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Research Article

Indications and Histologic Patterns of Biopsy-Proven Kidney Diseases in Vietnamese Adult Patients

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Keywords

- Kidney biopsy; Glomerular diseases; Histologic patterns

Abstract

Objectives

We present the first systematic description of indications and pathologies of kidney disease in Vietnam.

Patients and methods

Patients: We routinely performed renal biopsy in 146 adult patients referred to our renal center in Thong Nhat University Hospital, Ho Chi Minh City between March 2011 to October 2016 for asymptomatic urine abnormalities, nephrotic or nephritic syndromes, acute kidney injury or chronic kidney diseases of unknown causes.

Methods: Retrospective study.

Statistical analysis: SPSS 22.0 was used for analysis. The percentage and mean ± SE of the mean were used to describe categorical and continuous variables, respectively. Qualitative variables were compared by Chi-square or by Fisher's test as appropriate. P-values <0.05 were considered statistically significant.

Results

Kidney biopsies were indicated by nephrotic syndrome (NS) in 100 (68.49%), nephritic syndrome in 20 (13.70%), chronic kidney diseases (CKD) of unknown cause in 11(7.54%), asymptomatic urine abnormalities (AUA) in 8(5.48%), acute kidney insufficiency (AKI) in 7(4.79%).

Primary glomerular disease, secondary glomerular disease and tubulo-interstitial nephritis was 111(76.03%); 25(17.12%) and 6(4.11%) respectively. Among patients with primary glomerular disease, 41 (36.94%) cases were due to minimal change disease (MCD), 31(27.93%) focal segmental glomerulonephritis (FSGS), and 23(20.72%) IgA nephropathy. Membranous nephropathy (MN) accounted for only 8(7.21%) cases. Among the group of secondary glomerular disease, 14(56%) patients had lupus nephritis.

Conclusions

Our data showed that NS was the most common and asymptomatic urine abnormality was least common reasons for referral to our renal center for kidney biopsy. Primary glomerulopathy was most common cause of biopsy-proven kidney diseases. MCD, FSGS, and IgA nephropathy were the most common forms of primary NS.

ABBREVIATIONS

ANCA: Anti-Neurophil Cytoplasmic Antibodies; CKD: Chronic Kidney Disease; FSGS: Focal Segmental Glomerulosclerosis; MCD: Minimal Change Disease; MPGN: Membranoproliferative Glomerulonephritis; NS: Nephrotic Syndrome; PGN: Primary Glomerulonephritis; SGN: Secondary Glomerulonephritis; TIN: Tubulo-Interstitial Nephritis; TBM: Thin Basement Membrane

INTRODUCTION

Although the incidence of chronic kidney disease (CKD) is probably high in developing countries [1], little is known of the histologic patterns of renal disease. Data of histological patterns of renal disease does not exist in Vietnam due to several reasons such as the lack of trained nephrologists, renal pathologists and electron microscopy. In the extremely difficult situation, we attempt to illuminate the problems with renal diseases in Vietnamese. The present work is the first study of the indications and histologic patterns of renal disease revealed by routine kidney biopsies in a large hospital in South of Vietnam.

Kidney biopsy is an invasive diagnostic procedure with potential complications and costs. Hence, its indication varies across countries. International registries of renal biopsy show

that kidney biopsies are mainly indicated by asymptomatic urine abnormality and nephrotic syndrome [2-4]. Acute kidney injury and chronic kidney diseases are not the primary indications for kidney biopsy. Additionally, incidence and pathological patterns of kidney disease may vary across countries due to differences in the indication for biopsy and quality of medical care, as well as geographical, environmental, economic differences. However, most retrospective studies showed that IgA was the most common histological feature in Europe and the USA [5,6] but that the incidence of Focal Segmental Glomerulosclerosis (FSGS) is higher in Asia [7].

Vietnam is a tropical and developing country with 90.73 million people and lower middle income. Its unfavorable social and economic environments, including higher incidence of infectious diseases (hepatitis B and C, streptococcus, etc), pervasive pollution, lower food and water safety standards, and use of unmonitored, potential nephrotoxic herbal medications, may increase the risk of kidney diseases and may affect renal pathologies of renal diseases. In addition, the strategy of prevention and management of kidney diseases has not been available. Urinary analyses are not routinely scanned for kidney disease due to economic reasons, and insufficiency of primary health care. Kidney biopsies remain uncommon and have just been performed in some departments of nephrology in specific cases of renal diseases in large hospitals in Vietnam, and paid by health insurance with limitation of only around 30 USD for a case. Trained nephrologists and renal pathologists are not widely available. There are only four qualified renal pathologists up the country and two of them jointed this study in Ho Chi Minh City. Electron microscopy is not available at this moment. As well as, there are only around twenty nephrologists trained abroad who can be able to do kidney biopsy so that most of glomerular diseases are treated by steroid without kidney biopsy. As the result, these patients are suffered from severe complications due to long-term steroid prescription. In addition, most nephrologists lack of experience of application of results of biopsy in the clinical management for glomerular diseases. Therefore, renal diseases are usually diagnosed late, leading to high incidence of end stage renal disease.

In this study, we performed kidney biopsy for all patients referred to our department of nephrology, university hospital in Ho Chi Minh City for asymptomatic urine abnormalities, nephrotic syndrome, nephritic syndrome, acute kidney injury, and chronic kidney diseases of unknown causes. Clinical data for all patients is analyzed for indications of kidney biopsy and histological pattern is interpreted by two qualified renal pathologists.

PATIENTS AND METHODS

Patients

Kidney biopsies performed on 146 adult patients (81 male, 65 female) at Thong Nhat University Hospital, Ho Chi Minh City between March 2011 to October 2016 were included in the study. Patients were divided into two age groups: (1) young (15-60 years old) and (2) elderly (≥60 years old). Biopsies that yielded inadequate samples for meaningful histologic studies and patients younger than 15 years at the time of biopsy were excluded from study.

Methods

For each biopsy, demographic information (name, date of birth, and gender) were collected. Medical histories were taken for each patient, noting past history of renal disease, diabetic mellitus, hypertension, and systematic lupus erythematous, as well as use of medications or herbal remedies. At the time of visit, blood pressure, body weight, and presence of edema or gross hematuria were noted. Results of previous lab tests including urine volume; serum creatinine; estimated creatinine clearance by Cockcroft and Gault formula; fasting glucose; lipid profile; serum protein and albumin; serum electrolyte; coagulation profile; anti-HIV, anti-HCV; and HBsAg serology; 24-hours proteinuria; and hemoglobin serum C3, C4, ANCA and ANA as indicated per clinical situations were also noted at the time of kidney biopsy and of visit. Finally, a kidney ultrasound was taken at the time of biopsy.

Across patients, the clinical indications for kidney biopsy in the study were asymptomatic urine abnormalities, nephrotic syndrome, nephritic syndrome, acute kidney injury, and chronic chronic kidney disease of unknown causes [2]. Asymptomatic urine abnormalities were defined as mild to moderate proteinuria (150 mg to 3000 mg per day) and/or hematuria (>2 RBC/ high-power field in spun urine or > $10x10^6$ cells/liter) and absence of clinical manifestations. Nephrotic syndrome was defined as proteinuria > 3.5g/day and hypoalbuminemia <3.5g/dL with or without edema. Nephritic syndrome was defined as an abrupt onset of hematuria, oliguria, moderate proteinuria (<3g/day), associated with edema, and hypertension. Acute kidney insufficiency was defined as a rapid deterioration of renal function without past history of kidney disease. Chronic kidney disease was defined as renal insufficiency lasting for > 3 months.

Kidney biopsy was performed by nephrologists with ultrasound guidance and automated biopsy gun. All renal biopsy specimens were prepared by experienced technicians and examined by two trained renal pathologists. All renal tissues were quickly processed by fixing in buffered formalin 10% then alcohol increasing concentration up to 100% for dehydrating, then xylene before going to paraffin 60 degree Celcius for embedding. For light microscopy observation, the tissues were cut into many sections in 2 microns thickness and stained 2 slides with haematoxylin-eosin, 2 slides with periodic-acid Schiff, 2 slides with Trichrome, and 2 slides with silver-methenamine. Congo red was stained whenever amyloidosis was suspected. For Immunofluorescence, we use polyclonal antisera against human IgG, IgM, IgA, C3, C1q, kappa and lamda light chain. Electron microscope examination was not performed due to lack of facilities.

Incomplete records, inadequate biopsies (<10 glomeruli in the specimen for light microscopy when there were no typical findings in immunofluorescence or absence of a glomerulus in immunofluorescence) and repeat biopsies were excluded. Clinical and pathological data were collected.

Diagnosis

Pathological diagnoses were classified into five groups: primary glomerulonephritis (PGN), secondary glomerulonephritis (SGN), tubulo-interstitial nephritis (TIN), vascular nephropathy,

and miscellaneous [8], [9]. PGN was classified into eight groups: (1) IgA, (2) Membranous Nephropathy (MN), (3) Focal Segmental Glomerulosclerosis (FSGS), (4) Minimal Change Disease (MCD), (5) Membranoproliferative glomerulonephritis (MPGN), (6) Crescentic glomerulonephritis defined as crescentic glomerulonephritis not fulfilling the criteria for systemic diseases, (7) mesangioproliferative non IgA nephropathy. The diagnosis of PGN was made by exclusion: the patient's serology was negative for human immunodeficiency virus (HIV), hepatitis B and C, syphilis, anti-neurophil cytoplasmic antibodies (ANCA), anti-nuclear antibodies; there were no known associated systemic disease at the time of renal biopsy; nephropathy had an acute onset or was a chance discovery; and the symptoms (proteinuria with or without nephrotic syndrome, hematuria, hypertension, azotemia) occurred in a previously healthy person with non-antecedent illness [10].

SGN was classified into five groups: (1) immune-mediated glomerulonephritis such as Lupus nephritis, Vasculitis, Henoch-Schonlein purpura, and Goodpasture syndrome, (2) Glomerulonephritis caused by dysgammaglobulinemia or paraproteinemia such as renal amyloidosis, light-chain deposit diseases, myeloma kidney and essential mixed cryoglobulinemia (3) Glomerulonephritis associated with infectious diseases (non-streptococcal glomerulonephritis, endocarditis, hepatitis B, C, HIV, etc.), (4) Glomerulonephritis in the framework of metabolic (Diabetes Mellitus), and (5) hereditary disorders such as Alport syndrome, Fabry disease, thin basement membrane (TBM). The diagnosis of SGN was made if the nephropathy was discovered in the course of a specific disease and is often associated with extra-renal signs [10]. Miscellaneous pathologies included end-stage renal diseases, acute tubular necrosis.

Ethics approval

Thong Nhat Hospital Medical scientific committee Number TN-14-01-2011.

Patient consent

All patients provided written informed consent before inclusion.

Statistical analysis

SPSS 22.0 was used for analysis. The percentage and mean ± SE of the mean were used to describe categorical and continuous variables, respectively. Qualitative variables were compared by Chi-square or by Fisher's test as appropriate. P-values <0.05 were considered statistically significant.

RESULTS

Discussion

This retrospective study is the first systematic description of clinical indications for renal biopsy and of pathological patterns of biopsy-proven kidney disease in Vietnam. Our data showed that NS accounted for the majority of the indication for biopsy (68.49%), while asymptomatic urine abnormality was the least common (5.48%). Primary glomerulopathy was the most common cause of biopsy-proven kidney diseases (76.03%). MCD, followed by FSGS and IgA also were the most common forms of primary NS. Only a small minority of patients was diagnosed as MN (7.21%) (Tables 1-6).

Our study demonstrated a very low incidence of patients with asymptomatic urine abnormality (5.48%) and a very high incidence of NS (68.49%) were indicated for kidney biopsy. A literature review indicates that nephrotic syndrome, asymptomatic urine abnormality, nephritic syndrome, acute kidney injury and chronic kidney diseases of unknown causes were the clinical indications for kidney biopsy. Karnib et al., (2010) showed that the most common indication for renal biopsy was hematuria and/or proteinuria and that NS accounted for only 27.9% and 37.9% in the young adults and elderly group, respectively [11]. These differences may be related to lower incidence of urinary test screening by primary care providers in primary health care clinics, schools in Vietnam as well as lower referral rate of patients with asymptomatic urinary abnormality to nephrologists. Furthermore, most referred patients had had severe kidney insufficiency, especially among the elderly, 91.43% of whom had a creatinine clearance below 60 mL/min, higher than the 36.94% in the younger group. Our finding is consistent with those of Goretti Polito [2], Naumovic [12], Okpechi [13].

The high incidence of primary GN in our study is comparable with that reported by Naumovic (2009), which showed that PGN accounted for approximately two-thirds of all performed biopsies [12]. However, Goretti Polito et al (2010) reported a lower incidence of primary glomerulopathies (48.03%) in their large study of 9,617 renal biosies [2]. Our data also showed low incidence of non-glomerular renal disease. Tubulo-interstitial nephritis (TIN) accounted for only 4.11% of all biopsies (Table 3). The most common causes of TIN were potential nephrotoxic herbal medications (Table 1). Due to high use of traditional medications among our population, some of which may be nephrotoxic, we recommend a public awareness program to educate the public about the potential harmful effects of these products. This finding is in accordance with the studies of Li in China (6.5%) [14] and of Chang in Korea (6.4%) [15].

Interestingly, primary MN was infrequent in our study (7.21%) even in elderly patients with NS. Besides the 2 cases of membranous lupus glomerulitis (Table 5), the other 8 cases of membranous GN (Table 4) show no mesangial or subedothelial deposits or deposits in tubular basement membrane both in light microscopy and in immunofluorescence. We found no clinical conditions that could suggest a secondary membranous glomerulitis. We did not have anti-Phospholipase-A2-Receptor antibody to confirm that these cases were primary membranous glomerulitis. We also lack electron microscopy to rule out any subendothelial or mesangial deposits present in secondary membranous glomerulits. According to Couser, MN accounted for 30% of biopsies in adults and 15-50% of total cases of NS of allages [16]. In Singapore, Woo also reported lower incidence of MN [17]. The low number of biopsied patients included in our data, however, do not allow us to address this point and additional research is needed. By contrast, we noted a significantly high incidence of FSGS in both primary glomerular diseases (27.93%) and primary nephrotic syndrome (34.19%). This finding is comparable with other studies (e.g. Zaza [8] and Haas [18]). Future studies of the etiology and management of FSGS are needed in our population.

Table 1: Baseline characteristics of the patients with renal biopsy.

Baseline characteristics of the patients	All (n=146)	Elderly group (n=35)	Younger group (n= 111)	p
Age ($\overline{X}$ ±SD, years)	42.91±18.58	68.57±7.01	34.82±12.80	0.000
Age ≥ 60 years old, n(%)	35(23.97)			
Male, n (%)	81(55.48)	27(77.14)	54(48.65)	0.002
Body weight ($\overline{X}$ ±SD)	57.83±9.38	59.20±8.55	57.39±9.62	0.416
Patients from rural regions, n(%)	72(49.32)	13(37.14)	59(53.15)	0.072
Hypertension*, n (%)	47(32.19)	22(62.86)	25(22.52)	0.000
Proteinuria > 3.5g/day*, n (%)	68(46.85)	20(57.14)	48(42.24)	0.107
Past history of, n(%) Diabetes Mellitus Hypertension Nephrotic syndrome	 18(12.33) 47(32.19) 50(34.25)	 13(37.14) 21(60.00) 10(28.57)	 4(4.50) 26(23.42) 40(36.04)	 0.000 0.000 0.275
Past history of taking potential nephrotoxic herbal medications, n(%)	16(10.96)	6(17.10)	10(9.01)	0.151
Cl Cr ($\overline{X}$ ±SD, mL/min)*	61.14±36.37	31.38±19.76	70.53±35.39	0.001
Cl Cr ($\overline{X}$ ±SD, mL/min)* < 60mL/min, n(%)	73(50.00)	32(91.43)	41(36.94)	0.000
HBsAg positive and/or anti-HCV, n(%)	5(3.52)	1(2.86)	4(3.60)	

* At the time of kidney biopsy

Table 2: Distribution of clinical syndromes among native kidney diseases.

Clinical syndromes	All (n=146)	Elderly group (n=35)	Younger group (n=111)	p
Nephrotic syndrome, n(%)	100(68.49)	29(82.86)	71(63.96)	0.026
Asymptomatic urinary abnormalities, n(%)	8(5.48)	0(0)	8(7.21)	0.105
Acute kidney injury with unknown cause, n(%)	7(4.79)	3(8.57)	4(3.60)	0.219
Chronic kidney disease with unknown cause, n(%)	11(7.54)	2(5.71)	9(8.11)	0.483
Nephritic syndrome, n(%)	20(13.70)	1(2.86)	19(17.12)	0.023

Table 3: Percentages (%) of the different categories of renal diseases.

Categories of renal diseases	All (n=146)	Elderly group (n=35)	Younger group (n=111)	p
Primary glomerulonephritis (PGN), n(%)	111(76.03)	25(71.43)	86(77.48)	0.302
Secondary glomerulonephritis (SGN), n(%)	25(17.12)	7(20.00)	18(16.22)	0.483
Tubulo-interstitial nephritis (TIN), n(%)	6(4.11)	2(5.71)	4(3.60)	0.443
Miscellaneous, n(%)	4(2.74)	1(2.86)	3(2.70)	0.423

Table 4: Distribution of primary glomerular disease.

Type of primary Glomerular disease	All (n=111)	Elderly group (n=25)	Younger group (n=86)	p
MCD, n(%)	41(36.94)	9(36.00)	32(37.21)	0.592
FSGS, n(%)	31(27.93)	10(40.00)	21(24.42)	0.075
IgA nephropathy, n(%)	23(20.72)	3(12.00)	20(23.26)	0.094
Membranous nephropathy, n(%)	8(7.21)	1(4.00)	7(8.15)	0.544
Mesangioproliferative non IgA, n(%)	3(2.70)	1(4.00)	2(2.32)	
Crescentic GN, n(%)	3(2.70)	1(4.00)	2(2.32)	
Miscellaneous, n(%)	2(0.90)	0(0)	2(2.32)	

Table 5: Distribution of secondary glomerulonephritis (n=25).	
Type of secondary glomerular disease	**n(%)**
Immue-mediated GN (Lupus nephritis) Class I Class II Class III Class IV Class V	14(56.00) 1 2 2 7 2
Diabetic nephropathy	5(20.00)
GN associated with infectious diseases	4(16.00)
Renal involvement of Non-Hodgkin Lymphoma	1(4.00)
Renal Amyloidosis (AL- Amyloidosis)	1(4.00)

Table 6: Histologic patterns of primary nephrotic syndrome (n=79).	
Histologic patterns	**n(%)**
MCD	39(49.37)
FSGS	27(34.19)
IgA	4(5.06)
MN	8(10.12)
Mesangioproliferative non IgA	1(1.26)

Over time, the incidence of various primary GN may change within the same geographic area. High frequency of FSGS in our study may be due to the fact that more kidney biopsies are performed in the elderly and particularly in patients with diabetes mellitus suspected and primary glomerulopathy. Woo (2010) reviewed 2,586 renal biopsies and found that there was a decrease in mesangial proliferative glomerulonephritis and a dramatic increase in FSGS [9]. Additionally, our results showed that the prevalence of IgA was still high and associated with more severe level of renal function loss. In fact, this prevalence might be higher if higher incidence of urinary test screening in community and higher referral rate of patients with asymptomatic urinary abnormality to nephrologists for kidney biopsy. Our findings are in accordance with those of Chang in Korea (28.3%) [15].

In our study, the most common cause of secondary GN was lupus among young, female patients and diabetes mellitus among elderly patients. Other causes such as cancer were not common, probably due to the small size of study sample.

Our limitations of this study are the small size of study sample and the lack of electron microscope examination so that we could not be able to make diagnosis of thin basement membrane, to distinguish certainly secondary and primary FSGS, MPGN.

CONCLUSIONS

This retrospective study is the first systematic report of indications and of pathological pattern of biopsy-proven kidney disease in a large center in Vietnam. Our data showed that NS was the most common and asymptomatic urine abnormality was least common reasons for referral to our renal center for kidney biopsy. Primary glomerulopathy was most common cause of biopsy-proven kidney diseases. MCD, followed by FSGS, and IgA nephropathy were the most common forms of primary NS. Membranous nephropathy was still uncommon. Lupus nephritis was most common cause of secondary glomerular disease.

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Availability of data and materials

Please contact author for data requests.

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Authors' contributions

Bach Nguyen carried out the design of the study, performed kidney biopsy, and collected the data. Huynh Ngoc Linh and Tran Hiep Duc Thang examined the renal tissues. All authors read and approved the final manuscript

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