CASE REPORT

HBV associated nephrotic syndrome: resolution with oral lamivudine

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A 6 year old boy presenting with a five month history of fever, lethargy, and anorexia, was found to have hepatitis B associated membranous glomerulonephropathy and nephrotic syndrome. After two months treatment with oral lamivudine, his proteinuria cleared and serum albumin and aminotransferases normalised, associated with disappearance of hepatitis B e antigen (HBeAg) and appearance of anti-HBeAg antibodies. After 12 months, without side effects, lamivudine was discontinued. He remains well 11 months off treatment.

Worldwide, hepatitis B (HBV) infection is an important cause of nephrotic syndrome. The typical renal lesion is membranous glomerulonephropathy (HBVMN). Previous studies showed improvement with alpha interferon (IFN) therapy.^{1–8} Lamivudine is a nucleoside analogue inhibitor of HBV DNA polymerase, which has advantages over IFN for HBV treatment, having less frequent side effects and oral route of administration. To our knowledge, this is the first reported case of HBV associated nephrotic syndrome treated with lamivudine therapy.

CASE REPORT

The patient, a child of mixed race (mother white, father white/Filipino), migrated to Australia from South Africa at 2½ years of age. Before leaving South Africa, he had received childhood vaccinations at a community clinic and sutures for a minor laceration at a local hospital. He presented at 6 years, 3 months of age with a five month history of recurrent fever, lethargy, and anorexia. There was no other significant past medical or family history. He looked well, with weight 19.5 kg (25th percentile) and height 110 cm (3–10th percentile). There was mild digital clubbing, leuconychia, and palmar erythema, but no other peripheral stigmata of chronic liver disease. He was normotensive. The abdomen was soft and non-tender. Borderline hepatomegaly was present (liver span 9 cm), but there was no splenomegaly, renal mass, ascites, or peripheral oedema. Physical examination was otherwise unremarkable.

Persistent heavy proteinuria (urinary albumin/creatinine ratio 390 mg/mmol (normal <5)) and intermittent microscopic haematuria were noted. Serum albumin was persistently decreased at 24–26 g/l. Urea and creatinine were normal. Complement levels were reduced: C3 0.63 g/l (normal range 0.89–1.73) and CH50 25% (normal range 56–174). Renal and abdominal ultrasound was normal. Mild elevations of serum aminotransferases were noted: alanine aminotransferase (ALT) 77 U/l (normal range 17–63), aspartate aminotransferase (AST) 61 U/l (normal range 15–45). Bilirubin, γ glutamyl transferase, alkaline phosphatase, and coagulation were normal. Autoantibodies (antinuclear, antineutrophil cytoplasmic, and antiglomerular basement membrane) were

Figure 1 Electron micrograph of the renal biopsy showing membranous glomerulonephropathy. There is gross effacement of foot processes over thickened glomerular basement membranes. Numerous large electron dense subepithelial deposits are seen in the glomerular basement membranes, with basement membrane material seen between the deposits (stage 2) and focally fusing over the deposits (stage 3). In addition, some capillary loops show small subendothelial deposits. The mesangium shows moderate expansion with medium dense mesangial deposits.

negative and he was seronegative for Epstein-Barr and cytomegalovirus. HBV infection was confirmed with positive HBV surface antigen (HBsAg), HBV e antigen (HBeAg), and HBV core antibody. Antibodies to HBeAg and HBsAg were negative. His mother and four siblings were HBV seronegative.

Renal biopsy (fig 1) showed stage 2 membranous glomerulonephropathy. Immunoperoxidase staining for HBsAg and HBV core antigen (HBcAg) was negative; however, HBeAg staining was not available. Investigations for other causes of liver disease were negative, including α_1 antitrypsin phenotype, serum copper, ceruloplasmin, and serology for hepatitis A and hepatitis C. A liver biopsy (fig 2) showed mild to moderate lobular hepatitis (Scheuer score lobular activity 2) with mild patchy piecemeal necrosis (Scheuer score portal activity 2) and minimal portal fibrosis (Scheuer score 1). Immunoperoxidase staining was positive for HBV core antigen.

Abbreviations: HBeAg, HBV e antigen; HBsAg, HBV surface antigen; HBV, hepatitis virus B; HBVMN, hepatitis virus B membranous glomerulonephropathy; IFN, interferon; Ig, immunoglobulin

Figure 2 Histological examination of the liver biopsy showing mild to moderate lobular hepatitis with mild patchy piecemeal necrosis and minimal portal fibrosis (H&E stain; original magnification $\times 120$).

Figure 3 Serial measurements showing normalisation of serum albumin concentration (solid line) and urinary albumin/creatinine ratio (dashed line) during treatment with lamivudine.

Lamivudine was commenced at 50 mg twice daily, without side effects. Within two months, the patient seroconverted from HBeAg positive to anti-HBe antibody positive, associated with a transient increase in serum aminotransferases. Serum aminotransferase and albumin levels subsequently normalised and proteinuria cleared (fig 3). Lamivudine was discontinued after 12 months. The patient remains HBsAg positive, HBeAg negative. HBV DNA levels (Roche Amplicor Monitor PCR Assay) dropped from 150 800 genomes/ml pretreatment, to undetectable levels during treatment, rising to 1000 copies/ml at follow up nine months off lamivudine. Liver function tests remain normal.

DISCUSSION

In areas where HBV infection is endemic, infection may be acquired vertically or in early life. Our patient probably acquired infection horizontally, with the possibility of iatrogenic infection. The risk of progression to chronic hepatitis is inversely related to age at the time of infection.⁹ Most children infected with HBV by their first birthday will become chronic carriers, placing them at highest risk of eventual complications.⁹ In a long term study, 185 Italian and Spanish children, the majority of whom acquired the disease by horizontal transmission in early childhood, were followed for an average of 13 years; 83% cleared HBeAg on follow up, but only 6% cleared HbsAg.¹⁰ Fifty one (31%) had received specific treatment (nine levamisole, 21 corticosteroids, 21 IFN), but as a group their outcomes did not differ significantly from untreated patients. Recent research in adults suggests that the earlier the development of HBe antibodies (HbeAb), the lower the risk of hepatocellular carcinoma.¹¹

Hepatitis B associated membranous glomerulonephropathy is a distinct entity occurring frequently in hepatitis B prevalent

areas of the world. The disease affects both adults and children who are chronic carriers of hepatitis B virus, with or without a history of overt liver disease. Persistent proteinuria is the typical presentation, and as seen in our patient this is frequently in the nephrotic range. In a large series from South Africa, 76% of children with membranous nephropathy had associated HBV infection.¹² Immunofluorescence findings are characteristic of immune complex disease, with granular deposits of IgG, IgM, and C3 along glomerular capillary walls. While HBsAg has been identified in a proportion of cases,^{13–14} HBeAg is the most likely antigen in immune complexes found in glomerular capillary walls.^{15–17} Such testing was unavailable for our patient. There is conjecture as to whether immune complexes are preformed in the circulation, then deposited in glomeruli, or if they form in situ within capillary walls. The finding of viral RNA in glomerular cells supports the latter theory.¹⁸

The natural history of most cases of HBV associated nephrotic syndrome in children, without specific antiviral treatment, is of gradual improvement. Overall, only 1.4%¹⁹ to 2.8%²⁰ progress to end stage renal disease. In contrast, almost one third of adults with HBVMN eventually progress to renal failure.²¹ In children, the average duration of proteinuria in one study was 30 months. The cumulative probability of remission was 64% at four years and 84% at 10 years.²⁰ Remission of nephrotic syndrome parallels elimination of HBV antigens, especially HBeAg, with resolution of proteinuria occurring within six months of clearing the antigen (HBeAg) in the majority of cases.^{20–22} However, spontaneous clearance of HBV antigens is slow. In a follow up study of 46 black South African children positive for both HBeAg and HBsAg, only 22% had spontaneously cleared both HBsAg and HBeAg after three years, and these had remission of nephrotic syndrome.¹⁹ Our patient seroconverted from HBeAg positive to anti-HBe antibody positive within three months of starting lamivudine (two years after presentation) concurrent with a decline in the amount of proteinuria.

Membranous glomerulonephropathy in childhood is often idiopathic, but may be secondary to a variety of causes (such as HBV, congenital syphilis, systemic lupus nephritis, and other autoimmune diseases). Secondary membranous glomerulopathy generally improves with treatment of the underlying cause, while idiopathic forms may respond to immunosuppressive treatment with corticosteroids and/or cyclosporin. These agents are ineffective in HBVMN.^{16–20} Reported experience with antiviral treatment for HBVMN has thus far been limited to trials of IFN.^{1–8, 22–24} In 20 Chinese children (all HBeAg+/HBsAg+), treated with IFN alfa 2b, 5–8 $\times 10^6$ U subcutaneously three times per week for a year, all achieved sustained remission of proteinuria by three months, and none relapsed after IFN was discontinued.⁸ Sixteen (80%) seroconverted from HBeAg positive to anti-HBe positive, 12 of whom also cleared HBsAg. This was associated with development of anti-HBsAg antibody in eight (40% of entire group). In contrast, 20 controls given placebo all had persistent proteinuria at three months. However, at two years follow up, one third of controls had remission of proteinuria, despite all remaining positive for both HBeAg and HBsAg. These results are interesting, as in general less than 50% of children treated with IFN for chronic HBV liver disease show sustained clearance of HBeAg.^{25–29}

Disadvantages of IFN include expense, the requirement for subcutaneous injection, and frequent side effects such as fever, headache, malaise, myalgia, as well as occasional blood dyscrasias, alopecia, and neuropsychiatric disturbance. In contrast, the incidence of adverse events with lamivudine is considered similar to placebo.

Lamivudine is a nucleoside analogue, which has been proven to be safe and effective against hepatitis B in both adults and children,^{30–36} producing similar rates of HBeAg clearance to IFN therapy.³⁷ In children, a dose of 3 mg/kg/day produced drug concentrations and viral DNA inhibition similar to the standard 100 mg/day adult dose.³⁰ Preliminary data suggest that virologic and biochemical responses achieved in

children with HBV using lamivudine therapy are as durable as spontaneous seroconversion.³⁶

Prolonged lamivudine treatment may result in the development of drug resistant HBV mutations, as a result of amino acid substitutions in the YMDD (tyrosine-methionine-aspartate-aspartate) nucleotide binding locus of HBV polymerase,³⁸ emerging in up to one third of patients in the first year of treatment.^{36 37 39 40} The clinical significance of such mutations is as yet unclear, as emergence of such mutations is generally not reflected in exacerbation of alanine aminotransferase levels or deterioration of histologic score.^{36 40 41} Also, seroconversion to HBeAb positive has been reported in both adults⁴⁰ and children³⁶ with YMDD mutants during lamivudine treatment. The current strategy is to use lamivudine therapy for 12 months,³⁶ although the optimum duration of therapy in children remains to be defined. In general, monotherapy with either lamivudine or interferon leads to sustained viral suppression in less than half of the patients treated for chronic HBV infection, hence the recent trials of combination therapy using lamivudine with IFN which have shown increased rates of seroconversion with minimal occurrence of drug resistant strains.^{34 42}

Lamivudine treatment has been successful in adults with HBV associated polyarteritis nodosa, another immune complex disease,⁴³⁻⁴⁵ and lamivudine has also been successfully used in combination with other antiviral agents to treat HIV associated nephrotic syndrome in a child.⁴⁶ In this instance we chose lamivudine in preference to IFN because of its oral route of administration and fewer side effects, and having achieved HBe Ag seroconversion, normal liver function tests, and undetectable levels of HBV DNA, 12 months therapy was deemed appropriate to minimise the development of mutant forms of the virus.

In general, patients with raised serum aminotransferases between two and five times the upper limits of normal respond best to antiviral treatments for HBV, whether monotherapy with lamivudine^{33 36} or IFN,⁴⁷ or combination therapy.³⁷ However, in HBVMN, antiviral treatment may be associated with resolution of proteinuria and HBeAg seroconversion, even when serum transaminases are normal.⁶ Our patient had moderately increased transaminases when treatment was introduced. These increased prior to seroconversion, then rapidly declined. Antiviral drugs may have additional therapeutic effects on glomerulonephropathy because of immunomodulatory effects.⁴⁸ The cell mediated immune response to HBV is defective in children with HBVMN,⁴⁹ and both IFN⁵⁰ and lamivudine^{51 52} enhance this immune response.

We cannot exclude the possibility that our patient may have spontaneously seroconverted without antiviral treatment, but his prompt clearance of HBeAg and proteinuria, with return of normal serum albumin and transaminase levels, was likely caused by lamivudine treatment. Without antiviral medication, the reported rate of spontaneous remission (clearance of proteinuria with or without seroconversion) is 50% in 30 months.²⁰ We chose lamivudine in preference to IFN because of its oral route of administration and fewer side effects. However, lamivudine is also significantly less expensive than IFN.

This case shows resolution of HBV associated nephrotic syndrome with oral lamivudine treatment. Further assessment of this agent with randomised controlled trials in children with HBV associated membranous glomerulonephritis is indicated. Although it is cheaper than IFN, the current cost may limit its application in the developing world.

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