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ORIGINAL ARTICLE

Clinical and Pathologic Analysis of Kidney Damage in Patients With Nephrotic Syndrome in the Republic of Srpska

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Abstract

Background / Aim: Nephrotic syndrome (NS) is a clinical syndrome characterised by massive proteinuria > 3.5 g in 24 h urine, hypoalbuminaemia, hyperlipidaemia and oedema. Aim of this study was to determine the aetiology and frequency of kidney diseases that occur as the cause of NS in adults in the Republic of Srpska and the progression of renal insufficiency, disease outcomes and efficacy of applied therapy.

Methods: The retrospective study included patients aged 18 to 80 hospitalised between 2014 and 2018 due to clinically and laboratory-manifested NS. In patients with suspected primary glomerular disease, a kidney biopsy with immunofluorescent dyeing was performed. The first examination involved hospital admission and the next check-up six months after the first hospitalisation. Basic clinical parameters were followed: creatinine, clearance creatinine, albumin, total protein, cholesterol, total protein in 24 h urine and microscopy of urine during the first hospitalisation and repeated same laboratory findings on control. The progression of kidney failure during this period was assessed, as well as the efficacy of immunosuppressive therapy.

Results: In primary NS category membranous glomerulonephritis (MGN) was present at 40.7 % of patients, followed by focal segmental glomerulosclerosis (FSGS) 21.7 %, membranoproliferative glomerulonephritis (MPGN) 11.9 % and IgA glomerulonephritis (IgAN) 11.9 %. Nephroangiosclerosis was verified as the most common cause of secondary NS with 28.8 % and lupus nephritis 21.2 %, followed by ANCA-associated GN (11.5 %) and diabetic nephropathy (11.5 %). Thirty-four patients (21 %) died during the follow-up. Thirty-four patients (18.6 %) progressed to end stage renal disease during the five-year follow-up.

Conclusion: The pathology of kidney disease in older patients is often very complex; therefore, a kidney biopsy should be conducted at an early stage of kidney disease for the purpose of obtaining an accurate diagnosis, determining appropriate treatment and thus improving the prognosis of the patient.

Key words: Nephrotic syndrome; Aetiology; End stage renal disease; Follow-up; Outcome.

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Introduction

Nephrotic syndrome (NS) is one of the most common syndromes in nephrology, but at the same time it is challenging for nephrologists in terms of making a timely diagnosis and treatment. It is defined as an increase in protein over 3.5 g in 24 h urine with the advent of hypoalbuminaemia, oedema and hyperlipidaemia. Diseases that cause NS are generally categorised into those

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that primarily include the kidney (primary glomerular diseases) and those that secondary lead to kidney disease (secondary nephrotic syndrome). Studies show that NS aetiology in adults varies on many factors such as gender and race, but there are differences in geographic distribution as well. Focal segmental glomerulosclerosis (FSGS) appears as the most common cause of NS adults in the world.[1, 2] The Italian, Spanish and Japanese registries cite membrane nephropathy (MN) as the most common cause of NS is in the examined regions.[3-5] In terms of racial affiliation, FSGS is most common. Epidemiological studies have shown that patients with NS are vulnerable to a wide variety of adverse events: end stage renal disease (ESRD), thromboembolism, infection, malignancy, cardiovascular disease and all- cause mortality.[6] Immunosuppressive therapy is main treatment modality for patients with primary NS as suggested by clinical guidelines of primary NSs.[7] Systematic reviews of randomised controlled trials on immunosuppressive therapy in patients with MN, the most extensively studied glomerulonephritis (GN) in primary NS, clarified that some immunosuppressive drugs reduced all-cause mortality and risk of ESKD, although the number of trials with a high-quality design was relatively small and most trials did not have adequate follow-up and enough power to assess the prespecified definite outcomes.

The aim of the present cohort study was to clarify the incidence of major clinical outcomes in 177 patients with NS during the 5-year follow-up period. The outcomes of interest were remission and relapse of proteinuria, deterioration in kidney function (50 % and 100 % increases in serum creatinine level and ESKD), CVD, all-cause mortality and other adverse events associated with immunosuppressive therapy, including infection, diabetes, arteriovenous thrombosis, aseptic osteonecrosis and peptic ulcers. The results of the present study provide pivotal information to determine the clinical goals of the treatments for primary NS.

Methods

The research was conducted as a retrospective cohort study that included 177 respondents aged 18 to 80 who were hospitalised for clinical and laboratory manifestations of NS from 2014 to 2018. For the study, the consent of the Independent Ethics Committee of the Institute (EO) (No 01-9-291-2/18) was obtained on 07.06.2018. In most patients, kidney biopsies with immunofluorescent colouring were performed. The analysis of kidney biopsies was conducted by a pathologist admission in the University Clinical Centre of the Republic of Srpska (UCC RS) Banja Luka. The entire clinical properties, histological markings, laboratory results and parameters of monitoring each patient were collected for further analysis. The study included respondents who did not have an indicative kidney biopsy and have been treating with symptomatic therapy and been monitoring progression of kidney insufficiency.

Kidney biopsy was performed by a nephrologist, under real-time ultrasound control with a patient in a lying position. The preferred place to get kidney biopsies was the lower region of the left kidney. An automated biopsy gun was used for the biopsy and biopsies measuring 16 G or 18 G ensured the biopsy sample contained at least ten glomerulus.

Diagnostic criteria and pathological classification

Biopaths that were pathohistologically (PH) verified as GN were classified according to 1990 WHO criteria. Kidney biopsy samples were also processed and routinely coloured with haematoxylin and eosin (H&E), periodic acid-Schiff reaction (PAS), methenamine periodic acid Schiff (MPAS) or Masson's trichrome thaw (Masson) for subsequent light microscopic testing. Immunofluorescence dyeing was carried out with IgA, IgG, IgM, C3, C4, C1q, Fib and kappa and lambda light chains. Electron microscopy was not routinely performed.

Histological categories were classified as follows: Primary GN (PGN), which included minimal disease change (MCD), FSGS, membrane nephropathy (MN), IgA nephropathy (IgAN), membranoproliferative GN (MPGN), anti-glomerular basement membrane (GBM) GN. Further analysis was carried out by patients divided into four groups arbitrarily according to age at the time of the kidney biopsy (15-30, 31-45, 46-60 and ≥ 61).

Clinical data analysis

The following data was collected: gender, age, clinical and laboratory data, pathological diagnosis, treatment, clinical responses to treatment and tracking data. Basic laboratory parameters were monitored: creatinine, creatinine clearance,

serum albumins and total proteins, cholesterol, total proteins in 24 h urine and microscopy of urine during the first hospitalisation and repeated same laboratory after six months. Patients were collected according to data from the information system on admission to the hospital although some of them were already on therapy for NS and not all had nephrotic proteinuria. Due to the small sample and heterogeneous immunosuppressive therapy, it was not possible to adequately determine the degree of remission and draw appropriate conclusions, but the mortality and survival of the kidneys in these patients were determined.

Kidney survival was defined as the time until the first of any of the following events: the onset of dialysis, kidney transplantation or estimated glomerular filtration rate (eGFR) falls to < 15 mL/min at any point during follow-up after which treatment with replacement kidney function continues.

Statistical analysis of data

All of the study data was collected in a standard EXCEL database and the statistical analysis was conducted using commercial statistical software SPSS 18. The descriptive statistics parameters were presented as the mean ± standard deviation (SD), 95 % confidence interval (CI) and median. The statistically significant difference was assessed at a minimum level of $p < 0.05$. The normality of the distribution of continuous parameters was performed using the Kolmogorov-Smirnov test. Depending on the results of this test, the statistical significance between the groups was checked by the application of the Student t-test (alternatively the Mann-Whitney U-test). Some variables were represented in the frequency of certain markings (categories) and the statistical significance of the differences was determined by the application of the Chi Square test (Fisher test in case of expected frequencies < 5).

Results

Table 1 displays the general characteristics of the examined population.

Out of 177 respondents with NS, 124 had kidney biopsy. In 119 respondents, they were diagnosed with PH. The patient population included 108 men and 69 women and an average age was 51.97 ± 14.86 (range 18-80 years). The median results of laboratory tests for proteins in urine and albumins in the blood was 2.30 ± 0.94 g/24 h urine and 28.17 ± 8.66 g/L, respectively. The average value of the creatinine in the serum was 180.63 ± 148.17 (µmol/L), the value of total proteins in the serum was 53.57 ± 10.46 (g/L), cholesterol 7.01 ± 3.24 (mmol/L), serum triglycerides 2.64 ± 1.44 (mmol/L). Primary GN was more common than secondary GN (83 : 70). In 36 patients, haemodialysis treatment was indicated and 4 patients had kidney transplants. Microhaematuria was present in 106 patients (Table 2).

Table 1: Parameters of patients with nephrotic syndrome

Parameters	Result
Age	51.97 ± 14.86
Sex: male : female	108 : 69
Primary GN: Secondary: Other	83 : 70 : 18
Biopsy: yes : no	124 : 53
Haemodialysis: yes : no	36 : 139
Transplantation (yes : no)	4 : 170
Hypertension (yes : no)	147 : 30
Total proteins in serum (g/L)	53.57 ± 10.46
Albumins in serum (g/L)	28.17 ± 8.66
Creatinine in serum (µmol/L)	180.63 ± 148.17
Cholesterol in serum (mmol/L)	7.01 ± 3.24
Triglycerides in serum (mmol/L)	2.64 ± 1.44
Proteinuria (g / 24 h urine)	2.30 ± 0.94
Macrohematuria (yes : no)	106 : 71

GN: glomerulonephritis;

Table 2: Mortality and end-stage renal disease (ESDR) in patients with nephrotic syndrome

Parameters	Primary GN	Secondary GN	p-value	OR (95 % CI)
Diseased				
Yes	7	20	0.001	0.235 (0.093- 0.594)
No	79	53		
ESDR				
Yes	8	15	0.049	0.397 (0.158 -0.998)
No	78	58		

OR: Odds ratio; CI: Confidential interval; GN: glomerulonephritis;

Distribution of primary and secondary glomerulopathy

Figure 1 is showing that within the primary NS category membranous GN (MGN) was present in 40.7 % of patients, followed by FSGS 21.7 %, MPGN 11.9 % and IgAN 11.9 %. Other pathological types of primary GN were MCD 6.8 % and anti GBM GLN (1.7 %). Nephroangiosclerosis was verified as the most common cause of secondary NS with 28.8 % and lupus nephritis 21.2 %, followed by ANCA-associated GN (11.5 %) and diabetic

nephropathy (11.5 %). Multiply myeloma as the cause of secondary NS was verified in 5.8 % of respondents (Figure 2).

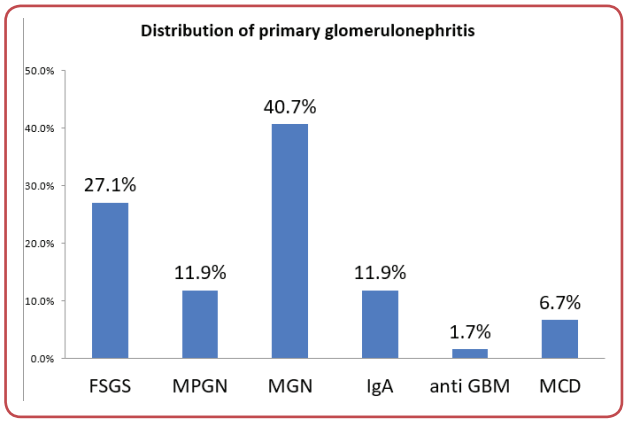

Figure 1: Distribution of primary glomerulonephritis
FSGS: focal segmental glomerulosclerosis; MPGN: membrane proliferation glomerulonephritis; MGN: membrane glomerulonephritis; IgA: immunoglobulin A nephropathy; Anti GMB: anti glomerular basement membrane glomerulonephritis; MCD: minimal lesion disease.

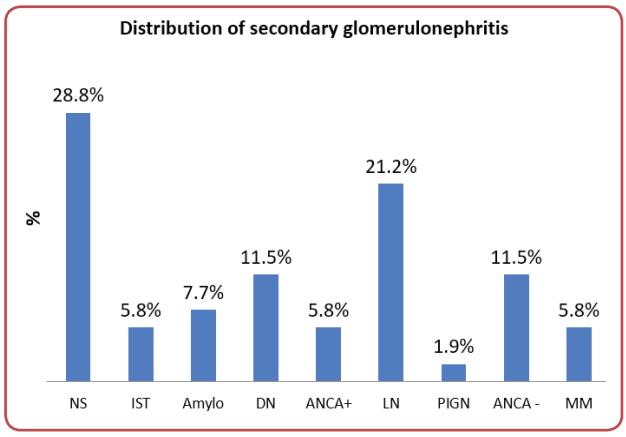

Figure 2: : Distribution of secondary glomerulonephritis
NS: nephroangiosclerosis; IST: chronic interstitial nephritis; Amylo: amyloidosis; DN: Diabetes Nephropathy; ANCA+: ANCA positive glomerulonephritis; ANCA-: ANCA negative glomerulonephritis; LN: lupus nephritis (LN), PIGN: post-infective glomerulonephritis; MM: multiply myeloma.

Mortality rate

Thirty-four patients (21 %) died during the follow-up. Deaths were more likely in patients with secondary NS and those aged 60 and above (Table 2) ($p < 0.001$ log-ranked test). The observed mortality was higher than those predicted for age and gender of the general population (Table 3). In patients with primary NS, the observed five-year mortality rate relative to the population was 8.9 % (95 % CI 0.0 %-4.6 %) versus 0.9 % (0.8 %-1.0 %) in patients under 60 and 38.33 % versus 9.4 % in those over 60 (Table 4). In primary NS, cardiovascular causes accounted for 28 % of deaths, compared to 18 % in the general population. Thirty-six patients (19.45 %) progressed to ESKD. The ESKD incident in 5 years was primary compared to secondary NS showed static significance relative to the general population (compared to WHO data) with high statistical significance p = 0.397, 95 % CI (0.158-0.998) (Table 3).

Table 3: Mortality of patients with nephrotic syndrome relative to the general population

Groups	Mortality	Whole group	p-value	OR (95 % CI)
NEFRO study	11	123	0.158	0.628 (0.332-1.196)
WHO	142	1000		

OR: Odds ratio; CI: Confidential interval;

Cause of death

Patients with primary NS were most likely to die from cardiovascular diseases, which were noted as the leading cause of death in 15 patients. Patients with secondary NS were relatively less likely to die from cardiovascular disease and were more likely to have died of cancer as the main cause of NS. Vein thromboembolism was recorded as one of the causes of death but is more often cited as a contributing factor to mortality in secondary NS.

ESRD

Thirty-four patients (18.6 %) progressed to ESKD during the five-year follow-up. ESRD during monitoring was more common in patients with secondary than primary NS. There was a competitive risk between progression in ESKD. In patients aged < 60, the risk of ESKD was higher than the risk of death. In patients aged 60 and over, the risk of mortality was higher than those of ESKD in patients with primary NS and equivalent to the risk of ESRD in patients with secondary NS. This competitive risk, ESRD rates (with 95 % CI) in 5 years

Table 4: Clinical and laboratory parameters related to end-stage renal disease (ESDR) in patients with nephrotic syndrome

Parameter	ESRD		p-value	OR (95 % CI)
	Yes	No		
Haemoglobin (g/L)				
< 120	15	40	0.026	2.859 (1.110-7.365)
≥ 120	8	61		
Phosphataemia (mg/dL)				
< 1	1	5		
1 - 2	7	71		
> 2	13	19		
Cholesterol (mmol/L)				
< 5	9	27	0.036	2.889 (1.039-8.030)
≥ 5	9	78		
Diabetes mellitus				
Yes	14	25	< 0.0001	4.445 (1.927-10.252)
No	16	127		

were 8.4 % (4.9 %-11.7 %) in primary NS and 35.1 % (24.3 %-44.5 %) in secondary NS. Progression to terminal kidney insufficiency correlates with lower basic eGFR risk of progression in ESRD (HR 2.4, 95 % CI 1.6-3.6), with lower haemoglobin < 120 g/L, as well as hyperphosphatemia and hypercholesterolemia and in patients with diabetes mellitus (Table 4).

Table 5: Distribution of renal insufficiency determined by creatinine clearance levels (Ccr) in patients with nephrotic syndrome

Ccr (mL/min)	N	%
0-15	5	3.79
16-30	22	16.67
31-45	17	12.88
46-60	17	12.88
> 60	71	53.79
Total	132	100.00

Table 6: Value of total proteins in 24 h urine on first hospitalisation and on control examination in patients with nephrotic syndrome

Total proteins in 24 h urine	First examination		Control examination	
	N	%	N	%
≤ 3.5 g	52	29.2	60	33.7
> 3.5 g	124	69.7	26	14.6
Total	176	98.9	86	48.3
No data	2	1.1	92	51.7
Total	178	100	178	100

Table 7: Impact of intervention on the value of creatinine clearance levels (Ccr) and proteins in 24 h urine (BIURET) in patients with nephrotic syndrome

Parameter	Mean	SD	t	df	p
BIURET - BIURET2	3.660	5.272	6.437	85	0.000
Ccr - Ccr2	3.575	34.052	0.793	56	0.431

A statistically significant decrease in the value of the biuret (from AS = 7.18 to AS = 3.52) is verified, p < 0.0005. The value of the eta square (0.33) indicates that the impact of the intervention is high. Values: BIURET: g/24 h urine, Ccr: mL/min

Patients were also categorised according to creatinine clearance levels (Ccr) in five groups: Ccr > 60 mL/min had 53.79 % of patients, Ccr 46-60 had 12.88 %, Ccr 31-45 mL/min had 12.88 % of patients, 16-30 mL/min 16.67 % and Ccr < 15 mL/min 3.78 % of patients (Table 5). Data on total protein in 24 h urine verified that 69.7 % of patients had nephrotic protein supplements at the beginning of the study and after the therapy was applied in 6 months, nephrotic proteinuria was 14.6 % indicating the efficacy of applied therapy (Table 6, 7).

Discussion

There is not a single national kidney biopsy registry in Bosnia and Herzegovina. Epidemiological data from different centres inevitably has geographical, racial and time variations. It is also possible to change the pattern of representation of GN within the same country is likely due to infection control, environmental pollution, increased awareness of disease and changes in life expectancy.

This study analysed the histopathological spectrum of diseases in patients with NS different ages and genders who underwent kidney biopsies. Of 124 patients with NS in this study, who were subjected to kidney biopsies, the most common primary GN was MN (40.7 %), then MPGN (11.9 %), the most common secondary cause of NS was nephroangiosclerosis 28.8 %, followed by lupus nephritis 21.2 %, diabetic nephropathy 11.5 %, and ANCA negative GN. A similar study was conducted in China,[8] 1,523 patients with NS were included and MN (20.7 %) was singled out as the most common cause. Similar studies in Spain, Italy and the United Arab Emirates reported that MN was the leading cause of the NS, however, the data was mainly from the 1990s. Therefore, it can be assumed that the MCD still occupies a significant part of the NHS in the last decades.[13] However, recent studies have found that the frequency of FSGS is gradually increasing world-wide which can be confirmed by this study as well.

IgAN was observed in 11.9 % of all adult patients in the present study, this finding is in line with other studies in India. However, IgAN was the most common type of glomerulopathy in other studies in China.[9,10] However, the prevalence of diagnosis varies with age. FSGS was the most common pathology in younger adults up to the age of 45. After that, MGN took the lead, followed by amyloidosis. Without the results of a kidney biopsy, treatment can be ineffective and in patients there would be progression of kidney weakness. Patients undergo kidney biopsies in the early stages of the disease according to prescribed indications in order to obtain an accurate pathology diagnosis.

The results of this study also suggest that patients with primary NS who receive appropriate immunosuppressive therapy may achieve full or PR. By test of paired samples, statistically significant reduction in the value of proteinuria in 24 h urine (from AS = 7.18 to AS = 3.52), p < 0.0005 was verified. The value of the eta square (0.33) shows

that the impact of the intervention was large, ie that immunosuppressive therapy has led to a positive effect in terms of reducing proteinuria in 24 h urine which is one of the parameters of slowing the progression of the underlying disease. In this research, MN (24.7 %) was the most common and clinically significant primary GN diagnosed in the group of older patients, followed by FSGS 27.1 % and IgAN (11.9 %). As the most common secondary glomerulopathy, data was recorded for lupus nephritis 21.2 %, diabetic nephropathy 11.5 % and ANCA negative GN.

MGN was the most common pathological type in older adults and a small part of MGN has been associated with malignant diseases and the use of specific drugs. Such findings underscore the need for a more detailed examination of kidney biopsies obtained from older people diagnosed with MN.

Limitation of the study

The study's deficiencies are a relatively small number of respondents. Therefore, the results cannot clearly show the specific spectrum of glomerular diseases that prevail in adults with NS. Besides, in the study was a significant percentage of patients with diabetes mellitus that did not have a kidney biopsy. In patients diagnosed with diabetic nephropathy, histological kidney analysis rarely provides additional information for treatment decisions. The limitation was the inability to perform electronic microscopy, as well. The main reasons for this were the unavailability of the method in our centre and the unavailability of another facility in which the patient could be referred for the same purpose.

Conclusion

The pathology of kidney disease in older patients is often very complex; therefore, a kidney biopsy should be conducted at an early stage of kidney disease for the purpose of obtaining an accurate diagnosis, determining appropriate treatment and thus improving the prognosis of the patient.

Acknowledgements

None.

Conflict of interest

None.

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