ORIGINAL ARTICLE

Characteristics of idiopathic nephrotic syndrome at an unusual age in a tertiary-level pediatric hospital in Guadalajara, Jalisco, México

Mildred Paola Ríos Moreno[1] and Germán Patiño García[2]

ABSTRACT

Background. Nephrotic syndrome (NS) is diagnosed by the presence of massive proteinuria, hypoalbuminemia, edema and hypercholesterolemia. Usual onset is between 2 and 10 years of age. This study was conducted to determine the features of idiopathic NS in patients at an unusual age.

Methods. A retrospective study was carried out in the Nephrology Department at the Pediatrics Hospital, Centro Medico Nacional de Occidente, Guadalajara, Mexico from January 2007-June 2009. Twenty three cases were analyzed to evaluate clinical features, biochemical parameters and histopathological spectrum. Medical management and outcome were established.

Results. We analyzed 10 patients <2 years of age and 13 patients >10 years of age. There were 11 females and 12 males. Mesangial proliferative glomerulonephritis was found in seven (30.4%) patients, diastolic hypertension in 16 (69.5%) patients, hematuria in 15 (65.2%) patients, and positive IgM immunofluorescence in renal biopsy in 13 (56.5%) patients. There were 13 patients who did not achieve remission (56.5%).

Conclusions. There was no gender predominance in idiopathic NS patients with unusual age presentation. Mesangial proliferative glomerulonephritis was the most common histopathological subtype.

Key words: nephrotic syndrome, infants, adolescents.

INTRODUCTION

Nephrotic syndrome (NS) is diagnosed according to the criteria of the International Study of Kidney Disease in Children (ISKDC): proteinuria >40 mg/m^2/h, hypoalbuminemia <2.5 g/dL, edema and hypercholesterolemia >200 mg/dL.[1,2] The cardinal manifestation of NS is massive proteinuria.[3] The incidence of NS is unknown in Mexico. About half of the patients are predominantly preschool males at a ratio of 1.5:1.[4] Only 1-6% of nephrotic patients begin their disease before the first year of life.[5] If NS occurs in children between 2 and 9 years of age without a familial history of renal disease and without the presence of systemic symptoms or associated nephritic factors, it is considered primary or idiopathic.[6]

The pathophysiological mechanism of NS fundamentally involves genetic predisposition, the presence of abnormal T cells with high concentrations of interleukin-2 and its receptors, and decrease in polyanionic charge of the glomerular membrane with the appearance of massive proteinuria.[7] Although NS may be associated with various kidney diseases, the most common presentation is primary NS.[8]

The clinical manifestations in congenital NS do not differ from primary NS.[5] The appearance of NS within the first 3 months of life has a poor prognosis.[9] Almost all children are premature and are usually small for gestational age. They often present with psychomotor developmental delay and failure to respond to aggressive medical treatment.[10] The clinical presentation in adolescents differs from that in childhood due to the presence of a significantly higher frequency of microscopic hematuria, resistance to steroids and histology different from minimal

[1] Pediatracs,
[2] Servicio de Nefrología Pediátrica, Unidad Médica de Alta Especialidad, Hospital de Pediatría,
Centro Médico Nacional de Occidente, Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, México

Correspondence: Dra. Mildred Paola Ríos Moreno
Pediatrics, Unidad Médica de Alta Especialidad
Hospital de Pediatría
Centro Médico Nacional de Occidente
Instituto Mexicano del Seguro Social
Guadalajara, Jalisco, México
E-mail: mildred126@yahoo.com.mx

Received for publication: 8-30-10
Accepted for publication: 5-17-11

change disease. No differences have been reported in the biochemical parameters at the time of NS presentation in adolescents.[10,11]

In 1970 the ISKDC reported that the most frequent histological lesion in biopsies of children with primary NS was minimal change disease in 80% of cases.[3,12] The five histological lesions described in the NS are minimal glomerular lesions (MGL), diffuse mesangial proliferation (DMP) and focal segmental glomerulosclerosis (FSGS), mesangiocapillary or membrane proliferative glomerulonephritis (MPGM) and membranous nephropathy (MN).[4] Renal biopsy (RB) is currently deferred in pediatric patients with primary NS due to the high prevalence of MGL and its excellent response to steroids; therefore, its empiric administration serves as a diagnostic test[13] associated with high precision of the histological findings.[14] However, the histological pattern is changing. There has been a dramatic increase in FSGS in children.[15] In the congenital infantile NS the glomerular lesion can range from increased cellularity (glomerulitis) up to focal and global sclerosis.[5]

This study was carried out in order to determine the characteristics of patients with primary NS at unusual ages in the Nephrology Department of the Hospital of Pediatrics, Centro Medico Nacional de Occidente (CMNO), Guadalajara, Jalisco, Mexico from January 2007 to June 2009.

PATIENTS AND METHODS

We conducted a 30-month retrospective study from January 2007 to June 2009. The sample size was established for convenience. We included patients from the Nephrology Department with a diagnosis of NS according to the criteria of the International Study of Kidney Disease in Children (ISKDC): massive proteinuria, hypoalbuminemia <2.5 g/dL, edema and hypercholesterolemia >200 mg/dL, <2 years or >10 years of age, and subjected to RB and with adequate histopathological results and complete medical record. Exclusion criteria were patients with secondary NS. The study was conducted in the Nephrology Department of the Hospital of Pediatrics and the Department of Pathology of the Medical Unit of High Specialty, CMNO, IMSS, Guadalajara, Jalisco, Mexico. We reviewed pathology records and determined the number of RB pediatric patients as well as the clinical diagnosis for which it was performed. We reviewed the medical records that met the inclusion criteria. Patients were divided into two age groups: patients ≤24 months and patients ≥10 years of age. Variables analyzed were chronological age in months (for patients >12 months it was expressed in years), age in months at the time of diagnosis (for patients >12 months it was expressed in years), place of origin and residence [place of birth and housing according to inhabitants, urban population (>2500 inhabitants) and rural population (<2500 inhabitants)], gender and birth weight (kg).

The following variables were established in accordance with their registration in the clinical record at the time of initial care in the unit: systolic blood pressure, diastolic blood pressure, presence of edema [excess fluid in the various organs or tissues described as mild (if it affected only one area of the body), moderate (if it affected two specific areas), severe (if three or more areas were affected) or generalized]. The method of detection of massive proteinuria was recorded as well: the collection of urine for 24 h >40 mg/m^2/h, the value of the urinary ratio (protein mg/dL/mg creatinine/dL) >2 in isolated urine samples, positivity of 3 or more + on urine dipstick or report of >300 mg/dL in the urinalysis. Systemic arterial hypertension (SAH) was considered when blood pressure level was >95th percentile for age, gender and height according to the IV Report of the NIH (U.S.) for the prevention, diagnosis, evaluation and treatment of hypertension in children and adolescents (Fourth Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure in Children and Adolescents).

The following variables relates to blood levels reported in the medical record during care provided in the unit:

1) Albuminemia, cholesterolemia, serum creatinine, urea (BUN), sodium, potassium, calcium, phosphorus, triglycerides, glucose, hemoglobin (Hg), hematocrit (Hct), platelets, leucocytes, uric acid, thrombin time (TT) and partial thromboplastin time (PTT).
2) Creatinine clearance calculated by the Schwartz formula: glomerular filtration in mL/min/1.73 m^2 = (T x k)/Pcr where T = height in cm, Pcr = plasma creatinine and k = constant of proportionality that depends on the urinary excretion of creatinine per unit of body size. The value of this constant varies according to age: term newborn to 1 year = 0.45, low birth weight newborns to 1 year = 0.33, older children and adolescent females = 0.55, adolescent males = 0.77

3) Serum level of C3 complement reported as high (>180 mg/dL), low (<90 mg/dL), normal (90-180 mg/dL). Serum level of C4 complement reported as high (> 40 mg/dL), low (<10 mg/dL), normal (10-40 mg/dL).
4) Hematuria (the presence of five or more erythrocytes per microscopic field in centrifuged urine), glucosuria (presence of >50 mg/dL of glucose in a urinalysis).
5) Treatment prior to the performance of RB (administration of any corticosteroid or immunomodulatory medication at the onset of symptoms and prior to the completion of the RB in the unit).
6) RB reported immunofluorescence, decreased GFR (<89 mL/min/1.73 m^2, according to the 2002 classification of the National Kidney Foundation).
7) Clinical picture without remission (persistent massive proteinuria despite medical management).
8) Histological findings in RB.

Annual records were reviewed in the area of outpatient and inpatient visits and the prevalence of NS at nontraditional ages was established. For statistical analysis, measures of central tendency (mean and median) and measures of dispersion (standard deviation and extreme values) and frequency and percentage analysis were used.

RESULTS

During the study period, 168 RB were performed, and 56 (33.4%) were primary NS. There were 43 biopsies performed on patients outside of the usual ages. Twenty NS patients outside the usual ages and with results of RB were not included in the study due to the following conditions: NS was secondary to lupus (11 patients), did not meet the four diagnostic criteria for NS (six patients), clinical record was incomplete (one patient), result of RB was unable to be assessed (one patient), NS was secondary to congenital cytomegalovirus and diagnosed at autopsy (one patient). Twenty three patients fulfilled the inclusion criteria and formed the basis for this study. The place of origin and residence of all patients (n = 23) were urban geographical areas.

The following describes the general characteristics and history of the study population. The study group was comprised of 10 patients aged ≤24 months. Median age at diagnosis was 18 months (Table 1). With regard to blood chemistry, a median serum albumin of 1.85 g/dL and serum cholesterol of 265 mg/dL were observed. Detection of massive proteinuria was performed by the dipstick method for urinalysis (>300 mg/dL) in 80% of patients. Hypocalcemia corrected with albumin levels occurred in 20% with an asymptomatic course (Table 2). Glomerulonephritis (GN) with diffuse mesangial proliferation and focal segmental glomerulosclerosis were the most frequent histopathological lesions (30% each, Table 3). Prednisone was given as a treatment prior to the completion of the RB in eight patients (80%). Seven patients did not go into remission, four of whom received prednisone and cyclophosphamide as treatment and three received only prednisone (Table 4).

A total of 13 patients made up the group aged ≥10 years. The median age was 12 years (Table 5). Median serum albumin was 2 g/dL and cholesterol was 360 mg/dL. Massive proteinuria detection was performed by the method of dipstick urinalysis (>300 mg/dL) in 61.5% of patients (8/13). Hypocalcemia corrected with albumin levels occurred in 30.7% (4/13) with an asymptomatic course (Table 2). GN with diffuse mesangial proliferation was the most common histopathological lesion in 30.8% (4/13) (Table 3). Five patients received prednisone as treatment prior to performing RB in those five patients. Failure of remission occurred in six patients, of whom three patients received prednisone and cyclophosphamide. One patient received prednisone, cyclophosphamide, mycophenolate mofetil and cyclosporine. Another patient received prednisone, cyclophosphamide and cyclosporin and the last patient received prednisone, cyclophosphamide and immunoglobulin (Table 4).

SAH occurred in 69.5% of cases studied (16/23) and hematuria occurred in 65.2% (15/23). IgM positive immunofluorescence was observed in 56.5% (13/23) of biopsies performed. Decreased glomerular filtration was observed in 39.1% (9/23) of patients. Complete remission of the clinical picture was not achieved in 56.5% because 13 patients were steroid resistant. There was no gender predominance. The most frequently associated histological lesion was GN with diffuse mesangial proliferation in seven patients (30.4%) (Tables 3 and 4). It was documented that on outpatient visits to the Nephrology Department of the Pediatric Hospital (CMNO, IMSS) there were 13,419 consultations from January 2007 to June 2009, of which 829 were for NS. This represented 6.1% of all consulta-

Table 1. General characteristics and history of 10 patients with NS ≤24 months of age (Nephrology Department, Hospital of Pediatrics, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, January 2007–June 2009)

Variable	*Frequency*	*Percentage*	*Mean (SD)*	*Median*	*Minimum-Maximum*
Chronological age (months)			46.4 ± 17.734	43	20–83
Age at time of diagnosis (months)			17 ± 6.164	18	2–24
Gender					
Male	5	50%			
Female	5	50%			
Birth weight (kg)			3.817 ± 0.440	3.225	2.53–4.1

NS, nephrotic syndrome.

Table 2. Hematological and laboratory blood results of 23 patients with NS at unusual ages (Nephrology Department, Hospital of Pediatrics, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, January 2007 – June 2009)

	Group ≤24 months of age			*Group ≥10 years of age*		
Variable	*Mean (SD)*	*Median*	*Minimum-Maximum*	*Mean (SD)*	*Median*	*Minimum-Maximum*
Albumin (g/dL)	1.83 ± 0.437	1.85	1.3–2.5	1.98 ± 0.362	2	1.3–2.5
Cholesterol (mg/dL)	283 ± 67.918	265	202–375	348.3 ± 111.60	360	205–548
Creatinine (mg/dL)	0.43 ± 0.156	0.45	0.2–0.7	1.13 ± 1.031	0.9	0.4–4.1
Urea (mg/dL)	34.82 ± 21.555	33.3	5.3–74	68.96 ± 77.304	30.2	14.8–246
Sodium (mmol/L)	135.5 ± 7.891	136	124–152	133.15 ± 4.487	134	124–139
Potassium (mmol/L)	4.3 ± 0.569	4.3	3.2–5.1	4.36 ± 0.977	4.2	3.1–7
Calcium (mg/dL)	7.97 ± 1.359	8.05	5.3–10	7.69 ± 1.367	7.5	5–10.7
Calcium corrected with albumin (mg/dL)	9.3 ± 0.992	8.9	7–10.8	8.9 ± 1.005	8.2	6.76–11.5
C3 complement (mg/dL)	119.13 ± 42.576	123	42.6–176	108.26 ± 43.216	111	19.3–186
C4 complement (mg/dL)	23.62 ± 17.503	15.85	3.23–63.60	24.21 ± 10.198	23.9	9.63–51
Triglycerides (mg/dL)	321 ± 268.59	203.5	57–802	261.61 ± 108.96	204	115–454
Glucose (mg/dL)	73.3 ± 21.571	73	35–106	85.61 ± 17.523	79	64–124
Hemoglobin (g/dL)	12.83 ± 2.496	13.5	8.2–15.6	13.79 ± 1.669	13	11.6–16.7
Hematocrit (%)	37.04 ± 7.388	39	23.7–46.10	40.53 ± 5.661	37.9	32.8–50.56
Platelets (1000/µL)	443.73 ± 236.80	473	322.20–850	305.17 ± 120.80	314	271–541
Leucocytes (1000/µL)	9.62 ± 7.831	9.86	7.6-19.5	8.59 ± 6.039	6.8	5.48–19.3
Uric acid (mg/dL)	6.06 ± 2.734	4.95	3.5–11.6	6.33 ± 2.942	5.3	3.3–12.5
Thrombin time (sec)	10.5 ± 1.185	10.75	8.7–12.6	11.04 ± 1.213	11.0	9.6–14.4
Thromboplastin time (sec)	43.67 ± 10.385	43.75	25.5–55.7	36.1 ± 7.903	35.2	27-54
Creatinine clearance according to formula of Schwartz (mL/min/1.73 m^2)	109.5 ± 28.032	120	64–154	130 ± 65.249	126	21–231

NS, nephrotic syndrome.

Table 3. Histopathological lesions of 23 patients with NS at unusual ages (Nephrology Department, Hospital of Pediatrics, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, January 2007–June 2009)

	Group ≤ 24 months		*Group ≥10 years*		*Both groups*
Anatomopathological diagnosis	*Frequency*	*Percentage*	*Frequency*	*Percentage*	*Total (%)*
MGL or MCD	1	10	2	15.4	3 (13.04)
DPGN	3	30	4	30.8	7 (30.43)
FSGC	3	30	3	23.1	6 (26.08)
MPGN	0	0	3	23.1	3 (13.04)
MN	0	0	1	7.7	1 (4.34)
Other lesions					
NC1q	2	20	0	0	2 (8.69)
CNF	1	10	0	0	1 (4.34)
Total	10	100	13	100	23 (100)

NS, nephrotic syndrome, MGL, minimal glomerular lesion or MCD, minimal change disease; DPGN, diffuse proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; MPGN, membrane proliferative glomerulonephritis; MN, membranous nephropathy; NC1q: Nephropathy due to C1q; CNF, congenital nephrotic syndrome of the Finnish type.

Table 4. Clinical and biochemical characteristics in different subtypes of renal histopathology of 23 patients with NS at unusual ages (Nephrology Department, Hospital of Pediatrics, Centro Medico Nacional de Occidente, Guadalajara, Jalisco, January 2007–June 2009)

	MGL or MCD (n = 3)	*DPGN (n = 7)*	*FSGS (n = 6)*	*MPGN (n = 3)*	*MN (n = 1)*	*CNF (n = 1)*	*NC1q (n = 2)*	*Total n = 23 (%)*
Gender								
Male	2	3	3	1	1	1	1	12 (52.1)
Female	1	4	3	2	-	-	1	11 (47.8)
Severe edema	1	4	2	-	-	1	1	9 (39.1)
SAH	2	3	3	1	-	-	1	10 (43.4)
DAH	2	6	3	2	-	1	2	16 (69.5)
Hematuria	2	6	3	3	-	1	-	15 (65.2)
Glycosuria	1	-	1	-	1	1	1	5 (21.7)
Immunofluorescence IgM (+)	2 (NR1)	5 (NR 2)	3 (NR3)	2	-	NR	1	13 (56.5)
Decrease of glomerular filtration	1	2	3	2	-	-	1	9 (39.1)
Managed with three or more medications	1	-	1	1	1	-	-	4 (17.3)
Panel without remission	2	2	4	1	1	1	2	13 (56.5)

NS, nephrotic syndrome; SAH, systemic arterial hypertension; DAH, diastolic arterial hypertension; MGL, minimal glomerular lesion or MCD, minimal change disease; DPGN, diffuse proliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; MPGN, membrane proliferative glomerulonephritis type I; MN, membranous nephropathy; NC1q, nephropathy due to C1q; CNF, congenital nephrotic syndrome of the Finnish type; NR, not reported.

tions recorded and the third leading cause of medical care in the service. In the area of nephrology inpatient admissions, there were 2,410 admissions recorded of which 234 (9.7%) corresponded to NS and was established as the third leading cause of hospitalization. The total number of patients with NS at nontraditional ages during the study period was 56 and a prevalence of 2.32 cases/100 patients hospitalized in the Nephrology Department of the hospital.

DISCUSSION

Our results showed that NS was the most frequent clinical indication for performing RB in the Nephrology Department of our hospital. This finding is comparable with the results of the study by Benitez et al.[16] who carried out a review of 356 patients undergoing RB. They reported, as the most frequent reason for the indication of an RB in patients with primary glomerulopathies, asymptomatic urinary abnormalities and NS.

This review provides information about the clinical, biochemical and histopathological characteristics of NS in 23 patients of ages not commonly found and indicated that diffuse mesangial proliferation is a histopathological lesion found most frequently in NS in patients ≤24 months or patients ≥10 years. However, in the group of patients ≤24 months the same percentage of focal segmental glomerulosclerosis and diffuse mesangial proliferation was found, probably due to the small size of the sample. This differs from that reported by Gulati et al.[1] and Hogg et al.[17,18] who identified segmental and focal glomerulosclerosis as the histological lesion of greatest frequency in adolescents with NS. It also differs from that reported by Sibley et al.[9] who found that Finnish type congenital NS is the main histological lesion in children whose ailment begins during the first year of life. There is only one national report of a group of 18 patients <12 months of age with NS published by Alcalá Carbajal and Mota Hernández where the main histological lesion in 12 of the cases was reported as minimal change disease.[19] Also, NS that occurs at an unusual age is often accompanied by hypertension, hematuria, poor prognosis due to absence of remission and IgM antibody positive for RB. This may be due to the high frequency reported of injuries to the glomerular complex. Another important point is that no gender predominance was found in either study group. A proportion of ~1:1 was similarly reported in two studies: Vachvanichsanong et al. in their review of characteristics of 10 children with congenital and infantile NS[20] and the study of Baqi et al. of 29 adolescent patients with NS.[21] The high prevalence of NS in nontraditional ages reported in our study was probably due to the fact that the investigation was performed in a tertiary-level referral center. Because the sample size was small, additional studies should be done for further validation.

In conclusion, we mention the following:

No gender predominance was found in patients with NS at nontraditional ages.

GN with diffuse mesangial proliferation was the most frequent histopathological lesion in these patients and was associated with SAH, hematuria, poor outcome due to lack of remission and immunofluorescence of IgM positive in the RB.

REFERENCES

1. Gulati S, Sural S, Sharma RK, Gupta A, Gupta RK. Spectrum of adolescent-onset nephrotic syndrome in Indian children. Pediatr Nephrol 2001;16:1045-1048.
2. Kumar J, Gulati S, Sharma AP, Sharma RK, Gupta RK. Histopathological spectrum of childhood nephrotic syndrome in Indian children. Pediatr Nephrol 2003;18:657-660.
3. Santos F. Síndrome nefrótico. Bol Pediatr 2006;46(suppl 1):19-23.
4. Academia Mexicana de Pediatría. Comité de Expertos en Nefrología. Síndrome nefrótico en niños. Bol Med Hosp Infant Mex 2000;57:522-536.
5. Rodríguez E, Ríos G, Saieh C, Puga F. Síndrome nefrótico congénito. Rev Chil Pediatr 1984;55:37-39.
6. Bolaños L, De Castaño I. Características clínicas e histopatológicas del síndrome nefrótico primario. Colomb Med 2005;36:29-33.
7. International Study of Kidney Disease in Children. Nephrotic syndrome in children: prediction of histopathology from clinical and laboratory characteristics at time of diagnosis. Kidney Int 1978;13:159-165.
8. Eddy AA, Symons JM. Nephrotic syndrome in childhood. Lancet 2003;362:629-639.
9. Sibley R, Mahan J, Mauer SM, Vernier RL. A clinicopathologic study of forty-eight infants with nephrotic syndrome. Kidney Int 1985;27:544-552.
10. Hamed RM, Shomaf M. Congenital nephrotic syndrome: a clinico-pathologic study of thirty children. J Nephrol 2001;14:104-109.
11. Salguero E, Bocángel D. Síndrome nefrótico primario. Rev Soc Boliv Pediatr 1999;38:35-38.
12. Hinkes BG, Mucha B, Vlangos CN, Gbadegesin R, Liu J, Hasselbacher K, et al. Nephrotic syndrome in the first

year of life: two thirds of cases are caused by mutations in 4 genes (NPHS1, NPHS2, WT1, and LAMB2). Pediatrics 2007;119:e907-e919.
13. Finn LS, Symons JM, Smith JM. Nephrotic syndrome in the newborn. Am J Kidney Dis 2003;42:1318-1323.
14. Filler G, Young E, Geier P, Carpenter B, Drukker A, Feber J. Is there really an increase in non-minimal change nephrotic syndrome in children? Am J Kidney Dis 2003;42:1107-1113.
15. Bonilla-Félix M, Parra C, Dajani T, Ferris M, Swinford RD, Portman RJ, et al. Changing patterns in the histopathology of idiopathic nephrotic syndrome in children. Kidney Int 1999;55:1885-1890.
16. Benitez O, Fuentes J, Pérez I, Cuervo R, Valdés A. La biopsia renal en el diagnóstico de las glomerulopatías. Rev Cubana Med 2002;4:87-92.
17. Hogg RJ. Adolescents with proteinuria and/or the nephrotic syndrome. Adolesc Med Clin 2005;16:163-172.
18. Hogg RJ, Silva FG, Berry PL, Wenz JE. Glomerular lesions in adolescents with gross hematuria or the nephrotic syndrome. Report of the Southwest Pediatric Nephrology Study Group. Pediatr Nephrol 1993;7:27-31.
19. Alcalá Carbajal O, Mota Hernández F. Nature and prognosis of nephrotic syndrome in the 1st year of life. Bol Med Hosp Infant Mex 1982;39:99-104.
20. Vachvanichsanong P, Mitarnun W, Tungsinmunkong K, Dissaneewate P. Congenital and infantile nephrotic syndrome in Thai infants. Clin Pediatr (Phil) 2005;44:169-174.
21. Baqi N, Singh A, Balachandra S, Ahmad N, Nicastri A, Kytinski S, et al. The paucity of minimal change disease in adolescents with primary nephrotic syndrome. Pediatr Nephrol 1998;12:105-107.