—Case Reports—

Seroconversion of Hepatitis B Envelope Antigen by Entecavir in a Child with Hepatitis B Virus-related Membranous Nephropathy

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Abstract

Membranous nephropathy (MN) is caused by subepithelial deposition of immune complexes in the glomerular basement membrane, with secondary MN arising in association with infection. In secondary MN caused by hepatitis B virus (HBV), seroconversion has been known to occur after the onset of MN, particularly in children. In patients with high serum concentrations of HBV DNA, treatment with interferon-α2b or a nucleoside analog has been reported to induce seroconversion and suppress HBV-DNA levels. We treated a 7-year-old boy who presented with proteinuria and liver dysfunction. He had a history of HBV infection since shortly after birth, as his mother was HBV-positive, and he was neither vaccinated nor treated with immunoglobulin at birth. Chronic hepatitis related to HBV was diagnosed following percutaneous needle biopsy of the liver. Percutaneous renal biopsy revealed HBV-related glomerulonephritis with diffuse global subepithelial and focal segmental mesangial and subendothelial deposits. Therefore, HBV-associated MN was diagnosed. Treatment with the nucleoside analog lamivudine was started to reduce serum HBV-DNA levels, but lamivudine was discontinued and treatment with entecavir was started at a dosage of 0.5 mg/day after 6 weeks because of possible adverse effects. Tests for HB envelope antibody were positive in week 16 of treatment, and proteinuria had resolved by week 22. Elevated levels of aspartate aminotransferase and alanine aminotransferase were seen with both treatments but were probably attributable to the developing immune response to HBV. In the present case, HBV levels needed to be reduced to: 1) lower elevated serum HBV-DNA titers, which put the patient at high risk of hepatocellular carcinoma; and 2) remove the immune complexes causing MN. Use of nucleoside analogs to suppress the HBV load may facilitate early remission of MN, and entecavir therapy did not cause any serious adverse reactions in this case. Given the advent of lamivudine-resistant HBV, entecavir appears promising for patients with elevated serum levels of HBV DNA.

Key words: entecavir, hepatitis B, basement membrane, children

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Introduction

Membranous nephropathy (MN) is caused by subepithelial deposition of immune complexes in the glomerular basement membrane. This entity can be classified into 2 types: idiopathic (or primary) MN and secondary MN, which is caused by infections, such as hepatitis B virus (HBV), or by autoimmune disorders, such as systemic lupus erythematosus.

In secondary MN caused by HBV, seroconversion can occur after the onset of MN, particularly in children. In patients with high serum concentrations of HBV DNA, treatment with interferon (IFN)-α2b or a nucleoside analog induces seroconversion and suppress HBV-DNA levels.

To the best of our knowledge, this report is the first of a pediatric case of HBV-associated MN treated with entecavir monotherapy.

Case Report

The patient was a 7-year-old boy who presented with proteinuria and liver dysfunction.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Normal range</th>
<th>Pretreatment</th>
<th>Posttreatment 16 weeks</th>
<th>Posttreatment 22 weeks</th>
<th>Posttreatment 26 weeks</th>
<th>Posttreatment 38 weeks</th>
<th>Posttreatment 44 weeks</th>
</tr>
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<tr>
<td>WBC</td>
<td>40–80 ×10³/µL</td>
<td>81</td>
<td>124</td>
<td>103</td>
<td>117</td>
<td>78</td>
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<tr>
<td>Hemoglobin</td>
<td>14–18 g/dL</td>
<td>116</td>
<td>11.6</td>
<td>11.2</td>
<td>11.5</td>
<td>11.5</td>
<td>11.3</td>
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<tr>
<td>Platelets</td>
<td>20–40 ×10³/µL</td>
<td>20.9</td>
<td>33.3</td>
<td>27.4</td>
<td>29</td>
<td>33</td>
<td>24.8</td>
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<tr>
<td>Urea</td>
<td>3.2–7.5 mg/dL</td>
<td>4.9</td>
<td>4.5</td>
<td>5</td>
<td>4.5</td>
<td>4.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.6–1.2 mg/dL</td>
<td>0.24</td>
<td>0.37</td>
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<td>0.25</td>
<td>0.27</td>
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<tr>
<td>AST</td>
<td>10–28 IU/L</td>
<td>43</td>
<td>57</td>
<td>46</td>
<td>48</td>
<td>28</td>
<td>25</td>
</tr>
<tr>
<td>ALT</td>
<td>5–33 IU/L</td>
<td>49</td>
<td>83</td>
<td>53</td>
<td>53</td>
<td>15</td>
<td>13</td>
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<tr>
<td>γ-GTP</td>
<td>16–73 IU/L</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Total protein</td>
<td>6.7–8.5 g/dL</td>
<td>6.0</td>
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<td>6.7</td>
<td>6.8</td>
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<tr>
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<td>3.8–5.5 g/dL</td>
<td>2.8</td>
<td>3.1</td>
<td>3.3</td>
<td>3.6</td>
<td>4.3</td>
<td>3.9</td>
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<tr>
<td>HBs Ag</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<tr>
<td>HBs Ab</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
<td>(-)</td>
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<tr>
<td>HBe Ag</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
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<td>(+)</td>
<td>(-)</td>
</tr>
<tr>
<td>HBe Ab</td>
<td>(-)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
<td>(+)</td>
</tr>
<tr>
<td>HBV-DNA/RT-PCR</td>
<td>&lt;2.1 logopies/mL</td>
<td>≥9.0</td>
<td>3.5</td>
<td>3.4</td>
<td>2.4</td>
<td>&lt;2.1</td>
<td>&lt;2.1</td>
</tr>
<tr>
<td>Urine protein</td>
<td>&lt;0.2 g/day</td>
<td>0.9</td>
<td>0.3</td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
<td>&gt;0.1</td>
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</tr>
</tbody>
</table>

Case Presentation

Family history
The boy’s mother was infected with HBV and had positive serum results for HB envelope (HBe) antigen (Ag) but negative results for HBe antibody (Ab). The reverse transcriptase polymerase chain reaction (RT-PCR) yielded ≥9.0 log copies/mL of HBV DNA.

Past history
The boy had undergone a urinary screening test at the age of 3 years which revealed grade 1+ hematuria and 1+ proteinuria. His mother was infected with HBV and transmitted the infection to her son, as he had not been immediately vaccinated and thus did not receive hepatitis B antibodies at birth.

Physical examination
No obvious abnormalities, such as hepatosplenomegaly or jaundice of the bulbar conjunctiva, were identified.

Laboratory examination (Table 1)
Laboratory studies obtained the following results: white blood cell (WBC) count, 8,100/µL; hemoglobin, 11.6 g/dL; platelets, 20.9 × 10⁹/µL; creatinine, 0.24 mg/dL; aspartate aminotransferase (AST), 43 IU/L; and alanine aminotransferase (ALT), 49 IU/L. A
Seroconversion of HBe Antigen

One small sample of liver tissue included slightly enlarged portal areas with lymphocyte infiltration and fibrosis (A, hematoxylin and eosin [HE], ×200). Lymphocytes in portal areas (asterisk) extended irregularly into adjacent hepatic lobes beyond the limiting plate of hepatocytes, indicating piecemeal necrosis and development of interface hepatitis (B, HE, ×600). In hepatic lobes, focal spotty necrosis was seen in areas of hepatocyte loss with lymphocyte infiltration (arrowhead), indicating moderate inflammatory activity, representing grade A2 in Inuyama's new classification of chronic hepatitis (C, HE stain, ×600). Insert in C shows acidophilic degeneration of hepatocytes (Masson trichrome stain, ×800). Fibrosis of portal areas extended into hepatic lobes, sometimes with formation of portal-to-portal (P-P) bridging fibrosis (arrow) (D, Reticulin silver impregnation, ×200). Periportal fibrosis and P-P bridging fibrosis were noted with intact architecture of hepatic lobules, indicating stage F2 according to Inuyama's new classification of chronic hepatitis. Ground-glass appearance of hepatocytes was not prominent in hepatic lobes. However, with Victoria blue stain (E, ×600) and immunostaining for HBsAg (F, ×600), hepatocytes with cytoplasmic staining were detected in hepatic lobes (arrow). In addition, with immunostaining for HBeAg (G, ×600), hepatocytes showing staining in the nucleus (arrow) or cytoplasm (arrowhead) or both were also evident in hepatic lobes. A polyclonal rabbit anti-HBsAg antibody (MLB, Nagoya, Japan) and a monoclonal anti-HBeAg antibody (Kokusai Shiyaku, Kobe, Japan) were used for immunohistochemical staining.

Liver Biopsy

Percutaneous needle biopsy of the liver was performed to determine the pathological characteristics of the liver in the carrier status of HBV. A liver biopsy showed enlargement of portal areas with lymphocyte infiltration and fibrosis (Fig. 1). Portal inflammation extended into hepatic lobes with piecemeal necrosis, and focal spotty necrosis and acidophilic bodies were seen in the hepatic lobes. Periportal fibrosis and portal-to-portal bridging fibrosis were noted with intact architecture of the hepatic lobes. Victoria blue stain and immunohistochemical staining for HBsAg and HBeAg showed the presence of HBV in scattered hepatocytes. We diagnosed hepatitis B-related chronic hepatitis, representing A2, F2, according to
Specimens from light microscopy (A, Periodic acid-methenamine-silver [PAM], ×200; B, Periodic acid-Schiff [PAS], ×600; C, PAM stain, ×800) contained 53 glomeruli, of which 3 glomeruli showed obsolescence (arrowhead in A). Several glomeruli showed mild hypertrophy (arrow in A). All glomeruli showed diffuse thickening of the glomerular capillary walls. Mild focal segmental proliferative lesions were also noted in some glomeruli (arrowhead in B). Diffuse and global subepithelial deposits along the glomerular basement membrane were noted with diffuse global spike formation (arrow in C). No obvious tubulointerstitial or arteriolar lesions were evident.

Immunofluorescence study was performed with fluorescein isothiocyanate (FITC)-conjugated antibodies against immunoglobulin (IgG, IgA, IgM, C3, C1q, and C4) (all antibodies were purchased from MBL, Nagoya, Japan), and nonconjugated monoclonal antibody against HBeAg (Kokusai Shiyaku, Kobe, Japan). Immunofluorescence staining (D–F, ×600) showed granular deposition of IgG (4+) and C3 (4+) in global peripheral and segmental mesangial areas. Deposition of IgM (2+), C1q (2+), and C4 (1+) was also noted in global peripheral and segmental mesangial areas. Importantly, HBeAg was present in global peripheral and segmental mesangial areas.

Electron microscopy (G, ×6,000; H, ×8,000; I, ×30,000) revealed diffuse but irregularly sized and distributed subepithelial electron-dense deposits. There were subepithelial deposits (arrow in G). Mesangial deposits (arrowheads in H) and a few subendothelial deposits (arrow in H) were also evident. No organized structures could be detected in the deposits.

the new Inuyama classification¹.

**Renal Biopsy**

Percutaneous renal biopsy was performed to determine the pathological characteristics of the renal disorder. Under light microscopy, all glomeruli showed diffuse thickening of the glomerular capillary walls with diffuse and global but irregular spike formation (Fig. 2A–C). Mild focal segmental proliferative lesions were also noted in some glomeruli. Light microscopy indicated MN with focal segmental proliferative lesions. Immunofluorescence
staining showed strong intensity of granular deposits of immunoglobulin (Ig)G, C3, and HBeAg in global peripheral and segmental mesangial areas (Fig. 2D–F). Sparse deposits of IgM, C1q, and C4 were also noted in a similar pattern. Electron microscopy revealed diffuse subepithelial and a few subendothelial and mesangial electron-dense deposits without organized structures (Fig. 2G–I). We therefore diagnosed hepatitis B-related glomerulonephritis with diffuse global subepithelial and focal segmental mesangial and subendothelial deposits.

Clinical Course

The boy started undergoing regular blood and urine screening on an outpatient basis, but stopped attending the clinic after 2 years. He resumed screening again after proteinuria was found on a school urine test while in the first year of elementary school.

After hypoproteinemia, hypoalbuminemia, and proteinuria were diagnosed, the patient underwent a renal biopsy and was found to have MN. An elevated serum concentration of HBV DNA and the results of liver biopsy led to a diagnosis of HBV-related chronic hepatitis based on the Inuyama classification. Treatment was started with the aims of lowering the HBV-DNA level and achieving seroconversion. The patient was scheduled to undergo IFN therapy with a nucleoside analog, but treatment was canceled because the serum HBV-DNA level first had to be decreased. The patient was therefore treated with a nucleoside analog without IFN therapy.

Figure 3 shows that treatment with lamivudine was started with a common pediatric dose of 70 mg/day, which succeeded in lowering the serum HBV-DNA level after 2 weeks. The dose was then increased to 100 mg/day, but AST and ALT levels increased, and the patient had occasional headaches. Whether these events represented adverse reactions is unclear, but the drug was changed as a precautionary measure. The 2009 guidelines of the Japan Society of Hepatology recommend using the nucleoside analog entecavir to detect mutant strains of lamivudine-resistant HBV.

Therefore, lamivudine was discontinued, and entecavir was started at a dosage of 0.5 mg/day 6
weeks after the start of treatment (week 6). Levels of both AST and ALT increased, but these changes were regarded as immune responses, and treatment with entecavir was continued. Tests for HBeAb were positive 16 weeks from the start of treatment with lamivudine, and proteinuria had resolved by week 22. Increases in AST and ALT levels from week 28 were again attributed to immune responses, but the frequency of treatment with entecavir was reduced to every other day. By week 38, tests for HBeAg were negative, and AST and ALT levels had returned to baseline values. The headaches that had persisted since the start of treatment with lamivudine also subsided after the frequency of entecavir administration was reduced to every other day. The elevated AST and ALT levels were ascribed to the immune response of the patient to HBV. In fact, tests for HBeAb were positive after the first increase in AST and ALT levels and were negative for HBeAg after the second increase. Furthermore, HBV DNA continued to be undetectable in the serum after the frequency of treatment with entecavir was changed to every other day. No adverse events associated with entecavir were encountered. As previous reports have described, we scheduled the dose of entecavir to be tapered and for treatment to be finished 6 months after seroconversion. Entecavir was started with an oral dose of 0.5 mg given once daily. Then entecavir was administered at a dose of 0.5 mg given once every other day. Serum HBV-DNA levels were monitored at 4-week intervals. To detect the onset of fulminant hepatitis B early, we will monitor hepatic function with clinical and laboratory studies, including measurements of HBV-DNA levels, for at least several years after a nucleoside analog is discontinued.

Discussion

MN is a form of glomerulonephritis that was first classified by Ehrenreich and Churg in 1968. MN is believed to be caused by the subepithelial deposition of immune complexes. Two types can be classified: idiopathic (or primary) MN and secondary MN, which is caused by infections, such as HBV, or autoimmune disorders, such as systemic lupus erythematosus. MN rarely affects children. Yoshikawa et al. have reported that 7 of 16 Japanese children (43%) with HBV-related MN showed nephrotic syndrome.

The genotype distribution for HBV in Japan is 1.7% for HBV/A, 12.2% for HBV/B, 84.7% for HBV/C, and 1% for HBV/D. As such, HBV/B and HBV/C are the predominant genotypes, and many Japanese patients with HBV/C reportedly show high serum concentrations of HBV DNA, persistent HBeAg positivity, and chronic hepatitis. Moreover, the HBV/C genotype predominates among cases of HBV-related hepatocellular carcinoma (HCC) in Japan.

Genotype distributions of HBV were investigated in 118 children in Japan. Genotype C (86%) was the most frequent, followed by genotypes B (9%), D (2.5%), and A (1.0%). Transmission routes of HBV to children were from mothers in 91 patients (77%), fathers in 8 (6.5%), mother or father in 1 (1%), family members other than the parents in 5 (4%), and unknown in 13 (11.5%). In 88 (97%) of 91 children with mother-to-infant transmission, the genotype was C. The proportion of children with genotype C who were infected by their mothers was significantly higher than those of children with genotypes B, D, or A (P<0.01).

In the present case, the patient’s mother had a chronic HBV infection that had not been treated. Her son had received neither HBV vaccine nor immunoglobulin at birth and contracted HBV as a result. The patient exhibited seroconversion after starting treatment with entecavir at 7 years of age. The improvements in hepatic function and the normalization of urinary findings were attributed to the natural course of the disease and the effects of entecavir therapy. Approximately 75% of children with HBV infection undergo seroconversion before reaching adulthood. While this seroconversion reportedly occurs after the onset of HBV-related MN, previous studies have identified elevated serum levels of HBV DNA as a major risk factor for HCC. No previous pediatric studies of entecavir appear to have reported how HBV DNA changes and whether the risk of HCC decreases after seroconversion. In
adults, the risk of HCC increases with the severity and duration of infection, with an annual incidence of less than 0.5% in carriers and of 6% in patients with cirrhosis. The incidence of HCC in Japanese children has been not reported, because HCC usually develops in late adulthood. Children with chronic HBV infection are at long-term risk for liver cirrhosis and HCC. The risk of HCC is positively correlated with the level of serum HBV DNA. The suppression of HBV DNA may reduce the risk of HCC. We believe that patients should be treated with a nucleoside analog to prevent HCC. Some reports suggest that HCC develops in childhood.

In the present case, the need to reduce the HBV level was twofold: 1) to lower elevated serum HBV-DNA titers, which greatly increase the risk of HCC; and 2) to remove the immune complexes causing MN.

According to the new Inuyama classification, candidates for HBV antiviral therapy are patients with necroinflammatory activity of A2 (moderate activity) or greater and fibrosis of F2 (bridging fibrosis) in liver biopsy tissue.

A 1994 guideline by Shiraki et al. on the treatment of pediatric HBV states that patients who test positive for HBeAg, have persistently elevated aminotransferase levels for 6 months or more, and show severe piecemeal necrosis, bridging necrosis, or intralobular inflammation in liver biopsy tissue. The guidelines recommend that treatment should be aimed at sustaining HBeAg negativity and normalizing aminotransferase levels.

In the 2011 guidelines, the eligibility criteria for treatment are an ALT level ≥31 IU/L and a HBV-DNA titer ≥5 log copies in HBeAg-positive patients. In patients younger than 35 years, the guidelines recommend that patients with a baseline serum HBV-DNA level of ≥7 log copies/mL should undergo: 1) long-term IFN therapy (i.e., 24–48 weeks) and 2) entecavir therapy. Furthermore, IFN is recommended as the first-line therapy for genotypes A and B (as stated above, genotype C is the most common in Japan).

Regarding pharmacotherapy, the 2011 guidelines recommend IFN as the first-line therapy in patients younger than 35 years. However, the guidelines also state that an HBV-DNA titer ≤10^4 copies/mL is preferable to enhance the therapeutic efficacy of IFN. In the present case, treatment with a nucleoside analog was started because serum HBV-DNA levels exceeded 10^6 copies/mL. Although most studies of nucleoside analogs have focused on the use of lamivudine, issues with drug tolerance have meant that the most recent guidelines now recommend entecavir as the first-line therapy.

Pawlowska et al. have reported that 24 weeks of treatment with entecavir suppresses HBV-DNA levels in a substantial proportion of children with chronic HBV infection who had been treated ineffectively. In that study, 0.5 or 1 mg of entecavir was administered to 30 children (25 boys, 5 girls) once a day for 24 weeks. The median HBV-DNA level decreased from 7.8 × 10^5 to 6.3 × 10^3 in HBeAg-positive patients (n=22). Furthermore, HBV DNA was undetectable in 5 of the 22 patients after 24 weeks of therapy. That HBV DNA had decreased to undetectable levels in the first 4 weeks of treatment suggests that early disappearance of HBV viremia predicts a favorable treatment response.

Meanwhile, a report by Hasahor et al. described HBeAg seroconversion in a 10-year-old Saudi boy treated with entecavir. The patient was HBSAg-positive, HBsAb-negative, HBeAg-positive, HBeAb-negative, and HBeAb-positive. The pretreatment HBV-DNA titer was ≥5.0 log copies/mL, and the ALT level was 119 U/mL. The HBV genotype was type D. At 6 years of age, the patient was treated with 4 mg/kg/day of lamivudine for 6 months but achieved no improvement in HBV-DNA load and showed no seroconversion. When the boy was 8 years old, treatment with oral entecavir was started at a dosage of 0.5 mg/day. At 12 weeks, HBV-DNA levels were undetectable, and seroconversion of HBeAg was seen. Entecavir therapy was continued for 1 year. At the time of writing, HBV DNA remained undetectable in serum, and HBeAg seroconversion had been maintained.

Another case report by Connor et al. described the resolution of HBV-associated nephrotic syndrome with oral lamivudine in a 6-year-old boy. The patient was HBsAg-positive, HBsAb-negative, HBeAg-positive, HBeAb-negative, and HBeAb-positive.
positive with an ALT level of 77 U/L and an AST level of 61 U/L. Lamivudine was administered at 30 mg twice daily, without side effects. Within 2 months, seroconversion from HBeAg-positive to anti-HBe Ab-positive had occurred. When lamivudine was discontinued after 12 months, the patient was HBeAg-negative, and HBV DNA had fallen to undetectable levels, but proteinuria did not resolve immediately.

In a report on an adult patient, Yang et al.18 chronicled the course of HBV-related MN in a 32-year-old man receiving entecavir monotherapy. The patient was HBsAg-positive, HBeAg-positive, and HBeAb-positive with an ALT level of 102 IU/L and an AST level of 63 IU/L. The HBV-DNA level was 4.2 × 10^5 copies/mL. Urinary protein excretion was 4.66 g/24 hours. After 2 months of treatment, no HBV DNA was detectable. After 3 years of entecavir therapy, virological tests showed HBeAg seroconversion. After 4 years of entecavir therapy, proteinuria had decreased to 0.52 g/24 hours. Previous report19 suggests that lamivudine was administered for 12 months. The follow-up continued for 24 months after the initial treatment19. In our case, preventing the onset of fulminant hepatitis was important. We scheduled the dose of entecavir to be tapered and for treatment with entecavir to be finished 6 months after seroconversion. Entecavir was started orally at a dose of 0.5 mg once daily. Then entecavir was administered at a dose of 0.5 mg every other day. Serum HBV-DNA levels were monitored at 4-week intervals.

These studies and case reports demonstrate that treatment with nucleoside analogs can reduce serum HBV DNA to undetectable levels, where they remain after seroconversion even without treatment. Moreover, no adverse events were observed in any of these studies. Although these findings are promising, further investigations of patients treated with entecavir are needed in the future. Long-term follow-up is necessary whether nucleoside analogs affect the sex organs in patients who discontinue treatment.

Conclusions

Childhood MN is often caused by immune complexes comprising an HBV-related Ag (often HBeAg) and the corresponding Ab. This condition is commonly resolved by seroconversion of the HBeAg. In the present case report, urinary findings and hepatic function both normalized after seroconversion. The use of nucleoside analogs to suppress the HBV load may have facilitated early remission of MN. Entecavir therapy did not cause any serious adverse reactions, and serum HBV DNA was undetectable after 38 weeks of treatment.

The existing literature on children with HBV has tended to focus on the use of lamivudine. However, given the emergence of lamivudine-resistant mutant strains of HBV, entecavir appears set to become the preferred treatment option for patients with elevated serum levels of HBV DNA.

Conflict of Interest: No competing financial interests exist.

References

Seroconversion of HBe Antigen


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