

Primary nephrotic syndrome in children in Cape Town, South Africa

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Background. Histopathological patterns of childhood primary nephrotic syndrome (PNS) and clinical response to steroids have been associated with certain race groups in parts of South Africa. However, there are no recent studies of childhood PNS in Cape Town.

Objectives. To describe the demographics, histological subtypes and steroid response of patients with PNS who underwent kidney biopsies at Red Cross War Memorial Children's Hospital (RCWMCH) over a 10-year period.

Methods. Details of patients with PNS who underwent kidney biopsies in the Paediatric Nephrology Department at RCWMCH between 2006 and 2015 were retrospectively recorded.

Results. A total of 103 patients were included in the study. Most patients were either of mixed race (42%) or black (36%), with a mean age of 6.8 years and a male-to-female ratio of 1.19:1. The most identified histopathological subtype was mesangioproliferative glomerulonephritis (MesPGN; 60% ($n/N=62/103$)). Of the patients with focal segmental glomerulosclerosis (FSGS), MesPGN and minimal change disease (MCD) 45% ($n/N=43/95$) were steroid-resistant, and 54% ($n/N=51/95$) were steroid-sensitive. There was no significant association between any race group and steroid response. Patients with FSGS were more likely to be black, while MCD was more common in mixed-race patients ($p=0.04$). There was no difference in the likelihood of being mixed race or black between patients with FSGS and MesPGN ($p=0.472$).

Conclusion. MesPGN was the most common histopathological subtype found in our study. There was no significant association between race and steroid response. Patients with FSGS were more likely to be black than mixed race when compared with MCD patients. Race was not otherwise significantly associated with any histopathological subtype.

Keywords. nephrotic syndrome; mesangioproliferative glomerulonephritis; steroid-sensitive; steroid-resistant.

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Childhood nephrotic syndrome is reported to have an incidence of 1 to 7 per 100 000 children under the age of 16 years.^[1] While some patients have a single episode and may not be attended to by a paediatric nephrologist, especially in lower- and middle-income countries, several patients tend to have a chronic relapsing course. There are numerous histopathological subtypes of primary nephrotic syndrome (PNS) namely minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), mesangiocapillary/membranoproliferative glomerulonephritis (MPGN), mesangioproliferative glomerulonephritis (MesPGN) and membranous nephropathy.

The most common subtype in younger patients is reported to be MCD, while focal segmental glomerulosclerosis (FSGS) is more common in older patients.^[2,3] Patients with PNS can be classified according to their clinical response to corticosteroid treatment, i.e. steroid-sensitive nephrotic syndrome (SSNS) or steroid-resistant nephrotic syndrome (SRNS). Between 20% and 60% of those with SSNS may also develop steroid-dependent nephrotic syndrome (SDNS) or frequently-relapsing nephrotic syndrome (FRNS).^[4,5] Not all patients who present with PNS undergo kidney biopsies and the criteria for performing biopsies in these patients vary between centres.

MCD has been associated with SSNS and FSGS, as well as SRNS in some studies.^[1,6-9] Studies conducted in other parts of South Africa

(SA), i.e. outside of Cape Town, have demonstrated associations between race and histopathological subtype on biopsy, as well as race and steroid response.^[6-9] Cape Town has a population of ~3.74 million people with most people belonging to the race group referred to as mixed race (42%).^[10] Mixed race refers to descendants of blacks, whites and slaves from West Africa, East Africa and the Far East.^[6] As there are no recent studies of childhood nephrotic syndrome in Cape Town, the aim of the present study was to describe the demographic characteristics as well as the histopathological subtypes and steroid response of patients with PNS who underwent kidney biopsies over a period of 10 years at Red Cross War Memorial Children's Hospital (RCWMCH) in Cape Town, SA.

Methods

Our study population included all patients with PNS who underwent kidney biopsies at RCWMCH between January 2006 and December 2015. Patients were identified from the departmental clinical database, which contains details of all patients who had kidney biopsies, the indication for the biopsy, as well as the biopsy result. Patients with congenital nephrotic syndrome and secondary causes of nephrotic syndrome, e.g. systemic lupus erythematosus, were excluded from the study.

In our nephrology department any patient with nephrotic syndrome (who has had a secondary cause excluded as far as

possible), in an atypical age group (under 1 year old or over 10 years old), or who has SRNS, SDNS, FRNS will undergo a kidney biopsy.

Hospital folders of patients were reviewed, and clinical and demographical data was recorded on an Excel spreadsheet. Race was determined from the clinician's knowledge of the patient over many years. We defined SRNS, SSNS, SDNS and FRNS according to the KDIGO Clinical Practice Guidelines.^[4]

Data were analysed using SPSS version 3.0 (SPSS Inc., USA). Numerical data that were normally distributed were reported as the mean with minimum and maximum values. Categorical variables were compared using Student's *t*-test and logistic regression. Confidence intervals (CIs) were reported for statistically significant results.

Ethics

Ethical approval was obtained from the University of Cape Town's Human Research and Ethics Committee (ref. no. HREC 026/2016).

Results

During the study period, 110 patients underwent kidney biopsies for PNS. The mean (range) age was 6 years (3 weeks - 15 years). Congenital nephrotic syndrome was diagnosed in 5 patients and 2 patients had features of IgA nephropathy (considered a secondary cause of nephrotic syndrome) and diffuse global sclerosis. These 7 patients were excluded from further analysis.

Fifty-six (54%) were male and 47 (46%) were female with a ratio of 1.19:1. There was no significant association between sex and histopathological subtype in our study (Table 1). The most common histopathological subtype in our cohort was MesPGN (60%; *n*/N=62/103), followed by FSGS (17%; *n*/N=18/103).

Our study population was reflective of the population of Cape Town, as most patients were either black (36%; *n*/N=38/103) or of mixed race (42%; *n*/N=43/103). MesPGN was the predominant histopathological subtype across all race groups in our study. Of the 62 patients with MesPGN, 40.3% (*n*/N=25/62) were black and 37.1% (*n*/N=23/62) were of mixed race. Of the 18 patients with FSGS, 55.6% (*n*/N=10/18) were black and 33.3% (*n*/N=6/18) were of mixed race.

Logistical regression revealed that patients with FSGS were significantly more likely to be black than mixed race when compared with patients with MCD (Exp B = 0.180; 95% CI 0.035 - 0.928; *p*=0.04); similarly, patients with MesPGN were more likely to be black than mixed race compared with those with MCD although this did not reach significance (95% CI 0.067 - 1.129; *p*=0.073). There

was no difference in the likelihood of being mixed race or black between patients with FSGS and MesPGN (95% CI 0.204 - 2.080; *p*=0.472).

When analysing histopathological subtypes and steroid response the group MPGN was excluded owing to small numbers. Forty-five percent of our patients had SRNS and 54% had SSNS (Table 2). One patient was lost to follow-up and therefore we could not determine his steroid responsiveness. Of the patients with MesPGN, 58% (*n*/N=36/62) had SSNS and 40% (*n*/N=25/62) had SRNS. Most (83%) of those with FSGS had SRNS and most (80%) of the patients with MCD had SSNS.

Patients with FSGS were 20 times more likely to have SRNS than those with MCD (Exp B = 20; 95% CI 3.403 - 117.559; *p*=0.001). Similarly, patients with FSGS were 7 times more likely to have SRNS compared with children with MesPGN (Exp B = 7.2; 95% CI 1.884 - 27.511; *p*=0.004). Patients with MCD were 75% less likely to have SRNS overall (95% CI 0.710 - 10.868; *p*=0.032). There was no significant difference in steroid response between patients with MCD and MesPGN (95% CI 0.710 - 10.868; *p*=0.142).

Indian and unknown groups were excluded from the analysis of the association between steroid response and race owing to small numbers (Table 3). No significant association was found between any race and steroid response.

Discussion

The results of patients with PNS who underwent kidney biopsies at our centre show that MesPGN was found in more than half the patients who underwent biopsies (60%), followed by FSGS (17%) and MCD (15%). Most patients in our study were either of mixed race (42%) or black (36%), which was reflective of the population in Cape Town but different from the findings of studies conducted elsewhere in SA^[6-9,11]

In a similar study^[7] conducted in Durban, most patients were black and FSGS was the predominant histopathological subtype found among both steroid-resistant and steroid sensitive patients who underwent biopsies. Nandlal *et al.*^[8] subsequently showed that the incidence of FSGS was increasing across all race groups in Durban.

In Pretoria, most patients who underwent biopsies for childhood nephrotic syndrome were black. MCD was the predominant histopathological subtype found overall and FSGS was more likely to be seen in black patients v. white patients.^[9] Similarly, a study in Johannesburg (including mostly black patients) identified MCD as the most common histopathological subtype and reported that

Table 1. Demographic characteristics of patients biopsied for PNS

Characteristic	Histopathological subtype				Total (<i>n</i> =103), <i>n</i> (%) [*]
	FSGS (<i>n</i> =18), <i>n</i> (%) [*]	MPGN (<i>n</i> =8), <i>n</i> (%) [*]	MesPGN (<i>n</i> =62), <i>n</i> (%) [*]	MCD (<i>n</i> =15), <i>n</i> (%) [*]	
Mean (range) age at time of biopsy, years	5.71 (1.09 - 12.20)	9.35 (4.5 - 13.42)	6.96 (0.81 - 14.86)	8.09 (1.7 - 14.58)	
Sex					
Male	11 (61)	5 (63)	34 (55)	6 (40)	56 (54)
Female	7 (39)	3 (37)	28 (45)	9 (60)	47 (46)
Ethnicity					
Black	10 (55.6)	0	25 (40.3)	3 (20)	38 (36)
Mixed race	6 (33.3)	4 (50)	23 (37.1)	10 (66.7)	43 (42)
White	0	2 (25)	7 (11.3)	1 (6.7)	10 (10)
Indian	0	0	1 (1.6)	1 (6.7)	2 (2)
Unknown	2 (11.1)	2 (25)	6 (9.7)	0	10 (10)

PNS = primary nephrotic syndrome; FSGS = focal segmental glomerulosclerosis; MPGN = membranoproliferative glomerulonephritis; MesPGN = mesangioproliferative glomerulonephritis; MCD = minimal change disease.

^{*}Unless otherwise specified.

Table 2. Steroid response according to histopathological subtype

Steroid response	Histology			Total (N=95), n (%)
	FSGS (n=18), n (%)	MesPGN (n=62), n (%)	MCD (n=15), n (%)	
SRNS	15 (83)	25 (40)	3 (20)	43 (45)
SSNS	3 (17)	36 (58)	12 (80)	51 (54)
Unknown*	-	1 (2)	-	1 (1)

FSGS = focal segmental glomerulosclerosis; MesPGN = mesangioproliferative glomerulonephritis; MCD = minimal change disease; SRNS = steroid-resistant nephrotic syndrome; SSNS = steroid-sensitive nephrotic syndrome.

*One patient was lost to follow-up and therefore steroid response could not be determined.

Table 3. Steroid response according to race

Steroid response	Race			Total (n=98), n (%)
	Black (n=41), n (%)	Mixed race (n=45), n (%)	White (n=12), n (%)	
SRNS	21 (51)	22 (49)	6 (50)	49 (50)
SSNS	19 (46)	23 (51)	6 (50)	48 (49)
Unknown*	1 (3)	-	-	1 (1)

SRNS = steroid-resistant nephrotic syndrome; SSNS = steroid-sensitive nephrotic syndrome.

*One patient was lost to follow-up and therefore steroid response could not be determined.

the highest rate of FSGS was seen in black patients.^[11]

In other parts of Africa, MesPGN was not noted to be a predominant histopathological subtype in patients who underwent biopsies for childhood nephrotic syndrome. In Kano, Nigeria, the most common histopathological subtype was FSGS^[12] and in Sudan it was MCD.^[13]

Differences in patient cohorts in terms of race in the SA studies reflects the population differences of each province, e.g. Cape Town has a large mixed-race population and Durban has a large Indian population. Other differences, such as steroid responsiveness and age, could be explained by varying biopsy criteria among the centres, as well as inclusion and exclusion criteria for the respective studies. If MesPGN was considered a variant of MCD it would explain the predominance of MCD in the present study and this would be in keeping with the previously mentioned studies conducted in Pretoria^[9] and Johannesburg.^[11]

Most of our patients who had FSGS were black (55.6%) in keeping with other studies, while most of our patients with MCD were mixed race (67%). In our study there was no significant association between histopathological subtype and race, except that patients were more likely to be black than mixed race if they had FSGS v. if they had MCD. This could indicate possible genetic causes of FSGS in our black population. There was no significant difference in the likelihood of being black or mixed race between patients with MesPGN and FSGS.

MesPGN was the predominant histopathological subtype among both our steroid-sensitive and steroid-resistant groups, which differed from findings in Durban, where FSGS was the predominant histopathological subtype in these groups.^[6-8] The vast majority (83%) of our patients with FSGS were steroid-resistant and most of our patients with MCD were steroid-sensitive (80%). Patients with MCD were overall significantly less likely to have SRNS, whereas patients with FSGS were 20 times more likely than those with MCD to have SRNS and 7 times more likely than those with MesPGN to have SRNS. There was no significant difference in steroid response between patients with MesPGN and MCD. Furthermore, there was also significant association between race and steroid response in our study population. This finding was in contrast to Durban-based studies,^[7,8] where black patients were significantly more likely to be steroid-resistant, regardless of their histopathological subtype, compared with Indian patients.

The present study revealed unique patient characteristics in Cape Town regarding childhood PNS, with MesPGN being the predominant histopathological subtype across all races and in both the steroid-resistant and steroid-sensitive patients who underwent kidney biopsies. Race and steroid response were not significantly associated with MesPGN in this study.

Study strengths and limitations

Limitations of the present study include its single-centre and retrospective nature.

Patients with MCD and SSNS who do not develop FRNS or SDNS, and therefore do not undergo a biopsy, were underrepresented in our study population. Furthermore, race was determined by physician recall and may not have been accurate in all cases. The quality of the biopsy samples was not reviewed in terms of number of glomeruli and presence of corticomedullary junctions. Strengths of the study include the analysis of a fairly large and robust data set.

Conclusion

MesPGN was the predominant histopathological subtype in patients who underwent kidney biopsies for PNS in Cape Town irrespective of race and steroid response. There was an increased likelihood of being black v. mixed race in patients who had FSGS, compared with patients with MCD only, who were more likely to be of mixed race. There was no other significant association between race and histopathological subtype. Patients with FSGS were more likely to be steroid-resistant and those with MCD were more likely to be steroid-sensitive. Recommendations for future studies include a multi-centre, prospective study of childhood PNS in SA investigating responses to second-line agents, e.g. calcineurin inhibitors, as well as the genetic causes of SRNS in our population.

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