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GLOMERULAR DISEASES IN MADINA REGION;

NEED OF ANTI PLA-2 RECEPTOR ANTIBODY, AS MEMBRANOUS NEPHROPATHY APPEARING AS PREDOMINANT PRIMARY GLOMERULAR DISEASE.

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ABSTRACT… Objectives: To get useful information and epidemiological data for clinical practice and investigations regarding glomerular disease frequencies in Madina region. **Study Design:** Single-center retrospective study. **Setting:** King Fahd Hospital Madina. **Period:** 01 year (March 2016- March 2017). **Methods:** All native renal biopsies were studied. Only glomerular disease patterns were analyzed. The diagnosis of each case was based on histological, immunopathological and clinical features. **Results:** A total of 44 biopsies were Included. Primary glomerular diseases was found in 52.27% of all biopsies studied. The most common primary disease was Membranous Nephropathy which accounts for 20.45%. Focal and Segmental Glomerulosclerosis (FSGS) (9%), Minimal change disease (4.54%), C3 glomerulopathy (4.54%), IGA Nephropathy (4.54%), Non-IgA Mesangial Proliferative GN(2.27%), Crescentic Glomerulonephritis (GN) (2.27%), Post Infectlous GN(2.27%), Thin Basement Membrane Nephropathy(2.27%) as primary GN. Secondary glomerular diseases in 47.73%. Lupus Nephritis corresponded to 34.09% of the entire series. **Conclusions:** FSGS has been the most frequent type of glomerulopathy in Saudi Arabian population according to previously available data from local studies but in our study the cases of Membranous Nephropathy were high .Lupus Nephritis remain above the list as a cause of secondary glomerular disease. The reasons for these findings are unclear but this information is an important contribution towards understanding the prevalence of renal diseases In Saudi Arabia.

Key words: Glomerular diseases, Glomerulonephritis, Glomerulosclerosis.

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INTRODUCTION

Glomerular disease is a common cause of end stage renal disease in both underdeveloped and developed countries. The patterns of glomerular injury varies widely from country to country and even from region to region within a country. Recent advancements occurred in therapeutic decision making for diagnosis of glomerular diseases like AntiPLA2 receptor antibodies in serum and in renal tissue. The management[1,2,3,4,5] revolves around it, along with strong association with the HLA DQA1 Allele has been found in pts with idiopathic membranous nephropathy. Similarly the MEST-C score in IGA nephropathy[6,7,8] guided the prognosis and the aggressiveness to the approach regarding management. Similarly in C3 glomerulopathy[9] emergence of Eculizimab, and MMF in its treatment has emphasized for proper diagnosis, plus different types of FSGS regarding their response to treatment and questionable implications regarding there variable prognosis.

Epidemological review of renal diseases, helps to identify the incidence and prevalence of glomerular and other renal diseases, their etiology, the causal relationship which can be ethnic, genetically related or environmental factors which can play a part in disease. The clinical features, the diversity in renal biopsy indications and histopathological data are all valuable tools to study. So the study was designed to review our renal biopsy data to look at the spectrum of glomerular in the Madina Region.

King Fahd Madina is a tertiary centre for the western Saudi Arabia, which has a population of

locals and immigrants.

This study highlights the diagnoses from renal biopsies in the community. The histopathological services available to us were light microscopy and immunofluorescence.

METHODS

It was a single centre retrospective study. All the biopsies came from patients living in our geographic region (Madina) and were performed over 1 year (march 2016 to march 2017). They were evaluated by means of light microscopy and Immunofluorescnce, using standard procedures.

Electron microscopy (EM) was not available but one case of suspected thin basement nephropthy was sent to higher centre which was later confirmed.

The diagnosis was made through light microscopy and immunofluoroscence. After exclusion total of 44 native renal biopsies were examined over 1 year period. The biopsies were seen by two pathologists and the consensus diagnosis was made. All the relevant stains, hematoxylin-eosin (H&E), periodic acid-Schiff (PAS), silver, masson trichrome and in selected cases, with other histochemical stains (congo red).

The renal diseases were classified according to the standard WHO criteria.[10] Clinical data was retrieved from electronic medical records. The glomerular diseases were classified as primary or secondary on the basis of clinical and lab data. Serological diagnosis for glomerular disease including workup for paraproteinemia was performed in all the relevant cases.

Data analysis. To predict the distribution of the data, descriptive statistics was used. Glomerulopathies and its histological types were plotted against their relative frequencies. Age was used with its mean and range. One of the most widely used software: Statistical Package for Social Sciences (SPSS) was used to analyze the data with its version 11.5.

RESULTS

Data were collected from 51 renal biopsies.

2 cases (3.9%) Had diagnoses of non-glomerular diseases which was tubulointerstitial nephritis.

In 3 cases (5.8%) there was not an enough tissue for a precise diagnosis.

In 2 cases (3.9%) no precise diagnosis could be achieved even though there was sufficient tissue material because of advanced glomerulosclerosis.

Excluding these 7 cases, a total of 44 biopsies were finally included in the study.

The patients mean age was 34 (range: 12-70) median 41.0, 23 cases (52%), the age was between 12 to 30, 13 cases (29.5%) age range was 31-45, 5 cases (11.3%) age range was between45 -60, and in 3 cases (6.8%), the age was > 60 years. The distribution of renal biopsies according to the patients' ages can be seen in Table-I, 50% of the patients were female.

	n	Percentage
12-30	23	52
31-45	13	29.5
45-60	5	11.3
Greater than 60	3	6.8

Table-I. Age distribution

Table-I Distribution of age groups among patients with primary and secondary glomerulopathies (n=44)

Indication for renal biopsy was nephrotic syndrome followed by non-nephrotic range proteinuria with or without hematuria, asymptomatic hematuria and AKI where glomerular vasculitis was suspected. The indication of biopsy in patients with diabetes were. if there is absence of diabetic retinopathy or, acute kidney injury or nephrotic range proteinuria or Less than 5 years history of diabetic nephropathy, active urine sediment or signs or symptoms of systemic disease.

The frequency of primary glomerular diseases was more among males: 57% and females 43%

respectively. Secondary glomerular diseases were more frequent among females (61%). The most common primary diseases were membranous nephropathy (20.45%), focal and segmental glomerulosclerosis (FSGS) (9%), minimal change disease (4.54%), C3 glomerulopathy (4.54%), IGA nephropathy (4.54%). Non-IgA mesangial proliferative GN (2.27%), crescentic glomerulonephritis (GN) (2.27%). PostInfectIous GN (2.27%) and thin basement membrane nephropathy (2.27%) as primary GN. Lupus nephritis corresponded to 34.09% of the entire series. Antigbm was 4.54 percent, Diabetic nephropathy 4.54 percent, HUS/TTP was 2.27 percent and ANCA vasculitis 2.27 percent. Table-II.

DISCUSSION

The results from the renal biopsy data has provided us to find the most common glomerulopathies in the region. This database consists of all the patients living in the Madinah region. The sample is relatively from a homogenous population and the patients in the database are a mix of Saudi and Immigrants. The geographical origin of the Immigrants is mostly Asians. Clinical features, skin color do not correlate with genomic ancestry.[11]

This data serves to be the first of its kind on renal biopsy in Saudi Arabia. Since, there is no national database available of glomerulopathies at present; we cannot be sure whether this Madinah regional sample represents the entire Saudi Arabia population and provides the true frequency of glomerulopathies in Saudi Arabia.

The country does not possess a national database of renal biopsies or glomerulopathies hence we cannot say whether this is a good representation of pathology in the population.

FSGS is the commonest glomerulopathy among Saudi population as reported by mitwali[12] and nawaz[13] and represents 40 % to 27 % of primary glomerulopathies. Our study shows totally contrasting results of predominant Membranous Nephropathy. Other authors have reported similar frequencies of FSGS.[14] Contrary to the available literature, IgA nephropathy cases were reportedly low in our study group, accounted for 4.54% of primary glomerulopathies and this might be due to usual clinical practice of not biopsing microscopic haematuria and isolated proteinuria (<1gm). ACEi or ARB are still the standard treatment protocol in these patients. Thus the proportion of IgA nephropathy was lower than in series from Romania,[15] Czech Republic,[16] Australia,[17]Denmark,[18] United States,[19] China,[20] Italy,[21] Brazil,[22] France,[23] Japan[24] and Korea.[25]

	Total N (%)	% of Primary Or Secondary	M (%) of Relative Disease	F (%) of Relative Disease
Primary Glomerular Diseases	23(52.27)		61	39
Membranous GN	9(20.45)	(39.1)	55	45
FSGS	4(9)	(13)	50	50
Minimal Change Disease	2(4.54)	(8.6)	50	50
C3 Glomerulopathy	2(4.54)	(8.6)	100	
IGA Nephropathy	2(4.54)	(4.34)	100	
Mesangial Proliferative	1(2.27)	(4.34)		100
Crescentic GN	1(2.27)	(4.34)	100	
* Postinfectious GN	1(2.27)	(4.34)		100
Thin Basement Membrane n	1(2.27)	(4.34)		100
Secondary Glomerular Diseases	21(47.73)		38	62
Lupus Nephritis	15(34.09)	(71)	20	80
Antl-GBM Disease	2(4.54)	(9.5)	50	50
Diabetic Nephropathy	2(4.54)	(9.5)	100	
TMA	1(2.27)	(4.7)	100	
Anca Vasculitis	1(2.27)	(4.7)	100	0

Table-II. Presents the frequency analyses.

Reports from India also showed membranous nephropathy only second behind FSGS.[26] Study from Oman also revealed membranous nephropathy as second to FSGS.[27] The reason for this high incidence of membranous nephropathy among our biopsied patients is unknown. A limitation of the study was other than the clinical , lab work and radiological work up we did not have access and availability of AntiPLA2 receptor antibodies/thromospondin A antibodies[28] neither in the serum nor in the biopsy which not only differentiates between primary and secondary membranous with the antibodies present mainly in primary membranous with 100 percent sensitivity and 80 percent specificity, only a few anecdotes of secondary membranous nephropathy associated with hepatitis B, sarcoidosis and cancer had Anti PLA2 receptor antibodies which the experts of the field think that it is an association rather than causation of membranous nephropathy. Similarly now the whole management of primary membranous nephropathy revolves around the titres, and disappearance of these antibodies, and the activity of the disease also depends upon simultaneous presence of these antibodies in serum and biopsy, if the antibodies are present only in biopsy and not in serum the disease seems to be inactive.

Similarly membranous GN has higher proportions in the Italian database (23.4%)[21] and Che Sao Paulo database (20.7%).[22] Membranous GN and minimal change disease, which are two of the most prevalent histological diagnoses among nephrotic patients, accounted for lower proportions of primary glomerulopathies in series from Europe, United States, Australia and Asia,[15-20] Another limitation of the study was unavailability of electron microscopy in all cases except in one case were it was send outside , which was important to differentiate between minimal change disease and stage 1 membranous, to differentiate between primary and secondary FSGS ,to see the diffuseness of the foot process in primary.[29] The conundrum of primary vs secondary is critical not only for the diagnosis but also for therapeutic purposes because this decision virtually drives all subsequent aspects of patient management. C3 consensus[30] also requires EM to differentiate between DDD and other C3, since prognosis seems to be worse in DDD. Another limitation of the study was the adequacy of glomeruli in our study (less than 15). According to sanjeev sethi, with glomeruli less than 15, FSGS cannot be ruled out with reasonable confidence.[31] It is possible that genetic and environmental factors, race and frequency of infections play a key role in this difference between populations which led to dominance of membranous nephropathy in our study.

Secondary causes with predominant Lupus Nephritis (71 %) was in complete agreement with studies of mitwali[12] and Nawaz.[13] Other causes of secondary glomerular disease were infrequent to have any conclusions.

The reason for including post infectious GN in the primary glomerulopathies are that some coexisting unknown factors can cause the glomerular disease. Extrarenal manifestations sometimes are not detected.

Standard of care in renal biopsy examination should include light microscopy, IF and electron microscopy. Madina region, does not have electron microscope, so the only tools which we have available are light microscopy and IF, analyzed by experienced renal pathologists. Cases in which electron microscopy was needed was send to mayo clinic Rochester.

As the biopsy resources as well as biopsy policies differ, the occurrence and incidence of glomerular diseases varies. Such behavior is validated when the histological diagnosis is made. There is not a single widely accepted epidemiology of glomerular disease. There are centers that take biopsies only when the pathological diagnosis would have a considerable affect on the therapy. They also take biopsies with subjects having signs of progressive renal diseases. Hence, the variation in the incidence of glomerulopathies can be explained by these different factors. Talking about our center, when a sign of renal dysfunction or proteinurea is exhibited by a patient, renal biopsy is carried out. Patients with hematuria alone, many of the doctors do not take

renal biopsy. Hence, this might predict the low occurrence of renal biopsy in our study of IGA nephropathy.

Hence, it is evident that there exists some internal biases in doctors when selecting patients for biopsy as well as the availability of resources. This can be seen from the results in the many reports published worldwide. However, the differences might also be due the difference in race, genetics and occurrence of the infection or environmental factors. Therefore, the results from our study are not applicable to other relevant populations.

The incidence of glomerular diseases varies according to the biopsy resources and biopsy policies. These are reflected in the histological diagnoses that are made. There is no universally valid "epidemiology" of glomerular disease.[32,33] Some centers only take biopsies when the pathological diagnosis would affect the therapy, or in subjects with signs of progressive renal disease,[34,35] Many differences in specific proportions (or incidence) of glomerulopathies can probably be explained by these confounding factors. In our center, renal biopsy is carried out on patients with any sign of renal dysfunction or proteinuria of any level. Nonetheless, among patients with hematuria alone, many nephrologists do not undertake renal biopsy. This may be a reason for the low incidence in our study of IGA nephropathy.

Thus, the different results in many reports worldwide could indicate bias in selecting patients for biopsy or resources for renal tissue study, or in other factors. Nevertheless, many differences are probably due to differences in population genetics, race, environmental factors and frequency of infection or biopsy rate. Therefore, our results are not relevant to other populations.

CONCLUSION

In conclusion, Membranous Glomerulopathy is the commonest entity diagnosed on biopsy in primary glomerular disease in adult from our region. In secondary glomerulopathies Lupus predominates as all the previous studies of Saudi Arabia. This study provides a contribution towards understanding the epidemiology of glomerular diseases in Madina with possible implications for the planning of future research.

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