

HEALTH CARE WORKERS AND HEPATITIS B

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INTRODUCTION

In the pre-vaccination era transmission of hepatitis B virus (HBV) in medical settings was a severe public health problem. A high rate of infections of health care workers (HCW) with HBV was observed and 5-10 % of the infected subjects usually became chronic HBV carriers. HBV transmission was especially frequent in areas with direct contacts to blood such as surgery, hemodialysis units, or oncology wards. In contrast to hepatitis C, transmission of HBV from patient to HCW can be prevented by vaccination. Therefore, the number of HBV infections of HCW dropped significantly during the last 20 years (17). This sustained decline in the incidence of hepatitis B among persons with occupational exposure can be attributed hepatitis B vaccination of HCWs (19), graduates of medical school (7), and emergency medical technicians (18). Introduction of a series of measures to prevent exposure to HBV in addition contributed to the reduction of the rate of HBV infections (2). As a result, the incidence of HBV infection among HCWs is now lower than among the general population (11, 16). As more than 95% of vaccinees develop protective antibodies, the risk of vaccinated HCW to acquire HBV during their professional activities is minimal. However, not all HCW are vaccinated or are responders to vaccine and, therefore, are at risk to acquire HBV infection. In Germany each year about 60 HCW who acquired hepatitis B by exposure at work are registered by the health care insurance.

HCW, who became HBV carriers due to infection in early childhood or exposure during their career prior to the beginning of HBV vaccination, represent a potential risk for their patients (24). Hasselhorn and Hoffmann reviewed number of accidents in which HCW, predominantly medical doctors, had infected 404 patients (13). Similar findings are reported by Koziol et al. (16). A most recent, unpublished transmission study in Germany showed that this is an ongoing problem. Thus, one HBV positive surgeon infected more than 100 patients with HBV during an 8 year period. To estimate the magnitude of the problem we calculated the number of HBV carriers among medical doctors in Germany. Assuming the prevalence of HBsAg in the German population of 0.6 % (35) we have to expect about 1800 HBsAg carriers among 290000 medical doctors in Germany. In the subgroup of surgeons (n=16,000) or gynaecologists (n=15,000) the number of carriers would be about 100. This number will gradually decrease over time due to systematic vaccinations of medical students. Nevertheless, there is an urgent need to formulate the recommendations on our attitude to the HBV positive HCWs (24). In this paper the residual risk of transmission of HBV from HCW to the patients will be discussed.

Determination of Infectivity

The transmission rate of HBV is directly correlated with the viral titer in the blood, blood products, or body fluids. High viremia is also correlated to HBe antigen positivity in patients. It has been known since many years that the risk of a virus transmission from HBe- antigen positive mothers (HBV titres of 10^8 to 10^9) to their offspring is more than 95%, while the transmission rate from anti-HBe positive mothers (HBV titres of 10^3 to 10^5) is less than 25 %. As there is no good tissue culture system for HBV to determine the infectivity of serum or body fluids, the only way to establish the HBV titer of a given inoculum is the experimental infection of chimpanzees with the serial dilutions of the virus-containing material. A number of such studies have been performed in the 70's (32). The infection after intravenous inoculation of these animals was determined by seroconversion to anti-HBc/anti-HBs. HBV/HBeAg positive sera demonstrated HBV titers up to 10^8 chimpanzee infection doses per ml (CID50). In contrast, the virus titers in pools of anti-HBe positive sera usually did not exceed 10^1 per ml (32).

Soon after the introduction of highly sensitive techniques for identification of HBV DNA it has been shown that the virus genome titre determined by hybridisation or quantitative PCR corresponds quite well to the infectivity titre in chimpanzees (36). In these studies the CID50 was one log less than the titre of viral DNA determined by quantitative PCR. In view of the existence of e-minus mutants, negative results for HBeAg in a given HCW are not sufficient to exclude the high infectivity of his serum. According to some observations, the plasma of several patients with HBe minus mutants may contain rather high titres of HBV (12). Many isolates of HBV genotype G, which is most prevalent in mediterranean countries, are unable to express HBeAg (15). Thus, in addition of determination of HBeAg, an assessment of HBV DNA titers in serum or plasma by quantitative assays was suggested to be used as a possible indicator of infectivity.

Methods for Quantitative Determination of HBV DNA

Quantitative determination of HBV DNA levels in peripheral blood has been increasingly used during the last few years to monitor the efficacy of the antiviral therapy. An objective measure of virus load is also of paramount importance for a prediction of a likelihood of viral transmission from an infected individual. A number of techniques for HBV DNA quantification are being used nowadays, including the Quantiplex HBV DNA Assay (bDNA) (Chiron), the Amplicor HBV Monitor Test (Roche), and the Digene Hybrid Capture System HBV DNA Assay (Digene) (4, 21). At present, the Roche Monitor test is the only assay to maintain the linear detectability below 10^5 copies per ml and, therefore, is most suited for investigation of individuals of lower infectivity (10). One should mention, however, the necessity of at least duplicate testing of all probes. Several trials were organized by WHO to evaluate performance of HBV DNA quantification in different labs. A good correlation of determined genome equivalents and a high sensitivity in the majority of participants was observed (29-31).

Proof of Transmission

Transmission of HBV by HCW to patients is not only a public health or insurance problem but also a legal issue. Therefore the proof of HBV transmission from HCW to a patient should be unequivocal. There are many ways of acquiring hepatitis B like mother-child transmission, sexual contacts, family contacts, i.v. drug use, and blood units (11). These modes of transmission have to be excluded in the investigation of HCW-Patient-transmission. Transmission can be proven by direct comparison of the sequence of the HBV genome of the HCW and the recipient patient. Typing of genomes obtained from HCW and patient is a first step in the verification of transmission (23). Different genotypes make a transmission highly unlikely. Genotype A is most prevalent in Northern Europe therefore sequencing of HBV isolates has to be performed in most instances. There is a high probability of transmission when an identical sequence is found in the HCW and the patient. However, sequencing of short fragments of genomes of HBV after PCR amplification is not always sufficient e.g. core region (20) or S gene (37) to determine identity of isolate of HCW and recipient. Uy et al. have shown that the preS1 sequence of genotype A was identical in four of seven instances of a presumed transmission in Northern German patients (37).

The best proof of identity of different isolates is obtained by sequencing the full length genomes (5, 22, 33). However, in some instances e.g. low viremia only parts of the genome can be amplified and sequenced. The optimal region to do subgenomic sequencing remains to be determined. In addition to the isolates from the HCW and the patient several isolates from the same area have to be determined to exclude other routes of transmission.

The S-region is optimal to determine the genotype and in some instances reveals nucleotide exchanges peculiar to the investigated case. However, due to the high conservation of the HBs sequence in a given geographic region identical fragments can often be found in presumed recipients of HBV in an infection chain and uninvolved patients that had no contact with the source (37). In contrast, the preC region is less stable during chronic infection and can accumulate abundant and rare variants in an infection source. Thus, if the abundant variant is transmitted to the recipient, the identification of the infection chain is facilitated due to higher likeliness of peculiar exchanges in this region. However, if the variant which is less abundant in the source is transmitted, a proof of transmission can be extremely difficult because of the difficulties in detecting the low abundant variant in a large majority of wild type or other variants (20). The proof that sequence identity indicates high probability of a specific transmission is illustrated by a transmission event in which a surgeon infected most probably over 100 patients during a period of seven years (Ritter et al., unpublished results), nine patients became chronic HBV carriers. Eight of these nine patients were chronically infected with HBV of genotype D and of identical sequence (s-gene) when compared to the isolate from the surgeon (S. Schaefer, personal communication). This sequence was detected only once by comparing it to 450 HBV genomes present in the gene bank. The probability that all eight patients had by chance the identical sequence but are infected from different sources is extremely low. In addition, this case demonstrates that the

probability of a false correlation decreases with the number of patients being infected by the same HCW.

Determination of the Risk to Transmit HBV in Medical Setting

There are several determinants of risk of HBV transmission from HCW to patients during invasive surgical procedures: prevalence of HBV positivity in medical staff, frequency of percutaneous injuries, frequency of a sharp object's recontact with susceptible patients, and frequency of HBV transmission after exposure e.g. by needle stick injuries. The risk estimate for HBV in this model including all four determinants is 2400 transmission of HBV per 1 million of surgical procedures (1). For comparison, the corresponding risks for hepatitis C is about 140 per million (26, 27) and for HIV, is about 24 per million (1) of surgical procedures. In this calculation the influence of differences in surgeons HBV titres was not considered, although this factor should also play an important role and should have evident impact on the rate of HBV transmission. Overall, the available estimates indicate that the risk of transmission of the virus from infected medical personnel to patients is much higher for HBV than for HCV or HIV.

Indication for Look Back Investigations in a Suspected Transmission Event

When patients develop acute hepatitis after blood transfusion a look back investigation is usually initiated as a standard procedure. The same approach probably should be employed when a patient developed acute hepatitis after hospitalisation (with or without surgery) or after treatment in a private practice. The initiation of a look back study depends very much on the physician treating the patient during acute hepatitis B. The predominant risk factors for HBV infection nowadays are heterosexual and homosexual exposure and i.v. drug use which accounts for 80.8 % of cases when a risk factor could be identified (11). If all these risk factors have been excluded, a look back should be initiated. The look back should include testing for markers of a HBV infection of all HCW of a given hospital and other patients who have been treated approximately at the same time and at the same ward where the index patient has been treated. Amplification and sequencing of the HBV isolates obtained from patients and HCWs has to be performed (see above). In contrast to hepatitis C, where more than 70 % of patients develop a chronic HCV infection, in HBV transmission only 5 to 10 % of infected subjects develop persistent viremia. This makes it sometimes difficult to prove a transmission of HBV from HCW to a patient when the look back starts month or even years after exposure and no samples have been taken during acute phase of the patient infection. In those instances epidemiological data have to be taken in consideration to provide evidence for the possible occurrence of a transmission event. However, the results of such epidemiological investigations can not be considered as unequivocal proof of transmission. The likelihood of transmission is high when the incubation period between exposure and appearance of clinical symptoms is in the right time frame, when several patients who have been operated by the same HBV positive surgeon at the same operating theatre were involved, when the surgeon was highly viremic and HBeAg positive, and when he has done exposure prone surgery. Other sources of infection with HBV in this patient e.g. HBsAg positive family members, history of a blood transfusion, i.v. drug use, sexual contacts with infected subjects, have to be also investigated and excluded.

Recommendations

Public health authorities of different countries have established recommendations for HBV positive HCWs (e.g. CDC (3), England (8), Germany (6), Netherlands). There is a general consensus that HBeAg-positive HBV carriers should not perform exposure prone surgery or similar treatment of patients. It has been shown that all cases in which transmission of HBV occurred, the titre of HBV was $\geq 10^7$ genome equivalents (34). The only one exception has been reported from England (8). These results prompted the British authorities to establish recommendations which exclude surgeons who have HBV titres $>10^3$ from performing a spectra of medical procedures. In the Netherlands 10^5 genome equivalence have been chosen as a limit (H. Zaaijer, personal communications). In Germany and other European countries no final decision on this important issue has been reached.

Therapy of Chronic Hepatitis B in HCW

Two major forms of therapy for chronic hepatitis B, interferon-alpha or antiviral drugs like nucleoside analogues, have been established. This therapy can dramatically reduce a viral load by several logs. HCWs who are high level carriers of HBV without symptoms of chronic hepatitis may be included in therapy studies with interferon-alpha or nucleoside analogues e.g. Lamivudine to reduce viremia or even eliminate HBV. One major problem with nucleoside analogues treatment is a high frequency of YMDD mutants in the polymerase gene which occur in about 30 % of patients one year after treatment. Therefore, frequent quantification of HBV DNA least two or three quantifications per year in HCW has to be performed to

exclude mutations and rise of viral titre. and to prevent a risk for patients.

Prevention

Transmission of HBV from HCW to patient can be prevented first of all by vaccination and control of their immunity. Neglect of hygienic measures to prevent exposure to HBV/HCV is still a source of transmission (28, 38). Therefore these measurements have to be enforced in the education of HCW. HBV carriers among HCW have to be identified by testing all staff members of a hospital or private practice and medical students when they enter medical school, prior to start of work. HCWs that are not vaccinated or are non responders to vaccine should be frequently tested for possible infection during their career. HBeAg-positive HBV carriers should be recommended not to start a career in the health care system or, at least, to select a type of work where the risk of transmission is minimal or absent (9).

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