Effect of Hepatitis B Virus Infection of Membranous Nephropathy††

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Abstract—To elucidate the effect of HBsAg on MN, 107 cases of MN admitted to SNUH from 1979 Jan. to 1985 Dec. were evaluated according to the markers of HBV.

Positive rate of HBsAg in MN was 48% which was higher than normal population and primary GN. Males were affected 4 times greater than females. MN with HBs antigenemia differed from MN without the antigen by having a lower incidence of nephrotic syndrome and azotemia. Serologically, positive rate of rheumatoid factor, ANA and rate of C4 decrement was higher in HBsAg positive patients, indicating the active participation of immune responses. Light microscopy demonstrated MPGN III-like lesions showing subendothelial deposit and double contour with mesangial hypercellularity, segmental change, tubular atrophy and interstitial fibrosis. Immunofluorescent microscopy showed frequent deposits of IgA and IgM in HBsAg positive group, and HBsAg, HBCAg were demonstrated in 76.9% and 31.4% of them.

Although the exact pathogenesis is not clear, the participation of multiple antigen and antibody system including HBsAg and HBCAg was clear, as well as the participation of hepatic dysfunction caused by liver cirrhosis on immune complex of rheumatoid factor, IgA deposit, subendothelial deposit have been proved to meet a concerted effect in the characterization of HBsAg related MN showing lupus-like features.

Key word: Hepatitis B virus, Membranous nephropathy

INTRODUCTION

Most of the patients with membranous nephropathy (MN) do not present with any known causes, about 30% of them are associated with systemic illnesses such as sarcoidosis, malignancies, drugs or infections.

Hepatitis B virus (HBV) infection as a cause of MN was first demonstrated by Combes et al. (1971), who proved the existence of HBsAg in a glomerulus by indirect immunofluorescent method. Thereafter, HBsAg, HBCAg (Slusarczyk 1980) and HBeAg (Takekoshi 1979, Ito 1981, Fruse 1982, Collins 1983) deposed in glome ruli had been proved, and this idea has been advanced that immune complexes formed by the BHBV antigens are deposited on the epithelial side of glomerular basement membrane (Kohler 1973).

Although this causal relationship between HBV infection and MN is well established its clinical and pathological characteristics remained uncertain because most of the reports had been limited in number and to the pediatric patients. In Korea, where the positive rate of HBsAg is 5 to 12% (Kim 1975, Ahn 1983, Yu 1984) among the general population, it seems likely that many cases of MN which had been considered as idiopathic could well be the result of secondary lesions to HBV infection. If this could be proven it would lay an important ground on which the clinical and patho-
logical differences between the idiopathic and HBV
related MN could be better understood, especially
in explaining the features of MN in Korea.

To elucidate the relationship of HBV infection to
MN, we investigated clinical and pathological find-
ings of MN patients based on studies of the pat-
terns of HBV markers.

PATIENTS AND METHODS

1. Patients

107 patients of MN and 11 patients with lupus
nephritis WHO class V membranous lupus were
included for observation. The selection criteria were
those diseases such as neoplasms, diabetes, amy-
loidosis or syphilis. Systemic lupus erythematosus
was diagnosed by American Rheumatism Associa-
tion (ARA) criteria. Pathological criteria for MN
were to Ehrenreich and Churg (1968). These
criteria are: 1) thickening of glomerular capillary
wall; 2) absence of intra or extracapillary prolifera-
tion and exudation; and 3) demonstration of sub-
epithelial and/or intramembranous deposit. Focal
cell proliferation were included.

The patients were divided into four groups
according to the patterns of HBV markers as fol-

Group I: HBsAg, HBsAb and HBCab are all nega-
tive

Group II: HBsAg is negative, HBsAb and/or
HBCab are positive.

Group III: HBsAg is positive regardless of the
results of HBsAb or HBCab tests

LN Class V: Lupus nephritis WHO Class V

Accordingly, 16 patients (15.0%) were Group I,
40 patients (37.4%) were Group II, and 51 patients
(47.7%) were Group III (Fig. 1).

2. Methods

clinical data were obtained by retrospective study
of historical medical records. Hypertension was de-
defined as diastolic pressure > 90 mmHg. Proteinuria
was evaluated with 24-hour quantitative measure-
ments performed on most patients, and nephrotic
syndrome was defined as proteinuria > 0.05 g/kg/
day. Hematuria was defined as centrifuged urine
specimen containing > 10 red cells per HPF.

On evaluation for clinical courses, patients who
were followed-up for more than 25 weeks were
included using the criteria mentioned by Noel
(1979) with some modifications. Remission was de-
defined as the total absence of urinary abnormalities
with normal renal function. Improvement was de-
defined as disappearance of clinical symptoms, per-
sisting mild proteinuria or hematuria with normal
renal function. Progressive disease was defined as
increment of serum creatinine level during the
course of follow up.

Standard biochemical methods were used for the
estimation of creatinine, protein, albumin, and
cholesterol. HBsAg, HBsAb and HBCab in the sera
were tested with radioimmunoassay. Rheumatoid
factor was measured with Latex test kit from latron
company. To measure cryoglobulin, approximately
5 ml of serum was incubated for 48 hours at 4°C.
CH50 was measured by a hemolytic technique
(Mayer 1961). C3 and C4 were determined by ra-
dial immunodiffusion using commercial anti C3 and
anti-C4 serum (Zehningwerke).

Liver biopsies were perfomed in 23 patients us-
ing Vim-Silverman needle.

The renal biopsy tissues obtained by percu-
taneous needle biopsy were evaluated with light
microscopy and with immunofluorescence in each
case; in selected cases, electron microscopy was
also used. Specimens for light microscopy were
fixed with Zenker’s solution, embedded in paraffin,
and cut into 2 μ sections. Sections were stained
with hematoxylin and eosin, periodic acid-Schiff
(PAS), silver-methanamine (PASM) and Masson’s
trichrome. A portion of renal tissue was embedded
in OCT compound (Lab-Tek PRODUCTS) and shaped
frozen in dry-ice and acetone. The forzen sections
of 4 μ thickness were stained with fluorescien-
isothiocyanate FITC conjugated antiseras to human
IgG, IgM, IgA, C3 and fibrinogen (Hyland, Costa
Mesa, Co.) in frozen tissues prepared as above.
Goat anti-HBsAg and rabbit anti-HBcAg were used

![Fig. 1. Groups of MN according to the HBV markers (Group I: HBsAg, HBsAb, HBCab are all nega-
tive; Group II: HBsAg is negative, HBsAb and/or
HBCab are positive; Group III: HBsAg is positive
regardless of the results of HBsAb or HBCab).](attachment:image)
for primary antibodies. Tissues for electron microscopy were fixed in glutaraldehyde, post-fixed in osmium and embedded in Epon. Ultrathin sections were cut on an LKB ultramicrotome, stained with lead citrate and uranyl acetate and examined on a TelsaBS 613 electron microscope. Abnormalities were graded semiquantitatively on a scale of 0 to 3+ as well as classified according to the criteria of Ehrenreich and Churg (1968).

RESULTS

1. Age and sex distributions

The mean age of Group I was 34.3 (range: 18-59) yr, Group II, 31.8 (range: 17-56) yr and Group III, 37.4 (range: 17-62) yr. Although there were no differences in age between the groups, the male to female sex ratio showed a higher incidence in males in Group II and Group III compared with that of Group I (Fig. 2).

2. Clinical findings

The incidences of clinical findings on admission had no differences among the groups (Table 1).

3. Laboratory findings

The massive proteinuria defined by 24 HU protein > 50 mg/kg were found in 81.3% of Group I, 65.0% of group II and 28.5% of group III. Hypercholesterolemia was observed at 81.3%, 55.0% and 46.9% of Group I, II and III, respectively (Table 2). In Group III, SGOT was elevated in 52.6% (20/38), SGPT in 56.4% (22/39), and HBeAg was found in 81.0% (34/42). Liver disease was confirmed in 27 patients by biopsy or endoscopy. The distribution of liver disease was: AVH 1 case, CAH 8 cases, normal 1 case, CPH 8 cases and LC 9 cases.

Table 1. Clinical findings of the patients with membranous nephropathy on admission (%)

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>LN class V**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (&gt;140/90)</td>
<td>25.0</td>
<td>35.0</td>
<td>33.3</td>
<td>13.6</td>
</tr>
<tr>
<td>Edema</td>
<td>62.5</td>
<td>75.0</td>
<td>66.7</td>
<td>54.6</td>
</tr>
<tr>
<td>Oliguria (&lt;500 ml/d)</td>
<td>12.5</td>
<td>27.5</td>
<td>11.8</td>
<td>54.6</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>25.0</td>
<td>25.0</td>
<td>27.5</td>
<td>9.1</td>
</tr>
</tbody>
</table>

*LN class V: lupus nephritis WHO Class V

Table 2. Laboratory findings of patients with membranous nephropathy on admission (% abnormal)

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>LN class V**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine &gt; 1.4 mg/dl</td>
<td>50.0*</td>
<td>22.5</td>
<td>23.5</td>
<td>26.4</td>
</tr>
<tr>
<td>24 HU Prot &gt; 0.05 mg/kg</td>
<td>81.3*</td>
<td>65.0*</td>
<td>28.6</td>
<td>36.4</td>
</tr>
<tr>
<td>Hematuria &gt; 10 HPF</td>
<td>56.3</td>
<td>35.0</td>
<td>56.9</td>
<td>72.7</td>
</tr>
<tr>
<td>Reversed A/G Ratio</td>
<td>56.3</td>
<td>37.5</td>
<td>43.1</td>
<td>72.7</td>
</tr>
<tr>
<td>Albumin &lt; 2.5 mg/dl</td>
<td>50.0</td>
<td>50.0</td>
<td>33.3</td>
<td>72.7</td>
</tr>
<tr>
<td>Cholesterol &gt; 270 mg/dl</td>
<td>81.3*</td>
<td>55.0</td>
<td>46.9</td>
<td>36.4</td>
</tr>
</tbody>
</table>

*p < 0.05, compared with Group III

**LN class V: lupus nephritis WHO Class V
Table 3. Serologic findings of the patients on admission (% abnormal)

<table>
<thead>
<tr>
<th>Serology</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>LN class V**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Factor</td>
<td>0.0*</td>
<td>3.6*</td>
<td>36.4</td>
<td>18.2</td>
</tr>
<tr>
<td>Cryoglobulin</td>
<td>16.7</td>
<td>23.5</td>
<td>13.5</td>
<td>55.6</td>
</tr>
<tr>
<td>ANA</td>
<td>0.0</td>
<td>0.0</td>
<td>7.4</td>
<td>54.8</td>
</tr>
<tr>
<td>Complement 3</td>
<td>0.0</td>
<td>0.0</td>
<td>4.1</td>
<td>72.7</td>
</tr>
<tr>
<td>Complement 4</td>
<td>0.0</td>
<td>0.0*</td>
<td>15.6</td>
<td>72.7</td>
</tr>
<tr>
<td>CH50</td>
<td>28.3</td>
<td>12.1*</td>
<td>39.0</td>
<td>77.8</td>
</tr>
</tbody>
</table>

*p < 0.05, compared with Group III
**LN class V: lupus nephritis WHO class V

Table 4. Clinical course of the patients who were followed-up for more than 25 weeks (number of patients, %)

<table>
<thead>
<tr>
<th>Clinical course</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>LN class V**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>3(30.0)</td>
<td>5(16.2)</td>
<td>3(10.3)</td>
<td>1(14.3)</td>
</tr>
<tr>
<td>Improved</td>
<td>4(40.0)*</td>
<td>14(45.2)</td>
<td>1(3.4)</td>
<td>1(14.3)</td>
</tr>
<tr>
<td>Stable</td>
<td>2(20.0)</td>
<td>7(22.6)</td>
<td>19(65.5)</td>
<td>5(71.4)</td>
</tr>
<tr>
<td>Progress</td>
<td>1(10.0)</td>
<td>5(16.1)</td>
<td>6(20.7)</td>
<td>0(0.0)</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
<td>31</td>
<td>29</td>
<td>7</td>
</tr>
</tbody>
</table>

*LN class V: lupus nephritis class V

The serologic profile of group III showed the following characteristics: a difference in RA positive rate compared with group II, and the reduction rate of C4 and CH50 were more common than in group II (Table 3).

In group III, RA positivity was related to liver cirrhosis and decrement in C4 (P < 0.05*). Among 22 patients upon whom both RA test and liver diagnosis were performed the incidences of liver cirrhosis was 44% (4/9) for RA positive group, but 8% (1/13) for RA negative group. C4 was reduced in 33% (5/15) of RA positive patients but 7% (2/21) in RA negative patients. Among 7 patients with decreased C4 levels, 6 had positive results for rheumatoid factor. Cryoglobulin or HBeAg test results showed no correlation with the results for rheumatoid factor or complement levels.

4. Clinical course

As the average periods from disease onset to the performance of renal biopsy were 9.2 months for group I, 16.2 months for group II, and 20.4 months for group III, there were no statistical differences among the groups.

The clinical courses for the patients who were followed-up for more than 25 weeks also showed no statistically significant difference among groups in the remission or the progression rate (Table 4). Six progressed patients of group III showed higher incidence of azotemia (66.7%) than the patients whose renal function were normal (8.9%) upon admission, and the incidences of hypertension,

![Fig. 3. Stage of MN of the 107 patients and 11 lupus nephritis class V cases.](image-url)
Fig. 4. Light microscopic findings of group III showing mesangial hypercellularity (right), segmental sclerosis (middle) and tubular atrophy (left).

Table 5. Light microscopic findings of patients in each group (% abnormal)

<table>
<thead>
<tr>
<th>Findings</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>LN classV*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GLOMERULUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>43.8</td>
<td>65.0</td>
<td>52.9</td>
<td>45.5</td>
</tr>
<tr>
<td>Hypercellularity</td>
<td>0.0</td>
<td>2.5</td>
<td>13.7</td>
<td>45.5</td>
</tr>
<tr>
<td>Mes. expansion</td>
<td>31.3*</td>
<td>32.5*</td>
<td>68.6</td>
<td>100.0</td>
</tr>
<tr>
<td>Duplication</td>
<td>25.0*</td>
<td>15.0*</td>
<td>82.3</td>
<td>63.6</td>
</tr>
<tr>
<td>Segmental sclerosis</td>
<td>18.8</td>
<td>15.0</td>
<td>31.4</td>
<td>18.0</td>
</tr>
<tr>
<td>Crescent</td>
<td>6.3</td>
<td>5.0</td>
<td>5.9</td>
<td>36.4</td>
</tr>
<tr>
<td><strong>TUBULE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrophy</td>
<td>18.8*</td>
<td>17.5*</td>
<td>47.1</td>
<td>54.6</td>
</tr>
<tr>
<td><strong>INTERSTITIUM</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>37.5</td>
<td>27.5</td>
<td>43.1</td>
<td>81.8</td>
</tr>
<tr>
<td>Inflammation</td>
<td>31.3</td>
<td>32.5</td>
<td>29.4</td>
<td>90.9</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>12.5</td>
<td>12.5</td>
<td>25.5</td>
<td>36.4</td>
</tr>
</tbody>
</table>

*p<0.05, compared with Group III

severity of proteinuria or the stage of MN gave no statistically meaningful differences compared with other patients.

5. Morphologic findings

In accordance to the stage of MN classified by Ehrenreich and Churg (1968) advanced lesions of stage II and IV were 25% in Group I, 32.5% in Group II and 62.7% in group III (Fig. 3).

On light microscopic examination, group III was conspicuous from Group I and II in respect to showing frequent mesangial hypercellularity, mesangial expansion, duplication of capillary walls, segmental changes, tubular atrophy and interstitial fibrosis (Fig. 4, Table 5).

The site of electron-dense deposits evaluated by light and electron microscopy showed massive deposits in subendothelial and mesangial area in Group III. This observation suggested that Group III be divided into two subgroups according to the main site of the deposits, that is, mainly subepithelial (Class V) and subendothelial (Class IVa). Thirty patients were belonged to the former (Lee's class
Fig. 5. Morphologic findings of a patient in group III showing classical findings of MN (Lee, SH).

Fig. 6. Findings of a patient in group III showing massive subendothelial deposit, as well as subepithelial deposit (Kim IS).
Table 6. Site of deposit confirmed by light and electron microscopic examinations (%)

<table>
<thead>
<tr>
<th>Site of deposit</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>LN class V**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subepithelial</td>
<td>100.0</td>
<td>100.0</td>
<td>94.2</td>
<td>100.0</td>
</tr>
<tr>
<td>Mesangial</td>
<td>18.8*</td>
<td>22.5*</td>
<td>80.4</td>
<td>90.9</td>
</tr>
<tr>
<td>Subendothelial</td>
<td>18.8*</td>
<td>12.5*</td>
<td>71.6</td>
<td>72.7</td>
</tr>
</tbody>
</table>

*p<0.05, compared with Group III

Table 7. Immunofluorescent findings of the patient (% deposit more than 1+)

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>LN class V**</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>capillary</td>
<td>82.8</td>
<td>96.2</td>
<td>86.4</td>
<td>80.0</td>
</tr>
<tr>
<td>mesangium</td>
<td>0.0</td>
<td>3.9</td>
<td>11.4</td>
<td>20.0</td>
</tr>
<tr>
<td>IgM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>capillary</td>
<td>18.2*</td>
<td>23.0*</td>
<td>56.8</td>
<td>30.0</td>
</tr>
<tr>
<td>mesangium</td>
<td>0.0</td>
<td>3.9</td>
<td>22.7</td>
<td>30.0</td>
</tr>
<tr>
<td>IgA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>capillary</td>
<td>0.0*</td>
<td>11.5*</td>
<td>36.4</td>
<td>70.0</td>
</tr>
<tr>
<td>mesangium</td>
<td>0.0</td>
<td>0.0*</td>
<td>18.8</td>
<td>20.0</td>
</tr>
</tbody>
</table>

*p<0.05, compared with Group III
**LN class V: lupus nephritis WHO class V

Table 8. Positive rates of HBsAg and HbcAg demonstrated by PAP method in group III (number of patients (% positive))

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Tested</th>
<th>Positive</th>
<th>Positive Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>capillary</td>
<td>26</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>mesangium</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>total</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>HbcAg</td>
<td>capillary</td>
<td>28</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>mesangium</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>total</td>
<td>13</td>
<td>13</td>
</tr>
</tbody>
</table>

Table 9. Effect of LC on MN group III (chi square test)

<table>
<thead>
<tr>
<th>C4</th>
<th>RA Factor</th>
<th>IgA(Cap)</th>
<th>IgA(Mes)</th>
<th>Class IVa*</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>LC*</td>
<td>1</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>nonLC</td>
<td>3</td>
<td>12</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>X²</td>
<td>0.10</td>
<td>4.09</td>
<td>3.88</td>
<td>8.03</td>
</tr>
</tbody>
</table>

*Class IV: MN with extensive subendothelial deposits without mesangial, endocapillary or mesangiocapillary proliferations.
V, Fig. 5), and 28 patients to the latter (Lee’s class IVa, Fig. 4). there were no clinical differences between the two including the ages, serologic results and clinical courses except for a higher association with LC in class IVa(<0.10, $X^2=3.63$).

On immunofluorescent microscopic examination, Group III showed higher rate of lgM and lgA deposit than those of group I and group II (p<0.05). The rates of mesangial involvement were found in 9.1% of Group I, 8.7% of Group II, and 36.4% of Group III (P<0.05*).

In Group III, HBsAg was demonstrated in 76.9%(20/26), 20 in capillary, 13 in mesangium. HBCAg was found in 46.4%(13/28) of cases, 9 in capillary, 8 in mesangium 4 in capillary and mesangium (Table 8).

6. Relation to liver cirrhosis
To evaluate the effect of hepatic dysfunction on HBsAg related MN, above findings were studied in relationship to liver cirrhosis. Liver cirrhosis was frequently combined with rheumatoid factor positivity, lgA deposit and class IVa lesions. Cryoglobulin, ANA, and complements were not influenced by terminal liver disease (Table 9).

DISCUSSION

Hepatitis B virus infection as a cause of MN is well defined by seroepidemiologic studies. The positive rate of HBsAg in MN is reported to be about 45% (Kleinknecht 1979, Nagy 1982), with a wide range of variations according to the region and the age of the study groups. However, the positive rates in MN were higher than control populations. We observed HBsAg in 48% of MN, which was higher than 5-12%(Kim 1975, Ahn 1983) of general population and 24% of primary glomerulonephritis (Ahn 1984). Among the 257 cases with glomerulonephritis with HBV antigen in their glomeruli reported in English literature, 148 cases (58%) were MN. This suggested that the association between MN and HBs antigenemia is more than casual.

The most outstanding difference among the groups was the sex difference. The male to female ratio in Group I was similar to those of other reports (Glassok, 1986). Among the HBsAg related MN, more than 80% of male predominance has been reported (Takekoshi 1978, Kleinknecht 1979, Levi 1980, Hsu 1983, Vecchio-Blanco 1983, Myata 1984). Since the male to female ratio was high in both Group II and III in this series, and reported as 4:1 in HBsAg carriers in Korea (Ahn 1983), it suggested that the male preponderance could be attributed to higher chances of environmental exposure to the antigen or to possible association with cross reactivity between male sex antigen and HBsAg, rather than to association with the glomerulonephritis itself.

Eighty percent of MN is manifested by nephrotic syndrome (Mallik 1983) and this also applies to HBsAg related MN in pediatric patients (Takekoshi 1978, Kleinknecht 1979, Hsu 1983, Seggie 1984). In diagnosing NS in patients with liver disease, there are difficulties in determining the diagnostic standard, because serum albumin level may be reduced and the increase of serum cholesterol level may not be marked in the presence of liver disease. Therefore we made the diagnosis of nephrotic syndrome based on the definition of syndrome as 24 HU with protein more than 0.05g/kg, and on such bases Group III included 29% of nephrotic syndrome, which was lower than Group I or II. Azotemia was rare in Group III in spite of higher incidences of advanced lesions of MN stage III and IV in Group III compared with Group I and II. Other differences in clinical findings were negligible.

Proper evaluation of clinical course was impossible, because there were only few patients who were followed-up for more than 25 weeks. Slow or benign course in HBsAg related MN than in idiopathic group in pediatric patients (Wyznska 1979, Wiggelinkhuizen 1983) was reported as apparent. If it is true (Kleinknecht 1979) then age, in addition to azotemia would be a factor for prognosis. Remission with disappearance of circulating virus antigen (Kecht 1978, Luciani 1980, Nagata 1981, Yamashita 1985, Cadrobbi 1985) was not found in this series.

The complement levels in HBsAg related MN remain to be settled. While some reported hypocomplementemia, others did not (Combres 1971, Kohler 1974, Ainsworth 1974, Kamph 1978, CPC 1978, Kleinknecht 1979, Stratta 1979, Silver 1979, D’amico 1981, Nagy 1982, Cadrobbi 1985). The involved complements were C3(Takekoshi 1979, Cogan 1977, Yoshikawa 1985), C4 (Wiggelinkhuizen 1983, Cadrobbi 1985, Southwest Group 1985) or both (Scully 1982, Collins 1983). The mechanisms of hypocomplementemia in HBsAg related MN are likely due to i) consumption by immune complex formation(Thomas 1979) ii) decreased production in liver (Kourilsky 1973, Notch 1976) and there was no correlation between liver cirrhosis and hypocomplementemia, we ascribe
hypocomplementemia as secondary to increased consumption. However, the participation of decreased production could not be excluded unless radiolabelled complement test or measurement of actiation product were performed, as all of the 7 patients with C4 decrement had elevated SGOT and SGPT.

Chronic liver disease is known as one of the conditions showing more than 30% positivity for rheumatoid factor. Hepatocellular disease in general shows 60–86% positivity and viral hepatitis 71 to 94% (Ziegenfuss 1971, Morris 1978). Some IgM rheumatoid factors comprised of HBsAg HBsAb or HBeAg containing immune complexes (Anderson-Visona 1980). A few case reports (Scully 1982, Collins 1983).

The morphological pictures in HBsAg positive MN can be characterized by mesangial expansion and cell proliferation, double contour, subendothelial and mesangial deposits, segmental changes, tubular atrophy, interstitial fibrosis, and IgM and IgA deposits. These features are not the same as in idiopathic MN previously reported (Porch 1973, Glassok 1986) except for the IgM deposit described in Row (1973) and in some series as being found in over 1/3 of biopsies. The lesions we observed showed much similarity with those of MPGN III except that there was no C3 decrease, mesangial interposition or marked diffuse hypercellularity. Such findings were meaningful, however, cannot be a characteristic for HBs related MN, because the so-called “atypical”, “mixed membranous and proliferative” or “intramembranous” membranous nephropathy had been mentioned in association with systemic disease (Cameron 1979). These features of MN with HBs antigemia were prominent in some cases but in others the morphologic lesions were not different from the idiopathic type. Moreover, marked subendothelial and mesangial deposits were not frequently noted in MN with HBs antigemia among the pediatric patients (Takekoshi 1978, Ito 1981, Fruse 1982). The 3 reports we found (Choi Y 1985, Yoshikawa 1985, Southwest 1985) with observation of subendothelial or mesangial deposits were by electron microscopy, and was different from our series, because they can be visualized clearly by light microscopy as well as electron microscopy. In adults, although the number of reported cases are few, mesangial cell proliferation (Combes 1971, Morzychka 1979, Scully 1982, Collins 1983, Myata 1984), subendothelial deposits, and mesangial deposits (Kohler 1974, Glassok 1982, Collins 1983) were frequently described.

The distinguishing factors noted are 1) age, 2) antigen involved, 3) route of infection, and 4) state of liver disease. As for age, there was no difference in mean age between MN according to its groups and subgroups of MN with HBs antigemia differentiated by main site of deposition, i.e. subendothelial or subepithelial.

The involvement of the antigens, HBsAg, HBCAg and HBeAg were proposed in the literatures, but it is not settled as of yet which antigen plays the main role in provoking MN. In pediatric patients, the relation between HBeAg and MN was demonstrated, its pathogenesis appropriately described as being due to the size of immune complexes of HBeAg small enough to deposit subepitheli ally provoking typical membranous lesions (Takekoshi, 1979). In adults, 7 out of 11 cases reviewed had HBsAg in their glomeruli (Combes 1971, Kohler 1974, Ainsworth 1974, Cogan 1977, Kamph 1978, D'Amico 1981, Scully 1982, Collins 1983); this is different from pediatric cases in which demonstration of HBsAg is rare (Takekoshi 1979, Ito 1981, Fruse 1982), but well correlated with the PAP staining results of ours, which suggesting participation of the multiple antigen-antibody system of HBV infection including HBsAg and HBCAg operating simultaneously inducing morphologic features look like those of lupus nephritis.

The vertical transmission of HBV (Takekoshi 1979) and the severity of associated liver disease may participate also in the production of the characteristic lesion of HBsAg related MN. Mild liver disease was mentioned among the pediatric patients (Takekoshi 1979, Kleinhecht 1979, Hsu 1983), but not in adult cases (Kohler 1974 et al). This series showed the effect of liver cirrhosis on immunologic markers such as rheumatoid factors, IgA deposit and subendothelial deposit. In literatures, it was reported that LC without HBs antigemia was associated with mesangial changes (Eknoyan 1978, Morzychka 1979), mesangial (Eknoyan 1978), subendothelial deposits (Eknoyan 1978, Wilkinson 1982), double contour (Fisher 1959, Jones 1961, Notch 1976, Wilkinson 1982) or IgA deposit (Callard 1975, Eknoyan 1978, Berger 1978, Woodroffe 1981). These findings support the view that advanced liver disease probably plays a role in contributing to the lesion formation of HBsAg related MN; whether it provokes the forma-

plexes remains yet unclear. Had dealt with rheumatoid factor, and many had commented on the relation of HBV immune complex and cryoglobulinemia (McIntosh 1976, Notch 1976, Levo 1978, Tiku 1979). However, the positive rate in MN did not show any differences for each groups. Therefore, cryoglobulin as a marker for active disease in HBV related MN serves no meanings, but is rather related to proliferative lesions (Notch 1976 or induces glomerulonephritis of mixed essential cryoglobulinemia (Levo 1979, Kumer 1982, Lee 1983). ANA of which the positivity was by 14-65% (Jain 1976, Morris 1978) showed higher positive rate in Group III than Group I or II; may be reflect a active immune response, even though HBV induced immune complexes may not been single contributing factor (Boucher 1964).

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HBV抗原 및 항체에 따른 모양성간질성신염의 임상 및 병리학적
소견의 비교 연구

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B형간염감염이 악성사구체신염에 미치는 영향을 알아보고 위하여, 1979년 1월부터 1985년
12월 사이에 서울대학교 병원 내과에 입원하여 신생경을 시행하여 악성사구체신염으로 진단받
했던 107명과 양성경 신염 class V 11명의 임상, 병리적 소견을 비교 검토하였다.

107례를 HBV 표식자에 따라 분류해보면 HBsAg가 양성인 경우는 51례(47.7%)였고 HBsAg
가 양성인 환자의 임상소견은 유사한 군에 비하여 신증후군과 뼈 증, 크레아티닌치의 상승이 적
았다. 혈청학적으로는, 양성인 군에서 rheumatoid factor, ANA양성률과 C4 감소율이 증가되
었다. 병리조직학적으로는 mesangial, subepithelial deposit와 subendothelial deposit의 상
당수 관찰되었고 double contour, mesangium의 확장, 신세뇨관 상피의 변성성 변화가 훨씬하
였으며, 면역혈청 고식사 IgA의 침착을 볼 수 있었다. HBsAg은 76.9%에서, HBsAg은 31.
4%에서 PAP법으로 증명되었다.

HBV에 의한 악성사구체 신염의 병태생리에 관하여는 아직 잘 밝혀져있지 않으나, HBsAg
와 HBcAg을 포함한 여러 항원 항체체에 의한 면역 복합체가 관여한 가능성이 증명되었으며,
아울러 갑상선의 변성, 갑상선의 구체화, HBsAg유발성 사구체신염의 임상적 병리학적 변화 등에
RA factor나 IgA침착에 관여한 것으로 사료되었으며 이와 같은 system의 복합작용은 갑상성
신염에서와 유사한 임상 병리적 소견을 나타내게 하는 것으로 생각된다.