



## NEPHROTIC SYNDROME IN NAMIBIAN CHILDREN

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**Background and objectives.** Patterns of nephrotic syndrome vary between regions and countries, and influence approaches to management. In the mid-1970s the University of Stellenbosch became involved in providing tertiary care to Namibia, including a paediatric nephrology service. The aim of this study was to document the clinical, pathological and outcome features of nephrotic syndrome in Namibian children.

**Subjects.** Seventy black Namibian children with nephrotic syndrome were managed from 1975 to 1988. Sixty-eight renal specimens (67 biopsies and 1 autopsy specimen) were evaluated.

**Results.** Twenty-nine of the 70 children (41.4%) were hepatitis B virus (HBV) carriers, of whom 25 (86.2%) were male. Of the 29, 26 had predominantly membranous glomerulonephritis (MGN), 1 mesangiocapillary glomerulonephritis (MCGN), and 1 focal segmental glomerulosclerosis (FSGS); 1 child in advanced renal failure was not biopsied. Five children (7.4%) showed minimal change disease (MCD), 11 (16.2%) FSGS and 15 (22.1%) diffuse mesangial proliferative glomerulonephritis (DMP). The remaining 10 children showed diffuse glomerulosclerosis (6), MCGN (3) and endocapillary proliferative GN (1). Four of the 5 children with MCD went into remission on immunosuppressive treatment. Of the 15 with DMP, 4 improved spontaneously and only 1 of those treated did not improve. Only 2 of those with FSGS improved on treatment. The children with HBV-associated MGN and MCGN were offered symptomatic rather than specific treatment. Thirteen children presented with degrees of chronic renal failure. Eight are known to have died, 3 of relentless nephrotic syndrome and 4 (of whom 3 were HBV carriers) of end-stage renal failure. One child died of penicillin anaphylaxis.

**Conclusions.** The pattern of nephrotic syndrome in black Namibian children differed greatly from the non-African pattern elsewhere in that MCD was uncommon and HBV-associated GN was the most common single group. The most

frequent pattern of HBV-associated GN was MGN with some mesangiocapillary features showing marked male predominance. MCD and DMP were potentially treatable and could only be identified by biopsy. HBV carrier rates exert a major influence on the proportions of morphological subgroups of nephrotic syndrome in children. As these HBV carrier rates alter in future due to the influence of vaccination and urbanisation, the relative size of nephrotic subgroups seems likely to alter.

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For the past 25 years it has been known that black children with nephrotic syndrome (NS) from southern Africa do not show the same renal morphology or clinical response as other children. In most other children, minimal change nephrotic syndrome (MCNS) is the most frequent cause and is usually responsive to steroids. Features of NS in black children in southern Africa have included a relatively low prevalence of MCNS, a high but variable prevalence of hepatitis B virus (HBV)-associated membranous glomerulonephritis (MGN), and substantial groups of children with focal segmental glomerulosclerosis (FSGS) and diffuse mesangial proliferative glomerulonephritis (DMP).<sup>1,2</sup>

When in the mid-1970s Tygerberg Hospital and the University of Stellenbosch Medical School became involved as a tertiary referral centre for Namibia, the clinicopathological spectrum of nephrotic syndrome in black Namibian children was unknown. This paper documents a 14-year involvement in the management of Namibian children, emphasising the value of serological and renal biopsy data in guiding towards rational appropriate treatment.

### MATERIALS AND METHODS

Seventy black children with nephrotic syndrome from six ethnic groups in Namibia were evaluated at Tygerberg Hospital near Cape Town from 1975 to 1988. Sixty-three children were seen from 1980 to 1988 (average 7 per year): 45 children were Ovambo (64.2%), 9 Damara (12.9%), 8 Kavango (11.4%), 4 Herero (5.7%), 2 Nama and 2 Bushmen. This distribution approximately represents the ethnic population groups in Namibia, with the Ovambo constituting 46.1% of the total population of 960 000 in 1980.<sup>3</sup> The policy during this period was for all children presenting with nephrotic syndrome at regional hospitals in Namibia to be referred to our hospital for evaluation and management.

The age of the children varied between 1 year 10 months and 15 years (average 7.2 years); 24% were aged under 5 years, 46% 5 - 9 years and 30% 10 - 15 years. There were 48 male (68.6%) and 22 female children (31.4%).

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The children were all subjected to a thorough examination and evaluation before biopsy and further management, which was supervised by the same paediatric nephrologist over the entire period (AJvB). The criteria for nephrotic syndrome were standard, including oedema, serum albumin below 30 g/l (levels were mostly below 25 g/l), hypercholesterolaemia and heavy proteinuria (> than 1 000 mg/m<sup>2</sup>).

From 1975 to 1986 the method used for HBV serological testing was radio-immunoassay using Abbott (Chicago, USA) kits, Ausria-125 and Ausria II-125. From 1987 to 1988 Abbott's enzyme-linked immunoassay was used.

Of the 70 children, 67 had renal biopsies performed and in 1 a postmortem specimen was evaluated. One child with a steroid-resistant, relentless nephrotic syndrome died before a biopsy could be done and 1 hepatitis B carrier in end-stage renal failure was not biopsied.

Renal biopsy material for light microscopy, electron microscopy and immunofluorescent studies was dealt with according to standard methods and procedures as previously described.<sup>4</sup> The following antibodies were used for HBV testing: HBs (Dako B560), HBc (Dako Polyconal B586) and HBe (mouse monoclonal, Institute of Immunology, Tokyo).

## RESULTS

### Clinical features

Twenty-nine of the 70 children tested (41.4%) were found to be HBV carriers. Of these 29, 25 were boys (86.2%) and 4 were girls (13.8%). Twenty-one of the HBV carriers were Ovambo children. The ages of the HBV carriers varied from 3 to 15 years, with an average of 6.6 years. When the HBV carriers were excluded, 23 of the remaining nephrotic children were male (56.1%) and 18 were female (43.9%), a ratio of 1:1.3.

Three children had positive serology for syphilis. All three came from the same geographical area (Tsumeb/Grootfontein), possibly an area of endemic syphilis.

Malaria was not a factor, with neither clinical nor blood film evidence of the disease in any of these children. On clinical examination no child showed features of systemic lupus erythematosus and the antinuclear factor was negative in all of them.

All the children by definition showed proteinuria, but 53 of the 70 (70.3%) also had haematuria in varying degrees of severity. Twenty (31%) were hypertensive at presentation and 13 showed evidence of varying severity of chronic renal impairment/failure, as further described in the section 'Course and management'.

### Histological classification

This is set out in Table I and is based on 68 renal specimens (67 biopsies and 1 postmortem). The classification is essentially

**Table I. Histopathological classification of nephrotic syndrome**

	No. of cases	%
Minimal change	5	7.4
Focal segmental glomerulosclerosis (1 HBV)	11	16.2
Proliferative glomerulonephritis		
Mesangial proliferative glomerulonephritis	15	22.0
Endocapillary proliferative glomerulonephritis	1	1.5
Mesangiocapillary glomerulonephritis (1 HBV)	3	4.4
Membranous glomerulonephritis (26 HBV-positive, 1 syphilis)	27	39.7
Diffuse sclerosing glomerulonephritis	6	8.8
Total	68	100

according to the most recent World Health Organisation (WHO) classification.<sup>5</sup>

It can be seen that the minimal change group (7.4%) is far smaller than in most non-African series. Twenty-eight of the biopsied children were HBsAg-positive. The morphological patterns seen in these biopsies were categorised as MGN in the 26 cases where subepithelial deposits were found ultrastructurally, with one case each of MCGN and FSGS. Those classified as MGN in association with HBV showed a morphological range usually more complicated than idiopathic membranous, with a mixture of membranous and mesangiocapillary features. The glomeruli showed not only subepithelial deposits but also always mesangial deposits and sometimes subendothelial deposits. Varying degrees of mesangial interposition were also frequently observed. This spectrum of morphology is part of a larger detailed study on HBV-associated glomerular disease, with some of the findings from the latter study published in abstract form.<sup>6</sup> In the context of this series, the membranous group and the mesangiocapillary case were viewed as HBV-associated glomerular disease. Of the 26 children with HBV MGN, 23 were boys, giving a female/male ratio of 1:7.6 compared with 1:1.3 for the non-HBV nephrotic group, a very marked male predominance in this subgroup. The remaining MGN example was associated with positive serology for syphilis.

Tubuloreticular bodies, which were first described in renal biopsies, particularly in connection with systemic lupus erythematosus, have been found in a high proportion of HBV MGN cases, usually in glomerular endothelial cytoplasm.<sup>7</sup>

This was also true in this series, where 26/28 of the biopsies of the HBV cases were positive (92.8%). In order to place this figure in perspective, we re-examined our ultrastructural sections of the other 39 biopsies for these bodies for a similar time at high magnification. They were positive in 15/39 cases (38%) spread across the other categories. This constitutes a statistically significant difference (chi square:  $P < 0.001$ ).

Immunofluorescence staining was available in most of the



biopsies and showed predominantly IgG, IgM and C3 positivity, particularly in the membranous, mesangial proliferative, mesangiocapillary and diffuse sclerosing subgroups, with less positivity in the FSGS category and only 1 of the minimal change group showing small amounts of C3. As part of a wider study on HBV MGN, a subgroup of these biopsies was stained for HBV antigens. Immunofluorescence staining using anti-HBs antibodies was positive in 9/17 (53%) HBV-associated MGN cases. It has since been shown that this antibody is not specific and cross-reacts with nonspecific proteins making these findings unreliable.<sup>8</sup> Staining for HBe was positive in 6/7 cases (86%) and 5/7 cases (71%) for HBe in a granular capillary wall pattern that correlated with the membranous subepithelial deposits.

### Course and management

All 5 children with MCD, average age 5.8 years, received steroids; 2 of the 5 also required cyclophosphamide. Four went into complete remission but 1 died of relentless nephrotic disease after 2 weeks on therapy.

Of the 15 children with a DMP, average age 7.3 years, 4 went into spontaneous biochemical remission and were not treated. Ten were treated with steroids, with 6 of the 10 also requiring cyclophosphamide. Six of the treated children went into complete remission, 3 showed biochemical improvement, and 1 did not respond. The remaining child, with positive serology for syphilis, responded partially to penicillin.

Seven of the 11 children with FSGS, average age 9.1 years, were treated, all with prednisone and 4 also with cyclophosphamide, but only 2 showed complete or biochemical remission and 1 died of relentless nephrotic disease.

The children in the remaining clinicopathological groups of HBV MGN, mesangiocapillary GN and end-stage disease were offered supportive therapy only. Of the HBV group, 3 presented with degrees of renal failure (1 MGN, 1 mesangiocapillary, 1 unbiopsied). A fourth child with MGN presented with normal renal function but later deteriorated. Three of these 4 are known to have died of renal failure. Despite recent efforts to trace these children via a paediatrician in Windhoek, no further follow-up could be established.

Of the 13 children presenting with chronic renal failure, 2 had FSGS (1 HBV carrier), 2 MCGN, 6 diffuse sclerosing GN and 3 HBV-associated disease (1 MGN, 1 MCGN and 1 unbiopsied).

Eight children are known to have died, 3 of relentless nephrotic syndrome (1 from MCD, 1 FSGS, 1 unbiopsied), 1 from penicillin anaphylaxis and 4 (3 of whom were HBV carriers) from end-stage renal failure.

### DISCUSSION

It is well known that the causes of nephrotic syndrome in

children vary from country to country and even between ethnic groups within countries. A recent review on renal problems in black South African children provides data with which to compare this series of Namibian children.<sup>2</sup> Thomson contrasted a group of 720 black nephrotic children biopsied in Johannesburg and Pretoria with 234 children from Durban (Table II). Among the former group, FSGS was the most frequent biopsy diagnosis (31%), similar to the 29% among the Durban children where it was the second most frequent diagnosis. In the Namibian children, FSGS was the third largest group (16%). The minimal change subgroup (24%) was the Gauteng region's second largest group while in Durban this group (14%) was the third largest group. In Namibia the MCD group was 5th and comprised 7% of the total, less than in Gauteng and Durban. One of the clearest differences between these two large South African centres was in the prevalence of membranous GN, almost always associated with HBV. In Durban this was the single largest group (40%) while in Gauteng (13%) this subgroup was third. In Namibia and Durban the membranous group was largest (40%), but in Namibia the mesangial proliferative group (22%) was second, as opposed to FSGS in Durban.

Is there an explanation for these striking differences in HGV MGN incidences in different series of black South African children? It was previously suggested that the differences may be related to inland or coastal factors, with the coastal areas having higher rates.<sup>2</sup> However, the inland Namibian (Ovambo) group, with a high incidence, seems to disprove this hypothesis. The differing incidences seem more likely to reflect underlying HBV carrier rates, which show prominent rural-urban differences. For example, there is evidence that HBV carrier rates among children in rural areas of KwaZulu-Natal (18.5%) are higher than those in peri-urban areas of Durban (10%).<sup>9</sup> In this epidemiological study, there was no significant difference between male and female children with regard to

Table II. Nephrotic syndrome pathology in black southern African children

	Namibia (over 14 yrs)	Durban (over 20 yrs)	Gauteng- Johannesburg (over 10 yrs), Pretoria (over 11.5 yrs)
Patient numbers	68	234	720
Diagnosis (% per group)			
Membranous	39.7	40.2	13.5
Mesangial proliferative	22.1	7.3	13.2
FSGS	16.2	28.6	31.3
MCD	7.4	13.7	24.4

Based on table by Thomson.<sup>2</sup>



prevalence of HBsAg. The consistent predominance of male children in HBV membranous GN series may, therefore, have causes other than simply higher male carrier rates. A survey in Soweto revealed a remarkable difference in the HBV carrier rate between urban children at 0.97% (boys 1.5%, girls 0.57%) compared with the accepted figure of 15% for rural children in southern Africa.<sup>10</sup> These rates were derived before the Durban peri-urban figure of 10% and are almost certainly a factor in the differing membranous GN patterns. The reason for this striking difference (1% v. 10%) between these two major populations of urban black children is not yet clear, but a probable factor is that Soweto is a more established urban area. In summary, the overall proportion of HBV MGN in a childhood nephrotic population appears to reflect the underlying HBV carrier rate in that population, which seems to be influenced by urbanisation.

A survey of the HBV carrier state in black children in Ovamboland (northern Namibia) was undertaken between 1981 and 1983 (in the middle of our study period) by a research group from another institution.<sup>11</sup> HBsAg was detected in 17% of adult males and 11% of mothers. Only 1% of children less than 6 months old were HBsAg-positive compared with 13% of children over the age of 1 year. In view of this finding, among others, it was concluded that later horizontal transmission seemed to be more important than neonatal maternal-infant transmission. Although the carrier rate among the Ovambo children was high (13% over 1 year of age), the proportion of Ovambo nephrotic children who were HBV-positive (21/45, 46.6%), being considerably higher, supports an association of HBV with the nephrotic syndrome and specifically the membranous type of picture.

## CONCLUSION

The pattern of nephrotic syndrome in black Namibian children differs greatly from the pattern among Western (non-African industrialised world) children. MCD is uncommon. MCD and DMP are potentially treatable with immunosuppressives and can only be identified by biopsy. Not unexpectedly, FSGS responded poorly to treatment in this series. New approaches to treatment are being attempted in other centres.<sup>12</sup> HBV is a common associated factor with a significant male predominance. All but one patient with MGN were HBV carriers. The morphology of the HBV-associated membranous pattern often shares features with the mesangiocapillary appearance, including mesangial deposits and proliferation, subendothelial deposits and mesangial interposition. It seems probable that, influenced by urbanisation and immunisation, future changes in HBV carrier rates may lead to changing patterns of childhood nephrotic histopathology in southern Africa.

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