SHORT COMMUNICATION

Gender Disparity in Infections of Hepatitis B Virus

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ABSTRACT

Gender differences prevail in the infections caused by the Hepatitis B virus. Four hundred and seventy two patients with HBV infection were selected for the study. The frequency of hepatic infection in males was 79.5% (n=375) and in females 20.5% (n=97), with a male to female ratio of 3.8:1. Out of 472 patients, 49% had acute hepatitis, 26% were carriers, 18% had chronic hepatitis, 6% had cirrhosis and 3% patients had hepatocellular carcinoma. Male dominance was found to be consistent in all categories of patients. When the patients were divided into groups according to age, the male to female ratio increased during the reproductive years. There may be an influence of estrogen in the protection and defense of hepatic cells against the development of chronic liver disease.

Key words: *Hepatitis. Liver diseases. Hepatitis B virus. Gender.*

Clinical studies around the world support the view that chronic hepatitis B appears to progress more rapidly in males than in females. It has been observed that with the exception of autoimmune liver diseases, cirrhosis and HCC are predominately diseases that tend to occur in men and postmenopausal women. The hepatitis B virus has been extensively studied, but the mechanisms of chronicity and pathogenicity in liver and extra hepatic tissue is still poorly understood, as the regulation of gene expression. HBV is transmitted by prenatal, parenteral, and sexual routes. Fifteen to 40% of chronically infected people may develop cirrhosis and hepatocellular carcinoma (HCC).[1] The remaining individuals become inactive carriers, otherwise defined as asymptomatic or healthy carriers. In general, evaluating the risk factors in Pakistan, we find that men are exposed to infected razors and syringes. However, they have greater opportunities for seeking medical help. Compared to men, women are more exposed to syringes, blood and blood products, especially during pregnancy and delivery and piercing of nose and ear and thus run higher risk of infections such as HBV, HCV and HIV.

Serum samples, were randomly collected after taking informed consent from 500 patients attending Ziauddin University Hospital (ZUH) and Pakistan Medical Research Council (PMRC) where they were undergoing treatment for various hepatic conditions due to HBV infection. Prior to this, the approval of the Ziauddin University ethical review committee was obtained. All patients were HBsAg positive as diagnosed by ELISA (MUREX kit by Abbott Laboratories). Data was compiled from patients with HBV-related liver disease such as acute, chronic, cirrhosis and HCC.

To evaluate the dominance of gender in HBV related hepatic infection, the data was further divided into groups according to age. Data analysis was done on SPSS version 10. Frequency and percentages were used to obtain relevant descriptive statistics for qualitative variables in different age groups of either gender.

Out of 500 patients, 472 were finalized. Patient characteristics included the incidence of hepatic infection in 79.5% males (375/472) and in 20.5% females (97/472) with an overall male to female ratio of 3.8:1. Out of 472 patients, 233(49%) had acute hepatitis 122 (26%) were HBV carriers, 86 (18%) had chronic hepatitis, 27 (6%) had cirrhosis and 14 (3%) patients had HCC. Male dominance was found consistently in all categories of patients.

The evaluation of the dominance of male gender on the basis of the ratio of different age groups, showed that the male to female ratio was maximum (7.1:1), between the ages of 36-40 years. The ratio was minimum at the age of 51 years and above, and under 15 years (Table I).

Table I: The frequency of hepatitis B in males and females and ratio of occurrence according to age.

Ages (years)	Female n=97 20.5%	Male n=375 79.5	Ratio Male:Female 3.8:1	Total n=472
Under 15	11 (11.3%)	26 (6.9%)	2.4:1	37 (7.8%)
16-20	17 (17.5%)	48 (12.8%)	2.8:1	65 (13.8%)
21-25	16 (16.5%)	61 (16.3%)	3.8:1	77 (16.3%)
26-30	14 (14.4%)	55 (14.7%)	3.9:1	69 (14.6%)
31-35	9 (9.3%)	57 (15.2%)	6.3:1	66 (14.0%)
36-40	7 (7.2%)	50 (13.3%)	7.1:1	57 (12.1%)
41-50	11 (11.3%)	48 (12.8%)	4.4:1	59 (12.5%)
51-above	12 (12.4%)	30 (8.0%)	2.5:1	42 (8.9%)

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It was observed that the overall male to female ratio was approximately 4:1, but the difference in ratio widened to approximately 7:1 when evaluation was done separating the reproductive age group from the younger (under 15 years) group (2.4:1) and the menopausal (51 years and above) group (2.5:1) (Figure 1). These results are in accordance with a Japanese study in which male-to-female ratio was examined in patients with HBV associated HCC.[2] When the subjects were divided into different age groups, as younger or older than the menopausal age of 50 years, the younger group had only 10.5% females compared to 32.8%, in the older group. The fact that HCC is more prevalent in men than in women suggests that estrogen may play an important role in the development of HCC. It was observed that variant estrogen receptors (ER) were expressed more in male patients than in female HCC patients. This leads to loss of estrogen responsiveness thus making cirrhosis largely a disease of men and postmenopausal women, with the exception of autoimmune liver diseases.[3]

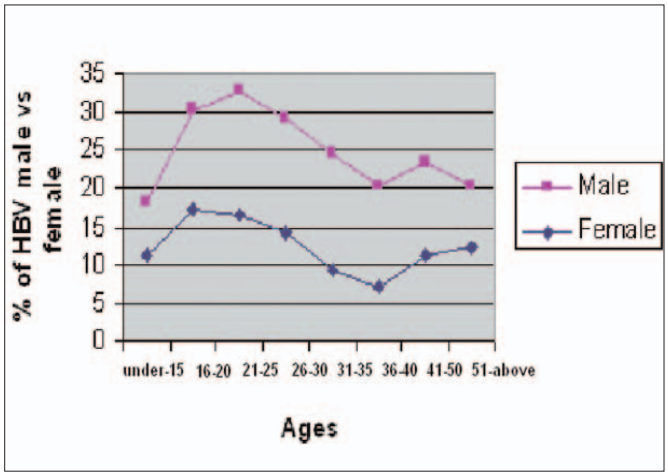

Figure 1: The frequency of hepatitis B in males and females.

Estrogen exerts its function through its two nuclear receptors, estrogen receptor and ß (ER and ERß). Activation of ERs is responsible for many biological processes, including cell growth, differentiation and apoptosis. Estrogen receptors are expressed in the liver of both healthy individuals and patients with HCC, with no difference in the pattern of expression. The mutant form with the entire exon 5 deleted (ER5) is preferentially expressed in patients with HCC compared with patients with normal livers.[4] The presence of the liver ER5 transcript also correlates with a higher clinical aggressiveness of the tumor in comparison with tumors characterized by wild-type ER (wt ER) transcript. ER5 encodes the hormone-independent AF-1 domain, as well as the DNA Binding Domain (DBD). The role of ER5 in ER signaling is still unknown. It can be hypothesized that HBx inhibits ER signaling through manipulation of ER signaling, possibly through recruitment of histone deacetylase 1 (HDAC1).

The risk factors for males with hepatic fibrosis include gender and age > 50 years, as important for HCC development.[4] Conversely, premenopausal women, without the risk factors of male gender and older age, are least vulnerable to HCC.

A study on experimentally induced carcinomas demonstrated the suppressive effect of estradiol on chemical hepatocarcinogenesis induced by dimethylnitrosamine (DEN)-2-acetylaminofluorene (AAF)-partial hepatectomy (PH) and thus occur at a higher rate in male rats and mice.[5] Estrogen regulates IFN-γ-inducible Interferon regulatory factor-1 (IRF-1), an important transcription factor that mediates interferon- (IFN-γ)-induced cell-signaling events in lymphoid cells.[6] IFN-γ is a potent cytokine with immunomodulatory and antiproliferative properties. Therefore, female subjects, particularly before menopause, may produce antibodies against HBeAg and HBsAg at a higher frequency than males with chronic HBV infection.

Furthermore, estradiol has also been reported to inhibit reactive oxygen species (ROS) generation and antioxidant enzyme loss via the suppression of NADH/NADPH oxidase activity. This blocks hydrogen peroxide-induced TGF-γ expression, activation of AP-1 and NF-κB, and proliferation and transformation of cultured rat hepatic stellate cells (HSCs). Thus, by suppressing NADH/NADPH oxidase activity, estradiol prevents the autocrine loop of ROS and TGF-β by HSCs as well as HSC activation, besides exerting a cytoprotective effect against hepatocyte injury.[7] These lines of evidence required further investigation of the relationship of estrogen with interleukin-6. Estrogen in female mice suppressed inflammation and decreased liver injury and excessive cell proliferation, resulting from dimethylnitrosamine (DEN) exposure that can lead to liver tumors. When researchers removed IL-6 or estrogen from female mice, their liver cancer rates were equal to that of male mice.[8]

These lines of evidence suggest that the greater progression of hepatic fibrosis and HCC in men and postmenopausal women may be due, at least in part, to the lower production of estradiol and a reduced response to the action of estradiol.

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