



Etiologies of Glomerular Diseases in Thailand: A Renal Biopsy Study of 506 Cases

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Background: The nationwide renal registry has not yet been organized in Thailand, and the literature contains no registry of renal pathologic finding across the Southeast Asian (SEA) countries in the modern era when electron microscopy (EM) is routinely available.

Objective: The aim of the present study was to examine the prevalence of renal pathology in Thai population

Material and Method: The authors revieThe authorsd the case file and renal biopsy specimens of King Chulalongkorn University Hospital to identify all adult native renal biopsy specimens received from January 2001 to December 2004, investigating prevalence and clinical and histological data. Biopsy of renal graft and in cases of trauma and tumors The authorse excluded. Most of the biopsy specimens obtained The authorse analyzed using light microscopy (LM), immunofluorescence (IF), and EM. Final diagnosis was made for each patient based on clinicopathologic correlations.

Results: A total of 506 native renal biopsies were processed during this period, 69.8 % were female and 30.2% were male. Their age average was 37 ± 14.2 (13-80) years. The most common indications for renal biopsy were nephrotic syndrome and SLE (36.8 %, 34.5 %, respectively), followed by asymptomatic hematuria/proteinuria in 10.9 % of patients. Secondary glomerular diseases were dominant against primary diseases in all but elderly age group (> 50 years), particularly LN. Among primary glomerular diseases, the prevalence of IgAN, focal segmental glomerulosclerosis, and membranous nephropathy were 31.0%, 24.9%, and 13.1%, respectively. The provisional clinical diagnosis was correct in three fourths (73.2%) of the SLE cases. Postbiopsy complications occurred in 3.3% (17/506). Gross hematuria was seen in 2.3% (12/506), and perinephric hematoma in 0.79%. Three of them required blood transfusion but none of them died and required an invasive procedure for resolution. The major complications were 2 folds less than regular prevalence (0.6% compared to 1.3%).

Conclusion: Although the data was collected from single center where EM is routinely performed, the authors believe that IgAN is the commonest primary GN in SEA countries. The authors are looking forward to seeing the nationwide registry data in Thailand and other SEA countries.

Keywords: Renal biopsy, Glomerular disease, Nephrotic syndrome

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Rapid advances in medicine and therapeutics have led to an increasing knowledge of diseases and the ways they affect the kidney. Important decisions

and pathogenesis insights are based on the interpretation of the changes in renal biopsies. The epidemiologic knowledge of renal disease provides initial therapeutic guidance in clinical practice. Hence, the renal biopsy has performed routinely in Thailand for more than 30 years; a nationwide renal registry has not yet been organized, and the literature contains no registry

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of renal pathologic finding among the Southeast Asian (SEA) countries in the modern era when electron microscopy (EM) is routinely available. Although, sparse data came from many Asian countries: Japan^(1,2), China⁽³⁾, Korea⁽⁴⁾, India⁽⁵⁾, United Arab Emirates⁽⁶⁾, etc but the spectrum of renal pathological changes may not be same among the SEA countries. The authors therefore report the epidemiologic data of renal biopsies containing EM information from single center (King Chulalongkorn University Hospital), which is one of the biggest hospitals in Thailand and is affiliated with the Thai Red Cross Society. It is located in the capital city, Bangkok, equipped with 1,200 in-patient beds.

Material and Method

Method

The authors reviewed the case file and renal biopsy specimens of King Chulalongkorn University Hospital to identify all adult native renal biopsy specimens received from the period that EM was available in our center, January 2001 to December 2004. A total of 506 native renal biopsies were process during this period; 7 of these were performed and received from outside private hospital. If the patients receive more than one biopsy, only the first or the final diagnosis was included in the data. Among the cases, 69.8 %weres female and 30.2% weremale. Their age average was 37 ± 14.2 (13-80) years. Most of the specimens were obtained from native kidney by using spring-loaded biopsy devices under ultrasound guidance. Open biopsy was done if this procedure was indicated for medical reasons. Biopsy of renal graft and in cases of trauma and tumors were excluded. All the biopsy specimens obtained were prepared and examined by the same group of clinicians and technicians. Analysis included light microscopy (LM), immunofluorescence (IF), and EM. EM was omitted when the diagnosis made by LM and IF was convincing. Final diagnosis was made for each patient based on clinicopathologic correlations.

To evaluate the incidence of renal diseases according to indications of biopsy, the authors categorized indications into 7 subgroups: 1) asymptomatic hematuria/proteinuria (including single and recurrent gross hematuria, as well as persistent microscopic hematuria; 2) nephrotic syndrome (defined by 24-hr urine protein ≥ 3.5 gm/day/1.73 m², UPCr ≥ 3 , or 4+ on dipstick; with or without edema); 3) rapidly progressive glomerulonephritis (including either nephritic syndrome or urinary abnormalities, together with acute renal failure); 4) renal dysfunction (defined by doubling of serum creatinine in both abrupt onset and insidious

onset, with or without oligo-anuria) of un-determining cause, 5) systemic lupus erythematosus (SLE), 6) diabetes with unusual renal manifestations, and 7) other non specified indications. The authors also subclassified the incidence of renal diseases according to age range into 3 groups 1) young adult (age between 15 to 35 years); 2) middle-aged adult (between 36-50 years; 3) old aged (more than 50 years) to.

The histological diagnosis were classified into two categories according to Richard Bright tradition: 1) primary glomerular diseases including minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), mesangiocapillary glomerulonephritis (MPGN), membranous nephropathy (MN), IgA nephropathy (IgAN), post-streptococcal glomerulonephritis (PSAGN), and non-IgA mesangial proliferative glomerulonephritis included cases with increased mesangial cellularity with negative IF for IgA with or without immune complexes in EM. 2) secondary glomerular diseases defined as the disease occur as part of a multisystem disorder such as lupus nephritis (LN), diabetic nephropathy (DN), deposition diseases (including light chain deposits, immunotactoid glomerulopathy, fibrillary glomerulopathy, post-infectious GN, and collagen type III depositions), cryoglobulinemia, Henrich-Schnelein purpura, vasculitis, anti-glomerular basement membrane disease, etc. Non diagnosed renal diseases included inadequate material, unclassified nephropathy, and end-stage kidney disease. Miscellaneous were non-glomerular diseases including benign nephrosclerosis, malignant nephrosclerosis, thrombotic microangiopathies, acute tubulointerstitial nephropathy, myeloma kidney, etc and glomerulopathies from toxic substances and preclampsia-eclampsia.

Statistical Analysis

Data were tested for normal distribution with the Kolmogorove-Smirnov test. The values are expressed as medians when the parameters did not fit into a normal (Gussian) distribution. The calculations were performed by using SPSS 11 for Window .

Results

Over 4 years, the authors recorded 506 renal biopsies from adult > 15 years. The number of case distributed according to age group was: 269 young adult (age 15-35 years), 149 middle age (36-50 years) and 88 old age (.50 years). In about half of the cases underwent renal biopsy because of nephrotic syndrome. The indications of renal biopsy are summarized



in Table 1. Nephrotic syndrome and SLE were the most frequent clinical syndromes which induced the nephrologists to perform renal biopsy (36.8 %, 34.5 %, respectively), followed by asymptomatic hematuria/proteinuria in 10.9 % of patients. The relative distribution of renal diseases according to patient's age group and indications of renal biopsy are demonstrated in Table 2 and 3. In some patients more than one clinical syndrome was found; the authors therefore collected a total of 536 clinical syndromes (for example NS associated with renal insufficiency). Declined glomerular filtration rate was presented in 42 patients (7.8%).

Forty-two biopsies (7.8%) were performed in patients presenting with RPGN. Most of the patients were classified as immune-complex associated GN which composed of IgAN (26.2%), post-infectious GN (19%), cryoglobulinemic GN (11.9%). Pauci-immune crescentic GN was accounted only 9.5% of the cases.

Primary and secondary glomerular disease was noted in 213, and 287 patients, respectively. There were 2 biopsies showing normal renal tissue which arbitrarily classified as miscellaneous groups. Secondary glomerular diseases were dominant in all but

Table 1. Clinical indications for renal biopsy in King Chulalongkorn University Hospital

Clinical diagnosis	Number of renal biopsies (%)
Asymptomatic hematuria/proteinuria	10.9
Nephrotic syndrome	36.8
Rapidly progressive glomerulonephritis	7.9
Renal dysfunction of un-determining cause	7.9
Diabetes with unusual renal manifestations	1.3
Systemic lupus erythematosus	34.5
Other non specified indications	0.8

Table 2. Percentage of glomerular diseases distributed by age group in patient presenting with nephrotic syndrome

Histopathologic diagnosis	Age 15-35 years N = 86 (%)	Age 36-50 years N = 63 (%)	Age > 50 years N = 47 (%)
MCD	19.8	6.3	10.6
FSGS	22.1	27.0	29.8
MN	7.0	20.6	14.9
MPGN	1.2	6.3	4.3
IgAN	23.3	12.7	6.4
Non-IgA mesangial proliferative GN	10.5	7.9	10.6
LN	9.3	3.2	8.5
DN	1.2	6.3	2.1
Post-infectious GN	4.7	4.8	2.1
Deposition diseases	0.0	1.6	4.3
Congänital glomerulopathies	1.2	0.0	0.0
Miscellaneous	0.0	0.0	2.1
Unknown	0.0	3.2	4.3

Table 3. Percentage of glomerular diseases distributed by age group in patient presenting with asymptomatic urinary abnormalities

Histopathologic diagnosis	Age 15-35 years N = 25 (%)	Age 36-50 years N = 21 (%)	Age > 50 years N = 12 (%)
MCD	0.0	0.0	8.3
FSGS	4.0	19.0	0.0
IgAN	80.0	47.6	41.7
Non-IgA mesangial proliferative GN	0.0	14.3	25.0
LN	4.0	0.0	16.7
DN	0.0	4.8	0.0
Congenital glomerulopathies	4.0	9.5	0.0
Miscellaneous	4.0	0.0	8.3
Unknown	4.0	4.8	0.0



elderly age group. Among the secondary disease, LN was the leading pathologic lesion in all age group, followed by post-infectious GN, diabetic nephropathy, and deposition diseases, respectively. The remaining secondary glomerular diseases such as, cryoglobulinemic GN, Henrich-Schönlein purpura, vasculitis, anti-glomerular basement membrane disease, pauci-immune crescentic GN, and other types of lesions contributed to a minority (17.1%).

IgAN and FSGS were the two commonest primary glomerular diseases. Both of which comprised half of the group, followed by MN (13.1%), non-IgA mesangial proliferative GN (13.1%), MCD (12.2%), post-streptococcal GN (2.3%), and MPGN (1.4%). The order was reorganized if the authors subcategorized primary glomerular disease by age range. In this regards, FSGS was the leading prevalence in middle and elderly adult, followed by MN similar to the prevalent data from European countries and the US. Alport disease was diagnosed in 1.8% of the cases.

The most common histologic lesions associated with primary nephrotic syndrome depended on age group (Table 4). IgAN was predominant in young adult but FSGS was in middle-aged and elderly adult. With no doubt, the prevalence of MPGN and congenital was decreasing across the age. Approximately 95% of the MCD patients entered remission after 4 months of steroid treatment but half of them remained in

remission after long-term follow up. On the contrary, MN (64.7%) and FSGS (34.5%) were resisted to steroid (Table 5). Only 2 cases of primary MPGN were available for evaluation of steroid treatment. All of which were steroid resistance.

In 177 patients (not including the 7 biopsy specimens that were inadequate or show normal finding), the nephrologists provided prebiopsy provisional diagnosis of lupus nephritis. The clinical diagnosis was correct in three fourths (73.2%) of the cases. In the remaining fourth, the pathologic diagnosis was different from the clinical provisional diagnosis. Most of them were IgA nephropathy (4.9%), followed by diffuse global sclerosis (3.8%), and FSGS (3.3%). Moreover, 2 of which included rather different disease, pauci-immune crescentic glomerulonephritis. The disease that is able to imitate most of glomerular diseases.

Seven diabetic patients biopsy performed because clinician suspected there were different biopsy lesions (for instance unexplained hematuria associated with NS). Only 2 out of 7 biopsies confirmed their clinical diagnoses which were IgAN, and pauci-immune crescentic GN. All of the remains revealed diffuse and nodular diabetic glomerulosclerosis with Kimmelstiel-Wilson nodule. Of interest, 2 of them were concomitant injured from AIN.

Postbiopsy complications occurred in 3.3% (17/506). Gross hematuria was seen in 2.3% (12/506),

Table 4. Percentage of primary glomerular diseases distributed by age group in patient presenting with nephrotic syndrome

Histopathologic diagnosis	Age 15-35 years N = 75 (%)	Age 36-50 years N = 45 (%)	Age > 50 years N = 37 (%)
MCD	21.3	8.9	16.2
FSGS	24.0	31.1	32.4
MN	8.0	31.1	18.9
MPGN	2.7	0.0	0.0
IgAN	29.3	17.8	10.8
Non-IgA mesangial proliferative GN	12.0	11.0	21.6
Congenital glomerulopathies	2.7	0.0	0.0

Table 5. Percentage of steroid responsiveness in distinct primary nephrotic syndrome

Histopathologic diagnosis	Complete remission (%)	Steroid dependence (%)	Steroid resistance (%)
MCD	36.4	59.1	4.6
FSGS	37.9	27.6	34.5
MN	17.6	17.6	64.7
IgAN	18.8	50.0	31.3
Non-IgA mesangial proliferative GN	37.5	50.0	12.5



and perinephric hematoma in 0.79%. Three of them required blood transfusion but none of them died and required an invasive procedure for resolution.

Discussion

The present report provides the epidermiologic data of adult renal diseases, diagnosed by native renal biopsy, in Thailand during the era that EM is available for assisting diagnosis. In no doubt, the incorporation of ultrastructural techniques should give additive information and make a clearer diagnosis. The most important role of EM in a diseased glomerulus is the search for discrete electron-dense “immune-type” deposits which help clinicians distinguish the immune-mediated from non immune-mediated glomerular diseases. Moreover, the EM is the only morphologic technique which pathologist uses to make specific diagnosis of hereditary nephropathies and rare deposition diseases.

Besides DM and SLE patients, most of the cases (83%) presented with renal failure or nephrotic range proteinuria. Only 16.8% of patients presented with asymptomatic hematuria or proteinuria, in contrast with the results from Spanish⁽⁷⁾, French⁽⁸⁾, and Japanese registries⁽¹⁾. This might imply that our renal biopsy was performed more frequently in the more severe of each nephropathy due to the late referral from general practitioners or low threshold of renal biopsy. Or it reflects true racial variation.

LN was the most common cause of secondary glomerular diseases far beyond any other secondary glomerular diseases in our center, particularly in young female. In the young adult, their prevalence surpassed IgAN's. This high prevalence is similar to the results from Australia⁽⁹⁾ and from other Asian countries such as China⁽³⁾, the United Arab Emirates⁽⁵⁾ but totally different from the US⁽¹⁰⁾ and South American⁽¹¹⁾ countries. It might indicate that the present report lacked knowledge about the size of the served population to calculate the exact incidence of the distinctive renal pathologies or Thailand is absent of strict national uniform indication of renal biopsies, at least in certain situations of NS and/or asymptomatic urinary abnormalities.

As the authors all expected, IgAN was a major cause of primary glomerular disease similar to the data from any other Asian country^(1, 3), notably among patient who presented with asymptomatic hematuria/proteinuria and RPGN. Of interest, IgAN also was the most common biopsy-proven renal diseases in patient presenting with NS.

Still, the presented findings comparing clinical and biopsy diagnoses suggest that a renal biopsy is needed for accurate diagnosis of renal diseases. In more than 90% of the patients in the present study, renal biopsy uncovered the cause of glomerular diseases, which in the majority of cases was a potentially treatable, although often severe, disease. In fact, it emphasizes the importance of setting up and maintaining a nationwide renal registry, and the need for a more aggressive nationwide policy towards kidney biopsies, especially in patients with asymptomatic urinary abnormalities, or with mild renal insufficiency. Periodic review of the data accrued should help identify the prevalence of the various glomerulopathies encountered in clinical practice in Thailand, leading focused research efforts on glomerulopathies prevalent in the region, and eventually resulting in substantial benefits in patient care.

Clearly, the patient population in the present study is not truly representative of the overall population in Thailand who develop renal disease because many of these patients, particularly those with clinical evidence supporting a diagnosis of ischemic or toxic ATN, obstructive nephropathy, acute pyelonephritis, and some cases of drug induced interstitial nephritis, do not undergo a renal biopsy and are treated on the basis of the clinical diagnosis. Moreover, the thresholds of renal biopsy in patients who present with glomerular syndromes in Thailand depend on availability of a renal pathologist, clinical practice guideline, and culture.

In conclusion, the presented data was collected from a single center where EM is routinely performed; the authors believe that IgAN is the commonest primary GN in SEA countries. The authors look forward to seeing the nation wide registry data in Thailand and other SEA countries.

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อุบัติการณ์ของโรคไตอักเสบที่ได้รับการวิเคราะห์ชิ้นเนื้อไตทางพยาธิวิทยาในประเทศไทย : รวบรวมผู้ป่วยจำนวนทั้งสิ้น 506 ราย

เกลิงศักดิ์ กาญจนบุษย์, ทรงเกียรติ หลิวสุวรรณ, วิภาวี กิติโกวิท, อัมภาศ ลิพนวนิชกุล, ยัยยศ อวิหิงสานนท์, เกื้อเกียรติ ประดิษฐ์พรศิลป์, สมชาย เขียมอ่อง, เกรียง ตั้งสง่า, วิศิษฐ์ สิตปรีชา

ไตอักเสบเป็นโรคที่พบได้บ่อยและเป็นสาเหตุสำคัญนำมาซึ่งภาวะไตวายอย่างเรื้อรังทั้งภายในประเทศและในต่างประเทศ ทั้งๆที่เป็นโรคที่สามารถรักษาให้หายขาดหรือชะลอการเสื่อมของไตได้หากได้รับการวินิจฉัยและรักษาอย่างถูกต้อง ทันทีที่ และจำเพาะเจาะจง ต้นเหตุของไตอักเสบชนิดนี้มีมากมาย การวินิจฉัยที่ถือว่าเป็นมาตรฐานในปัจจุบันคือ การเจาะชิ้นเนื้อไตเพื่อวิเคราะห์ทางพยาธิวิทยา (renal biopsy) แม้ว่าการวิเคราะห์ชิ้นเนื้อไตทางพยาธิวิทยาจะทำกันมานานต่อเนื่องหลายสิบปี แต่ยังไม่มีการรวบรวมอุบัติการณ์ของโรคภายในประเทศและในแถบภูมิภาคเอเชียอาคเนย์อย่างเป็นระบบ (nationwide registry)

รายงานฉบับนี้ถือว่าเป็นรายงานที่มีการรวบรวมยอดผู้ป่วยไตอักเสบจำนวนมากที่สุดในประเทศและในแถบภูมิภาคที่ชิ้นเนื้อของผู้ป่วยทั้งหมดได้รับการวิเคราะห์ทางพยาธิวิทยาอย่างสมบูรณ์ (ได้รับการตรวจด้วยกล้องจุลทรรศน์อิเล็กตรอน) รวมจำนวนผู้ป่วยทั้งสิ้น 506 ราย ในโรงพยาบาลจุฬาลงกรณ์ ตั้งแต่ วันที่ 1 มกราคม พ.ศ. 2544 ถึงวันที่ 31 ธันวาคม พ.ศ. 2547 ประกอบด้วยผู้ป่วยเพศชายจำนวน 153 ราย และเพศหญิง จำนวน 353 ราย มีอายุเฉลี่ย 37 ปี มูลเหตุสำคัญที่ทำให้อายุรแพทย์โรคไตเลือกเจาะเนื้อไตชิ้นเนื้อในผู้ป่วยเหล่านี้คือภาวะเนฟโรติก (36.8%) รองลงมาคือ สงสัยว่าโรค SLE จะลุกลามมายังเนื้อไตของผู้ป่วย (ร้อยละ 34.5%) พบอุบัติการณ์ของ secondary glomerular disease (GN) มากกว่า primary GN (287 ราย เทียบกับ 213 ราย) โรคที่เป็นสาเหตุสำคัญของ secondary GN คือ lupus nephritis คล้ายกับหลายรายงานจากประเทศในแถบเอเชีย ส่วนโรคที่เป็นสาเหตุสำคัญของ primary GN ก็คือ IgAN (ร้อยละ 31.0) รองลงมาคือ FSGS (ร้อยละ 24.9) และ membranous nephropathy (ร้อยละ 13.1) ซึ่งต่างจากรายงานที่ได้จากหลายประเทศในชาติตะวันตก และที่สำคัญพบอุบัติการณ์ของโรคที่เกี่ยวข้องกับภาวะการติดเชื้อลดลง

อายุรแพทย์โรคไตมักเลือกที่จะทำการวิเคราะห์ชิ้นเนื้อไตเมื่อผู้ป่วยมีอาการมากแล้ว ดังจะเห็นได้จาก ร้อยละ 83 ของผู้ป่วย (ไม่รวมผู้ป่วยที่ได้รับการตรวจเนื่องจากป่วยเป็นโรค SLE หรือ โรคเบาหวาน) จะได้รับการเจาะตรวจเมื่อมีอาการเนฟโรติก หรือเมื่อมีการทำงานของไตบกพร่องไปแล้ว พบผู้ป่วยเพียงร้อยละ 16.8 เท่านั้นที่แพทย์ทำการเจาะเนื้อไตเนื่องจากตรวจพบเพียงความผิดปกติของปัสสาวะ นอกจากนี้มีเพียงร้อยละ 29.8 ของผู้ป่วยที่มาพบแพทย์ด้วยอาการทางคลินิกของภาวะเนฟโรติกเท่านั้นที่ตอบสนองต่อสเตียรอยด์อย่างถาวร

แต่เป็นที่น่าสนใจคือพบภาวะแทรกซ้อนที่เกิดจากการเจาะเนื้อไตเพียงน้อย (เพียงร้อยละ 3.3) ในจำนวนนี้มีผู้ป่วยเพียง 3 รายเท่านั้นที่ต้องได้รับเลือด คิดเป็นร้อยละ 0.6 ไม่มีผู้ป่วยรายใดเลยที่ต้องเข้ารับการผ่าตัดแก้ไขหรือเสียชีวิต ผู้ป่วยทั้งหมดสามารถฟื้นตัวจากภาวะแทรกซ้อนได้ ซึ่งน้อยกว่ารายงานจากต่างประเทศ ที่มีอัตราการเกิดภาวะแทรกซ้อนอย่างรุนแรงร้อยละ 1.3 และเสียชีวิตร้อยละ 0.2

ด้วยเหตุที่วิเคราะห์ชิ้นเนื้อไตมีความสำคัญต่อการวินิจฉัยโรคและอุบัติการณ์ของภาวะแทรกซ้อนจากการวิเคราะห์ที่จำเป็นอย่างยิ่งที่จะต้องเร่งส่งเสริมให้มีการวินิจฉัยภาวะไตอักเสบแต่เนิ่น ๆ และควรมีการรวบรวมและตั้งฐานข้อมูลของประเทศ เพื่อพัฒนาการวิจัยภายในประเทศให้ก้าวหน้าทัดเทียมอารยประเทศต่อไปในภายภาคหน้า