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Hepatitis B-associated nephrotic syndrome in Jamaican children

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Summary Between December 1984 and November 1996, 171 children under 12 years old presented to the University Hospital of the West Indies with nephrotic syndrome. Hepatitis B surface antigen (HBsAg) was found in ten (6%) of these children, eight of whom had membranous nephropathy (MN), and one each had mesangial proliferative glomerulonephritis (MesN) and minimal change nephrotic syndrome (MCNS). Only those children with MesN and MCNS were steroid-sensitive. The HBsAg-positive status was identified incidentally on screening. At a mean follow-up of 34 months, seven of ten children had experienced complete or partial remission and three had persistent nephrotic syndrome, although none was in renal failure. Six of the ten had biochemical hepatitis. All the children were still HBsAg-positive. Hepatitis B virus (HBV) is a factor contributory to nephrotic syndrome in Jamaican children. As diagnostic clinical markers for HBV-associated nephropathy are usually absent, all children presenting with nephrotic syndrome should be screened for HBsAg. A policy should be implemented in Jamaica for screening pregnant women and at-risk groups for HBsAg, as well as for immunising susceptible neonates, in order to reduce the incidence of HBV-associated pathology.

Introduction

Hepatitis B virus (HBV) infection is ubiquitous.The prevalence of asymptomatic carriers is highest in countries or areas of low socio-economic status and high levels of overcrowding. Jamaica is an island in the Western Caribbean with an estimated population of 2.6 million, 31% of whom are under 14 years of age.[1] The society is multi-racial and consists primarily of Blacks of African descent, followed by East Indians, Chinese, Syrians and Caucasians. The island is divided into fourteen administrative parishes. At the time of the study, hospitals in six parishes provided consultation in general paediatrics, but only the University Hospital of the West Indies (UHWI) offered a paediatric nephrology service and served as the referral centre for patients with problematic renal disease.

In December 1984, protocols were introduced at UHWI to standardise the investigation and management of paediatric renal disease. This included routine screening for HBsAg. By November 1996, ten children with nephrotic syndrome had been detected as HBsAg-positive. There had been no documentation of HBV-associated renal disease in Jamaican children prior to this study, nor were there any data on the prevalence of HBV in the child population.

This case series documents the clinicopathological features of these ten HBsAg-positive nephrotic children and explores the factors associated with HBV infection in this group.

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Materials and Methods

One hundred and seventy-one children less than 12 years of age who presented consecutively for the first time with nephrotic syndrome to UHWI between December 1984 and November 1996 were enrolled in the protocol. Independent records of these children were compiled by one of the authors. All of them were screened for secondary nephropathy by measuring anti-streptolysin O titre, anti-nuclear factor, VDRL, C3 complement and HBsAg. Haemoglobin (Hb), Hb electrophoresis and liver function tests (alkaline phosphatase, gamma glutamyl transferase, serum glutamic oxalo-acetic transaminase and bilirubin levels) were determined. Blood urea, creatinine, electrolytes, serum proteins and 24-hour urine protein measurements were also performed on all patients. Glomerular filtration rate (GFR) was estimated by the Schwartz formula.[2] It was not possible to determine C4 levels, CH 50, circulating immune complexes, hepatitis Be antigen or any hepatitis B antibodies.

During follow-up, management of all the HBsAg-positive children was supervised by the paediatric nephrology service. The specific follow-up outcome measures documented were response to steroids, remission, relapse and complications.

The date of onset of nephrotic syndrome was determined by the date of onset of oedema. Nephrotic syndrome was diagnosed when serum albumin was <25 g/l with proteinuria >50 mg/kg/day.[3,4] Renal impairment was defined as GFR <80 ml/min/1.73 m^2. Steroid sensitivity was diagnosed as remission occurring within 28 days of daily prednisone at 2 mg/kg/day in divided doses,[4] and steroid resistance as failure to attain remission during this period of treatment.[4] Remission was deemed spontaneous if it occurred without steroid therapy or after steroids were tapered or discontinued. Complete remission was defined as resolution of proteinuria, hypoalbuminaemia and oedema.[4,5] Partial remission was resolution of hypoalbuminaemia and oedema but with persistent, asymptomatic, non-nephrotic proteinuria.[5] Hypertension was defined according to guidelines established by the Second Task Force on Blood Pressure Control in Children.[6] Anaemia was defined as haemoglobin <12 g/l for age >6 years and <11 g/l for ages 1–5 years. Hepatomegaly was diagnosed when the liver span was greater than the mean for age[7] and splenomegaly when the spleen was palpable. Percutaneous renal biopsy was performed in all HBsAg-positive children, with informed consent, and renal biopsy specimens were processed by methods previously described.[8] Histological appearances were classified according to accepted pathological criteria.[9,10]

The parents or guardians of the HBsAg-positive children were interviewed to determine possible modes of transmission and susceptible contacts. Requests were made to screen all contacts for HBsAg. The Public Health Department of the Ministry of Health was notified and immunisation of seronegative contacts was arranged with the relevant health centres.

Results

Ten (6%) of the 171 nephrotic children were HBsAg-positive. Other serological tests were negative in these children, and haemoglobin electrophoresis in nine of the ten was AA. The other child had no fixed sickled cells on blood film. There were seven boys and three girls, all of African descent. Two were from Kingston and St Andrew and the others lived in rural parts of other parishes. Paediatricians referred all ten children. Thirty-nine close contacts were identified but only 16 individuals from eight families consented to be tested. The average (SD) number of close contacts per household was five (three). Sixty per cent of the HBsAg-positive children came from households of six or more members. None of the eight mothers tested was HBsAg-positive. The only HBsAg-positive close contact documented was the 12-year-old brother of the boy with

MCNS. Only three contacts attended for hepatitis B immunisation (all from the same family). There was no history of jaundice, hepatitis or blood transfusion in any patient, mother or other family members. No child had been sexually abused or used illicit drugs. Four children had a past or present history of skin sepsis.

The mean age at diagnosis of nephrotic syndrome in the HBsAg-positive children was 6 years. The mean time interval from onset of symptoms to diagnosis of nephrotic syndrome was 2.1 months (range 1 week to 6 months) and 6.9 months from onset of symptoms to diagnosis of HBsAg-positivity (range 1 month to 2.5 years). HBV infection was not suspected or diagnosed before referral to UHWI.

Membranous nephropathy was the predominant histological appearance in eight of the ten children and included pure membranous nephropathy (PMN) (four) and membranous with mesangial proliferation (Mmes) (four). There was one case each of pure mesangial proliferative glomerulonephritis (MesN) and minimal change nephrotic syndrome (MCNS). Children with PMN were older than those with MesN and MCNS. Electron microscopy was available for six renal biopsies. Four showed diffuse subepithelial and/or intramembranous electron-dense deposits, and in two of these the deposits had focal mesangial extension. In the remainder, electron-dense deposits were absent and the typical ultrastructural findings of MCNS and MesN were evident. Immunofluorescence studies could be performed in only two patients (both with MN). There was bright staining of peripheral capillary loops to antisera against IgG, and C4 in both, and to C3, IgM and IgA in one. Both were negative for fibrinogen. C3 immunofluorescence was unavailable in the second child.

Anaemia and gross and microscopic haematuria were present only in the MN group. Hypertension was noted in four children, two of whom had PMN. One child with PMN had splenomegaly and subsequently developed progressive splenomegaly and worsening liver function tests. His liver histology revealed portal triaditis only. At initial presentation to UHWI, four children had abnormal liver function tests, though none was symptomatic of liver disease. Neither clinical nor biochemical hepatitis was noted at presentation or on follow-up in the child with MCNS. Hypocomplementaemia was documented in seven children including six of the eight in the MN category (Table 1).

At a mean follow-up period of 34 months after diagnosis of nephrotic syndrome (range 4–89 months), no child had renal impairment, one was persistently hypertensive (PMN subgroup) and six had developed

TABLE 1. *Clinical features at presentation.*

Parameters	Patients by histological type			
	PMN (4)	Mmes (4)	MesN (1)	MCNS (1)
Mean age at diagnosis (yrs)	8.2	5.9	1.3	2.3
Anaemia	2	1	–	–
Microscopic haematuria	2	2	–	–
Gross haematuria	2	2	–	–
Hypertension	2	1	1	–
Reduced GFR	–	2	1	–
Abnormal liver function tests	2	1	1	–
Hypocomplementaemia	3	3	1	–

Figures in parentheses show the number of patients in each group. PMN, pure membranous nephropathy; Mmes, membranous with mesangial proliferation; MesN, mesangial proliferative glomerulonephritis; MCNS, minimal change nephrotic syndrome; GFR, glomerular filtration rate.

TABLE 2. *Clinical features at follow-up.*

Parameters	Patients by histological type			
	PMN (4)	Mmes (4)	MesN (1)	MCNS (1)
Mean duration (mths)	36	27	27	68
Hypertension	1	–	–	–
Reduced GFR	–	–	–	–
Abnormal liver function tests	3	2	1	–
Hypocomplementaemia	2	1	–	–
Full remission	1	3	1	1
Partial remission	1	–	–	–
Persistent nephrotic syndrome	2	1	–	–

Figures in parentheses show the number of patients in each group. PMN, pure membranous nephropathy; Mmes, membranous with mesangial proliferation; MesN, mesangial proliferative glomerulonephritis; MCNS, minimal change nephrotic syndrome; GFR, glomerular filtration rate.

deranged liver function tests, though no child became jaundiced. All remained HBsAg-positive. Hypertension resolved after a mean 7.5 months (range 2 weeks to 14 months). Hypocomplementaemia persisted in three children, all of whom had MN; it resolved in the others after a mean 5.5 weeks.

Six of the ten children experienced full remission and one had partial remission. The two with MesN and MCNS continued to have steroid-sensitive relapses with intervening periods of full remission. Four children in the MN category received steroids (prednisone 2 mg/kg/day in divided doses followed by alternate-day dosing for 3–4 weeks). In all of them, steroids had been started prior to the diagnosis of HBsAg-positivity. None of the four was initially steroid-sensitive, but three subsequently (off steroids) had complete spontaneous remissions and one a partial remission. After a spontaneous remission, one child with Mmes had two steroid-sensitive relapses. An untreated 5-year-old boy with PMN had two relapses after spontaneous remission. Remission in the children with MN occurred at either 2 or 9 months after the onset of nephrotic syndrome, regardless of whether or not steroids were given. However, the only childen who failed to remit were those who had never received prednisone.

Discussion

This case series represents the first documentation in the Caribbean literature of HBV nephropathy in children. The actual number of children affected might be underestimated as only children from parishes served by paediatricians were referred. It is possible that children in other parishes might have been misdiagnosed and treated as idiopathic nephrotic syndrome, despite atypical clinical features such as steroid resistance. Currently, the prevalence of HBV infection in Jamaican children is unknown. The occurrence of HBV infection in this series of children with nephrotic syndrome underscores the need for evaluation of the true prevalence of HBV infection in the wider childhood population. Routine antenatal screening for HBV is also not done. We propose that this be introduced in the antenatal period to identify and treat susceptible neonates.

The most commonly described renal pathology in HBV infection is membranous nephropathy.[11–15] Membranoproliferative glomerulonephritis, MesN and MCNS have also been described.[12,15,16] Since the clinical presentation of nephrotic syndrome and steroid sensitivity followed the pattern of idiopathic disease, it is conceivable that

HBV infection in our two children with MesN and MCNS coincided with rather than caused the renal disease.

The clinical features of HBV nephrotic syndrome are seldom distinguishable from those of idiopathic disease,[5] although the older age at presentation, gross haematuria, hypocomplementaemia and elevated liver enzymes are 'soft' diagnostic clues.[14–17] However, clinical diagnostic criteria are notoriously unreliable. Our series supports this observation and, without routine screening for HBsAg, these children would have been missed, as was the case at their primary hospital. In HBV MN, transaminase levels are usually elevated, although jaundice is uncommon. Histopathological changes in the liver vary from chronic active persistent hepatitis to the minor inflammatory abnormalities seen in our patients.[14,16,18] The deranged liver function tests in six children during follow-up is cause for concern and careful monitoring for more serious liver disease is warranted as long as HBsAg carriage persists.

The long-term outcome in HBV MN is reported to be good,[11,13,17] with spontaneous remission occurring in up to 86% within 5 years of onset of symptoms.[11,13,17,19] Renal function is well preserved,[17,18] although progression to chronic renal failure has been described.[11,14,19] Although remission is said to coincide with HBsAg seroconversion to the HB antibody-positive and HBsAg-negative states,[13,16,19] remission occurred in our patients without seroconversion. The role of steroids in treating this disease is debatable. The consensus is that they have no beneficial effect in the management of HBV MN and are not recommended.[11,17,19] Steroids have been shown to prolong the HBV carrier state and have the potential risk of enhancing viral replication.[19] However, in our two (MesN and MCNS) cases in whom HBV infection appeared to be coincidental with idiopathic renal disease rather than causative, discretion was exercised and steroids used judiciously. The treatment of HBV nephropathy remains unsatisfactory. Most recently, interferon has been used in some centres with variable success.[11,16,17] Economic constraints would limit the use of such treatment options in our centre.

Based on data from blood bank donors[20] and antenatal clinic attendees,[21] it would appear that Jamaica falls into the low prevalence group for HBsAg. HBV may be transmitted parenterally, sexually, vertically or horizontally.[12,19,22] In eastern Asia, vertical transmission is the predominant route of childhood infection,[12] while in Senegal[23] and Taiwan[13] horizontal transmission appears more common. All the mothers tested in our series were HBsAg-negative, but, because of our inability to test for antibody to HBsAg or anti-hepatitis B core antigen, we might have missed those who had seroconverted. The only HBsAg-positive contact identified was a sibling of a patient whose mother tested HBsAg-negative. The possibility of horizontal transmission cannot be excluded.

Our series demonstrates that HBV-associated nephropathy contributes to the spectrum of nephrotic syndrome in Jamaican children. We recommend that routine screening for HBsAg be performed as part of the diagnostic evaluation of all children with nephrotic syndrome. HBV is not innocuous. As the true prevalence of HBV infection island-wide is unknown, one should not be led into complacency by the low prevalence suggested by blood bank data. HBV infection is preventable. The screening of pregnant women for HBV, therapeutic intervention in susceptible neonates and hepatitis B immunisation of infants and children would help reduce HBV-associated pathology. Current national budgetary constraints in Jamaica would, however, dictate that priority be given to high-risk groups.

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