www.nephropathol.com DOI: 10.15171/jnp.2017.49 J Nephropathol. 2017;6(4):304-308

Journal of Nephropathology

Histologic patterns of primary adult onset nephrotic syndrome and their clinical characteristics; a single center study from South India

Gurudev Konana[1], Vijay Varma[1*], Mahesh Eswarappa[1], Sonika Puri[1], Gireesh Mathihally[1], Rakesh Madhyastha[1], Sujeeth Reddy[1], Vijaya Mysorekar[2], Clement Wilfred[2]

[1]Department of Nephrology and [2]Department of Pathology, M.S. Ramaiah Medical College, Bengaluru, India

ARTICLE INFO

Article type:
Original Article

Article history:
Received: 28 December 2016
Accepted: 11 April 2017
Published online: 5 May 2017
DOI: 10.15171/jnp.2017.49

Keywords:
Nephrotic syndrome
Renal
Biopsy
Minimal change disease
Focal segmental glomerulosclerosis
Glomerulonephritis
IgA nephropathy

ABSTRACT

Background: The histologic pattern causing nephrotic syndrome (NS) and their clinical outcome varies depending on age, sex, race, socioeconomic status and geographic location. There has been a changing trend in the histologic spectrum of NS in the last few decades, in India as well as worldwide.

Objectives: The objective of the present study was to see the histologic spectrum of adult NS in our institution and to compare it with data from other centers.

Patients and Methods: All adults (≥ 18 years) with nephrotic range proteinuria who underwent renal biopsy from August 2012 to February 2015, were consecutively included in this prospective study. NS caused by diabetes and other secondary glomerular diseases were excluded.

Results: Eighty (65.4%) patients were males and 42 (34.4%) were females. The median age at the time of biopsy was 36 years (interquartile range [IQR]: 24.8–45). The most common lesions were minimal change disease (MCD) in 40.2%, membranous nephropathy (MN) in 24.6% and focal segmental glomerulosclerosis (FSGS) in 16.4% of the patients. MCD was observed mostly commonly in the age group 18-35 years and MN was seen mostly commonly in age group 36-55 years.

Conclusions: MCD still continues to be leading cause of NS in south Indian adults as evidenced from previous studies from this region. Other common causes include MN and FSGS. The incidence of MPGN is on the decline.

Original Article

Implication for health policy/practice/research/medical education:
Our study is a showcase of the different histologic spectrum of primary nephrotic syndrome (NS) in South Indian adults. Minimal change disease (MCD) is the most common lesion found in our patients as opposed to data from other developed nations where focal segmental glomerulosclerosis (FSGS) is an emerging entity and the most common lesion. Also the incidence of membranoproliferative glomerulonephritis was very low in our population which probably is indicative of better infectious control practices that we use these days. Our study highlights that heterogeneity in the histologic spectrum of NS is influenced by region, race, genetic and environmental factors.

Please cite this paper as: Konana G, Varma V, Eswarappa M, Puri S, Mathihally G, Madhyastha R, et al. Histologic patterns of primary adult onset nephrotic syndrome and their clinical characteristics; a single center study from South India. J Nephropathol. 2017;6(4):304-308. DOI: 10.15171/jnp.2017.49.

1. Background

Nephrotic syndrome (NS) accounts for the most common indication for renal biopsy in our nephrology practice. In single center biopsy series by Das et al (1), and Narasimhan et al (2), NS accounted for 49% and 65% of cases respectively, for whom renal biopsy was performed. It is defined as a syndrome comprising of proteinuria more than 3.5 g/d, hypoalbuminemia, edema, hyperlipidemia, and lipiduria. The histologic pattern causing NS and their clinical outcome varies depending on age, sex, race, socioeconomic status and geographic location (2-4). Also there has been a

*Corresponding author: Vijay Varma, Email: vijay.varma8@gmail.com

changing trend in the histologic spectrum of NS in the last few decades, in India as well as worldwide with a notable increase in incidence of focal segmental glomerulosclerosis (FSGS) with a decrease in the incidence of minimal change disease (MCD) (2,3,5,6). Data from Indian chronic kidney disease (CKD) registry show that 13.8% of CKD are caused by chronic glomerulonephritis. This data indicates a high burden of glomerular disease in a developing country like India and the role of prompt diagnosis, treatment and follow up which go a long way in preventing the progression of disease (7). Improvements in imaging techniques and biopsy needles have optimized the efficacy and minimized the risk of complications associated with renal biopsy making it an indispensable tool for diagnosis of NS.

2. Objectives

The aim of the present study was to find the histologic spectrum of adult NS in our institution and to compare it with data from other centers.

3. Patients and Methods

3.1. Study population

M.S Ramaiah Medical College is a tertiary care center in North Bangalore catering to referrals from Karnataka, Andhra Pradesh, Tamil Nadu, Orissa and West Bengal. All adults (≥ 18 years) with nephrotic range proteinuria, who underwent renal biopsy from August 2012 to February 2015, were consecutively included in this prospective study. Nephrotic range proteinuria was defined as proteinuria >3.5 g/1.73 m^2 body surface area per day. NS caused by diabetes and other secondary glomerular diseases were excluded. Blood samples were checked for blood sugars, hemoglobin, platelet counts, serum creatinine (sCr), blood urea, total protein, serum albumin (SA), lipid profile, coagulation profile, HIV, hepatitis B surface antigen and anti-hepatitis C virus antibody for all patients.

Additional investigations such as antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid, complement levels C3 and C4 as well as anti-neutrophil cytoplasmic antibody were performed as and when indicated. All patients underwent an ultrasound guided renal biopsy under local anesthesia using 18G automatic spring loaded biopsy gun. Patients were observed for 24 hours for procedure related complications. The biopsy material was subjected to histopathology with hematoxylin and eosin stain and immunofluorescence (IF). IF examination was done by direct method using fluorescein isothiocyanate conjugated antibodies against immunoglobulin G, A and M, complement C3, C1q, kappa and lambda light chains.

3.2. Ethical issues

1) The research followed the tenets of the Declaration of Helsinki; 2) informed consent was obtained, and 3) the research was approved by the ethical committee of Ramaiah Medical College, Rajiv Gandhi University of Health sciences, Bengaluru, India.

3.3. Statistical analysis

The data was analyzed using SPSS Version 18.0. Descriptive statistics of demographic variables were analyzed and reported as mean values (standard deviation; SD). The data of variables such as 24 hour urinary protein and serum creatinine was skewed, so descriptive statistics were reported as median values (interquartile range, IQR). Analysis of variance (ANOVA) test was used to compare demographic data between the three major histologic patterns and post hoc test was done for comparison between any two combinations among the three major histologic patterns. Kruskal-Wallis test (non-parametric test) was used to compare the median 24-hour urinary protein and serum creatinine between the three major histologic patterns. Kaplan–Meier curves were used to calculate the median time for complete remission, partial remission and relapse. *P* values of <0.05 were considered to indicate statistical significance.

4. Results

A total of 122 patients who presented with NS were included for analysis. Eighty (65.4%) patients were males and 42 (34.4%) patients were females with a male to female ratio of 1.90:1. The median age at the time of biopsy was 36 years (IQR: 24.8–45). Majority of the patients (76.3%) were found to be less than 45 years of age. The histologic patterns causing NS are presented in Table 1. The most common lesions were MCD in 40.2% (n = 49), membranous nephropathy (MN) in 24.6% (n = 30) and FSGS in 16.4% (n = 20) of the patients. IgA nephropathy (IgAN) in 7.4% (n = 9), non IgA mesangioproliferative glomerulonephritis (MesPGN) in 4.1% (n = 5), diffuse proliferative glomerulonephritis (DPGN) in 3.3% (n = 4), IgM nephropathy in 2.5% (n = 3) and membrano-proliferative glomerulonephritis (MPGN) in 1.6% (n = 2) of the patients constituted the remainder of the histologic spectrum.

Among the 80 males, the most common pathology was MCD (33.8%) followed by MN (28.8%). The same trend was observed even among females. In terms of renal diagnosis by age distribution, MCD

Table 1. Histological spectrum of adult onset nephrotic syndrome (N = 122)

Primary pathology	Cases No. (%)	Gender (Male: Female)	Age at renal biopsy Median (range)
Minimal change disease	49 (40.1)	27:22	31 (22.5-43.5)
FSGS	20 (16.3)	14:6	35 (23-44.3)
Membranous GN	30 (24.5)	23:7	43.5 (36-53)
IgA nephropathy	9 (7.3)	6:3	33 (29.5-45)
MPGN	2 (1.6)	0:2	-
DPGN	4 (3.2)	3:1	-
Mesangioproliferative	5 (4.0)	5:0	-
IgM nephropathy	3 (2.4)	2:1	-

was observed mostly commonly in the age group 18-35 years, followed by 36-55 years age group. Whereas MN was seen mostly commonly in age group 36-55 years with similar distribution in age groups 18-35 years and 55-75 years. FSGS showed variable distribution in different age groups (Figure 1).

The baseline demographic data of the patients with the three major histologic patterns of NS (MCD, MN and FSGS) are shown in Table 2. The FSGS patients had significantly higher systolic blood pressure (BP) and diastolic BP compared to MCD and MN patients ($P<0.001$ [systolic BP], $P=0.002$ [diastolic BP]). On the other hand, the MN patients exhibited significantly increased daily proteinuria (g/d) (median: 9.5 IQR [6.6–12], 5.6 [4.1-6.9]for MCD, 4.5 [3.9–5.4]) for FSGS, $P<0.001$) and lower SA levels ($P<0.001$) when compared to MCD and FSGS patients. MCD patients had significantly lower serum creatinine (mg/dL) levels at presentation (median: 0.90 IQR [0.86 – 1.0], 1 [0.97–1.27] for FSGS, 1 [0.90–1.10] for MN, $P=0.029$) than FSGS and MN patients.

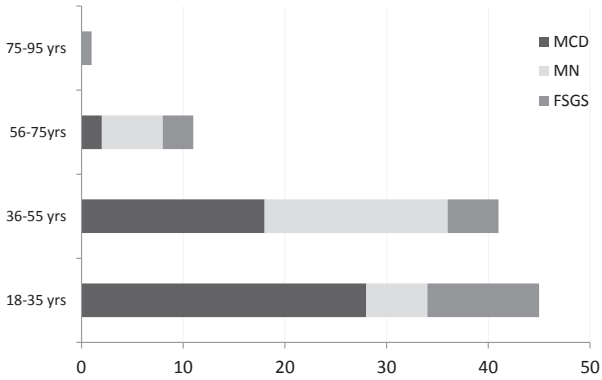

Figure 1. Distribution of three major pathological types of NS in our study population by age.

5. Discussion

The etiologies of NS vary between different countries and also within the same country. In the present study conducted at a single center in south India, MCD (40.2%) was found to be the most common histologic pattern causing NS. This is contrary to the results of several recent Indian studies from North India (5), and Eastern India (8), and South India (2) which report the incidence of MCD as 14.8% (fourth most common in their study), and 23.9% (second most common in their study) and 11.6% respectively. While all three studies report FSGS as the most common pattern with a frequency of 30.6% and 27.4% in the first two studies, Narasimhan et al reported a lower frequency of 17%. It is also possible that relative frequency of MCD incidence itself might have increased in our area. Studies from other Indian centers done from 1971–2008 (1,9-11), which included south Indian centers noted showed that MCD was the most common etiology of NS, supporting the findings from our study. The reason for this could be due to differences in the genetic and environmental factors within various regions of the country, as well as center level variations in the indications and threshold for performing renal biopsy. Rathi et al have studied the changing histologic spectrum of adult NS over 5 decades in north India and found that there was nearly five-fold increase in the incidence of FSGS, 3-fold increase in MN and a 10-fold reduction in DPGN while there was no major change in incidence of other diseases (5). Also they had used electron microscopy (EM) in about one fourth of the patients, which can explain the increased diagnosis of FSGS and MN, which are otherwise likely to be misdiagnosed as MCD. Studies done in the United States have clearly demonstrated increasing incidence of FSGS in both African-American and white populations, making it the most common cause of NS in their adult population (3,12-14).

The incidence of MPGN in our study was low (3.3%). There are other studies which support this trend of declining incidence of MPGN probably owing to better infection control and lifestyle practices over time (2,9). The fact that we did not use EM could be one of the reasons for such a low incidence in our study group.

In our study IgAN was seen in 7.4% of the patients,

Table 2. Demographics of the patients with the three major pathological types of NS in our study population

Parameter	MCD Mean (SD)	FSGS Mean (SD)	MN Mean (SD)	P value	MCD vs FSGS	MCD vs MN	FSGS vs MN
Height (cm)	169.2 (5.5)	167.8 (6.7)	166.5 (4.5)	0.127	-	-	-
Weight (kg)	65.3 (9.9)	64.6 (5.4)	66.6 (8.7)	0.701	-	-	-
Systolic BP (mm Hg)	123.7 (10.1)	142.6 (15)	134.8 (12.1)	<0.001	<0.001	<0.001	0.025
Diastolic BP (mm Hg)	79.5 (4.6)	85.8 (10.2)	81.5 (5.8)	0.002	<0.001	0.179	0.025
Total protein (g/dL)	5.6 (0.5)	5.9 (0.3	5.4 (0.5)	<0.001	0.003	0.122	<0.001
Albumin (g/dL)	1.9 (0.4)	2.3 (0.3)	1.8 (0.5)	<0.001	<0.001	0.105	<0.001
Serum TC (mg/dL)	273.5 (29)	261.7 (22)	280 (37.5)	0.203	-	-	-
Serum HDL-C (mg/dL)	41.9 (7.2)	43 (5.1)	45.2 (8.2)	0.217	-	-	-
Serum LDL-C (mg/dL)	140.5 (16.9)	125.9 (13.9)	144.7 (19)	0.004	0.006	0.356	0.001
TG (mg/dL)	298.7 (35.5)	283.9 (20.8)	295.2 (43)	0.395	-	-	-
Hb%	13.3 (0.73)	12.9 (1)	13.6 (1.4)	0.069	-	-	-

following the trend of a low prevalence as reported by other Indian studies (4.5%-14%) (1,5,8-11). However IgAN is a very common cause of NS in countries like China and Korea (20%–28%) (4,6,15).

The age wise distribution of renal diseases seen in our study, is similar to the findings in the study by Narasimhan et al (2), where predictably MCD is seen predominantly in younger population, while MN is seen in more older population (35-55 years). Registry data from some European countries like Italy (16) and Spain (17), and also recent data from Asian countries like China (15) and Japan (18), have also reported similar age trends for MN. The incidence of MN in these studies ranged from 20.7% in the Chinese study to 44.1% in the Italian registry data. In our study, MN was the second most common group constituting 24.6 % of all the cases of adult NS.

6. Conclusions

In our study primary NS occurred in adults younger than 45 years of age, more so in males. There is considerable heterogeneity in the histologic spectrum of NS which is influenced by region, race, genetic and environmental factors. MCD still continues to be leading cause of NS in south Indian adults as evidenced from previous studies from this region. Other common causes include MN and FSGS. The incidence of MPGN is on the decline.

Limitations of the study

The main limitation of our study was our inability to perform electron microscope for our cases owing to non-availability of this facility at our center and poor affordability of our patient population. The other limitations were the small sample size, this being a single center study and lack of data on complications related to renal biopsy.

Authors' contribution

GK, VV, ME, GM, VM and CW conducted the design of the research and acquisition of information. VV, SP, RM and SR analyzed the data and drafted the manuscript. All authors read, revised, and approved the final manuscript.

Conflicts of interest

There were no points of conflicts to declare.

Funding/Support

No fund or support received for this study.

References

1. Das U, Dakshinamurty KV, Prayaga A. Pattern of biopsy-proven renal disease in a single center of south India: 19 years experience. Indian J Nephrol. 2011;21(4):250-7. doi: 10.4103/0971-4065.85482.
2. Balakrishnan N, John GT, Korula A, Visalakshi J, Talaulikar GS, Thomas PP, et al. Spectrum of biopsy proven renal disease and changing trends at a tropical tertiary care centre 1990-2001. Indian J Nephrol 2003;13:29-35.
3. Haas M, Meehan SM, Karrison TG, Spargo BH. Changing etiologies of unexplained adult nephrotic syndrome: a comparison of renal biopsy findings from 1976-1979 and 1995-1997. Am J Kidney Dis. 1997;30(5):621-31.
4. Chu F, Chen G, Liu Y. Pathological patterns of primary nephrotic syndrome in Central China: a retrospective study of 627 cases. Ren Fail. 2014;36(4):514-9.doi: 10.3109/0886022X.2014.882736.
5. Rathi M, Bhagat RL, Mukhopadhyay P, Kohli HS, Jha V, Gupta KL, et al. Changing histologic spectrum of adult nephrotic syndrome over five decades in north India: A single center experience. Indian J Nephrol. 2014;24(2):86-91. doi: 10.4103/0971-4065.127892.
6. Chang JH, Kim DK, Kim HW, Park SY, Yoo TH, Kim BS, et al. Changing prevalence of glomerular diseases

in Korean adults: a review of 20 years of experience. Nephrol Dial Transplant. 2009;24(8):2406-10.doi: 10.1093/ndt/gfp091.
7. Rajapurkar MM, John GT, Kirpalani AL, Abraham G, Agarwal SK, Almeida AF, et al. What do we know about chronic kidney disease in India: first report of the Indian CKD registry. BMC Nephrol. 2012;13:10. doi: 10.1186/1471-2369-13-10.
8. Golay V, Trivedi M, Kurien AA, Sarkar D, Roychowdhary A, Pandey R. Spectrum of nephrotic syndrome in adults: clinicopathological study from a single center in India. Ren Fail. 2013;35(4):487-91. doi: 10.3109/0886022X.2013.768939.
9. Date A, Raghavan R, John TJ, Richard J, Kirubakaran MG, Shastry JC. Renal disease in adult Indians: a clinicopathological study of 2,827 patients. Q J Med. 1987;64(245):729-37.
10. Agarwal SK, Dash SC. Spectrum of renal diseases in Indian adults. J Assoc Physicians India. 2000;48(6):594-600.
11. Aggarwal HK, Yashodara BM, Nand N, Sonia, Chakrabarti D, Bharti K. Spectrum of renal disorders in a tertiary care hospital in Haryana. J Assoc Physicians India. 2007;55:198-202.
12. Swaminathan S, Leung N, Lager DJ, Melton LJ, 3rd, Bergstralh EJ, Rohlinger A, et al. Changing incidence of glomerular disease in Olmsted County, Minnesota: a 30-year renal biopsy study. Clin J Am SocNephrol. 2006;1(3):483-7. doi: 10.2215/CJN.00710805
13. Kitiyakara C, Kopp JB, Eggers P. Trends in the epidemiology of focal segmental glomerulosclerosis. SeminNephrol. 2003;23(2):172-82. doi: 10.1053/snep.2003.50025.
14. Korbet SM, Genchi RM, Borok RZ, Schwartz MM. The racial prevalence of glomerular lesions in nephrotic adults. Am J Kidney Dis. 1996;27(5):647-51.
15. Zhou FD, Shen HY, Chen M, Liu G, Zou WZ, Zhao MH, et al. The renal histopathological spectrum of patients with nephrotic syndrome: an analysis of 1523 patients in a single Chinese centre. Nephrol Dial Transplant. 2011;26(12):3993-7. doi: 10.1093/ndt/gfr166.
16. Gesualdo L, Di Palma AM, Morrone LF, Strippoli GF, Schena FP, Italian Immunopathology Group ISoN. The Italian experience of the national registry of renal biopsies. Kidney Int. 2004;66(3):890-4.doi: 10.1111/j.1523-1755.2004.00831.x
17. Rivera F, Lopez-Gomez JM, Perez-Garcia R, Spanish Registry of G. Clinicopathologic correlations of renal pathology in Spain. Kidney Int. 2004;66(3):898-904. doi: 10.1111/j.1523-1755.2004.00833.x
18. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, et al. Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan. ClinExpNephrol. 2011;15(4):493-503. doi: 10.1007/s10157-011-0430-4.

Copyright © 2017 The Author(s); Published by Society of Diabetic Nephropathy Prevention. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.