Type B and non-B viral hepatitis in Jerusalem*

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In a two-year survey of adult patients hospitalized with acute viral hepatitis in Jerusalem, 27% were reactive for the hepatitis B surface antigen (HB_sAg) by radioimmunoassay and therefore diagnosed as having hepatitis B. The majority of patients (73%) were non-reactive for HB_sAg and their diagnosis was non-B hepatitis ("type unspecifiable"). Thirty-one per cent of patients with hepatitis B and only 5% of patients with non-B hepatitis had histories consistent with parenteral transmission of hepatitis by blood transfusion or drug use. An additional 19% of the patients with hepatitis B had possible parenteral exposure and 50% had no obvious parenteral exposure, indicating that non-parenteral transmission of the hepatitis B virus (HBV) may be a significant epidemiological factor (50–69%) in the Jerusalem area. The prominent role of non-parenteral transmission of HBV is further evidenced by the relatively high prevalences of HB_sAg (0.97%) and antibody to hepatitis B surface antigen (anti-HB_s) (19.0%) in healthy blood donors. These findings are consistent with the view that personal contact and intra-familial spread may be important factors in the epidemiology of HBV and indicate that non-parenterally transmitted HBV contributes significantly to endemic viral hepatitis in the Jerusalem area.

Sero-epidemiological surveys during recent years have documented the worldwide distribution of the hepatitis B virus (HBV) and its non-parenteral transmission as a significant factor in endemic and sporadic cases of acute viral hepatitis (*1*). In the eastern Mediterranean area, where "infectious" hepatitis is known to be endemic, acute cases are typically of short incubation, are non-parenterally transmitted, and affect the indigenous population primarily in early childhood (*2*). In Israel statutory notification of viral hepatitis to the Ministry of Health has provided considerable data on the epidemiology, morbidity, and mortality of endemic viral hepatitis (2–4). The availability of a serological test specific for HBV infection, namely the test for the hepatitis B surface antigen (HB_sAg), provided the opportunity for the present study of the role of HBV in acute viral hepatitis in a defined Israeli population. This report summarizes a two-year survey of HB_sAg in patients hospitalized with acute viral hepatitis in a large hospital in Jerusalem. Simultaneous surveys of HB_sAg and antibody to HB_sAg (anti-HB_s) in healthy blood donors are reported as indicators of the HBV carrier state and the role of HBV in subclinical hepatitis in the same community.

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MATERIALS AND METHODS

Population selection

Patients with acute viral hepatitis were identified and included in the study prospectively at the time that HB_sAg tests were requested. Subsequently, the clinical findings, laboratory tests, and pathology records for all patients admitted to the Hadassah University Hospital between March 1973 and March 1975 were reviewed to ensure the completeness of case findings and to confirm diagnoses of acute viral hepatitis. All patients were hospitalized at the Hadassah University Hospital, a 700-bed general hospital with 25 000 admissions annually, which serves both Jewish and Arab communities in Jerusalem and environs and receives referrals from the

Worker's Sick Fund (Kupat Holim), government health clinics, and hospital outpatient departments. The study population is considered to be representative of acute viral hepatitis in adults in the area, since it is the usual practice in Jerusalem to hospitalize all referred patients with jaundice.

During the 24-month study period, 4039 voluntary blood donors from the community attending the hospital's blood bank were screened for HB_sAg. Seven hundred of these blood donors were tested also for anti-HB_s.

Radioimmunoassay (RIA) for HB_sAg

Sera from all patients hospitalized with acute viral hepatitis were tested for HB_sAg by RIA, using a modification of the direct solid-phase radioimmunoassay (*5*), consisting of polystyrene beads coated with guinea-pig anti-HB_s as the solid-phase, and human anti-HB_s ^{125}I as the radio-labelled antibody (Ausria II 125^R, Abbott Laboratories). Initially, 0.2 ml of test sera were incubated for 16 h at room temperature with the antibody-coated beads in plastic test wells. The wells and beads were aspirated to remove unreacted reagents and rinsed with 10 ml of distilled water using a semi-automatic rinsing and dispensing system (Pentawash, Abbott Laboratories). The beads were re-incubated with 0.2 ml of ^{125}I-labelled human anti-HB_s for 1 h at 45°C. Unbound radio-labelled antibody was aspirated and the test wells and beads were rinsed with 10 ml of distilled water. The beads were transferred to clean tubes and counted for 1 min in an automatic gamma-counter. A specimen whose reactivity on two separate determinations was at least 2.1 times that of the mean of 7 negative controls was considered to be reactive for HB_sAg.

Radioimmunoassay (RIA) for anti-HB_s

Seven hundred blood donors were tested for anti-HB_s by RIA, consisting of polystyrene beads coated with HB_sAg/*ad* and HB_sAg/*ay* as the solid phase and ^{125}I-HB_sAg as the radio-labelled antigen (Ausab™, Abbott Laboratories). The antigen-coated polystyrene beads were incubated initially with 0.2 ml of test serum in plastic test wells for 18 h at room temperature. Subsequently, the wells and beads were aspirated and rinsed with 10 ml of distilled water using the Pentawash dispensing system. The beads were re-incubated with 0.2 ml of ^{125}I-HB_sAg for 4 h at room temperature, followed by aspiration and a 10-ml rinsing with distilled water to remove excess radio-label. The beads were transferred to clean tubes and counted for 1 min in an automatic gamma-counter. Specimens whose reactivity on two separate determinations was at least 2.1 times that of the mean of 7 negative control specimens were further tested for specificity by incubation with an equal volume of standardized reagent HB_sAg (subtypes *ad* and *ay*). The specimens were considered to be specifically reactive for anti-HB_s if the reactivity of the test sera after incubation with HB_sAg was reduced by 50% or more, when compared with incubation of the test sera with HB_sAg-negative controls.

Counterimmunoelectrophoresis (CEP) for HB_sAg

All sera from blood donors were tested for HB_sAg by CEP using horse anti-HB_s and pre-punched agar gel plates (Austigen II™, Hyland Laboratories), as previously described (*6*). Sera were inactivated at 56°C for 15 min before electrophoresis. Precipitin lines were read at 15 min and 24 h after electrophoresis.

RESULTS

During the two-year study period, 1610 serum specimens from patients with suspected liver disease

Table 1. Routes of infection

Clinical data	Hepatitis B		Non-B hepatitis	
	No.	%	No.	%
Probable parenteral transmission				
blood transfusions	7		3	
parenteral drug use	6		3	
	13	31	6	5
Possible parenteral transmission				
dental care	3		4	
hospital or paramedical employment	3		2	
needle injection	1			
surgery	1			
	8	19	6	5
Probable non-parenteral transmission				
contact with jaundiced person	2		28	
travel in hyperendemic area	1		4	
no known contact	18		69	
	21	50	101	90
Total patients	42	100	113	100

Table 2. Comparison of type B and non-B hepatitis

Clinical data	Hepatitis B [a]	Non-B hepatitis [a]
Age (years)	25 (2/12–75)	21 (4–75)
Length of hospital stay (days)	24 (9–52)	10 (3–63)
Serum bilirubin [b] (mg/100 ml; [c] normal range 0–0.9)	12.0 (1.5–58.0)	8.4 (1.0–33.0)
Serum glutamic oxaloacetic transaminase [b] (milli-units/ml; normal range 20–50)	2360 (75–8720)	1460 (80–8000)
Serum cyanocobalamin [b] (pg/ml)	3000 (890–4000)	3000 (830–4000)

[a] Median value (range).
[b] Highest values measured during hospitalization.
[c] To convert to μmol/l, multiply by 1.71×10^{-2}.

were tested for HB_sAg. Of these unselected patients, 155 subsequently satisfied the clinical and laboratory criteria for the diagnosis of acute viral hepatitis.

Viral hepatitis type B

Forty-two (27%) of the 155 patients with acute viral hepatitis were reactive for HB_sAg by RIA and were therefore classified as having viral hepatitis type B. Thirteen patients (31%) with hepatitis B had histories consistent with parenteral transmission of viral hepatitis by blood transfusions or parenteral drug use (Table 1). Eight additional patients (19%) with hepatitis B had possibly been exposed parenterally during dental treatment, hospital employment, or medical care. All the blood components implicated in post-transfusion hepatitis B were obtained from volunteer donors and had been prescreened for HB_sAg by CEP, although not by RIA. Twenty-eight patients (67%) with hepatitis B were males and 14 (33%) were females. The median age of patients with hepatitis B was 27 years and there was a predominance of males in all age categories. Since the study population was selected on the basis of hospitalization for presumptive liver disease, it was to be expected that all patients with hepatitis B were overtly ill and had laboratory evidence of acute hepatic injury (Table 2). One of the 42 patients with hepatitis B died of hepatic coma. The 41 surviving patients with hepatitis B were discharged from hospital after a median of 24 days.

Non-B hepatitis

One hundred and thirteen patients (73%) with acute viral hepatitis whose sera were non-reactive for HB_sAg by RIA were diagnosed as having viral hepatitis, type unspecifiable ("non-B"), in conformity with the recently suggested nomenclature for patients in this clinical category without a specific serological diagnosis (*7*). Six of these patients (5%) had histories of blood transfusions or intravenous drug use during the previous 6 months and were considered to represent cases of probable parenterally transmitted non-B hepatitis (Table 1). An additional 6 patients (5%) had histories consistent with possible non-parenteral transmission of non-B hepatitis. Seventy-seven (68%) of the patients with non-B hepatitis were males and 36 (32%) were females. One of the 113 patients with non-B hepatitis died in hospital, and the remaining 112 patients were discharged from hospital after a median of 10 days. While there was considerable heterogeneity in the clinical courses of patients in both groups, the average (median) patient with non-B hepatitis was younger, was less jaundiced, and had a briefer hospital stay than his counterpart with hepatitis B (Table 2). Abnormally elevated serum cyanocobalamin levels (Table 2) correlated well with clinical evidence of acute hepatocellular injury in both type B and non-B hepatitis, confirming the previously described usefulness of this test as a sensitive and specific index of liver cell damage (*8*).

HB_sAg and anti-HB_s in blood donors

During the 24-month study period the prevalence of HB_sAg, determined by CEP, for healthy blood donors was 0.97% (39 reactive sera per 4039 volunteer blood donors) (Table 3). The prevalence of anti-

Table 3. Hepatitis B surface antigen (HB_sAg) and antibody to hepatitis B surface antigen (anti-HB_s) in blood donors

Test	No. tested	No. reactive	Prevalence (%)
HB_sAg	4039	39	0.97
Anti-HB_s	700	133	19.0

HB_s, determined by RIA, was 19.0% (133 reactive sera per 700 blood donors) (Table 3).

DISCUSSION

Specific serological diagnostic criteria for the etiological classification of acute viral hepatitis are essential for elucidating regional and worldwide epidemiological patterns and for planning immunization programmes (*1*). From other hospital-based surveys of acute viral hepatitis, it appears that in most non-endemic regions of Europe approximately 40–60% of patients admitted to hospital with acute viral hepatitis are diagnosed as having hepatitis B (*9–15*). In the USA an estimated 18–46% of all reported cases of viral hepatitis are of type B (*16*). In contrast, in Iraq (*17*), Egypt (*18*), India (*19*, *20*), and Ethiopia (*21*), where " infectious " hepatitis is known to be endemic, the majority of patients have non-B hepatitis and only 10–20% of patients hospitalized with acute viral hepatitis are diagnosed serologically as having hepatitis B. Our finding that only 27% of patients hospitalized with acute viral hepatitis had type B confirms the prevailing opinion (*2*, *4*) that endemic viral hepatitis in Jerusalem is predominantly " infectious ", i.e., non-B. A history of probable parenteral transmission of viral hepatitis was more common in patients with hepatitis B (31%) than in those with non-B hepatitis (5%) (Table 1). An additional 19% of the patients with hepatitis B had possible parenteral exposure and 50% had no obvious parenteral exposure, indicating that non-parenteral transmission of HBV may be a significant epidemiological factor (50–69%) in our community. High rates of non-parenteral transmission of HBV have been reported also from other parts of the world (*22–25*), where personal contact and intra-familial spread are considered to be the primary modes of non-parenteral transmission.

The majority of patients with acute viral hepatitis in the present study (73%) were non-reactive for HB_sAg and were therefore diagnosed as having non-B hepatitis (type unspecified). Each of these patients satisfied the conventional clinical and epidemiological criteria for the diagnosis of non-parenterally transmitted viral hepatitis type A. However, in the absence of a specific serological diagnosis of hepatitis A virus (HAV) infection, and in view of the unreliability of clinical and epidemiological data alone for establishing precise etiological diagnoses of viral hepatitis (*7*, *26–28*), we consider the suggested designation of these cases as " non-B " hepatitis (type unspecificable) (*7*) to be the most appropriate.

The prevalence of anti-HB_s in the hospital's volunteer blood donor population (19.0%) is higher than that reported for volunteer blood donors in the USA (3.5–14.4%) (*29–31*) and is considered to reflect subclinical HBV infection in our community. This finding is consistent with the known local endemicity of viral hepatitis, the apparently significant role of non-parenteral transmission of HBV, and the relatively high HB_sAg carrier rate (0.97%) in the Jerusalem area.

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RÉSUMÉ

HÉPATITES VIRALES DE TYPE B ET D'AUTRE ORIGINE À JÉRUSALEM

Entre 1973 et 1975, chez tous les malades admis à l'Hôpital de l'Université Hadassah à Jérusalem, et soupçonnés de présenter une affection hépatique, on a recherché l'antigène de surface de l'hépatite B (HB_sAg) afin d'étudier les aspects épidémiologiques et cliniques de l'hépatite B et de l'hépatite d'autre origine dans cette région. Sur 155 malades répondant aux critères cliniques et de laboratoire de l'hépatite virale aiguë, 42 (27%) étaient positifs en ce qui concerne HB_sAg et l'on a posé pour eux le diagnostic d'hépatite B; les 113 autres (73%) ont été considérés comme ayant une hépatite d'autre origine. Pour 13 (31%) des malades atteints d'hépatite B et 6 (5%) des malades ayant une hépatite d'autre origine, l'anamnèse était compatible avec une transmission parentérale de l'hépatite virale. Chez 8 autres sujets (19%) ayant une hépatite B, une exposition parentérale était possible et chez 21 (50%), il n'y avait pas d'indice net d'exposition parentérale, ce qui montre que la transmission non parentérale du virus de l'hépatite B (HBV) est un facteur épidémiologique important (50 à 69%) dans la région de Jérusalem. Le fait que la prévalence de HB_sAg (0,97%) et celle de l'anticorps anti-HB_s (19%) étaient relativement élevées chez les donneurs de sang en bonne santé constitue un autre indice du rôle important de la transmission non parentérale de l'infection à HBV. Ces résultats montrent que ce virus a un rôle considérable dans l'hépatite virale endémique dans cette région, et sont compatibles avec l'hypothèse selon laquelle la propagation intrafamiliale pourrait être un facteur notable dans l'épidémiologie du HBV.

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