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Epidemiological Review of Kidney Biopsy during 30 years - Single Center Experience

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Abstract

Introduction. Renal biopsy represents a diagnostic method that provides an acurrate diagnosis and adequate treatment of different renal diseases. The first biopsy in our Center was done in June 1982, but it has been performing routinely since 1984. The aim of this study was to report the histopathological features of biopsy proven kidney disease during the past 30 years.

Methods. During 30 years, a total of 563 biopsies were performed, of which 530(94%) were succesfull. Data about gender, age, clinical syndrome and histopatological finding were collected from the medical records.

Results. The mean age of our patients was 48±11 years, 53% were man (No=272). In the first decade (1982-1994) we performed 118(mean age 50±13), in the second (1995-2004) 208 (mean age 46±14), and in the third decade (2005-2014) 189 renal biopsies (mean age 50±16). Mean number of glomeruli per biopsy was 18±11. There were only two serious complications. The most common clinical syndromes as indication for renal biopsy were: nephrotic proteinuria (41%) followed by asymptomatic urinary abnormalities (AUA-14.8%), chronic renal failure (CRF-13.8%), acute kidney injury (AKI-12.8%), nephritic syndrome (7.6%), systemic lupus erytematosus (SLE-4.5%), isolated haematuria (2.7% of the cases) and other (2.9%). The major histological groups identified were: primary glomerulonephritis (GN) (62.3%), secondary GN (21.2%), and other (16.5% of the cases). The most common primary glomerulonephritis (PGN) were focal segmental glomerulosclerosis-FSGS (19.4%) followed by IgA nephropathy-IgAN (18.8%), membranous GN-MGN (16.4%) and mesangial proliferation-MesGN (16%). Interstitial changes were present in 55% of biopsy samples in the first, in 66% in the second and in 63% in the third decade. Blood vessel changes were present in 39% of biopsy samples in the first, in 62% in the second and in 72% in the third decade.

Conclusions. The most frequent finding among PGN was mesangioproliferative GN (including IgAN, alltogether 34.8%) followed by FSGS and MGN. Apart from succesful biopsies, there are several aspects to be improved in the future including expanding indications and earlier procedure during the course of chronic kidney disease-CKD.

Key words: kidney biopsy, epidemiology, single center experience

Introduction

Renal biopsy represents a diagnostic method that provides acurrate diagnosis and also adequate treatment of different renal diseases. The first renal biopsy was performed in 1901, but its' usage as a routine procedure started in the 1950s [1,2]. Since glomerulonephritis (GN) is a relatively rare disease with a large number of subtypes, many nephrology centers are seeing a limited number of certain histological forms of glomerulonephritis annually. Therefore the collection of data for extended periods is of great help in the study of the epidemiology of GN. Establishment of national renal biopsy registers modeled on Italian or Spanish register, should be the main objective regarding understanding local GN epidemiology [3,4]. The aim of this single Center study was to report clinical syndromes at the time of renal biopsy and histopathological features over the past three decades.

Materials and methods

The first biopsy in our Center was done in June 1982, but it has been routinely performing since 1984. Over te last 30 years, a total of 563 biopsies were done. Data collected from medical records included gender, age, clinical syndrome at the time of renal biopsy and histopathological finding. For better epidemiological analysis, the re-

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porting period was divided into three decades: Ist decade (1982-1994), IInd decade (1995-2004) and IIIrd decade (2005-2014).

Clinical and laboratory parameters observed at the time of renal biopsy were reported as follows:

1. nephrotic proteinuria: >3.5 g/24h;
2. asymptomatic urinary abnormalities (AUA): persistent low-grade proteinuria (<3.5 g/24 h) with or without microhaematuria;
3. chronic renal failure (CRF): elevated serum creatinine for more than 6 months;
4. isolated haematuria: presence of micro-or macrohaematuria, without any proteinuria;
5. nephritic syndrome: combination of haematuria, arterial hypertension and reduced renal function (sCr >110 mmol/l);
6. acute kidney injury (AKI) defined as sudden and rapid deterioration of renal function;
7. systemic lupus erythematosus (SLE): already diagnosed SLE with onset of renal symptoms;
8. other; in some patients, more than one clinical syndrome was found but the most prominent was taken as dominant clinical syndrome.

Histopathological analysis of the biopsy samples was based on light microscopy and immunohistochemistry except during the period 1992-1999, when it was made only on the basis of light microscopy (71 biopsy samples, 13.7%).

Histological diagnoses were clasiffied into three main categories:

1. Primary glomerulonephritides (PGN) including membranous GN (MGN), focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), membranoproliferative GN (MPGN), minimal change disease (MCD), crescentic GN (CGN, defined as CGN not fulfilling the criteria for systemic disease), proliferative endocapillary GN (PEGN), mesangioproliferative non-IgA GN (MesGN) and unclassified GN.
2. Secondary Glomerulonephritides (SGN) including immune-mediated GN such as systemic lupus erythematosus (SLE), Henoch–Schonlein purpura (HSP), necrotizing vasculititis (NV) and Goodpasture's syndrome (GPS); GN caused by dysgammaglobulinemia or paraproteinemia such as renal amyloidosis (AM), light-chain deposit disease (LCDD), myeloma kidney (MM) and essential mixed cryoglobulinemia; GN associated with infectious diseases (non-streptoccocal GN, endocarditis, shunt GN and others); metabolic disorders, particularly diabetic nephropathy (DN).
3. Other types of GN including vascular diseases benign and malignant nephroangiosclerosis (NAS), hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (HUS/TTP), renal scleroderma and cortical necrosis; acute and chronic tubulointerstitial nephritis (TIN) and acute tubular necrosis; hereditary nephropathies, i.e. Alport syndrome (AS), Fabry's disease, thin basement membrane glomerulopathy (TBM) or other hereditary diseases; end-stage renal disease (ESRD) of undetermined cause; miscellaneous and unclassified nephropathies and normal histopathological findings.

Pediatric patients were not included since our Center does not cover pediatric level of care.

Statistical calculations were performed using the SPSS 20.0 software program. The Kolmogorov-Smirnov test was performed for making assumptions about the distribution of data which were expressed as percentages for categorical values and mean values for continuous variables. Chi-square test and one-way ANOVA test were used to analyze the differences in various baseline variables between the groups of patients. Chi-square (or Fishers' exact test where appropiate) followed by post-hoc analysis of adjusted residuals were used for analysis of variable differences overall and between three decades. A p-value <0.05 was considered statistically significant, and z-value >1.96.

Results

Out of 563 biopsies, 530 were successful (515 primary and 15 re-biopsy) and 33 were unsuccessful due to inadequate samples. We have recorded only two serious complications that were related to the procedure: one led to splenectomy and one to nephrectomy. During the first 12 years, we made about 118 biopsies and then the

Table 1. General data about patients and biopsies performed in our Center during the past three decades (re-biopsies excluded)

	Total	Decades (years)			p***
		1982-1994	1995-2004	2005-2014	
Biopsy No	515	118	208	189	
Gender (men/women)	272/243 (53%/47%)	61/57 (52%/48%)	111/97 (53%/47%)	100/89 (53%/47%)	0.958
Age, years (mean±SD)	48±11	50±13	46±14	50±16	0.163
Glomeruli No / biopsy	18±11	10.5±6.1	16.8±9.1	22.3±11.4	<0.00
Interstitial changes (yes/no)*	260/149 (63%/37%)	18/15 (55%/45%)	124/64 (66%/34%)	118/70 (63%/37%)	0.433
Blood vessel changes (yes/no)**	259/141 (65%/35%)	11/17 (39%/61%)	114/71 (62%/38%)	134/53 (72%/28%)	0.002

* data were available for 409 biopsies, ** data were available for 400 biopsies, *** according to Chi-square test or one-way ANOVA where appropriate

number increased to about 200 biopsies in the next two decades. Of all patients, 272 (53%) were men, and 243 (47%) women; mean age 48±11 years. Mean age at the moment of renal biopsy was slightly decreasing from 50 years in the first decade to 46 years in the second and than in the third it was almost similar as in the first. The average number of glomeruli per biopsy was significantly increasing over the years (10.5 in the first decade, 16.8 in the second and 22.3 in the third) and interstital changes were present in 63.6% of biopsy samples with the peak in the second decade (66%). Blood vessel changes were found in 39% of biopsy samples in the first, in 62% in the second and in 72% in the third decade with a statistical significance (χ^2=12.66) (Table 1).

The most common clinical syndromes at the time of renal biopsy are presented in Table 2. During the entire period of observation, nephrotic syndrome was the most common indication for renal biopsy (211 patients, 41%) followed by AUA (15%), CRF (14%) and ARF (13%). Over time, the representation of individual indications for renal biopsy changed significantly (χ2=24.88; p=0.036) due to increase in the number of patients with a biopsy performed for nephrotic proteinuria and chronic renal failure (in the second and the third decade) and also lupus in the third decade and significantly decreased number of biopsy in patients who had isolated hematuria in the second and the third decade. Number of patietns with AUA also decreased but without statistical significance (Table 2).

Table 2. Clinical syndromes at the time of renal biospy in past three decades (re-biopsies excluded)

	Total	Decades (years)		
	No 515	1982-1994	1995-2004	2005-2014
Nephrotic proteinuria	211(41%)	49(41.5%)	70(33.7%)*	92(48.7%)*
Asymptomatic urinary abnormalities	76(14.8%)	21(17.8%)	32(15.4%)	23(12.2%)
Chronic renal failure	71(13.8%)	13(11.0%)	39(18.8%)*	19(10.1%)
Nephritic syndrome	39(7.6%)	10(8.5%)	19(9.1%)	10(5.3%)
Isolated hematuria	14(2.7%)	6(5.1%)	4(1.9%)**	4(2.1%)**
Acute kidney injury	66(12.8%)	14(11.9%)	31(14.9%)	21(11.1%)
Systemic lupus erythematosus	23(4.5%)	3(2.5%)	7(3.4%)	13(6.9%)*
Other	15(2.9%)	2(1.7%)	6(2.9%)	7(3.7%)

*significantly increased vs. other decades, **significantly decreased vs. other decades

Table 3. Presence of major groups of biopsy proven renal diseases in past three decades (re-biopsies excluded)

Group	Total	Decades (years)		
	No 515	1982-1994	1995-2004	2005-2014
Primary glomerulo-nephritides (PGN)	321(62.3%)	83(70.3%)	126(60.6%)	112(59.3%)*
Secondary glomerulo-nephritides (SGN)	109(21.2%)	19(16.1%)	38(18.3%)	52(27.5%)**
Other	85(16.5%)	16(13.6%)	44(21.2%)	25(13.2%)

*significant decrease vs. first decade, **significant increase vs. first decade

Table 3 shows the presence of the three major biopsy proven groups of renal diseases. The most common finding was PGN in 62.3% of patients. During the years this number changed (χ^2=12.01; p=0.017) due to a significant decrease in the prevalence of PGN from 70.3% in the first to 59.3% in the third decade. At the same time the presence of SGN significantly increased from 16.1% to 27.5% of patients.

Table 4. Presence of primary glomerulonephritis in past three decades (re-biopsies excluded)

Primary glomerulonephritides	Total	Decades (years)		
	No 321	1982-1994	1995-2004	2005-2014
Membranous GN (MGN)	53(16.4%)	16(19.3%)	16(11.8%)	22(19.6%)
Focal segmental glomerulosclerosis (FSGS)	62(19.4%)	15(18.0%)	28(22.0%)	19(17.0%)
IgA nephropathy (IgAN)	61(18.8%)	12(14.4%)	29(22.8%)	20(17.9%)
Membranoproliferative GN (MPGN)	25(7.7%)	4(4.8%)	9(7.1%)	12(10.7%)
Minimal change disease (MCD)	12(3.7%)	7(8.4%)	2(1.6%)	3(2.7%)
Crescentic GN (CGN)	31(9.9%)	5(6.0%)	13(10.2%)	14(12.5%)
Proliferative endocapillary GN (PEGN)	22(6.9%)	8(9.6%)	11(8.7%)	3(2.7%)
Mesangioproliferative non-IgA GN (MesGN)	51(16.0%)	15(18.0%)	20(15.7%)	16(14.3%)
Unclassified GN	4(1.2%)	1(1.2%)	0(0%)	3(2.7%)

Among PGN, the most common finding was mesangial PGN (IgA and non-IgA 34.8%) followed by FSGS (19.4%) and MGN (16.4%). During the years, the number of patients with different histologically confirmed PGN did not differ significantly (χ^2=25.135; p=0.067). Although without statistical significance, the number of patients with MCD, PEGN and MesGN decreased and the number of patients with histologically confirmed IgAN, MPGN and CGN increased (Table 4).

Among 515 biopsies, SGN was found in 109 biopsy samples and during the years the number significantly increased from 19 to 52 (Table 3). Over the time, incidence of different SGN did not change significantly (χ^2= 0.281; p=0.991). Most of them were immune-mediated GN (60.7%). Diabetic nephropathy was confirmed in 15 patients with increase in incidence over the years (14% overall; decade I: 11.8%; decade II: 15.1%; decade III: 13.7%) (Figure 1).

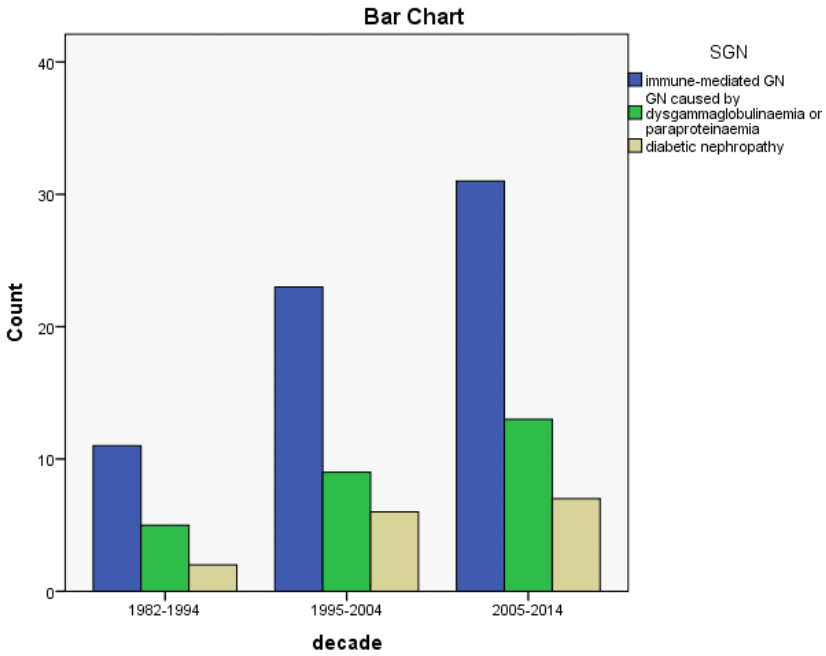

Fig. 1. Number of different SGN in the past three decades (No=109)

Table 5 represents the incidence of GN from the third category. Over time, there were no statistically significant changes in overall incidence in different types of these GNs (χ^2=10.461; p=0.401) although TIN finding decreased over time (25% in the first, 14% in the second and 7.7% in the third decade) and ESRD increased (6.2% of biopsy samples in the first decade and then increased up to 23.3% and 19.2% in the second and third decade, respectively). Vascular nephropathy is the major finding in this category (25.0% in the first, 34.9% in the second and 30.8% in the third decade).

Table 5. Presence of non-primary and non-secondary GN

Variable	Total	Decades (years)		
	N^0=85	1982-1994	1995-2004	2005-2014
Vascular diseases	27(31.8%)	4(25%)	15(34.9%)	8(30.8%)
Tubulointerstitial nephritis (TIN)	12(14.1%)	4(25%)	6(14.0%)	2(7.7%)
Hereditary nephropathies	2(2.4%)	0(0%)	0(0%)	2(7.7%)
End-stage renal disease (ESRD)	16(18.8%)	1(6.2%)	10(23.3%)	5(19.2%)
Miscellaneous	19(22.4%)	4(25%)	9(20.9%)	6(23.1%)
Unclassified nephropathies	9(10.6%)	3(18.8%)	3(7.0%)	3(11.5%)

Discussion

This report provides insight in the diagnosis obtained by renal biopsies performed in a single Center for more than 30 years. There were few serious complications and a small number of glomeruli per sample indicating the efficiency of the method applied in our Ccenter. We found a slight predominance of male patients and the mean age at the moment of renal biopsy was 48 years. According to some other reports, male patients were also bioptied more frequently than female (Romanian data-51.5%; Clinical Center Serbia-51.2%; Pisa, Italy-59%; Czech data-57.9%; Turkish data-55%). The mean age at the moment of renal biopsy was almost one decade higher in our patients than in that reported by others (two Romanian Centers-38.5±15.2; Clinical Center Serbia-

39.1±13.8 years, Turkey-40.8±14.6 years) (5-9). This difference can be explained by different attitudes regarding the biopsy of the elderly.

The main clinical syndrome as indication for renal biopsy in our patients was nephrotic proteinuria (41%), followed by AUA (14.8%), CRF (13.8%) and AKI (12.8%). Our result is similar to that from other registries and studies [4-6,8,9]. Some differences could be explained by the differences in local policies regarding kidney biopsy and by different understanding/interpretation of overlaping clinical syndromes as the main indication for renal biopsy. Also, some of the studies included pediatric patients which may explain the difference in age between our and their findings.

Our data are in concordance with other reports regarding the incidence of PGN and SGN (3,5-8,10). In our study PGN was found in 62.3% of patients and over the years this number decreased from 70.3% in the first to 59.3% in the third decade. At the same time the presence of SGN increased from 16.1% to 27.5% of biopsy samples. Simillar data have been shown in Chinese single center study where PGN desreased from 78.3% in 1985 to 66.8% in 1999 while SGN increased from 21.7% to 33.2% of biopsy samples [10].

The most frequent PGN in our patients was FSGS (19.4%) followed by IgAN (18.8%), MGN (16.4%) and MesGN (16%). Altogether, the mesangial proliferation was the most common finding (IgAN and MesGN, 34.8%). Schena *et al.* also reported that IgAN (36.9%) and FSGS (21.7%) were the most frequent PGN [3]. Single center experience from the Nephrology Clinic, Clinical Center Serbia also showed that the majority of patients had mesangial proliferation (IgAN 12.2% and non-IgAN 25.1%) followed by FSGS and MGN with the same percentage (both 18.9%) [6]. Spanish register also revealed that IgAN (15.2%) and FSGS (10%) were the most common PGN as well as Autralian data where IgAN participated with 34.1% of all PGN followed by FSGS (16.9%). According to data from Finland, IgAN was found in 34.9% of biopsy samples, followed by MesGN (11.6%) and MGN (11.6%) [4,11,12]. Chinese single center study analyzed over 13,000 biopsies and IgAN and MesGN had the highest incidence (IgAN 45.2%, MesGN 25.6%). On the other hand, Romanian investigators have shown that MPGN was the most common PGN in their patients (29.4%), followed by MesGN (incuding IgAN, 28.9%) and FSGS (11.5%). Also they reported that annual prevalence of MPGN was constantly decreasing during the study period (from 1995 to 2004). They agreed with the French authors' hypothesis that the socioeconomic conditions are strongly related to MPGN prevalence and that improvement in income, sanitation, social and medical infrastructure are followed by a decrease in MPGN [5,13]. In our group of patients MPGN had a constant increase in incidence over the years (from 4.8% to 10.7%) despite the fact that our country was under economic sanctions in the second decade, but not at the end of the study period and these 10.7% in the last decade can be still compared to data from some western European countries such is Italy [3]. According to Czech data IgAN accounted for 34.5% of all PGN, followed by MCD (12.5%) and MesGN (11.3%). Turkish register revealed somewhat different results since MGN was the most frequent PGN with prevalence of 28.8%, followed by FSGS (19.3%) and IgAN (17.2%) [9]. This finding could be explained by their indications for renal biopsy where 57.8% of patients (vs. ours 41%) underwent renal biopsy due to NS. It is well known that FSGS is the most common cause of NS.

According to our report, immune-mediated GN was the most common SGN. The incidence in our group was 60.7% while in the Czech register it was 71.6% and in the Chinese report over 90%.

In the group of patients with non-PGN non-SGN, vascular nephropathy was the most common finding (31.8%), followed by miscellaneous (22.4%), ESRD (18.8%) and TIN (14.1%). In the study of Naumovic *et al.* VN was also the most frequent finding (40.1%) followed by TIN (28%) and miscellaneous (13%) non-PGN non-SGN [6]. According to the Romanian register, 48% of patients from this group were 'miscellaneous' followed by VN (31%) and TIN (21%) [5]. The small numbers of TIN could possibly be explained by the fact that diagnosis of TIN is based mainly on clinical data and by procedures that are less invasive than renal biopsy.

One of the limitations of this study is its retrospective design. The novel biopsy analyses include more precise data (index of chronicity, index of activity, different scoring systems), however these data could not be compared over decades. In addition, therapy, follow-up and patients' outcome are not provided by this analysis.

Conclusion

In conclusion, we have shown that primary and secondary GNs have similar incidence and the similar distribution of major histological forms to other European countries. The most frequent PGN was mesangioproloferative GN (including IgAN, alltogether 34.8%), followed by FSGS and MGN. Apart from succesful biopsies, there are several aspects to be improved in the future including expanding indications and earlier procedure during the course of CKD.

Conflict of interest statement. None declared.

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