

REVIEW ARTICLE

Occult Hepatitis B Infection in Chronic Hemodialysis Patients: Current Concepts and Strategy

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The prevalence of end-stage renal disease has increased dramatically in developing countries, and this has been accompanied by the widespread utilization of chronic hemodialysis in its management prior to kidney transplantation. Within this group, the interjection of hepatitis B virus (HBV) infection represents a significant co-morbidity event that has led to several outbreaks of hepatitis B. Occult hepatitis B (OHB) is a variant of conventional hepatitis B that is manifested by the presence of HBV DNA in blood and/or tissue in the absence of hepatitis B surface antigen (HBsAg). It is postulated that its impact on chronic hemodialysis patients also might be of importance. Unfortunately, there are only a limited number of published studies on this topic and, in most cases, only prevalence data are reported without descriptions of histopathology or outcome measurements. In this paper, we have reviewed this information. Based on the scarcity of available data, HBV DNA assessment with highly sensitive assays might be informative in this target population, especially among those hemodialysis patients who present with isolated antibodies to the hepatitis B core antigen (anti-HBc) or who are hepatitis C virus (HCV) RNA positive, since HCV coinfection appears to worsen the outcome. Clearly, more precise studies need to be performed to answer questions concerning the impact of OHB in chronic hemodialysis patients.

Keywords: Hemodialysis, HBV, Occult Hepatitis B

Introduction

Hepatitis B virus (HBV) replication in the absence of a detectable hepatitis B surface antigen (HBsAg) and occasionally other HBV serologic markers has been called occult hepatitis B (OHB). It is not a new concept and has been recognized since the 1980s ⁽¹⁾. The application of highly sensitive and specific tests for HBsAg and HBV DNA has helped to refine the diagnosis of OHB and to promote its emergence as an important clinical entity. OHB has been shown to cause posttransplant hepatitis B in patients who receive livers from donors with OHB ⁽²⁻⁵⁾ and to be associated with cryptogenic chronic liver disease and hepatocellular carcinoma (HCC) ⁽⁶⁻¹⁰⁾, especially in hepatitis C virus (HCV) co-infected patients. Mechanisms that are responsible

for controlling viral replication in the absence of detectable HBsAg utilize elements derived from both the host and the virus. Among these are mutations in the HBsAg gene that block export or detection of

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the antigen, integration of the HBV genome into the host DNA that can affect the expression of proteins, repression or inefficiency of viral replication resulting from mutations that occur in the polymerase domain, development of circulating immune complexes, and coinfection with other viral agents that down-regulate HBV replication and protein synthesis (reviewed by Hollinger and Sood (11)).

End-stage renal disease (ESRD) is a significant problem in almost all countries and the prevalence has increased considerably in developing countries (12). For example, in Iran its prevalence has increased from 238 per million population in 2000 (13) to 357 per million in 2006 (14), with about fifty percent of these patients undergoing hemodialysis. Among the hemodialysis group, regardless of location, HBV infection is a significant co-morbid event sometimes leading to outbreaks of hepatitis B (15-17), even though multiple measures are often implemented to reduce new infection such as HBV vaccination, execution of infectious disease control measures, isolation of HBV-positive patients, and the use of dedicated dialysis machines (18-24). The aim of this review is to summarize the role of OHB in chronic hemodialysis patients.

End Stage Renal Disease and Traditional Hepatitis B Infection

Although the prevalence of HBV in patients with ESRD undergoing dialysis has decreased significantly during the past few decades (18), it still remains a distinct clinical problem due to the immunosuppressive nature of renal disease that often leads to chronicity of the virus and an opportunity for nosocomial spread of the infection among dialysis patients. In this regard, studies have demonstrated a connection between HBV genotypes and subtypes and certain dialysis centers (24) providing a molecular linkage between the virus and the environment.

Several factors are associated with the increased transmission of HBV among hemodialysis patients in nonendemic areas such as low vaccination rates against HBV, using the same machines for HBV infected and uninfected patients, the presence of undiagnosed hepatitis B among HBV negative groups (25, 26) and preparation of injectable medications in the dialysis treatment room (23). Unlike hemodialysis patients, however, the risk of HBV infection is significantly lower among patients undergoing peritoneal dialysis (27). These findings highlight the possible risk of procedure-related infection in hemodialysis patients although the role of transfusions cannot be excluded especially in countries where hepatitis B is endemic.

The higher incidence and prevalence of HBV infection in hemodialysis patients makes vaccination a powerful and desirable tool for prevention of the disease among these high risk individuals. Previous studies have suggested that vaccination can reduce infection risk by 70 percent (28). However, it is important to consider that the rate of antibody seroconversion following vaccination of patients with ESRD is suboptimal and correlates directly with the level of renal function (29).

The majority of dialysis patients acutely infected with HBV have a relatively mild clinical course (30). They are often asymptomatic and have normal or only slightly elevated serum aminotransferase levels. HBV infection also does not have an adverse effect on outcomes among those undergoing peritoneal dialysis (31). Chronicity following the acute infection has been shown to occur in up to 80% of patients with renal failure compared to a 1-3% rate of chronicity that occurs in healthy adults (30). Although the course of disease is mild in most acutely infected cases, some genotypes might result in severe hepatitis with a higher fatality rate (32).

In hemodialysis patients with chronic HBV infection, clinical manifestations are usually similar to those without renal failure. However, aminotransferase levels (alanine aminotransferase [ALT]/aspartate aminotransferase [AST]) usually need to be interpreted after adjusting for the level of renal failure since uremia typically depresses these enzymes. Only a few studies are available pertaining to the histological findings in hemodialysis patients infected with HBV (33, 34). Although piecemeal necrosis, portal inflammation or fibrosis observed in liver biopsies from HBV-infected hemodialysis patients are generally comparable to the histology observed in HBV-infected patients devoid of renal failure, some reports have indicated that the histology and clinical course may be worse in the dialysis patients (30).

Occult HBV Infection in Chronic Hemodialysis Patients

In 1985, detection of HBV DNA in the serum of patients with chronic liver disease in the absence of conventional serologic markers by Brechot *et al.* (1) led to the recognition of occult HBV infection. Subsequently, Lai *et al.* (35) discovered that 31% of uremic patients on long-term dialysis had isolated antibodies to the hepatitis B core antigen (anti-HBc), several of whom had elevated ALT levels suggesting the possibility of subclinical hepatitis B even though HBV DNA was not detected using an assay of unknown

sensitivity. Prior to that observation, however, Hoofnagle *et al.* (36) had reported transmission of HBV following transfusion of blood with isolated anti-HBc. In the early 1990s, Sanchez-Quijano *et al.* (37) and Joller-Jemelka *et al.* (38) detected HBV DNA in 42% and 40% of subjects with persistently isolated anti-HBc. In 1997, Cabrerizo *et al.* (39) analyzed serum and peripheral blood mononuclear cells (PBMC) from 33 HBsAg-negative hemodialysis patients for HBV DNA. They found HBV-specific nucleic acid in 58% of the sera and in 54% of the PBMC, and this occurred more often in those with anti-HBV antibodies. They concluded that the absence of HBsAg in their dialysis patients may have been due to the presence of HBsAg-antibody to hepatitis B surface antigen (anti-HBs) immune complexes, as previously reported (38), although S gene mutations preventing detection of HBsAg by conventional assays could not be excluded.

The prevalence of OHB in hemodialysis patients in a North American population was reported to be 3.7% (40) compared to 4.9% in India (Table 1) (41). In Italy, the prevalence ranged from 0% in a large cohort of 213 dialysis patients (42) to 26.6% in another cohort (43) while in Turkey prevalence rates of 2.7% (44) and 12.4% (45) have been recorded. As can be inferred from these reports, it is evident that the prevalence of OHB in hemodialysis patients is diverse, and several factors can be established as the determinants such as selection bias, sensitivity and specificity of the tests, vaccination rates, health care measures and hemodialysis machine isolation for HBV-positive patients. It also is of interest to compare these prevalence rates to the prevalence of HBsAg, anti-HBc, HCV RNA and occult hepatitis C in the same population (Table 1). As can be seen, the prevalence of OHB bears little direct relationship to overt HBV or HCV or to occult hepatitis C in the same cohort, except for the fact that the presence of one agent often corresponds to the detection of another. As a result, it is very important to rule out OHB in dialysis patients who are HBsAg-negative

but who display evidence of HCV RNA or anti-HBc reactivity, regardless of whether the ALT is elevated.

Cabrerizo and colleagues (46) detected OHB in serum and PBMC from 85% of 13 hemodialysis patients. Within this cohort, the viral DNA appeared to be transcriptionally active in 5 of the 11 PBMC samples based on detection of covalently, closed, circular (ccc) HBV DNA. In addition, these investigators found deletions in the pre-S1 region of the viral genome which affects the S promoter region that may be responsible for reducing the synthesis of HBsAg.

Occult Hepatitis B in Chronic HCV Infected Hemodialysis Patients

Current studies that have examined the influence and prevalence of OHB in chronically infected patients with HCV point toward a significant association. Higher grades of liver involvement and a poorer response to anti-HCV therapy also appear to accompany these coinfections. However, due to a scarcity of well-designed cohort studies, adequate conclusions can only be arrived at following further research on the subject (47). In a study from Turkey (48), OHB was reported in 12 out of 33 treatment naive hemodialysis patients (36%) with chronic HCV and, in half of these, tyrosine-methionine-aspartate-aspartate (YMDD) variants of the HBV polymerase motif were present. However, in other hemodialysis units in Turkey, results were either negative (47) or showed no difference among those with or without anti-HCV reactivity in the serum (49). The latter authors were unable to find any risk factors in their chronic hemodialysis patients that might distinguish patients with OHB from those who are HBV DNA negative such as hemodialysis duration, demographic features, and biochemical parameters. In Greece (50), OHB was detected in 20% of 49 HCV RNA positive patients on maintenance hemodialysis compared to 6% of 48 patients with normal renal function ($P = 0.07$).

Table 1. Reported prevalence of occult hepatitis B in hemodialysis patients compared to HBV and HCV infections in the same cohort.

Authors	Publication Year	Country	Study Population	Occult Hepatitis B	HBsAg	Anti-HBc	HCV Infection	Occult Hepatitis C
Minuk, GY (40)	2004	America	241	9 (3.7%)	2 (0.8%)	21 (8.7%)	- ^a	-
Fabrizi, F (42)	2005	Italy	213 ^b	0 (0%)	11 (1.9%)	216 (36.9%)	120 (20.5%)	-
Yakaryilmaz, F (43)	2006	Turkey	188	5 (2.7%)	32 (17%)	12 (6.4%)	45 (23.9%)	9 (4.8%)
Altindis, M (44)	2007	Turkey	153	19 (12.4%)	-	32 (20.9%)	40 (26.1%)	-
Jain, P (41)	2008	India	102	5 (4.9%)	6 (5.9%)	-	3 (2.9%)	27 (26.5%)
Di Stefano, M (43)	2009	Italy	128	34 (26.6%)	-	-	15 (11.7%)	-

^a – Data not available.

^b – HBV DNA was measured in a subset of dialysis patients (213 of 585) whereas the other data are from the entire cohort.

Possibilities for this trend may be a lower prevalence of HBV vaccination in the hemodialysis group, impaired immune function observed in uremic patients, a high risk of parenteral exposure and lower titers of anti-HBs.

Summary and Recommendations

Currently available evidence suggests a relatively high prevalence of OHB in hemodialysis patients. Conventional serologic testing used in most hemodialysis centers is not able to identify the occult infection. Considering the potential transmissible nature of OHB among this population via the mucosal, parenteral or percutaneous routes, identification seems appropriate employing real-time PCR for HBV DNA. As a rule, hemodialysis patients with chronic hepatitis C or who have an isolated anti-HBc response are among those with the greatest possibility of having an OHB infection.

It is noteworthy that the extent of liver disease in ESRD patients undergoing hemodialysis is largely unknown and thus needs further investigation. A potentially important contributing factor to the development and progression of liver disease in this population is the immunosuppression that accompanies renal failure. The association of so many of these cases with chronic HCV confounds the issue. Therefore, studies designed to evaluate the clinical and histological pattern of disease progression are of utmost importance because this knowledge might suggest the need for more aggressive treatment in these patients. Currently, however, there is a paucity of data on how to manage hemodialysis patients with OHB once they are detected. Therefore, the need for guidelines is apparent.

There is even less information concerning the impact of occult hepatitis B infection in renal transplant patients undergoing immunosuppression. However, if the outcome is similar to the abortive infection usually seen in orthotopic liver transplant patients exposed to OHB in the absence of anti-HBV therapy, then this may be less of an issue than what has been observed in transplant patients with HBsAg-positive hepatitis (51).

Studies concerning outcome, based on the prevalence of different genotypes of HBV or the presence of mutants in ESRD patients, are also lacking. Additionally, the relationship between serum transaminase level and disease severity and progression has not been studied, but based on what has been reported for renal transplant patients with chronic hepatitis C (52,53), we anticipate that elevated levels of ALT may be associated with lower patient

and graft survival and more histological injury to the liver. Obviously, more investigations need to be performed in order to provide sufficient data for patient management.

Conclusions

Based on current epidemiologic data, we have limited information on the clinical impact and therapeutic management of OHB in chronic hemodialysis patients. In most situations, only prevalence studies which do not include histopathology or outcome events are available. This absence of data needs to be rectified. In addition to HBsAg testing, HBV DNA assessment is encouraged in this population, especially among those hemodialysis patients who are HCV RNA positive or who have an isolated anti-HBc test result. Such an approach could effectively help diminish the incidence and outbreaks of HBV in dialysis centers.

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