Hepatitis-B Virus-Associated Nephropathies in Adults: A Clinical Study in Thailand

Suraphan Panomsak MD*, Songkiat Lewsuwan MD*,
Somchai Eiam-Ong MD*, Talerngsak Kanjanabuch MD*

** Division of Nephrology, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital*

Hepatitis B virus (HBV)-associated glomerulonephropathy (HBV-GN) has been increasingly reported, especially in adults. In the present study, the authors investigated the clinical and histopathology features of patients who suspected HBV-GN in 24 patients and age ranging from 23 to 74 years (mean 43 years).

Asymptomatic hematuria was the most common presentation (54%); followed by edema and hypertension at equal percentages of 50%. The nephrotic syndrome was presented in 43%, the nephrito-nephrotic syndrome in 3.5%. Clinically suspected rapidly progressive GN was found in 14%. Renal insufficiency was determined in 30%. The most common pathologic finding was IgA nephropathy (IgAN 29%), followed by membranous nephropathy (21%), focal segmental glomerulo sclerosis (FSGS 11%), membranoproliferative GN (11%), post-infectious GN (11%). Liver disease activity also tended to be mild or had no symptoms of hepatitis. The authors remission rates both complete and partial were 75% (higher than the usual report), notwithstanding treatment. The authors achieved a sustained complete remission in half of the patients (3 in 6 cases) treated with steroid alone and 2 out of 7 cases (28.6%) treated with anti-viral therapy. Spontaneous remission was demonstrated in 2 (1 with IgAN + FSGS, and 1 with post infectious GN) out of 6 patients (33.3%). None of the patients in both treatment groups turned to ESRD that occurred in 2 cases receiving non-specific treatment. Of note, all of the patients who received anti-viral therapy or corticosteroid and had complete follow up were in remission either complete or partial.

Keywords: *HBV, Nephopathy, Glomerulonephritis*

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Extra-hepatic manifestations of hepatitis B-virus (HBV) infection have increasing recognition and expanding prevalence. One of the most common is HBV associated nephropathies (HBV-AN)[1]. Most of the reported HBV-AN are glomerular diseases, including membranous nephropathy (MN)[2-4], mesangiocapillary proliferative glomerulo nephritis (MPGN), non-IgA mesangial proliferative glomerulo nephritis (GN), minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), and IgA nephropathy (IgAN). Those may occur in pure form or sometimes overlapping. The most common glomerular pathologic finding is MN, which resolved spontaneously in many cases of children, but such is uncommon in adults[5,6]. Significant percentages of adults (30%) may progress to renal failure. As many as 10% required maintenance dialysis[7,8]. Antigen-antibody immune complexes against either HBs, HBc, or HBe together with com-plement components have been demonstrated in the glomerular basement membrane (GBM) and mesan-gium[9]. Perhaps they reflect the pathogenesis of the HBV-GN. Liver disease tends to be mild in patients with HBV-AN[10]. In fact, the severity of the renal disease does not correlate with the severity of liver disease or level of HBV replication. Even though, Thailand is classi-fied as an endemic area of HBV infection, no one has reported the pathologic finding and clinical outcome of HBV-AN. The authors, therefore, present the clinicopatho-

Correspondence to : Kanjanabuch T, Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University Hospital, Bangkok 10330, Thailand. Phone: 0-2256-4321, Fax: 0-2252-6920, E-mail: golfnephro@hotmail.com

logical and follow-up findings in 24 patients with suspected HBV-AN.

Material and Method

From the renal biopsy registry done at King Chulalongkorn Memorial Hospital, Bangkok, Thailand from 1997 to 2005, forty four of 985 biopsies were selected according to the positive serology of HBsAg. Eight were excluded due to inadequate tissue to make a final conclusion. Eight biopsies from the patients who had clinical or laboratory features of systemic lupus erythematosus or any other systemic conditions causing GN at the time of biopsy or later were further excluded. Finally, 28 biopsies from 24 patients were left to review the clinical manifestation, clinical outcome, and pathologic finding. Four patients were rebiopsied due to reappearance of proteinuria. HBV infection defined as persistent appearance of HBsAg or serum HBV DNA > 10^5 copies/ml. Tests for HBsAg, anti-HBs, and anti-HBc were performed using an enzymatic immunoassay.

Complete remission (CR), defined as disappearance of proteinuria and returned to normal serum protein levels, were categorized into sustained CR (defined by no relapse within one year after remission) and non-sustained CR (with at least one relapse during the first year of the follow-up period). Partial remission was described as absence of edema, decrease in proteinuria (less than 2 g but remained above 300 mg per day), and normal serum albumin concentrations. Chronic renal insufficiency was defined by a persistence of serum creatinine level higher than 1.7 mg/dL in males and 1.5 mg/dL in females. Nephrotic syndrome was diagnosed when daily proteinuria was larger than 3 g and plasma albumin level was below 2.5 g/dL. Prednisolone 2 mg/kg per day was given as a treatment for 8 patients. Four patients received no treatment. The patient with IgAN received interferon-α2a and lamivudine in addition to an initial month of prednisolone treatment. All patients but 4 were followed for a period ranging from 5 to 120 months.

Pathological material consisted of renal biopsies in 13 patients and renal necropsy samples in 1 patient. All patients had renal biopsies prior to treatment. Liver tissue for examination was available in 4 patients. Renal tissue samples were routinely processed and stained with Hematoxylin-Eosin (H&E), Periodic Acid-Schiff (PAS), Masson's trichrome, Jones's silver, and Congo red stains. For direct immunofluorescence, frozen sections of the fresh tissue samples were stained with antisera against human C3, C4, C1q, IgG, IgA, IgM, kappa, lamda, and fibrinogen. The streptavidin-biotin peroxidase method was used for immunohistochemical staining with antibody against HBsAg. All renal tissue samples were studied by light and immunofluorescence microscopy. Electron microscopy was available in 4 patients, supporting the tissue diagnosis. Time to rebiopsy ranged from 0-17 years. (average 7.25 years).

Results

From a total of 24 patients, males were slightly predominant (M:F = 14:10) and age ranged from 22 to 74 years with a median age of 39.8 years. The clinical presentation varied from asymptomatic hematuria and proteinuria (39%), nephrotic syndrome (43%), and rapidly progressive glomerulonephritis (14%). Half of the patients had edema and hypertension. In 11 patients having no symptom, 3 of them had only hematuria, the other 3 had only proteinuria, and 5 had both. Renal insufficiency was found in 7 patients (30%), most of them were IgAN (3 in 7). Three of those were classified as RPGN, whose histopathologies were MPGN, post-infectious GN, and IgAN.

ANA was falsely positive in one of 17 tests, which was found in only one patient with HIV and HBV co-infection. The C3 levels were low in 4 of 10 patients tested, C4 levels were done in 2 of 5, and CH50 levels were done in 3 of 11. HBsAg was positive in all cases. HBV DNA was tested in 11 patients and HBeAg was tested in 18 patients, only 4 of 11 patients (36%) and 14 of 18 patients (77%) had a high level of HBV DNA (more than a hundred thousand copies/mL) and positive HBeAg, respectively. Three patients had mild elevated levels of ALT and AST. Hepatomegaly was hardly found (only 1 in 24 cases) and splenomegaly was not found. Liver biopsies were done in three cases and all resulted in chronic hepatitis with mild activity while one case developed liver cirrhosis. The pertinent clinicopathological findings of patients are summarized in Table 1.

The most common pathologic finding was IgAN (8 biopsy episodes in 7 patients), followed by MN (6 biopsies in 5 patients), FSGS (3 cases), MPGN (2 cases), post infectious glomerulonephritis (2 cases), MCD (1 case), and IgM nephropathy (1 case). Two patients had combined lesions, one was a combination of MN and MPGN, and the other was FSGS and IgAN (Table 2). All patients, who had repeated kidney biopsy, had no change in pathology following treatment (Table 3).

All patients with MN had positive HBeAg, while half of IgAN (2 in 4 tests) did. Of interest, one of

Table 1. Clinical manifestations in HBV-associated glomerulopathy

No	Age/Sex	Manifestations	HT	Hematuria	UA_alb	UPCR	TP_24hr	BUN	Cr	AST/ALT	Renal biopsy	Treatment	Final outcome
1	23/M	NS	none	Microscopic	3+	0.38	-	17	1.5	28/24	IgAN	steroid, endoxan, 3TC	PR
	34/M	AP	none	Non	-	-	1.25	14	1.3	21/20	IgAN	no treatment	Stable
2	74/F	NS	none	Microscopic	3+	2.08	1.76	17	1.4	-	MCD	steroid	PR, but frequent relapse
3	26/M	NS	none	Non	Trace	0.49	-	10	0.5	43/54	FSGS, hilar type + AIN	steroid, 3TC	PR
4	55/F	AH	yes	Microscopic	2+	2.19	-	14	0.8	30/35	IgMN	steroid	CR,
5	23/M	NS	none	None	2+	4.08	-	21	0.9	32/24	MN	steroid, endoxan	PR byadd endoxan
6	30/M	Nephrito-NS	none	Microscopic	0	0.38	0.80	18	1.2	-	MPGN	steroid	MPGN->CR, then became cirrhosis,
	47/M	AP	yes	None	0	0.38	0.09	15	1.0	76/154	Non-IgA mesangial proliferative GN	3TC	PR
7	40/M	NS	none	None	-	-	-			41/31	FSGS	steroid	Lost follow up
8	57/F	AH+AP	yes	Microscopic	3+	5.57	-	43	2.9	-	IgAN	steroid	Died, due to sepsis
9	33/F	NS	none	None	2+	5.59	12.80	8	0.6	-	MN	steroid	CR
10	55/M	AH	yes	Microscopic	1+	0.25	-	18	1.4		IgAN	no	stable GFR
11	45/M	CGN	yes	None	3+	3.04	2.17	32	4.0	76/83	FSGS	no	ESRD
12	29/F	AH+AP	none	Microscopic	3+	2.52	-	9	0.7	-/13	IgAN	no	loss to follow up
13	55/M	AH	none	Microscopic	-	0.26	-	18	1.8	26/33	IgAN	no	Stable
14	51/F	AH+AP	none	Microscopic	2+	2.55	1.33		0.6	22/28	MN	no	Increase proteinuria
	52/F	AH+AP	none	Microscopic	2+	-	1.36		0.6	28/22	MN	3TC	cirrhosis
15	51/F	AP	none	None	3+	0.17	2.27	16	1.2	17/19	IgAN +FSGS	no	CR
16	47//M	AH+AP	yes	Microscopic	-	2.19	-	15	1.4	29/32	IgAN	no	Stable GFR and protienuria
17	58/M	NS	yes	Microscopic	2+	-	8.40	10	0.8	35/18	MN+MPGN	3TC	PR by 3TC, then developed YMDD mutant
18	46/M	NS	none	None	2+	-	4.27	9	1.2	49/49	MN	3TC	CR by 3TC
19	32/M	NS	yes	None	4+	-	11.04	6	0.6	-	MN	steroid	CR by steroid
20	36/M	NS r/o RPGN	yes	Macroscopic	-	4.60	-	74	6.2	21/20	MPGN	endoxan	PR after PE + IFN
	36/M	fail biopsy	yes	Macroscopic	-	4.60	-	74	6.2	21/20	MPGN	endoxan	PR after PE + IFN
21	31/F	NS	yes	Microscopic	2+	1.86	0.94	24	1.2	15/14	Post-infectious GN	no	Spontaneous CR
22	28/F	RPGN	yes	Macroscopic	3+	7.50	2.96	142	6.3	31/39	Post-infectious GN	no	loss follow up
23	22/F	CRF	yes	Macroscopic	4+	-	-	140	38.0	-	Cresentic GN	no	ESRD
24	37/M	RPGN	none	Macroscopic	2+	-	3.07	41	3.5	22/25	IgAN	no	loss follow up

Abbreviation: AP = asymptomatic proteinuria; AH = asymptomatic hematuria; UPCR = urine protein creatinine ratio; 3TC = Lamivudine

MN had "full house" IF staining. HBsAg stain in renal biopsy was checked in two patients, one (MN) was positive for HBsAg and one (MPGN) was negative for HBsAg.

Seven patients received prednisolone treatment (MN = 3, IgAN = 1, FSGS = 1, MCD = 1, and IgMN = 1); one of them received additional oral cyclosphosphamide. Half of the group with steroid treatment alone obtained sustained CR (1 = IgM and 2 = MN) and the remaining 3 cases were PR.

Seven of the remaining patients were treated with anti-viral drugs, 6 had lamivudine and one had interferon-alpha (IFN-α). None of them used combination therapy. The majority, one IFN-a- and four lamivudine-treated patients, had partial response. One case developed YMDD mutation. Only two cases achieved sustained CR, one occurred with simultaneous seroconversion and the other had liver cirrhosis. Of note, all patients receiving the treatment achieved remission either complete or partial.

No specific treatment (ACEI, fish oil, or neither) were prescribed in 10 patients. Two cases obtained sustained CR and the other 2 had progressively declined GFR to ESRD. The remaining 2 cases had stable proteinuria and GFR.

Table 2. Histological diagnosis of HBV-positive patients (N = 28)

Histological diagnosis	Number (%)
IgA nephropathy	8 (29)
Membranous nephropathy	6 (21)
Focal segmental glomerulosclerosis	3 (11)
Mesangiocapillary proliferative GN	3 (11)
Post-infectious GN	2 (7)
Minimal change nephropathy	1 (3.5)
IgM nephropathy	1 (3.5)
Non IgA-mesangial proliferative GN	1 (3.5)
Crescentic GN	1 (3.5)
IgAN + FSGS	1 (3.5)
MGN + MPGN	1 (3.5)

Discussion

Many types of HBV-AN have been disclosed in the authors' series, including MN, MPGN, IgAN, non-IgA mesangial proliferative GN, FSGS, MCD, and IgAN. However, the majority of cases were IgAN. This is inconsistent with previous reports[6,7] that demonstrated MN being the most common. In the study done in the same geographical area with the highest endemicity of HBV infection had also the highest incidence of IgA nephropathy[3]. Several Chinese studies showed association between the HBV and IgAN[9-11]. In the present study, HBV infection might play an important role in the occurrence of IgAN. Since, in Thailand, the incidences of both IgA nephropathy and HBV infection are high; therefore, coincidence might not truly demonstrate the cause-effect relationship.

The pathogenesis of HBV-GN is not fully understood[21,22]. The demonstration of HBsAg and HBeAg in the glomerular deposits suggests an immune complex mechanism leading to glomerular injury. Simultaneously spontaneous renal remission and seroconversion of HBeAg to anti-HBeAg seems to be additional evidence of an immune complex mechanism[8,22]. In the present study, the authors excluded other primary causes of GN with positive for HBsAg and suspected that HBV might play a pathogenetic role in those patients.

The tendency for low C3 and C4 levels in HBV-GN has been occasionally reported, suggesting the activation of the classical complement pathway. Recently, it has been demonstrated that patients with HBV-related MN had inadequate cellular immune response to HBeAg, causing defective clearance of viral particles and virus-infected cells[21]. Thus, the free

Table 3. Pathologic changes in patient with repeated kidney biopsy

Cases	Time between Bx	Indications	1st biopsy results	2nd biopsy result
1	11 years	NS	IgAN 12/22 global sclerosis, 6/22 segmental sclerosis	IgAN 13/20 global sclerosis 7/20 segmental sclerosis; focal TBM
6	17 years	PP	MPGN	MPGN
14	1 years	PP + PH	MN	MN
20	2 days	Inadequacy*	MPGN	MPGN with curvilinear substructure deposits by EM

* There are inadequate amount of kidney tissue on first biopsy, PP = Persistant proteinuria, PH = Persistant hematuria

form of HBeAg is filtered and deposited in sub-epithelial zone of the GBM where it subsequently and locally combines with the anti-HBe antibody, leading to HBV-related MN. In the present study, all of the MN patients had HBeAg positive, but due to laboratory limitation the authors could not demonstrate HBeAg-immune complex in GBM. Thus the incidence of HBV-AN may be overestimated.

The clinical presentations were consistent with previous reports. Edema and hematuria are the leading presentations. Males are slightly predominating. Liver disease activity also tended to be mild or have no symptom of hepatitis, thus liver disease activity might not be related to clinical glomerulopathy.

Treatment of HBV-AN remains controversial[12-14]. It is claimed that steroids might induce the replication of HBV, might prolong the persistence of liver injury, and might lead to acute hepatic decompensation[14-16]. Nevertheless, other authors reported favorable effects of steroids on prognosis of patients with MPGN or MN-associated with HBV infection[17]. There have been conflicting reports of interferon treatment alone for HBV-AN[12,13]. Although, there have been no large series suggesting a definite beneficial effect on HBV-AN, a small group of patients may respond well to this treatment[11,12].

Remission rates both complete and partial in the patients were higher than in the literature with an average rate of 75% (30-60%), notwithstanding treatment. The authors achieved a sustained CR in half of the patients (3 in 6 cases) treated with steroid alone and 2 out of 7 cases (28.6%) treated with anti-viral therapy. Spontaneous remission was demonstrated in 2 (1 with IgA + FSGS, and 1 with post infectious GN) out of 6 patients (33.3%). None of the patients in both treatment groups turned to ESRD which occurred in 2 cases receiving non-specific treatment. Of note, all of the patients who received anti-viral therapy or corticosteroid and had complete follow up were either in complete of partial remission. Undoubtedly, the presented evidence strongly supports the benefit of the specific treatment against non-specific treatment. However, the questions remain whether anti-viral therapy has beneficial effect beyond corticosteroid treatment in the HBV-AN since there were no flares of HBV in patients receiving corticosteroid. Further study needs to be explored.

Conclusion

The manifestations of the presented HBV-AN seem like the previous literatures, but the pathological findings of the kidney showed that IgAN was more common than other pathologies. Besides, the presented remission rate was higher, even without specific treatment.

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รายงานการศึกษาผู้ป่วยโรคไตอักเสบที่เกิดจากการติดเชื้อไวรัสตับอักเสบบีในประเทศไทย

สุรพันธ์ พนมศักดิ์, ทรงเกียรติ หลิวสุวรรณ, สมชาย เอี่ยมอ่อง, เถลิงศักดิ์ กาญจนบุษย์

รายงานการศึกษาผู้ป่วยไวรัสตับอักเสบบีที่มีการอักเสบของเนื้อไต จำนวน 24 รายที่ได้รับการพิสูจน์ชิ้นเนื้อไตยืนยันในโรงพยาบาลจุฬาลงกรณ์ พบว่าผู้ป่วยส่วนใหญ่มีปัสสาวะเป็นเลือด (ร้อยละ 54) รองลงมา ได้แก่ ภาวะบวม (ร้อยละ 50), ความดันโลหิตสูง (ร้อยละ 50), กลุ่มอาการเนฟโฟรติก (ร้อยละ 43) ผู้ป่วยร้อยละ 14 เท่านั้นที่มีการสูญเสียการเนื้อไตอักเสบอย่างรุนแรงและรวดเร็ว ผู้ป่วย 14 ใน 18 ราย (ร้อยละ 74) ตรวจพบ HBeAg ร่วมกับ HBsAg ซึ่งบ่งชี้จำนวนเชื้อไวรัสตับอักเสบชนิดบีที่มีอยู่เป็นจำนวนมากในร่างกายของผู้ป่วย ที่น่าสนใจคือพบภาวะตับอักเสบร่วมด้วยไม่บ่อย ส่วนใหญ่พบพยาธิสภาพของเนื้อไตเป็นชนิด IgA nephropathy (ร้อยละ 29) รองลงมาคือ membranous nephropathy (ร้อยละ 21), membranoproliferative GN (ร้อยละ 11), และ focal segmental glomerulosclerosis (ร้อยละ 11) ตามลำดับ ต่างจากรายงานที่เผยแพร่จากประเทศแถบยุโรปซึ่งพบภาวะ membranous nephropathy เป็นลำดับแรก ๆ ภาวะไตอักเสบสามารถหายจนเกิด complete remission และ partial remission ได้สูงถึงร้อยละ 75 ทั้ง ๆ ที่มีผู้ป่วยเพียง 1 ใน 3 เท่านั้นที่ได้รับยาต้านไวรัส นอกจากนี้ยังพบผู้ป่วยจำนวน 2 รายที่หายเองโดยไม่ได้รับยาใด ๆ ได้เพียงการรักษาประคับประคอง