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RESEARCH

NATIVE RENAL BIOPSIES PERFORMED IN OLDER ADULTS ARE INCREASING: TWELVE YEARS EXPERIENCE OF EGE UNIVERSITY

ABSTRACT

Introduction: Determination of the frequency and prevalence of biopsy proven nephropathies in older adults and adults is important for epidemiological studies.

Materials and Method: Predominant glomerulonephritis (GN) in native renal biopsies of adults and older adults (≥65 years) were evaluated.

Results: Among a total of 1702 renal biopsies (males 52%, ages 16-82, mean 40±15 years), 121 (7%) were performed in persons ≥65 years old. The mean age at the time of renal biopsy increased from 37.3±16.8 in 1996 to 44±16.1 years in 2009. The leading indications for biopsy in older and younger age groups were nephrotic syndrome (NS) (46.5% vs. 39.8% respectively), asymptomatic urinary abnormalities (20.9% vs. 33.4% respectively) acute renal failure (15.1% vs. 7.4% respectively) and hematuria (4.7% vs. 10.9% respectively). The etiologies of NS were amyloidosis, membranous GN and focal segmental glomerulosclerosis (FSGS) in both age groups. Primary GN was the predominant etiology in both age groups. Above 65 years, membranous (14.8%) and crescentic (9.9%) GNs were predominant while below 65 years IgA nephropathy (9%) was predominant. Among secondary GNs, amyloidosis (19%) and lupus nephritis (11.7%) were also predominant in the elderly and the younger persons respectively.

Conclusion: The current data represents the experience of a single center. Such registries will allow epidemiologic studies to answer several open questions regarding both prevention and treatment of nephropathies in different age groups.

Key Words: Aged; Biopsy, Fine-Needle; Glomerulonephritis.

ARAŞTIRMA

YAŞLILARA YAPILAN NATİV BÖBREK BİYOPSİLERİ ARTMAKTADIR: 12 YILLIK EGE ÜNİVERSİTESİ DENEYİMİ

ÖZ

Giriş: Yaşlı ve gençlerde biyopsi ile gösterilmiş nefropatilerin sıklığı ve prevalansı ile ilgili veriler epidemiyolojik çalışmalar için önemlidir.

Gereç ve Yöntem: Erişkin ve yaşlılarda (≥65 yıl) görülen glomerülonefritler (GN) incelenmiştir.

Bulgular: Toplam 1702 böbrek biyopsisi (%52'si erkek, yaş aralığı 16-82, ortalama 40±15, 121'i (%7) ≥65 idi. 1996-2009 yılları arasında böbrek biyopsisi sırasında yaş ortalaması 37.3±16.8'den 44±16.1'a yükselmişti. Yaşlı ve gençlerde biyopsi endikasyonları nefrotik sendrom (NS) (%46.5 ve %39.8) nefrotik olmayan proteinüri (%20.9 ve %33.4) akut böbrek yetmezliği (%15.1 ve %7.4) ve hematüri (%4.7 ve %10.9) idi. NS etiyolojisi her iki grupta amiloidoz, membranöz GN ve fokal segmental glomuloskleroz (FSGS) idi. Primer GN'ler her iki grupta da daha fazlaydı. 65 yaş üzerinde, membranöz (%14.8) ve kresentik (%9.9) GN'ler belirgin iken, 65 yaş altında IgA nefropatisi (%9) daha belirgindi. Sekonder GN'lerden amiloidoz (%19) yaşlılarda ve lupus nefriti (%11.7) gençlerde belirgindi.

Sonuç: Mevcut bulgular tek merkez deneyimini yansıtmaktadır. Bu tür kayıtlar değişik yaş gruplarında nefropatilerin önlenmesinde ve tedavisinde bir çok açık soruya yanıt aramada epidemiyolojik çalışmalara öncülük edebilir.

Anahtar Sözcükler: Yaşlı; Biyopsi; İnce-İğne; Glomerülonefrit.

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INTRODUCTION

Renal biopsy was introduced into regular clinical practice by Iverson and Brun in 1951 and since then it has been a useful tool in assessing the diagnosis, giving a prognosis and guiding the treatment of many renal diseases (1).

There is no strict definition of the term "older adults" but most gerontologists consider the age 65 as the chronological cut-off point between adulthood and older adulthood. Renal diseases, in general, become more common with aging, particularly due to urinary tract obstruction, infection and atherosclerosis. Glomerular diseases are also prevalent. The types of glomerular diseases observed in the older adults generally reflect those seen in the whole population. However, prevalence of certain conditions; renal complications of type 2 diabetes, amyloidosis, renal para-neoplastic syndromes and adverse effects of therapeutic agents may increase among the older adults. This contribution will specifically address glomerular diseases in the aged population and will focus on specific issues of geriatric care which need to be embraced by practicing nephrologists.

In this article we reviewed glomerular pathologies observed in renal biopsies of aged patients who later developed a glomerular disease, over a 12 year period in our center.

MATERIALS AND METHOD

This is a single center retrospective study concerning adults' native kidney biopsies at Ege University. From January 1996 to May 2009, a total of 1702 adult native renal biopsies were evaluated with the permission of pathology and nephrology departments. Renal biopsy cores were processed according to the standard techniques. Paraffin sections were prepared and stained with hematoxylin and eosin, periodic acid Schiff, Masson trichrome, Kongo red and Jones silver methenamine stains.

Renal biopsy specimens were analyzed with light and immunofluorescence microscopy. Only minimal changes were observed, the disease couldn't be specified and the specimens were probably classified under the group with normal biopsy findings due to the unavailability of electron microscopic evaluation.

Renal biopsy indications were categorized as follows:

(I) Nephrotic proteinuria defined as ≥3.5g/24h excretion of protein.

(II) Asymptomatic urinary abnormalities (AUA): persistent low grade proteinuria (<3.5g/24h) with or without microhaematuria.

(III) Isolated haematuria: presence of micro or macrohaematuria, without any proteinuria.

(IV) Nephritic syndrome: combination of haematuria, arterial hypertension and reduced renal function.

(V) ARF was defined as a sudden increase (several days to weeks) in serum creatinine of ≥0.3mg/dl (≥26.4 µmol/l) or ≥50% from baseline and/or reduction in urine output<0.5 ml/kg/hr for more than 6 hours.

(VI) CRF was considered when elevated serum creatinine persisted for >6 months and/or bilateral small kidneys or unilateral small single kidney was examined with radiological imaging techniques.

Renal diseases were classified in four major categories: primary glomerulonephritis (GN), secondary GN, tubulointerstitial nephropathies and chronic GN.

Primary GNs were classified as follows: focal segmental and proliferative glomerulonephritis with or without glomerulosclerosis (FSPGN), membranoproliferative glomerulonephritis (MPGN), diffuse proliferative glomerulonephritis (DPGN), mesangio proliferative glomerulonephritis (MesPGN), membranous glomerulonephritis (MGN) and focal segmental glomerulosclerosis (FSGS). Chronic GNs were defined as non specific sclerotic glomeruler lesions.

Data Analysis

Data were stored on a database Excel file. Qualitative variables were compared by Chi-square or by Fisher's test as appropriate. p-values< 0.05 were considered statistically significant. All analyses were performed using the SPSS statistical software package (Version 15; SPSS, Inc., Chicago, IL, USA).

RESULTS

Approximately 7450 (native and transplant) renal biopsies were performed at the Adult Nephrology, Renal Transplantation and Pediatric Nephrology Departments of Ege University. Transplant kidney biopsies (n=4250) and pediatric renal biopsies (n=1413) were excluded from the analysis. Due to inadequate data collection or insufficient sample material, a few biopsies (5%) were excluded and finally 1702 adult native renal biopsies were included.

The mean age at the time of renal biopsy was 40±15.3 years (range 16-82) and males were slightly more prevalent (51.7%) than females. From 1996 to 2009 mean age at the

time of renal biopsy increased from 37.3 to 44 years in a steady state (see figure 1). One hundred and twenty one (7.1%) with a median age of 69 (range 65-82) were in the older adults group. Five hundred and thirty five (31.4%) were middle aged (45-64 years) and 1046 (61.5%) were young (16-44 years).

In the older adults group and the adults group; nephrotic syndrome (NS) (46.5% vs. 39.8% respectively), asymptomatic urinary abnormalities (20.9% vs. 33.4% respectively), acute renal failure (15.1% vs. 7.4% respectively) and hematuria (4.7% vs. 10.9% respectively) were the mainindications for kidney biopsy.

Etiology of NS was amyloidosis (40% vs. 29.2%), MGN (22.5% vs. 15.56%) and FSGS (17.5% vs. 15.21%) in older adults and adults respectively (Figure 3). Membranous (14.8%) and crescentic (9.9%) GNs were predominant in older adults (p=0.03 and p=0.004 respectively). IgA nephropathy (9%, p= 0.008) was more prevalent in adults. The percentage of biopsies with normal histology under light microscope were 6.7% vs. 8.8 in older adults and adults respectively (p>0.05). The major cause of secondary glomerulonephritis was amyloidosis in older adults (19%, p= 0.002) and lupus nephritis (11.7%, p= 0.001) in adults (Table 1).

Diagnosis of secondary pathologies (systemic diseases), such as vasculitis, increased in time from 2.17% to 6.58%. Rates of chronic GN (from 3.18% to 7.89%) and TIN (from 1.92% to 5.26%) also increased. Among all primary pathologies, only the rate of MGN decreased (from 9.6% to 9.21%) in time (Figure.1).

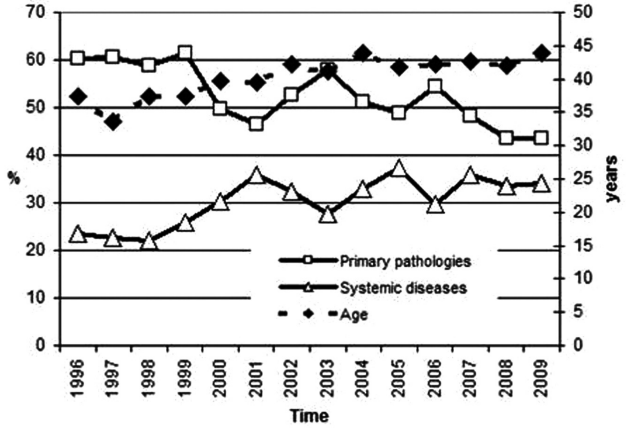

Figure 1— Annual percentage of primary and secondary renal pathologies.

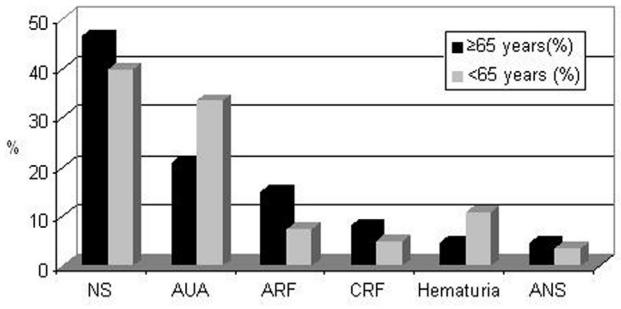

Figure 2— Renal biopsy indications.
NS: nephrotic syndrome, (AUA): asymptomatic urinary abnormalities, ARF: acute renal failure. CRF: chronic renal failure, ANS: acute nephritic syndrome.

DISCUSSION

This report provides information on occurrence of renal diseases diagnosed by renal biopsy in an aged population during a period of 12 years at Ege University. Renal biopsy registers can provide very important information on the epidemiology of renal diseases. However differences in geographical and ethnic characteristics and indications for renal biopsy with variations in categorization of the clinical syndromes and pathological classification among studies are sources of bias which hamper making comparisons and drawing accurate conclusions. The Italian national registry (2) considers only three clinical syndromes (urinary abnormalities, NS and acute nephritic syndrome), while the Spanish renal biopsy registry includes hypertension among the seven clinical syndromes

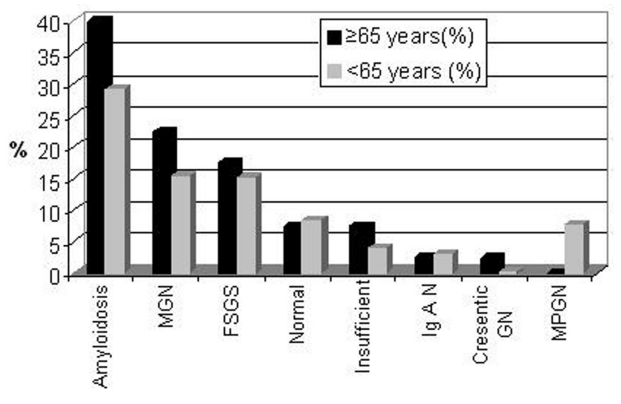

Figure 3— Etiology of nephrotic syndrome.
GN: Glomerulonephritis, MGN: Membranous glomerulonephritis, FSGS: Focal segmental glomerulosclerosis.

Table 1— Renal Biopsy Findings According to Age

	Age ≥65 years		Age <65 years		Total		p
	%	n	%	n	%	n	
Primary pathologies	**51.24**	**62**	**52.50**	**830**	**52.41**	**892**	**0.87**
Normal histology (light microscopy)	6.61	8	8.79	139	8.64	147	0.51
FSGS	9.92	12	10.31	163	10.28	175	0.98
Membranous GN	14.88	18	8.73	138	9.17	156	0.03
IgA Nephropathy	1.65	2	9.04	143	8.52	145	0.01
MesPGN	0	0	0.57	9	0.53	9	0.86
DPGN- Post infectious GN	4.13	5	3.73	59	3.76	64	0.98
MPGN	2.48	3	4.43	70	4.29	73	0.43
Crescentic GN	9.92	12	3.92	62	4.35	74	0.00
FSPGS	2.48	3	2.91	46	2.88	49	0.99
Systemic diseases	**31.40**	**38**	**30.93**	**489**	**30.96**	**527**	**0.99**
Amyloidosis	19.01	23	11.64	184	12.16	207	0.02
GP-AGBM	0.83	1	0.25	4	0.29	5	0.79
SLE	1.65	2	11.70	185	10.99	187	0.00
Diabetic nephropathy	2.48	3	1.64	26	1.70	29	0.75
Vasculitis	4.96	6	3.10	49	3.23	55	0.39
TMA-HUS	0.83	1	0.70	11	0.71	12	0.69
HT	2.48	3	1.33	21	1.41	24	0.52
Myeloma	0	0	0.51	8	0.47	8	0.92
Chronic GN	**5.79**	**7**	**5.19**	**82**	**5.23**	**89**	**0.94**
ATN	**1.65**	**2**	**0.76**	**12**	**0.82**	**14**	**0.60**
AIN	**1.65**	**2**	**0.44**	**7**	**0.53**	**9**	**0.86**
CIN	**0**	**0**	**0.25**	**4**	**0.24**	**4**	**0.67**
TIN	**3.31**	**4**	**3.61**	**57**	**3.58**	**61**	**0.93**
Insufficient material	**4.13**	**5**	**5.69**	**90**	**5.58**	**95**	**0.60**
Non diagnostic	**0.83**	**1**	**0.63**	**10**	**0.65**	**11**	**0.75**
Total	**7**	**121**	**93**	**1581**	**100**	**1702**	

FSGS: Focal segmental glomerulosclerosis, GN: Glomerulonephritis, MesPGN: Mesangio proliferative glomerulonephritis, DPGN: Diffuse proliferative glomerulonephritis, MPGN: Membranoproliferative glomerulonephritis, FSPGS: Focal segmental proliferative glomerulosclerosis, GP-AGBM: Good pasture-Anti glomerular basement membrane disease, SLE: systemic lupus erythematosis, TMA-HUS: Thrombotic microangiopathy-hemolytic uremic syndrome, HT: Hypertension, ATN: Acute tubular necrosis, AIN: Acute interstitial nephritis, CIN: Chronic interstitial nephritis, TIN: Tubulo-interstitial nephritis.

analyzed (3). Our indications for renal biopsy were grouped according to six clinical syndromes as described above. Histopathological diagnoses were grouped according to a combination of the Italian and Spanish methods.

In this study, we analyzed 1702 renal biopsies from native kidneys, starting from the year 1990, when percutaneous renal biopsies became standard practice in our clinic. Of the renal biopsies, 121 (%7) were performed in patients ≥65 years. Sanches et al. published a study of 2375 renal biopsies but only 2.6% of them were performed in patients older than 60 years of age (4).

In general, indications for renal biopsy in older adults and the entire population were similar. NS was found to be the most common indication for renal biopsy in older adults (5). We showed that NS, (46.5% vs. 39.8%); AUA, (20.9% vs. 33.4%); ARF, (15.1% vs. 7.4%) and hematuria (4.7% vs. 10.9%) were the major indications for biopsy in older adults and adults respectively.

Another study from Ege University Pediatric Nephrology Unit addressing the indications for renal biopsy performed by percutaneous technique reported the indications for children. Four hundred and fifty eight renal biopsies in 374 patients

(189 boys, 185 girls) aged one month-15 years (average: 7.4±4.1 years) during the period between January 1994 and December 2004 were evaluated. The most common renal biopsy indication was nephrotic syndrome in 175 (46.8%) of the cases (6). These data are in line with a Japanese study where nephrotic syndrome was found to be the most frequent clinical manifestation among 1850 cases (7). As expected, the incidence of acute or chronic renal failure increased significantly with age. Conversely, in the Italian registry, AUA was more common than nephrotic syndrome. This may be due to tendency of performing biopsy to asymptomatic hematuria or proteinuria (8).

Data from a survey of 12 published series, representing older adult patients with NS, were tabulated by Cameron as follows: MGN was observed in 37.3%, minimal change was observed in 12.6%, amyloidosis was seen in 11.8% and the others, FSGS, MPGN and diabetic nephropathy, were seen in 38.3% (9).

A study from the department of Nephrology, Gulhane School of Medicine, reviewed 632 patients who had undergone renal biopsy between 2000 and 2007. Thirty of these patients were 65 years or older. The most common indication for renal biopsy was acute renal injury and acute on chronic renal disease (53.3%), nephrotic syndrome (40%) and non-nephrotic proteinuria (6.6%) (10).

As for amyloidosis, 90% of them were AA amyloidosis, which was reported to be very frequent among secondary forms of GN, at a rate of 19% vs. 11.6% in older adults and adults respectively, pointing out the geographical characteristics of Turkey where Familial Mediterranean Fever is common (11). In a study from Italy carried out between 1996 and 2000, 373 amyloidosis cases were selected. In contrast to our results AL was the prevalent type: 237 (53.9%) were affected from AL (primary) amyloidosis, 104 from AA (secondary) amyloidosis and 6 from AF (heredofamilial) forms. In 26 cases the type of amyloidosis remained undetermined. Median age ranged between 63 and 65 years in all groups (12).

As the other causes of NS, MGN and FSGS rates were 22.5% vs. 15.56% and 17.5% vs. 15.21% in older adults and adults respectively (Table 1).

MG in the aged population is most often idiopathic; however it may also occur in association with other diseases, most notably malignant neoplasia or following exposure to certain drugs. All older adult patients with nephrotic syndrome found to have underlying membranous glomerulonephritis should undergo a careful and complete physical examination with imaging procedures with special attention to lungs, breasts, lymph nodes, skin and the prostate. Stools should be assessed for occult blood in at least three occasions, a standard chest x-ray (or computerized tomography of the chest) should be performed and a mammogram should be performed in females. A prostatic surface antigen should also be measured in males. Additional diagnostic studies are not indicated unless the preliminary evaluation is suspicious. The association between the malignancy and membranous glomerulonephritis may appear during, before or after the onset of nephrotic syndrome. The morphologic appearance of membranous glomerulonephritis in association with malignancy is no different from that found in the idiopathic disorder (13). In older adults, prostate and gastric adenocarcinomas were found among the 18 patients who were diagnosed as MGN. In addition to the other non specific treatments eight were given corticosteroids, six were treared with immunosuppressive agents (cyclophosphamide, cyclosporine or azathioprine) and one was treated with intravenous immunoglobulins.

Considering the experience of other authors (14) who reported gross hematuria in 5–7% or severe perirenal hemorrhage in 0.2–1.4% there was no age related risk regarding the post biopsy complications. We recorded clinically serious post-biopsy complications of gross hematuria or perirenal hematoma in 2 patients from the older adults group (%1.7) and 28 patients from the other group (1.6%).

Contrary to other reports (15) we did not observe a significant decrease in complication rates when the biopsy gun was used, but we do not know whether or not a smaller gauge needle was used in the gun. Although some authors (16) did not observe any serious complications using the biopsy gun, we believe that despite these newer devices, the risk of renal biopsy as an invasive procedure remains. USG-guided biopsy was predominant in our series but many biopsies are still performed under X-ray guidance throughout the world, despite the wide availability of USG. This may be the result of local policy, perhaps influenced by good personal experience with particular techniques. USG guidance was also reported to be predominant (85%) in Europe (1).

Renal biopsy is feasible and may be indicated in elderly patients, as long as contraindications are respected (17-18). We respect the frail older patients and in some cases we are conservative regarding biopsy. But in most cases histological diagnosis is necessary to clarify a clinical situation, confused by previous co-morbidities and may help us choose the appropriate therapeutic intervention. Glomerulonephritis in the elderly is not uncommon, is difficult to diagnose without histology, and often requires specific and sometimes aggressive therapies.

Although the present data represents the experience of a single centre, it may help design epidemiologic studies to answer several open questions in both prevention and treatment of nephropathies in older adults.

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