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Lupus Nephritis in Children: 21-Year Experience of a Single Center in Belarus

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Abstract: The article presents a historical and prospective analysis of the clinical and paraclinical data of a cohort of children suffering from systemic lupus erythematosus (SLE) with kidney damage, observed in a single center for 21 year. The case histories of 62 patients (51 girls and 11 boys) with a diagnosis of SLE and lupus nephritis (LN) who were monitored and treated at the Byelorussian Center for Pediatric Nephrology and Renal Replacement Therapy of the 2nd Children's Clinical Hospital in Minsk in the period from 1998 to 2019 yrs. We evaluated the initial manifestations of the disease, age of the onset, time of diagnosis (from the first symptom to the diagnosis), clinical manifestations at the time of diagnosis, the duration of SLE and treatment at the time of kidneys biopsy, as well as the activity of the disease. During the observation period (from 3 months up to 12 years) the frequency of extrarenal and renal exacerbations was analyzed, and the activity, treatment and outcome were evaluated. Male gender and early debut are factors worsening the prognosis of the disease (55% of boys showed progression of CRF). In children, the disease proceeds with a high degree of activity, rapid multi-organ involvement, requires more aggressive therapy with prescription of several immunosuppressive agents, which increases the risk of infection. Nephritis is an unfavorable prognostic criterion and is crucial in determining the volume of therapy for SLE. Noncompliance in therapy, social status were factors of an unfavorable outcome in children. Timely diagnosis and aggressive intervention to suppress the activity of the disease should be used to prevent chronic irreversible damage. Children with SLE and kidney damage are at high risk for early development of cardiovascular disorders. Steroid-sparing strategies must be actively implemented in clinical practice in order to prevent severe side effects.

Keywords: Systemic Lupus Erythematosus, Lupus Nephritis, Children

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multisystem involvement and a chronic relapsing course [1, 2]. Childhood onset lupus includes patients with a debut of the disease under the age of 18 and has a number of features. In particular, the ratio of girls and boys (5-8: 1) is less pronounced compared with adults, the clinical phenotype is characterized by a higher activity and frequency of renal, hematological and neuropsychiatric symptoms, multi-organ lesion and worse prognosis [3, 4]. Lupus nephritis (LN) is considered as one of their unfavorable prognostic criteria [1, 5, 6].

The purpose of this study is a historical and prospective analysis of the clinical and paraclinical data of a cohort of children with SLE, LN at the onset of the disease and with long-term follow-up, treatment and outcome to assess factors that affect the prognosis of the disease.

2. Method

The case histories of 62 patients (51 girls and 11 boys) with a diagnosis of SLE and LN who were monitored and treated at the Byelorussian Center for Pediatric Nephrology and Renal Replacement Therapy of the 2nd Children's Clinical Hospital in Minsk in the period from 1998 to 2019 yrs. Patients were divided into two groups: 1st historical and 2nd prospective, including years of observation 1998-2012 and 2013-2019 respectively. All patients noted at least four of the proposed 11 diagnostic criteria of the American College

of Rheumatology (ACR) 1997, from 2013 year with added SLICC criteria [5]. The diagnosis of lupus nephritis was verified morphologically with using of ISN/RPS 2004 classification [6]. We evaluated the initial manifestations of the disease, age of the onset, time of diagnosis (from the first symptom to the diagnosis), clinical manifestations at the time of diagnosis, the duration of SLE and treatment at the time of kidneys biopsy, as well as the activity of the disease. During the observation period (from 3 months up to 12 years) the frequency of extrarenal and renal exacerbations was analyzed, and the activity, treatment and outcome were evaluated. Statistical analysis was performed using the software package Statistica10.0 and Microsoft Excel.

3. Result

The 1st group included 8 boys and 22 girls with average age of the onset of the first signs of the disease 12,8±2,7 months (from 6 to 17 years, median 13,5), the 2nd group (3 boys and 29 girls) 12,2±0,5 months (from 6 to 17 years, median 12,5). For the 1st group the time from debut to diagnosis was from 1 to 60 months, median 6, for the 2nd group – from 2 weeks to 77 months, median 2 (p=0,005). Kidneys involvement was confirmed at the onset for the 1st group in 16/30 (53%), for the 2nd group in 14/32 (44%). From all patients 3 girls were of Caucasian ethnicity, the others were Slavs. Five girls had a positive family history in terms of autoimmune diseases, including SLE in aunt (n=2) and chronic glomerulonephritis (GN) with renal failure in aunt (n=2).

Among the triggering factors dominated infection, insolation, allergy, and among the first symptoms were general non-specific (70% and 62,5% for the 1st and 2nd groups respectively): fever, growing weakness, malaise, loss of appetite, weight loss, lymphadenopathy. Arthritis was the most common initial extrarenal manifestation in both groups (37% and 65,6% respectively). Skin lesions and hematological involvement were observed in one third of patients in both groups.

By the time of admission, the percentage of joint and skin manifestations decreased, but hematological, immunological and visceritis symptoms joined. In nine children with cytopenia at the first onset alone, a significantly longer average time to diagnosis (up to 5 years) was observed compared with patients having other clinical manifestations of SLE (p=0.005), positive anti-nuclear (ANA) and against double-stranded DNA antibodies appeared later. High (44.4%) or moderate (55.6%) activity was observed, and no cases of low activity were noted.

During follow-up from the moment of appearance of the first signs of SLE, a decrease in skin and joints involvement is distinguished, the frequency of renal damage significantly increases. Chronic cutaneous lupus in children has not been identified, unlike in adults, where it is predominant. The number of ACR criteria has increased from 6 to 9. For the 1st and 2nd groups respectively serositis was seen in 12 and 6 cases, neurolupus – in 6 and 2, antiphospholipid syndrome (APS) in 8 and 6, endocarditis in 4 and 3, hepatitis in 3 and 4. Both in the 1st and in the 2nd groups' pulmonitis in 6 cases, Raynaud's phenomenon in 2 patients were observed. Pancreatitis in one patient of the 1st group was confirmed. Arterial hypertension (AH) was detected in 87,1% (54/62).

At the time of admission at our Hospital everyone had urinary syndrome and / or signs of renal failure, which was the indication for kidneys biopsy. Acute renal failure (ARF) in dynamics occurred in three children. Kidney damage at the onset of SLE was observed in 44-53%, over a maximum of five years LN developed in 100% of patients. The diagnoses for referral to our hospital were: for the 1st group - acute GN with nephrotic syndrome (NS), hematuria and hypertension (n=8), acute pyelonephritis (n=4), acute tubulointerstitial nephritis (TIN) (n=2), ARF (n=2). For the 2nd group: acute pyelonephritis (n=2), nephropathy with hematuria and proteinuria (n=2), acute GN with nephritic syndrome (n=1), urinary tract infection (n=1), NS (n=1), IgA nephropathy (n=1), acute TIN (n=1), dysmetabolic nephropathy (n=1).

Morphological study of renal tissue with the allocation of the class, indices of activity and chronicity was carried out according to the Morphological classification of the International Society of Nephrologists and Pathologists ISN/RPS 2004, before the appearance of this classification WHO 1995 criteria were used (table 1).

Table 1. *LN classes.*

LN class	1st historical group	2nd prospective group
I	-	- (only 1 in transplanted kidney)
II	4	2
III	3	1
IV	20	28
V	2	1
VI	-	-
IV+VI	1	-

In most cases in our patients (66,7% in the 1st group and 87.5% in the 2nd group) a highly active diffuse-proliferative class IV of nephritis were noted. High activity index (8-16) was observed in 10 from 16 patients (62,5%) of the 1st group and (8-17) in 15 from 32 patients (47%) of the 2nd group. Less common was a high chronicity index (above 4), which we can use as a good prognostic factor (25% for the 1st group and 12,5% for the 2nd group).

Repeated biopsy was performed only in five patients from the 1st group: in one case due to uninformative of the 1st study, in one due to suspected transformation of kidney damage class, in one suspected cyclosporin nephrotoxicity, in one for the evaluation of progression, in one primary diagnosis was TIN, but later extrarenal symptoms developed.

According to the results of Echo-CG for the 2nd group it was found that during the manifestation of the disease changes were detected in five children, while when calculating left ventricular mass index (LVMI) and left ventricle relative wall thickness (LVRT), signs of myocardial remodeling were found in 14 (45.2%): dilated LV myocardial hypertrophy (n=10), concentric LV myocardial hypertrophy (n=3), concentric remodeling (n=1). With repeated Echo-CG

in 50% of children (7/14), calculated indices returned to normal: signs of dilated hypertrophy persisted in two; dilated was replaced by concentric hypertrophy in two. In four patients with a normal ultrasound picture and calculated indices at the onset of the disease, repeated examination revealed signs of myocardial remodeling - concentric LV myocardial hypertrophy (n=3) and concentric remodeling (n=1), two of them reached end stage renal disease (ESRD). Ultrasound signs of LV hypertrophy were detected in only one patient with ESRD.

LVMI in children with SLE, LN before the start of immunosuppressive (IS) and hypotensive therapy exceeded 95th percentile (according to the gender and age of the child) in 13 children (42%), while during remission and on hypotensive therapy it persisted in 6 (19.3%) (p=0.01). An increase in LVRT over 0.4 before the onset of IS and hypotensive therapy was noted in 13% (4/31); during remission remained in 3.2% (1/31, p=0.005). LV hypertrophy according to the results of Echo-CG during follow up remained in two patients.

A tendency to an increase in complex intima-media thickness (TCIM) in SLE patients was revealed: the median of TCIM of the right artery was 0.5 (0.3-0.81 mm, 25-75% confidence interval (CI) 0.4-0.58, on average 0.5±0.03) in comparison with the healthy (0.03-0.5, CI 0.35-0.5, on average 0.4 ± 0.02) median 0.4 (p=0.005). The median TCIM of the left artery in SLE was 0,5 (0.3-0.88 mm, 25-75% CI 0.4-0.6, on average 0.5±0.03) versus median 0.4 (0.03-0.6 mm, 25-75% CI 0.35-0.5, on average 0.4 ± 0.02) in the healthy (p=0.01).

The results of the study of metabolic parameters in children with SLE, LN from the 2nd group are shown in the table 2.

Table 2. *Metabolic parameters in children with SLE, LN.*

Serum concentration, IU	Groups	Concentration	M±m	Median	25-75% CI	p<0,05
Adiponectin, ng/ml	SLE, LN	1,07-65,26	19,42 ±2,47	14,75	9,75-21,78	0,001
	Healthy	17,6-601	142,88±26,66	93,98	44,33-206,3	
Leptin, pg/ml	SLE, LN	925-2246	1898,82±72,58	2081,0	1577-2150	0,001
	Healthy	51,5-2360	1296,72 ±140,43	1313,7	830,7-1906,6	
Obestatin, pg/ml	SLE, LN	47,7-282,6	178,75,82±10,5	189,45	133,9-220,4	0,009
	Healthy	14,6-294,3	121,14±18,4	69,31	48,4-252,0	
Osteoprotegerin, ng/ml	SLE, LN	0,7 -399	21,89±79,1	2,15	1,3-4,1	0,005
	Healthy	1,4 -3,2	1,82±0,78	1,5	1,4-1,6	
Vitamin D, 25 (OH) D, ng/ml	SLE, LN	1,6-22,7	8,88±0,98	8,0	4,6-12	0,001
	Healthy	5,03-53,89	24,1±2,57	20,85	12,7-30,4	

Treatment. As an induction therapy plasma exchange was used in 13 children from the 1st group and in 1 from the 2nd group, puls therapy with Methylprednisolone in 15 and 2, Cyclophosphamide in 8 and 22 respectively, oral Prednisolon in all cases. As a maintaince therapy combination of oral Prednisolon with Endoxan in one of the 1st group and one of the 2nd group, Methotrexate in 3 and 1, Cyclosporine A in 11 and 3, Azathioprine 16 and 21 respectively. Leukeran was used in 15, Plaquenile in 2 from the 1st group only. Delagil in 1, MMF in 2 and Rituximab in 1 from the 2nd group.

We began to use the KDIGO protocols for the treatment LN after 2012 year. Before this we used a variety of cytostatic agents in therapy. Thanks to the introduction of the protocol, the active manifestations of SLE, LN can be suppressed within from 5 to 11 months for the patients from the 2nd group, median 6 (6.8 ±1.6) in comparison with the 1st group (6-24 months, median 13.5, 14.3±5.7), p=0,001, reducing the duration of hospitalization.

Prior to kidneys biopsy treatment received 23/30 in the 1st group and 6/32 from the 2nd group. Kidneys biopsy should be performed before therapy, because the treatment may alter the morphology of renal inflammation and the volume of therapy depends on the class and index of activity.

Outcome. 4 from 62 (6.5%) died due to infectious complications, often associated with treatment incompetence: the 1st group - 2 girls, the 2nd group - 2 children: one foreigner boy, one girl at another Hospital.

The duration of historical analysis for the 1st group averaged 41.8 ± 36.4 months (from 3 to 144, median 33 months). The progression of chronic renal failure (CRF) for this group was observed in 5 from 8 (63%) males, and in 4 cases with an early manifestation of the disease before age of 8. CRF stage 1 was observed at 2 patients, stage 2-3 at 2 patients. ESRD developed in one boy three years after the onset of SLE, LN. He was on hemodialysis (HD), then on peritoneal dialysis (PD), later he was transplanted (Tx) with rejection of the cadaveric kidney, at the age of 20 he was sent to adult service on HD. In 2 girls, after acute renal failure, partial renal function was limited.

All patients during follow up received CS (only 1 girl remained on monotherapy with CS) in combination with cytostatic: 15 leukeran, 11 cyclosporin A, 16 azathioprine. There was a change in cytostatic agent in almost all children (only 2 were sent to the adult service with prednisone and azathioprine without changing the cytostatic). We confirm the literature data that monotherapy with CS is not able to change the course of LN in a favorable direction and the addition of cytostatic agent is necessary. Episodes of herpes infection were confirmed in 33.3%. In case of pulse therapy with cyclophosphamide (CYC) in synchronization with plasmapheresis every other day (3-5 sessions), 3 patients developed severe leukopenia with addition of viral and bacterial infections and life-threatening condition in one case, what allows recommend not to use CYC in this mode because of a high risk of infectious complications.

Steroid diabetes developed in three girls. Death of two

girls (at the time of diagnosis of SLE both had 9 ACR criteria, LN class IV, severe cytopenia, APS) due to infectious complications, their social status and lack of compliance with therapy: they admitted in severe conditions, were non-complacence, independently canceled treatment, refused to implementation of recommendations.

The duration of analysis for the 2nd group averaged 41.7 ± 27.4 months (from 4 to 108, median 38 months). In this group three patients reach ESRD. One of them was a foreigner boy who first entered to our Hospital with CRF 3-4 stage (CKD 4-5), later transplanted, after 7 months died in his home country due to infection. One girl with overlap syndrome (Juvenile rheumatoid arthritis at 8 years old, later urinary syndrome, refusal of hospitalization and treatment, SLE was diagnosed at the age of 15 yrs) and first admission to our Hospital was with CRF3 (CKD 4), later successfully Tx and transfer to adult service. And another girl arrived with 1-2 stage CRF, debut was with pulmonary damage, ESRD after 4,5 years, Tx, currently remains under our observation. Steroid diabetes developed in 4 from 32.

Adverse outcome was seen in the 1st group in 7/30 cases (23,3%), in the 2nd group - 4/32 (12,5%). Continuously recurring course was more often observed in the 1st (n=16), in comparing with the 2nd group (n=2).

4. Discussion

SLE survival over the past 20 years has increased significantly due to the rational use of glucocorticoids and cytostatic agents: in 1950 the 5-year-old was no more than 30%, today is approximately 93.3% [11]. The development of diagnosis and treatment of SLE leads to an improved prognosis, however, the comparison with the general population shows a two-five times higher risk of death in children with SLE. Long-term follow-up of patients with childhood SLE is not well understood due to the transition to an adult clinic [2, 3, 7-10]. We followed up the course of SLE, LN in children for a fairly long time (up to 12 years), and in some up to a young adult age (20, 26 and 31 years). Currently a 26-year-old young woman has a two-year-old healthy girl and a stable remission of SLE, LN.

Analysis of demographic data shows that gender ratio in childhood onset SLE is different from adults: out of 62 children 11 were boys and male gender may act as an unfavorable prognostic factor (55% of boys showed progressive relapsing course of nephritis to ESRD). Most cases develop in adolescence, which is also consistent with the literature data. Analysis of the onset of the disease showed a clear predominance of general nonspecific symptoms, joints, skin and hematological manifestations, which corresponds to the literature data [10-14].

The presence of typical skin rashes, especially on the face, significantly speeds up the diagnosis. Joint syndrome is not specific, therefore, when arthritis is the first sign even in childhood, SLE must be included in the diagnostic search, especially if it is combined with hematological changes. Autoimmune hemolytic anemia and thrombocytopenia as the only initial signs can ultimately manifest as SLE many years after the debut, deserving of rigorous clinical observation with periodic determination of ANA [1-4, 7-11]. Evaluation of the disease activity confirmed that childhood SLE is characterized by high and moderate degree with a rapid multi-organ involvement, which demonstrates the presence of from 6 to 9 ACR criteria during the period of active manifestation of the disease.

During the observation period from 1 up to 3 episodes of extrarenal exacerbations occurred, most often associated with excessive insolation or infection, progression to ESRD of continuously recurring active nephritis with long-term persistent nephrotic proteinuria in 12,5%.

Previously we did not have the possibility to determine the concentration of anti-nuclear antibodies and we often used glucocorticoids in small doses and for a short time, which significantly delayed the diagnosis and, of course, influenced the course of the disease.

Damage of the kidneys acts as a factor aggravating the prognosis. The maximum within 5 years from the onset of SLE, nephritis occurred in 100% of patients, in 48 of 62 cases it was highly active class IV, requiring aggressive high-dose immunosuppressive therapy of CS and cytostatics (in synchronization with plasmapheresis in 14 children).

Almost all patients from the 1st group underwent a change in cytostatic agent due to insufficient response or side effects. Progression of chronic renal failure occurred in 6 out of 11 (55%) of males, four of them had an early manifestation of the disease before 8 years of age. In 2 girls, after acute renal failure, partial renal function was limited.

In addition to damage caused by systemic inflammation, it is also necessary to take into account the addition of side effects associated with the use of CS and CA [11-15]. Early involvement of several organs, high activity of the disease requires high dosages of CS and CA. Doses of medications used in childhood are higher than in the treatment of adult disease. Severe infections developed in patients using the CYC pulse therapy regimen every other day in synchronization with plasmapheresis even after second or third CS injections, while other children received pulse CYC therapy 1 time per month for 6 months or ones per 14 days during 3 months without similar side effects).

Our experience confirms numerous data from other centers about the advantage of induction therapy with high doses of CS or CYC and long-term supportive treatment with low doses of CS and azathioprine, steroids alone are not able to change the course of LN in a favorable direction. Pulse therapy with CYC should not be carried out every other day because of the high risk of cytopenia and infectious complications in an immunosuppressive patient. The treatment strategy has changed; we adhere to the recommendations of Eurolupus about the pulse of CYC in a dose of 400-500 mg/m^2 once every 14 days or 1 time per month with dose 500-1000 mg/m^2. Cyclosporin A (with maintaining the serum concentration between 80-150 ng/ml) has shown insufficient effectiveness in the treatment of SLE, LN may be due to the relatively low occurrence of other

classes of nephritis except the fourth, requiring more aggressive therapy.

It is of concern that among the most significant side effects (exogenous hypercorticism, osteoporosis, infection), steroid diabetes is common (in 7 from 62, 11.3%). Herpetic infection was observed quite often, in one third of children, which should be considered in the treatment of the patient.

Metabolic disorders in the case of active SLE, LN are characterized by an increase in lipid atherogenicity with a decrease in high density lipoproteins and adiponectin, an increase in triglycerides, total cholesterol, low and very low density cholesterol, and increase in the level of leptin and obestatin. Metabolic problems are aggravated by an increase in serum uric acid and glucose, the development of steroid diabetes, hypovitaminosis D, as well as arterial hypertension, which contributes to the development and progression of atherosclerosis processes. The results of a myocardial and vascular wall remodeling study demonstrate that children with SLE and kidney damage are at high risk for early development of cardiovascular disorders. It seems advisable to calculate of LVMI, LVRT, measure TCIM during follow up for the purpose of timely diagnosis and preventive measures.

Morphological classification of LN ISN/RPS 2004 is mainly devoted to changes in the glomeruli of the kidneys, but we should not underestimate the contribution of tubulointerstitial lesions to the development of renal inflammation. As we can see in the 1st group, acute renal failure was noted in five children, two of which were registered at the onset.

5. Conclusion

Analysis of demographic data shows that gender ratio in childhood onset SLE is different from adults: out of 62 children 11 were boys (5,6: 1). Most cases develop in adolescence. Male gender and early debut are factors worsening the prognosis of the disease (55% of boys showed progression of CRF). In children, the disease proceeds with a high degree of activity, rapid multi-organ involvement, requires more aggressive therapy with prescription of several immunosuppressive agents, which increases the risk of infection. An analysis of the onset of the disease emphasizes that patients with autoimmune cytopenia require careful follow up because of the possible development of SLE. During the observation, percentage of patients with renal damage increases, therefore, monitoring of renal function should be carried out in all individuals with SLE, especially with an early debut. Nephritis is an unfavorable prognostic criterion and is crucial in determining the volume of therapy for SLE. Noncompliance in therapy, social status were factors of an unfavorable outcome in children. Timely diagnosis and aggressive intervention to suppress the activity of the disease should be used to prevent chronic irreversible damage. Children with SLE and kidney damage are at high risk for early development of cardiovascular disorders. Steroid-sparing strategies must be actively implemented in clinical practice in order to prevent severe side effects. Recommended duration of immunosuppressive therapy to date remains unknown.

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