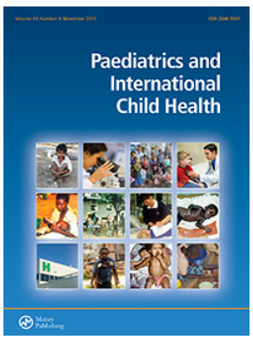

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Kidney disease in hepatitis B surface antigen-positive children: experience from a centre in south-west Nigeria and a review of the Nigerian literature

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ABSTRACT

Background: Kidney disease is an important extra-hepatic manifestation of hepatitis B virus (HBV) infection. However, there is paucity of recent literature on kidney disease in children and adolescents with HBV infection from several parts of sub-Saharan Africa including Nigeria.

Objective: To review the pattern of kidney disease in hepatitis B surface antigen (HBsAg)-positive children and adolescents seen at a tertiary hospital in south-west Nigeria.

Methods: A retrospective study was undertaken of HBsAg-seropositive children with kidney disease managed at University College Hospital, Ibadan, from January 2004 to December 2015. Patients were identified from the paediatric nephrology unit admissions and the renal histology registers.

Results: 24 children and adolescents were studied, 17 of whom were male (70.8%), and the median age was 10.0 years (range 3–15). Ten (41.7%) had nephrotic syndrome, five (20.8%) had non-nephrotic glomerulonephritis, five (20.8%) were in end-stage renal disease (ESRD), including a patient with posterior urethral valves, and four had acute kidney injury secondary to acute tubular necrosis. Renal histology was available for 10 patients: nine had nephrotic syndrome associated with minimal change disease in six, focal segmental glomerulosclerosis in two and one had membanoproliferative glomerulonephritis. The patient with non-nephrotic glomerulonephritis had diffuse global sclerosis.

Conclusion: The pattern of kidney disease in HBV-positive children demonstrated a predominance of nephrotic syndrome, followed by non-nephrotic glomerulonephritis, ESRD and acute kidney injury. Better diagnostic facilities and treatment are required. Prevention of HBV infection by universal childhood immunisation is the ultimate goal.

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ELISA, enzyme-linked immunosorbent assay; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; IgA, immunoglobulin A; KDIGO, Kidney Disease Improving Global Outcomes; MCD, minimal change disease; MPGN, membranoproliferative glomerulonephritis

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Introduction

Kidney disease is an important extrahepatic manifestation of hepatitis B virus (HBV) infection and various forms of glomerular disorders have been described in patients with chronic HBV disease. These include membranous nephropathy, membranoproliferative glomerulonephritis (MPGN), mesangial proliferative glomerulonephritis, immunoglobulin A (IgA) nephropathy, focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) [1,2]. In children, the most commonly reported association between HBV and kidney disease has been with membranous nephropathy [1,2].

The prevalence of HBV-associated glomerulonephritis tends to parallel the prevalence of HBV infection. HBV-associated glomerular disease has been reported from regions with low, medium and high hepatitis virus endemicity [3–5]. However, the greatest number of reports, and therefore the sources of greatest detail, are from South-East Asia and South Africa during periods of high regional endemicity of HBV infection [2,6–9]. The pattern usually observed in children is that the disease occurs mainly in males and membranous nephropathy is the most common histopathology. Spontaneous regression of nephrotic syndrome occurs in 30–60%

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of patients with HBV membranous nephropathy and it usually coincides with seroconversion of the anti-HBe antigen. The disease, however, runs a benign course in most children and only a minority (1.4–2.8%) progress to end-stage renal disease (ESRD).

It is unclear whether the higher rates of renal disease reported in South Africa and South-East Asia compared with other parts of sub-Saharan Africa are because of better access to facilities for HBV detection and renal investigations rather than a higher prevalence of chronic HBV infection [10,11]. Additionally, in highly endemic settings, a decline in HBV infection rates and HBV-associated glomerular disease has been recorded following the introduction of universal childhood HBV immunisation [2].

Reports on the prevalence of HBV infection in Nigerian children estimate that the rate of HBsAg seropositivity in children and adolescents was 6.7–40% before introduction of the HBV vaccine into the National Programme on Immunisation in 2004 (Table 1). A recent meta-analysis of the prevalence of HBV infection in Nigeria noted a pooled prevalence of 11.5% in children aged <12 years [12]. The current high prevalence may have been associated with logistical problems associated with ensuring universal and timely immunisation against HBV infection leading to delayed administration of HBV vaccines [13–15].

Management of several forms of kidney disease in many sub-Saharan African countries is a challenge because of the poor socio-economic conditions. There is limited access to diagnostic facilities, immunosuppressive medication and renal replacement therapy. Documentation of positive HBsAg in Nigerian children with kidney disease creates additional challenges in terms of the financial burden of laboratory investigations for diagnosing and monitoring the HBV infection, and limited facilities for renal histology. In addition, financial constraints restrict the choice of and access to antiviral agents. These challenges also contribute to limited data on HBV infection and kidney disease in Nigerian children (Table 2).

A description of the clinical spectrum of kidney disease in HBsAg-positive patients is an important initial step towards understanding the challenges, designing interventions and assessing the outcome of any interventions. This article reviews the clinical and histological spectrum of kidney disease in HBsAg-positive children and adolescents attending University College Hospital Ibadan (UCH).

Methods

A retrospective analysis of case records of HbsAg-seropositive children and adolescents with kidney disease managed by the Paediatric Nephrology Unit, UCH between January 2004 and December 2015 (144 months) was undertaken. HBsAg screening is routinely performed in patients who are scheduled for haemodialysis and in those with nephrotic syndrome. In addition, screening for HBsAg is usually requested in the evaluation of children with diseases of the kidney and the urinary tract when the disease is not a congenital anomaly.

HBsAg-positive patients with kidney disease were identified from the paediatric nephrology admissions and renal histology registers. Results of chemical pathology investigations and HBsAg were also extracted.

Laboratory investigations

HBsAg was determined using third-generation ELISA kits at the Department of Medical Virology, University of Ibadan. Hepatitis B surface antigen status was determined by rapid screening kit in the Department of Haematology, UCH.

At UCH, renal biopsy is usually undertaken in patients with suspected secondary nephrotic syndrome, and in patients with chronic kidney disease (CKD) and non-nephrotic glomerulonephritis (provided they are not in end-stage renal disease or do not have shrunken kidneys on ultrasound). During the study, renal biopsy was sometimes limited by caregivers' financial constraints. In the earlier stage of the study, the non-availability of renal biopsy needles was a barrier. Renal diseases were diagnosed histologically using haematoxylin and eosin stain along with three special stains which were periodic acid schiff (PAS), Masson's trichrome and Jones silver stains. Renal biopsies were analysed by light microscopy only. Immunofluoresence or electron microscopy was not undertaken on any of the biopsy samples as these facilities are not available. In addition, laboratory investigations and treatment in many patients were limited by financial constraints as payment is usually out-of-pocket [21].

Definitions

Nephrotic syndrome was defined as massive proteinuria and hypo-albuminaemia with hyperlipidaemia [22]. Massive proteinuria was defined as 24-hour urinary protein >40 mg/m^2/h or protein dipstick of ≥3+ [22].

Hypertension was defined as blood pressure ≥95th percentile for age, gender and height [23]. Non-nephrotic glomerulonephritis consisted of hypertension, azotaemia and proteinuria with or without haematuria. Glomerulonephritis included both nephrotic syndrome and non-nephrotic glomerulonephritis [22]. Chronic kidney disease was staged according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines [24].

In patients with clinical features of septicaemia or haemoglobinuria, acute kidney injury (AKI) was attributed to acute tubular necrosis. ESRD was defined as the need for dialysis or death from renal failure in patients with clinical features of underlying chronic kidney disease [16,24].

Table 1. Studies on the prevalence of HBsAg in Nigerian children (hepatitis B virus vaccine was introduced into the Nigerian Programme on Immunisation in 2004).

Authors	Year	Location	Com/hosp-based	Sample size	Type of study	Age	Population	Prevalence of HBsAg
Francis et al. [30]	1971	Ibadan	Com	423	Cross-sectional	4–20 yrs	School children	6.7%
Fakunle et al. [31]	1981	Zaria	Hosp	242 (61 aged <10 yrs)	Cross-sectional	NA	Children & adults	45.9% in children <10 yrs
Abdurrahman et al. [10]	1983	Zaria	Hosp	Cases (NS): 50 Controls: 61	Case-control	NA	Children NS cases & controls	Cases: 36% Controls: 45.9%
Johnson et al. [32]	1986	Ibadan	Hosp	122	Cross-sectional	6 m–14 yrs	Children	15.6%
Abiodun et al. [33]	1989	Benin	Hosp	Cases (HB S): 143 Controls: 161	Case-control	6 m–12 yrs	Children	HbS: 39.2% Controls: 19.3%
Abiodun et al. [34]	1991	Benin	Hosp	437	Cross-sectional	2 m–15 yrs	Children	10.8%
Angyo et al. [35]	1995	Jos	Hosp	501	Cross-sectional	6 m–12 yrs	Children	19.5%
Angyo et al. [36]	2001	Jos	Hosp	Cases (HB S): 507 Controls: 501	Case-control			Cases: 22.7% Controls: 19.6%
Chukwuka [37]	2004	Nnewi	Com (urban)	237	Cross-sectional	5-12 yrs	Children	7.6%
Bukbuk [38]	2005	Maiduguri	Com (rural)	150	Cross-sectional	10–13 yrs	Children	44.7%
Odusanya [39]	2005	Sabongidda-ora	Com (rural)	Cases (HBV vaccinated): 223 Controls: 219	Case-control	1–4 yrs	Children	Cases: 1.3% Controls: 4.6%
Agbede [40]	2007	Ilorin	Hosp	70	Cross-sectional	<1–5 yrs	Children	10%
Alikor et al. [41]	2007	Portharcourt	Hosp	251	Retrospective study of HBsAg requests	≤16 yrs	Children	12.4%
Onakewhor et al. [42]	2009	Benin	Hosp	620	Cross-sectional	Neonates	Neonates	0.96%
Ugwuja *et al* [43]	2009	Abakaliki	Com.	785	Cross-sectional	12–17 yrs	Children	4.1%
Adoga et al. [44]	2010	Abuja & Nasarawa	Hosp-based	1891 (1056 aged ≤ 20 yrs)	Cross-sectional	≤10–60 yrs	Children & adults	5.1% in patients aged ≤20 yrs
Okonko [25]	2012	Ibadan	Hosp	217		<10–17 yrs	Children	0.5%
David et al. [45]	2012	Ekiti	Com	1000	Cross-sectional	9–20 yrs	Children	11.5%
Sadoh et al. [14]	2013	Benin	Hosp	153		1–90 days	Children	16.3%
Sadoh et al. [13]	2014	Benin	Hosp	150	Cross-sectional	2 m–15 yrs	Children	13.8%
Jibrin et al. [46]	2014	Sokoto	Hosp	Cases (HB S): 300 Controls: 300	Case-control	6–15 yrs	Children	Cases: 17.3% Controls: 10.7%
Musa et al. [12]	2015	NA	NA	NA	Metanalysis		Children & adults	11.5% in children aged ≤12 yrs
Ikobah et al. [47]	2016	Calabar	Com	749	Cross-sectional	11–19 yrs	Children	1.2%
Nwokedi et al. [48]	2010	Kano	Hosp	6395 (adults and children)	Retrospective	<10 to >50 yrs	Children & adults	19.5% in patients aged <10 yrs
Bukbuk et al. [49]	2016	Maiduguri	Com	836 (175 aged <10 yrs)	Cross-sectional	0–56 yrs	Children & adults	24.9% in children aged <10 yrs

Notes: Com, community; HBsAg, hepatitis B surface antigen; Hb S, sickle cell anaemia; hosp, hospital; NA, not available; NS: nephrotic syndrome. (Hepatitis B virus vaccine was introduced into the Nigerian Programme on Immunisation in 2004).

Table 2. Studies of hepatitis B infection and kidney disease in Nigerian children.

Authors	Year	Location	Type of study	Sample size	HBsAg seropositive *n* (%)	Renal histology in HBsAg-seropositive patients with kidney disease	Other remarks
Abdurrahman et al. [10]	1983	Zaria	Case-control	Cases (NS): 50	Cases: 18 (36)	MPGN: 9	Histology in cases with HBsAg in kidneys
				Controls: 61	Controls: 28 (45.9)	QMN: 5 PGN: 2 CGN: 1 Miscellaneous: 1	MPGN: 8 PGN: 2 CGN: 1 MCD: 1
Anochie et al. [19]	2003	Port Harcourt	Case series: CRF	45	2 (4.4)	NA	The two HBsAg-seropositive children had NS
Ladapo et al. [18]	2012	Lagos	Case report	1	1 (100)	MN	Sustained remission of NS following treatment with lamivudine
Asinobi et al. [16]	2014	Ibadan	Case series: ESRD	53	4 (7.5)	NA	
Ladapo et al. [17]	2014	Lagos	Case series: NS	108	0	NA	
Asinobi et al. [20]	2015	Ibadan	Case series: renal histology	1997–2001: 22 2006–2013: 56	1997–2001: 0 2006–2013: 7 (12.5)	MCD: 4 FSGS: 2 MPGN: 1	
Present study	2016	Ibadan	Case series	24	24 (100%)	MCD: 5 FSGS: 2 MPGN: 1 DGS: 1	

Notes: CGN, chronic glomerulonephritis; CRF, chronic renal failure; DGS, diffuse global sclerosis; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; HBsAg, hepatitis B surface antigen; MPGN, membranoproliferative glomerulonephritis; MCD, minimal change disease; NS, nephrotic syndrome; QMN, quartian malaria nephropathy; PGN, proliferative glomerulonephritis.

Statistical analysis

Categorical data were described using proportions. Non-categorical data were analysed as median and range. All analyses were undertaken using the IBM SPSS (International Business Machines Statistical package for social sciences) data editor version 21.

Ethics approval

Ethics approval was granted by the University of Ibadan/University College Hospital Ethics Committee. Data were anonymised.

Results

Patients

A total of 24 children and adolescents, 17 male (70.8%), with ages ranging from 3 to 15 years (median 10.0) were studied. Ten (41.4%) had nephrotic syndrome, five (20.8%) had non-nephrotic glomerulonephritis, five (20.8%) were in ESRD, and four (16.7%) had acute kidney injury (AKI) secondary to acute tubular necrosis.

Nephrotic syndrome

The patients with nephrotic syndrome were 3–12 years. Eight of the ten were male. Renal biopsy results were MCD in five, FSGS in two and MPGN in one. Two of the patients with nephrotic syndrome also had CKD stage G3a, and another had CKD stage G2.

Non-nephrotic glomerulonephritis

Five patients had non-nephrotic glomerulonephritis. Three of the patients with non-nephrotic glomerulonephritis had background CKD. Chronic kidney disease was G3a in one of the patients and stage 1 in the other two. One of the patients with CKD had diffuse global sclerosis on renal biopsy. The two other patients had acute glomerulonephritis, one of whom also had clinical features of rapidly progressive glomerulonephritis.

End-stage renal disease

Five other patients were in ESRD when they were found to be HbsAg-positive. One of them had undergone ablation of the posterior urethral valves at the age of 12 years. Another patient had nephrotic syndrome and had defaulted from follow-up for approximately 3 years. End-stage renal disease was secondary to non-nephrotic glomerulonephritis in three patients.

Acute tubular necrosis

Four patients had AKI secondary to acute tubular necrosis. In two, the acute tubular necrosis was secondary to intravascular haemolysis and one other patient had sickle cell anaemia and sepsis.

Discussion

There are few reports of the spectrum of kidney disease in HBsAg-positive Nigerian children (Table 2). In the

present study, there were 24 HbsAg-positive children and adolescents with renal disease over a 12-year period (2004–2015). The findings in this study are in part different from observations by Ladapo et al. in Lagos as they did not document positive serum HBsAg in 108 children with nephrotic syndrome who were seen between 2008 and 2013 [17]. The different HBsAg seropositivity in both studies may relate to differences in the study period, study population and prevalence of HBsAg positivity in Lagos and Oyo States.

There is heterogeneity in the prevalence of HBsAg in different parts of Nigeria, ranging from 0.5 to 46.8 in different parts of the country, as shown in a previous meta-analysis [12] and in Table 1. A recent study from Ibadan showed a low rate of HBsAg seropositivity in children attending a secondary health facility [25]; however, our study was undertaken in a tertiary centre with a potentially higher rate of HBsAg among attendees. Differences in access to immunisation, sociocultural practices and prevalence of risk factors for vertical and horizontal transmission of HBV infection may account for the differences. Additionally, the prevalence of HBV infection varied between different time periods [12] with an annual decline of 0.8% noted between 2000 and 2013 which might be related to the introduction of routine childhood HBV immunisation in 2004.

In a study published in 1983 before the inclusion of HBV vaccination in the Nigerian immunisation schedule, Abdurrahman and colleagues in Northern Nigeria found an HBsAg prevalence of 36% in patients with nephrotic syndrome and a higher prevalence of 45.9% in controls. However, their renal histology findings demonstrated HBV antigens, immunoglobulins and C3 complements in the glomeruli of 12 of 18 patients with nephrotic syndrome and positive serum for HBsAg. The findings of HBV antigens in the glomeruli support an aetiological role for HBV in at least some of these cases [10].

While the nephrotic syndrome is the most common clinical renal disorder associated with HBV infection, patients with non-nephrotic glomerulonephritis and a nephritic/nephrotic picture have also been reported [2,10,26]. Consistent with previous reports [2,10,26], in this study there was a predominance of nephrotic syndrome and non-nephrotic glomerulonephritis in HBsAg-positive patients with kidney disease.

Hepatitis B membranous nephropathy usually runs a benign course with only a minority progressing to end-stage renal failure [2] In this study, however, a relatively high proportion of patients had ESRD. This is consistent with a previous report from Saudi Arabia in which four of seven children with HBV-associated membranous nephropathy developed ESRD [27].

The role of hepatitis B infection in patients with AKI is not clear. Fulminant hepatitis has been associated with AKI, but it was not documented in any of our patients [28]. On the other hand, non-fulminant HBV infection is a rare cause of acute kidney disease [29]. To more accurately delineate the role of hepatitis B infection in children with AKI, additional serology for hepatitis B antigens and antibodies will be required and renal biopsy undertaken in selected patients.

The study has several limitations. Firstly, HBsAg was the only available seromarker of HBV infection, thus limiting characterisation of HBV infection in the patients. Secondly, renal biopsy was not undertaken in all patients with glomerulonephritis, and, when renal histology was undertaken, it was limited to light microscopy only; facilities for immunofluorescence or electron microscopy were not available. The presence of HBsAg could not therefore be demonstrated on renal histology, and patients with HBV-related nephropathy were not identified. The study, however, provides recent data on the spectrum of kidney disease in HBV-positive Nigerian children, and potential areas of support and further research.

Prospective, multi-centre studies are required to further describe the role of HBV infection in children in sub-Saharan Africa. Potential areas of support for HBsAg-seropositive children with kidney disease include access to other viral markers of HBV infection such as HBV DNA viral load, and renal histology including immunofluorescence and electron microscopy. Antiviral agents should be made available for the treatment of affected children.

To conclude, the spectrum of kidney disease in HBsAg-seropositive children and adolescents in Ibadan is described. Patients with HBsAg will require support in the areas of access to other markers of HBV infection, renal histology and antiviral therapy. Universal immunisation of children to prevent HBV infection and related kidney disease is the ultimate goal.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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