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Spectrum of Biopsy Proven Renal Disease – Referral Hospital Experience in a Developing Nations: Analysis Based on 624 Renal Biopsies

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Abstract: ***Background: The spectrum of biopsy-proven renal disease(BPRD) varies according to the race, age, sex, demography, geographic area, infectious diseases, socioeconomic condition, from centre to centre, indication of renal biopsy and gives information that is useful for clinical practice. A nation-wide renal registry is not yet organized in India and there is a scarcity of information on the pattern of biopsy proven renal disease. Objectives: To study the epidemiology of biopsy proven renal disease (BPRD) and to look for any changing trends in renal disease in comparison to other studies. Material and Methods: A retrospective analysis of the histopathological reports of all native kidney biopsies performed from 2008 – 2014(n=624)at a tertiary care hospital in South India. All renal biopsies were studied by light and immunofluorescence microscopy and also special stains wherever required. Results: A total of 624 cases were analyzed in the study. Patient's age ranges from 4 months to 68 years. The male: female ratio was 1.07:1.The most common clinical indication for renal biopsy was NS (39%).Out of all, primary glomerular disease (PGD) was the most common BPRD, accounting for60.25% of the total cases. Minimal change disease 20.47(%) was the commonest PGD followed by focal segmental glomeruloscleros is (18.35%) and membranous nephropathy (16.22%). Tubulointerstitial nephritis (TIN) (16.66% total BPRD)is the second most common BPRD. Acute TIN accounts for56.73%of the total TIN. Secondary glomerular disease (SGD) is third most common. SGD accounts for 13.78% of total BPRD. Lupus nephritis (62.79% of total SGD) was the commonest SGD followed by HUS/TTP (12.76%total SGD). In our study DN(10.46% total SGD) is third most common SGD. Chronic renal parenchymal changes (5.12% total BPRD) and vascular disease (4.17% total BPRD)were less common. Conclusion: This study provides epidemiological biopsy data in renal diseases in South India and provides information about some important trends in changing prevalence of renal disease pattern.***

Keywords: Epidemiology, biopsy-proven renal disease (BPRD), glomerular diseases, Change in spectrum.

1. Introduction

Renal biopsy has a definitive role in the confirmation of diagnosis in various renal diseases. [1]. Histopathologica ldiagnosis following renal biopsy is not only helpful in diagnosis, butalso useful in treatment planning and prognostication (2).Analysis of biopsy proven renal disease (BPRD) provide understanding about epidemiological patterns and their demographic distribution which in turn provides a basis for further research in identifying risk factors in the development and progression of renal diseases. The incidence and prevalence of biopsy proven renal disease has geographic, demographic variance and differs with geographic area, age, sex, race and socioeconomic conditions. Changing patterns of renal diseases are also influenced by locally prevalent infections and variance in indication for renal biopsy.(3,4) Evidence from different regions of world indicates a changing pattern of glomerular disease over the last few decades(5-18).Renal biopsy registries ,where existing , are helpful in reporting changing pattern of renal diseases in the last few decades .Due to lack of national registry epidemiological spectrum of biopsy proven renal diseases (BPRD) are limited in India. The aim of the present study is to analyze the epidemiological and clinical outcomes of biopsy proven renal diseases over five years duration among people belonging to low socioeconomic status in a tertiary care hospital at Visakhapatnam, Andhra Pradesh, India.

2. Material and Methods

Aretrospective, observational study to analyze histopathology of renal biopsies was done at King George hospital, Visakhapatnam, Andhra Pradesh, India between January 2008 and December 2014. After recording the demographic and clinical details, a thorough biochemical and immunological analysis was done. Coagulation profile was done for all cases. After taking informed consent renal biopsy was done under strict aseptic conditions with automated spring loaded biopsy device (BARD) under ultrasound guidance. After renal biopsy, patients were observed for 24 hours for any untoward reactions and consequences of renal biopsy and post renal biopsy ultra sound was done for all cases for evidence of any hematomas and collections .All biopsies were evaluated by light microscopy; immune fluorescence study was done using IgG, IgM, C3, C4, fibrinogen stains. Special stains were used wherever required. Indications for renal biopsy were nephrotic syndrome, acute nephritic syndrome (ANS), asymptomatic urinary abnormalities (AUA), isolated hematuria, acute kidney injury with delayed recovery (>3 weeks) , and rapidly progressive renal failure..[19] A repeat renal biopsy was done where there is inadequate or inconclusive specimen .A total of 624 native kidney biopsies were performed during this period. Provisional diagnosis in relation to clinical findings and laboratory investigations were regrouped into major clinical syndromes. Classification based on histological categories were as follows: I) primary glomerular disease(PGD) which included minimal change

disease (MCD), FSGS, membranous nephropathy(MN), IgA nephropathy(IgAN), IgM nephropathy (IgMN), mesangioproliferative glomerulonephritis (MesPGN), membranoproliferative glomerulonephritis(MPGN),diffuse proliferative glomerulonephritis (DPGN), postinfectious glomerulonephritis (PIGN); (II) secondary glomerular disease (SGD) included lupus nephritis(LN), diabetic nephropathy (DN), amyloidosis (AM), Henoch–Schönleinpurpura (HSP), multiple myeloma (MM), systemic vasculitis (VAS),hemolytic–uremic syndrome(HUS)/ thrombotic microangiopathy (TTP); (III) tubulointerstitial nephritis (TIN) includes AIN, CIN, acute tubular necrosis (ATN);(IV) vascular nephropathy (VN) includes thrombotic microangiopathy(TMA), acute cortical necrosis, hypertensive changes;(V) Chronicrenal parenchymal changes are characterized by advanced glomerulosclerosis, arteriosclerosis, tubular atrophy/ loss, severe interstitial fibrosis and some degree of cystic change [20].In this study the data generated and analyzed was also compared with studies from India and different geographical regions of the world. We calculated the incidence of each type of renal disease. Qualitative data was expressed as numbers and percentages.

3. Results

A total of624 cases were included in this study,males51.92%(n: 323), females48.23(n:301)and male: female ratio of 1.07:1 with arange of 4months to 68years.Primary glomerular disease(PGD) accounted for 60.25%(n:376) of the total cases and was the most common BPRD followed by tubule interstitial nephritis (TIN)16.66%(n104) , secondary glomerular disease (SGD) 13.78%(n86),CKD 5.12%(n32)and vascular nephropathy (VN)4.17%(n26).Figure: 1shows distribution of BPRD.

The incidence of different types of primary glomerular disease (PGD)&sex distribution are shown in Table 1. PGD accounted for 60.25 %(n: 376) of the total cases and was the most common BPRD. Within the PGD most common cause was MCD 20.47% (n: 77) followed by FSGS 18.35 %(n: 69) and MN16.22 %(n :61).Most common cause of ANS was PIGN11.34 %(n:43).Figure 2.shows distribution of PGD along with sex.

Table 1: Incidence of different types of primary glomerular disease (PGD) &sex distribution

primaryglomerulonephritis(PGD)				
	M	F	Total	% of total PGN
MCD	48	29	77	20.47
FSGS	41	28	69	18.35
M.N	35	26	61	16.22
MPGN	27	14	41	10.9
PIGN	25	18	43	11.43
DPGN	6	16	22	5.85
MES.P.GN	9	13	22	5.85
IgA	14	8	22	5.85
C1Q	9	4	13	3.45
IgM NPHROPATHY	1	1	2	0.53
C3 GLOMRULOPATY	0	2	2	0.53
PAUCI IMMUNE	1	0	1	0.26
FIBRILLARY G.N	1	0	1	0.26
Total	217	159	376	100

Secondary glomerular disease (SGD):Lupus nephritis62.79 %(n: 54) was the most common BPRD fallowed by HUS/TTP 11% and DN 9%. Figure: 3show distribution of SGD along with sex. Tubulointerstitial nephritis (TIN): Acute TIN56.73% (n:59) was the most common BPRD. Figure: 4 shows distribution of TIN along with sex

Table 2& Figure: 5 shows over all Incidences of different glomerular diseases in north Andhra Pradesh, India.

INCIDENCE OF biopsy- proven renal disease (BPRD)				
	M	F	Total	% of total BPRD
MCD	48	29	77	12.33
FSGS	41	28	69	11.05
M.N	35	26	61	9.77
ACUTE TIN	36	23	59	9.45
LUPUS N	1	53	54	8.65
PIGN	25	18	43	6.89
MPGN	27	14	41	6.57
CHRONIC TIN	13	17	30	4.8
DPGN	6	16	22	3.52
MES.P.GN	9	13	22	3.52
IgA	14	8	22	3.52
CHRONIC GN	10	11	21	3.36
A.T.N	11	4	15	2.4
C1Q	9	4	13	2.08
A.CORTIAL NEROSIS	6	6	12	1.92
CKD	6	5	11	1.76
HUS/TTP	4	7	11	1.76
D.N	4	5	9	1.44
HTN NPHROPATHY	5	2	7	1.12
T.M.A	3	4	7	1.12
multiple myeloma (MM)	1	2	3	0.48
IgM NPHROPATHY	1	1	2	0.32
C3 GLOMRULOPATY	0	2	2	0.32
AMYLOIDOSIS	2		2	0.32
HSP		1	1	0.16
HIV N	1		1	0.16
PRIMARY HYPEROXALURIA	1		1	0.16
AUTE PYELO NPHRITIS	1		1	0.16
VASICULITIS		1	1	0.16
SICKLE CELL N		1	1	0.16
PAPILLARY NECROSIS	1		1	0.16
PAUCI IMMUNE	1	0	1	0.16
FIBRILLARY G.N	1	0	1	0.16
	323	301	624	100%

Table 2 shows over all Incidences of different glomerular diseases in north Andhra Pradesh, India.

4. Discussion

This study provides comprehensive information about the clinical syndromes, its occurrence and demographic pattern of different renal diseases diagnosed by renal biopsy during the period of 2008 to 2014 over a period of six years, in a single tertiary care referral centre in south India.

Tables 3 shows comparison of the basic data and some common diseases in this study with those of other studiesfrom the same region and other countries.

Table 3: Comparisons of some basic data and common diseases in this study with other studies

Comparisons of some basic data and common diseases in our series with other published studies									
Variables	Present study*	Nims(4) *	CMC[22]	PGI[23]**	Pakistan[21]*	China[24]	Korea[3]	Japan[9]***	UAE[5]
Duration	2008-2014	1990-2008	1986-2002		1995-2008	1979-2000	1987-2006	1985-1993	1978-1996
Total no.	624	1849	5415	2947	1793	10002	1818	1850	490
M:F	1.07:1	1.5:1	_	_	1.6:1	1:03	1.02:1	_	_
mean age	_	32.27±18.4	_	_	32.9±12.8	31.4±13	_	_	_
PGD	60.25	69.1	71	69	73	71	74		77.1
SGD	13.78	18.2		31	10.9	23	11.8	_	_
TIN	16.66	6.7	3.6	_	11.6	3.2	_	_	_
MCD	12.33	15.1	10.8	23	5.8	0.93	15.5	17.5	18.3
FSGS	11.05	10.5	16.8	9	21.2	6	5.6	4.6	18.3
Mes.PGN	3.52	5.2	7.3	3	1.9	25.62	_	_	_
MPGN	6.57	3.9	2.9	18	1.1	3.38	4	7.5	_
MN	9.77	7	9.5	10	17.2	9.89	12.3	10.6	20.1
Chroni GN	3.36	6.7	_	7	11.6	_	_	_	_
DPGN	3.52	4.7	_	_	19	_	_	41.9	_
IgA N	3.52	4.4	8.4	4	1.5	40	28.3	47.4	6.3
ESRD	1.76	2	4.2	_	_	_	0.5	1.3	_
LN	8.65	14.6	6.9	22	4.9	54.3	74	_	40.7
AM	0.32	1.5	1	39	4.6	2.2	_	_	33.3
DN	1.44	1.2	2.8	20	0.9	7.35	16.7	_	_
MM	0.48	0.4	_	_	_	0.89	_	_	_
HUS	1.76	0.3	_	_	0.6	_	_	_	_
VASULITIS	0.16	0.7	_	4	0.3	_	_	_	_

Indicates non availability of data for the particular variable.NIMS= Nizam's Institute of Medical Sciences, Hyderabad India, CMC = Christian Medical College, Vellore, India; UAE = United Arab Emirates; PGI = Postgraduate Institute of Medical Education and Research, Chandigarh, India. *These figures indicate percentage of total renal diseases. **Data for glomerular diseases only and percentage calculated out of total primary GD and secondary GD separately. ***Only primary GD. Rest of the studies percentage were calculated from total primary GD and secondary GD separately.

Similar to the majority of other studies worldwide, PGN was the predominant renal disease in our study (3, 4, 5, 21, 22, 23, 24), followed by TIN and SGN. CKD & vascular nephropathies were less frequent in majority of the studies. From this data and analysis, we did not observe any hereditary GD which may be due to the non availability of EM or it can be diagnosed by other noninvasive methods. We also observed a male predominance in the majority of cases except in SGN where there is strong female predominance. This reflects the increased prevalence of LN in the female population. All studies worldwide showed a similar pattern.

In this study NS was the most common clinical indication for renal biopsy accounting for 39% of the total cases which is similar to other studies around the world, including South India (4, 6,10,21,22, 25). However, asymptomatic urinary abnormality was more frequent in the Japanese study, because a greater tendency to biopsy in patients with hematuria and asymptomatic proteinuria (9).

In NS underlying etiology is widely variable in different regions of the world. In our study, the most common cause was MCD, followed by FSGS, MN, three most frequently diagnosed PGD, comprising 55% of the PGD in our study. This is similar with another South Indian study and studies from Bahrain and Morocco (4,12,23,26).MCD shows variable geographic distribution. Some European studies and a south Indian study from Vellore have shown a decline in the relative frequency of MCD (7, 25, 27, 28).A study from china shows very low incidence of MCD (24). It is the most common cause of NS in children with 80% of histological verified cases occurring in first decade and a male: female (M: F) ratio of 2:1. (29).In this study, MCD comprised20.47% of total PGD, peaked in the first decade of life and more common in males(M: F, 1.65:1).

FSGS shows increased prevalence from <10% to25% of PGN in the past 20 years with variable geographic distribution (3, 4, 9, 21, 22, 23, 24). FSGS is the second most common PGD (18.35%) with a M:F ratio of 1.34:1, findings which are similar to south Indian studies from Vellore and Hyderabad (4, 5). Studies from Pakistan, Brazil and Arab countries have quoted FSGS as the commonest PGN (4, 10, 21, 25).A South Indian study from Bangalore differed from present study where FSGS is third most common PGD (12.6%)(30).

MN is thought to be the most common PGD in adults. A review of different articles shows MN to be the third or fourth common cause of PGD (6, 9, 11, 12, 22, 24). In our study it was the third most frequent PGN (16.22%) and most common cause of NS in adults which is similar to other south Indian studies. Present study also supports the same. However, a south indian study from Bangalore differed from present study where MN is the second most common PGD (15.7%)(30).In many European Countries (Italy and Serbia), United Arab Emirates (UAE), and America MN is still the commonest cause of NS (5, 7, 27, 31).

IgA nephropathy represents 5.85% of total PGN, M: F (1.75:1) was uncommon in our study, a pattern similar to South Indian studies, including Pakistan and West Asian Studies.(4,12,21,25,32) However, IgANis the commonest PGN in Europe, West Germany and some East Asian countries like Japan Korea and china (3, 7, 24, 33, 35, 36). Though IgAN is considered as the most common glomerular disease worldwide, its detection rate varies depending on indications of biopsy and mass screening programs for a symptomatic urinary abnormalities , genetic and environmental influences(3). In CRF patients the number of biopsies is increasing when normal sized kidneys with intact corticomedullary differention by ultra sonogram. Some of these patients are diagnosed as chronic IgAN.

The incidence of MPGN is decreasing in different parts of the world probably due to the improved socioeconomic conditions, improved hygienic environments, universal precautions and vaccinations which eventually cause a reduction in infection rates, and reduction in the regional endemic diseases(4, 10, 12, 28).In our study MPGN comprised 10.9%of all PGN,M:F(1.9:1) which is slightly higher compared to other South Indian studies conducted at Vellore (5.2%),Hyderabad (7.5%) and Bangalore(9.4%)(4, 25, 30). It is attributable to the higher prevalence of infectious diseases like bacterial infection, hepatitis B and C and parasitic infection.

In our study c1q nephropathy comprised (3.45%of PGN) with male predominance, M:F(2.25:1). Most of the studies did not mention this category. In this study increased incidence of c1q nephropathy can be explained by the improved IF study technique in each biopsy. IgMN & Fibrillary G.N was the least common entity in our study. Most of the studies did not mention IgMNas a distinct category. A study fromPakistan reported that IgMN comprises 2.9% cases of PGD (21). The existence of both entities (IgM nephropathy and C1q nephropathy) is disputed by some renal pathologists.

TIN is found to be a relatively less frequent BPRD in many studiesacross the world. Compared with two south Indian studies Hyderabad India (6.7%) Vellore, India (3.6%), this study shows a relatively high frequency of TIN 16.66% of total BPRD and second common cause of total BPRD (4, 22). Of total BPRD (n: 59)), acute TIN(9.45%) is more common than chronic TIN. Similar to this study a south Indian study from Bangalore where TIN accounted for 20% of BPRD (30). This variation is mostly due to analgesic abuse and intake of native medication which comprises a mixture of plant products, heavy metals, other inorganic materials, is very popular in North Andhra Pradesh, India. We observed a higher incidence of ATN (2.4% of total BPRD)&cortical necrosis(1.92% of total BPRD)as compared to other studies which can be explained by aggressive performance of biopsy procedure in patients with ARF with prolonged recovery without an obvious etiology &non recovering ARF in obstetric patients, insect bites and snake bites.

The most common SGD in this study was LN comprising 62% of all SGD which is comparable with that reported in many studies across the world (3, 11, 21, 22, 24, 25). The second common SGD in our study was HUS/TTP (12.76% all SGD), with a female predominance M:F(0.57:1).This variation is mainly due to infections. The third common SGD in our study was DN (10.46%) with M: F (0.8:1) and it differs from other studies where it is second most common (4, 30).Compared with other studies this variation is mainly due to selection criteria for renal biopsy in these patients. The decreased incidence of diabetic nephropathy in this study may not be a true representative of the overall diabetic renal disease as only diabetic patients with unusual presentations were biopsied.

Multiple myeloma (MM3.48%) and amyloidosis (2.32%) occupy fourth & fifth place among SGD. Studies from Pakistan and UAE& Italy have reported a higher frequency of amyloidosis (5, 7, 21). However, despite the higher prevalence of tuberculosis and other infectious diseases, amyloidosis comprised only 2.32%of SGD in our study. Instead of performing renal biopsy amyloidosis can be confirmed by biopsies from other sites such as rectum, gum or abdominal fat.

Limitation: Drawing accurate conclusions were difficult due to several biases regarding demographical, geographical and racial characteristics, differences in indications for renal biopsy, the analyzed clinical syndromes and variations in histopathological classification. Hence, accurate comparison with different data is difficult.

5. Conclusions

This study documented the incidence of BPRD in north Andhra Pradesh, India .The pattern of PGD largely corresponds to the distribution pattern of other South Indian studies. The increasing incidence of worldwide FSGS is confirmed in this study. Comparison with worldwide studies there is a wide variation of major histological patterns of renal disease across the world. However, the most common secondary glomerular disease has been documented as LN almost across the world. This study also provides descriptive epidemiological biopsy data of south Indian population and highlights the changing trends in this region. The changing incidence of BPRD is probably contributed by an increased referral &health awareness, together with improved biopsy technique. For comparison of BPRD from different parts of India it is necessary to maintain a national registry.

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