

TABLE 1. Mammalian glucose transporters

Glucose transporter	Major sites of expression	K_m (mmol/L)	Proposed function
Active transport			
Sgt-1 (Na ⁺ -glucose cotransporter)	Small intestine, renal tubules	0.1-10	Active uptake of glucose
Facilitated diffusion			
Glut-1	Ubiquitous, but especially RBC, brain, HepG2 hepatoma cell line	1-2	Glucose uptake into cells
Glut-2	Liver, kidney, small intestine, and β cells of pancreas	15-20	Glucose homeostasis; likely mediates bidirectional transfer of glucose by hepatocytes
Glut-3	Many tissues, including brain	< 1	Unknown
Glut-4	Muscle and fat	~5	Insulin-responsive glucose uptake
Glut-5	Small intestine and kidney placenta, and kidney	1-2	Unknown
Glut-6	mRNA nontranslatable into a functional protein		Pseudogene

glut-1 was expressed only in one or two rows of hepatocytes surrounding the hepatic venule. Fasting for 3 days resulted in an increment in the levels of glut-1 apoprotein and messenger RNA (mRNA), whereas no major changes were observed in the levels of glut-2. Furthermore, the area of hepatocytes expressing glut-1 expanded to about three to five rows of cells surrounding the hepatic venule. Glucose administration and refeeding of the fasted rats resulted in a decrease in the number of hepatocytes expressing glut-1 to a control pattern. However, the concomitant administration of glucose and food in this study does not allow one to define the role of glucose in regulating the expression of glut-1 in acinar hepatocytes.

Various aspects of this paper are of considerable interest. The restricted expression of glut-1 to a few hepatocytes surrounding the hepatic venule provides an explanation for previous observations by various groups (3, 4) of low levels of expression of this transporter in the liver. In rat liver, mRNA levels of glut-1 represent about 1% to 3% of the mRNA levels of the glut-2 transporter (2). The restricted expression of glut-1 also reinforces the proposal that the one to two rows of hepatocytes surrounding the hepatic venule represent a different state of differentiation of liver cells. It should be remembered that glutamine synthetase is also exclusively expressed in these hepatocytes (5). Therefore these genes may represent suitable models for the study of the regulation of hepatocyte-specific gene expression. Finally, the presence in all hepatocytes of glut-2 with a K_m for glucose of 15 to 20 mmol/L points to a major role for this transporter in the bidirectional transport and regulation of glucose within the hepatic acinus. Furthermore, the location in the last two hepatocytes of a glucose transporter, glut-1, with a low K_m for glucose, and thus functioning under conditions of saturation, suggests that the role of this transporter may not be the regulation of the levels of glucose reaching the systemic circulation. In contrast to glutamine synthetase, this transporter may not act in a scavenger role. Rather, the

presence of this transporter at that location may indicate the need for glucose of those cells, suggesting that "the last hepatocyte" may survive in a very different metabolic state than more proximal hepatocytes.

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POTENTIAL IMPORTANCE OF THE SEXUAL TRANSMISSION OF NON-A, NON-B HEPATITIS

Alter MJ, Coleman PJ, Alexander WJ, Kramer E, Miller JK, Mandel E, Hadler SC, et al. Importance of heterosexual activity in the transmission of hepatitis B and non-A, non-B hepatitis. *JAMA* 1989;262:1201-1205.

ABSTRACT

To identify previously unrecognized sources for acquiring acute hepatitis B and non-A, non-B (NANB) hepatitis, we interviewed patients with these types of

hepatitis who were reported to two county health departments in the United States and matched control subjects for known and potential risk factors for acquiring hepatitis. Of 218 patients with hepatitis B and 140 patients with NANB hepatitis, 46% and 53%, respectively, had no commonly recognized source for infection. When these patients were compared with control subjects, significantly more patients with hepatitis B had multiple heterosexual partners, accounting for 14% of all hepatitis B infections; more patients with NANB hepatitis either had sexual or household contact with a person who had hepatitis in the past or had multiple heterosexual partners, accounting for 11% of all NANB infections. This is the first study to suggest that heterosexual transmission may play an important role in the spread of NANB hepatitis.

COMMENTS

Data from a nationwide surveillance of acute cases of hepatitis B and non-A, non-B (NANB) hepatitis reveal that commonly recognized risk factors only account for 50% to 60% of reported cases (1). Whereas sexual transmission of HBV has been well documented (2, 3), the role of person-to-person contact of NANB hepatitis has not been well defined, and sexual activity has not appeared to play an important role in the transmission of this type of hepatitis. It was the intention of the authors of this paper, therefore, to explore possible sources of infection for the large number of cases without identifiable risk factors and to evaluate the relative importance of sexual transmission for both disorders. To do this, all patients with acute viral hepatitis who were reported to two county health departments (Jefferson County, Birmingham, AL, and Tacoma-Pierce County, Tacoma, WA) were identified over a 12-mo period (March 1985 to February 1986). Standard serological criteria were applied to the diagnosis of acute hepatitis B (presence of IgM anti-HBc) and acute NANB hepatitis (absence of IgM anti-hepatitis A virus and IgM anti-HBc). Each patient was interviewed to identify both known and potential risk factors for either type of hepatitis during the preceding 6 mo. Patients with hepatitis B were considered to have a known source of infection if they had a history of blood transfusion; intravenous drug abuse; male homosexual activity; health care employment with frequent contact with blood; hemodialysis; or sexual or household contact with a hepatitis B case or carrier. Patients with NANB hepatitis were considered to have a known source of infection if they had a history of blood transfusion or intravenous drug use. For each patient who had no known source for acquiring hepatitis, two matched, noninfected control subjects were studied by use of the same questionnaire. An attempt was made to determine the prevalence of serological markers for viral hepatitis in household and sexual contacts of cases and in the control group.

During the 12-mo period of enrollment, 218 patients with hepatitis B and 140 patients with NANB hepatitis were located and interviewed. These individuals consti-

tuted approximately 90% of the total number of hepatitis B and NANB hepatitis cases reported to the Centers for Disease Control (CDC) during the study period. One hundred and eighteen of the hepatitis B patients (54%) reported a known source: intravenous drug use (26%), male homosexual activity (11%), heterosexual (9%) and household contact (4%) with a hepatitis B case or carrier, blood transfusion (2%), health care employment (2%) and hemodialysis (0.5%). Only age greater than 40 yr and black race were significantly associated with hepatitis B in the 100 cases with no known source of exposure. Controls were available for 76 of these 100 cases. Using a logistic regression analysis, the only factors that occurred significantly more frequently in the cases vs. controls were heterosexual activity with more than one sexual partner and history of unemployment. When heterosexual activity with multiple partners was applied as a risk factor to the original population of 218 patients, it accounted for an additional 14% of infections. The prevalence of serological markers indicating previous (but not recent) infection with HBV in the household and sexual contacts of hepatitis B cases was 20% vs. 9% for the control group.

In contrast to these results, 66 (47%) of the NANB cases reported a known source: blood transfusion (13%) and intravenous drug use (34%). The 74 cases with no known source of infection were more likely to be black women. Controls were available for 52 (70%) of the 74 patients without a known source of exposure. By logistic regression, the only factors that occurred significantly more frequently in this population when compared with controls were fewer years of education (threefold greater risk) and heterosexual activity with more than two sexual partners in the preceding 6 mo (11-fold greater risk). When household or sexual contact and heterosexual activity with multiple partners were applied as risk factors to the original population of 140 patients with NANB hepatitis, they accounted for an additional 11% of infections.

Hepatitis B and NANB hepatitis are similar epidemiologically, and certain high-risk situations such as intravenous drug use are particularly likely to result in infection with both viruses (4). It follows, therefore, that other behaviors associated with the acquisition of hepatitis B, such as sexual activity with multiple partners, should be associated with acquiring NANB hepatitis. At this time, however, evidence varies as to whether sexual contact is an important mode of transmission. Perhaps the strongest evidence for a limited risk from sexual transmission of NANB hepatitis is found in a large prospective study evaluating hepatitis B vaccine in homosexual men (5). In that study, the annual attack rate for NANB hepatitis was 2% among vaccine recipients and 1% among placebo recipients compared with an adjusted annual attack rate for HBV infection of 12% among placebo recipients. Further evidence against sexual transmission of NANB hepatitis comes from a recently published study by investigators at the National Institutes of Health (6). In this study, 5 of 42 sexual contacts of 44 index patients with chronic NANB

hepatitis were noted to have elevated ALT levels. However, all of the sexual contacts had elevated values on only one occasion, and in two instances minimal elevations were noted that could be attributed to potential hepatotoxins. Importantly, whereas 40 of the 44 index patients had antibody to hepatitis C virus (anti-HCV), none of the 62 household contacts, including the small group of sexual contacts with elevated ALT values, were positive for anti-HCV.

The study by Alter et al. at the CDC presents a different view of the relative importance of sexual transmission of NANB hepatitis. The authors conclude that heterosexual contact plays an important role in the spread of hepatitis B and NANB infection, accounting for 14% of all hepatitis B infections and 11% of the NANB cases in their study population. One should be cautious in extrapolating these results to all heterosexuals, however, because the frequency of sexual activity and the type of sexual behavior is likely to have a substantial effect on the transmission rates for both infections (2). This is supported by the findings of a recent study from Germany in which anti-HCV was demonstrated in 4.7% of 191 heterosexuals attending a clinic for sexually transmitted diseases compared with a prevalence of 0.51% in 390 blood donors (7). In the CDC study a greater risk of acquiring NANB hepatitis was associated with heterosexual activity with *more than two* sexual partners in the preceding 6 mo. Alter et al. did not define the average number of sexual partners during this time nor the prevalence of sexually transmitted diseases in their hepatitis cases. Thus the relationship between the level of heterosexual activity and the risk of acquiring NANB hepatitis could not be defined.

Because sexual transmission of blood-borne viruses generally is recognized to be more efficient between homosexual men when compared with heterosexual men and women and because homosexual men are a group at high risk of hepatitis B, it is not immediately evident why homosexual orientation was not identified as a risk factor for NANB hepatitis in the paper by Alter et al. Furthermore, the results of the CDC study differ with those of a recently reported study from Spain in which 8% of homosexual men were positive for anti-HCV compared with 1.2% of healthy pregnant women and 0% of random blood donors (8). Although not specifically commented on by Alter et al., the lack of an association between homosexual orientation and NANB hepatitis may have been substantially influenced during the period of the study by greater adherence to the practice of "safe" sex and avoidance of high-risk sexual behavior to prevent human immunodeficiency virus infection. Indirect support for this assertion is derived in a separate report from the CDC that describes the changing pattern of hepatitis B infection in various populations in the counties studied (including the two counties described in the present study) (9). In this report a decline in the number of reported cases of hepatitis B was observed in homosexual men (20% of reported cases in 1985 and 9% in 1986), and an increase in the number of reported cases was demonstrated in

heterosexual men and women (19% in 1985 and 26% in 1986).

How, then, are we to interpret the data on sexual transmission of NANB hepatitis? I believe that when the existing data are taken together one may reasonably conclude that sexual transmission of NANB hepatitis does occur. However, the infection is inefficiently spread in this manner and occurs at a much lower frequency than with hepatitis B. The relatively low prevalence of anti-HCV in homosexual men stands in marked contrast to the high prevalence (50% to 60%) of serological markers for past or active hepatitis B in this population (10). The most plausible explanation for this discrepancy in the frequency of sexual transmission is that this is caused by a marked difference in viral levels in the body fluids of the two infections. The results of chimpanzee inoculation experiments suggest that 10^2 to 10^4 viral particles/ml of blood are generally found in chronic NANB infection (11), whereas it is known that the corresponding number in chronic hepatitis B may be as high as 10^7 to 10^8 complete, infective particles. It is known that HBV DNA and HBeAg-positive carriers of HBsAg are more infectious for their sexual contacts and other household contacts (3). In the future, detection of HCV RNA by polymerase chain reaction using primers specific for the nucleocapsid or other structural regions of the virus may identify those hepatitis C carriers who are significantly more likely to transmit infection to their intimate contacts. Although it is difficult to be sure that the results of the study by Alter et al. apply to all heterosexual and homosexual behavior, it is, nonetheless, an important paper because it raises our awareness of the potential importance of sexual transmission of NANB hepatitis. It provides the best evidence to date that a proportion of so-called "sporadic" cases of this infection are due to person-to-person transmission.

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THYROXINE-BINDING GLOBULIN, HYPERTHYROXINEMIA AND HEPATOCELLULAR CARCINOMA

Huang M-J, Liaw Y-F. Thyroxine-binding globulin in patients with chronic hepatitis B virus infection: different implications in hepatitis and hepatocellular carcinoma. *Am J Gastroenterol* 1990;85:281-284.

ABSTRACT

To determine serum thyroxine-binding globulin (TBG) levels, we used radioimmunoassay, and compared the results obtained with other tests in 231 patients with chronic hepatitis B virus infection to evaluate its clinical implications. All of these patients were hepatitis B surface antigen (HBsAg)-positive. Among them, 38 patients had hepatocellular carcinoma (HCC), 18 had chronic persistent hepatitis, 70 had chronic lobular or active hepatitis (grouped as CAH), 31 had active cirrhosis (AC), 25 had inactive cirrhosis, 20 had decompensated cirrhosis, and 29 were "healthy" HBsAg carriers. Twenty-seven patients with acute hepatitis, 12 with cancer metastasis to the liver, and 81 normal adults served as disease or normal controls. The results showed that serum TBG level increased significantly in patients with CAH, AC, or HCC. Serum TBG did not correlate with albumin or bilirubin level, but correlated with alanine aminotransferase (ALT) positively in patients with CAH ($p < 0.001$) and negatively in patients with HCC ($p < 0.01$) (slope difference $p < 0.05$). Serial determination of serum TBG and ALT also showed parallel changes in 15 patients with CAH, but not in nine patients with HCC. In contrast, the fall and rise of serum TBG levels in patients with HCC coincided with tumor resection and recurrence. The data suggest that serum TBG elevation in patients with hepatitis activity is the result of hepatocellular damage, whereas that in patients with HCC is due to increased synthesis. Whether serum TBG elevation without concomitant rise of ALT could be used as a marker of HCC awaits further study.

COMMENTS

The article under comment focuses attention on the relevance in HCC of thyroxine-binding globulin (TBG), the major transport protein of thyroxine (T_4) in human plasma. In addition, a recent case report describes a

patient with HCC in whom greatly raised serum T_4 levels were responsible for weight loss and weakness that had been attributed initially to hyperthyroidism (1). The patient was, however, euthyroid clinically, and hyperthyroidism was excluded by the finding of a normal-free T_4 index and a low triiodothyronine (T_3) resin uptake and 24-hr ^{131}I uptake by the thyroid gland. The serum level of thyroid-stimulating hormone (TSH) was normal. A high concentration of TBG was measured in the patient's serum, and the euthyroid hyperthyroxinemia was ascribed to increased binding of T_4 to this protein.

When larger numbers of patients with HCC are studied, it becomes evident that raised serum T_4 concentrations are not uncommon. Seven of 39 of our patients (18%) (2) had a raised level, as did 22% (12 of 59) of those of Alexopoulos et al. (3). These patients, too, were euthyroid clinically and had normal-free T_4 indices, low T_3 resin uptakes, normal serum TSH concentrations and raised serum TBG levels. Although the cause of the high serum concentration of TBG in patients with HCC has not been established with certainty, the protein is almost certainly synthesized and secreted by the malignant hepatocytes (2). TBG is normally derived from hepatocytes (4), and HCC cells growing in tissue culture have been shown to produce the globulin (5). Apart from HCC, other causes of increased hepatic secretion of TBG are congenital, increased serum estrogen levels and various forms of benign hepatic disease (6). A high circulating level of the binding protein is the most common explanation for euthyroid hyperthyroxinemia. The number of patients with increased TBG values in our series (2) and that of Alexopoulos et al. (3) was 17 (44%) and 15 (25%), respectively. Thus T_4 levels are less often raised in patients with HCC and elevated serum TBG levels than would be expected. A probable explanation for this phenomenon is suggested by the finding of a reduced mean T_4 TBG ratio in such patients (2), indicating a lesser affinity of binding of T_4 to the TBG produced by malignant hepatocytes.

Ironically, in the only reported situation of a patient with both HCC and hyperthyroidism, although the serum TBG concentration was elevated, free T_4 and T_3 levels were increased, and circulating levels of TSH were inappropriately raised (7). The hyperthyroidism was attributed to ectopic synthesis by the tumor of a substance that stimulated the release of TSH from the pituitary gland.

Huang and Liaw found that 71% of 38 patients with HCC had raised serum TBG levels. With this prevalence, and the 69% reported by Terui et al. (8), it has, not surprisingly, been suggested that TBG be used as a serum marker for this tumor. In other published series, however, lower prevalences—25% (3), 32% (9) and 44% (2)—were recorded. Thus the sensitivity of TBG as a marker for HCC falls far short of that of α -fetoprotein and of other tumor markers such as des- γ -carboxy prothrombin and tumor-specific isoenzymes of γ -glutamyltransferase. Moreover, increased serum concentrations of TBG often occur in a variety