Van Med J 31 (3): 172-178, 2024
DOI: 10.5505/vmj.2024.66375

Associations of Raynaud's Phenomenon in Juvenile Onset Systemic Lupus Erythematosus

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Abstract

Introduction: Raynaud's phenomenon (RP) is associated with mild disease in adults with systemic lupus erythematosus (SLE). Although RP is more frequently reported in juvenile onset SLE (jSLE) clinical associations were not studied. We aimed to investigate whether the presence of RP is associated with clinical and serological features at onset and outcomes in children with SLE.

Methods: Medical charts of children diagnosed with jSLE were reviewed. The presence of RP was evaluated by the presence of patients reporting symptoms, and patients were compared according to the presence of RP.

Results: Among the 52 included patients, 13 (25.0%) displayed RP. The clinical and laboratory features did not significantly differ according to the presence of RP. However, positive anti-dsDNA (76.9% vs. 35.8%), anti-RNP (53.8% vs. 17.9%), and anti-centromere (23.0% vs. 2.5%) antibodies were more frequently observed in patients with RP than in those without. RP was not found to be associated with initial disease severity, flare rate, remission, or damage accrual.

Conclusion: RP was associated with certain serological features. However, RP was not strongly associated with clinical features. Moreover, neither disease severity nor disease outcomes differed according to the presence of RP in children with SLE.

Key words: Anti-ribosomal P protein autoantibodies; outcomes; raynaud phenomenon; severity; systemic lupus erythematosus.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a relapsing nature. A diagnosis of SLE before 16 years of age is called juvenile SLE (jSLE) and comprises 15–20% of all patients with SLE (1). jSLE differs from its adult counterparts with more frequent major organ/system involvement and serological activity with a higher rate of damage accrual in a relatively shorter time (1,2). Skin is among the most frequently involved organs and can be seen in up to 85% of patients with SLE. Although not included in the classification criteria, Raynaud's phenomenon (RP) is regarded as a cutaneous manifestation of SLE (3).The term RP is used to describe the constellation of symptoms following the sequence of blanching, cyanosis, and erythema due to vasospasm of the small vessels of the distal extremities, especially the fingers (4). Although believed to be rare, RP can be seen in healthy children, predominantly in females, mostly aged 12–15 years (5). In a survey-based study of 720 children, symptoms suggesting RP were reported by 18% of girls and 12% of boys (6). Although the exact prevalence of RP in patients with jSLE is unknown, observation of RP in SLE seems to be more frequent than that in healthy individuals (2,7). The presence of RP is higher in the presence of systemic sclerosis-specific autoantibodies, especially anti-centromere autoantirbodies, in autoimmune diseases, including SLE (8). Previous studies have shown contrasting results regarding whether RP in patients with SLE is associated with a milder or more severe disease course (9,10). In this study, we aimed to investigate the association between RP and clinical and laboratory features in patients with jSLE and determine whether the presence of RP is associated with disease outcomes.

Materials and Methods

Medical records of children diagnosed with jSLE between January 2012 and December 2021 were reviewed. Patients who fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for Systemic Lupus Erythematosus (11) were included. Patients with

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Received: 15.03.2024, **Accepted:** 15.05.2024

other antinuclear antibody-associated diseases were excluded. Demographic, clinical, and laboratory features associated with SLE at disease onset were extracted from medical charts. The diagnosis of RP was based on the presence of patient-reported classical symptoms of RP, and patients were grouped according to the presence of RP. The Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) was used to assess disease activity at the baseline and at each visit (12). In addition to disease activity, every visit to all patients was assessed for the presence of flares and remission. The term flare was used for new-onset hematological, renal, nervous system, or musculoskeletal involvement or worsening of a previous manifestation that required pulse methylprednisolone, new immunosuppressive, and/or an increase in prednisolone dose of more than 10 mg (13). The flare rate is calculated by dividing the total number of flares by the observation period. Remission was defined according to the definition of remission in SLE (DORIS), and patients with clinical SLEDAI=0, physician global assessment <0.5, on stable immunosuppressants and/or biologics with a prednisolone equivalent dose of glucocorticoid <5 mg/day were accepted as having attained remission (14). SLE-associated cumulative damage was assessed using the SLICC/American College of Rheumatology Damage Index (SDI) at the last visit (15). Written consent was obtained from all patients participating in our study in accordance with the Declaration of Helsinki.

Ethical approval : Ethical approval was obtained from the Karadeniz Technical University Medical Faculty Clinical Research Ethics Committee.

Staistical analysis: Descriptive statistics are presented as frequencies with percentages and means with standard deviations or medians with interquartile ranges (IQR). Data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared using the Student's t-test or Mann-Whitney U test according to the distribution of the data. Analysis of categorical variables was performed using Fisher's exact test. The level of significance was set at p value < 0.05. All statistical analyses were conducted using the SPSS software version 23.0.

Results

Fifty-two patients with juvenile-onset systemic lupus erythematosus were included in the study. Of the patients, 43 (82.7%) were female, and the median follow-up duration was 40.7 (interquartile range (IQR): 17.2-59.0) months. The mean age at diagnosis was 13.2 ± 3.3 years. The hematological system was the most frequently observed systemic involvement in 35 (69.0%) patients, followed by musculoskeletal involvement in 31 (59.6%), and cutaneous involvement in 26 (50.0%). Kidney involvement was observed in 24 (46.2%) patients. The median SLEDAI score at onset was 13.4 (IQR: 7-18.75). While low complement C3 levels were observed in 42 (80.0%) patients, low

Table 1: Demographical, clinical, and laboratory features of 52 patients with jSLE

Demographics	n (%)
Age at diagnosis (years) mean ± SD	13.2 ± 3.3
Female	43 (82.7)
Duration of follow-up (months) median (IQR)	40.7 (17.2-59)
Clinical Features	
Hematologic involvement	35 (68.8)
Constitutional symptoms	30 (57.7)
Musculoskeletal involvement	31 (59.6)
Cutaneous involvement	26 (50)
Kidney involvement	24 (46.2)
Oral/nasal ulcers	14 (26.9)
Raynaud phenomenon	13 (25.0)
Neurologic involvement	9 (17.3)
Serositis	7 (13.5)
Non scarring alopecia	8 (15.4)
SLEDAI at onset median (IQR)	13.4 (7-18.75)
Laboratory Features	
Low complement C3	42 (80.8)
Low complement C4	26 (50.0)
Lymphopenia	25 (48.1)
Leukopenia	19 (36.5)
Thrombocytopenia	17 (32.7)
Hypergammaglobulinemia	17 (32.7)
Positive Coombs test	25 (48.1)
Autoimmune hemolytic anemia	15 (28,8)
Serological Features	
Antinuclear antibody	51 (98.0)
Anti-Sm antibody	25 (48.1)
Anti-dsDNA antibody	24 (46.2)
Anti-RNP antibody	14 (26.9)
Anti-SSA antibody	11 (21.2)
Anti-phospholipid antibodies	11 (21.2)
Anti-ribosomal-P antibody	9 (17.3)
Anti-centromere antibody	4 (7.7)
Anti-SSB antibody	1 (1.9)

jSLE: juvenile onset systemic lupus erythematosus, **n:** number, **SD:** standard deviation, **SLEDAI:** systemic lupus erythematosus disease activity index

complement C4 levels were present in 26 (50.0%) patients. A positive antinuclear antibody was observed in 98 percent of patients. Extractable nuclear antigen panel investigation revealed that anti-Smith antibody was the most commonly observed autoantibody in 25 (48.1%) patients, followed by anti-dsDNA antibody in 24 (46.2%) patients. A positive anti-RNP antibody result was observed in 14 patients (26.9 %). All the patients received hydroxychloroquine and oral prednisolone. Pulse methylprednisolone was used in 29 (55.8%) patients, cyclophosphamide in 18 (34.6 %), and mycophenolate mofetil in 10 (19.2 %) across the entire patient cohort. In addition to these treatments, methotrexate in 4 (7.7%) and tacrolimus, intravenous immunoglobulin, and rituximab in 3 (5.8%) patients were employed. Demographic, clinical, and laboratory features of the cohort are presented in Table 1. Among the patients, four (two with RP) died within the first 3 months of treatment; thus, these patients were not included in the analysis of remission, flare ratio, and damage. A comparison of demographic and clinical features according to the presence of RP revealed no significant differences (Table 2).

Table 2: Comparison of demographical, clinical and laboratory features according to presence of Raynaud's phenomenon in patients with jSLE

	Patients with RP n: 13 (%)	**Patients without RP n: 39 (%)**	***p* value**
Gender (female)	12 (92.3)	31 (79.4)	0.42
Age of diagnosis, (years) mean±SD	14.6 ±1.3	12.8±3.7	0.20
Duration of follow up, (months) median (IQR)	36 (15-66)	41 (17-58)	0.94
Clinical features			
Fever	3 (23.0)	18 (46.1)	0.19
Oral/nasal aphthous	3 (23.0)	11 (28.2)	1.00
Alopecia	3 (23.0)	5 (12.8)	0.39
Serositis	2 (15.3)	5 (12.8)	1.00
Cutaneous involvement	8 (61.5)	18 (46.1)	0.52
Musculoskeletal involvement	9 (69.2)	22 (56.4)	0.52
Renal involvement	7 (53.8)	17 (43.6)	0.54
CNS involvement	2 (1.5)	7 (1.8)	1.00
SLEDAI at onset median (IQR)	12.0 (8.5-23.5)	11.0 (5.0-18.0)	0.35
Laboratory features			
Autoimmune hemolytic anemia	5 (3.8)	10 (2.5)	0.48
Leukopenia	4 (30.8)	15 (38.5)	0.74
Thrombocytopenia	3 (23.0)	14 (35.9)	0.50
Low complement C3	12 (92.3)	30 (76.9)	0.41
Low complement C4	9 (69.2)	17 (43.6)	0.19
Coombs positivity	7 (53.8)	18 (46.1)	0.75

jSLE: juvenile onset systemic lupus erythematosus, **RP:** Raynaud's phenomenon n: number **SD:** standard deviation, **IQR:** interquartile range, **CNS:** central nervous system, **SLEDAI:** systemic lupus erythematosus disease activity index, *p* value:< 0.05, Mann-Whitney U test, Fischer's exact test

Table 3: Comparison of hematological indices, inflammatory markers and complement levels at disease onset in patients with jSLE according to presence of Raynaud's phenomenon

	Patients with RP	**Patients without RP**	***p* value**
Hemoglobin (g/dL) mean ± SD	10.2±1.7	10.5±2.4	0.59
Leukocytes ($x10^9$/L) median (IQR)	4.5 (3.0-5.9)	4.20 (2.9-9.5)	0.59
Lymphocytes ($x10^9$/L) median (IQR)	1.0 (0.6-1.3)	1.05 (0.75-1.9)	0.11
Thrombocytes ($x10^9$/L) median (IQR)	220 (112-285)	157 (71-287)	0.36
Sedimentation (mm/hr) median (IQR)	53.0 (27.5-80.5)	43.0 (18-72)	0.47
Complement C3 (g/L) median (IQR)	64 (21.5-76.5)	71 (45-88)	0.31
Complement C4 (g/L) median (IQR)	6.0 (5-15)	10 (5-13)	0.51

jSLE: juvenile onset systemic lupus erythematosus, **RP:** Raynaud's phenomenon, **IQR:** Interquartile range, **SD:** Standard deviation, ***p* value:**< 0.05, Mann-Whitney U test, Fischer's exact test

In addition, the treatments did not differ according to the presence of RP in terms of pulse methylprednisolone, cyclophosphamide, and mycophenolate mofetil. In addition, hematological indices, such as hemoglobin, leukocyte count, thrombocyte count, and inflammatory markers at onset, were not statistically different between patients with and without RP (Table 3). Assessment of the autoantibody profile revealed significantly more frequent positive anti-dsDNA (76.9% vs. 35.8%, p = 0.02), RNP (53.8% vs. 17.9%, p = 0.02), and centromere (23.0% vs. 2.5%, p = 0.04) antibodies in patients with RP than in those without (Table 4). Remission was observed in 34 (70.8%), patients and 23 (47.9%) patients had damage associated with SLE at the last visit. Comparison of outcomes such as flare rate, frequency of remission, patients with

Table 4: Comparison of autoantibody profile and outcomes according to presence of Raynaud's phenomenon in jSLE

Serological features	Patients with RP n:13 (%)	Patients without RP n:39 (%)	*p* value
Anti-dsDNA	10 (76.9)	14 (35.8)	0.02
Anti-Sm	8 (61.5)	17 (43.5)	0.34
Anti-RNP	7 (53.8)	7 (17.9)	0.02
Anti SS-A	2 (15.3)	9 (23.0)	0.70
APLA	5 (38.4)	6 (15.3)	0.11
Anti-Ribosomal p	3 (23.0)	6 (15.3)	0.67
Anti-centromere	3 (23.0)	1 (2.5)	0.04
Outcomes	n: 11 (%)	n: 37 (%)	
Flare rate$^{\alpha}$, median (IQR)	0.03 (0- 0.11)	0.02 (0- 0.05)	0.39
Patients with remission	7 (63.6)	27 (73.0)	0.71
Damage, median (IQR)	0 (0-1)	1 (0-2)	0.25
Patients with damage	4 (36.4)	19 (51.4)	0.49

jSLE: juvenile onset systemic lupus erythematosus, **RP:** Raynaud's phenomenon **n:** number, **dsDNA:** double stranded deoxyribonucleic acid, **Sm:** smith, **RNP:** ribonucleoprotein, **SS-A:** Sjogren syndrome type A antigen, **APLA:** anti-phospholipid antibodies, IQR: interquartile range, ***p* value:**< 0.05, Mann-Whitney U test, Fischer's exact test **$^{\alpha}$:** count of flares per months of observation period

damage, and SDI score were not significantly different according to the presence of RP in children with SLE.

Discussion

This study showed that RP in children with SLE is associated with serological features of the disease. However, disease severity at onset, clinical manifestations, and disease outcomes were not related to the presence of RP. Raynaud's phenomenon was observed in 25% of children with SLE in our study. In adults, frequency of RP might be observed up to 60% of SLE patients (7,16,17). In addition, RP is more frequently reported in childhood-onset disease than in adults (2). Knowledge of the frequency of RP in jSLE is scarce, and in our study, the frequency of RP was lower than that reported in the literature. However, this might be a result of environmental factors such as temperature and sunlight exposure, which might affect the clinical features of RP. Studies suggested that RP was associated with a milder disease in adult patients with SLE (10,18,19). In a comparative study, RP was less frequently observed in patients with a poorer prognosis (9). Pavlov-Dolijanovic et al. (20) showed that frequency of CNS involvement and peripheral neuropathy were significantly higher in adults with RP. Another study with a small sample size reported that major organ involvement, such as the kidney, CNS, and cardiovascular system; age of onset; and disease duration did not differ according to the presence of RP. However, pulmonary arterial pressure was higher in the presence of RP, with more frequent musculoskeletal involvement (21). In addition, alopecia was found to be associated with the presence of RP in two adult studies (21,22). In a recent study, the presence of RP was shown to be associated with a particular phenotype with more frequent CNS involvement, a positive anti-RNP antibody, less frequent kidney involvement, and hemolytic anemia in adults with SLE (7). Unlike adults, our results were not suggestive of a milder disease at onset, differences in clinical manifestations, or a better prognosis in the presence of RP in children with SLE. Since jSLE is associated with a more severe disease with more frequent major organ involvement, the absence of such an association is not surprising in childhood-

onset disease. However, the existence of a relationship between RP and disease serology in our study raised suspicion of a possible association between RP and clinical manifestations. Anti-dsDNA antibody is one of the serological marker found in patients with SLE and used in classification, could be used for the assessment of the disease activity and has a role in the pathogenesis (23,24). Despite this, our study showed a higher frequency of positive dsDNA antibodies in children with SLE, and positive dsDNA antibodies were not found to be associated with RP in adults (18). However, autoantibodies appear in distinct clusters with significant clinical differences in jSLE patients and are different from adult-onset diseases (25). Similar to our results, several studies showed an association between anti-RNP antibodies and presence of RP in adults with SLE (7,26,27). In contrast, a recent study of 510 SLE patients reported no significant association between RP and autoantibodies (28). In addition, anti-RNP antibodies are associated with the interferon signature (29). Thus, the more frequent detection of anti-RNP in children with RP is expected to be associated with clinical consequences. In addition, anti-phospholipid antibodies were shown to be associated with the presence of RP in adults with SLE (30). However, our study did not reveal a similar result, which might be due to the limited sample size.

Study limitations: The retrospective nature and limited sample size were notable limitations of this study. In addition, the diagnosis of RP is clinically based, and the typical episodic nature of RP results in a reliance on patient-reported symptoms (4). Furthermore, it is unclear whether the presence of RP is associated with SLE or is incidental, as seen in healthy individuals. In addition, we did not evaluate the treatment response of RP, whether it persisted throughout the course, which might be regarded as a limitation. Moreover, hydroxychloroquine dose and medication adherence might affect disease outcomes, which were not investigated in the present study.

Conclusions

In conclusion, the presence of RP is associated with certain serological features, and although this study showed no clinical associations, these serological features might have clinical relevance in children with RP. However, neither disease severity nor disease outcomes appear to be associated with the presence of RP in children with SLE.

Ethical approval: Ethics Committee permission was obtained from Karadeniz Technical University Medical Faculty Clinical Research Ethics Committee with the decision dated 10.03.2023 and numbered 2023/35

Conflict of Interest: The authors declare no conflicts of interest regarding this study.

Financial disclosure: No financial support was received for this study.

Author contributions: Concept (OB, HK), Design (OB, HK, MK), Data Collection and/or Processing (OB, HK), Analysis and/or Interpretation (OB, HK), Drafting the article (OB,HK), Final approval of the version to be submitted (OB, HK, MK).

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