

A Cross-Sectional Study to Compare Differences on Clinical and Laboratory Findings in Children with Seropositive and Seronegative Lupus

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Abstract

Background: Lupus is an inflammatory and autoimmune disease that involves various tissues and organs of the body. Identification of diagnostic elements to rapid identification of seronegative lupus cases is very important in order to prevent morbidity and progression of disease. This study aimed to compare clinical and laboratory findings of seropositive cases with seronegative lupus patients.

Methods: This cross-sectional analytic study was performed on 43 children (17 seronegative and 26 seropositive) with lupus who were admitted to Ali Asghar Hospital during 2007-2017. Seropositive patients had anti-nuclear antibody (ANA) titration $>1/80$, while seronegative patients had ANA titration $<1/80$ (at the time of disease diagnosis). Clinical and laboratory findings were compared between two groups.

Results: Serositis in patients with ANA⁻ was significantly higher than ANA⁺ (41.17% vs. 23.07%; $p = 0.042$). ANA⁻ group had higher autoimmune disease history than ANA⁺ group (42.85% vs. 15.0%; $p = 0.041$). The family history of the disease in the ANA⁻ group was greater than ANA⁺ group (50% vs. 23.52%). The percentage of hypertensive patients in ANA⁻ group was higher than ANA⁺ group (52.94% vs. 26.92%; $p = 0.037$). Neurologic symptoms in ANA⁺ and ANA⁻ groups were 38.46% and 17.64%, respectively ($p = 0.043$). The frequency of patients with thrombocytopenia in ANA⁺ group was significantly greater than ANA⁻ group (32% vs. 12.5%; $p=0.041$). There was no significant difference in other clinical and laboratory findings between two groups.

Conclusion: Seronegative lupus patients had higher percentage of musculoskeletal symptoms, autoimmune disease history, familial history of disease, and hypertension, while neurological and thrombocytopenia symptoms were higher in seropositive patients compared to seronegative cases. Therefore, evaluation of these factors can be helpful to diagnosis of seronegative patients.

Introduction

Lupus is a chronic inflammatory disease in which the autoimmune system attacks various tissues and organs of the body (e.g. joints, skin, kidneys, blood cells, brain, heart and lungs) and causes serious damage [1]. Lupus is usually divided through several categories, including systemic lupus erythematosus (SLE), skin involvement lupus, drug-induced lupus erythematosus, neonatal lupus erythematosus and pediatric lupus [2]. It is usually accompanied by symptoms such as fatigue, fever and arthritis [3]. Lupus in children is usually somewhat similar to adult lupus; however, children are often involved in the disease for a longer period of time before a definitive diagnosis [4, 5]. Since children are sick for a longer period of time before lupus diagnosis, their internal organs are more likely to be involved and hurt at the time of diagnosis [5]. The risk of kidney involvement in children with lupus is approximately twice more than adult patients [4]. Therefore, children suspected of be involved with lupus need serious care strategies than adults [6]. Symptoms in pediatric lupus are highly various with more abnormal clinical presentation compared to adults [7]. In Some cases the disease is presented with typical symptoms such as fever, rash

(40 to 60% of cases) and renal dysfunction [8]. Others may be presented with fatigue and pain. Some children look good, but their urine sample may have blood or other invisible problems that can help a physician to diagnose it [9]. The other clinical symptoms are light sensitivity (35 to 50% of cases), alopecia (15 to 30% of cases), oral ulcers (20 to 30% of cases), arthritis (60 to 70% of cases), central nervous involvement (20 to 45% of cases), respiratory problems (15 to 40% of cases), and pericarditis (10 to 15%) [7, 10]. The laboratory findings of pediatric lupus usually contain hyper-gammaglobulinemia, anemia, leukopenia or lymphopenia, thrombocytopenia, hypo-albuminemia, and increased erythrocyte deposition [7, 11]. The presence of anti-dsDNA (in 50 to 85% of cases) is commonly used to confirm the diagnosis. Although the positive result of anti-nuclear antibodies (ANA) test is needed for definitive confirmation of the diagnosis in more than 90% of cases, there are also many ANA positive children without lupus [12]. On the other hand, there are children with lupus who may have negative ANA test result. These children with seronegative lupus usually comprise 1–5% of the lupus patients [13].

Despite these clinical and laboratory tests, there are still patients with negative serological test results which make the precise diagnosis difficult for clinicians. Therefore, evaluating of clinical and laboratory test results in children with seronegative lupus is very helpful to find out valuable findings (s) for rapid diagnosis of the disease. In this study, we aimed to consider clinical and laboratory findings of children with lupus (including seronegative and seropositive cases) who referred to Ali Asghar Hospital from the year of 2007 to 2017 to find out appropriate elements to identify seronegative patients.

Materials And Methods

In this cross-sectional analytic study, all seronegative and seropositive Systemic Lupus Erythematosus patients aged less than 16 years who were admitted to Ali Asghar Hospital (Tehran, Iran) from the year of 2007 to 2017 were included. The study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1397.256). At the beginning of the study, a checklist was provided in which information on demographic and basic clinical data of all patients such as age, sex, BMI, systolic (SBP) and diastolic blood (DBP) pressures, family history of diseases, history of drug consumption, and family history of autoimmune diseases were recorded. Patients with incomplete clinical and laboratory documents were excluded from the study. Eventually, 43 patients (17 seropositive and 26 seronegative) were selected for further evaluations. Patients were divided into two groups of ANA positive (titration $>1/80$) and ANA negative (titration $<1/80$) at the time of the disease diagnosis. Patients in both groups were considered phenotypically for general, cutaneous and musculoskeletal symptoms, as well as for neuropsychological, gastrointestinal, pulmonary and renal symptoms, and renal biopsy test results. Furthermore, the laboratory and immunological test results of patients in each group, including CBC, proteinuria, hypergammaglobulinemia, hematuria, direct coombs test, complements levels, and serum antibodies (e.g. Anti-dsDNA, Anti-phospholipid antibodies, p-ANCA and c-ANCA) were compared.

Statistical analysis

All quantitative data were analyzed using the descriptive program and presented as Mean \pm SD. Crosstabs and Chi-Square tests were used to compare the percentage or frequency of findings between two groups. The comparison of the mean of quantitative data between two groups was analyzed using independent sample-t test. In this study, $p < 0.05$ was considered statistically significant. The SPSS software (IBM, version 19) was applied for data analysis.

Results

A total of 43 cases with mean age of 10.81 ± 3.16 years (ranged from 1 to 15 years old) and BMI of 18.25 ± 2.63 kg/m² (ranged from 13.36 kg/m² to 24.49 kg/m²) were included into the study. Overall, 13 patients (30.2%) were boys and 30 cases (69.8%) were girls.

Comparison of the basic demographic and clinical findings of cases between ANA⁺ and ANA⁻ is summarized in Table 1. Totally, 26 patients (60.46%) were ANA⁺ and 17 cases (39.53%) were ANA⁻. There was no significant in the mean of age ($p=0.42$), BMI ($p=0.3$) and sex distribution ($p=0.55$) between ANA⁺ and ANA⁻ groups. The percentage of girls in both groups was significantly higher than boys ($p < 0.05$). Twenty-five (58.13%) out of 43 patients had at least one of the general symptoms such as fatigue, anorexia, weight loss, fever and lymphadenopathy. The prevalence of general symptoms in ANA⁺ and ANA⁻ groups was 53.84% and 64.7%, respectively ($p=0.39$). Overall, cutaneous examination of all patients showed that 29 patients (67.44%) had at least one of the mucocutaneous manifestations, including malar rash, photosynthesis, oral ulcer, nasal ulcer and maculopapular rash. The frequency of cutaneous manifestation in ANA⁺ and ANA⁻ groups was 69.23% and 64.7%, respectively ($p=0.79$). Thirteen patients (30.23%) had at least one of the neuropsychological manifestations, including convulsion, psychosis, headache, depression, and anxiety. The incidence of neuropsychological symptoms in patients in the ANA⁺ group was approximately twice that of the ANA⁻ group (38.46% vs. 17.64%; $p=0.043$). Seventeen patients (39.53%) had at least one of the gastrointestinal symptoms, including hepatosplenomegaly, intestinal vasculitis, pancreatitis, abdominal pain, and rectal surgery. The distribution of gastrointestinal symptoms in ANA⁺ and ANA⁻ groups was 38.46% and 41.17%, respectively ($p=0.62$). Twenty-three patients (53.48%) had at least one musculoskeletal manifestations such as arthritis, synovitis, arthralgia and myalgia. The frequency of musculoskeletal symptoms in ANA⁻ group was slightly greater than ANA⁺ group (64.7% vs. 46.15%; $p=0.09$). Seventeen patients (39.53%) had at least one of the renal symptoms such as edema, nausea, vomiting, ascites and oliguria. The distribution of renal complaints in ANA⁺ and ANA⁻ groups was 38.46% and 41.17%, respectively ($p=0.68$). The information of the history of autoimmune disease (such as hypothyroidism, vitiligo) was available for 27 patients (20 in ANA⁺ and 7 in ANA⁻ group). Patients in the ANA⁻ had significantly higher percentage of autoimmune disease history compared to those in the ANA⁺ group (42.85% vs. 15.0%; $p=0.041$). The information of family history of the autoimmune disease was available for 21 patients (17 in ANA⁺ and 4 in ANA⁻ group). The family history of the autoimmune disease in ANA⁻ group was relatively higher than that in ANA⁺ group (50% vs. 23.52%; $p=0.29$). The prevalence of patients with

hypertension in ANA⁻ group was significantly higher than ANA⁺ group (52.94% vs. 26.92%; p=0.037). Thirteen patients (30.23%) had serositis (7 patients in ANA⁺ and 6 patients in ANA⁻ group). The prevalence of patients with serositis in ANA⁻ group was significantly higher than ANA⁺ group (41.17% vs. 23.07%; p=0.042). The frequency of patients with leukopenia or lymphopenia in ANA⁺ and ANA⁻ group was 40.0% and 31.25%, respectively (p=0.68). The frequency of patients with thrombocytopenia in ANA⁺ group was significantly greater than ANA⁻ group (32% vs. 12.5%; p=0.041). Although there was no significant difference in the frequency of positive and negative results of direct Coombs between two groups, the direct positive Coombs in ANA⁺ group was relatively higher than ANA group (43.75% vs. 20%; p=0.34). There was no significant difference in the frequency of dsDNA test result between two groups; however, patients in ANA⁺ had slightly higher percentage of dsDNA positive compared to those with ANA⁻ (80% vs. 66.66%; p=0.34). Anti-phospholipid antibody test result didn't show a significant difference between two groups (p=0.21). Most patients in both groups (88.88% in ANA⁺ and 100% in ANA⁻) had negative anti-phospholipid antibody test result. There was no significant difference in the p-ANCA and c-ANCA test results between two groups.

Table 1
The basic demographic and clinical characteristics of patients

Variables	ANA⁺	ANA⁻	p-value
Age at diagnosis (year)	10.50 ± 3.68	11.29 ± 2.14	0.42
BMI (kg/m ²)	17.91 ± 2.68	18.79 ± 2.55	0.30
Gender			
Boys (%)	7 (26.9%)	6 (35.29%)	0.55
Girls (%)	19 (73.37%)	11 (64.7%)	
General symptoms	14 (53.84%)	11 (64.7%)	0.39
Cutaneous symptoms	18 (69.23%)	11 (64.7%)	0.79
Neuropsychological symptoms	10 (38.46%)	3 (17.64%)	0.043
Gastrointestinal symptoms	10 (38.46%)	7 (41.17%)	0.62
Musculoskeletal symptom	12 (46.15%)	11 (64.7%)	0.09
Renal symptoms	10 (38.46%)	7 (41.17%)	0.68
History of autoimmune disease			
Yes (%)	3 (15%)	3 (42.85%)	0.041
No (%)	17 (85%)	4 (57.14%)	
Family history			
Yes (%)	4 (23.52%)	2 (50%)	0.29
No (%)	13 (76.47%)	2 (50%)	
Hypertension			
Yes (%)	7 (26.92%)	9 (52.94%)	0.037
No (%)	19 (73.07%)	8 (47.05%)	
Serositis			
Yes (%)	6 (23.07%)	7 (41.17%)	0.042
No (%)	20 (76.92%)	10 (58.82%)	
Leukopenia or lymphopenia			
Yes (%)	10 (40%)	5 (31.25%)	0.68
No (%)	15 (60%)	11 (68.75%)	

Variables	ANA ⁺	ANA ⁻	p-value
Thrombocytopenia			
Yes (%)	8 (32%)	2 (12.5%)	0.041
No (%)	17 (68%)	14 (87.5%)	
Direct coombs			
Positive (%)	7 (43.75%)	1 (20%)	0.34
Negative (%)	9 (56.25%)	4 (80%)	
dsDNA			
Positive (%)	20 (80%)	10 (66.66%)	0.34
Negative (%)	5 (20%)	5 (33.33%)	
Anti-phospholipid antibodies			
Positive (%)	1 (11.11%)	0	0.21
Negative (%)	8 (88.88%)	5 (100%)	
p-ANCA			
Positive (%)	1 (12.5%)	1 (14.28%)	0.97
Negative (%)	7 (87.5%)	6 (85.71%)	
c-ANCA			
Positive (%)	8 (100%)	6 (100%)	1
Negative (%)	0	0	

Comparison of the mean levels of C3, C4 and CH50 complements between ANA positive and negative groups is shown in Table 2. There was no significant difference in C3 ($p = 0.086$), C4 ($p = 0.51$) and CH50 ($p = 0.58$) levels between the two groups. However, approximately 76% of patients in the ANA⁺ had reduced C3, whereas this was 50% for patients in ANA⁻ group. 64% of patients in ANA⁺ group had decreased C4 level, while it was declined in 57.14% of in ANA⁻ group.

Table 2
Comparison of the complement levels between two groups

		ANA		p-value
		Positive	Negative	
C3	Increase	0	2 (14.28%)	0.086
	Decrease	19 (76%)	7 (50%)	
	Normal	6 (24%)	5 (35.71%)	
C4	Increase	1 (4%)	2 (14.28%)	0.51
	Decrease	16 (64%)	8 (57.14%)	
	Normal	8 (32%)	4 (28.57%)	
CH50	Increase	1 (5.88%)	0	0.58
	Decrease	9 (52.94%)	6 (46.15%)	
	Normal	7 (41.17%)	7 (53.84%)	

Comparison of the renal biopsy between two groups is shown in Table 3. Renal biopsy results were available for 29 patients (17 patients in ANA⁺ and 12 patients in ANA⁻ group). Overall, there was no significant difference in the renal biopsy results between the two groups ($p = 0.84$). 16 patients in ANA⁺ had lupus nephritis of varying degrees and only one patient had a normal biopsy. 11 patients in ANA⁻ group had lupus nephritis of varying degrees and only one patient had a normal biopsy. 5.88% of patients in ANA⁺ and 8.33% of patients in ANA⁻ group had normal biopsy results. The highest frequency of renal involvement in both groups was class IV (47.05% of patients in ANA⁺ and 50.0% of patients in ANA⁺ group). The second highest frequency in both groups was related to class V (17.64% in ANA⁺ and 16.66% in ANA⁻ group). 17.64% of patients in ANA⁺ and 8.33% of patients in ANA⁻ had class II.

There was no significant difference in the frequency of proteinuria between two groups ($p = 0.42$). The frequency of proteinuria in ANA⁺ and ANA⁻ patients was 82.6% and 78.57%, respectively. There was no significant difference in the frequency of normal, sub-nephrotic (nephritic) and nephrotic state between two groups ($p = 0.41$). The most common form of proteinuria in ANA⁺ was nephritic (52.17%), whereas the most common form proteinuria in ANA⁻ group was nephrotic (42.85%). There was no significant difference in the frequency hematuria between two groups ($p = 0.48$). 81.25% of ANA⁺ patients and 91.66% of ANA⁻ patients had hematuria.

Discussion

In this study, 26 patients (60.46%) were seropositive (ANA⁺) and 17 patients (39.53%) were seronegative (ANA⁻). The frequency of seronegative patients in our study was somewhat more than other previous

studies because this research was conducted in long period of time at the Ali Asghar Pediatric Hospital, a referral center in Iran in which many patients even from neighboring countries are referred for diagnostic and treatment procedures. Furthermore, we compared the clinical and laboratory findings of patients at the time of diagnosis and we didn't intend ANA⁻ patients who had been changed to ANA⁺ in the course of the disease because the purpose of this study was to identify the underlying factors for the diagnose of the disease and seroconversion was not the purpose of this study. We also found that the proportion of female patients in both groups was nearly twice as high as that of boys, indicating a higher incidence of Lupus in girls than boys. Many studies reported that the incidence of lupus in girls is higher than boys [6, 12, 14]. For example, Murashima *et al.*, [15], showed that the incidence of ANA⁺ was significantly higher in girls than boys; and 9 out of 10 patients who had ANA⁺ at the second visit were girl. In another study, Moradinejad *et al.*, [16] reported that the ratio of female to male with SLE was 8 to 1 and aged between 0 3 to 16 years(sample size=45). In another study, Hiraki *et al.*, [17]examined 256 children with SLE and revealed that the ratio of girls to boys with SLE was 4.7, which is somewhat consistent with the results of our study. Salah *et al.*, [18] showed that the ration of girls to boys with SLE was 2.7 which is in line with our results. In our study, although the percentage of girls with SLE was higher than boys, there was no significant difference in sex distribution between ANA⁺ and ANA⁻ groups.

So far, very few studies have compared the results of clinical and laboratory findings between patients with lupus, especially between seropositive and seropositive children. The results of our study didn't show a significant difference in general symptoms such as fatigue, anorexia, weight loss, fever and lymphadenopathy between the ANA⁺ and ANA⁻ groups. The frequency of general symptoms in ANA⁺ and ANA⁻ patients was 53.84% and 64.7%, respectively. Our study also did not show a significant difference in the frequency of skin symptoms between the two groups. Interestingly, the results of our study showed a significant difference in the frequency of neuropsychiatric symptoms, including convulsion, psychosis, headache, depression, anxiety, and between the two groups. The incidence of neurological symptoms in ANA⁺ group was approximately twice that of the ANA⁻ group. The frequency of neurological symptoms in patients in ANA⁺ and ANA⁻ groups was 38.46% and 17.64%, respectively. Thus, the results of this study suggest that neuropsychiatric manifestations can be one of the diagnostic tools used in the differentiation of seropositive and seronegative SLE patients.

The results of our study did not show a significant difference in the frequency of gastrointestinal involvement, including HSM, intestinal vasculitis, pancreatitis, abdominal pain. The frequency of gastrointestinal presentations in ANA⁺ and ANA⁻ groups was 38.46% and 41.17%, respectively. Although there was no significant difference in the frequency of musculoskeletal symptoms between two groups, its prevalence was somewhat higher in ANA⁻ patients (64.7%) than ANA⁺ (46.15%). Therefore, it seems that musculoskeletal symptoms may also be a useful diagnostic tool for the differentiation of seropositive and seropositive patients; however, further studies with larger sample sizes are needed to confirm it. The frequency of renal complaints, including edema, nausea, vomiting, ascites, and oliguria in ANA⁺ and ANA⁻ groups was 38.46% and 41.17%, respectively, and didn't show a significant difference.

Numerous studies have investigated the prevalence of clinical symptoms in patients with SLE. Moradinejad *et al.*, [16] reported that the most common type of symptoms in children with SLE was skin and musculoskeletal involvements, kidney problems and hematologic abnormalities by 88.8%, 77.7%, 64.4% and 55.5%, respectively. The prevalence of heart disease, central neurological involvement and lung disease was 26%, 17%, and 11%, respectively. Hiraki *et al.*, (18) reported that the most common clinical findings in children with SLE were arthritis (67%), malarial rash (66%), nephritis (55%), systemic involvement, and central nervous system (27%). In another study, Ramírez Gómez *et al.*, [19] examined 230 children under the age of 18 with SLE and reported that malarial rash, fever, oral ulcers, thrombocytopenia and hemolytic anemia and neuropsychiatric problems were the most common clinical symptoms in these patients. Salah *et al.*, (19) considered 207 children aged 2 to 16 years with SLE and showed that nephritis (67%), hematological findings (44.9%), photosynthesis (44%), arthritis (39%), malarial rash (38.2%), cervicitis (32.9%), and neurological findings (24.25%) were significantly increased during the follow-up. Sibbitt *et al.*, (11) demonstrated that the most common clinical symptoms in children with SLE were headache (72%), mental disorders (57%), consciousness disorders (55%), seizures (51%), acute perturbation (35%), emotional disorders (21%), central nervous system involvement (15%), cerebrovascular disease (12%), psychosis (12%), chorea (7%), syndrome Demineralization (4%), and myelopathy (1%). Deborah *et al.*, [20] reported that the most common clinical findings in children with SLE included fever (37- 100%), lymphadenopathy (13-45%), weight loss (-32%). 21%), mucocutaneous (60-90%), musculoskeletal (60-90%), nephritis (48-78%), NPSLE (15-95%), gastrointestinal problems (24-40%), hematological disorders (50%-100%), heart problems (25-60%), and pulmonary problems (18-81%).

Another finding of our study was related to the history of autoimmune disease between two groups. Patients in ANA⁻ group had higher autoimmune disease history compared to ANA⁺ group (42.85% vs 15.0%). It is clinically valuable and can be helpful for the prognosis and distinguish of seronegative from seropositive patients. However, further studies with larger sample size should be undertaken. In our study, although there was no significant difference in the family history of the disease between two groups, patients in ANA⁻ group had somewhat higher family history of the disease (50% compared to 23.52%).

Interestingly, the results of our study showed a significant difference in the frequency of hypertension between two groups. The frequency of hypertensive patients in ANA⁻ group (52.94%) was significantly higher than those in ANA⁺ group (26.92%). This data suggests that a history of hypertension can be considered as one of the risk factors for the possibility of lupus seronegative. Along with hypertension, our results showed that the prevalence of serositis ANA⁻ group (41.17%) was significantly higher than patients in ANA⁺ group (23.07%). We didn't find significant difference in other parameters such as CBC, complements levels, direct coombs, renal biopsy result, prevalence of proteinuria and hematuria, as well as prevalence of leukopenia and lymphopenia between two groups; however, the prevalence of patients with thrombocytopenia in ANA⁺ group was significantly higher than those in ANA⁻ group (32% vs. 12.5%). There was no significant difference in the serum antibodies levels including anti-dsDNA, antiphospholipid antibodies, p-ANCA and c-ANCA between two groups. Similarly, Murashima *et al.*, [15] found non-significant difference in the prevalence of anti-DNA and anti-phospholipid antibodies in children with SLE

and the control group. Therefore, it seems that investigating several risk factors such as autoimmune and family history of the disease together, hypertension, serositis and musculoskeletal symptoms can be considered for the diagnosis seronegative patients from seropositive patients.

Conclusion

According to the results of this study, seronegative lupus patients compared with seropositive patients have higher percentage of musculoskeletal symptoms, autoimmune disease history, familial history of disease, and hypertension, whereas neurological and thrombocytopenia symptoms were higher in seropositive patients compared to seronegative cases. Therefore, evaluation of these factors can be helpful to diagnose and differentiate of seronegative from seropositive patients. Since one of the limitations of this study was related to small sample size, it is worthwhile to conduct another comprehensive study with larger sample size to confirm the diagnostic role of these factors in seronegative lupus children.

Declarations

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Conflicts of interest/Competing interests: The author declare they have no conflict of interest

Availability of data and material: Not applicable

Code availability: Not applicable

Authors' contributions: **SSH**, the acquisition, analysis and interpretation of data for the article.. **RS**, contributed the data and designed analysis. **RH**, Approved the version to be published **MSH**, collected the data.

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Iran University of Medical Sciences (No.IR.IUMS.FMD.REC.1397.256).

Informed consent: Written informed consent was obtained from the parents.

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