus can be transmitted parenterally and may possibly cause transfusion-associated hepatitis. A high prevalence of hepatitis G virus RNA has been found in subjects with frequent parenteral exposure, including intravenous drug users, patients on haemodialysis, and patients with haemophilia. Hepatitis G virus RNA can also be found in the blood of apparently healthy subjects. Hence, the clinical significance of this virus is still unclear and more information is awaited.

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