Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2020;45(1):200-207
DOI: 10.17826/cumj.638611

ARAŞTIRMA / RESEARCH

The frequency of avascular necrosis in juvenile systemic lupus erythematosus

Çocukluk çağı başlangıçlı sistemik lupus eritematozus hastalarında avasküler nekrozis sıklığı

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Cukurova Medical Journal 2020;45(1):200-207

Abstract

Purpose: Avascular necrosis (AVN) is a debilitating complication of juvenile systemic lupus erythematosus (jSLE). The aim of this study was to evaluate the frequency and clinical characteristics of patients with AVN in jSLE from a single center.

Material and Methods: Fifty-eight jSLE patients diagnosed according to the American College of Rheumatology classification criteria were included in this retrospective study. Disease activity of jSLE patients was measured by SLE Disease Activity Index-2K (SLEDAI-2K), organ damage was determined by the pediatric version of the systemic lupus international collaborating clinics/American College of Rheumatology damage index (pedSDI) at last visit.

Results: Among 58 jSLE patients, the female patients accounted for 86.2% (n=50). Mean baseline SLEDAI-2K score was 21.47±8.96. The number of patients with at least one damage item of pedSDI was 24 (41.4%), in which 5 patients (8.6%) had AVN. There were no statistical differences between the groups except baseline complement 3 (C3) level was significantly lower in patients with AVN.

Conclusion: Baseline low C3 level might be a predictor for AVN development in jSLE patients.There is unmet need for multicenter studies investigating possible risk factors of AVN in jSLE patients.

Keywords:. Juvenile systemic lupus erythematosus, avascular necrosis, complement 3.

Öz

Amaç: Avasküler nekrozis (AVN), çocukluk çağı başlangıçlı sistemik lupus eritematozusun (jSLE) yıkıcı bir komplikasyonudur. Tek merkezden yapılan bu çalışmanın amacı jSLE hastalarında AVN sıklığını ve bu hastaların klinik özelliklerini belirlemektir.

Gereç ve Yöntem: Amerikan Romatoloji Koleji'nin sınıflama kriterlerine göre tanı almış 58 jSLE hastası bu geriye dönük çalışmaya dahil edildi. jSLE hastalarının hastalık aktiviteleri SLE hastalık aktivite indeksi baz alınarak (SLEDAI-2K) ölçüldü. Organ hasarı Amerikan Romatoloji Koleji'nin SLE hastalarında uyguladığı hasar indeksinin çocukluklardaki versiyonu kullanılarak son muayenede belirlendi.

Bulgular: Elli sekiz jSLE hastasının %86,2 (50)'si kız hastaydı. Ortalama bazal SLEDAI-2K skoru 21,47±8,96 idi. En az bir organda hasarı olan hasta sayısı 24 (%41,4) idi, bunlardan 5 tanesinde (%8,6) AVN vardı. AVN olan ve olmayan hastalar arasında çeşitli değikenlere göre istatistiksel anlamlı bir farklılık saptanmadı. Sadece bazal kompleman 3 (C3) düzeyi AVN hastalarında, AVN olmayan hastalara göre anlamlı olarak düşüktü.

Sonuç: Bazal düşük C3 düzeyi jSLE hastalarında AVN gelişimini tahmin etmede ön görücü olabilir. jSLE hastalarında AVN gelişimi için muhtemel risk faktörlerini inceleyen çok merkezli çalışmalara ihtiyaç vardır.

Anahtar kelimeler: Çocukluk çağı başlangıçlı sistemik lupus eritematozus, avasküler nekrozis, kompleman 3.

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Geliş tarihi/Received: 26.10.2019 Kabul tarihi/Accepted: 15.01.2020 Published online: 15.02.2020

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disease with various clinical manifestations[1,2]. Among all SLE patients, 15-20% have a disease onset in childhood namely juvenile SLE (jSLE)[3]. Disease severity and outcome of jSLE patients are more severe than adult onset SLE due to the higher frequency of central nervous system and renal involvement; requiring more intense immunosuppressive treatments[4]. In the past two decades, with achieving early diagnosis and improved treatment modalities, jSLE patients might live longer with a chronic disease. Therefore, organ damage secondary to the sequelae of disease activity, side effects of medications, or comorbid conditions becomes more apparent[5,6]. The outcome of jSLE patients is measured by the pediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (PedSDI)[7]. Avascular necrosis (AVN), which is also known as osteonecrosis, is one of the items of PedSDI[7].

Avascular necrosis is a debilitating disorder that characterized by interruption of the blood supply which leads to death of the bone marrow and trabecular bone, presenting with joint pain, bone destruction, and loss of function[8]. It is a well-known complication of SLE since its first determination in 1960 and has been reported in 1.4-40% of jSLE patients[1-4,9-14]. The most common affected sites are femoral head, femoral condyles, proximal tibia, and the bones of foot and ankle[8]. AVN is multifocal in 57-81% of the affected patients, which is characterized by the involvement of three or more anatomic sites[8].

There are several reports on risk factors related to the AVN development in adult SLE patients, in which corticosteroid treatment, hypertriglyceridemia, hypertension, and neuropsychiatric involvement have been suggested to influence AVN development[8,15]. However, only a few reports have described the frequency and risk factors for AVN development in jSLE patients so far[11,12]. Therefore, the aim of this study was to describe the frequency of AVN in jSLE patients and compare the characteristic features of those patients according to the presence of AVN in a single center from Turkey.

MATERIALS AND METHODS

This is a retrospective study. Fifty-eight jSLE patients, who were diagnosed between January 2006 and February 2019 prior to their 18th birthday included in this study. We have extended our previous reported data focusing more on AVN and organ damage by including more jSLE patients[1].

The jSLE patients were diagnosed according to the revised 1997 criteria of American College of Rheumatology (ACR) classification criteria of SLE and followed by the same pediatric rheumatologist regularly[16].

Neuropsychiatric involvement was identified according to 1999 ACR neuropsychiatric lupus criteria[17]. Renal biopsy findings were classified by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) 2003 classification criteria[18]. Disease activity of jSLE patients was measured by SLE Disease Activity Index-2K (SLEDAI-2K) at every clinical visit.

Organ damage of the patients was determined by the pediatric version of the systemic lupus international collaborating clinics/American College of Rheumatology damage index (pedSDI) at last visit[7]. All patients' demographic and clinical features, baseline laboratory parameters, and therapies prescribed were collected from their medical files. Laboratory parameters included complete blood count (CBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA), anti-double-stranded DNA (Anti-dsDNA), level of complement 3 and 4 (C3, C4), anticardiolipin immunoglobulin G and M (aCL IgG, aCL IgM), and serum concentration of 25-hydroxycholecalciferol (vitamin D). The cumulative corticosteroid dose as methylprednisolone for each patient was also calculated from their medical files. The patients who have clinical symptoms, such as pain, limping, and arthritis, were undergone further investigations, including plain radiograph and/or magnetic resonance imaging (MRI). The diagnosis of AVN was confirmed by a radiologist with MRI findings.

The study protocol was approved by the Cukurova University Medical Faculty Ethical Committee (Number: 89, Date: 14 June 2019). Informed consent was obtained from all the enrolled patients' parents.

Statistical analysis

All statistical analyzes were performed by SPSS software version 20.0. Patient demographic data, clinical characteristics, and treatment information were analyzed descriptively. The significance of the difference between patients with and without AVN was determined utilizing the independent Student's t test for continuous variables and Mann Whitney U test for categorical variables. Categorical variables were presented as numbers and percentages, whereas continuous variables were expressed as mean and standard deviation (SD) and as median and minimum-maximum where suited.

RESULTS

The present study included 58 jSLE patients. The proportion of the female patients was 86.2% (n=50) and the female to male ratio was 6.2:1. Mean age at the time of diagnosis of jSLE was 12.6 years ±3.2 and median diagnostic delay of jSLE was 1.98 months (range, 0.53-35.9). While the median disease duration of jSLE was 2.87 years (range, 0.61-9.9), the median disease duration until the diagnosis of AVN has been established was 1.79 years (range, 0.70-6.04). Demographic and disease characteristics, laboratory data of all jSLE patients were given in Table 1 in detail.

Table 1. Demographic and disease characteristics, laboratory data of all juvenile systemic lupus erythematosus patients.

Demographic characteristics	
Female/Male, *n (%)*	50 (86.2)/8 (13.8)
Parental consanguinity, *n (%)*	14 (24.1)
Age at diagnosis, mean±SD	12.6 years ±3.2
Diagnostic delay, median (range)	1.98 months (0.53-35.9)
Age at study time, mean±SD	16.06 years ±2.7
Disease duration, median (range)	2.87 years (0.61-9.9)
Age at the AVN diagnosis, mean±SD	16.71 years ±1.72
Duration of medication at the time of AVN diagnosis, median (range)	21.5 months (7.36-72.5)
Clinical characteristics	
Constitutional symptoms, *n (%)*	53 (91.4)
Raynaud phenomenon, *n (%)*	17 (29.3)
Mucocutaneous involvement, *n (%)*	54 (93.1)
Musculoskeletal involvement, *n (%)*	37 (63.8)
Renal involvement, *n (%)*	41 (70.7)
Neuropsychiatric involvement, *n (%)*	14 (24.1)
Serositis, *n (%)*	8 (13.8)
Hematological involvement, *n (%)*	43 (74.1)
Cardiac involvement, *n (%)*	6 (10.3)
Hypertension, *n (%)*	7 (12.1)
Laboratory data	
Total Leucocyte count median, (c/mm3), median (range)	4760 (760-16800)
Hemoglobin level median (g/dl), median (range)	10.4 (5.5-13.7)
Platelet count median (c/mm3), median (range)	136000 (16000-760000)
Erythrocyte sedimentation rate (mm/h), median (range)	33.5 (2-140)
C-reactive protein level median (mg/dl), median (range)	0.3 (0.1-25.9)
Antinuclear antibody positivity, *n (%)*	51 (87.9)
Anti-dsDNA positivity, *n (%)*	28 (48.3)
aCL IgG positivity, *n (%)*	10 (17.2)
aCL IgM positivity, *n (%)*	13 (22.4)
Hypocomplementemia, *n (%)*	53 (91.4)

SD; standard deviation, AVN; avascular necrosis, Anti-dsDNA; anti-double-stranded DNA, aCL; anticardiolipin, Ig; immunoglobulin.

While mean baseline SLEDAI-2K score was 21.47±8.96, median last visit SLEDAI-2K score was 0 (range, 0-7). The number of patients having at least one damage item of pedSDI was 24 (41.4%) in which AVN was observed in 5 (8.6%) patients (Table 2). All of jSLE patients with AVN were female and had

multifocal involvement, including femoral heads, femoral condyles, distal femur, proximal tibia, and small bones of ankles. All patients were given methylprednisolone and median cumulative methylprednisolone dose was 13.4 gram (range, 1.9-58). Disease activity, damage score, and medications data of jSLE patients were given in Table 2, elaborately.

Table 2. Disease activity, damage score and medications data of juvenile systemic lupus erythematosus patients.

Disease activities and damage scores	
Baseline SLEDAI-2K, mean±SD	21.47±8.96
Last SLEDAI-2K, median (range)	0 (0-7)
pedSDI ≥ 1, *n (%)*	24 (41.4)
Mean PedSDI score±SD (range)	0.57±0.90 (0-5)
Growth failure, n (%)	13 (22.4)
Avascular necrosis, *n (%)*	5 (8.6)
Cataract, *n (%)*	4 (6.9)
Nephrotic proteinuria, *n (%)*	3 (5.1)
Delayed puberty, *n (%)*	2 (3.4)
Facial scar, *n (%)*	1 (1.7)
Pericardiectomy, *n (%)*	1 (1.7)
Shrinking lung, *n (%)*	1 (1.7)
ESRD, *n (%)*	1 (1.7)
Medications data	
Cumulative methylprednisolone dose gram, median (range)	13.4 (1.9-58)
Oral corticosteroid, *n (%)*	58 (100)
Pulse corticosteroid, *n (%)*	23 (39.7)
Hydroxychloroquine, *n (%)*	55 (94.8)
Cyclophosphamide, *n (%)*	34 (58.6)
Mycophenolate mofetil, *n (%)*	48 (82.8)
Rituximab, *n (%)*	19 (32.8)
Azathioprine, *n (%)*	5 (8.6)
Methotrexate, *n (%)*	5 (8.6)
Tocilizumab, *n (%)*	1 (1.7)
Plasmapheresis, *n (%)*	8 (13.8)

SLEDAI-2K; Systemic Lupus Erythematosus Disease Activity Index, PedSDI; pediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index, ESRD; end stage renal disease.

Disease characteristics of patients were compared according to the presence of AVN. There were no statistically significant differences between patients with and without AVN according to gender, age at diagnosis, diagnostic delay, disease duration, and clinical characteristics, including proliferative nephritis, neuropsychiatric involvement, hematological involvement which were given in Table 3.

Baseline laboratory parameters and medication data were also compared between patients with and without AVN. Baseline SLEDAI-2K scores did not differ between patients with and without AVN. There were not statistically significant differences between patients with and without AVN according to ANA positivity, anti-dsDNA positivity, aCL IgG and IgM positivity, CBC values, ESR and CRP levels, vitamin D levels. Although baseline C4 level did not differ between the groups according to the presence of AVN, baseline C3 level was statistically lower in patients with AVN than without.

Patients with and without AVN were also compared according to median cumulative methylprednisolone dose, cyclophosphamide, mycophenolate mofetil, and rituximab use. There were no statistically significant differences between the groups. Comparison of baseline laboratory parameters and medication data between patients according to the presence of AVN were given in Table 4 in detail.

Table 3. Comparison of disease characteristics between patients according to the presence of avascular necrosis

	Avascular necrosis		
Parameters	**Yes**	**No**	**p-value**
Gender (F/M), n (%)	5 (100)/0 (0)	45 (84.9)/8 (15.1)	0.462
Disease duration years, median (range)	1.92 (1.47-6.04)	2.90 (0.51-9.96)	0.535
Age at diagnosis, median (range)	15.13 (12.86-15.52)	12.99 (5.13-17.92)	0.277
Diagnostic delay months, median (range)	2.10 (0.95-6.01)	1.97 (0.53-35.98)	0.914
Constitutional symptoms, *n (%)*	5 (100)	45 (90.6)	0.626
Raynaud phenomenon, *n (%)*	2 (40)	15 (28.3)	0.461
Mucocutaneous involvement, *n (%)*	5 (100)	49 (92.5)	0.690
Oral aphthosis, *n (%)*	4 (80)	28 (52.8)	0.248
Malar rash, *n (%)*	5 (100)	44 (83.0)	0.416
Photosensitivity, *n (%)*	5 (100)	45 (84.9)	0.462
Musculoskeletal involvement, *n (%)*	2 (40)	35 (66)	0.246
Renal involvement, *n (%)*	3 (60)	38 (71.7)	0.461
Neuropsychiatric involvement, *n (%)*	2 (40)	12 (22.6)	0.348
Hypertension, *n (%)*	1 (20)	6 (11.3)	0.487
Hematological involvement, *n (%)*	4 (80)	39 (73.6)	0.614
Proliferative glomerulonephritis, *n (%)*	2 (40)	23 (51.1)	0.500

F; female, M; male, Mann-Whitney U test was used for data comparison. Significant p values (<0.05) are presented in bold.

Table 4. Comparison of baseline laboratory parameters and medication data between patients according to the presence of avascular necrosis.

	Avascular necrosis		
Parameters	**Yes**	**No**	**p**
Baseline SLEDAI-2K, median (range)	33 (9-36)	21 (5-49)	0.433
ANA positivity, *n (%)*	4 (80)	47 (88.7)	0.727
Anti-dsDNA positivity, *n (%)*	4 (80)	24 (45.3)	0.209
aCL IgG positivity, n (%)	1 (20)	9 (17)	0.914
aCL IgM positivity, n (%)	1 (20)	12 (22.6)	0.936
Baseline C3 level (mg/dl), median (range)	30 (7.4-60.8)	62 (15-149)	0.040
Baseline C4 level (mg/dl), median (range)	5 (4.3-10.9)	6.4 (4-57.8)	0.146
Leucocyte count, (c/mm3), median (range)	3770 (760-7010)	4920 (1800-16800)	0.372
Hemoglobin level median (g/dl), median (range)	10.5 (6.5-13)	10.4 (5.5-13.7)	0.872
Platelet count median (c/mm3), median (range)	143000 (20000-227000)	218000 (16000-760000)	0.086
Erythrocyte sedimentation rate (mm/h), median (range)	30 (2-120)	34 (2-140)	0.963
C-reactive protein level (mg/dl), median (range)	0.4 (0.1-13.9)	0.3 (0.1-25.9)	0.265
25-hydroxycholecalciferol, median (range)	18.8 (11-21.7)	15.3 (2.4-63.1)	0.768
Cumulative methylprednisolone dose, median (range)	8.7 (5.9-48.7)	13.9 (1.9-58)	0.440
Pulse methylprednisolone, *n (%)*	3 (60)	20 (37.7)	0.433
Cyclophosphamide use, *n (%)*	3 (60)	21 (58.5)	0.957
Mycophenolate mofetil use, *n (%)*	4 (80)	44 (83.0)	0.914
Rituximab use, *n (%)*	2 (40)	17 (32.1)	0.788

ANA; antinuclear antibody, Anti-dsDNA; anti-double-stranded DNA, SLEDAI-2K; Systemic Lupus Erythematosus Disease Activity Index, C3; complement 3, C4; complement 4, aCL IgG; anticardiolipin immunoglobulin G, aCL IgM; anticardiolipin immunoglobulin M, Mann-Whitney U test was used for data comparison. Significant p values (<0.05) are presented in bold.

DISCUSSION

In this study, AVN was observed in 8.6% of jSLE patients and baseline C3 level of patients with AVN was significantly lower than those without AVN. Other than baseline C3 level, there were no statistical difference between the groups of patients with and without AVN in terms of age at diagnosis, disease duration, disease characteristics, laboratory parameters and medication data, including cumulative methylprednisolone dose.

To date, there have been many reports on risk factors for AVN development in SLE patients[19,20]. Although the results of studies are different, the use of corticosteroid, cumulative corticosteroid dose, immunosuppressive agents, neuropsychiatric involvement, antiphospholipid antibodies have been associated with AVN development in SLE patients[19,20]. However, there are few reports on the frequency and risk factors for AVN development in jSLE patients.

The first report on AVN in jSLE patients was published in 1974 by Bergstein et al[14]. Thirty-five jSLE patients, in which 9 were symptomatic, evaluated by X-ray survey and 14 patients (all female, 40%) were diagnosed with AVN. Radiographically, avascular necrosis was defined as mottling of the bone trabecular pattern, subchondral demineralization, depression or fragmentation, and irregular areas of sclerosis. While cumulative dose of prednisone was significantly associated with diagnosis of AVN, duration of immunosuppressive therapy, disease severity, central nervous system involvement, Raynaud's phenomenon, and vascular thrombosis was not linked to AVN[14]. In the present report the frequency of AVN in jSLE patients was 8.6%, which was lower than the previous report. Considering the date of the study the technique used in the diagnosis, the very high frequency of AVN in previous report might be due to technical misinterpretation.

The frequency of AVN was reported as 17.5% in 40 jSLE patients by Castro et al., in 2011[8]. They prospectively performed whole body MRI to all patients, in which only one patient was symptomatic. They compared disease activity, corticosteroid use, vasculitis, Raynaud's phenomenon, and lipid profile between patients regarding the presence of AVN. No statistical differences were found between groups in these regards. However, they concluded that the small sample size of jSLE patients make the interpretation difficult on the risk factors for AVN development[8]. The frequency of AVN in jSLE patients in the previous study was also higher than out study. In the present report, MRI was only performed to symptomatic patients. Because whole body MRI was performed to all patients, AVN might be diagnosed more accurately in the previous report which could explain the difference between the frequency of AVN in present study.

The frequency of AVN was reported as 6% of 617 jSLE patients by Yang et al[12]. Rate of central nervous system involvement, proliferative nephritis, cumulative prednisone dose, immunosuppressive treatments, including micofenolate mofetil, cyclophosphamide, and azathiopurine were significantly higher in the AVN group than without. However, disease activity, malar rash, arthritis, Raynaud's phenomenon, and ANA positivity did not differ between the groups[12]. Moreover, Gurion et al. enrolled 201 jSLE patients, in which the frequency of AVN was 8.5%[11]. Hypertension, nephritis, vitamin D deficiency, and elevated serum triglyceride were risk factors for developing AVN. However, disease activity, disease duration, corticosteroid use, and anti-phospholipid profile were not associated with AVN development[11]. The frequency of AVN in jSLE patients in the last two studies were similar to our study. However, the risk factors related to AVN development differ among studies.

As mentioned above, the frequency of AVN in jSLE patients ranges between 1.4-40%. The frequency of AVN in our report was within the range. The frequency of AVN in Turkish jSLE patients was solely given in a report of 112 jSLE patients, which was higher than our report (n=18, 16% vs n=5, 8.6%)[4]. However, the report did not mention about the risk factors related to the AVN development in jSLE patients. Multiple risk factors have been associated with AVN development in jSLE, particularly corticosteroid use, cumulative corticosteroid dose, central nervous system involvement, proliferative nephritis, cumulative prednisone dose, immunosuppressive treatments[12,14]. In our study, only baseline C3 level was significantly lower in AVN group than without. The risk factors related to the AVN development in jSLE patients were various and inconsistent between studies[8,11,12,14].

SLE is an immune complex disease linked to classical complement pathway activation, hyperconsumption of C3 and C4 proteins. Low C3 level was reported to be the strongest risk factor for thrombosis and

associated with both venous and arterial thrombosis in adult SLE patients[21]. Moreover, low C3 level was reported to be associated in cardiovascular events in adult SLE patients[22]. The baseline C3 level of the patients with AVN was found to be lower than those without in the present report. These findings together and pathogenesis of the disease let us think that baseline low C3 levels might be associated with AVN development in jSLE patients. However, the data on AVN development in jSLE patients are scarce and inconsistent probably due to the rarity and complexity of jSLE. Although baseline low C3 level was associated with the presence of AVN in the present report, in contrast to the findings of previous reports, age at diagnosis, disease duration, disease characteristics, laboratory parameters and medication data, including cumulative methylprednisolone dose did not influence the AVN development. In view of the heterogeneity of the results of the studies in adult and juvenile SLE, further multicenter, prospective studies including more jSLE patients are needed to clarify the frequency and risk factors associated with AVN particularly in jSLE patients.

The strength of this study is being the first one which investigated the frequency and characteristic features of AVN in such rare disease among Turkish children. Nevertheless, we acknowledge that there are limitations of our study, including the enrollment of the small number of jSLE patients, the retrospective design of the study, and lack of the standardized screening procedure in asymptomatic patients.

In conclusion, baseline low C3 level might be a predictor for AVN development in jSLE patients; however, age at diagnosis, disease duration, disease characteristics, laboratory parameters and medication data, including cumulative methylprednisolone dose did not influence the AVN development in this report. The diversity of the different studies on AVN development let us think that AVN is likely a result of a multifactorial process.

Acknowledgment

Teşekkür: Pediatrik Romatoloji hakkındaki bilgi ve deneyimlerini bizimle paylaşan ve akademik alanda gelişmemizi teşvik eden yakın zamanda kaybetmiş olduğumuz mentorumuz Profesör Mustafa Yılmaz'a içtenlikle teşekkür ediyoruz.

Yazar Katkıları: Çalışma konsepti/Tasarımı: SB, RMKE; Veri toplama: SB, RMKE; Veri analizi ve yorumlama: FCP, SB; Yazı taslağı: SB; İçeriğin eleştirel incelenmesi: RMKE, AKB; Son onay ve sorumluluk: SB, RMKE, FCP, EM, BA, DD, DUA, AKB; Teknik ve malzeme desteği: -; Süpervizyon: DUA, AKB; Fon sağlama (mevcut ise): yok.

Etik Onay: Çalışma protokolü Çukurova Üniversitesi Tıp Fakültesi Etik Kurulu tarafından onaylanmıştır (Sayı: 89, Tarih: 14 Haziran 2019)

Hakem Değerlendirmesi: Dış bağımsız.

Çıkar Çatışması: Yazarlar çıkar çatışması beyan etmemişlerdir.

Finansal Destek: Yazarlar finansal destek beyan etmemişlerdir.

Author Contributions: Concept/Design : SB, RMKE; Data acquisition: SB, RMKE; Data analysis and interpretation: FCP, SB; Drafting manuscript: SB; Critical revision of manuscript: RMKE, AKB; Final approval and accountability: SB, RMKE, FCP, EM, BA, DD, DUA, AKB; Technical or material support: -; Supervision: DUA, AKB; Securing funding (if available): n/a.

Ethical Approval: The study protocol was approved by the Cukurova University Medical Faculty Ethical Committee (Number: 89, Date: 14 June 2019)

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors declared no conflict of interest.

Financial Disclosure: Authors declared no financial support

Acknowledgment: We sincerely thank to our recently lost mentor, Professor Mustafa Yılmaz, who shared his knowledge and experience on Pediatric Rheumatology with us and encouraged us improving in academic field.

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