Review

Hepatitis B Virus-associated Nephropathy
An International Data Analysis

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Introduction. Hepatitis B virus (HBV)-associated nephropathy is one of the manifestations of HBV infection. However, since it is not common, the patient populations of reports are usually limited. In order to have a more perfect understanding of the disease, we conducted this analysis of data published in articles of the English literature on HBV-associated nephropathy.

Materials and Methods. We conducted a comprehensive search for the available publications on HBV-associated nephropathy through the PubMed. The patients were defined as pediatric when they were 18 years old or younger. The definition criteria for complete remission were in part different between studies, but a generalized definition was taken as a significant decrease in the proteinuria to levels around normal with no relapse episodes in 1 year after remission.

Results. Overall, 119 patients from 10 reports were included into this analysis. All of the patients using lamivudine experienced remissions compared to those receiving other treatment modalities (P = .001), of whom 72.7% (16 of 22) had complete remission (P = .08). None of lamivudine recipients lost their kidneys (P = .04). Pediatric patients were more frequently positive for hepatitis B envelop antigen (P = .001). Immunoglobulin A nephropathy was more frequent among adult patients (P = .01), and membranous nephropathy in children (P = .01). Children represented significantly higher levels for aspartate aminotransferase (P = .004) and alanine aminotransferase (P = .002).

Conclusions. Lamivudine therapy can effectively be used to stop progression of HBV-associated nephropathy. Pediatric patients represent different serological and laboratorial test results compared to their adult counterparts. Future studies with larger patient population are needed to confirm our findings.

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INTRODUCTION

Hepatitis B virus (HBV) infection has been shown to cause several extrahepatic lesions, especially through deposition of immune complexes in different organs.[1-5] The precise mechanisms by which only some of patients with chronic HBV infection develop nephritis is not well known. The diagnosis of HBV-associated nephropathies is made by serologic evaluations for HBV antigen and antibodies and immunohistochemical demonstration of HBV-related antigens as well as immune complexes in a kidney biopsy specimen.[6] The isolation of immune complexes from kidney biopsies suggests that this complication may be a hypersensitivity reaction to

the viral infection.

Hepatitis B virus-related nephropathy is one of the HBV infection manifestations that is repeatedly observed by the physicians from all over the world.[7-15] The association between chronic HBV infection and glomerular diseases was first described in 1971 by Combes and coworkers,[6] and since then, several morphological patterns for glomerular lesions have been reported.[7-16]

Hepatitis B virus-associated nephropathy predominantly occurs in childhood and mainly in men[17]; however, the number of reports is very limited. In this analysis of the studies published so far, we included data of 10 articles on HBV-associated nephropathy, in order to review the issue in a larger patient population and have a more precise conclusion on the international experience on the disease.

MATERIALS AND METHODS

We conducted a comprehensive search for the available data through the PubMed, in order to collect all articles on the HBV-associated nephropathies. Keywords used for the search were *hepatitis B virus + kidney disease*, *hepatitis B virus + renal disease*, and *hepatitis B virus + nephropathy*. Only full-text of articles whose data were well presented enough to conduct an analysis based on the method of our study was included. Articles which were suitable to be included were those provided distinct data for each of their subjects, separately. When the articles' full text was not available online or we had not institutional subscription to the journal, emails containing request for the article were sent to the corresponding authors. A questionnaire was developed to collect data from different published studies. Finally, data from 10 published studies were used to make a data bank and were included in the final analysis.[7-16] Because different studies presented different data from their patients, we were only able to use the available data for our analyses.

The following data were collected: gender, age, morphologic patterns for glomerular lesions, treatment agents, virological evaluations (for hepatitis B surface antigen, hepatitis B envelop antigen [HBeAg], and anti-hepatitis B envelop antibody [HBeAb]), serological evaluations (for albumin, blood urea nitrogen, creatinine, alanine aminotransferase [ALT], and aspartate aminotransferase [AST]), outcome (death and kidney failure), and follow-up time. Renal lesions for HBV-associated nephropathy in the studied reports were membranous nephropathy, mesangioproliferative glomerulonephritis, focal and segmental glomerulonephritis, proliferative glomerulonephritis, postinfection glomerulonephritis, crescentic glomerulonephritis, minimal change glomerulonephritis, and immunoglobulin A (IgA) nephropathy. Because some patients had more than one kidney specimen morphologies for their pathology reports or got multiple remedial agents, we separately analyzed each of the mentioned glomerulopathies or administered agents for different variables.

The patients were defined as pediatric when they were 18 year old or younger. Complete remission definition was in part different between studies, but a significant decrease in the proteinuria to levels around normal with no relapse episodes in 1 year was the criteria founded in all studies.

The software used for data analyses was the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA). Statistical differences between patients' subgroups were performed by using chi-square and Fisher exact tests for proportions and the Student *t* test for continuous data. The 1-way analysis of variance was used for comparisons between more than two groups. All statistical tests were performed at the .05 significance level.

RESULTS

Overall, 119 patients from 10 reports were included into this analysis. The mean age of the studied patients was 35.9 ± 14.7 years (range, 2 to 74 years), of whom 9 (9.4%) were pediatric patients, 57 (59.3%) were male, and 23 had missing data. Lamivudine had been used for 22 patients (18.5%). The patients were under follow-up for a mean duration of 23.3 ± 25.3 months (range, 1 to 180 months), with missing data for 41 patients. Of 57 patients whose final outcome was reported, 5 (8.8%) lost their kidney and 1 (1.8%) died. Eleven patients (19.3%) had no remission after medical therapy, 9 of whom had membranous nephropathy and IgA nephropathy, and focal and segmental glomerulonephritis was the pathologic diagnosis of kidney specimen for the other 2 patients. Eleven patients (19.3%) experienced a partial remission,

while 29 (24.4%) achieved complete remission.

Kidney biopsy specimen morphologies were as follows: IgA nephropathy in 60 (50.4%), membranous nephropathy in 41 (34.5%), proliferative glomerulonephritis in 6 (5%), focal and segmental glomerulonephritis in 6 (5%), mesangioproliferative glomerulonephritis in 3 (2.5%), postinfectious glomerulonephritis in 2 (1.7%), minimal change glomerulonephritis in 1 (0.8%), and crescentic nephropathy in 1 (0.8%).

Of 72 patients (60.5%) tested for hepatitis B surface antigen, 39 (54.2%) were positive; of 94 patients (79.0%) with reported HBeAg results, 33 (35.1%) were positive; and of 89 patients (74.8%) who also had anti-HBeAb results, 24 (27.0%) were positive. There were no significant differences between the two genders in their serologic and pathologic results; however, all those with focal and segmental glomerulosclerosis were men (P = .07) and HBeAg was more frequently observed among men (P = .09). Compared with patients receiving other therapies, all of the patients using lamivudine experienced remissions (P = .001), of whom 72.7% (16 of 22) had complete remission (P = .08); none of lamivudine recipients lost their kidneys (P = .04). Because most patients whose outcomes were determined had no defined follow-up duration, we were not able to conduct survival analysis.

The Table summarizes characteristics for pediatric and adult patients with HBV-associated nephropathy. Comparing pediatric patients with adults, we found that pediatric patients were more frequently positive for HBeAg (78% versus 21%, P = .001). While IgA nephropathy was more frequent among adult patients (67% versus 22%, P = .01), membranous nephropathy was more likely to occur in children (56% versus 16%, P = .01). Moreover, among all laboratory measurements, children represented significantly higher levels of AST (87.5 ± 22.6 U/L versus 41.6 ± 26.8 U/L, respectively; P = .004) and ALT (164.4 ± 151.7 versus 43.4 ± 32.8 U/L, respectively; P = .002).

DISCUSSION

Because HBV-associated nephropathy does not essentially improve in all patients without medical therapy, and it may impact the overall outcome of the patients, considerable attempts have been made to find effective therapeutic methods and to resolve the related complications. This analysis of 119 patients from 10 studies showed that lamivudine therapy was significantly associated with better outcome; all patients receiving lamivudine had partial or complete remission, and none of them lost their kidneys. Although because of the inevitable uncontrolled nature of our analysis, as well as missing data, one may assume that patients with unfavorable outcome might have

Differences in Study Variables Between Pediatric and Adult Patients*

Variable	Children	Adults	*P*
Male gender	67	56	.73
Lamivudine use	57	28	.19
Pathologic diagnosis			
FSGS	22	5	.09
IgA nephropathy	22	67	.01
Membranous nephropathy	56	16	.01
Proliferative nephropathy	0	7	.99
Laboratory results			
HBsAg positive	78	51	.16
HBeAg positive	78	17	.001
HBeAb positive	20	27	.99
Blood urea nitrogen, mg/dL	20.5 ± 12.0	29.0 ± 35.9	.64
Serum creatinine, mg/dL	0.6 ± 0.3	3.0 ± 7.2	.09
AST,U/L	87.5 ± 22.6	41.7 ± 26.8	.004
ALT, U/L	164.4 ± 151.7	43.4 ± 32.8	.002
Serum albumin, mg/dL	2.3 ± 0.5	2.3 ± 0.9	.96
Complete remission	100	61	.07

*Data are summarized after excluding missing data. Values are presented as percents for all variables except for laboratory studies (mean ± standard deviation). FSGS indicates focal segmental glomerulosclerosis; IgA, immunoglobulin A; HBsAg, hepatitis B surface antigen; HBeAg, hepatitis B envelop antigen; HBeAb, hepatitis B envelop antibody; AST, aspartate aminotransferase; and ALT, alanine aminotansferase.

not receive appropriate therapies, the observed higher outcome for lamivudine users may not certainly show superiority of lamivudine over other agents; however, this finding overall shows that lamivudine therapy can effectively induce remission in HBV-associated nephropathies. Moreover, when we repeated analysis with patients receiving only steroids and interferon, we did not find such a relationship (although the number of subjects was less in the latter therapeutic groups).

Corticosteroids have been used in patients with HBV-associated nephropathy mainly for symptomatic relief of proteinuria.[18,19] However, there is no evidence on a potential positive impact of corticosteroids administered at the onset of nephrotic syndrome in HBV-associated nephropathy.[20] On the other hand, withdrawal of corticosteroids can exacerbate liver function in patients with chronic HBV infection.[21] There are studies in favor of using corticosteroids to achieve remissions,[21] while other studies have not shown protective roles for corticosteroids.[22]

Interferon-alpha (IFN-alpha) has antiviral, antiproliferative, and immunomodulatory effects.[23] Evidence suggests that 3 to 6 months of IFN-alpha therapy is beneficial in HBeAg-positive patients.[24] There are several reports in favor of using IFN-alpha in patients with HBV-associated nephropathy.[23-26] A study showed that patients who did not respond to corticosteroid treatment well responded to IFN-alpha therapy becoming free of proteinuria.[27]

The clinical manifestations of HBV-associated nephropathy tend to be different in pediatric and adult patients. Several pediatric chronic carriers of HBV are asymptomatic, and in some of them, HBV nephropathy is detected by routine urine and serological screening.[1] The other common clinical presentation in children is the nephritic syndrome with a strong predominance in male children.[28,29] We also found that pediatric patients were more likely to represent HBeAg in their sera compared to adult patients. Evidence indicates that HBeAg is the primary antigen related to the subepithelial deposits in patients with HBV-associated nephropathy.[28-30] Takekoshi and colleagues[31] suggested that HBeAg in association with IgG is essential in the pathogenesis of HBV nephropathy. Another study showed that in the absence of HBeAg, the disease remains subclinical.[32]

Another major finding of this study was that pediatric patients were more likely to develop membranous nephropathy in relation with HBV infection, while adult patients more frequently had IgA nephropathy. To our knowledge, this is a new finding that has never has reported elsewhere. This finding can represent some clues toward the pathogenesis of HBV-associated nephropathy and help to find better methods for prevention and treatment of the disease. Moreover, pediatric patients were found to significantly represent higher levels of AST and ALT; we did not find similar reports in the literature on this issue as well.

CONCLUSIONS

Lamivudine therapy can be effectively used to stop progression of HBV-associated nephropathy. Pediatric patients represent different serological and laboratory test results compared to their adult counterparts. Future studies with larger patient populations are needed to confirm our findings.

CONFLICT OF INTEREST

None declared.

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