

Nephrotic Syndrome in South African Children: Changing Perspectives in the New Millennium



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The epidemiological landscape of nephrotic syndrome (NS) in South Africa has changed drastically in the New Millennium. Although the pattern of disease in the 3 main non-Black racial groups (White, Indian, and Mixed race) mirror that seen in Western countries, Black African children show a pattern of disease that is at variance with these 3 racial groups. The incidence of infectious diseases, particularly hepatitis B virus associated nephropathy has sharply declined to being almost extinct in Black children in the New Millennium whereas HIV-related nephropathy surfaced. However, following the widespread use of anti-retroviral therapy, its incidence has also decreased dramatically. Focal segmental glomerulosclerosis (FSGS), which was once uncommon, has, in the New Millennium, emerged as one of the most challenging forms of NS across all racial groups, particularly in Black children. Although the introduction of calcineurin inhibitors, mycophenolate mofetil and monoclonal antibodies (e.g., rituximab) has improved the outcome of children with FSGS, the response in Black children is less than optimal, with those having single gene mutations being universally unresponsive to all forms of immunosuppression.

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KEY WORDS: children; hepatitis B; HIV; nephrotic syndrome

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Nephrotic syndrome (NS) is one of the most commonly encountered glomerular diseases in children and a major contributor to the workload of pediatric nephrologists. The estimated worldwide incidence of the disease is 4.7 per 100,000 children (range 1.15–16.9).^{1,2} Worldwide, research has shown that certain ethnic groups, specifically South Asians and Africans, have a higher incidence of NS, suggesting environmental and/or genetic influences on the disease.³ Also, strong racial differences with regard to histopathological subtypes, response to treatment, and outcome have been documented in studies from South Africa.^{4,5}

South Africa is described as a “Rainbow Nation,” given its ethnic diversity; in the last century, the apartheid government segregated individuals according to race, with 4 major races being recognized: Black, Indian, White, and Mixed race (descendants from Black, White, and slaves from West and East Africa

and from the Far East).⁶ During the late 1970s, the profile of the disease described showed a pattern of disease in Indians, Whites, and those of Mixed race being similar to that in the Western world.^{5,7–9} The conspicuous features of NS in Black children, however, differed from that of the other 3 racial groups: there was a paucity of minimal change disease (MCD) on histopathology, a high incidence of steroid resistance irrespective of histopathological pattern, with a less satisfactory outcome, and an identifiable causative agent in many children.^{5,7,8} The high prevalence of infections, lower socio-economic status, environmental factors, inequality of access to health care services, and genetic factors were postulated as possible reasons for these differences.

In this narrative review of NS in South Africa, we aim to highlight the changing spectrum in the epidemiology, histopathological pattern, management, and outcome of children with NS prior to the New Millennium and that reported in the literature thereafter.

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Literature Search Strategies and Data Collection

Search engines such Google Scholar and PubMed were explored, and other studies were identified through reference lists of relevant publications. The search

terms included “nephrotic syndrome”; “children”; “South Africa”; “HIV”; and “hepatitis B”. The search was customized to publications before 2000 and after 2000 (i.e., the New Millennium). Inclusion criteria included the following: all children 1 to 16 years old with NS in South Africa, and only English-language articles or those available in English translation. The following were excluded: patients >16 years old; non-English-language articles; no abstract available or access to full-text article; combined pediatric and adult data where it was difficult to extract pediatric data; non-South African studies; and case reports. Reports on children with congenital or infantile NS were also excluded from this review, as these were only case reports.

Information extracted included year of publication, region of study, authors, study period, sample size, NS (primary NS, hepatitis B-associated NS, and HIV-associated nephropathy) prevalence, age, sex, race, renal histopathology, treatment, and outcome.

Data Collection

All descriptive information was extracted and tabulated on an Excel Spreadsheet (Microsoft Office for Windows, version 10; Microsoft Corporation, Redmond, WA).

Publication Results

There were a total of 43 publications on NS published from 1972 to June 2018: 25 publications before 2000 and 18 publications after 2000. A total of 24 publications were on primary NS (14 from KwaZulu-Natal and 9 from Gauteng) (Table 1), and 14 publications were on hepatitis B-associated nephropathy (9 from KwaZulu-Natal, 2 from Gauteng, and 3 from the Western Cape) (Table 2). There were 5 publications on HIV-associated nephropathy (4 from KwaZulu-Natal and 1 from the Western Cape) (Table 3). One publication was excluded because no text or abstract was available.

Nephrotic Syndrome in South Africa Before 2000

Primary Nephrotic Syndrome

In the 1970s, there were several reports that documented the profile of NS in children in South Africa.^{5,7,8,10,11} This was during the apartheid era, when population groups were segregated based on color. The juxtaposition of different population groups, namely, White, Black, Indian, and Mixed race, each with its own unique background and environmental experiences, showed distinct differences in the disease pattern, with striking differences in the distribution of the various histopathological types of NS within these population groups. In addition, the clinical trajectory of the disease in Black children was at variance with

that in other regions in Africa and that described in developed countries.⁵

Adhikari *et al.* and Coovadia *et al.* reported a startling contrast of the histopathological lesions seen in Black and Indian children. In addition, neither group corresponded to what was described in earlier reports from other regions in Africa. The majority of Black African patients had evidence of glomerular damage, with no Black child having evidence of MCD on histopathology. Membranous and membranoproliferative lesions were the most common findings that were associated with unresponsiveness to steroids. The majority of Indians (90%) had MCD, which was steroid sensitive. There were 41 children (9 Black and 32 Indian) who did not undergo biopsy.^{8,11}

In a follow-up study, Adhikari *et al.* reported on the absence of “true” MCD in Black South African children. The authors reported 15 (13%) of 115 Black children having biopsy-confirmed MCD on histopathology based on light microscopy findings. A total of 53% of Black children with MCD failed to respond to a standard course of oral corticosteroids or cyclophosphamide. These patients also had a much older peak age of presentation compared to Indian children (7–8 years). The lack of responsiveness to oral corticosteroids and cyclophosphamide in Black children with obvious glomerular lesions prompted the authors to conclude that such immunosuppressive therapy should be avoided in these children.⁷

In 1 of the largest series of NS, reported by Bhimma *et al.*, from Durban, South Africa of 636 children over a 20-year period (1976–1995; 306 Black children, 307 Indian, and 23 Mixed race), typical steroid-sensitive NS was found to be uncommon among Black children, with only 14.4% showing steroid sensitivity. In Black children, there was a poor correlation between histopathological findings of MCD and steroid response. Eighteen (56%) of 32 Black children with MCD on biopsy were steroid resistant. In contrast, 127 of 135 (94.1%) Indian children with biopsy-proven MCD were steroid sensitive. In children of Mixed race, 5 (21.7%) had steroid-sensitive disease.⁵

In a report by Prinsloo from Pretoria of 60 black children with NS in 47 of 60 children who received steroids, 15 (32%), including 6 of 9 children with MCD, responded to treatment.¹² This group of Black children had a paucity of MCD on biopsy, confirming the findings by Adhikari *et al.*⁷ and Coovadia *et al.*⁸ van Biljon reported that in 67 children with NS, 74% had MCD, and 11 children with clinical and biochemical data in keeping with MCD did not undergo kidney biopsy and were presumed to have MCD. Only 2 black children had MCD, the most common histopathological finding being FSGS in Black children.¹³ Kala *et al.* also

Table 1. Publications of primary nephrotic syndrome in South Africa before and in the New Millennium

Year	Period	Author	Study region (province)	No. of NS patients	Mean age and range (mo)	Race				Histopathology					
						Black	Indian	Mixed race	White	MCD	FSGS	MN	MesCap	MesProl	Other
Before 2000															
1972 ^a	1961–1965	Levin <i>et al.</i>	Johannesburg (Gauteng)	37	<120	37									
1976 ^b	1968–1974	Adhikari <i>et al.</i>	Durban (KwaZulu-Natal)	51	6 (14–132)	30	21			11	1	17	16	4	2
1979 ^c	N/A	Coovadia <i>et al.</i>	Durban (KwaZulu-Natal)	130		74	56			42	64				
1983 ^b	1966–1980	Adhikari <i>et al.</i>	Durban (KwaZulu-Natal)	171	(84–96)	115	56			57					
1985 ^c	N/A	Adhikari <i>et al.</i>	Durban (KwaZulu-Natal)	77		44	33			20		12			
1986 ^c	1973–1985	Prinsloo	Pretoria (Gauteng)	60	75 (8–144)	60				9	10	5		10	11
1992 ^c	N/A	Adhikari <i>et al.</i>	Durban (KwaZulu-Natal)	125	45 (25–168)										
1993 ^b	1982–1988	Kala <i>et al.</i>	Johannesburg (Gauteng)	40	55 (21–89)	40					40				
1994 ^b	N/A	Ramjee <i>et al.</i>	Durban (KwaZulu-Natal)	56	86 (12–180)	19	37			32	19				
1995 ^c	1986–1994	van Biljon	Pretoria (Gauteng)	67	51 (3–144)	14	3	6	44	57	2				
1995 ^c	1981–1993	Kala <i>et al.</i>	Johannesburg (Gauteng)	343	73 (14–141)	343				82	8				
1996 ^c	N/A	Ramjee <i>et al.</i>	Durban (KwaZulu-Natal)	40							10	14		5	
1997 ^b	N/A	Ramjee <i>et al.</i>	Durban (KwaZulu-Natal)	57	72 (12–180)						26				
1997 ^d	N/A	Ramjee <i>et al.</i>	Durban (KwaZulu-Natal)	33						4	10	14		5	
1997 ^b	1976–1995	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)	636	74 (18–180)	306	307	23		168	136	26	22	21	
1997 ^b	1997	Adhikari <i>et al.</i>	Durban (KwaZulu-Natal)	7	67 (36–96)	3	4				7				
1997 ^b	1977–1997	Thomson	Durban/Pretoria/ Johannesburg	720	<192	720				197	291			42	20
New Millennium															
2001 ^b	1970–1997	Adhikari	Durban (KwaZulu-Natal)	75	65	43	32				75				
2006 ^b	2002–2006	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)	20	55 (25–90)	8	12				20				
2011 ^b	1986–2009	van Biljon	Johannesburg (Gauteng)	358	58 (0,5–144)	278	80			109	80	14	13		22
2013 ^b	2003–2011	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)	4	107,5 (61–142)	4						4			
2016 ^d	1996–2010	Parbhoo	Johannesburg (Gauteng)	440	44 (12–162)	100	5	4		112					
2017 ^b	2004–2013	Bakhief <i>et al.</i>	Johannesburg (Gauteng)	163	63 (24–192)	111	22	16	14	69	57			6	

FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MesCap, mesangiocapillary; MesProl, mesangioproliferative; MN, membranous nephropathy; NS, nephrotic syndrome; SR, steroid resistant; SS, steroid sensitive.

^aExcluded from study because no abstract/full text was available.

^bFull-text publication and abstract available.

^cAbstract only.

^dThesis.

Table 2. Publications on hepatitis B–associated nephropathy in children in South Africa before and in the New Millennium

Year	Study period	Author	Study region (province)	No. of NS patients	No. of HBV patients	Mean age and range (mo)	Race				Histopathology					
							Black	Indian	White	Mixed race	MCD	FSGS	MN	MesCap	MesProl	Other
Before 2000																
1983 ^a	N/A	Wiggelinkhuizen	Cape Town (Western Cape)	114	28	72 (24–144)					14	4	28	4	19	1
1983 ^b	N/A	Adikhari <i>et al.</i>	Durban (KwaZulu-Natal)	31	3	48–132										
1986 ^b	1973–1985	Prinsloo ^c	Pretoria (Gauteng)	60	4	75 (8–144)	60				9	10	5		10	11
1987 ^a	1969–1985	Wiggelinkhuizen	Cape Town (Western Cape)	388	46	74 (1–156)	20			43				63		
1988 ^b	N/A	Milner <i>et al.</i>	Johannesburg (Gauteng)	45	14	56 (18–30)								14		
1993 ^a	1981–1998	Coovadia <i>et al.</i>	Durban (KwaZulu-Natal)	178	57	6–144	178				32	14	60		30	41
1994 ^a	1969–1990	Gilbert	Cape Town (Western Cape)	81	71	79 (13–164)								70	1	
1998 ^a	1976–1996	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)	131	93	86 (20–200)	131							70		
1999 ^a	1995–1997	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)		31	96 (24–156)	31							31		
New Millennium																
2001 ^a	1995–1997	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)		31	96 (24–156)	31							31		
2002 ^a	1995–1997	Sithebe <i>et al.</i>	Johannesburg (Gauteng)		29	96 (24–156)	29							29		
2002 ^a	1995–1998	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)		30	96 (24–192)	30							30		
2002 ^a	1995–1998	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)		30	96 (24–192)	30							30		
2002 ^a	1997–1999	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)	39	24	(0–192)	39							36	2	1
2003 ^a	1984–2001	Bhimma <i>et al.</i>	Durban (KwaZulu-Natal)		119	84 (12–168)								119		

FSGS, focal segmental glomerulosclerosis; HBV, hepatitis B virus; MCD, minimal change disease; MesCap, mesangiocapillary; MesProl, mesangioproliferative; MN, membranous nephropathy; NS, nephrotic syndrome.

^aFull-text publication and abstract available.

^bAbstract only.

^cStudy included primary and hepatitis B–associated NS.

Table 3. Publications on HIV-associated nephropathy in children in South Africa in the New Millennium

Year	Period	Author	Study region (province)	No. of NS patients	HIV NS	Mean age and range (mo)	Race					Histopathology				
							Black	Indian	Mixed race	MCD	FSGS	MN	MesProl	MesCap	Other	
Before 2000																
1997 ^a	1977–1997	Thomson ^b	Durban/Pretoria/Johannesburg	720	N/A	<192	720				197	291	42		20	
New Millennium																
2007 ^c	1996–2005	Kala et al.	Johannesburg (Gauteng)	60	60	78				1	7			1		
2007 ^c	N/A	Nourse et al.	Cape Town (Western Cape)	14	14	67 (6–192)	12		2			5		4	5	
2012 ^a	2001–2010	Ramsuran et al.	Durban (KwaZulu-Natal)	71	51	80 (4–156)	50		1		4	64				
2017 ^d	N/A	Gulu et al.	Durban (KwaZulu-Natal)	70	14	82 (40–109)	56					56				
2018 ^a	2005–2011	Asharam et al.	Durban (KwaZulu-Natal)	64	64	84 (24–169)	31	33		1	50			7	6	
2018 ^a	N/A	Nandlal et al.	Durban (KwaZulu-Natal)	34	13	168 (98–195)	13					34				

FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; MesCap, mesangiocapillary; MesProl, mesangio proliferative; MN, membranous nephropathy; N/A, not available; NS, nephrotic syndrome.

^aFull text publication and abstract available.

^bReport included primary NS and HIV-associated NS.

^cAbstract only.

^dThesis.

reported a high incidence of steroid sensitivity in children from Johannesburg compared to Durban. In all, 82 Black African children (23.9%) had MCD; spontaneous remission occurred in 5 (6.1%); 56 (68.2%) had steroid sensitive disease with complete remission, 5 (6.1%) had partial remission after treatment with oral steroids, and 11 (13.4%) were nonresponsive.¹⁴

In the earlier reports of NS in children in South Africa FSGS was rarely reported.^{7,12,15} Thus, from being a marginal therapeutic issue in the 1970s and 1980s, by the late 1990s, FSGS had become the single most difficult form of NS to manage. Bhimma et al., in their review of NS over a 20-year period, reported FSGS as the second most common histopathological variety of NS (28.6%),⁵ much higher than the 3.7% reported by Adhikari et al. in 1976,¹¹ in line with worldwide trends showing a rising incidence of FSGS.^{16–18} In keeping with published reports, these authors recorded only 6 children (4.4%) responding to steroids, which prompted the use of i.v. immunosuppressive therapy in these patients.^{5,10} In a review of kidney problems in Black South African children, Thomson reported a slightly higher incidence of FSGS (31.3%) in Johannesburg, FSGS being the most common histopathological form of NS in Black children in this region.¹⁹

Kala et al. reported the prevalence of tuberculosis (TB) to be 37.5% in 40 children with FSGS compared to 6% in a comparable group of children with MCD. After a mean follow-up period of 2.4 years, the mean estimated creatinine clearance of children with FSGS and TB was significantly reduced by 46% compared to the initial value in children with FSGS and TB but remained stable in the group with FSGS without TB. These authors concluded that TB is relatively common in Black South African children with FSGS and that this may have a deleterious effect on kidney function.²⁰

Based on the unusual characterization of NS in Black African children and the typical features among Indian children, Adhikari et al. further explored associations between human leukocyte antigen (HLA) and NS in 20 Indian children with MCD and 12 Black African children with membranous NS.²¹ HLA Bw44, which is part of HLA B12, was found at a significantly higher frequency in Indian children with MCD than in controls (45% vs. 12% respectively; $P < 0.004$; relative risk [RR] = 5.8). Black African children had a significantly increased frequency of HLA Bw21 compared with controls (15% and 1% respectively; $P < 0.004$; RR = 22.1). The majority of Black African children with membranous nephropathy were hepatitis B carriers (9 of 11 HBsAg positive). The authors concluded that the interactions between genetic factors and environmental influences were central to the pathogenesis of NS in

both groups of children with their respective forms of NS.²¹

In a further series of experiments, Ramjee *et al.* undertook an investigation of the pathogenesis of NS and the use of noninvasive tests to predict the response to steroids and underlying kidney histopathological diagnosis in children with NS. Direct measurements of pore size was determined by detecting fixed anionic sites using polyethyleneimine on the glomerular basement membrane and an indirect measure of membrane charge on red blood cells using Alcian blue in 40 children with NS compared to controls. The authors found a reduced membrane charge in children with NS. The reduction in membrane charge was greater in steroid-resistant children. Excretion of glomerular proteins was restricted by size (≤ 80 kd) in children with steroid-resistant NS but was not restricted in FSGS, membranous nephropathy, and membranoproliferative glomerulonephropathy. These authors also reported on the distribution of glomerular anionic sites using polyethyleneimine and ultrastructural changes in the adjacent glomerular basement membrane of 33 children with NS. They found a moderate inverse correlation between anionic site numbers and proteinuria (estimated by urinary protein:creatinine ratio) in children with MCD only ($r = -0.6$). These findings suggest that the main cause of proteinuria was likely to be depletion of negative charge on the glomerular basement membrane in steroid-sensitive NS and distortion of capillary pore size in other histopathological forms of NS, with probable overlap of these mechanisms, especially in FSGS.^{22,23} To evaluate the use of a noninvasive test to distinguish between steroid-sensitive and steroid-resistant NS, Ramjee *et al.* compared electrophoretic patterns of urinary proteins in 32 children with steroid-sensitive NS to 19 children with biopsy-proven FSGS who were steroid resistant.²⁴ The urinary electrophoresis of all 32 children with steroid-sensitive NS (presumed MCD) revealed albumin and transferrin bands only, whereas 19 children with FSGS showed additional excretion of IgG and low-molecular-weight proteins (lysozyme, β_2 -microglobulin) irrespective of histopathological pattern. Based on these findings, the authors concluded that sodium dodecyl sulfate (SDS)–polyacrylamide gel electrophoresis (PAGE) was useful in distinguishing steroid-sensitive from steroid-resistant NS.²⁴

In another set of experiments, these authors compared the reliability of conventional selectivity index of serum and urinary transferrin and IgG against other tests of urinary proteins, namely, SDS-PAGE and isoelectric focusing (IEF). A total of 31 children with steroid-sensitive NS were compared with 26 children

who had biopsy-proven FSGS and who were steroid resistant. SDS-PAGE and IEF revealed excretion of albumin and transferrin only, with homogeneous anionic charge, respectively, in steroid-sensitive NS but unrestricted excretion of additional proteins IgG, β_2 -microglobulin, and lysozyme with heterogeneity of electrical charge in FSGS.²⁵ With SDS-PAGE and IEF, the authors were able to predict all children who had steroid-sensitive NS and FSGS; the selectivity index test predicted all steroid-resistant patients with FSGS but was able to predict only 41.7% of the patients with steroid-resistant NS. Therefore, the negative predictive value for steroid-sensitive NS was 58.8% by selectivity index and 100% by SDS-PAGE and IEF; the positive predictive value was 100% by selectivity index, SDS-PAGE, and IEF. Based on these findings, the authors concluded that SDS-PAGE and IEF of urinary proteins were useful in distinguishing steroid-sensitive from steroid-resistant NS (i.e., FSGS).²⁵

Hepatitis B–Associated Nephropathy

In the early 1970s, Coovadia and Adhikari studied the clinico-pathological pattern of NS in Black African and Indian children and reported that Black children had obvious structural glomerular lesions and were unresponsive to steroids.^{8,11} Membranous nephropathy was the most frequent histopathological form of NS among Black children.²⁶ At about the same time, Wiggelinkhuizen *et al.* reported on the incidence of persistent hepatitis B surface antigen (HBsAg) in 114 children.²⁷ Of 28 patients of membranous nephropathy, 25 were HBsAg carriers; 24 were male. Only 9 of the remaining 86 children with nephropathies other than membranous nephropathy were HBsAg positive. The 14% incidence of membranous nephropathy was much higher than that reported by the International Study of Kidney Diseases in Childhood (ISKDC). In a subsequent report of 388 children with NS from the same center in Cape Town, Wiggelinkhuizen *et al.* reported membranous nephropathy to be present in 63 children (16.2%). A higher incidence of membranous nephropathy was found in Black children and those of Mixed race (52.9% and 20.9% respectively in male and 25% and 5.6% respectively in female children). Membranous nephropathy was absent in White and Indian children. Corticosteroids and other immunosuppressants were ineffective means of treatment and not without complications. These authors surmised that the frequent occurrence of membranous nephropathy was related to the high prevalence of predisposing infections in the infected population groups (Black African and Mixed race), and that socio-economic rather than ethnic factors were important.²⁸ Milner *et al.* reported the presence of hepatitis BsAg and eAg in serum of all children

with HBV—membranous nephropathy (HBV-MN), but only 54% of these children had HBV-DNA particles demonstrable in their serum.²⁹

It was only in 1993 that Coovadia *et al.* from Durban reported on the strong association between HBV and membranous nephropathy and concluded in their report that hepatitis B “s” and “e” antigen carriage in Black African children was strongly associated with membranous nephropathy. These authors reported on 178 Black African children, with 60 children (34%) having membranous nephropathy and 57 (95%) being HBsAg positive and 52 (86%) HBeAg positive. Given the strong association of HBV carriage and membranous nephropathy, these authors concluded that the strength of such an association in these patients permits reliable prediction of membranous nephropathy from serological tests for HBsAg and HBeAg, obviating the need for kidney biopsy.³⁰ Subsequent reports by Gilbert *et al.* and Bhimma *et al.* further corroborated this strong association between HBV and membranous nephropathy.^{31,32} Gilbert *et al.* showed that the cumulative probability of remission was 64% at 4 years and 84% at 10 years, with remission occurring within 6 months of clearing the HBeAg in the majority of cases. Steroids and cyclophosphamide had no beneficial effect in the 70 children with MN reported in this series; 9 had a decline in estimated glomerular filtration rate (eGFR) of more than 25% between first presentation and last follow-up. Thirteen patients had an eGFR of <80 ml/min per 1.73 m² at last clinic visit, 5 with an eGFR of <50 ml/min per 1.73 m². Two patients progressed to end-stage kidney disease. The lack of evidence of HBV infection in the mothers of the children supported the notion that HBV-associated membranous nephropathy (HBV-HBVMN) is primarily a complication of horizontal transmission of HBV infection.^{31,33}

Little is understood of the biosocial context in which HBV-associated nephropathy (particularly membranous nephropathy) develops. Bhimma *et al.* undertook 2 studies to determine the ecology of HBVMN by evaluating HBV status and proteinuria in family members and household contacts of index children with HBVMN to test the hypothesis that HBV carriage and asymptomatic proteinuria are closely linked and may be causally associated.^{32,34} In a study of 152 family members and 43 household contacts of 31 index cases of Black children with biopsy-proven HBVMN, they found strong clustering of HBV in family members, up to 37% of HBV-infected individuals in multiple families of index HBVMN cases, compared to 19.9% in households of children with HBV carriage alone in the same population. In all, 53 (27%) of the family members and household contacts had a protein:creatinine ratio greater than the physiological limit of 0.2 (mg/dl

protein and mg/dl creatinine). The frequency of abnormal proteinuria was not significantly different in those with (22 [30.5%] of 72) or without (33 [32%] of 104) HBV carriage. This lack of association remained when carriers were classified into those who were HBsAg positive only and those with active viral replication (HBsAg and/or HBeAg and/or HBV DNA; $P = 0.07$). Although family members were more predisposed to HBV carriage than household contacts, both had an equal frequency of abnormal proteinuria ($P = 0.48$). In addition, there were no differences in the genotype of the virus in the index cases and those found in the households.³⁴

Pattern of Proteinuria

These authors undertook more detailed analysis of the pattern of proteinuria detected in these household subjects using SDS-PAGE. Both IgG and haptoglobulin on SDS-PAGE were suggestive of membranous nephropathy.³⁵ In all, 72 (37%) of the 195 family members and household contacts were HBV carriers; 21(29%) of these carriers had evidence of proteinuria on SDS-PAGE. A total of 28 (41%) of the 68 members of the study group who were HBV negative and 27% of the controls also showed proteinuria on SDS-PAGE. This lack of association between HBV carriage and proteinuria remained when controlled for sex and family relationship. Those having a pattern of proteinuria suggestive of membranous nephropathy were more likely to have an abnormal protein:creatinine ratio ($P = 0.001$). The lack of association between HBV carriage and abnormal proteinuria (protein [mg/dl]:creatinine [mg/dl] ratio >0.2 or IgG and haptoglobulin on SDS-PAGE) led the authors to the conclusion that HBV alone is not sufficient for the development of HBVMN. It was postulated that in HBV carriers, additional interactions between socio-environmental conditions and possible genetic factors in specifically vulnerable individuals might be responsible for the development of HBVMN.³⁶

Genetic Factors

To determine the genetic basis for the development of membranous nephropathy, the authors investigated 30 Black children with biopsy-proven HBVMN. Human leukocyte antigen class I and II frequencies of the study subjects, when compared to controls who were healthy blood donors from the same population, showed a significantly increased frequency of HLA DQB1*0603 in patients with HBVMN compared to controls ($\chi^2 = 13.65$, P value corrected for the number of antigens detected (P_c) = 0.001; relative risk [RR] = 4.3). DRB1*07 and DQB1*02 were increased in frequency in the study subjects but failed to reach statistical significance. There was no significant difference

in the frequencies of class I antigens in the study group compared to controls. Based on the significant frequency of class II antigens (HLA DQB1*0603), a possible genetic predisposition to the development of HBVMN was proposed.³⁷

A total of 14 children with HBVMN from the above cohort who were positive for HLA DQB1*0603 had 70 of their family members studied to test for an association between this gene, HBV carriage, and the development of abnormal proteinuria, using the mean probability ratio (lod scores). There was a lack of association between HLA DQB1*0603 with either HBV carriage or abnormal proteinuria in family members, suggesting that other factors may play a role in predisposing children to these 2 disorders. Putatively, the main effect of HLA DQB1*0603, which distinguishes HBVMN from family members, is the degree of proteinuria, which is a reflection of the severity of glomerular basement membrane damage.^{37,38} Taken together, it would appear that the pathogenetic mechanism by which individuals with chronic HBV infection develop nephropathy are probably dependent on interactions among viral, host, and environmental factors. Viral characteristics do not appear to play a major role in the development of nephropathy, but further studies are needed to determine the role of viral genotype in the development of membranous nephropathy.

Treatment

To evaluate the efficacy of interferon- α 2b (IFN α 2b) treatment in children with HBVMN, Bhimma *et al.* undertook an open-label, observational study of 24 Black African children with biopsy-proven HBVMN. Five children defaulted treatment and were excluded. The IFN α 2b was administered for 16 weeks. Response to treatment was defined as loss of HBeAg, decrease in proteinuria, and prevention of deterioration in renal and liver function. A control group of 20 patients was followed up for the same period. Ten (52.6%) of the treated children responded with clearance of HBeAg by 40 weeks. None cleared HBsAg. All responders showed remission of proteinuria, 90% maintained normal kidney function, and 1 child (10%) showed improvement of kidney function. HBV DNA levels decreased in this group. Nine patients did not clear HBeAg, none showed remission of proteinuria, and 2 showed deterioration of kidney function. Liver enzymes rose during treatment but subsequently declined irrespective of response to therapy. No serious side effects were encountered. Only 5% of controls showed spontaneous clearance of HBeAg, and none had remission of proteinuria. The authors concluded that Black children with HBV-associated nephropathy showed accelerated clearance of HBeAg with

remission of proteinuria following treatment with IFN α 2b. IFN α 2b was well tolerated.³⁹

In summary, the key findings with respect to NS in South Africa prior to the New Millennium were as follows:

- Black children had a spectrum of disease that differed from those of other racial groups and children in Western countries.
- There was a paucity of MCD.
- The majority of patients were steroid resistant.
- In several patients, there was an identifiable cause, particularly HBV.
- HBVMN was the most common cause of NS seen along the East Coast of South Africa, with a lower prevalence inland.
- There was an absence of schistosomal nephropathy.
- The natural history of Black children with HBV nephropathy was that of spontaneous remission following clearance of the HBeAg, with a small number progressing to chronic kidney disease, and with IFN α 2b therapy showing accelerated clearance of the virus. The pathogenetic mechanisms by which individuals developed HBV nephropathy are dependent on interactions among virus, host and environmental factors.

Nephrotic Syndrome in South Africa in the New Millennium

The histopathological landscape of NS has dramatically changed in the New Millennium despite a fairly stable incidence of the disease in the last 30 years.⁴⁰ There are several factors that have contributed to this change; these include, among other things, an increasing reported incidence of FSGS,^{40–45} the introduction of the hepatitis B vaccine into the Expanded Programme on Immunisation on 1 April 1995, the HIV epidemic that began ravaging Africa from the latter part of the 1980s, and the more widespread use of antibiotics and antiviral agents leading to a decline in the incidence of secondary forms of NS from infectious diseases. The outcome of NS has further been affected by the introduction of newer immunosuppressive agents such as calcineurin inhibitors (cyclosporin and tacrolimus), mycophenolate mofetil, and monoclonal antibodies such as rituximab.

Primary Nephrotic Syndrome

As stated previously, the different histopathological types and treatment responses of the primary forms of NS in South Africa have been associated with differences in ethnicity and geographic location. In a retrospective review of 163 children (aged 2–16 years) with idiopathic NS in Johannesburg, Black children had the highest incidence of FSGS (37.8%) whereas White

children had mainly MCD (64.3%). Minimal change disease was the most common histopathological lesion seen in steroid-sensitive NS, whereas FSGS was the most common lesion (65.2%) observed in children who had steroid-resistant NS.⁴⁰ In another report on 129 children with MCD from another center in Johannesburg, 4 children did not undergo biopsy and the records of 13 children could not be traced, leaving 112 children to be included into the study. Of the children, 89% were Black African, with the remaining 11% comprising children who were mixed race, Indian, and White.⁴⁶ Both studies reported a higher rate of MCD in Black children, with a more favorable response to steroids compared to that reported by Bhimma *et al.* from Durban.⁵ Other studies performed locally and abroad, however, have found a much lower rate of MCD (<36%).^{41,47–49} It is possible that this difference in the rate of MCD may be due to differences in the indications for kidney biopsy in the different centers (the most common indication being steroid resistance).

In line with reports from many other pediatric centers, FSGS in South Africa has been reported to be increasing across all racial groups.^{16,17,40,50} In a study by Bakhiet *et al.* from Johannesburg, FSGS was found to have a rate of 43.2%, higher than previously reported from other centers in South Africa, namely 28.5% in Durban, 25.0% in Pretoria, and 31.3% in a previous study from Johannesburg.^{5,40,41,51}

The treatment and prognosis of FSGS has changed in recent decades. In addition, it is now well established that many patients have single gene mutations in structural proteins of the podocytes. New research has shown that whereas the genetic forms of FSGS are predominantly resistant to immunosuppression, the immunological forms are responsive.⁵² Prior to the New Millennium, the only available agents used for the treatment of steroid-resistant NS were oral steroids, cyclophosphamide, and cyclosporin (used in a limited number of patients because of cost). More intensive therapy in the 1990s included pulse methylprednisolone in conjunction with oral steroids and cyclophosphamide or pulse cyclophosphamide given with low-dose oral steroids or pulse methylprednisolone and adjunctive therapy using angiotensin-converting enzyme antagonists.^{5,10,46}

In the New Millennium, tacrolimus and mycophenolate mofetil were added to the armamentarium of treatment for difficult-to-treat primary NS, with rituximab being used in a handful of patients mainly with steroid-dependent NS because its usefulness in steroid-resistant NS is less than optimal and it is extremely costly.⁵² Bhimma *et al.* conducted a study in 20 children with steroid-resistant FSGS treated with tacrolimus in combination with low-dose steroids,

angiotensin-converting enzyme antagonists, folic acid, and multivitamin supplementation as well as lipid-lowering agents when required. At the end of the treatment period, 40% of children were in complete remission, 45% were in partial remission, and 15% failed to respond. Three children progressed to end-stage kidney disease and died of end-stage kidney disease at least 6 months after cessation of tacrolimus treatment, as they did not qualify for renal replacement therapy. At last hospital follow-up, 25% of children were in complete remission, 50% in partial remission, and 10% in relapse. The authors concluded that tacrolimus is a safe and effective form of treatment for FSGS but that, as with cyclosporin, some children tend to relapse upon discontinuation of treatment.⁵³

The high rate of steroid resistance in Black South African children compared to other racial groups has spurred the need to further elucidate the genetic basis for this racial disparity in steroid-resistant NS and FSGS histology for Black children with NS from South Africa compared to other racial groups. Considering the high rate of steroid resistance in children of Black ancestry, Asharam *et al.* hypothesized that *APOL1* renal risk variants, which were found only in African ancestry haplotypes or founder mutations in *NPHS2*, might be responsible for the higher rate of steroid-resistant NS in Black children compared to Indian or White children. These investigators undertook a study in 64 unrelated Indian and Black children, 49 with steroid-resistant NS and 15 with steroid-sensitive NS. Findings from this study showed that *NPHS2 260E/E* was present in one-third of Black children with FSGS and was absent in all those with steroid-sensitive NS as well as controls with no kidney disease. All those with *NPHS2 260E/E* mutation were unresponsive to therapy. The authors concluded that genotyping *V260E* in Black children from South Africa with NS would identify a sizable proportion of Black children with steroid-resistant FSGS, potentially sparing these children the use of steroids and other immunosuppressive agents as well as the need to undergo kidney biopsy, which is an invasive procedure.⁵⁴

Hepatitis B–Associated Nephropathy

Prior to the introduction of the HBV vaccine, HBVMN was the most common form of NS seen in Black children in Durban.⁵ Although membranous glomerulonephritis is an occasional complication of hepatitis C virus infection, it is rarely described in children. Sithebe *et al.* reported on 5 Black African children with HBVMN co-infected with HBV and hepatitis C virus. These patients had a disease pattern and natural history similar to children with HBVMN. Co-infection with HBV and hepatitis C virus may be explained by

simultaneous infection with both viruses, although another explanation might be that children with HBVMN are at increased risk for hepatitis C virus infection.⁵⁵

Immunization, together with active screening and appropriate treatment of HBV infection, is important in HBV infection control programs, with the potential to eradicate HBV infection and reduce the incidence of HBV-related diseases. In a study by Bhimma *et al.* from Durban, HBVMN was used as an endpoint to assess the medium- to long-term efficacy of HBV immunization.⁵⁶ The study was conducted over a 6-year period from April 1995 following the introduction of the HBV vaccine into the South African Expanded Programme on Immunisation, to the year 2000. The average annual incidence in the immediate post-immunization period, as expected, showed no significant decline in the incidence of HBVMN. The average annual rate ratio per 10⁵ child population was 0.43 per 10⁵ for 1996 to 1998 and 0.25 per 10⁵ for 1998 to 1999 ($P = 0.14$; RR = 1.3; 95% confidence interval [CI] = 0.9–1.9). When the average annual rate for the pre-immunization period 1984 to 1995 (0.22) was compared to that for the 5-year postimmunization period 2000 to 2001 (0.03), there was a sharp decline per 10⁵ child population ($P = 0.003$; RR = 0.12; 95% CI = 0.03–0.5). The HBV vaccine coverage rates during this period were 85.4%, 78.2%, and 62.0% for the first, second, and third doses, respectively, in children aged 12 to 23 months.^{56–58} From being 1 of the most common forms of NS in Black children along the coastal regions of South Africa, with HBVMN accounting for 43% of all cases of NS in Black children, following the introduction of the HBV vaccine into the Expanded Programme on Immunisation, the disease has now almost disappeared (R. Bhimma, personal communication, 2015).

HIV-Related Kidney Diseases

One of the major differences in the spectrum of NS in the New Millennium has been the emergence of HIV-related kidney diseases. The HIV epidemic has ravaged Africa for almost 4 decades, with sub-Saharan Africa and South Africa in particular bearing the greatest burden of the disease.⁵⁹ Initially, kidney disease in HIV-infected children presented as acute kidney injury, electrolyte abnormalities, and tubular dysfunction usually secondary to severe diarrheal diseases.⁵⁹ The initial reports of kidney disease in children with HIV/AIDS was by Kala *et al.* from Johannesburg in 60 children. Kidney biopsy was performed in 52 children (86.7%), with 50% having HIV immune complex kidney disease (HIVICK), 11.5% FSGS, and 1.9% MCD. In all, 33% of children had

pulmonary tuberculosis, which was the main complication resulting in high mortality in children with HIV-associated nephropathy (HIVAN; HIV-associated FSGS).⁶⁰

In 1 of the largest series of children with HIV-related nephropathy reported from Africa, Ramsuran *et al.* reported 71 children with HIV infection and chronic glomerular disease. All children except one were Black African. Given the fact that KwaZulu-Natal is the epicenter of the HIV epidemic, the authors suggested that all children with NS be screened for HIV.⁶¹ This was followed by a report by Nourse *et al.* from Cape Town in 14 children with HIV-infection and nephropathy presenting with NS.⁶²

It is well known that kidney disease is more frequent and progresses more rapidly to end-stage kidney disease in people of African descent. Qulu *et al.* undertook a study to determine the role of genetic variants at the *APOL-1* locus in the development of FSGS in children with primary FSGS and HIVAN, to determine the genetic basis for the increased risk of kidney diseases with its propensity for progression to end-stage kidney disease. A total of 163 Black children (aged 1–16 years) were enrolled: 14 with HIVAN, 56 with primary FSGS, 17 HIV-infected children with no kidney disease, and 76 normal children. The results of the study showed no significant associations between *APOL-1* risk variants and primary FSGS or HIVAN in children in KwaZulu-Natal, South Africa.⁶³

Kidney biopsy is currently the gold standard for the diagnosis of HIV-infected kidney diseases. Unfortunately, it is invasive, with attendant complications. This presages the need for noninvasive biomarkers for early detection of HIV-related kidney diseases. Nandlal *et al.* undertook a study in 34 children (13 with HIVAN and 21 with primary FSGS) and compared them to 35 controls (19 HIV-positive children and 16 HIV-negative children with no kidney disease). Urinary concentration of kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18) and glutathione *S*-transferase (GST- π) were quantified using BioPlex assay. The results showed a significant increase in urinary KIM-1 levels was observed in the HIVAN group compared with the HIV-positive ($P = 0.0039$) and HIV-negative ($P = 0.0438$) control groups. There was no significant increase in KIM-1 levels on comparison of the idiopathic FSGS group with the control groups (HIV-positive and HIV-negative children) ($P = 0.0737$ and $P = 0.1757$, respectively). No statistically significant differences were noted in urinary IL-18 and GST- π levels across all study groups. The authors concluded that KIM-1 may be a useful biomarker to detect kidney disease in HIV-1-infected children.⁶⁴

In summary, the main findings in the spectrum of NS in the New Millennium are:

- Steroid resistance remains high in Black children irrespective of histopathological type, with high levels of unresponsiveness to all forms of immunosuppression and early progression to end-stage kidney disease, although a slightly higher response of Black African children to steroids has now been documented.
- Identifiable causes such as hepatitis B and post-streptococcal glomerulonephritis are now markedly reduced or not seen.
- Primary FSGS, which was once a marginal issue, is now 1 of the most common forms of NS in Black children, with a rising incidence also being documented in other racial groups.
- The introduction of newer intensive therapies for FSGS has included, among other things, calcineurin inhibitors, mycophenolate mofetil, and rituximab. Although the outcome of steroid-resistant NS following the introduction of newer immunosuppressive agents in the New Millennium has had a positive impact in non-Black children, in Black children, especially those with identifiable genetic mutations, the outcome remains abysmal.
- The introduction of HIV-related kidney diseases including HIVAN, HIVICK, and MCD presenting with NS have been followed by a considerable decline in the frequency of HIVAN since implementation of antiretroviral therapy with low rates of perinatal transmission.
- There has been a sharp decline in the incidence of HBV-related nephropathy following the introduction of the HBV vaccine into the expanded program on immunization.

Conclusion

There has been a major paradigm shift in the histopathological spectrum and outcome of NS from the early 1970s to what has been reported in the New Millennium. There is a rising incidence of FSGS in all racial groups, whereas hepatitis B and HIV nephropathy are on the decline. Steroid resistance remains high in Black children, irrespective of histopathological type, although a slightly higher response rate has been documented in some centers. In those having genetic mutations, almost all are resistant to any form of immunosuppression. The introduction of newer immunosuppressive agents in the New Millennium has had a positive impact on the outcome of steroid-resistant NS in non-Black children, with the response in Black children being less favorable.

DISCLOSURE

All the authors declared no competing interests.

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