

Lupus nephritis in children – 10 years' experience

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Abstract

Systemic lupus erythematosus (SLE) in children is usually more severe than it is in adults and there is a higher incidence of renal involvement. We described 18 children (16 girls, 2 boys) with lupus nephritis (LN), whose average age was 14.4 ± 1.81 years. Disease activity was assessed according to SLEDAI (SLE Disease Activity Index). Renal biopsy was classified according to the INS/RPS (International Society of Nephrology/Renal Pathology Society). The patients were treated with steroids (100%) and pulses of cyclophosphamide (88.9%) or mycophenolate mofetil (11.1%), next azathioprine or mycophenolate mofetil with prednisone in reduced doses. In children with renal/multi-organ insufficiency and/or septicaemia, renal replacement therapy (27.8%), and plasmapheresis (22.2%) were used in the initial treatment. The SLEDAI initial activity was high in 44.4% and moderate in 55.6% of children. LN manifested as: nephrotic syndrome (83.3%), microhaematuria (100%), leukocyturia (60%), hypertension (72.2%), and acute renal injury (83.3%); mean GFR was 54.55 ± 33.09 ml/min/1.73 m². In the renal biopsy, class IV LN according to INS/RPS was mainly diagnosed (82%). At the end of follow-up, mean observation time 32.1 ± 23.36 months: mean GFR was 90.87 ± 12.13 ml/min/1.73 m², proteinuria disappeared in 66.7% and decreased in 33.3% of children to the average of 1.7 g/day (range: 0.5-4.0 g/day), hypertension was observed in 83.4% of children. Intensive immunosuppressive treatment with pulses of cyclophosphamide in early stage of LN in children is very effective.

Key words: acute kidney injury, cyclophosphamide, lupus nephritis, children.

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Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that is caused by the loss of tolerance to one's own antigens and the production of autoantibodies forming immune complexes that are deposited in various organs, which induces an inflammatory response. SLE development is triggered by genetic, environmental, infectious, and hormonal factors [1, 2]. Women are more frequently affected than men (incidence ratio: 8-13 : 1) [1-4]. SLE onset before puberty and in the elderly is uncommon [1, 5-10]. The incidence in children was estimated at 0.36-0.9/100,000 children/year, morbidity: 3.3-24/100,000 children/year [5].

The diagnosis of SLE is currently performed with the use of SLICC criteria (Systemic Lupus International Collaborating Clinics) [11]. SLE manifests with a broad spectrum of clinical signs, high variability of severity, and various response to implemented treatment [1, 3, 5, 11-15].

Lupus nephritis (LN) develops in approx. 50-70% adults with SLE and 37-82% of children [5-8]. At the early

stages of SLE the clinical signs of LN occur only in 25-40% of patients [1-3, 5-8] and may present as minor abnormalities in the urine (microhaematuria and/or proteinuria and/or leukocyturia) or as nephrotic syndrome, nephritic syndrome, hypertension, or renal failure [1-3, 7-10].

Prior to the decision of treatment of LN it is recommended to perform renal biopsy [1-3, 16, 17]. Nowadays, renal histological examination is classified with the use of the ISN/RPS scale (International Society of Nephrology/Renal Pathology Society) [16].

The treatment of adults and children with active SLE may be divided into two stages [17-19]:

1) remission induction, aiming at the fastest possible (usually 3-6 months) regression of symptoms [3, 17-22] by the administration of immunosuppressive drugs: cyclophosphamide [23-28] or mycophenolate mofetil [29-31] combined with glucocorticosteroids [17-19, 22-27], cyclosporin A [32], rituximab [33]; new biological therapies (belimumab, epratuzumab, ocrelizumab) [34-37], and in particular clinical situations – plasmapheresis and renal replacement therapy [3, 17-20];

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2) supportive treatment with the fewest drugs administered in the lowest effective doses, which maintains the remission.

There are no clear guidelines as regards the duration and ways of termination of supportive treatment [3, 17-21]. The minimal period of three years of supportive treatment is recommended in LN patients with a complete or at least partial response to treatment. Drugs which may be used in the supportive treatment are azathioprine (AZA) [17, 18, 27, 28] or mycophenolate mofetil (MMF) [17, 18, 29-31] and then prednisone in monotherapy [17, 18]. Moreover, long-term administration of an antimalarial drug (chloroquine) is recommended because it reduces the risk of renal exacerbations, permanent renal injury, thrombotic episodes, and the number of deaths [3, 17, 20, 38]. If LN occurs with proteinuria of over 0.5 g/day or hypertension, it is necessary to introduce the inhibitors of renin-angiotensin-aldosterone system [17-20]. However, in spite of treatment, 10-20% of LN patients develop end-stage renal failure [3, 5-8, 17, 18].

The development in SLE diagnosis and treatment leads to an improvement in the prognosis [1-3, 6, 10, 13-15]. However, the comparison with the general population shows a 2-5-fold higher risk of death in SLE patients. The clinical factors of poor prognosis in SLE include: young age at onset, initial high activity of the disease, severe nephropathy, and central nervous system involvement [1-3, 5, 9, 10]. Data collected worldwide show that the clinical course of SLE in children is more severe in comparison with adults [1, 5, 10].

The aim of the study was to assess the clinical and morphological presentation and treatment outcomes in children with LN in a paediatric nephrology centre during 10 years.

Material and methods

The study included 18 children (16 girls and 2 boys) with SLE diagnosed at the average age of 14.4 ± 1.86 years. The children were hospitalised due to LN in the University Hospital in the years 2004-2014.

The following elements were considered in the assessment: the age of SLE onset, the type of non-renal manifestations, the age of LN onset, clinical picture of nephropathy (microhaematuria, leukocyturia, proteinuria, nephrotic syndrome, hypertension, renal failure), activity of disease, renal biopsy result, recurrences of the disease, and complications.

SLICC criteria were used in SLE diagnosis [11]. According to these criteria the patient may be diagnosed with SLE if at least four clinical and immunological criteria are met, including at least one clinical and one immunological criterion, or if biopsy confirms the diagnosis of LN with the presence of ANA or anti-dsDNA antibodies. The criteria do not need to be met simultaneously.

The assessment of the activity of disease was performed with the SLEDAI scale (SLE Disease Activity Index) [13].

The activity of disease was classified as high with the score of ≥ 25 points, moderate with 16-24 points, and low with ≤ 15 SLEDAI points.

Renal biopsy was performed in 17 children with LN. Biopsy was not performed before treatment in a 17.5-year-old girl with severe mental impairment and critical state. LN histological presentation was classified according to ISN/RPA [16].

Treatment

Prior to obtaining renal biopsy results all the children with LN were administered prednisone (Encorton) at 1.5-2 mg/kg/day (max. 60 mg/day) and/or pulses of intravenous methylprednisolone (MP) 10-15 mg/kg (max. 1000 mg/pulse), then prednisone 1 mg/kg/day with the dose reduced individually.

Induction therapy included cyclophosphamide (CYP) pulses in 16 children and MMF in two children. Fourteen children were administered intravenous CYP according to the National Institute of Health-NIH guidelines [22] at a dose of 750 mg/m² (max. 1000 mg/infusion) modified according to leukocytosis and GFR levels. The regimen was: once a month for six months, then once every three months. Two children were administered CYP according to Euro-Lupus regimen [23], i.e. six infusions of 500 mg every two weeks. Prednisone at 1 mg/kg/day was administered between CYP pulses. Two children were administered MMF at a maximum dose of 1200 mg/m² with prednisone at 1 mg/kg/day.

Apart from immunosuppressive drugs, the induction therapy in five children with renal failure and/or multi-organ failure and/or septicemia was combined with renal replacement therapy: haemodialysis (HD), continuous veno-venous haemodiafiltration (CVVHDF) and plasmapheresis (PE) – four children. All the children with proteinuria were administered an angiotensin-converting-enzyme inhibitor (ACEI): enalapril maleate at 2.5-10 mg/day or angiotensin receptor blocker (ARB): losartan 25-50 mg/day. Hypertension was treated with ACEI, ARB or beta-blocker: amlodipine at 2.5-10 mg/day. Chloroquine at 250 mg/day has been in use since 2010.

Supportive treatment included AZA for 2-5 years or MMF for 2 years with prednisone at an individually decreased dose, then prednisone as monotherapy.

At baseline all the patients underwent the following tests: complete blood count, glucose, urea levels, C3 and C4 complement component, ANA and ds-DNA antibody titres, creatinine, and creatinine clearance (calculated with Schwartz equation). Microhaematuria and proteinuria were assessed in urine analysis and in 24-hour urine collection.

Prior to the treatment all the patients underwent ophthalmological examination, chest X-ray, ECG, and abdominal ultrasound. Throughout LN treatment with immunosuppressive drugs and prednisone ophthalmological

Table 1. Clinical date, renal biopsy results, and treatment in children with lupus nephritis

N	Sex	Age of onset (yrs)	ANA titre	SLEDAI – points	GFR ml/min/1.73 m ²	AKI	HT	NS	Renal biopsy	MP iv pulses	CYP		MMF	AZA	P	CHLOR					
											NIH	Euro-Lupus					Time/ yrs	Time/ yrs			
		Onset a year	After	Total	Extra-renal	Renal	Onset	End of obs.	INS/IRPS	NIH	μ pulses/total dose (g)	Time/ yrs	Time/ yrs								
1	F	15	2560	160	26	14	12	68.5	96.5	+	+	+	+	IV-S(A)	9	6	6.0	2	20 mg/48 h	+	
2	F	16	1280	320	22	14	8	106.5	105.5	0	+	0	+	V	10	0		2 ⁱ	2	12.5 mg/24 h	+
3	F	14.8	1280	320	26	14	12	96.7	105	0	+	+	+	IV-S(A)/V	3	0	6	3.0	20 mg/48 h		
4	F	13.7	1280/5120	1280	26	14	12	73.88	81.1	+	+	0	+	IV-S(A)	9	9	6.75	2 ^s	2	12.5 mg/24 h	+
5	F	15.2	320	160	16	8	8	57	63	+	+	+	+	VI	3	6	3.0	2	12.5 mg/48 h	+	
6	F	10.5	2560	640	20	8	12	60.71	92.6	+	+	+	+	IV-S (A)(C)V	6	6	4.5	2 ^s	2	15 mg/48 h	+
7	M	15.5	1280	0	28	16	12	18.3-0	73.5	+	+	+	+	IV-G(A)	10	0	6	3.0	30 mg/24 h	+	
8	F	17.5	1280	320	29	17	12	23.0-0	91.1	+	0	+	+	0	10	4	2.0	2	60 mg/48 h	+	
9	F	16	5120	640	30	18	12	23	97	+	+	+	+	IV-G(A)	6	6	5.0	2	60 mg/25 mg	+	
10	F	12	2560	320	20	12	8	78.9	88.5	+	0	+	+	IV-S(A)	6	0		2 ⁱ	2	15 mg/24 h	+
11	F	14	1280	80	24	20	4	34.69	95.8	+	0	0	+	III (A)	0	3	3.0	2	12.5 mg/48 h	+	
12	M	15	2560	0	32	16	16	27.0-0	91	+	+	+	+	IV-S(A)/V	13	13	9.65	2	15 mg/48 h		
13	F	15	640	80	16	8	8	77	106	+	+	+	+	IV-S(A)/V	5	6	6.0	2	20 mg/48 h	+	
14	F	10.5	1280/2560	0	19	11	8	100	94	0	0	+	+	IV-G(C)	4	11	9.0	5	15 mg/24 h		
15	F	12	160	0	17	9	8	54	86	+	+	+	+	IV-G(C)	8	1	0.5	3	15 mg/48 h		
16	F	14.3	1280	1280	29	21	8	50	73	+	+	+	+	IV-G(A)	11	8	6.0	2	10 mg/48 h		
17	F	15.8	1280	80	21	9	12	51	90	+	+	+	+	IV-S (C)	3	9	8.1	2	10 mg/48 h		
18	F	13.1	1280	80	24	12	12	50	106	+	0	+	+	IV-G(C)	3	8	8.0	2	15 mg/48 h		
Average		14.38 ±1.86			23.6 ±4.98	13.4 ±4.10	10.2 ±2.82	54.55 ±33.09	90.87 ±12.13	n = 15	n = 13	n = 15	6.6 ±3.55	6.9 ±3.13	5.5 ±2.71	6	3.0	n = 4	n = 12	n = 11	

LN – lupus nephritis, n – number, F – female, M – male, yrs – years, SLEDAI – SLE Disease Activity Index, obs. – observation, AKI – acute renal injury, HT – hypertension, NS – nephrotic syndrome, INSRPS – International Society of Nephrology/Renal Pathology Society classification, G – global, S – segmental, (A) – active, (C) – chronic, MP iv – intravenous methylprednisolone pulse, CYP – cyclophosphamide pulse, NIH – National Institute of Health-NIH guidelines, Euro-Lupus – Euro-Lupus regimen, MMF – mycophenolate mofetil, i – induction, s – supportive, AZA – azathioprine, P – prednisone, CHLOR – chloroquine

examination was performed every six months and densitometry every 6-12 months.

LN remission was reported if serum creatinine normalized appropriately for the child's age and GFR was >90 ml/min/1.73 m², proteinuria <0.5 g/day, ANA ≤ 1 : 80.

Results

Clinical data of 18 LN children, renal biopsy result, and the type of treatment are presented in Table 1. The average observation period until 18 years of age was 33.4 ±26.13 months in 15 children and 16.3 ±16.19 months in the remaining three children.

During the prodromal period of SLE the following non-specific clinical manifestations were reported: weakness in 10 children (55.6%), recurrent fever in 10 children (55.6%), body weight reduction in seven children (38.9%), headache in four children (22.2%), and recurrent diarrhoea in three children (16.7%). The most common initial SLE clinical manifestations in the study group were: haematologic in 14 children (77.8%), musculoskeletal in 13 children (72.2%), and cutaneous in 12 children (66.7%). The involvement of vital organs was reported in eight children (44.4%) including: heart in four children (pericarditis in two children, Libman-Sacks endocarditis in one child, dilated cardiomyopathy in one child), central nervous system in five children (headache in three children, convulsions in two children, depressive symptoms in one child), and respiratory insufficiency in one child. The results of ANA testing showed the titres from 1 : 160 to 1 : 5120 (Table 1). The presence of ds-DNA was reported in 11 children (61.2%), the reduction of C3 complement in 12 children (66.7%), and C4 in 14 children (77.7%).

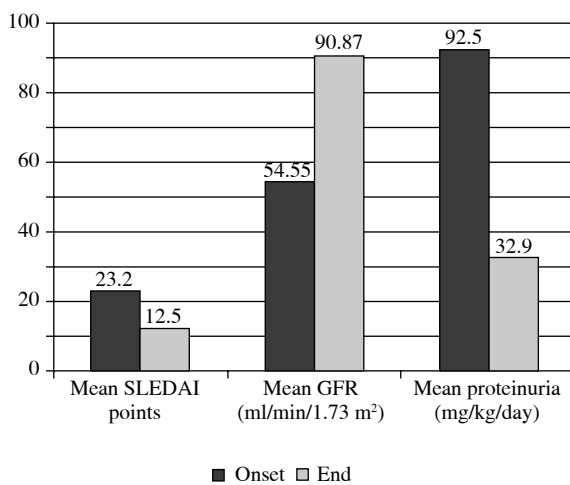


Fig. 1. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), glomerular filtration rate (GFR) and mean proteinuria at the onset and at the end of observation of children with lupus nephritis

The average activity of disease at onset according to SLEDAI was 23.2 ±4.98 points (Fig. 1) and was assessed as high in 44.4% of children and moderate in 55.6% children. The ratio of non-renal to renal symptoms was 57% : 43% (Table 1).

The signs of LN were reported in the first four months (average: 79 ±77.6 days) since SLE onset. 8 children (44.4%) had LN at onset. All the children had microhaematuria and proteinuria at the average level of 92.5 ±66.4 mg/kg/24 h. Nephrotic syndrome was diagnosed in 15 children (83.3%), hypertension in 13 children (72.2%), and acute renal injury in 15 children (83.3%). Average GFR was 54.55 ±33.09 ml/min/1.73 m² (Table 1). Two children had anuria in the course of LN. 60% of children had sterile leukocyturia (Fig. 2).

Renal biopsy was performed in 17 children between days 7 and 64 (average – 38 days) after the onset of nephropathy. Renal biopsy most commonly revealed LN class IV according to ISN/RPS (Table 1).

Induction therapy

Seventeen children were administered 3-13 (average: 6.6 ±3.55) MP pulses, and one child was treated with oral prednisone. Sixteen children (88.9%) were administered intravenous CYP. Fourteen patients treated with intravenous CYP according to NIH regimen were administered the average of 107.2 ±61.79 mg/kg/treatment (i.e 5.5 ±2.71 g/treatment). CYP pulse therapy lasted for the average of 9.6 ±7.66 months and depended on the clinical status of the patient and the activity of disease. One girl (patient 15, Table 1) developed pneumonia with underlying *Aspergillus* infection, which excluded her from further CYP treatment. She was continued on oral steroids in combination with AZA. Two girls (patients 8 and 11) were administered

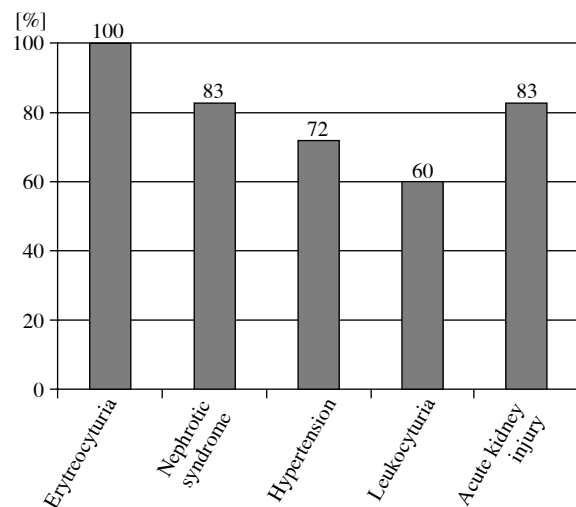


Fig. 2. Clinical presentation lupus nephritis in children

only four and three CYP pulses, respectively, before they turned 18 and were transferred to nephrological centres for adults. The remaining children obtained 6-13 CYP pulses. The highest number of CYP pulses (13) were administered over 27 months to a boy (patient 12) who, at the critical state at the beginning of the disease (septicaemia, multi-organ failure, pulmonary oedema, dilated cardiomyopathy, anuria), was treated with CVVHDF and plasmapheresis (nine procedures). A similar induction treatment regimen: CYP (500 mg/infusion), plasmapheresis (6-9 procedures) and renal replacement therapy (HD – two children, CVVHDF – two children) was implemented in four children (patient 7, 8, 10, 16). Throughout CYP treatment according to NIH regimen, the following complications were observed: leukopaenia in 10 children (71.4%), nausea in 10 children (71.1%), hair thinning in eight children (57.4%), menstruation disorders in four girls (30.8%), shingles in four children (28.5%), oral fungal infections in three children (21.4%), recurrent herpes in three children (21.4%), pneumonia/aspergillosis in one child (7.1%), and recurrent enterobiasis in one child (7.1%). Three children (21.4%) treated according to this regimen experienced one recurrence of the disease after six months, three and five years after onset. These recurrences were related with pharyngitis, bronchitis, and CMV infection. Intravenous MP was effectively used in each case.

Two children treated according to Euro-Lupus regimen (patients 3 and 7) with 3 g of intravenous CYP over three months did not develop any complications. At the end of observation period these children had the nephrotic proteinuria reduced to 0.8-1.0 g/day and GFR at 63-105 ml/min/1.73 m². Both patients had hypertension which was well-controlled with antihypertensive drugs.

Two children in induction therapy received MMF: a girl (patient 2) with membranous LN (class V according to ISN/RPS) and a girl (patient 10) with neurological symptoms and LN class IV-S(A). They both developed transient leukopaenia during MMF therapy with no other adverse effects. Proteinuria regressed and diminished to < 0.5 g/day and renal function normalised in these children. Both patients had hypertension which was well-controlled with drugs.

Eleven children (61.1%) were administered 250 mg of chloroquine over 1-2 years with no adverse effects.

During supportive treatment 12 children were administered AZA for 2-5 years and two children – MMF for two years. AZA was effectively substituted with MMF in one girl who had a tendency towards leucopaenia (patient 6).

Supportive treatment included prednisone in doses reduced individually (Table 1). During chronic steroid treatment the following manifestations were observed: transient glucose intolerance in one child (5.6%), cataract in two children (11.1%), osteoporosis in four children (22.2%), and hypertension in 72.2% of children.

Microhaematuria and leukocyturia regression were observed in all the children and a complete LN remission in

seven children (38.9%), during the first year of treatment. The average duration of observation was 32.1 ± 23.36 months (7 months – 7.3 years). During that period renal function improved in all the children (final average GFR at 90.87 ± 12.13 ml/min/1.73 m² vs. baseline average GFR 54.55 ± 33.09 ml/min/1.73 m²), including GFR normalisation in 12 children (66.7%), proteinuria regression in 66.7% of children, and proteinuria reduction in 33.3% of children down to 32.9 ± 11.67 mg/kg/day (Fig. 1). Hypertension that was well-controlled with drugs was observed in 83.4% children. Fifteen children were transferred to nephrological centres for adults when they turned 18 years old. The lowest GFR in the group was 63 ml/min. Three girls are still being treated: patient 9 is currently receiving CYP pulses according to NIH, and two other girls are undergoing supportive treatment: MMF and prednisone (patient 6), AZA and prednisone (patient 4).

Discussion

The onset of SLE in children from the study group was at the average age of 14.4 years. As regards the gender – girls dominated (8 : 1), which is consistent with the literature [1-3, 7-10]. The initial activity of SLE was moderate-high according to SLEDAI, with the predominance of non-renal signs (57%). It is stated that in the early period the clinical signs of renal diseases occur only in 25-40% of SLE patients [1-3], being more common in children than in adults [5-8] and their presence translates into poorer prognosis both in adults [1-3] and in children [5-10]. In the study group, nephropathy was present at onset or developed in the first four months since SLE onset. All the patients had microhaematuria, and 89% children presented with a severe LN onset: nephrotic syndrome, renal failure, and hypertension. Additionally, in eight children we observed the involvement of vitally important organs.

Renal biopsy was performed in our patients in the early stage of SLE. Therefore, the assessment of active and chronic abnormalities conducted according to ISN/RPS revealed the predominance of active abnormalities (mainly class IV) in histopathological examination, which could influence treatment results. In proliferative LN it is necessary to combine immunosuppressive drugs with glucocorticoids at high doses [17-20]. According to numerous authors, children are administered higher doses of steroids in comparison with adults [5, 6]. 94.4% of patients in this study group were administered pulses of methylprednisolone at onset.

According to EULAR/ERA-EDTA guidelines [18], it is necessary to administer high doses of intravenous CYP in the induction of remission in proliferative LN with poor prognostic factors, i.e. severe deterioration of renal function, the presence of cellular crescents, and/or fibrinoid necrosis in renal biopsy [16-20]. The induction therapy in 88.9% of children in this study group involved the intra-

venous administration of CYP and administration of MMF only in 11.1% of children. MMF is considered the first-line treatment in African Americans and Hispanic patients due to its more marked effectiveness, and also in young patients due to a lower risk of infertility and in patients with lupus membranous nephropathy [5-8, 18-20, 30, 31].

The minimum of 25% of proteinuria reduction and normalisation of C3 and/or C4 complement components after eight weeks and serum creatinine reduction and proteinuria < 1 g/day after six months of induction therapy are considered good prognostic factors of LN [18]. Microhaematuria and leukocyturia regression were observed in all the children in our group and a complete LN remission in seven children (38.9%) during the first year of treatment.

According to the literature, even half of LN patients experience the recurrence after obtaining a complete or partial remission [1, 3, 5-8, 18]. The recurrence was observed in only 16.7% of children in our study group. Each LN exacerbation, particularly a nephritic one, can lead to permanent renal injury. Therefore, it is recommended to treat all LN exacerbations as a new renal involvement [18]. Amaral *et al.* [8] conducted an analysis and demonstrated an increased risk of renal involvement in the course of juvenile SLE and an increased risk of mortality compared to patients with adult-onset symptoms. In his group, the most common class of histopathological lesions in adolescents and adults was class IV, which was consistent with the results of the present study.

According to the data of Institute of Rheumatology in Warsaw, 138 children were treated for SLE in the years 1985-2005 [10]. The assessment of the course of the disease in those children revealed a decreased initial activity of disease according to SLEDAI scale, renal involvement and epilepsy were less common, while psychosis and the presence of anti-ds-DNA antibodies were more common. Mortality was most frequently due to generalised infections (renal failure was indicated as one in previous years).

High initial activity of SLE was observed in the present study group of children with LN. At the onset of the disease about one third of children required renal replacement therapy or plasmapheresis due to renal/multi-organ failure and/or septicemia. There were no deaths of LN children with renal failure in our group. Induction therapy with intravenous CYP in the majority of children resulted in a final average GFR of 90.87 ±12.13 ml/min/1.73 m² and proteinuria regression in 66.7% of children. However, hypertension was present at the end of observation in 83.3% of children.

Conclusions

Microhaematuria, nephrotic syndrome, hypertension, and renal injury are frequent manifestations of lupus nephritis in children. Induction therapy with intravenous cyclophosphamide is an effective treatment in the prolif-

erative forms of lupus nephritis in children. Long-term assessment of the course of lupus nephritis in Polish children requires multi-centre cooperation and evaluation of new immunosuppressive agents including MMF and rituximab.

The authors declare no conflict of interest.

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