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Clinical and Laboratory Investigation of Children with Systemic Lupus Erythematosus (SLE) Referring to Lupus Clinic of Dr. Sheikh Hospital, Mashhad, Iran

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Abstract

Background: Systemic lupus erythematous (SLE) is a multisystemic and autoimmune inflammatory disease characterized by production of autoantibodies against different cellular components. We aimed to investigate children with SLE in terms of clinical symptoms and laboratory findings who referred to Lupus clinic.

Materials and Methods: In this cross-sectional study, 36 children with SLE referring to lupus clinic of Dr. Sheikh hospital, Mashhad-Iran, were enrolled for one year. Clinical symptoms and involvement of different organs were completely checked and recorded at the time of diagnosis of lupus disease based on questionnaire information. The patients with nephritic manifestations of lupus underwent needle biopsies of kidneys, with the samples being examined by light microscope and immunofluorescence to investigate the extent of renal involvement. The main course of treatment included steroid- cyclophosphamide (injection and oral), hydroxychloroquine - mycophenolate (Cellcept) and Azathioprine. Then, response or lack of treatment response as well as the extent and severity of relapse were recorded based on questionnaire.

Results: In this study, out of 36 lupus patients, 30 were female (83.3%). The mean age was 9.15±4.28 years. Lupus nephritis, musculoskeletal manifestations, hematological manifestations, cutaneous manifestations, and neurological manifestations existed in 20 (55.6%), 11 (30.6%), 9 (25.0%), 7 (19.4%), and 4 (11.1%), respectively. There was no significant relationship between the age plus gender and lupus clinical manifestations. However, there was a significant relationship between relapse of disease and lupus nephritis ($p<0.05$).

Conclusion: The results of this study indicated that nephrological, musculoskeletal, hematological, and neurological manifestations are among the most common manifestations of childhood onset lupus. Concerning the diversity of symptoms in patients with lupus, performing precise examinations especially renal examinations is recommended.

Key Words: Children, Clinical symptoms, Laboratory results, Systemic Lupus Erythematous.

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1- INTRODUCTION

Systemic lupus erythematosus (SLE) is a type of multisystemic autoimmune disorder with unknown etiology, which is associated with production of antibodies against different tissues. The clinical course, activity and relapse of the disease are characterized by the level of antibody serum; in clinical practice, its manifestations include mild skin complaints, joint pains, and even risky kidney failure or different types of cytopenia (1). Definite diagnosis of the disease is based on the set of signs and symptoms. Renal, psychoneurological, cardiovascular problems as well as coagulation and hematological disorders cause mortality of these patients. Nevertheless, most of them reveal joint and skin problems earlier than its internal and laboratory signs (2-5).

In a community-based study, SLE prevalence in Iran has been estimated to be 40 per 100,000 (6). When the involvement of different organs in the patients grows and treatment response decreases or the disease is associated with frequent relapses, it leads to more severe complications and more morbidity and mortality (7-9). So far, the etiology of lupus has not been understood completely, though different factors including genetic, environmental, hormonal, and others are involved in its development (10).

The prevalence of lupus in children and teenagers is 1-6 per 100,000, which is far higher in Asian races (11). Lupus mostly develops in the female gender, such that the female to male ratio before adolescence is 2-5:1 and in reproductive years is 9:1 (10, 11). Childhood onset lupus before age of five is rare and is usually diagnosed during adolescence. Around 20% of all patients with lupus are diagnosed before the age of 16 (12, 13). Clinical manifestations of lupus during childhood or teenage period are different from those of adults. The most common clinical complaints in children with lupus include fever- fatigue- hematological disorders, arthritis, and arthralgia (14). Kidney disease in lupus is often asymptomatic, but it can be associated with edema, kidney failure, nephrotoxic syndrome, or with glomerulonephritis symptoms (15). Psychoneurological complications can emerge with silent or active lupus, and especially in teenagers who have already had mood disorders, it makes diagnosis complicated (15).

Different studies suggest that lupus and its resulting complications can lead to a significant reduction in the quality of life of patients, which is itself affected by various factors especially the severity of disease and the degeneration caused by it (16, 17). The earlier this disease is diagnosed, the better the quality of life of patients will be for the rest of their life, not to mention the therapeutic response, which also improves. Therefore, use of diagnostic methods capable of detecting this disease or treatment complications or the complications caused by the course of disease itself earlier is of high importance for improving the conditions of patients (18). This is especially evident in Third World countries, and therefore faster diagnosis and providing proper healthcare services in the course of the treatment and investigation of treatment complications confers special significance (19).

Since SLE is a multisystemic and chronic disease and can cause serious damage to many systems of the body and many times is associated with frequent relapses, thus early detection of this disease in children and teenagers, examination of clinical symptoms and laboratory findings, investigation of the extent of relapse and involvement of different organs are crucial (20, 21). Accordingly, this study was conducted with the aim of clinical and laboratory investigation of children with SLE referring to lupus clinic of Dr. Sheikh hospital.

2- MATERIALS AND METHODS

2-1. Methodology

In this cross-sectional study, 36 children with SLE referring to lupus clinic of Dr. Sheikh hospital (affiliated with Mashhad University of Medical Sciences) who had been diagnosed with SLE based on the American Rheumatology Association criteria (22, 23) were chosen as census and target-based, and included in the study for one year (Jan to Dec, 2018). For collecting the information associated with the clinical symptoms and laboratory findings of patients, systemically lupus erythematosus disease activity index (SLEDAI) was used (24). This questionnaire consists of a series of laboratory and clinical symptoms associated with lupus. Based on the questionnaire, a score lower than 6 represents inactive disease, while a score equal to or greater than 6 represents active disease. The recorded information included demographic characteristics (age, gender, etc.) along with clinical manifestations (musculoskeletal, mucous and cutaneous, psychological-neurological, pulmonary, cardiovascular, and hematological) plus paraclinical tests [(CBC and platelet count, ESR, CRP, serum creatinine and urine analysis, immunological tests such as measuring Anti-nuclear antibody (ANA) measurement, Anti-double-stranded DNA (Anti ds DNA), complement factors (CH50, C4, and C3)]. Indirect immunofluorescence method was used for Anti-ds DNA assessment. The complements were investigated by nephelometry method. The biopsy samples of kidneys were studied by optical immunofluorescence microscope. Lupus nephritis classification was performed based on WHO classification in 1982 (25). The type of the principal treatment included steroid, cyclophosphamide (injection and oral), hydroxychloroquine, and Cellcept across all studied patients. Then, response or lack of response to treatment along with the extent and severity of relapse were recorded based on questionnaire. In order to investigate the complications of consumption of steroids such as osteopenia and osteoporosis, bone densitometry (six months after drug consumption) was performed for the patients. Further, eye examination was conducted to test the possible side effects of hydroxychloroquine (3-6 months after the treatment). Chest X-ray, sonography of kidneys and urinary system, and echocardiography were also performed for all patients, and the patients were visited in 1-3-month intervals based on the severity of disease. In this study, ESR larger than 30 and Anti-ds DNA greater than 50 were considered as above the normal level. Further, C3 lower than 80 and C4 lower than 10 were regarded as below the normal level (22-25).

2-2. Inclusion criteria

This study included children and teenagers with SLE referring to lupus clinic of Dr. Sheikh hospital with an age equal to or younger than 18 years old.

2-3. Exclusion criteria

Exclusion criteria included death of patients for any reason during the investigation and renal transplantation of lupus patients suffering chronic kidney failure during the study.

2-4. Ethical considerations

This study was approved by the Ethics Committee of Mashhad University of Medical Sciences (TUMS) with the code T5250. In this study, the tests requested for patients were routine and no extra cost was incurred to the patients. All of the information acquired from the file of patients remained confidential. In this study, there was no special ethical prohibition. There was no inconsistency with international treaties regarding medical sciences such as Nuremberg and

Helsinki. All of the collected questionnaires remained confidential. The results were reported only in general. Finally, written informed consent form was taken from the parents of the patients to include them in the study.

2-5. Data analysis

The data were analyzed using SPSS software (version 22.0). For qualitative variables, frequency and percentage, while for quantitative variables, mean, standard deviation, median, and range of variations were used. In case of abnormal data distribution, nonparametric tests were employed. To compare the quantitative variables with each other, independent t-test, while to compare the qualitative variables with each other (comparing the frequency of lupus in male and female gender and others), chi-square test was utilized. P-value less than 0.05 was considered as statistically significant.

3- RESULTS

Out of the 36 studied patients, 6 (16.7%) were male and 30 (83.3%) were female. The mean age of patients was 9.15±4.28 years (median: 9, range: 0.5-18) (p=0.407). Note that 21 (58.3%) had an age range of 7-12 years.

3-1. Laboratory results

The laboratory results corresponded with clinical manifestations, and in all cases, lupus nephritis was represented with hematuria and proteinuria. Also, hematological manifestations were evident in most cases as pancytopenia. The mean level of complement component (C3) in 36 studied patients was 91.06±36.41 mg/dl, while the mean C4 complement level was 28.01±19.32 mg/dl. In 16.6% of patients, severe anemia (hemoglobulin less than 8 mg/dl) was observed. In this study, 7 had leucopenia and only 2 patients had leukocytosis. Three patients had thrombocytopenia, but thrombocytosis was not observed in any of the patients. The laboratory results are summarized in **Table.1**.

Table-1: Comparison of the results of lupus in patients studied by age group.

Lab Results	Sub-group	Number (%)
Hemoglobin, mg/dl	<10	6 (16.6)
	10-11.4	11 (30.5)
	>11.4	19 (52.9)
White blood cell, mm3	< 4000	7 (19.4)
	> 4000	29 (80.6)
Platelet, mm3	<150,000	3 (8.3)
	> 150,000	33 (91.7)
Anti-double stranded DNA	Positive	35(97.3)
	Negative	1 (2.7)
Antinuclear antibodies	Positive	35 (97.3)
	Negative	1 (2.7)
Antiphospholipid	Positive	2 (5.5)
	Negative	34 (94.5)
C3	<80	9 (25)
	>80	27 (75)
C4	<10	4 (11.1)
	>10	32 (88)

C3: Component 3; c4: Complement C4.

3-2. Clinical findings

The results of this study indicated that lupus nephritis Class III, musculoskeletal manifestations, and hematological manifestations existed in 20 (55.6%), 11 (30.6%), and 9 (25.0%) patients, respectively (**Figure.1**). The results revealed that the frequency of age groups of patients had no significant relationship with lupus manifestations in patients (p>0.05) (**Table.2**). The frequency of clinical manifestations of patients with SLE for each gender are shown in **Table.2** (p>0.05) (**Table.3**). The frequency of disease relapse for each gender is demonstrated in **Figure.2**. There was a significant relationship between relapse frequency and lupus nephritis (p=0.044). However, in other cases, none of the lupus manifestations had a significant relationship with disease relapse (p>0.05) (**Table.4**). In investigating the patients in terms of bone mineral density, 6 (16.7%), and 3 (8.3%) had osteopenia and

osteoporosis, respectively, while 18 (50.0%) were normal. Also, 9 patients (25.0%) did not refer for having their bone mineral density tested. Investigation of the ophthalmologic complications in the studied patients caused by lupus or because of consuming corticosteroids and hydroxychloroquine showed that 28 (77.7%) had no ophthalmologic complications. Four (11.1%) underwent no examination for such complications. On the other hand, one patient suffered Stevens-Johnson following cellcept intake, which, in eye examination, bilateral glaucoma was observed. One patient experienced retina involvement because of hydroxychloroquine. Two patients suffered eye involvement due to hypertension; one because of pigmentation changes in the eye choroid, and the other due to bleeding in the left eye macula. Finally, two patients had comorbidity of SLE and cataracts. One patient with hematological manifestations developed autoimmune hepatitis in the course of hospitalization, who underwent Intravenous immunoglobulin (IVIg) treatm ent accordingly. Two patients had comorbid SLE and antiphospholipid syndrome; one of them experienced thrombosis in the course of hospitalization and underwent anti-coagulation therapy. The other patient had comorbid SLE and diabetes + cataracts and hypothyroidism. Investigation of the cardiac status of the patients showed that two patients had considerable mitral regurgitatio (MR) and tricuspid regurgitation (TR), while one patient developed cardiac tamponade. Finally, two patients who were siblings and had lupus with cutaneous involvement showed reduced C1q in investigations, which indicated a genetic background.

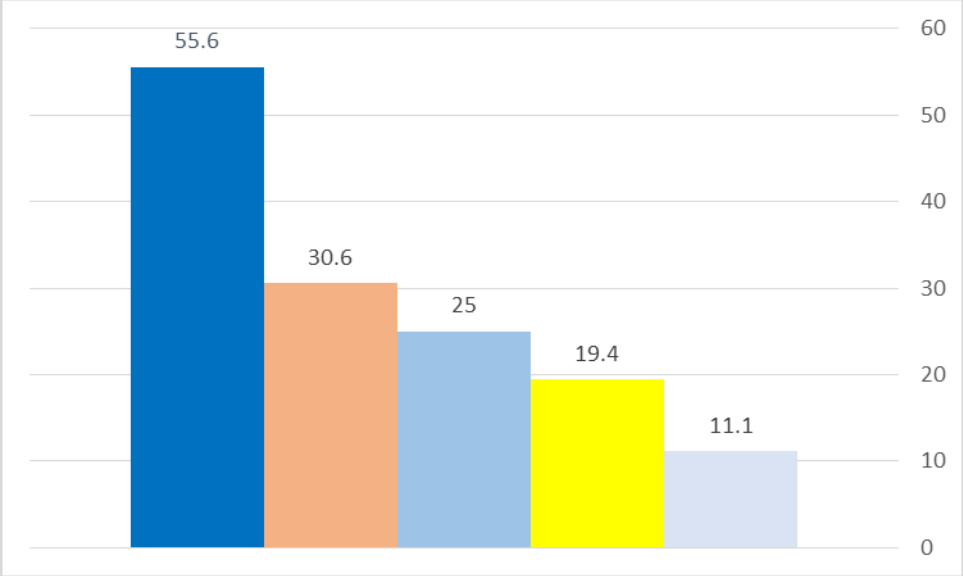

Fig.1: Clinical manifestations common in patients under study (percentage).

Table-2: Comparison of lupus manifestations in patients under study by age group.

Clinical protests	Yes/ No	Age Group, year			P-value
		< 6 (8 patients)	7-12 (21 patients)	13-18 (7 patients)	
Lupus Nephritis	Yes	7 (35)	8 (40)	5 (25)	0.069
	No	1 (6.3)	13 (81.3)	2 (12.5)	
Hematological manifestations	Yes	2 (22.2)	7 (77.8)	0	0.211
	No	6 (22.2)	14 (51.9)	7 (25.9)	
Neurological manifestations	Yes	0	3 (75)	1 (25)	0.536
	No	8 (25)	18 (56.3)	6 (18.7)	
Kutanese	Yes	1 (14.3)	5 (71.4)	1 (14.3)	0.733
	No	7 (24.1)	16 (55.2)	6 (20.7)	
Musculoskeletal manifestations	Yes	1 (9.1)	7 (63.6)	3 (27.3)	0.406
	No	7 (28)	14 (56)	4 (16)	

Table-3: Comparison of Lupus Proliferation in Patients Examined by Gender.

Clinical protests	Yes/ No	Male (6 patients)	Female (30 patients)	P-value
Lupus Nephritis	Yes	2 (10)	18 (90)	0.230
	No	4 (25)	12 (75)	
Hematological manifestations	Yes	1 (11.1)	8 (88.9)	0.606
	No	5 (18.5)	22 (81.5)	
Neurological manifestations	Yes	1 (25)	3 (75)	00.635
	No	5 (15.6)	27 (84.4)	
Kutanese	Yes	2 (28.6)	5 (71.4)	0.346
	No	4 (13.8)	25 (86.2)	
Musculoskeletal manifestations	Yes	1 (9.1)	10 (90.9)	0.418
	No	5 (20)	20 (80)	

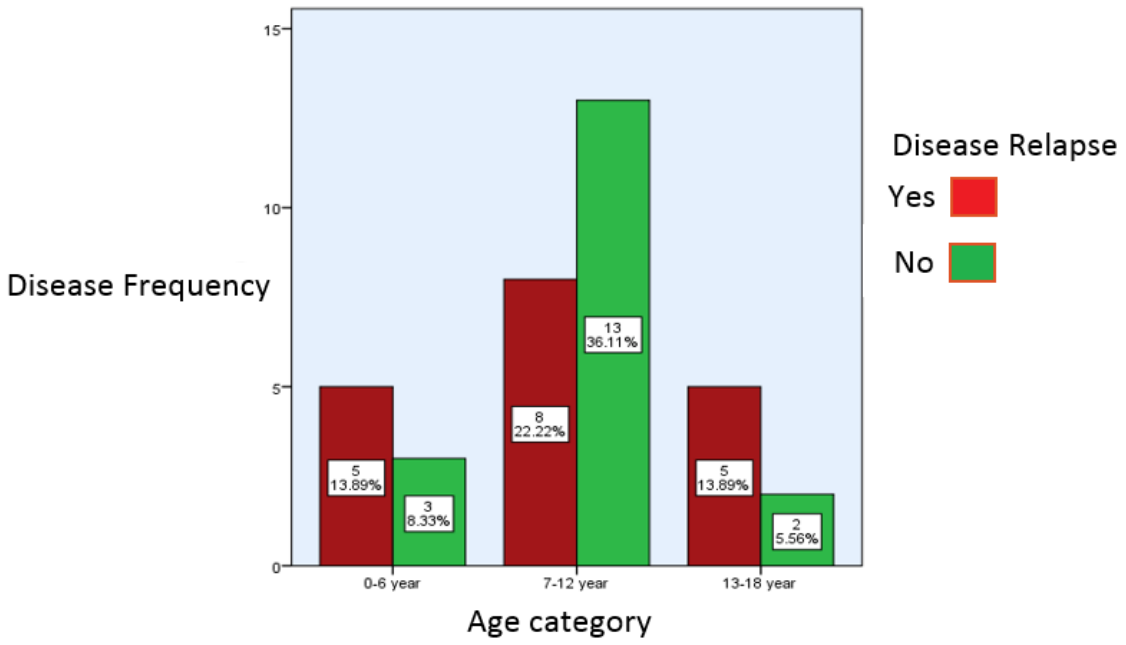

Fig.2: Frequency of recurrence of disease by age group in patients under study.

Table-4: Comparison of lupus manifestations in patients with recurrence of disease.

Clinical protests	Yes/ No	Recurrence of disease		P-value
		Yes, (18 patients)	No, (18 patients)	
Lupus Nephritis	Yes	13 (65)	7 (35)	0.044
	No	5 (31.3)	11 (68.7)	
Hematological manifestations	Yes	4 (44.4)	5 (55.6)	0.701
	No	14 (51.9)	13 (48.1)	
Neurological manifestations	Yes	2 (50)	2 (50)	0.999
	No	16 (50)	16 (50)	
Kutanese	Yes	5 (71.4)	2 (28.6)	0.206
	No	13 (44.8)	16 (55.2)	
Musculoskeletal manifestations	Yes	7 (63.6)	4 (36.4)	0.278
	No	11 (44)	14 (56)	

4- DISCUSSION

This study was performed with the aim of clinical and laboratory investigation of children with SLE referring to lupus clinic of Dr. Sheikh hospital. The results indicated that lupus nephritis class III, musculoskeletal manifestations, and hematological manifestations with involvement of 55.6%, 30.6%, and 25.0% of children were the most common manifestations of lupus in children, respectively. According to studies, kidney involvement occurs in 50-75% of patients with childhood onset lupus, and more than 90% of those who experience lupus during their childhood develop renal involvement during the first two years following the diagnosis (26). According to studies, using an aggressive treatment regimen, incidence of ESRD has decreased compared to past decades. However, still 10-20% has remained in the first 10 years of diagnosis (27, 28). Patients with ESRD need dialysis and in case of existence of a suitable donator, they can undergo renal transplantation. The study by Hiraki et al. showed that one third of patients with ESRD who received transplanted kidney during the first five years and 22% of others died within the same time period (29). In addition, there is also the risk of recurrence of nephritis in kidney transplantation (30). Overall, renal involvement is still considered an important cause of mortality which is associated with possible relapse of disease even after years of improvement (28). In this regard, in a study performed by Costagliola et al. in 2018, the number of patients with nephrological manifestations has increased considerably (from 36% of the time of diagnosis to 72.2% after 10 years of disease progression) (31). According to investigations, primary manifestations of nephrological disease range from proteinuria and microscopic hematuria to nephrotic range proteinuria, severe hypertension, peripheral edema, kidney failure, or acute kidney failure (26-29). In the present study, laboratory results were in line with clinical manifestations, and in all cases lupus nephritis was observed from the beginning of hematuria and proteinuria. Szymanik-Grzela et al. in investigating 18 children with lupus with involvement of kidneys (lupus nephritis) showed that 83% of these children developed acute kidney failure or nephritic syndrome at the beginning of the disease or during the first four months of the lupus. Further, 72% showed hypertension symptoms, and very good response of patients to cyclophosphamide pulse therapy was considerable (32). The findings of the present study showed that the musculoskeletal manifestations with 30.6% involvement was the second most common lupus manifestation in children. Studies performed in this regard have attributed musculoskeletal involvement to

the activity of lupus or secondary to the treatment. It has also been stated that arthritis occurs in 80% of patients with childhood onset lupus (33, 34). Avascular necrosis may occur in patients treated with corticosteroids (35). In addition, considerable prevalence of osteoporosis is associated with corticosteroid therapy with increased risk of fracture (33). In our study, more than 25% of patients had osteopenia and osteoporosis. Hematological manifestations with a prevalence of 25% was the third common manifestation of lupus in children in the present study. According to studies in this regard, cytopenia is common in childhood onset lupus, where more than 50% of patients experience the reduction of at least one cell line (26, 34). Mild leucopenia is the most common hematological sign, which is usually due to lymphopenia and less frequently neutropenia. While stable lymphopenia may be one of the features of active disease, neutropenia mostly develops in response to the treatment (such as in the course of cyclophosphamide treatment). Anemia can manifest in any form including chronic disease induced anemia in the form of normocytic normochromic anemia, iron deficiency anemia, or positive Coombs hemolytic anemia (36). In our study, laboratory findings were congruent with clinical manifestations, and in patients with hematological manifestations, in most cases pancytopenia was evident from the beginning. In the present study, two patients had comorbid antiphospholipid syndrome alongside lupus; one of them developed thrombosis in the course of hospitalization followed by ischemic cerebral accident and underwent anticoagulant therapy. According to studies, antiphospholipid antibodies exist in 40% of childhood onset lupus cases, which is overall associated with hyper-coagulation. Nevertheless, less than half of these patients experience a thrombolytic or thromboembolic accident (37). The most common accidents include deep vein thrombosis, cerebral vein thrombosis, and pulmonary embolism. Vascular accidents including stroke have been less observed (38). The most common antibody in lupus has been reported to be antinuclear antibody (ANA), which exists in more than 95% of patients with childhood onset lupus (39). In our study, only one patient was negative for ANA. The findings of the present study showed that neurological manifestations exist in 11% of patients. Lupus can involve both central and peripheral nervous system (40). In the present study, two patients experienced psychological manifestations during hospitalization (more disorders); one of them had hematological manifestations and the other had nephrological manifestations from the beginning of the symptoms.

5- CONCLUSION

According to the results of this study, nephrological, musculoskeletal, hematological, and neurological manifestations are among the most common manifestations of childhood onset lupus. Thus, concerning the importance of the issue and better understanding of disease manifestations for preventing the progress and possible damages to vital organs of the body, it is suggested that cohort studies with larger sample sizes as multi central be conducted, so that the necessary information for better recognizing the complications of this disease in children would be provided. Moreover, the results obtained from this study and those that will be performed in future in this regard can be used for long-term diagnostic and therapeutic planning in the country in order to prevent incidence of possible complications and incurrence of substantial costs to both the patients and the healthcare system of the country.

6- CONFLICT OF INTEREST: None.

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