Primary nephrotic syndrome in the new millennium in KwaZulu-Natal, South Africa

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Background. The outcome and response of idiopathic nephrotic syndrome (NS) to steroids have been linked to race.

Objectives. To determine the age of presentation, sex, race, histopathology, kidney function and disease status at the last hospital visit and correlate these with steroid response in Indian and black African children with idiopathic NS.

Methods. This is a retrospective review of 231 children aged 1 - 14 years, who were seen at Inkosi Albert Luthuli Central Hospital, Durban, South Africa (SA) from 2003 to 2018.

Results. The mean (standard deviation (SD)) age of presentation was 6.2 (3.4) years, with the majority of children (n=107; 46.3%) presenting at an early age (1 - 3 years) with a mean (SD) follow-up of 3.0 (2.4) years. One-hundred and twenty-one (52.4%) were males and 110 (47.6%) were females, with a male/female ratio of 1.1:1. There were 166 (71.9%) black African and 65 (28.1%) Indian children. The latter presented at a younger age than black African children (p<0.001). Seventy-six (32.9%) children were steroid sensitive (SS) and 155 (67.1%) were steroid resistant (SR). Black African children were more likely to be SR (odds ratio (OR) 2.0; p=0.02; 95% confidence interval (CI) 1.1 - 3.7). A kidney biopsy was performed in 209 (90.5%) children. Minimal change disease (MCD) was observed in 32 (13.9%) children and 162 (70.1%) had focal segmental glomerulosclerosis (FSGS). Black African children were slightly more likely to have FSGS; this, however, did not reach statistical significance (122/166 (73.5%) v. 40/65 (61.5%); OR 1.73; p=0.08; 95% CI 0.94 - 3.18). On comparing disease status at last hospital visit by race, 49/65 (75.4%) Indian and 94/166 (56.6%) black African children were in remission. At last hospital visit, black African children were less likely to be in remission than Indian children (OR 0.47; p=0.02; 95% CI 0.2 - 0.9), while 15/65 (23.1%) Indian and 47/166 (28.3%) black African children had relapsed, with no significant difference between the two groups. One (1.5%) Indian child and 25 (15.1%) black African children had end-stage kidney disease (ESKD) (OR 9.27; p=0.03; 95% CI 1.2 - 70.4) – the majority had FSGS. Sixteen (61.5%) received renal replacement therapy.

Conclusions. Our study shows a rising incidence of FSGS, with the majority of patients having SRNS, particularly black African children. This highlights the need for alternative efficacious therapy in the management of this disease. Also, a higher percentage of black African children with both MCD and FSGS were SS on histopathological examination, which was in keeping with reports from other regions in SA. There are still major challenges for the inclusion of all children into a chronic dialysis and transplant programme.

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Nephrotic syndrome (NS) is one of the most commonly encountered kidney diseases in childhood and one of the kidney diseases most frequently referred to a specialised centre for management by a paediatric nephrologist or a paediatrician with a special interest in childhood kidney diseases. The disease is characterised by heavy proteinuria (≥3+) on urinary dipstick analysis, or a random spot urine protein/creatinine ratio ≥200 mg/mmol, or a 24-hour urine protein excretion >40 mg/m^2/h, hypoalbuminaemia ≤25 g/L and oedema. The estimated worldwide incidence of NS is 4.7 per 100 000 children (range 1.15 - 16.9).[1]

It has been documented that there is a strong geographical variation in the pattern of the disease and that certain ethnic groups, specifically South Asians and Africans, have a higher incidence.[2] Several studies from South Africa (SA) have documented strong racial differences with regard to response to treatment, histopathological subtypes and outcome.[3-13]

In the previous millennium, from the late 1970s onwards, the spectrum of the disease documented in the four major racial groups in SA, i.e. African, Indian, white and mixed race (decedents from blacks, whites and slaves from West and East Africa and from the Far East),[14] showed distinct differences. While the pattern of the disease in Indians, whites and persons of mixed race was shown to be similar to that described in industrialised countries, black African children showed distinct differences.[3-6] The latter often had secondary identifiable causative agents, with a high prevalence of steroid-resistant (SR) disease, irrespective of the histopathological pattern.[3-5] The high prevalence of infections, lower socioeconomic status, environmental factors, inequality of access to healthcare services and genetic factors were postulated as possible reasons for these differences.

In this study, we report on the histopathological spectrum, response to steroids and outcome in children seen in the new millennium at a central hospital in KwaZulu-Natal Province, SA, and highlight differences in the pattern of disease in black African and Indian children.

Methods

This was a retrospective study in children (1 - 14 years old) referred to Inkosi Albert Luthuli Central Hospital (IALCH) in KwaZulu-

Natal from 2003 to 2018. IALCH is the central, tertiary/quaternary referral hospital for KwaZulu-Natal and its neighbouring provinces for children with complex and chronic kidney disorders.

Using the Meditech database, 420 children were identified as having NS, based on the International Classification of Diseases 10th Revision (ICD10) coding. One hundred and eighty-nine children were excluded; 99 were diagnosed with secondary NS (15 with the nephrotic phase of acute post-streptococcal glomerulonephritis, 62 with HIV nephropathy, 4 with IgA nephropathy, 6 with hepatitis B-associated nephropathy, 4 with systemic lupus erythematosus nephritis and 8 with crescentic glomerulonephritis of unknown aetiology); 38 children had congenital NS; 13 had infantile NS; records were incomplete for 7; and 1 patient refused a kidney biopsy. Twenty-seven children who had visited the hospital only once were excluded from the study, as their steroid response could not be accurately determined. Only 2 children of mixed race and 2 white children were seen at IALCH during the study period; they were also excluded from the study, as their steroid response could not be accurately determined. Only 2 children of mixed race and 2 white children were seen at IALCH during the study period; they were also excluded from the analysis (Fig. 1).

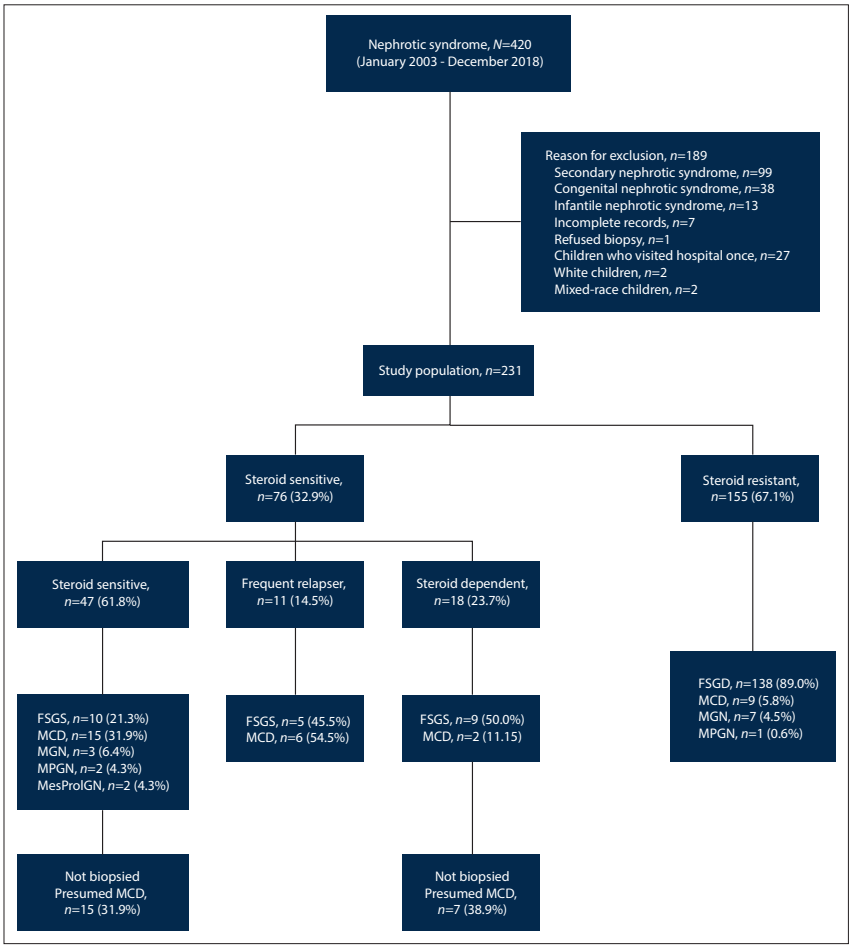

Fig. 1. Flow chart of the study. (FSGS = focal segmental glomerulosclerosis; MCD = minimal change disease; MGN = membranous glomerulonephritis; MPGN = membranoproliferative glomerulonephritis; MesProlGN = mesangioproliferative glomerulonephritis.)

Children with primary NS (*n*=231) comprised the study group. The following data were extracted from the hospital computer records: patient demographics, age at first hospital visit, age at diagnosis, clinical findings (including presenting symptoms, weight, height, blood pressure, urine dipstick analysis and any other significant clinical findings), laboratory data at first and last hospital visit, estimated glomerular filtration rate, kidney biopsy histopathological findings, response to steroids, use of immunosuppressive therapy other than steroids, disease status at last hospital visit, mode of dialysis therapy and kidney transplant (in children with end-stage kidney disease (ESKD). The children's areas of residence were classified as urban or rural according to the Statistics South Africa Census 2011 criteria.[15]

Investigations

The following investigations were performed to exclude secondary causes of NS: antistreptolysin O titre, hepatitis B screen for s- and e-antigens and antibodies, hepatitis A IgM, hepatitis C total antibody, cytomegalovirus IgM (if positive, a viral load was done), Epstein-Barr virus IgM, parvovirus B19 IgM, HIV IgG, rapid plasma reagin test for syphilis, antinuclear factor and serum complement (C3 and C4). A renal biopsy was performed in 209 children who frequently relapsed, and who were steroid dependant or SR. After 2 years a repeat kidney biopsy was done in children treated with calcineurin inhibitors (CNIs) to assess for CNI toxicity and disease progression. Kidney biopsies were examined by light microscopy, immunohistochemistry and electron microscopy in the Department of Anatomical Pathology of the National Health Laboratory Service at IALCH. In 22 children a kidney biopsy was not performed, as they had a clinical course suggestive of steroid-sensitive (SS) minimal change disease (MCD) NS and were classified as presumed MCD.

Blood pressure was measured using an appropriate-sized cuff, with the child at rest and seated upright. Systolic and diastolic blood pressures were measured using the oscillometric method, employing an automated blood pressure monitor Edan Model 3 (Edan, USA). Hypertension (HPT) was defined by the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents[16] as follows: normal <90th percentile; prehypertension ≥90th - <95th percentile or >120/80 mmHg in adolescents; stage 1 HPT if between ≥95th and 99th percentile plus 5 mmHg; and stage 2 HPT >99th percentile plus 5 mmHg. Glomerular filtration rate was estimated (eGFR) using the modified Schwartz formula,[17] and children were classified according to the Kidney Disease Outcomes Quality Initiative (KDIGO) guidelines for chronic kidney disease (CKD).[18] Daily oral prednisone at a dose of 2 mg/kg/day (maximum 60 mg) was administered as initial treatment and steroid response was assessed after 6 weeks. Children who frequently relapsed and were steroid dependant or SR were treated with additional immunosuppressants, including cyclophosphamide, CNIs (cyclosporin or tacrolimus) or mycophenolate mofetil.

Disease status at last hospital visit was categorised as follows:

Steroid-sensitive nephrotic syndrome (SSNS): Children whose proteinuria resolved for 3 consecutive days after 6 weeks of daily steroid therapy.

Steroid-dependent nephrotic syndrome (SDNS): Children who relapsed twice consecutively while on steroid therapy or within 2 weeks of steroid discontinuation.

Frequent-relapse nephrotic syndrome: Children who relapsed ≥2 times within 6 months of an initial response to steroids or ≥4 times in any 12-month period.

Steroid-resistant nephrotic syndrome (SRNS): Children with proteinuria persisting after 6 weeks of steroid therapy.

Remission: The absence of oedema and proteinuria on urinary dipstick analysis (protein = 0/trace) on 3 consecutive early-morning urine specimens, or alternately a random urine protein/creatinine ratio <0.05 g/mmol.

Relapse: The presence of oedema and proteinuria on urinary dipstick analysis (protein ≥2+) or protein/creatinine ratio >0.05 g/mmol for 3 consecutive days after a period of remission.

Renal function: This was assessed by an eGFR using the modified bedside Schwartz formula,[17] and classified according to the KDIGO guidelines for CKD.[18]

Data were captured on Excel version 16 (Microsoft, USA) and all children identifiers were removed. Data were imported into SPSS version 24 (IBM Corp., USA) for analysis. A descriptive analysis of the data included means, standard deviations (SDs), ranges, frequency distribution tables and proportions. A *p*-value <0.05 was considered statistically significant.

Ethical approval

Permission to perform the study was granted by the institutional hospital medical manager, and ethical approval was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (ref. no. BE435/16).

Results

Overall findings

A total of 231 children with primary NS treated over 16 years at IALCH were included in the study; 121 (52.4%) were males and 110 (47.6%) were females, with a male/female ratio of 1.1:1. There were 166 (71.9%) black African and 65 (28.1%) Indian children. Most children were diagnosed at an early age: 107 (46.3%) between 1 and 3 years, 69 (29.9%) between 4 and 7 years and 55 (23.8%) between 8 and 12 years ($p<0.001$), the mean (SD) age of presentation being 4.8 (3.3) years. The majority of children ($n=183$; 79.2%) were from an urban setting while 48 (20.8%) were from a rural setting. One hundred and six (45.9%) children were asymptomatic on initial presentation and 125 (54.1%) had varying degrees of oedema as their presenting symptom. Blood pressure assessment at first visit showed that 89 (38.5%) children were normotensive, 25 (10.8%) prehypertensive, 73 (31.6%) had stage 1 HPT and 44 (19.0%) stage 2 HPT.

Indian children presented at a younger age: 47/65 (72.3%) between 1 and 3 years compared with 60/166 (36.1%) black African children ($p<0.001$). Most black African children presented at an older age: 11/65 (16.9%) Indian v. 58/166 (34.9%) black African children presented between 4 and 7 years ($p=0.01$) and 7/65 (10.8%) Indian v. 48/166 (28.9%) black African children presented between 8 and 14 years ($p=0.004$). There was a significantly larger proportion of Indian males v. females (42 (64.6%) v. 23 (35.4%), respectively; $p=0.02$), whereas in black African children there was a significantly larger proportion of females v. males (87 (52.4%) v. 79 (47.6%), respectively; $p=0.02$). Sixty-five (100%) Indian children v. 118 (71.1%) black African children were from an urban setting, with all children from a rural setting being black African ($p<0.001$). There were no significant differences in body mass index or presence of oedema on initial presentation between the racial groups. On initial presentation, black African children were more than twice as likely to have stage 2 HPT than Indian children (37/66 (22.3%) black African v. 7/65 (10.8%) Indian; odds ratio (OR) 2.38; $p=0.05$; 95% confidence interval (CI) 1.0 - 5.6) (Table 1).

At last hospital visit, 76 (32.9%) children were SS (47/231 (20.3%) had infrequent relapses, 11/231 (4.8%) had frequent relapses, 18/231 (7.8%) were steroid dependent) and 155 (67.1%) were SR. A total of 29/65 (44.6%) children with SSNS were Indian and 47/166 (28.3%) were black African. Comparing children with SRNS, 36/65 (55.4%) were Indian and 119/166 (71.7%) were black African. The latter were more likely to be SR (OR 2.0; $p=0.02$; 95% CI 1.1 - 3.7).

The histopathological findings of kidney biopsies in 209 (90.5%) children who frequently relapsed, who were steroid dependent or SR are

Table 1. Demographics and clinical characteristics of children with primary nephrotic syndrome

Demographics	Indian ($n=65$), *n* (%)*	Black ($n=166$), *n* (%)*	*p*-value	OR	95% CI
Age at diagnosis, years					
1 - 3	47 (72.3)	60 (36.1)	<0.001	0.22	0.1 - 0.4
4 - 7	11 (16.9)	58 (34.9)	0.01	2.64	1.3 - 5.4
8 - 14	7 (10.8)	48 (28.9)	0.004	3.37	1.4 - 7.9
Residence					
Urban	65 (100.0)	118 (71.1)	<0.001	-	-
Rural	0 (0.0)	48 (28.9)		-	-
Sex					
Female	23 (35.4)	87 (52.4)	0.02	-	-
Male	42 (64.6)	79 (47.6)		-	-
Blood pressure					
Normal	31 (47.7)	58 (34.9)	NS	-	-
Prehypertension	5 (7.7)	20 (12.0)	NS	-	-
Stage 1	22 (33.8)	51 (30.7)	NS	-	-
Stage 2	7 (10.8)	37 (22.3)	0.05	2.38	1.0 - 5.6
BMI, median (IQR)	17.5 (16 - 20)	17.7 (16 - 19)	NS	-	-

OR = odds ratio; CI = confidence interval; NS = not significant; BMI = body mass index; IQR = interquartile range.
*Unless otherwise indicated.

shown in Fig. 2. There were no significant differences between the two racial groups in the occurence of MCD. One hundred and sixty-two (70.1%) children had focal segmental glomerulosclerosis (FSGS): 40/65 (61.5%) were Indian and 122/166 (73.5%) black African. Although the latter were slightly more likely to have FSGS, this did not reach statistical significance (OR 1.73; p=0.08; 95% CI 0.94 - 3.18). Fifteen (6.5%) black African children had other histopathological findings: 3/15 (20.0%) membranoproliferative glomerulonephritis, 10/15 (66.7%) idiopathic membranous glomerulonephritis and 2/15 (13.4%) mesangioproliferative glomerulonephritis (Table 2).

The mean (SD) follow-up of all children was 3.0 (2.4) years; Indian children were followed up for a mean (SD) of 3.5 (2.8) years and black African children for a mean (SD) of 2.8 (2.2) years. At last hospital visit, 143 (61.9%) children were in remission, 62 (26.8%) had relapsed and 26 (11.3%) had ESKD. Six of the 26 children with ESKD received peritoneal dialysis only, 2 received haemodialysis only, and 8 received haemodialysis and peritoneal dialysis. Four children received a live-related kidney donor transplant; 3 were females and all had SR FSGS. Ten of 26 (38.5%) children who did not receive renal replacement therapy included those who did not qualify for the programme; they were therefore referred to their base hospitals for palliative follow-up care. On comparing disease status at last hospital visit by race, 49/65 (75.4%) Indian and 94/166 (56.6%) black African children were in remission. Black African children were less likely to be in remission than Indian children (OR 0.47; p=0.02; 95% CI 0.2 - 0.9). On comparing Indian and black African children who were in relapse at last hospital visit, there was no significant difference between the two groups. One (1.5%) Indian child and 25 (15.1%) black African children had ESKD at last hospital visit. Therefore, black African children were more likely to have ESKD than Indian children (OR 9.27; p=0.03; 95% CI 1.2 - 70.4) (Table 2).

When stratified by kidney histopathology, at last hospital visit 28/32 (87.5%) children with MCD were in remission, 4 (12.5%) had relapsed, and none had progressed to ESKD. Of the children who infrequently relapsed, who did not undergo a kidney biopsy and were presumed to have MCD, 19/22 (86.4%) were in remission, 2/22 (9.1%) had relapsed and 1 (4.5%) was lost to follow-up and presented with ESKD. In children with FSGS on histopathology, 85/162 (52.5%) were in remission, 53/162 (32.7%) had relapsed and

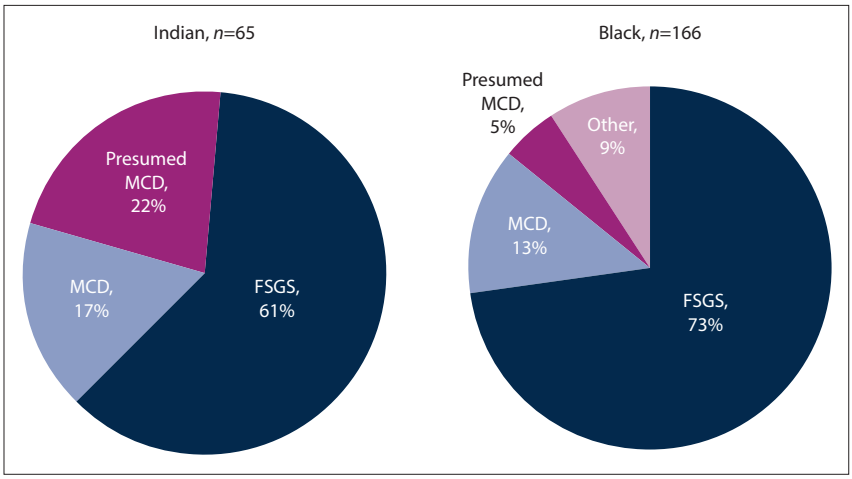

Fig. 2. Histopathology in Indian and black African children with primary nephrotic syndrome. (MCD = minimal change disease; FSGS = focal segmental glomerulosclerosis; other = membranoproliferative glomerulonephritis, membranous glomerulonephritis and mesangioproliferative glomerulonephritis.)

Table 2. Histopathological findings and disease status at last hospital visit in Indian and black African children with primary nephrotic syndrome*

	Steroid sensitive					
Histopathology	**Indian (n=29), n (%)**	**Black (n=47), n (%)**	**Total (n=76), n (%)**	**p-value**	**OR**	**95% CI**
Final biopsy assessment						
FSGS	9 (31.0)	15 (31.9)	24 (31.6)	NS	-	-
MCD	6 (20.7)	17 (36.2)	23 (30.3)	NS	-	-
Other†	0 (0.0)	7 (14.9)	7 (9.2)	NS	-	-
Disease status at last hospital visit						
Remission	24 (82.8)	44 (93.6)	68 (89.0)	NS	-	-
Relapse	5 (17.2)	2 (4.3)	7 (9.0)	0.08	0.21	0.04 - 1.18
ESKD	0 (0.0)	1 (2.1)	1 (1.0)	NS	-	-
	Steroid resistant					
	Indian (n=36), n (%)	**Black (n=119), n (%)**	**Total (n=155), n (%)**	**p-value**	**OR**	**95% CI**
Final biopsy assessment						
FSGS	31 (86.1)	107 (89.9)	138 (89.0)	NS	-	-
MCD	5 (13.9)	4 (3.4)	9 (5.8)	0.03	0.22	0.05 - 0.85
Other†	0 (0.0)	8 (6.7)	8 (5.2)	NS	-	-
Disease status at last hospital visit						
Remission	25 (69.4)	54 (42.0)	75 (48.4)	0.01	0.2	0.14 - 0.71
Relapse	10 (27.8)	45 (37.8)	55 (35.5)	NS	-	(0.70 - 3.58)
ESKD	1 (2.8)	24 (20.2)	25 (16.1)	0.04	8.84	(1.15 - 67.8)

OR = odds ratio; CI = confidence interval; FSGS = focal segmental glomerulosclerosis; NS = not significant; MCD = minimal change disease; ESKD = end-stage kidney disease.
*Fourteen (48.3%) Indian and 8 (17.0%) black African children did not undergo biopsy and were presumed to have MCD.
†Membranoproliferative glomerulonephritis, membranous glomerulonephritis, mesangioproliferative glomerulonephritis.

24/162 (14.8%) had progressed to ESKD. Of 15 children with other forms of histopathology, 11/15 (73.7%) were in remission, 3 (20.0%) had relapsed and 1 (6.7%) had progressed to ESKD. When stratified by race and histopathology, at last hospital visit 9/11 (81.8%) Indian children with MCD were in remission and 2 (18.2%) had relapsed. Twenty-one black African children had MCD, 19 (90.5%) were in remission and 2 (9.5%) had relapsed. For Indian children with presumed MCD, 12/14 (85.7%) were in remission and 2 (14.3%) had relapsed. For black African children with presumed MCD, 7/8 (87.5%) were in remission, none had relapsed and 1/8 (12.5%) had progressed to ESKD. Twenty-eight (70.0%) of 40 Indian children with FSGS were in remission, 11 (27.5%) had relapsed and none had progressed to ESKD. In 122 black African children with FSGS, 57 (46.7%) were in remission, 42 (34.4%) had relapsed and 23 (18.9%) had progressed to ESKD. None of the Indian children had histopathological findings on kidney biopsy other than FSGS or MCD. On comparing the frequency of FSGS in Indian and black African children who achieved remission, the former were more likely to be in remission (28 (70.0%) v. 57 (46.7%), respectively; p=0.01). Black African children with FSGS were more likely than Indian children to be in ESKD (23 (18.9%) black African v. 1 (2.5%) Indian; p=0.01). Fifteen black African children had other forms of histopathology, 11 (73.3%) were in remission, 3 (20.0%) had relapsed and 1 (6.7%) had progressed to ESKD (Table 3).

On comparing kidney function based on the stage of CKD between the initial presentation and last hospital visit, 12 (5.2%) children had an improvement in their kidney function, 151 (65.4%) remained unchanged and 68 (29.4%) progressed to higher stages of CKD. On comparing Indian and black African children whose kidney function improved, there was no significant difference between the two racial groups. In the group of children whose kidney function remained stable, 50/65 (76.9%) were Indian and 101/166 (60.8%) were black African, with the former being more likely to preserve kidney function than black African children (OR 0.47; p=0.02; 95% CI 0.24 - 0.90). In the group of children whose kidney function progressed to higher stages of CKD, 11/65 (16.9%) were Indian and 57/166 (34.3%) were black African. Therefore, black African children were more likely to progress to higher stages of CKD than Indian children (OR 2.56; p=0.01; 95% CI 1.24 - 5-29).

At the end of the study, there were 11 deaths; all were black African children. Eight children received renal replacement therapy and died from overwhelming sepsis. The remaining 3 children received palliative care; 1 died from severe sepsis due to peritonitis, whereas the cause of death in the remaining 2 was unknown. Seventy-three children were lost to follow-up; 54 (74.0%) were black African and 19 (26.0%) Indian. Seventy-nine children were discharged to their base hospital or to adult care; 51 (64.6%) were black African and 28 (35.4%) Indian. At last hospital visit 68 children were continuing care in the paediatric unit at IALCH; 50 (73.5%) were black African and 18 (26.5%) Indian.

Steroid-sensitive nephrotic syndrome

Seventy-six (32.9%) children had SSNS: 42 (55.3%) were males and 34 (44.7%) females, with a male/female ratio of 1.2:1; 47 (61.8%) were black African and 29 (38.2%) Indian. There were only minor differences in the number of children across the three age categories, with 27 (35.5%) diagnosed between 1 and 3 years of age, 20 (26.3%) between 4 and 7 years, and 29 (38.2%) between 8 and 14 years. The mean (SD) age of presentation in children with SSNS was 5.8 (3.6) years. Sixty-five (85.5%) were from an urban setting and 11 (14.5%) from a rural setting. Forty-two (55.3%) children were asymptomatic on initial presentation and 34 (44.7%) had oedema as presenting symptom. Blood pressure assessment at initial visit showed that 41 (54.0%) children were normotensive, 8 (10.5%) were prehypertensive, 19 (25%) had stage 1 HPT and 8 (10.5%) had stage 2 HPT. There was a significantly high number of Indian children with SSNS presenting between 1 and 3 years of age compared with black African children (20/29 (69%) v. 7/47 (14.9%), respectively; OR 0.08; p<0.001; 95% CI 0.03 - 0.24). Black African children presented at an older age: 14/47 (29.8%) black African v. 6/29 (20.7%) Indian between 4 and 7 years old (OR 1.63; p=0.38; 95% CI 0.5 - 4.9) and 26/47 (55.3%) black African v. 3/29 (10.3%) Indian children between 8 and 14 years (OR 10.7; p<0.001; 95% CI 2.8 - 40.4). All Indian children v. 36 (76.6%) black African children were from urban settings, with all children from a rural background being black African (p<0.001). Forty-two children were asymptomatic at initial presentation and 34 had oedema as presenting symptom, with no significant differences between the two racial groups. There were also no significant differences between the two racial groups with regard to their stage of HPT on initial presentation.

Twenty-two (28.9%) children with SSNS did not undergo percutaneous kidney biopsy, as they had infrequent relapses and were classified as presumed MCD (Indian: 14/29 (48.3%); black African: 8/47 (17.0%)). Black African children were less likely to have presumed MCD than Indian children (OR 0.22; p=0.01;

Table 3. Comparison of disease status at last hospital visit in Indian and black African children, stratified by histopathology

	Indian			
Histopathology	**Remission (*n*=49), *n* (%)**	**Relapse (*n*=15), *n* (%)**	**ESKD (*n*=1), *n* (%)**	**Total, *n***
FSGS	28 (70.0)	11 (27.5)	1 (2.5)	40
MCD	9 (81.8)	2 (18.2)	0 (0.0)	11
Presumed MCD	12 (85.7)	2 (14.3)	0 (0.0)	14
Other*	0 (0.0)	0 (0.0)	0 (0.0)	0
	Black			
	Remission (*n*=94), *n* (%)	**Relapse (*n*=47), *n* (%)**	**ESKD (*n*=25), *n* (%)**	**Total, *n***
FSGS	57 (46.7)	42 (34.4)	23 (18.9)	122
MCD	19 (90.5)	2 (9.5)	0 (0.0)	21
Presumed MCD	7 (87.5)	0 (0.0)	1 (12.5)	8
Other*	11 (73.3)	3 (20.0)	1 (6.7)	15

ESKD = end-stage kidney disease; FSGS = focal segmental glomerulosclerosis; MCD = minimal change disease.
*Other = membranoproliferative glomerulonephritis, membranous glomerulonephritis and mesangioproliferative glomerulonephritis.

95% CI 0.08 - 0.60). Twenty-three (30.3%) children with SSNS who underwent kidney biopsy had MCD on histopathology. Twenty-four (31.6%) children had FSGS; there was no significant difference between the two racial groups with regard to histopathological findings of MCD and FSGS. Seven (9.2%) children had histopathological findings other than MCD or FSGS – all were black African (Table 2).

The mean (SD) follow-up period for all children with SSNS was 2.4 (2.2) years; Indian children were followed up for a mean (SD) of 3.3 (2.5) years and black African children for a mean (SD) of 2.0 (1.9) years. At the last hospital visit, 68 (89.5%) children with SSNS were in remission, 7 (9.2%) had relapsed and 1 (1.3%) child had progressed to ESKD – therefore, disease status in this last child could not be classified. This black African child was lost to follow-up, presented 6 years later in ESKD, and subsequently died from severe sepsis. Comparing disease status at the last hospital visit, there was no significant difference between the two racial groups (Table 2).

When stratified by histopathological findings and disease status at last hospital visit, 23 (30.3%) children had MCD, 20 (86.9%) were in remission, 3 (13.0%) had relapsed and none had progressed to ESKD. Twenty-two (28.9%) children with SSNS who relapsed infrequently, did not undergo kidney biopsy and were classified as presumed MCD, 19 (86.4%) were in remission, 2 (9.1%) had relapsed and 1 (4.5%) had progressed to ESKD. Twenty-four (31.6%) children with SSNS had FSGS, 22 (91.7%) were in remission and 2 (8.3%) had relapsed. All 7 (9.2%) children with SSNS who had other histopathological findings on kidney biopsy were in remission.

On comparing kidney function between the initial presentation and last hospital visit, 6 (7.9%) children with SSNS had an improvement in their stage of CKD, 65 (85.5%) remained stable, while 5 (6.6%) progressed to higher stages of CKD. There were no statistically significant differences between the two racial groups with regard to their staging of CKD between first and last hospital visit.

At the end of the study, 1 black African child with SSNS died. Twenty children were lost to follow-up: 13 (65.0%) were black African and 7 (35.0%) Indian. Thirty-two children were discharged to their base hospital or to adult care: 20 (62.5%) were black African and 12 (37.5%) Indian. At last hospital visit 23 children were reveiving continuing care in the paediatric unit at IALCH: 13 (56.5%) were black African and 10 (43.5%) Indian.

Steroid-resistant nephrotic syndrome

A total of 155 (67.1%) children had SRNS: 79 (51.0%) were males and 76 (49.0%) females, with a male/female ratio of 1:1; 119 (76.8%) were black African and 36 (23.2%) Indian. Eighty (51.6%) children presented between 1 and 3 years of age, 49 (31.6%) between 4 and 7 years, and 26 (16.8%) between 8 and14 years, with a mean (SD) age at presentation of 4.3 (3.1) years. All Indian children v. 82 (68.9%) black African children were from an urban setting – all children from a rural setting were black African ($p<0.001$). Sixty-four (41.3%) children were asymptomatic on initial presentation and 91 (58.7%) had oedema as presenting symptom. Blood pressure assessment on initial presentation showed that 48 (31.0%) children were normotensive, 17 (11.0%) prehypertensive, 54 (34.8%) had stage 1 HPT and 36 (23.2%) stage 2 HPT. On comparison of the sexes, there were significantly more Indian than black African males (24/36 (66.7%) v. 55/119 (46.2%), respectively; $p=0.03$). There was a significantly higher number of Indian children presenting between 1 and 3 years than black African children (27/36 (75.0%) v. 53/119 (44.5%), respectively; OR 0.27; $p=0.002$; 95% CI 0.12 - 0.62). A greater number of black African than Indian children presented between 4 and 7 years (44/119 (37.0%) v. 5/36 (13.9%), respectively; OR 3.64; $p=0.01$; 95% CI 1.3 - 10). There was no significant difference between Indian and black African children who presented between 8 and 14 years of age. Sixty-four children were asymptomatic at initial presentation: 18/36 (50.0%) were Indian and 46/119 (38.7%) black African. There was no significant differences between the two racial groups regarding symptoms at initial presentation. Indian children were more likely to be normotensive than black African children (18/36 (50.0%) v. 30/119 (25.2%), respectively; OR 0.34; $p=0.006$; 95% CI 0.2 - 0.6). There were no significant differences at initial presentation when comparing prehypertension or stage 1 HPT between Indian and black African children. Although Indian children were less likely to have stage 2 HPT than black African children, this did not reach statistical significance.

All children with SRNS underwent percutaneous kidney biopsy, 9 (5.8%) had MCD, 138 (89.0%) had FSGS and in 8 (5.2%) there were other histopathological findings (Table 2). Indian children with SRNS were significantly more likely to have MCD than black African children (5/36 (13.9%) v. 4/119 (3.4%), respectively; OR 0.22; $p=0.03$; 95% CI 0.05 - 0.85). Thirty-one of 36 (86.1%) Indian and 107/119 (89.9%) black African children had FSGS, with no significant difference between the two racial groups. All 8 children with histopathological findings other than MCD or FSGS were black African: 1 (12.5%) had membranoproliferative glomerulonephritis and 7 (87.5%) idiopathic membranous glomerulonephritis (Table 2).

The mean (SD) follow-up period for all children with SRNS was 3.3 (2.6) years; Indian children were followed up for 3.6 (3.0) years and black African children for 3.1 (2.4) years. At last hospital visit, 75 (48.4%) children with SRNS were in remission, 55 (35.5%) had relapsed and 25 (16.1%) were in ESKD; therefore, disease status could not be classified in the latter group. On comparison of disease status at last hospital visit between the two racial groups, 25/36 (69.4%) Indian v. 50/119 (42.0%) black African children were in remission, with significantly more Indian children being in remission than black African children (OR 0.32; $p=0.01$; 95% CI 0.14 - 0.71). With regard to children who had relapsed, there was no significant difference between the two racial groups. One of 36 (2.8%) Indian and 24/119 (20.2%) black African children progressed to ESKD. Black African children were significantly more likely to progress to ESKD than Indian children (OR 8.84; $p=0.04$; 95% CI 1.15 - 67.8).

When stratified by histopathological findings and disease status at last hospital visit, of 9 (5.8%) children with MCD and SRNS, 8/9 (88.9%) were in remission, 1 (11.1%) had relapsed and none had progressed to ESKD. One hundred and thirty-eight (89.0%) children with SRNS had FSGS, 63 (45.7%) were in remission, 51 (37.0%) had relapsed and 24 (17.4%) had progressed to ESKD. Eight (5.2%) children had other forms of histopathological findings, 4 (50.0%) were in remission, 3 (37.5%) had relapsed and 1 (12.5%) had progressed to ESKD.

On comparing staging of CKD between the initial presentation and last hospital visit, 6 (3.9%) children with SRNS had an improvement in their CKD staging, 86 (55.5%) had no change, and 63 (40.6%) had progressed to higher stages of CKD. Ten of 36 (27.8%) Indian children and 53/119 (44.5%) black African children had progressed to a higher stage of CKD. Black African children were more likely to progress to higher stages of CKD than Indian children, although this did not reach statistical significance.

At the conclusion of the study, there were 10 deaths in children with SRNS – all were black African. Fifty-three children were lost to follow-up: 41 (77.4%) were black African and 12 (22.6%) Indian. Forty-seven children were discharged to their base hospital or adult care: 31 (66.0%) were black African and 16 (34.0%) Indian. Forty-five children at last hospital visit received continuing care in the paediatric unit at IALCH: 37 (82.2%) were black African and 8 (17.8%) Indian.

Discussion

To date, in the new millennium there have been only two major reports focusing on the spectrum of primary NS in SA children – one was confined to biopsy-proven MCD.[19,20] The most recent studies globally and in Africa focused on NS in general, SSNS (presumed MCD) or SRNS.[19-27] In this study, we focused on children with primary NS and report on the histopathological spectrum, response to steroids and outcome of these children seen at a central hospital in KwaZulu-Natal. We highlight the differences in the pattern of disease in black African and Indian children – two dominant racial groups seen in our hospital. There have been no other reports of primary NS in children from this region, except from Bhimma *et al.*,[14] who in 1997 focused on NS in general. We have excluded congenital and secondary forms of NS, as these will be reported separately.

The main findings in our study can be summarised as follows: there was a predominance of black African children, mainly from an urban setting, with just fewer than half being asymptomatic at the time of their first presentation to hospital. The clinical presentation at the initial visit, however, was similar in both racial groups. Overall, there were slightly more males than females; this difference was accentuated in Indian children, but there was a preponderance of black African female children, especially in the group with SRNS. The mean age of presentation was 4.8 years, with a mean follow-up of 3.0 years. On initial presentation, HPT was present in about half of the children, with black African children being two times more likely to have stage 2 HPT than Indian children. Just more than two-thirds of children had SRNS – black African children being two times more likely to have the condition than Indian children. With regard to SSNS, Indian children presented at an earlier age than black African children. With regard to SRNS, black African children presented at a significantly older age than Indian children. Indian children were more likely to relapse infrequently. Both racial groups with SSNS showed high rates of remission, with no statistically significant differences between the groups. Also, in children with SSNS, there were no significant differences in the histopathological pattern of disease in both racial groups. However, in children with SRNS, FSGS was more prevalent in black African children than Indian children; the former were less likely to achieve remission and more likely to progress to higher stages of CKD. All except 1 child who progressed to ESKD were black African, the majority having FSGS on histopathology.

In a previous general report on NS by Bhimma *et al.*,[14] Indian children comprised 48.2% of the study population; in our study it was 28.1%. Black African children now comprised 71.9% compared with 48.2% in the previous general report on NS from this region, with a very low representation of white and mixed-race groups. The preponderance of black African children in our study reflects not only the population demographics of the various racial groups in KwaZulu-Natal, but is also a reflection of the utility of public health services in the country in general. Other racial groups with a better socioeconomic background use private healthcare, which provides better facilities, turnaround times and an appropriate level of care, as there are paediatric nephrologists in private practice.

Whereas most SA studies, in keeping with those from the developed world, report a higher frequency of males than females with primary NS, our study showed more female than male black African children. This difference was most pronounced in black African children with SRNS.[14,19,21,28] Black African children also presented at an older age than those reported in other studies, both locally and internationally.[19,21-27] Furthermore, the mean (SD) age of presentation was 6.2 (3.4) years, which is slightly higher than that previously reported in SA children,[14,19] probably due to late diagnosis in our study group. Just fewer than half of the children in our study were asymptomatic at the time of initial presentation. While the majority with primary NS presented stereotypically with varying degrees of oedema, the large number of children who were asymptomatic at the time of initial presentation is probably due to our referral pattern. All children presenting to the central hospital are initially treated at a base hospital. Oedema in children would have been controlled prior to referral to the central hospital, the majority being referred for kidney biopsy and intensive treatment as they were SR.

The high frequency of HPT in the current study, particularly in black African children with SRNS, is in contrast to the much lower incidence reported by Bhimma *et al.*[14] This low incidence of HPT in previous studies may be due to resource limitations, with fewer children having blood pressure accurately measured and HPT documented. It could also possibly reflect the change in racial demographics – black African children being the predominant racial group in our study population, the majority having FSGS with SRNS and therefore being more likely to have HPT.[14] The high frequency of HPT, particularly in black African children with primary NS, is supported by a study from an academic hospital in Johannesburg, SA.[19]

One of the most striking differences in our study compared with previous reports from this region was the change in the histopathological pattern of disease and response to steroids. The burden of SRNS increased substantially from 30.5% previously reported by Bhimma *et al.*[14] to 67.1% in the current study. This increased burden of SRNS was mirrored by an increase in children with FSGS, with a concomitant decline in the incidence of MCD from 30.8% to 13.9%.[14] From being a marginal therapeutic issue in our centre, FSGS has now become the single most common histopathological finding in children with primary NS and a management problem. In our study, FSGS was diagnosed in 70.1% of children with primary NS, which is much higher than the previously reported figures of 3.7% (1976), 3.9% (1981) and 25% (1997) from other centres in SA, including our centre.[4,5,14] This increase in the incidence of FSGS, albeit exceedingly high, is in line with the increasing incidence of FSGS reported from many other paediatric nephrology units, where it accounts for 10 - 20% of children with primary NS.[29-31] A review of FSGS supports the view that there has been an authentic increase in the disease, as documented in other reports from geographically distinct regions.[32-34] The same process may be occurring in SA. However, the increase may also be due to better pathological identification of biopsy tissue, more biopsies being performed or improved access to health services in the new millennium. The low incidence of MCD in our study (13.9%) may not be a true reflection of the incidence of this disease in the general population. It may reflect selection bias, with only difficult-to-treat NS being referred to the central hospital, as well as centre-specific indications for biopsy, where only children with frequently relapsing, steroid-dependent or SRNS are biopsied. Similar to previous findings from this region, black African children were more likely to be SR than Indian children.[4,5,14]

An unusual finding in our present study was the larger number of black African children being steroid responsive, in keeping with reports from other regions in SA.[8,9] Of the 76 children with SSNS, 61.8% were black African compared with a previous study from this region, where only 14.4% of black African children had SSNS; 31.9% had FSGS compared with SSNS children from other races in the previous study.[14]

Only 1 child with presumed MCD, who may have been missed as having FSGS, as he was initially SS and lost to follow-up, presented 6 years later with ESKD. All except 2 children who progressed to ESKD

had FSGS, making it the most common histopathological form of NS to progress to ESKD, which is in keeping with the literature.[14,35,36] All except 1 child who progressed to ESKD were black African children, highlighting the more aggressive progression of kidney disease in children of African descent.[9,36,37] Indian children were more likely to preserve kidney function, while black African children were more likely to progress to higher stages of CKD.

Only about two-thirds of children with primary NS who progressed to ESKD qualified for some form of renal replacement therapy. Although this is an improvement from our previous experience of <10% of children having access to such therapy (R Bhimma – personal communication, 2019), it is probably a reflection of the plight of our children, with poor socioeconomic factors being one of the major determinants of eligibility for renal replacement therapy. The high cost of this therapy, lack of trained staff, late referral of children with comorbidities and lack of kidney donors due to religious beliefs make it increasingly difficult for all children with ESKD to be part of a programme for renal replacement therapy. In our centre, only children eligible for kidney transplantation are entered into a chronic dialysis programme.

Study limitations

There are several limitations to this study. This was a retrospective single-centre study of children with primary NS. Seven children with incomplete records and children >14 years of age were excluded from the analysis. There may have been children with primary NS not referred to the central hospital, lost to follow-up or who died before a referral from the base hospital. We did not fully evaluate the response to the different forms of therapy other than steroids. There is a strong selection bias, as only children with difficult-to-treat NS are referred to the central hospital. There is a dearth of white or mixed-race children who are not represented in the analysis owing to the small numbers seen in our centre. We were not able to document the complications of the disease accurately, except death, due to coding irregularities in the computer system.

Conclusions

Our study comprises one of the largest cohorts of children with primary NS from a single centre in KwaZulu-Natal and shows a rising incidence in FSGS, with the majority having SRNS, particularly black African children. This highlights the need for alternative efficacious therapy in the management of the disease. We have documented a higher percentage of black African children with both MCD and FSGS on histopathology who are SS, in keeping with reports from other regions of SA. Renal replacement therapy is currently more readily available, but there are still major challenges for the inclusion of all children into a chronic dialysis and transplant programme.

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