

ORIGINAL ARTICLE

CLINICAL AND PATHOHISTOLOGICAL CHARACTERISTICS OF LUPUS NEPHRITIS IN PEDIATRIC AND ADULT POPULATION

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Summary

Introduction: Systemic lupus erythematosus (SLE) is an autoimmune disease, characterized by abundant production of antibodies, deposits of immune complexes, and activation of the complement system, which disrupts the integrity and function of many organs, including the kidney. Although the frequency of SLE is less common in children, affected children develop lupus nephritis (LN) significantly more often, while in adults with SLE, LN occurs in 23% of cases, more often in males.

Aim: The aim of this study was to analyze clinical parameters (gender, frequency of LN as the first manifestation of SLE, proteinuria, and serum creatinine values) and pathohistological parameters (frequency of LN classes, activity and chronicity index values, immunoglobulin deposit intensity and complement components at immunofluorescence, and blood vessel lesions) in the pediatric and adult populations of LN patients.

Material and methods: The study included 218 biopsy samples of kidney tissue. Patients were divided into two groups: patients under 18 years of age (n=35) and those over 18 years of age (n=183).

Results: Mean values of serum creatinine in pediatric population (71.6±16.4 μmol/l) were statistically significantly lower (p<0.001) than in adults (115.5±64 μmol/l). Leukocyte interstitial infiltration was statistically significantly higher in the adult group (p=0.003). The average value of the chronicity index (p=0.002), as well as the tubulointerstitial parameters that determine it (tubular atrophy (p<0.001) and interstitial fibrosis (p=0.011)) were significantly higher in adults with LN. Leukocyte infiltration (p=0.003) and myoelastofibrosis (p<0.001) of blood vessels were statistically significantly more common in the adult population.

Conclusions: Serum creatinine values are significantly higher in the adult population of LN. Pathohistological findings indicate that glomerular LN lesions do not differ significantly with regard to activity and chronicity index in pediatric and adult populations, but the degrees of tubulointerstitial lesions are significantly higher, both in terms of activity and in terms of chronicity within the adult groups. Myoelastofibrosis and hyalinization of blood vessels as well as leukocyte infiltration of blood vessels, are statistically significantly more common in the adult population.

Keywords: Systemic lupus erythematosus, Lupus nephritis, pediatric population, adult population



INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by a distinctive production of large amounts of polyclonal antibodies, deposits of immune complexes, and activation of complement system, which disrupts the integrity and function of many organs, including the kidneys (1). SLE most often occurs in women in the reproductive period, while 10%-20% occur in the pediatric population (2). In the pediatric population, SLE usually occurs between the ages of 12 and 18, rarely before the age of 10, and even less often before the age of 5 (3-5). Lupus nephritis (LN) is usually not the first manifestation of SLE, but as many as 75% of patients with SLE develop some form of kidney lesion during the course of diseases (6). Kidney involvement is crucial in terms of morbidity and mortality due to the possible occurrence of chronic kidney disease (CKD), which in its terminal stage requires dialysis and/or transplantation (7). Although the incidence of SLE is lower in children, they are significantly more likely to develop lupus nephritis (42% of SLE patients), while in adults with SLE, lupus nephritis occurs in 23% of cases, more often in male patients (8-9).

According to the criteria established by the *American College of Rheumatology* (ACR 1997), the occurrence of proteinuria greater than 0.5g per 24 hours, or semi-quantitatively higher than 3+, and/or the presence of cylindruria in patients with SLE can be defined as the development of lupus nephritis (10). However, the gold standard for the diagnosis of LN is a renal biopsy, therefore the World Health Organization in 2018, based on morphological findings (optical-microscopic), classified lupus nephritis (ISN / RSP Code) in 6 classes: Class I - lupus nephritis with minimal lesions, Class II- mesangio-proliferative LN, Class III- focal proliferative LN, class IV- diffuse proliferative LN, class V- membranous LN and class VI - advanced sclerosing LN (11). Studies have shown that class IV LN is the most common pathohistological type, both in pediatric and adult populations, with prevalence of about 60% (12-14). Defining the classes of lupus nephritis, as well as determining the presence of active and chronic lesions in the glomeruli and tubulointerstitium, have an important prognostic significance (11). Therefore, in 2018, the activity index and chronicity index were introduced as mandatory parameters in the classification of lupus nephritis (11). These indexes are based on changes in the interstitium (inflammation, tubular atrophy, interstitial fibrosis), and not only changes in the glomeruli (15-17). Studies have shown that the indexes of activity and chronicity of LN increase with class, so classes IV, V, VI of LN could have similar index values. Class II LN has lower index values, and class IV has the highest activity variability (18). In patients with SLE, various alterations of renal vessels can be seen on glomerular capillaries, arterioles and/or renal arteries. Immune deposits are most commonly found in class IV LN (19).

In several cases, neutrophils infiltration is present, which may be accompanied by fibrinoid necrosis of glomerular basement membrane (20). In addition to the above mentioned morphological characteristics important for the diagnosis and classification of LN, there is a significant and characteristic finding of immunofluorescence (IF), which in these patients is often characterized by the presence of "full-house" phenomenon. This phenomenon implies that all routinely tested antibodies (IgA, IgG, IgM, C3, C1q, kappa, lambda) are positive for IF findings with moderate and/or strong intensity (++/+++), (11).

The aim of this study was to analyze clinical parameters (distribution by gender, frequency of LN as the first manifestation of SLE, values of proteinuria and serum creatine) and pathohistological parameters (frequency of LN classes, activity and chronicity index values, immunoglobulin deposit intensity and complement components immunofluorescence and blood vessel lesions) in pediatric (children and adolescents-younger than 18 years) and adult (adults-older than 18 years) populations of LN.

MATERIAL AND METHODS

The study used material from the Institute of Pathology of the Faculty of Medicine University of Belgrade. The study involved 218 renal biopsies diagnosed between 2003 and 2020. Clinical and laboratory data recorded at the time of biopsy data were collected from medical records. Patients were divided into two age-based groups: patients up to 18 years of age (n=35) and those older than 18 years (n=183).

Activity and chronicity indexes were determined based on the ISN/RPS criteria presented in **Table 1** (11).

Statistical analysis was performed using IBM SPSS software, version 26.0. We used the χ^2 test, Fisher's test, Student's *t*-test, and *Mann-Whitney U* test, and $p < 0.05$ was considered statistically significant.

RESULTS

Clinical parameters

In the group of patients consisting of children and adolescents, the mean age was 13.9 ± 2.6 years (median 14 years, range 6 to 18 years). In the adult population, the mean age was 37.9 ± 13.1 years (median 36 years, range 19 to 74 years).

Details of the clinical characteristics of patients with LN in the adult and pediatric population are shown in **Table 2**. Our study population was composed of 24.3% (n=53) males and 75.7% (n=165) females. Among males, 14.3% (n=5) were patients younger than 18 years, and 26.2% (n=48) were patients older than 18 years. In the female population, 85.7% (n=30) patients belonged to

Table 1. Criteria for determining the index of activity and chronicity of lupus nephritis lesions.

Activity index	Definition	Score
Endocapillary hypercellularity	Endocapillary hypercellularity in <25% (1+), 25% –50% (2+), or > 50% (3+) of glomeruli	0-3
Neutrophils/karyorrhexis	Neutrophil and/or karyorrhexis infiltration in <25% (1+), 25% –50% (2+), or > 50% (3+) of glomeruli	0-3
Fibrinoid necrosis	Fibrinoid necrosis in <25% (1+), 25% –50% (2+), or > 50% (3+) of glomeruli	(0-3)x2
Hyaline deposits	Wire loop lesions and/or hyaline thrombi in <25% (1+), 25% –50% (2+), or > 50% (3+) of glomeruli	0-3
Cellular/fibrocellular crescents	Cellular and/or fibrocellular crescents in <25% (1+), 25% –50% (2+), or > 50% (3+) of glomeruli	(0-3) x 2
Interstitial inflammation	Interstitial leukocytes in <25% (1+), 25% –50% (2+), or > 50% (3+) in the cortex	0-3
Total		0-24
Chronicity index	Definition	Score
Total glomerular sclerosis	Total glomerular sclerosis in <25% (1+), 25% –50% (2+), or > 50% (3+) glomeruli	0-3
Fibrous crescents	Fibrous crescents in <25% (1+), 25% –50% (2+), or > 50% (3+) glomeruli	0-3
Tubular atrophy	Tubular atrophy in <25% (1+), 25% –50% (2+), or > 50% (3+) glomeruli	0-3
Interstitial fibrosis	Interstitial fibrosis in <25% (1+), 25% –50% (2+), or > 50% (3+) in the cortex	0-3
Total		0-12

the pediatric group and 73.8% (n=135) of patients were adults.

It is known that LN may be the first manifestation of SLE. In our study, 34 patients had LN as the primary manifestation, and among them, 16.5% (n=30) were older than 18 years.

Although it was observed that the average value of proteinuria in children and adolescents on average was lower (2.5±2.1g/24h) compared to the average value of proteinuria in the adult population (7.2±6g/24h), the difference was not statistically significant, most likely due to the small number of patients from the group of younger subjects.

Mean values of serum creatinine in pediatric population (71.6±6.4 µmol/l) were statistically significantly lower (p <0.001) than the values in the adult population (115.5±64 µmol/l).

Pathohistological parameters

The distribution of pathohistological parameters is shown in detail in Table 3. Among the examined pathohistological parameters, which determine the LN activity index, glomerular lesions did not differ significantly in pediatric and adult populations, but the value of the

intensity of interstitial infiltration by leukocytes was higher in the adult group and covered mainly between 25-50% of the interstitium (p=0.003). The mean values of the chronicity index, as well as the tubulointerstitial parameters that determine it (tubular atrophy and interstitial fibrosis), were statistically significantly higher in adult LN (Table 3).

LN was associated with changes in blood vessels in both pediatric and adult populations. It was noticed that leukocyte infiltration and myoelastofibrosis of blood vessels were statistically significantly observed in the adult population. Necrosis of medium size blood vessels was observed only in the adult population (Table 3).

The frequency of classes did not significantly differ in pediatrics and adults. It was noticed that class IV LN was the most common pathohistological form of the disease in both examined populations. On the other hand, the majority of class V LN 21.3 (n=39) was detected in adult population, and one patient with class VI LN belonged to the same group (Table 3).

The absence of a “full-house” immunofluorescent finding was observed in 25 patients, of whom 15.6% (21/25) belonged to the adult LN population. On the other hand, a very similar distribution of positive full-house immunofluorescence findings was observed in

Table 2. Clinical parameters in patients with lupus nephritis.

	Children and adolescents	Adults	p	
Gender [n (%)]	Male	5 (14.3%)	48 (26.2%)	0.135
	Female	30 (85.7%)	135 (73.8%)	
Primary manifestation [n (%)]	no	30 (88.2%)	152 (83.5%)	0.495
	yes	4 (11.8%)	30 (16.5%)	
Serum creatinine [average value±SD]	71.6±16.4	115.5±64	<0.001*	
Proteinuria [average value±SD]	2.5±2.1	7.2±6	0.282	

Table 3. Pathohistological parameters in patients with lupus nephritis.

		Pediatrics [average value ± SD] [N (%)]	Adults	P
ISN/RPS activity and chronicity indexes				
<i>Activity index</i>		6.1±3	5.7±3	0.407
Endocapillary hypercellularity		1.9±1	1.9±0.7	0.745
Neutrophils/karyorrhexis		1.1±1	1±0.9	0.536
Fibrinoid necrosis		0.9±1.2	0.7±1	0.178
Cellular/fibrocellular crescents		0.6±0.8	0.7±1.3	0.696
Hyaline deposits		0.7±0.9	0.5±0.9	0.187
Interstitial infiltration		0.7±0.9	1.2±0.9	0.003*
<i>Chronicity index</i>		1.1±1.9	2±1.7	0.002*
Total glomerular sclerosis		0.3±0.7	0.5±0.7	0.098
Fibrous crescents		0.1±0.4	0.1±0.3	0.549
Interstitial fibrosis		0.3±0.7	0.7±0.7	0.011*
Tubular atrophy		0.4±0.6	0.9±0.7	<0.001*
Immunofluorescence (IF)				
IgA		2.2±1	1.9±1	0.235
IgG		2.3±0.4	2.2±0.9	0.687
IgM		2±0.9	1.8±0.9	0.229
C1q		2.1±1	1.9±0.9	0.177
C3		2.5±0.8	2.3±0.8	0.185
“Full-house” IF findings	no	4 (14.8%)	21 (15.6%)	0.923
	yes	27 (85.2%)	114 (84.4%)	
Myoelastofibrosis and hyalinization of blood vessels	not present	24 (70.6%)	47 (26.6%)	<0.001*
	present	10 (29.4%)	130 (73.4%)	
Infiltration of blood vessels	not present	27 (82%)	81 (46%)	0.002*
	present	7 (18%)	96 (54%)	
Necrosis of medium-size blood vessels	not present	34 (100%)	167 (94.4%)	0.157
	present	0 (0%)	10 (5.6%)	
ISN/RPS lupus nephritis classification				
Class I		1 (2.9%)	2 (1.1%)	0.153
Class II		8 (22.9%)	23 (12.6%)	
Class III		6 (17.1%)	19 (10.4%)	
Class IV		18 (51.4%)	99 (54.1%)	
Class V		2 (4.9%)	39 (21.3%)	
Class VI		0 (0%)	1 (0.5%)	

* -statistically significant difference;

these two groups of subjects, so the differences were not statistically significant p=0.923 (Table 3).

DISCUSSION

Lupus nephritis (LN) can lead to chronic kidney failure (CKF) and is one of the most serious manifestations of systemic lupus erythematosus (SLE) (7). Bearing in mind that SLE is more common in female population, studies indicate that LN is more common in men with SLE

(21,22). In a cohort of our subjects consisting of patients with LN, a significantly higher incidence was observed in female patients (male to female ratio was 1:3). Females were more frequent, and the ratio between the genders in the adult population was the same as in the cohort of all patients (1:3), while in the pediatric population the incidence of girls was six times higher than boys (1:6).

It was noticed that LN can be the primary manifestation of SLE up to 80% of cases in the pediatric population (23,24), while in the adult population the primary manifestation of LN in SLE is significantly rarer (35%–50%)

(3). The results of our study indicate a significantly lower incidence of LN as the primary manifestation of SLE in both populations of subjects (12% pediatric and 16% adult).

In our study, the value of serum creatinine was significantly higher in the adult population, but it is generally known that the values of serum creatinine are higher in the population of healthy adult individuals (25), as well as the frequency of comorbidities (hypertension and diabetes) that may contribute to the damage of kidneys and an increase in serum creatinine (26). Serum creatinine is not of great importance in terms of diagnosing LN, but a progressive increase in serum creatinine is associated with a poorer course of the disease (27-29). Also, serum creatinine is used as a parameter in the calculation of eGFR, (30) and it has been shown that lupus nephritis patients have lower eGFR values in the adult population (14). In the lack of data on the body height of pediatric patients, we were unable to determine their eGFR, and statistical analysis was not possible despite the existence of eGFR data in the adult group.

Proteinuria is also an important laboratory parameter in the process of diagnosing LN, although it does not have great specificity. The decline in proteinuria after therapy predicts a good further course of the disease (27-29). In our study, children and adolescents had on average lower values of proteinuria but compared to the values observed in the adult populations, a statistically significant difference was not observed. Our results are in accordance with the previously published data (14).

The histopathological analysis itself is of great importance, because it directly influences the definition of therapy and determines the prognosis (7). Pediatric population is at a higher risk of active LN development, based on activity index parameters (3). Although the values of the activity index and its parameters were not statistically significantly higher, a higher value of the parameters can be observed in the pediatric population. The chronicity index is statistically significantly higher in the adult population, which is due to the higher values of the score of tubular atrophy and interstitial fibrosis. However, studies have shown that the activity index has been shown to be a relatively weak indicator of further impaired renal function because lesions are potentially reversible and patients themselves respond differently to the same therapy (15,17,31,32). Certain studies have shown that the chronicity index correlates with the outcome of the disease only in class III LN (33).

Previous studies have indicated that among LN, class IV has the highest incidence (43% in pediatrics and 67% in adults). Although class II is the rarest in general population, among patients under the age of 18, class II accounted for 25% of all cases, while its frequency is lower in the adults with SLE and accounts for only 2.5%. Classes III and V have the same frequency in total population (15). In pediatric population, class III is present in 10%

of cases, and in the adult population in up to 15%, while class V in both populations have the same frequency (14%). This research did not cover classes I and VI (14). In our study, the distribution among classes is similar. Class IV of LN is also the most common class, without differences between populations (51.4% in pediatric LN and 54.1% in adult LN). When it comes to class II LN, our results show a slight difference in frequencies (22.9% in pediatrics and 12.6% in adults). A significant difference was noticed in class V (4.9% in patients younger than 18 and 21.3% in patients older than 18). Class I was three times more common in the pediatric population than in the adult population (2.9% and 1.1%).

In the adult population, vascular lesions are more common (14). We observed that leukocyte infiltration of blood vessels, as well as myoelastofibrosis and hyalinization of blood vessels are statistically significantly more common in the adult population as well. Infiltration of blood vessels occurs in the pediatric population in only 3%, while in the adult population it occurs in 39% of cases. Myoelastofibrosis and hyalinization of blood vessels occur in 62% of cases in adults, and in 5% of cases in pediatric population. Although the data were not statistically significant, fibrinoid necrosis of large blood vessels does not occur in the pediatric population, and in the adult population it occurs in only 6%.

“Full-house” immunofluorescent findings are characteristic for the LN as proven in our results, and the distribution among patient groups was almost identical (85.2% in pediatric and 84.4% in adult).

CONCLUSION

Serum creatinine values are significantly higher in the adult population of lupus nephritis. The histologic finding suggests that the glomerular lesions of LN do not differ significantly in terms of the activity index and chronicity index in the pediatric and adult population, but the tubulointerstitial lesions are significantly higher, both in terms of activity and chronicity in a group of adult patients. Myoelastofibrosis and hyalinization of blood vessels as well as leukocyte infiltration of blood vessels, are significantly more common in the adult population as well.

It is known that tubulointerstitial lesions determine the course and outcome of the disease and directly influence the occurrence of CKD and eventually kidney transplantation, however, for final confirmation of the influence of tubulointerstitial lesions on renal function, it is necessary to perform a follow-up study.

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KLINIČKE I PATOHISTOLOŠKE KARAKTERISTIKE LUPUS NEFRITISA U PEDIJATRIJSKOJ I ADULTNOJ POPULACIJI

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Sažetak

Uvod: Sistemski lupus eritematozus (SLE) predstavlja autoimuno oboljenje koje karakteriše obilna produkcija antitela, imunih kompleksa, kao i aktivacija sistema komplementa, koja remeti normalnu funkciju i rad mnogih organa, uključujući i rad bubrega. Iako je učestalost pojave SLE kod dece retka, jedna od najčešćih manifestacija kod obolele dece je lupus nefritis (LN), dok se kod odraslih obolelih od SLE, lupus nefritis javlja u 23% slučajeva i to češće kod muškaraca.

Cilj rada: Cilj ovog rada je bio da se analiziraju klinički (pol, učestalost LN kao prva manifestacija SLE, proteinurija i vrednosti serumskog kreatinina) i patohistološki parametri (učestalost klasa SLE, indeks aktivnosti i hroničnosti, intenzitet imunofluorescentnog bojenja imunoglobulina i kompleksa komplementa, kao i promene na krvnim sudovima) u pedijatrijskoj i adultnoj populaciji bolesnika sa LN.

Materijal i metode: U studiji je analizirano 218 uzoraka bubrežnog parenhima. Pacijenti su podeljeni u dve grupe: pacijenti mlađi od 18 godina (n=35) i pacijenti stariji od 18 godina (n=183).

Ključne reči: Sistemski lupus eritematozus, Lupus nefritis, pedijatrijska populacija, adultna populacija.

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Rezultati: Srednje vrednosti serumskog kreatinina u pedijatrijskoj populaciji ($71,6 \pm 16,4 \mu\text{mol/l}$) su bile statistički značajno niže ($p < 0,001$) nego kod odraslih ($115,5 \pm 64 \mu\text{mol/l}$). Intersticijalna infiltracija leukocitima bila je statistički značajno viša u grupi odraslih ($p = 0,003$). Prosečna vrednost indeksa hroničnosti ($p = 0,002$) kao i tubulointersticijski parametri koji ga određuju (tubularna atrofija ($p < 0,001$) i intersticijalna fibroza ($p = 0,011$)) bili su značajno viši kod odraslih sa LN. Infiltracija leukocitima ($p = 0,003$) i mioelastofibroza ($p < 0,001$) krvnih sudova bili su statistički značajno češći u populaciji odraslih.

Zaključak: Vrednosti kreatinina u serumu su značajno više u adultnoj populaciji LN. Patohistološki nalazi ukazuju na to da se glomerularne lezije LN ne razlikuju značajno u pogledu aktivnosti i indeksa hroničnosti u pedijatrijskoj i adultnoj populaciji, ali su stepen tubulointersticijalnih lezija značajno veći, kako u pogledu aktivnosti, tako i u pogledu hroničnosti kod adultnih pacijenata. Mioelastofibroza i hijalinizacija krvnih sudova, kao i leukocitna infiltracija krvnih sudova, statistički su značajno češće u adultnoj populaciji.