Evaluation of Primary and Secondary Raynaud's Phenomenon in Childhood

Çocukluk Çağı Birincil ve İkincil Raynaud Fenomeni Olgularının Değerlendirilmesi

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ABSTRACT

Objective: To evaluate the clinical, laboratory and capillaroscopic findings of pediatric patients with Raynaud's phenomenon.

Material and Methods: Ninety-five pediatric patients who were diagnosed with Raynaud's phenomenon between January 2014 and January 2021, were retrospectively examined. The demographic data, laboratory parameters and capillaroscopic findings of the patients were recorded. The capillaroscopic findings of the patients were classified as normal, nonspecific abnormalities and scleroderma pattern.

Results: Primary Raynaud's phenomenon was present in 84 (88.5%) patients, and secondary Raynaud's phenomenon was present in 11 (11.5%). Arthralgia, arthritis, rash and recurrent fever were significantly more common in secondary Raynaud's phenomenon (p=0.001, p=<0.001, p=0.01, p=0.035, respectively). Antinuclear antibody positivity >1/320 was significantly higher in the patients with secondary Raynaud's phenomenon (p=0.01). Of the 40 patients who had capillaroscopy performed, 2 had a scleroderma pattern, 19 had nonspecific changes, and 19 had normal nailfold capillaroscopic findings. Capillary irregularity, tortuous capillaries and increased branching were significantly higher in the secondary Raynaud's phenomenon cases (p=0.015, p=0.015, p=0.003, respectively).

Conclusion: Having antinuclear antibody titer >1/320 and detection of capillary irregularity, tortuous capillaries and increased branching may be useful in distinguishing primary and secondary Raynaud's phenomenon.

Key Words: Antinuclear antibody, Capillaroscopy, Pediatric, Raynaud's Phenomenon, Rheumatology

ÖZ

Amaç: Raynaud fenomeni ile takip edilen pediatrik hastaların klinik, laboratuvar ve kapilleroskopik bulgularını değerlendirmek.

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Ethics Committee Approval / *Etik Kurul Onayı*: This study was conducted in accordance with the Helsinki Declaration Principles.The study was obtained from Ankara City Hospital, No. 2 Clinical Research Ethics Committee (Approval number: E2-21-258).

Contribution of the Authors / Yazarların katkısı*: *SEZER M: Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in necessary literature review for the study, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar. ***CELIKEL E:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. ***AYDIN F:*** Constructing the hypothesis or idea of research and/or article, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study. ***EKICI TEKIN Z:*** Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in necessary literature review for the study, Reviewing the article before submission scientifically besides spelling and grammar. KURT T: Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***TEKGOZ N:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***KARAGOL C:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***COSKUN S:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***KAPLAN MM:*** Taking responsibility in patient follow-up, collection of relevant biological materials, data management and reporting, execution of the experiments. ***CELIKEL ACAR B:*** Constructing the hypothesis or idea of research and/or article, Planning methodology to reach the Conclusions, Organizing, supervising the course of progress and taking the responsibility of the research/study, Taking responsibility in logical interpretation and conclusion of the results, Taking responsibility in the writing of the whole or important parts of the study, Reviewing the article before submission scientifically besides spelling and grammar.

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Gereç ve Yöntemler: Ocak 2014 ile Ocak 2021 tarihleri arasında Raynaud fenomeni tanısı ile takip edilen 95 çocuk hasta geriye dönük olarak incelendi. Hastaların demografik verileri, laboratuvar parametreleri ve kapilleroskopik bulguları kaydedildi. Hastaların kapilleroskopik bulguları normal, nonspesifik anormallikler ve skleroderma paterni olarak sınıflandırıldı.

Bulgular: Birincil Raynaud fenomeni 84 hastada (%88.5), ikincil Raynaud fenomeni 11 hastada (%11.5) mevcuttu. Artralji, artrit, döküntü ve tekrarlayan ateş, sekonder Raynaud fenomeninde anlamlı olarak daha sıktı (sırasıyla p=0.001, p=<0.001, p=0.01, p=0.035). Sekonder Raynaud fenomeni olan hastalarda 1/320 titre ve üzerinde antinükleer antikor pozitifliği anlamlı olarak daha sıktı (p=0.01). Kapilleroskopi yapılan 40 hastanın 2'sinde skleroderma paterni, 19'unda nonspesifik değişiklik ve 19'unda normal kapilleroskopi bulguları vardı. İkincil Raynaud fenomeni olgularında kapiller düzensizlik, tortuyoz kapiller ve dallanma artışı anlamlı olarak daha sık saptandı (sırasıyla p=0.015, p=0.015, p=0.003).

Sonuç: Antinükleer antikor titresinin >1/320 olması ve kapiller düzensizlik, tortuyoz kapiller ve dallanma artışının saptanması, birincil ve ikincil Raynaud fenomenini ayırt etmede faydalı olabilir.

Anahtar Sözcükler: Antinükleer antikor, Kapilleroskopi, Pediatri, Raynaud Fenomeni, Romatoloji

INTRODUCTION

Raynaud's phenomenon (RP) is a vasospastic disorder characterized by recurrent transient vasospasm in the smaller arteries of the fingers and toes that results in triphasic color changes. The vasospasm causes blanching (whitening), followed by the dilation of the capillaries and venous stasis causing cyanosis (blue coloration). Finally, the arteries dilate, causing the return of blood flow and post-ischemic hyperemia (redness). The hands, feet, ears, nose and nipples can be affected (1). RP prevalence increases with age in children, especially among the girls (2). The prevalence of primary RP in the general population is 5-20%, while it is 15% in children who are 12-15 years old (3). In a multicenter report, the prevalence of RP was found to be 2.2% between 0 and 10 years of age and 20% between the ages of 10 and 20 (4).

Interactions between genetic, neural, vascular and intravascular factors are responsible for the pathogenesis of RP. The underlying defect in primary RP is considered to be a local fault in the vascular function of thermoregulation and excessive vasoconstriction (5). Secondary RP results out of acquired conditions involving endothelial damage that may be associated with structural deterioration (6).

According to its etiology, RP can be primary (80% of cases) or secondary. There is no associated disease in primary RP. Secondary RP is attributed to an underlying disease, most commonly connective tissue diseases (7). Risk factors for RP in children are living in cold climates, female sex, and positive family history. Some conditions associated with RP may be listed as rheumatological disorders (scleroderma, systemic lupus erythematosus, juvenile idiopathic arthritis, dermatomyositis, mixed connective tissue disease, Sjogren's syndrome, Takayasu arteritis), mechanical injury, arterial diseases, hematological diseases, infection, medication, and exposure to chemical agents (1, 8). The clinical symptoms of the underlying pathology are usually present at the time of examination. However, in connective tissue diseases like scleroderma, RP may occur as the first symptom years before other clinical findings (9). RP is a clinical sign in 70-80% of patients at presentation in juvenile systemic scleroderma (10). In several studies evaluating RP cases in children, the rates of connective tissue diseases were found to be 23.6% and 28% (11, 12).

The difference between secondary RP and primary RP is related to their severity and complications. Attacks in secondary RP are more severe and frequent, and they usually have an asymmetrical pattern. Primary RP usually develops at an earlier age than secondary RP. Digital ulceration, necrosis and ischemic self-amputations are common in secondary RP. Nailfold capillary microscopy is a powerful diagnostic tool that can be used for the differential diagnosis of primary and secondary RP (13, 14). In primary RP, capillaroscopic findings are likely to be normal. Antinuclear antibody (ANA) positivity and changes in capillaroscopy (capillary enlargement, decreased number of capillaries, avascular areas) are indicative of secondary RP (15). Primary RP patients may develop symptoms of collagen tissue diseases over time. Therefore, patients who are followed up with a diagnosis of RP should be evaluated in terms of systemic diseases and monitored carefully (16).

The aim of this study is to evaluate the clinical, laboratory and capillaroscopic findings of pediatric patients with primary and secondary RP.

MATERIAL and METHODS

Ninety-five patients diagnosed with RP in the pediatric rheumatology department of our hospital between January 2014 and January 2021 were included in the study. The international consensus criteria for the diagnosis of RP were used to diagnose the patients (17). The study was obtained from Ankara City Hospital, No. 2 Clinical Research Ethics Committee (Approval number: E2-21-258).

Patients over 18 years of age and those with secondary causes other than rheumatological diseases were excluded from the study. Patients who already had additional connective tissue disease at the time of diagnosis were excluded.

Data were collected from patient records retrospectively. Age at diagnosis, sex, clinical findings, duration of symptoms, trigger factors, concomitant diseases, family history and all initial laboratory parameters including hemoglobin (Hb), white blood

cell count (WBC), platelet counts (PLT), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), complement 3 (C3), complement 4 (C4), ANA, anti-dsDNA, extractable nuclear antibody (ENA) panel, antiphospholipid antibodies and capillaroscopic findings were recorded. The laboratory parameters of the patients had been recorded at the time of their admission. ANA was evaluated with the IFA method and ENA panel was evaluated using the immunoblot method. Values above 1/100 were considered ANA-positive. Among the antiphospholipid antibodies, the lupus anticoagulant, beta 2 glycoprotein, and anticardiolipin antibodies were tested.

Capillaroscopy was performed by experienced specialist rheumatologists. The capillaroscopic findings of the patients were classified as normal (capillary count >7, capillary morphology normal, no capillary enlargement, no avascular area), nonspecific abnormalities (one of these following: decrease in capillary number, capillary enlargement, abnormal morphology or microhemorrhage) and scleroderma pattern (early, active or late stage). More specifically the presence of giant capillaries (capillaries with an apical diameter ≥50 µm) or the combination of abnormal shapes with an extremely lowered number of capillaries points to a 'scleroderma pattern' (18, 19).

The clinical and laboratory data of the patients with primary and secondary RP were compared.

Statistical analyses

The statistical analyses were performed using the SPSS software version 25. The normal distribution of the variables was investigated using visual (histograms, probability plots) and analytical (Kolmogorov-Smirnov/Shapiro-Wilk tests) methods. Descriptive statics are presented using medians and interquartile ranges (IQR) for the non-normally distributed and ordinal variables and frequencies for the categorical variables. In the comparisons between groups, Mann-Whitney U test was used for the non-normally distributed variables and ordinal variables, and Chi-squared or Fisher's tests were used for the categorical variables. A p-value smaller than 0.050 was considered to show a statistical significance.

RESULTS

Ninety-five patients with RP, of which 68 (71.6%) were female patients (female-to-male ratio= 2.5:1), were included in the study. The median age of the patients was 15.5 years (IQR 13.9-16.5 years) at the onset of their disease. The patients were most frequently admitted to the hospital in February (n=15, 15.8%) and March (n=15, 15.8%). Where as cold was a trigger for all patients also, 3 (3.2%) patients were triggered by stress. The mean follow-up period for all patients was 2.6 months, where the mean follow-up period of the secondary RP patients was 7.9 months. The clinical and laboratory characteristics of the patients are shown in Tables I and II.

Primary RP was present in 84 (88.5%) patients, and secondary RP was present in 11 (11.5%). Among the secondary RP patients, the associated disease was SLE in 3 (27.2%) patients, scleroderma in 2 (18.2%) patients, juvenile dermatomyositis in 1 (9.1%) patient, and juvenile idiopathic arthritis in 5 (45.5%) patients.

Table I: Baseline clinical characteristics of Raynaud phenomenon patients.

	All patients (n=95)	Primary RP (n=84)	Secondary RP (n=11)	p
Gender, female*	68 (71.6)	59 (70.2)	9 (81.8)	0.723
Age at diagnosis (years) †	15.5 (13.9-16.5)	15.5 (13.9-16.6)	14.9 (12-16.4)	0.496
Duration of symptoms (month) † n=61	12 (2-24)	12 (2-24)	4 (1.6-12)	0.355
Biphasic pattern*	69 (72.6)	62 (73.8)	7 (63.6)	0.486
Triphasic pattern*	26 (27.4)	22 (26.2)	4 (36.4)	0.486
Arthralgia*	40 (42.1)	30 (35.7)	10 (90.9)	0.001
Arthritis*	17 (17.9)	8 (9.5)	9 (81.8)	<0.001
Skin eruption*	5 (5.3)	2 (2.4)	3 (27.3)	0.010
Malar rash*	5 (5.3)	4 (4.8)	1 (9.1)	0.467
Photosensitivity*	8 (8.4)	7 (8.3)	1 (9.1)	1.000
Dry mouth/dry eyes*	10 (10.5)	9 (10.7)	1 (9.1)	1.000
Apthous ulcers*	20 (21.1)	18 (21.4)	2 (18.2)	1.000
Alopecia*	3 (3.2)	2 (2.4)	1 (9.1)	0.312
Thickened of the skin*	4 (4.2)	1 (1.2)	3 (27.3)	0.004
Muscle weakness*	1 (1.1)	0 (0)	1 (9.1)	0.116
Headache*	6 (6.3)	6 (7.1)	0 (0)	1.000
Weight loss*	2 (2.1)	1 (1.2)	1 (9.1)	0.219
Recurrent fever/abdominal pain*	3 (3.2)	1 (1.2)	2 (18.2)	0.035

*****Number (percentage), †Median (Interquartile range)(IQR)*

Table II: Baseline laboratory characteristics of Raynaud phenomenon patients.

	All patients (n=95)	Primary RP (n=84)	Secondary RP (n=11)	p
WBC, 10^9/L*	6.64 (5.8-8)	6.62 (5.74-7.97)	6.68 (6.1-9.1)	0.926
Hemoglobin (g/dL)*	13.8 (13-14.8)	13.9 (13.1-14.9)	13 (12.9-14.1)	0.063
ESR, mm/h*	5 (4-8)	5 (4-7)	8 (4-15)	0.209
CRP, mg/dL*	0.07 (0.01-0.18)	0.03 (0.01-0.17)	0.18 (0.01-0.2)	0.213
C3 g/L*	1 (0.9-1.1)	1 (0.9-1.1)	0.9 (0.6-1.3)	0.383
C4 g/L*	0.19 (0.14-0.21)	0.18 (0.14-0.21)	0.2 (0.1-0.21)	0.671
ANA positivity† (>1/100 titer) n=94	40 (42.6)	32 (38.6)	8 (72.7)	0,050
ANA positivity† (>1/320 titer) n=94	20 (21.3)	14 (16.9)	6 (54.5)	0.010
Anti dsDNA positivity† n=86	1 (1.2)	0 (0)	1 (10)	0.116

Median (Interquartile range)(IQR), †Number (percentage),* ***ANA:* *Antinuclear antibodies,* ***C3:*** *Compleman 3,* ***C4:*** *Compleman 4,* ***CRP:*** *C-reactive protein,* ***ESR:*** *Erythrocyte sedimentation rate,* ***WBC:*** *White blood cell*

Table III: Capillaroscopic findings in RP patients.

	All patients (n=40)	Primary RP (n=35)	Secondary RP (n=5)	p
Capillaroscopy findings Normal*				0.049
Nonspesific changes and sclerodema pattern*	19 (47.5) 21 (52.5)	19 (54.3) 16 (45.7)	0 (0) 5 (100)	
Capillary loss*	1 (2.5)	0 (0)	1 (20)	0.125
Capillary disorganization*	11 (27.5)	7 (20)	4 (80)	0.015
Capillary enlargement*	16 (40)	13 (37.1)	3 (60)	0.373
Giant capillaries*	1 (2.5)	0 (0)	1 (20)	0.125
Tortuous capillaries*	11 (27.5)	7 (20)	4 (80)	0.015
Capillary branching*	8 (20)	4 (11.4)	4 (80)	0.003
Microhemoarrages*	7 (17.5)	5 (14.3)	2 (40)	0.204

*******Number (percentage)*

Color changes were biphasic in 69 (72.6%) patients, and triphasic in 26 (27.4%) patients. Twenty-one (22.1%) patients had pain and 40 (42.1%) had numbness. The most common findings accompanying RP were arthralgia (n=40, 42.1%), arthritis (n=17, 17.9%) and oral ulcers (n=20, 21.1%). Nine (9.5%) patients had a family history of rheumatic diseases (including 4 RP, 2 SLE, 1 systemic sclerosis, 1 Sjogren's syndrome and 1 rheumatoid arthritis). All patients with a family history were primary RP patients.

There was no significant difference between the primary RP and secondary RP patients in terms of their pattern of color changes, age of onset, complete blood count parameters or acute phase reactants. The positivity rate of ANA titer >1/100 was 42.6% (40 patients). The positivity rate of ANA titer >1/320 was significantly higher in the secondary RP patients (p=0.010). Positivity was detected in 27 of the 58 (46.6%) patients whose ENA panels had been tested. Of 27 patients with positive ENA panels, 8 (29.6%) had isolated DFS70, 3 (11.1%) had Scl70 or RNP-Sm or PCNA, 4 (14.8%) had CENP-B, 2 (7.4%) had Ribosomal P or SS-B or Ro-52 and 1 (3.7%) had Jo-1 positivity. There was no significant difference in terms of ENA panel positivity between primary and secondary RP. Antiphospholipid antibodies had been tested in 47 patients, and isolated Beta-2 glycoprotein IgM positivity was detected in 2 patients.

Among the 40 patients who had capillaroscopy performed, 2 had a scleroderma pattern, 19 had nonspecific changes, and 19 had normal nailfold capillaroscopic findings. Capillary irregularity, tortuous capillaries and increased branching were significantly higher in the secondary RP patients (p=0.015, p=0.015, p=0.003, respectively) (Table III).

Thirty-two (38.1%) of the primary RP patients and 5 (45.5%) of the secondary RP patients were treated with a vasoactive agent. Treatment response was observed in 90.3% of the primary RP patients and 80% of the secondary RP patients.

DISCUSSION

In our study, it was revealed that children diagnosed with RP with joint complaints, rash, fever, high-titer ANA positivity and capillaroscopy findings should also be followed up in terms of underlying rheumatological diseases. The importance of screening tests for ANA, more specific antibodies associated with connective tissue diseases, and nailfold capillaroscopy in

patients presenting with RP have been demonstrated in adult series, because the data suggest that these may be risk factors for developing a connective tissue disease. There are still no clear recommendations for RP in children, and the importance of screening tests and imaging techniques has been only partly elucidated.

In general, the prevalence of RP is higher in girls than boys and increases with age. Nigrovic et al. (11) reported that 80% of 123 children with RP were girls, with a mean age of symptom onset of 12.3±4.3 years. Pavlov-Dolijanovic et al. (12) showed that among 250 RP patients, 44% were between 10 and 16 years of age, and 140 (56%) were adolescents aged 17 to 20 years. Eighty-two percent of the patients were girls, and the female-to-male ratio was 5:1 (12). Similarly, in our study, RP was more common in girls (71.6%). The median age of the patients included in our study was 15.5 years at the onset of their disease.

It is sometimes difficult to diagnose RP in children, as some patients may not have triphasic color changes and parents may perceive the color changes in their child as a normal response to cold exposure. Although three-color changes are not experienced by every patient with RP, triphasic color changes in the fingers or toes may be seen with blanching followed by cyanosis and then reactive hyperemia. Monophasic color change is more common than biphasic and triphasic color changes which are typical attacks. "Definite RP" is defined as biphasic color changes in response to cold, while monophasic color changes accompanied by paresthesia or numbness are termed "possible RP". In any case, mainly disturbances of the cutaneous microcirculation lead to these color changes. Nigrovic et al. (11) showed the triphasic pattern in 24% of primary RP patients and 19% of secondary RP patients. Turan et al. (3) detected the triphasic pattern in 34.5% of patients. In our study, the triphasic pattern rate was found to be 26.2% in the primary RP patients and 36.4% in the secondary RP patients. There was no significant difference in the pattern of color changes between the primary and secondary RP patients. Similarly, Nigrovic et al. (11) reported that biphasic or triphasic color changes were less common than monophasic color changes and not more common in secondary than primary RP.

ANA positivity and capillaroscopic findings are the most important parameters associated with evaluating the progression of the condition connective tissue diseases (20). ANA positivity at low titers can also be found at different rates in the healthy population, depending on geographical differences (3, 21).

In our study, ANA was positive in 40 (42.6%) patients. While ANA positivity at a 1/100 titer was seen in 21.7% of the patients with primary RP, no significant difference was found between the primary and secondary RP patients. The rate of ANA positivity over 1/320 was significantly higher in the cases with secondary RP (p=0.010). Similarly, the rate of ANA positivity was found to be 25% in patients with primary RP in another study (11). A study in Italy found that 63% of patients with RP who developed rheumatological diseases at follow-up had an ANA titer above 1/160, and only 22% of patients with primary RP had this positivity (22). Patients with high-titer ANA positivity should be evaluated carefully in terms of underlying diseases.

Capillaroscopy is an important imaging technique in the differentiation of primary and secondary RP. According to the Pediatric Rheumatology European Society (PRES) Scleroderma Working Group recommendations, capillaroscopy should be performed at the time of diagnosis and the findings should be classified as normal, nonspecific changes and scleroderma pattern. Additionally, patients with ANA positivity, specific autoantibodies and/or nailfold capillary changes were considered to be at high risk and follow-up was recommended (20). Capillary enlargement, decreased number of capillaries, giant capillaries and avascular areas are indicative of secondary RP. In a large series of pediatric patients with RP, 211 of 250 children with RP were classified as having normal capillaroscopy findings, 29 patients were classified as having nonspecific capillary changes, and 10 patients had a scleroderma pattern according to capillaroscopy findings. The frequency of normal capillary findings in patients with primary RP was higher than that in patients with secondary RP. Nonspecific capillary changes had a similar distribution in both primary and secondary RP. A scleroderma pattern was found only in patients with secondary RP (12). Nigrovic et al. (11) stated that nailfold capillaries were nonspecific or abnormal in 23% of primary RP and 68% of secondary RP patients. In our study, 47.5% of the patients had normal findings, 47.5% had nonspecific changes, and 5% had scleroderma patterns among the 40 patients with capillaroscopy results. Capillary irregularity, tortuous capillaries and increased branching were significantly higher in the secondary RP cases.

Despite the large number of patients, the limitations of our study were its retrospective nature and limited number of secondary RP patients. Conducting the study with a larger number of patients with both primary and secondary RP would be more valuable in terms of the significance of the results. Because it was a retrospective study, only half of the patients had received capillaroscopy examination. Prospective, multicenter studies including long-term results of pediatric RP patients should be conducted.

In conclusion, having ANA titer >1/320 and detection of capillary irregularity, tortuous capillaries and increased branching may be useful to distinguish between primary and secondary RP. Patients with joint complaints, rash, fever, high-titer ANA positivity and capillaroscopy findings should be evaluated carefully in terms of underlying diseases.

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