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Low prevalence of HBV DNA in the liver allograft from anti-HBc-positive donors: a single-center experience

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Abstract

Allografts from donors positive for antibody to hepatitis B core antigen (anti-HBc⁺) can transmit hepatitis B virus (HBV) to the recipients. We aimed to study the prevalence of HBV DNA in liver allografts from anti-HBc⁺ donors. Between January 2003 and December 2008, this retrospective study identified 18 patients who received a liver from an anti-HBc⁺ donor. Pre- and post-transplantation HBV serology and serum HBV DNA level of the study subjects were reviewed. DNA extracted from liver biopsy tissue was used for PCR assay. Immunohistochemistry was also performed to determine viral protein expression. We observed a low prevalence of HBV DNA in allografts from anti-HBc⁺ donors even among patients who did not receive prophylaxis. Only one of 18 patients had detectable HBV DNA in the liver allograft. This recipient was seronegative for HBV before transplantation and did not receive prophylaxis after transplantation, and developed *de novo* hepatitis B. Of the five patients who were positive for both antibody to hepatitis B surface antigen and anti-HBc before transplantation and did not receive prophylaxis after transplantation, none developed HBV infection. Prophylaxis for HBV is important for seronegative recipients receiving a liver from an anti-HBc⁺ donor. Such prophylaxis may not be necessary for recipients who do not have detectable HBV DNA in the liver allograft.

Keywords

de novo hepatitis; hepatitis B virus DNA; liver transplantation; PCR; prophylaxis

After acute self-limiting hepatitis B virus (HBV) infection, the loss of hepatitis B surface antigen (HBsAg) from the serum and the development of antibody to hepatitis B surface antigen (anti-HBs) are generally believed to reflect viral clearance. However, HBV deoxyribonucleic acid (DNA) and possibly HBV virions may present in serum and peripheral blood mononuclear cells for more than five yr after complete clinical and serological recovery from acute hepatitis B (1). Bläckberg et al. reported that HBV DNA could be detected by polymerase chain reaction (PCR) in two of four liver specimens from the patients who had acute self-limited HBV infection 30 yr earlier (2). These findings suggest that patients may have occult HBV infection despite complete serological and clinical recovery from acute hepatitis.

In some people, antibody to hepatitis B core antigen (anti-HBc) may be the only evidence of previous HBV infection. In a German study of 552 subjects who had “anti-HBc alone” serology, HBV DNA was detected in the serum of 44 of 545 (8.1%) and in the paraffin embedded liver tissue in 16 of 39 (41%) patients tested (3). In another study, HBV DNA was detected in the livers of 10 of 16 (62.5%) patients who had no active diseases but were positive for anti-HBc and negative for HBsAg (4). These findings suggest that livers from people who had HBV exposure before donation can potentially transmit HBV to recipients. Oliver et al. first reported occult HBV in donors as the source of infection in liver transplant recipients (5). Subsequently, multiple studies reported *de novo* HBV (DNH) infection developed after orthotopic liver transplantation (OLT) in recipients who had received a graft from anti-HBc-positive donors (6–10). DNH is defined as hepatitis B occurring in a recipient who does not have the infection before OLT. Because of the aforementioned risk of acquiring DNH infection, prophylactic therapy is recommended for recipients who receive a liver from anti-HBc-positive donors (11). This represents a costly burden to the recipients because the prophylactic therapy is usually maintained lifelong. According to a survey of 56 transplant centers in the United States, knowledge about HBV DNA status of the donor and/or liver would greatly influence prophylaxis for those accepting anti-HBc-positive donor livers (12). Of those who would accept an anti-HBc-positive liver, 16 of 27 (59%) centers indicated that knowledge of the HBV DNA status would change their protocol; 46% of these centers would decrease prophylaxis if HBV DNA was negative, 27% would increase prophylaxis if HBV DNA was positive, and 27% would not accept the liver if HBV DNA was positive (12). In the same study, nine of 28 centers (32%) who would not accept an anti-HBc-positive liver stated that knowing HBV DNA status would change their protocol in that they might consider accepting livers if HBV DNA was negative (12).

In this retrospective case–control study, we aimed to investigate the prevalence of HBV DNA in the recipients’ livers which came from anti-HBc-positive donors and assess post-transplant HBV reactivation events.

Patients and methods

Patients

Between January 2003 and December 2008, this institutional review board-approved retrospective study identified 21 patients who received a liver from an anti-HBc-positive donor. Three patients were excluded because of their positive hepatitis B status prior to the transplantation. Pre- and post-OLT hepatitis B serology including the status of HBsAg, anti-HBs, and anti-HBc of the patients were reviewed. The same serology of the corresponding donors was also reviewed. The serology tests were performed by certified laboratories following the standard protocol. Formalin-fixed, paraffin-embedded tissues from their first post-OLT liver biopsy were used for DNA extraction. The median time between the first liver biopsy and OLT was 17 d (range, one d–12 months) (Table 1). The median age of the patients at OLT was 53.5 (range, 34–62). Among the 18 patients, 72.2% were men. The indications of OLT included: 10 chronic hepatitis C (55.6%), five cryptogenic cirrhosis (27.8%), and three alcoholic hepatitis (16.7%). Six of these patients (33.3%) also had hepatocellular carcinoma (HCC). The median follow-up duration was 20.5 months (range, 6–49 months) (Table 1).

Patients with the following conditions can receive a liver allograft from an anti-HBc-positive donor at our institute.

1. Any patient who is anti-HBs-positive.
2. Any patient with HCC irrespective of his/her HBV serology.

3. Any patient who agrees to accept such allograft with an informed consent.
4. Other circumstances that dictate a need for urgent transplant with an informed consent.

Patients receiving a liver allograft from an anti-HBc-positive donor will receive prophylaxis and will be followed according to the following protocol.

1. Hyperimmune hepatitis B immunoglobulin (HBIG) of variable doses will be provided to every patient perioperatively (usually only one post-operative dose) unless he or she is already positive for anti-HBs from either vaccination or infection before OLT.
2. Lamivudine (LAM) 100 mg daily will be provided to every patient after OLT once he or she resumes oral medications.
3. Serological status of HBsAg, anti-HBs, and serum HBV DNA level will be monitored every three months for the first two yr and then every six months after OLT unless clinically indicated.
4. Patients will continue to take daily LAM indefinitely or until they develop evidence of HBV viremia or disease.

DNA extraction and PCR

Five formalin-fixed, paraffin-embedded tissue sections (5- μ m/each section) from the first post-OLT liver biopsy of each patient were used for DNA extraction. The sections were deparaffinized at ambient temperature by treatment with xylene twice (five min per treatment), 100% ethanol twice (two min per treatment), 95% ethanol once for two min, 75% ethanol once for two min, and finally double-distilled water for two min. Deparaffinized liver tissues were scraped off the slides and transferred to a 1.5-mL Eppendorf tubes. The tissues were incubated in EDTA lysis buffer containing proteinase K at 37°C overnight. DNA was purified according to the standard phenol/chloroform protocol. The purity and amount of the resulting DNA were measured by a spectrophotometer (Thermo Electron Corporation, Madison, WI, USA). One microgram of genomic DNA was used for each PCR reaction. The plasmid pCMV-HBV that contains the complete HBV genome and the genomic DNA extracted from a 50-yr-old woman liver who has chronic hepatitis B served as a positive control of the HBV PCR. PCR of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) gene served as an internal control of the template quality.

The sequences of the forward and reverse primers for HBV PCR are 5'-TGG AAG TTA TGG GTC CTT GC-3' and 5'-GTT GGC GAGAAA GTG AAA GC-3', respectively. The sequences of the forward and reverse primers for GAPDH PCR are 5'-CCA CCC AGA AGA CTG TGG AT-3' and 5'-ACT GAC ACG TTG GCA GTG G-3', respectively. PCRs were performed in 20- μ L reaction volume. Each reaction started with denaturalization at 94°C for four min, followed by 35 cycles of the three-step program (94°C for 30 s, 58°C for 30 s, 68°C for one min), and finished with a final extension at 68°C for seven min in the iCycler (Bio-Rad Laboratories, Hercules, CA, USA). The final PCR products were electrophoresed on a 1.5% agarose gel with ethidium bromide staining and visualized using a UV transilluminator.

Immunohistochemistry staining

Five-micron sections of formalin-fixed, paraffin-embedded liver tissues were stained for HBsAg and HBcAg at the Shands hospital clinical pathology laboratory following the

standard immunoperoxidase staining protocol. The staining was performed to confirm the positive PCR results.

Results

Among the 18 donors, eight had unknown anti-HBs status because the local organ procurement organizations where the donors were located did not check their donors for that (Table 2). In this study, we found a very low prevalence of HBV DNA in the allograft of the recipients who received a liver from an anti-HBc-positive donor. Among the 18 recipients, only one (patient 4) had detectable HBV DNA in the allograft by the PCR testing (Fig. 1). This female patient did not have any HBV seromarker before OLT and underwent OLT for cryptogenic cirrhosis. Despite our established protocol, she unfortunately did not receive any HBV prophylaxis after OLT because of oversight. To further confirm the PCR finding, we retrospectively performed immunohistochemistry staining of her liver tissue, which was positive for both HBsAg and HBcAg (Fig. 2). Consistent with the histology findings, she also became positive for serum HBsAg and anti-HBc (Table 2).

Another five recipients (patients 2, 3, 10, 15, and 16) also did not receive any prophylaxis for hepatitis B despite our protocol because of the same reason as that in patient 4. Except unknown status of anti-HBc in patient 10, all of these subjects were positive for both anti-HBs and anti-HBc before OLT. None of them had detectable HBV DNA in their allograft (Table 2). Patient 3 died after a complicated post-operative course at seven months after OLT. Before his demise, there was no evidence of DNH. Consistent with the negative PCR, his first liver biopsy performed at seven d post-OLT was also negative for HBsAg staining. The other four recipients (patients 2, 10, 15 and 16) all had their first liver biopsy within 30 d after OLT. Despite not taking HBV prophylaxis, all of these patients remained negative for serum HBV DNA during follow-up periods.

In addition to patient 3, there were two more recipients (patients 8 and 17) who died from different reasons after OLT (Table 2). Patient 8 was seroconverted for serum anti-HBc after OLT despite taking LAM. However, he continued to be negative for serum HBV DNA before death. Patient 17 remained negative for serum HBsAg before death. Based on our protocol, patient 13 received a single dose of HBIG post-operatively. She was positive for anti-HBs but negative for anti-HBc before OLT. Other than HBIG, she did not receive any HBV prophylaxis after the surgery. She was recently diagnosed with DNH based on positivity of serum HBV DNA. However, her previous liver biopsies obtained one and two yr prior to the diagnosis of DNH were both negative for HBV staining (data not shown) and PCR testing (Fig. 1). Interestingly, she was positive for anti-HBs before and became negative for the protective antibody after OLT. This seroconversion could probably be explained by her immunosuppressive state. She could have developed DNH although we cannot rule out the possibility that her HBV infection is not from the donor.

Discussion

Unlike the previous studies that involved non-transplant subjects (3, 4), we found a low prevalence rate of HBV DNA in the livers from anti-HBc-positive donors. Among the 18 patients who received livers from anti-HBc-positive donors, only one has positive PCR for HBV. In a study of liver transplant patients, Abdelmalek et al. reported a 29% prevalence rate of HBV DNA in the native livers of the recipients who were HBsAg-negative and anti-HBc-positive (13).

There are several potential explanations for the disparities between the low prevalence rate observed in our study and the high rate in the others. Different study populations may have

different characteristics that can potentially explain the variation in prevalence. Spontaneous viral clearance as reported by Kwon et al. is another possibility for the low prevalence of HBV DNA in the liver allograft observed in this study (14). In that retrospective study, 46.4% of the grafts from anti-HBc-positive donors had HBV DNA before transplantation. Despite the high prevalence rate, only 14.3% of the grafts remained positive for HBV DNA after transplantation (14). The observed low prevalence of HBV DNA in the allograft in this study could be partially attributed to the use of prophylaxis. Eleven of 18 (61.1%) patients received LAM either alone or with HBIG after their OLT. Different primers used for the PCR in our study could explain the observed low prevalence rate. As shown previously, different primer sets did not work equally on the same template (2, 4, 15). Nevertheless, we believe that our primers worked properly because we could detect HBV DNA in the liver tissue from a patient with chronic hepatitis B (Fig. 1). The quality of DNA templates could also affect PCR results. We extracted DNA from formalin-fixed, paraffin-embedded liver tissues in this study. During paraffin embedding, genomic DNA can be nicked and degraded, which causes fragmentation (15, 16). Fragmented DNA templates can be problematic for PCR. Therefore, we could not examine covalently closed circular DNA (cccDNA) of HBV in this study. Finally, sampling error during the liver biopsy could potentially explain the differences in prevalence rate among different studies.

There is a 38–100% risk of transmitting DNH from anti-HBc-positive donors to their recipients. When the cases identified in the published studies are pooled, the calculated risk is 73% (11). Even with the presence of anti-HBs in recipients before OLT, there is a 17% risk of developing DNH if they received a liver from an anti-HBc-positive donor (14). Because of the shortage of available liver grafts for patients listed for transplantation, grafts from anti-HBc-positive donors will continue to be used worldwide despite the high risk of transmitting hepatitis B to recipients. The traditional solution to the problem is to provide prophylaxis, including an antiviral nucleoside analog and variable duration of HBIG, to the recipients (11, 12, 17, 18). Our findings suggest that prophylaxis may not be necessary for everyone. Even with our established protocol, six of 18 patients in this study did not receive any prophylaxis after OLT because of oversight problems. Among the six patients, only one had detectable HBV DNA in the liver from the first post-OLT biopsy. This patient was negative for hepatitis B seromarkers before OLT and developed DNH during follow-up. The rest of the five patients were all positive for anti-HBs and anti-HBc before OLT. Based on our protocol, they did not need HBIG perioperatively but still need to take a nucleoside analog. Fortunately, none of these five patients had detectable HBV DNA in their liver after OLT and none of them had DNH during follow-up. Within the limits of our small data set, this study suggests that recipients who are positive for anti-HBs and anti-HBc before OLT may not need prophylaxis if they do not have detectable HBV DNA in their graft biopsies. On the other hand, recipients who are negative for HBsAg and positive for both anti-HBs and anti-HBc before OLT may not need long-term prophylaxis if they do not have detectable HBV DNA in their grafts.

Prior to the development of antiviral therapy, the observed risk of developing DNH was highest (50–75%) for recipients without past HBV exposure, lowest (0–5%) for recipients with both anti-HBc and anti-HBs, and intermediate (0–18%) for individuals positive for either anti-HBs or anti-HBc (18). Consistent with the above observations, patient 4, who developed DNH, belongs to the high-risk group and the other five patients who did not have DNH belong to the group of people who practice low-risk activities. It remains controversial about the use of prophylaxis to prevent DNH on recipients with HBV seromarker(s) before OLT. Abdelmalek et al. previously reported that prophylaxis is not warranted after OLT in HBsAg-negative and anti-HBc-positive recipients. No detailed donor information was available in that study. Twenty-nine percent of the recipients who were negative for HBsAg and positive for anti-HBc had HBV DNA in their liver before transplant. Of those whose

liver was HBV DNA-positive before OLT, 40% of them continued to have detectable HBV DNA in their graft after OLT. None of them developed DNH (13). Dodson et al. suggested that anti-HBs-positive recipients are resistant to DNH with an allograft from an anti-HBc-positive donor. However, HBV prophylaxis may be justified for recipients positive only for anti-HBc because they infrequently developed DNH when they received an allograft from an anti-HBc-positive donor (8). In agreement with Dodson et al., Prieto et al. also reported that the presence of anti-HBs in recipients before OLT offered protection against DNH when they received an allograft and an anti-HBc-positive donor. In that study, none of the four recipients who were anti-HBs-positive before OLT developed DNH after receiving a liver from an anti-HBc-positive donor compared with 15 of 26 recipients who were anti-HBs-negative (10).

In this study, two patients (patients 8 and 13) became seroconverted for anti-HBc after transplant. Both of them were anti-HBs-positive and anti-HBc-negative before transplant. We could not follow the clinical course of patient 8 because he died from lung cancer at 11 months after OLT. However, he remained negative for serum HBV DNA before death. Despite our prophylaxis protocol, patient 13 received one dose of HBIG intraoperatively and did not receive post-operative antiviral therapy. She became HBsAg-positive, anti-HBc-positive, and anti-HBs-negative during follow-up. Our findings suggest that anti-HBs positivity alone status in recipients may not provide protection against DNH when receiving a graft from anti-HBc-positive donor – the patient may need anti-HBc as well. Dickson et al. previously proposed that immunity to hepatitis B, at least as marked by the presence of anti-HBs, is not absolute and that cannot entirely prevent the transmission of HBV when an anti-HBc-positive liver is given to a vaccinated recipient or to a recipient with pre-existing antibodies to HBV (9).

There are several limitations present in this study. First of all, the study sample is small. Secondly, we could not determine the prevalence of HBV DNA in the donor graft prior to transplant because not every donor had liver biopsy peri-operatively. Therefore, we can neither confirm nor rule out the possibility of spontaneous viral clearance in the grafts as suggested by Kwon et al. (14). Thirdly, not every one of the recipients in this study underwent protocol liver biopsy at regular interval and hence the duration between the first biopsy and OLT varied among study subjects. For the same reason, we may not be able to study the prevalence longitudinally. Fourthly, some of the patients have a relatively short follow-up duration that may be too early for them to develop DNH infection. Longer follow-up duration is needed in the future studies. Finally, some of the donors had incomplete HBV serology and that needs to be addressed prospectively in the future studies.

In summary, we observed a low prevalence of HBV DNA in the post-transplant liver allografts from anti-HBc-positive donors. Our findings support the importance of post-OLT prophylaxis for recipients who have no HBV seromarkers and receive a liver from an anti-HBc-positive donor in this setting. However, we suggest that post-OLT prophylaxis may not be needed for recipients who are positive for both anti-HBs and anti-HBc and have no detectable HBV DNA in their allograft. Nevertheless, the importance of continuous monitoring for DNH cannot be overemphasized. Further prospective multicenter cooperative studies are needed to better define post-OLT prophylaxis strategies.

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Fig. 1. Detection of hepatitis B virus (HBV) DNA (upper) and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (lower) by PCR in liver tissues from selective patients. Lane information: M, 100-base pair marker; Pos, pCMV-HBV-positive control; 1, patient 2; 2, patient 3; 3, patient 4; 4, patient 5; 5, patient 6; 6, patient 7; 7, patient 8; Neg, reagent negative control; 8, positive control (the patient with chronic hepatitis B). Vertical arrow indicates patient 4. Horizontal arrows indicate the size of PCR products.

A.

B.

Fig. 2. Immunohistochemistry staining of HBsAg and HBcAg in liver tissues from patient 4. (A) HBsAg (400 $\times$) and (B) HBcAg (400 $\times$). Negative controls are shown in inserts. The positive staining is in brown color.

Table 1

Characteristics of recipients

Patient	Age (yr)	Gender	Indication for OLT	Biopsy ^a	Follow-up duration (months)
1	53	M	HCV/EtOH/HCC	6 d	11
2	62	M	HCV	6 d	13
3	53	M	HCV/HCC	7 d	7
4	53	F	Cryptogenic	8 months	29
5	58	M	Cryptogenic	13 d	25
6	55	M	Cryptogenic	1 month	31
7	58	F	EtOH	5 months	49
8	46	M	HCV/HCC	1 d	11
9	52	F	HCV	5 months	8
10	46	F	HCV/HCC	7 d	26
11	48	M	PSC	12 months	27
12	52	M	HCV/EtOH	4 months	35
13	54	F	AIH	12 months	36
14	57	M	HCV/HCC	6 d	9
15	58	M	Cryptogenic	18 d	13
16	56	M	HCV	6 d	16
17	55	M	HCV/HCC	4 months	6
18	34	M	Cryptogenic	17 d	44

Patient 3 died at seven months after OLT from complicated post-operative course that was not related to hepatitis B.

Patient 8 died at 11 months after OLT from lung cancer.

Patient 17 died at six months after OLT from an infection with Ehrlichiosis.

HCV, hepatitis C; EtOH, alcohol; HCC, hepatocellular carcinoma; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; OLT, orthotopic liver transplantation.

^aTime of the first liver biopsy after liver transplantation.

Table 2
Hepatitis B serology of donors and recipients; PCR results; and prophylactic therapy after OLT

Patient	Donor's serology			Recipient's pre-OLT serology			Recipient's post-OLT serology			PCR ^a	Prophylaxis
	HBsAg	Anti-HBs	Anti-HBc	HBsAg	Anti-HBs	Anti-HBc	HBsAg	Anti-HBs	Anti-HBc		
1	-	ND	+	-	+	-	- _b	+	ND	-	LAM
2	-	ND	+	-	+	+	- _b	ND	ND	-	-
3	-	ND	+	-	+	+	- _c	ND	ND	-	-
4	-	ND	+	-	-	-	+ _{b,c}	-	+	+	-
5	-	ND	+	-	+	+	- _b	±	ND	-	LAM
6	-	ND	+	-	+	ND	- _b	-	ND	-	LAM
7	-	ND	+	-	+	-	-	+	-	-	LAM
8	-	ND	+	-	+	-	- _b	+	+	-	LAM
9	-	-	+	-	+	-	- _{b,c}	ND	ND	-	LAM
10	-	-	+	-	+	ND	- _b	+	+	-	-
11	-	-	+	-	-	-	- _{b,c}	+ ^d	ND	-	HBIG, LAM
12	-	-	+	-	-	+	- _{b,c}	+ ^d	ND	-	HBIG, LAM
13	-	-	+	-	+	-	+	-	+	-	HBIG
14	-	+	+	-	+	+	- _b	ND	ND	-	LAM
15	-	+	+	-	+	+	- _b	+	ND	-	-
16	-	+	+	-	+	+	- _b	+	ND	-	-
17	-	+	+	-	+	+	-	ND	ND	-	LAM
18	-	+	+	-	-	-	- _{b,c}	-	ND	-	HBIG, LAM

Patient 3 died at seven months after OLT from complicated post-operative course that was not related to hepatitis B.

Patient 8 died at 11 months after OLT from lung cancer.

Patient 17 died at six months after OLT from an infection with Ehrlichiosis.

OLT, orthotopic liver transplantation; PCR, polymerase chain reaction; HBsAg, hepatitis B surface antigen; anti-HBs, hepatitis B surface antibody; anti-HBc, hepatitis B core antibody; ND, not done; LAM, lamivudine; HBIG, hyperimmune hepatitis B immunoglobulin.

^aPCR performed on liver tissue.

^bConfirmed by PCR performed on serum.

^cConfirmed by immunohistochemistry staining.

^dReceived HBIG perioperatively.