Clinicopathological Features of Atypical Nephrotic Syndrome in Jamaican Children

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ABSTRACT

Objectives: *To document the histopathological spectrum of atypical nephrotic syndrome in Jamaican children and to make clinicopathological correlations which will assist physicians in identifying patients needing nephrology consultation.*

Methods: *This was a retrospective review of renal biopsy data of Jamaican children who were referred to the University Hospital of the West Indies and the Bustamante Hospital for Children between January 1985 and December 2008. The study population consisted of children < 12 years old with atypical nephrotic syndrome.*

Results: *Biopsies were done in 157 children – 85 males and 72 females (mean age 8.91 ± 3.44 years). Indications for biopsy were steroid resistance (35%), frequent relapses (8.9%) and other atypical presentations (56.1%).*

Overall, mesangial proliferative glomerulonephritis (MesGN) was the commonest histology (49/157, 31.2%), followed by minimal change disease (MCD) (36/157, 22.9%) and diffuse proliferative glomerulonephritis (DPGN) (26/157, 16.6%). Infection was present in 38/157 (24%) cases. Diffuse proliferative glomerulonephritis was the predominant type associated with streptococcal infection (52.9%) while Hepatitis B was seen in 83% of cases of membranous nephropathy.

Conclusion: *Mesangial proliferative glomerulonephritis is the commonest histology seen in Jamaican children with atypical nephrotic syndrome. Most membranous nephropathy is Hepatitis B related. Hypertension with hypocomplementaemia, renal failure and anaemia are features of more serious renal disease (eg membranoproliferative glomerulonephritis and crescentic nephritis) rather than MCNS and should warrant urgent nephrology consultation for renal biopsy.*

Keywords: Atypical nephrotic syndrome, mesangial proliferative glomerulonephritis, renal biopsy

Características Clínico-patológicas del Síndrome Nefrótico Atípico en los Niños Jamaicanos

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RESUMEN

Objetivos: *Documentar el espectro histopatológico del síndrome nefrótico atípico en los niños jamaicanos y hacer correlaciones clínico-patológicas que ayuden a los médicos a identificar pacientes que necesitan la consulta de nefrología..*

Métodos: *Se trata de un estudio retrospectivo de datos de biopsias renales de niños jamaicanos remitidos al Hospital Universitario de West Indies y al Hospital Pediátrico Bustamante, entre enero de 1985 y diciembre de 2008. La población del estudio consistió en niños < 12 años de edad que padecían el síndrome nefrótico atípico.*

Resultados: *Se realizaron biopsias a 157 niños – 85 varones y 72 hembras (edad promedio 8.91 + 3.44 años). Las indicaciones para la biopsia se debieron a resistencia a los esteroides (35%), recaídas frecuentes (8.9%) y otras manifestaciones atípicas (56.1%).*

En general, la glomerulonefritis proliferativa mesangial (GNMes) fue la histología más común con 49/157 (31.2%), seguida por la enfermedad de cambio mínimo (ECM) con 36/157(22.9%) y la

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glomerulonefritis proliferativa difusa (GNPD) con 26/157 (16.6%). La infección estuvo presente en 38/157 (24%) de los casos. La glomerulonefritis proliferativa difusa fue el tipo predominante asociado con la infección estreptocóccica (52.9%), mientras que Hepatitis B fue observada en el 83% de los casos de nefropatía membranosa.

Conclusión: *La glomerulonefritis proliferativa mesangial es la histología que con mayor frecuencia se observa en los niños jamaicanos que padecen el síndrome nefrótico atípico. La mayoría de los casos de nefropatía membranosa guardan relación con la hepatitis B. La hipertensión con hipocomplementemia, la insuficiencia renal y la anemia son rasgos más bien de enfermedades renales más serias (p.ej, glomerulonefritis membranoproliferativa, nefritis crescéntica) que del síndrome nefrótico de cambios mínimos (SNCM) y debe asegurarse la consulta urgente con el nefrólogo para se realice una biopsia renal.*

Palabras claves: síndrome nefrótico atípico, glomerulonefritis proliferativa mesangial, biopsia renal

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INTRODUCTION

Jamaica is a Caribbean island divided into fourteen parishes. In 1997 (the mid-study-year of the present study), the island's population was 2.55 million of whom 25.6% (about 654 000) were children < age 12 years (1). The commercial heart of the island is located in the parishes of Kingston and St Andrew and it is here that the only hospitals offering paediatric nephrology service are found – namely the University Hospital of the West Indies (UHWI) and the Bustamante Hospital for Children (BCH). It is to these hospitals that all cases of complicated renal disease in children (including atypical nephrotic syndrome) from across the entire island are referred. In Jamaican hospitals, childhood is defined as age < 12 years so all children > 12 years of age are managed by the adult services.

Nephrotic syndrome (NS) is a common manifestation of renal disease in childhood, with an annual incidence of 2–7 new cases per 100 000 children in the Western hemisphere (2). Nephrotic syndrome in childhood is predominantly idiopathic and is represented histologically by minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), mesangial proliferative glomerulonephritis (MesGN), membranous nephropathy (MN) and membranoproliferative glomerulonephritis (MPGN) (3). Minimal change nephrotic syndrome (MCNS) is historically responsible for approximately 80% of cases in children under 6 years old (3, 4) and is characterized by its benign nature and steroid responsiveness (4). Children with features atypical for MCNS require renal biopsy for diagnosis and treatment.

Studies from India (5) and the USA (6) have shown an increase in the frequency of FSGS with time. The current study documents the histological spectrum of renal disease in Jamaican children < 12 years of age with atypical nephrotic syndrome between 1985 and 2008. Correlations will be made between clinical presentation and histological findings with a view to enabling physicians to determine which patients need to be referred for nephrology consultation. Histological trends observed during the period of the study will be recorded.

SUBJECTS AND METHODS

In the Jamaican hospital setting, childhood is defined as age < 12 years. All children in the island with complicated renal disease are referred to the paediatric nephrology services of either UHWI or BCH. Renal biopsies from these hospitals represent all the island's paediatric renal biopsies and are evaluated only at the UHWI, primarily by one pathologist (DS). Paediatric renal biopsy data from the Pathology Department of the UHWI are therefore representative of the entire Jamaican paediatric population.

A comprehensive retrospective review was conducted of histology reports for the first adequate renal biopsies performed in Jamaican children < 12 years of age in the 24-year period between January 1985 and December 2008. The study was approved by the University Hospital of the West Indies/University of the West Indies, Faculty of Medical Sciences (UHWI/UWI/FMS) Ethics committee. The current study analysed only the NS data from the overall review. Data were gathered solely from information recorded on the pathology requisition forms and included: age, gender, year of and indication for biopsy, renal histology, clinical and laboratory features. Indications for biopsy in children with NS were: a) age < 12 months, b) sustained hypertension, c) renal impairment, d) significant persistent renal failure, e) gross haematuria, f) steroid resistance g) abnormal serology (positive ANF, VDRL, ASOT, Hepatitis B surface antigen and HTLV-1 antibody) h) hypocomplementaemia and i) sickle haemoglobinopathy. Children with HIV nephropathy were not biopsied. From 1985–1992, frequent relapsers were also biopsied as was the practice then.

Steroid resistance was defined as failure to achieve remission after twenty-eight days of daily steroid use at a dose of 60 mg/m²/day (or 2 mg/kg/day). *Frequent relapses* were defined as 2 or more relapses in a 6-month period. Nephrotic syndrome was termed idiopathic if no cause was identifiable. The diagnosis of infection-related nephrotic syndrome was based on the data provided by the clinician on the histology requisition form and was supported by positive serology in all infections except Poststreptococcal

Glomerulonephritis (PSGN). In PSGN, the diagnosis was made either by posi-tive ASOT and hypocomplementaemia or in cases where either one or the other was negative, by the association of glomerulonephritis with skin sepsis. The anti-DNAse B and antihyaluronidase tests are not available in Jamaica. All cases of PSGN with nephrotic syndrome were biopsied. The term focal sclerosis included both FSGS and focal global sclerosis. Biopsy specimens were processed by light microscopy and when possible by immunofluorescence and electron microscopy. A biopsy was deemed adequate if there were ≥ 5 glomeruli but if the glomerular disease seemed difuse the diagnosis was made on as few as 2 glomeruli. Data were assessed using the Statistical Software Package for the Social Sciences version 14. Chi-squared test was used to assess categorical variables while Fisher's exact test was used for continuous variables.

RESULTS

Of the 270 paediatric renal biopsies performed during the twenty-four year period 1985 to 2008, nephrotic syndrome was the indication in 157 (57.4%). Immunofluorescence was available in 17.8% and electron microscopy in 33.8% of biopsy specimens. There was a slight male preponderance overall (85 males [54%] and 72 females [46%]). In the 153 children for whom age-related data were available, the mean age (years) was 6.91 ± SD 3.44. The most common age at biopsy was 2 years (22/153) with another peak at 11 years (19/153). Renal biopsies were performed on 7 children less than 12 months of age. Two of three patients with congenital NS (onset at age < 3 months) had steroid resistant FSGS (66%) while the other had MesGN. Of the 4 children with infantile NS (onset at age 4–11 months), 3 had MesGN and one MCD.

Indications for biopsy and associated histology: Most children were biopsied for steroid resistant NS (SRNS) [35%] or other features atypical for minimal change nephrotic syndrome (MCNS) [56.1%] while only 8.9% were biopsied for frequent relapses (FRNS). The commonest histological appearances overall were MesGN (31.2%) and MCD (22.9%) followed by DPGN (16.6%) and FSGS (10.8%) (Fig.1). Steroid resistant NS was due to MCD in the majority (36.4%) [20/55] followed by MesGN (30.9%) [17/55] and FSGS (14.5%) [8/55]. In 5 of the patients with steroid resistant MCNS, minimal change histology was associated with focal sclerosis, hypertensive changes, focal mesangial proliferation or mesangial sclerosis. MCNS was the commonest histology in FRNS (22%) [$p = 0.009$] (Fig. 2).

Aetiology: Nephrotic syndrome was deemed idiopathic (primary) in 63.6% (100/157). Secondary nephrotic syndrome was associated with infection in 67%, sickle haemoglobinopathy in 28%, systemic lupus erythematosus in 3.5%, and amyloidosis in 1.5%. In the group with idiopathic NS, the male: female ratio was 1:1 and the commonest histological appearance was MesGN (43%) followed by MCNS (29%) and FSGS (10%) and DPGN (8%).

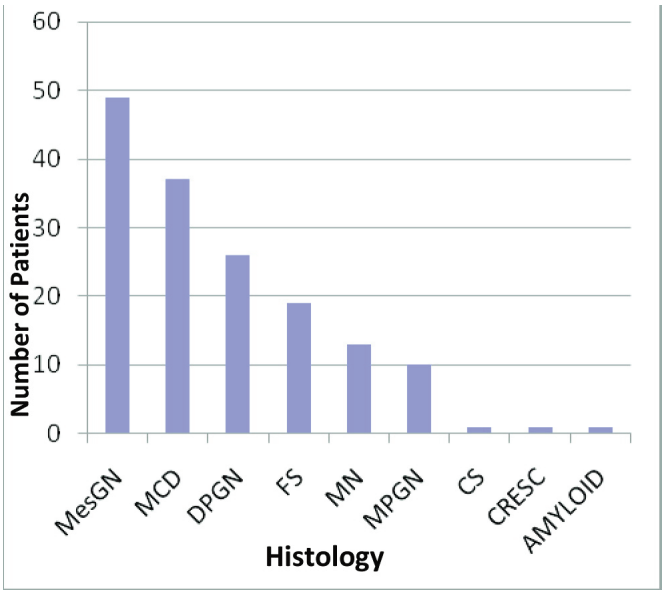

Fig. 1: Renal histology in Jamaican children with nephrotic syndrome

MesGN = Mesangial proliferative glomerulonephritis; MCD = Minimal change disease,
DPGN= Diffuse proliferative glomerulonephritis, FS = Focal sclerosis, MN =Membranous nephropathy, MPGN = Membranoproliferative glomerulonephritis, CS= Chronic sclerosing glomerulonephritis, CRESC = Crescentic glomerulonephritis, AMYLOID = Amyloidosis

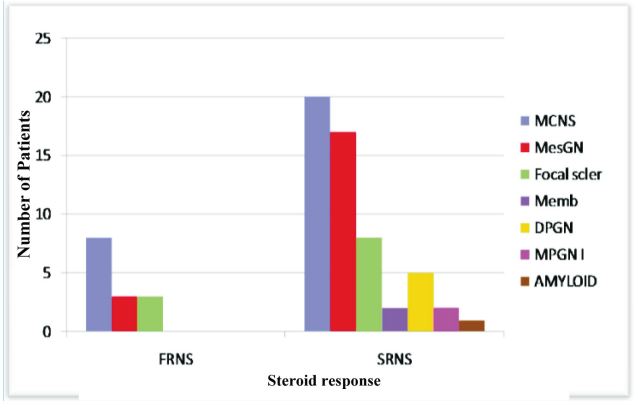

Fig. 2: Renal histology in frequently relapsing and steroid resistant nephrotic syndrome

FRNS = Frequently relapsing nephrotic syndrome, SRNS = Steroid resistant nephrotic syndrome, MesGN = Mesangial proliferative glomerulonephritis, MCD = Minimal change disease, DPGN = Diffuse proliferative glomerulonephritis, FS = Focal sclerosis, MN = Membranous nephropathy, MPGN = Membranoproliferative glomerulonephritis, CS = Chronic sclerosing glomerulonephritis, CRESC = Crescentic glomerulonephritis, AMYLOID =Ayloidosis

Histology in infection: Nephrotic syndrome was secondary to infection in 24% of the total population (38/157). Poststreptococcal GN (PSGN) was the commonest infection (10.8%)

(17/157), followed by Hepatitis B in 8.3% (13/157). There were four patients with cytomegalovirus infection (CMV), two sicklers with parvovirus infection and one child each with mumps and HTLV-1 infections. The most frequent histology associated with PSGN was DPGN (52.9%). Eighty-three per cent of membranous nephropathy was associated with Hepatitis B infection. Cytomegalovirus infection was represented by FSGS (50%) and by MCD and DPGN (25%) each. Mumps and HTLV-1 infections both showed DPGN histology.

Histology in sickle haemoglobinopathy: (Table 1). There were 13 patients with HbSS disease. The majority had DPGN (46.2%). Parvoviral infection occurred in 2 patients with HbSS and showed either MCD or MesGN. Streptococcal infection was confirmed in 3 patients with HbSS, two had DPGN while the other had MPGN1.

Table 1: Histology in patients with sickle haemoglobinopathy

Histology	Sickle Genotype			
	SS	AS	$S\beta^0$	Thalassemia
MesGN	1	2	0	
FSGS	2	0	0	
MPGN	2	0	0	
MCD	2	0	0	
DPGN	6	0	1	
Total	**13**	**2**	**1**	

SS – homozygous sickle cell disease, AS – sickle cell trait, $S\beta^0$ Thalassaemia – Sickle β^0 Thalassaemia

Associated features: Overall, hypertension was present in 50.1% of biopsied children, gross haematuria and infection in 20% and renal failure in 25%. Hypertension occurred in > 60% of cases with MPGN, and in all cases of crescentic glomerulonephritis. Anaemia was present in 30% of cases of MesGN and 15% of DPGN. Gross haematuria was observed in ≥ 25% of children with MPGN, MesGN and DPGN. Two children (6%) with MCNS had gross haematuria but both had associated mesangial proliferation. Renal failure was a feature of MPGN (80%) and crescentic glomerulonephritis (100%), but was also noted in 2 children with MCD – one had associated mesangial hypercellularity and the other had sickle cell disease. Hypocomplementaemia was noted in MPGN and Poststreptococcal GN (Table 2).

Trends with time: There has been no significant difference in the occurrence of MCNS: 14.3–16.7% ($X^2 = 0.51$), MesGN 23.8 – 37.5% ($X^2 = 0.78$) or FSGS: 11.9 – 16.7% ($X^2 = 0.86$) between the periods 1985–1988 and 2005–2008 respectively. DPGN was more common in the mid-1980s but decreased dramatically in the early 1990s.

Table 2: Clinicopathological correlates in Jamaican children with nephrotic syndrome

Clinical/Laboratory data	Histology %					
	MCD	FSGS	MesGN	MN	DPGN	MPGN
Hypertension	33	41	35	6	24	60
Renal failure	6	18	10	0	50	80
Anaemia	0	12	8	0	15	30
Gross haematuria	6	0	31	25	31	42
Low C3	3	12	0	6	4	66
Sickle haemoglobinopathy	6	12	6	0	27	20
Hepatitis B infection	3	0	0	83	0	10

DISCUSSION

Although the study reflects the histological data from all biopsied patients in the island, it cannot be used to determine incidence data on nephrotic syndrome in the island as a whole as patients with typical nephrotic syndrome would not have been biopsied and there might have been atypical cases from rural hospitals that might not have been referred for nephrology consultation or biopsy.

In the present series of Jamaican children with nephrotic syndrome, the main histology observed was MesGN (31.2%) which supports previous local paediatric data in which MesGN predominated *ie* 25% of biopsies between 1971–1981 (7) and 30% between 1984–1987 (8). This finding was also observed in children with idiopathic nephrotic syndrome. As immunofluorescence was only possible in 17% and electron microscopy in 33.8% of biopsies, IgA and IgM nephropathy which are represented histologically as MesGN may have been under-diagnosed. In the landmark study by the International Study of Kidney Disease in Children of an unselected population of nephrotic syndrome with a similar age distribution as in this study (majority preschool) MCD was the main histological appearance (4). This finding is not unexpected since, in the Jamaican study, children with features typical of MCNS were not biopsied. In the Jamaican series, as was the experience in India (5), FSGS, MesGN, membranous nephropathy and MPGN were commonest in children older than 6 years.

Paediatric studies from Turkey (48.9%) (9), Saudi Arabia (24%) (10) and Croatia (27.7%) (11), like Jamaica, also show a predominance of MesGN. The reason for this is unclear. In the Nigerian series (12), there was a high frequecy of post-infectious NS: Hepatitis B (30.6%) and malarial nephropathy (20.4%). Hepatitis B was represented histologically as MPGN in 25.5% and MN in 2% compared with the Jamaican series (MN 83.3% and MPGN 10%). In Nigeria, MCNS was rare (9.2%) while proliferative nephritis was common (19.4 %) (12). Histology is not uniform across continental Africa. In Durban, South Africa, Indian children were more likely to have MCNS (73%) while in African chil-

dren MN (36.5%) and proliferative GN (20.2%) were more common than MCNS (14%) (13). Although Jamaica and Trinidad share the same geographic location (the Caribbean) the histological pattern in nephrotic Trinidadian children (the majority of whom were of East Indian extraction) was predominantly MCD (14) compared with MesGN in Jamaican children who were mainly of African descent. This difference between the two islands may be based on ethnicity.

In the current series, FSGS was present in 10.8% of Jamaican children who had renal biopsies while in the earlier Swaby study (7) FSGS occurred in 17%. This is in contrast to previous studies done by White *et al* in 1970 in England (ethnicity not specified) where only 5.3% of renal biopsies showed either FSGS or MesGN (4).

Internationally, there has been an increase in FSGS with time (5, 6). In the USA, the incidence of FSGS rose from 23% before 1990 to 47% afterwards (6). This trend was not observed in the current Jamaican study, where the prevalence of FSGS remained fairly constant over the years varying from 11.9% (1985–1989) to 16.7% (2003–2008). In India, (5) FSGS (38%) was the most frequent histological pattern seen, followed by MCD (32%). In a USA study of Caucasians, Hispanics and African Americans, MCD predominated (35%) followed by FSGS [31%] (6). However, FSGS was more prevalent in African Americans. In light of that finding, the lower frequency of FSGS in Jamaican children who were predominantly of African heritage is unexpected.

During the periods 1985–1988 and 2003–2008, there was no statistical difference in the prevalence of MCNS and MesGN. There was a dramatic reduction in DPGN cases seen in 1985–1988 (28.6%) compared to the period 2005–2008 (8.3%), the greatest decline was noted in the period 1989–1992 when the prevalence fell to 7.1%. Since then, there have been very few DPGN cases, possibly due to the decline in streptococcal related nephrotic syndrome. This is supported by a reduction in streptococcal infections observed in the study group from 16.7% (1985–1988) to 7.1% (1989–1992) and 4.2% (2005–2008). Despite the reduction in PSGN, the frequency of MesGN remains constant. There have been no studies to date in Jamaican children to identify a genetic predisposition to MesGN, but one may theorize that chronic low grade infection of a yet unidentified source may be contributory. Patients with sickle cell disease had nephropathy of the diffuse proliferative type predominantly, which in the majority could not be positively correlated with infections. Only two of the six DPGN cases were associated with serologically confirmed streptococcal infection. The other cases of DPGN may have been referred too late for positive serology, since patients with features of atypical nephrotic syndrome were frequently referred for paediatric nephrology consultation only after a failed course of steroids. Two patients with HbSS disease had MPGN1with hypocomplementaemia. One was associated with streptococcal infection which was likely coincidental, since classically poststreptococcal nephropathy is of the diffuse proliferative type. MPGN secondary to sickle cell disease is normocomplementaemic (15). The presence of hypocomplementaemia is more suggestive of idiopathic MPGN rather than sickle nephropathy. In Jamaica, children with sickle nephropathy and nephrotic syndrome are biopsied and treatment determined by their histology. It is not assumed that their pathology is due to sickle nephropathy.

Classically, MCD is steroid sensitive (2, 3, 4) but in this series, it was the commonest pathology in SRNS. Possible explanations include the presence of mesangial proliferation and focal sclerosis, or a superficial biopsy which did not include juxtaglomerular glomeruli where FSGS begins.

In summary, MesGN remains the commonest histology seen in Jamaican children undergoing renal biopsy for nephrotic syndrome. Unlike the global experience, the frequency of FSGS in nephrotic syndrome has remained stable. In Jamaican children, pure minimal change disease was not associated with renal failure, anaemia or hypocomplementaemia. The presence of these clinical features enables the physician to predict clinically the patients who are more likely to have serious pathology such as membranoproliferative or crescentic glomerulonephritis, and hence to refer for early renal biopsy and specialist treatment. Prompt appropriate evaluation may prevent the progression to chronic kidney disease.

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