Risk Factors for Symptomatic Avascular Necrosis in Childhood-onset Systemic Lupus Erythematosus

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ABSTRACT. *Objective.* To examine the frequency and risk factors for symptomatic avascular necrosis (AVN) in childhood-onset systemic lupus erythematosus (cSLE).

Methods. A single-center, nested, matched, case-control design was used. There were 617 patients with cSLE followed at the Hospital for Sick Children (SickKids) Lupus Clinic between July 1982 and June 2013 included in the study. The AVN cohort consisted of 37 patients identified with clinical findings of symptomatic AVN and diagnosis was confirmed by 1 or more imaging modalities. Three controls were matched to each patient with AVN by date and age at diagnosis. Baseline clinical, laboratory, and treatment characteristics were compared between patients with AVN and controls by univariable analyses and if statistically significant, were included in a multivariable logistic regression model.

Results. A total of 37/617 patients (6%) developed symptomatic AVN in 91 joints during followup at SickKids. The mean duration to disease was 2.3 years. The hip was the most commonly involved joint (26/37, 70%). Compared with the matched non-AVN cohort, patients with AVN had a higher incidence of central nervous system (CNS) involvement and nephritis, required greater cumulative prednisone (PRED) from cSLE diagnosis to AVN, received a greater maximal daily PRED dose, and had more frequent use of pulse methylprednisolone therapy. Multivariable regression analysis confirmed major organ involvement (CNS disease and/or nephritis) and maximal daily PRED dose as significant predictors of symptomatic AVN development.

Conclusion. Patients with cSLE with severe organ involvement including nephritis and CNS disease and higher maximal daily dose of PRED are more likely to develop symptomatic AVN. (J Rheumatol First Release November 15 2015; doi:10.3899/jrheum.150464)

Key Indexing Terms:
AVASCULAR NECROSIS   OSTEONECROSIS   MAJOR ORGAN INVOLVEMENT
CHILDHOOD-ONSET SYSTEMIC LUPUS ERYTHEMATOSUS   RISK FACTORS

Systemic lupus erythematosus (SLE) is a chronic multi-system autoimmune disease with up to 20% of patients diagnosed in the first 2 decades of life[1]. Since its initial association with SLE by Dubois and Cozen in 1960[2], avascular necrosis (AVN) is now a well-recognized complication with prevalence reported in the range of 5–23% in childhood-onset SLE (cSLE) and up to 40% when magnetic resonance imaging (MRI) studies are performed on asymptomatic patients[3,4,5,6,7]. Previous studies in large adult SLE cohorts have reported symptomatic AVN between 9–12% of patients[8,9,10,11,12,13]. AVN likely stems from multiple

pathways resulting in compromised blood supply and necrosis of both medullary bone and surrounding cortex[14]. These ischemic changes lead to structural bone damage with accompanying pain and loss of function that may result in joint replacement[14,15].

Most studies in patients with SLE suggest that corticosteroid use is a major risk factor for AVN[9,11,13,16,17], although there are reports of AVN occurring in corticosteroid-naive patients[11,18]. It is unclear whether maximal corticosteroid dose[9,11,17], cumulative corticosteroid dose[11,19,20], duration of steroid therapy[10,15,19,20,21], or the use of intravenous (IV) high-dose pulse therapy[11,22,23] are most predictive of developing AVN. Several other risk factors for AVN have been inconsistently recognized, including disease activity, arthritis, Raynaud phenomenon, vasculitis, renal disease, neuropsychiatric [central nervous system (CNS)] symptoms, the presence of antiphospholipid antibodies [specifically the lupus anticoagulant (LAC)], and treatment with cytotoxic agents and even antimalarials[8,12,13,17,24,25,26,27].

There are few data on the frequency and risk factors for AVN in cSLE because most studies have been limited by small sample sizes[3,4,5,6,7]. Therefore, our objectives were to determine the frequency and risk factors for developing

symptomatic AVN in our large single-center cohort of patients with cSLE.

MATERIALS AND METHODS

A single-center, nested, matched, case-control study was conducted of patients with cSLE followed at the Hospital for Sick Children (SickKids) Lupus Clinic between July 1982 and June 2013. Clinical, laboratory, and treatment details have been prospectively collected using standardized forms, and these data are maintained in our divisional SLE database. SickKids Research Ethics Board approval (#1000010957) was obtained for our study.

Patients. Patients who fulfilled ≥ 4 of the 11 American College of Rheumatology (ACR) classification criteria for SLE[28,29] prior to their 18th birthday and were followed in the Lupus Clinic at SickKids were eligible for inclusion in our study. The AVN cohort consisted of 37 patients identified with clinical findings of symptomatic AVN and diagnosis was confirmed by 1 or more imaging modalities including plain radiograph, MRI, bone scan, and/or computed tomography (CT). AVN was suspected and investigations pursued when there was a rapid onset of swelling in 1 or more large joints, groin pain, or pain out of keeping with the current disease activity level, along with restricted range of movement. Although staffed by more than 1 physician throughout the years, 1 physician (EDS) had participated in the shared care of all patients seen since the clinic's inception. The imaging modality performed was dependent on the era of AVN diagnosis, with plain radiographs obtained initially for all patients. If the diagnosis of AVN was made by radiograph, then no further imaging was required unless symptoms changed (e.g., if suspicion of a loose body in the joint). In the earlier decades (1980s and 1990s), a patient may have had a bone scan if the diagnosis was uncertain. CT scans were also performed prior to the widespread use of MRI. MRI was ordered if plain radiograph was normal with persistent symptoms and suspicion of AVN, or to better delineate the extent of AVN, or for surgical assessment.

Three controls from the 580 patients with cSLE without AVN were matched to each patient with AVN. Matching was done by date of cSLE diagnosis and age at cSLE diagnosis (± 1 yr for both variables) to generate a matched non-AVN cohort (control) of 111 patients with cSLE. This matching ensured a similar length of followup and similar treatment regimens for the cases and controls. Variables of interest that were extracted at the time of AVN diagnosis were ascertained at an equivalent cSLE disease duration in the controls.

Data collection. Demographic, clinical, and laboratory features and therapies prescribed were extracted from the SLE database for each clinic visit up to the last followup for the patients with AVN and non-AVN control patients. Clinical variables were defined by the ACR classification criteria for SLE, except CNS involvement, which was defined as the presence of psychosis, acute confusional state, cognitive dysfunction, or another significant neuropsychiatric syndrome that required the addition of systemic immuno-suppression by the treating physician. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[30] or SLEDAI-2000 (SLEDAI-2K)[31] scores (for visits in 2002 or later) were calculated following all patient visits as a valid indicator of cSLE disease activity[32]. Scores were summarized over time using the adjusted mean SLEDAI (AMS)[33]. Cumulative corticosteroid dose (per kg of body weight) was calculated using available dosing information and patient's weight from each clinic visit.

Statistical analysis. Clinical, laboratory, and therapeutic variables previously reported to be associated with AVN were evaluated using descriptive statistics. Continuous variables are presented as means and SD or medians and interquartile range for parametric and nonparametric variables, respectively. Categorical variables are presented as frequencies and percentages. Correlations between variables were examined using the variance inflation factor to avoid multicollinearity. To compare characteristics between patients with cSLE with AVN and those without AVN, Student t test, chi-square, and Fisher's exact test were used as appropriate. Multivariable conditional logistic regression was performed to identify relevant risk factors for AVN. Variables in the final multivariable model were examined for interaction effects to generate a final model with independent predictors. Patients were followed from cSLE diagnosis until their transfer to adult rheumatology care or last followup (whichever was earlier). Statistical analyses were conducted using STATA (version 12.0, StataCorp). Differences at p < 0.05 were considered statistically significant, with Bonferroni correction used for multiple testing as noted.

RESULTS

Patients. Symptomatic AVN occurred in 37/617 (6%) of the entire cSLE cohort (Table 1). Thirty (81%) were women, and there was no significant difference in ethnicity (white vs non-white) between AVN and controls (p = 0.204). The mean age at diagnosis of AVN was 16.1 ± 2.1 years, with mean disease duration to AVN of 2.3 years (Table 1). When examined by era, 13 patients presented with new symptomatic AVN between 1985 and 1994, 12 patients between 1995 and 2004, and 12 patients between 2005 and 2014. Only 2/37 patients (5%) developed AVN prior to the onset of puberty. The controls were representative of the entire cSLE cohort because there were no significant demographic differences between these 2 groups (data not shown).

AVN developed in a total of 91 joints in the 37 patients (Table 2). Thirty patients (81%) had symptomatic AVN diagnosed in 2 or more sites, where 27 of these patients had involvement of bilateral symmetric joints. The hip was the most commonly involved joint (26/37, 70%) with bilateral involvement in 18 patients (49%). Nine of 37 patients (24%) who developed AVN underwent surgical treatment prior to transfer to adult care. Eleven total hip arthroplasties and 1 hip vascular graft were done in 8 patients, and the ninth patient had a total knee arthroplasty.

Clinical and laboratory features. The clinical characteristics of patients with AVN and controls are shown in Figure 1. To determine whether clinical or laboratory features were

Table 1. Patient demographics*. Values are n (%) or mean ± SD.

Characteristic	AVN, n = 37	Controls, n = 111
Female	30 (81)	82 (74)
Age at cSLE diagnosis, yrs	13.8 ± 2.5	13.8 ± 2.4
Age at AVN diagnosis, yrs	16.1 ± 2.1	N/A
Mean disease duration to AVN, yrs	2.3 ± 2.02	N/A
Mean followup†, yrs	6.89 ± 5.39	5.72 ± 5.09
Ethnicity		
South Asian	10 (27)	10 (9)
Other Asian‡	9 (24)	30 (27)
Black	9 (24)	12 (11)
White	8 (22)	40 (36)
Hispanic	0	1 (1)
Other	1 (3)	13 (12)
Unknown	0	5 (5)

* All comparisons between AVN cases and controls were nonsignificant. † Followup duration was defined as time from cSLE diagnosis to last visit date or June 2013, whichever was earlier. ‡ Includes Southeast Asian, East Asian, West Asian, and mixed Asian ethnicities. AVN: avascular necrosis; cSLE: childhood-onset systemic lupus erythematosus; N/A: not applicable.

Table 2. Distribution of AVN sites (no. patients)*.

Joint	Unilateral	Bilateral
Shoulder, glenohumeral	2	0
Elbow	0	1
Hip	8	18
Knee	3	14
Ankle	5	3
Talonavicular	1	0

* Thirty out of 37 patients had involvement of more than 2 joints, of which 27 had involvement of bilateral symmetrical joints. AVN: avascular necrosis.

predictive of developing AVN, we compared these between the AVN and control cohorts at the time of AVN diagnosis.

Clinical predictors previously associated with the development of AVN were compared between the groups by univariable analysis (Table 3). Using a Bonferroni correction for multiple comparisons, patients with AVN had a higher incidence of CNS disease (43% vs 19%, p = 0.003) and nephritis (68% vs 32%, p < 0.001) compared with controls. Twenty-one of the 25 patients (84%) with AVN who had nephritis had proliferative nephritis (World Health Organization Class III or IV, or proliferative/membranous overlap Class III/V or IV/V). Laboratory features from diagnosis to time of AVN were not significantly different between the patients with AVN and controls. In particular, there were no significant differences in the prevalence of LAC and anticardiolipin antibodies between the 2 cohorts.

Disease activity. Disease activity from diagnosis of SLE up to the time of AVN diagnosis, as measured by AMS, was not significantly different between patients with AVN and controls (p = 0.12; Table 3). Further comparisons of the AMS for the first 6 and 12 months from diagnosis were also not different between the patients with AVN and the controls (data not shown).

Medications. All patients with AVN received corticosteroid therapy at some point prior to AVN diagnosis compared with 86 (80%) of the controls at an equivalent disease duration (p = 0.003). One patient with AVN (and the 3 matched controls) was excluded from the medications analysis because of incomplete prednisone (PRED) data. Compared with controls with time-matched intervals, patients with AVN received greater cumulative PRED dose per kg during the first 3 and 6 months from cSLE diagnosis, and from time of cSLE diagnosis to AVN diagnosis (p < 0.001 for all 3 comparisons). Those developing AVN also received higher maximal daily PRED dose (1.25 ± 0.36 vs 0.71 ± 0.53 mg/kg, p < 0.001), and more frequent use of high-dose IV pulse methylprednisolone therapy (39% vs 10%, p < 0.001). High-dose (oral) corticosteroids, defined as ≥ 90 days of at least 0.5 mg/kg/day of PRED (consecutive or nonconsecutive days), were taken by 35 patients with AVN compared with 5 controls (p < 0.01). No patient received alternate day steroids.

Use of other medications also differed, whereby a greater proportion of patients with AVN received immunosuppressives (cyclophosphamide, azathioprine, or mycophenolate mofetil) compared with controls (89% vs 41%, p < 0.001), although there was no significant difference in the proportion of patients who took antimalarial drugs (78% vs 75%, p = 0.66; Table 3).
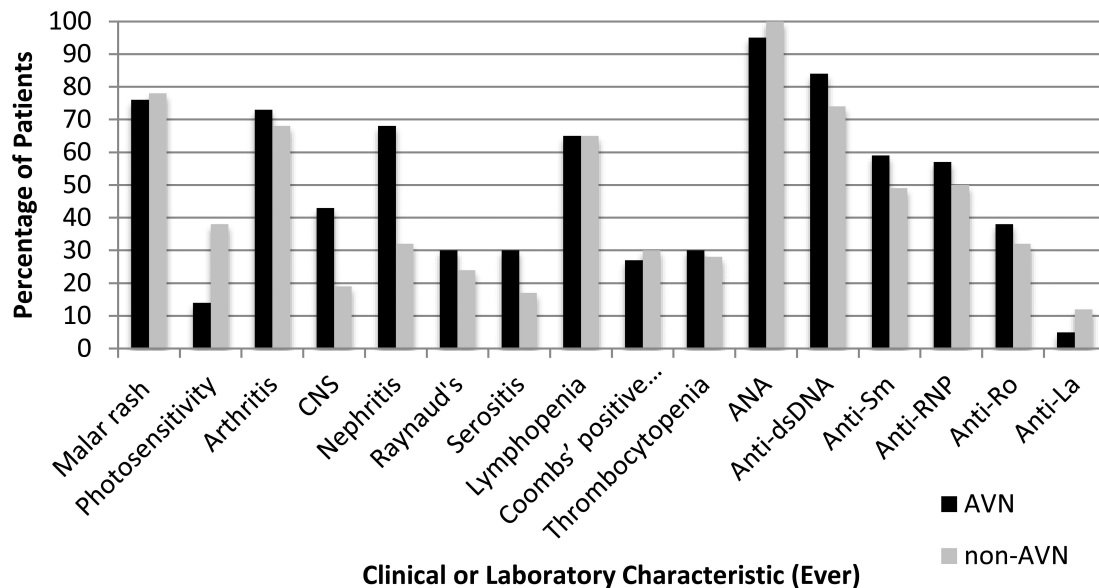

Figure 1. Clinical and laboratory characteristics of patients with AVN and without AVN. All variables were examined prior to AVN diagnosis for patients with AVN or matched disease duration for controls. CNS: central nervous system (involvement); ANA: antinuclear antibody; AVN: avascular necrosis; Coombs' positive: Coombs' positive hemolytic anemia.

Table 3. Clinical and laboratory predictors. Values are n (%) or mean ± SD unless otherwise specified.

Variable	AVN, n = 37	Controls, n = 111	p[†]
Clinical features, ever*			
CNS	16 (43)	21 (19)	0.003
Nephritis	25 (68)	36 (32)	< 0.001
Proliferative nephritis, Class III, IV, III/V, or IV/V	21 (57)	28 (25)	< 0.001
Raynaud	11 (30)	27 (24)	0.52
Laboratory features, ever*			
Lupus anticoagulant	5 (14)	16 (14)	1.00
Anticardiolipin antibodies	16 (43)	49 (44)	0.92
Coombs' positive hemolytic anemia	10 (27)	33 (30)	0.76
Adjusted mean SLEDAI**	6140 ± 5868	4679 ± 4516	0.12
Max daily PRED dose***, mg/kg	1.25 ± 0.36	0.71 ± 0.53	< 0.001
PRED dose at AVN diagnosis, mg/kg	0.30 ± 0.25	0.19 ± 0.24	0.01
Cumulative PRED dose, mg/kg	364 ± 53	232 ± 36	< 0.001
Cumulative dose over 3 mos	69 ± 42	40 ± 42	< 0.001
Cumulative dose over 6 mos	116 ± 62	71 ± 68	< 0.001
Antimalarial[‡]	29 (78)	83 (75)	0.66
Immunosuppressives[‡]	33 (89)	46 (41)	< 0.001

[†] P value significant if < 0.0033 (Bonferroni correction). * All clinical and laboratory characteristics were present prior to AVN diagnosis or matched disease duration for controls. ** Adjusted mean SLEDAI (AMS) from diagnosis of cSLE to AVN diagnosis or matched disease duration for controls. *** Corticosteroid therapy analysis includes 36 AVN and 108 matched controls. Data for 1 patient with AVN was unavailable between cSLE and AVN diagnosis. [‡] Antimalarial drugs: hydroxychloroquine or chloroquine; immunosuppressives: cyclophosphamide, azathioprine, or mycophenolate mofetil. AVN: avascular necrosis; CNS: central nervous system; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; PRED: prednisone; cSLE: childhood-onset systemic lupus erythematosus.

Multivariable analysis. All clinically important variables presented in Table 3 in addition to age and sex were included in the final multivariable model. Maximum PRED dose was included in the multivariate model rather than the dichotomous variable of high-dose corticosteroid. Conditional logistic regression was conducted with symptomatic AVN as the outcome. In the final model, these remained as independent risk factors: maximal daily dose of PRED in mg/kg, history of CNS symptoms, nephritis (stages II to V), and use of IV pulse methylprednisolone therapy (Table 4A). Interaction between variables in the model was examined, and the correlated variables were combined to form a final model consisting of 2 independent predictors: major organ involvement (renal and/or CNS) and maximum daily PRED dose in mg/kg (Table 4B).

DISCUSSION

AVN is a significant morbidity in cSLE, often leading to joint replacement and substantial disability. We observed symptomatic AVN in 6% of our patients. The majority of our patients who developed AVN (35/37, 95%) did so after the onset of puberty at an average age of 16.1 years and a disease duration of 2.3 years. Although patients who developed AVN had a similar age at disease onset as our entire SLE population, our observation of predominantly postpubertal patients developing AVN is consistent with a cSLE study that observed AVN on MRI in 49% of joints in adolescents (15–20 yrs old) as compared with only 6% of joints in patients 14 years or

Table 4A. Clinical predictors in the multivariate regression model.

Variable	OR estimate (95% CI)	p
Nephritis	6.6 (1.8–24.6)	0.005
History of CNS symptoms	7.7 (2.0–30.3)	0.003
Prior IV pulse methylprednisolone	8.2 (1.6–42.7)	0.012
Maximal daily PRED dose	6.6 (1.8–24.2)	0.004

Table 4B. Final clinical predictors in the model after examining for interaction effects.

Variable	OR estimate (95% CI)	p
Major organ involvement, CNS/renal	9.1 (2.8–29.9)	< 0.001
Maximal daily PRED dose, mg/kg	9.9 (2.4–40.8)	0.002

R^2 = 0.4335. CNS: central nervous system; IV: intravenous; PRED: prednisone.

younger within the first year following the initiation of corticosteroids[34]. Young children have a richer vascular supply from red marrow and growth plate, and with aging, red marrow is converted to fatty marrow and growth plate is ossified, thereby increasing the susceptibility to ischemic injury of AVN[25,34,35].

AVN typically occurs in weight-bearing joints, most commonly the hip or knee[15]. We observed involvement of multiple joints in 81% of our affected patients, with bilateral involvement of hip and knee more frequent than unilateral

involvement. These findings are consistent with the existing adult and pediatric literature[7,11,13,36].

We have observed that maximal daily PRED dose, rather than duration of corticosteroid or cumulative PRED dose, was most predictive of AVN by multivariate analysis. Although both maximal daily PRED dose and cumulative PRED dose were significant in the univariate analysis, the maximal daily PRED dose was more important in determining risk for AVN. Prior studies reported cumulative corticosteroid dose to be predictive of AVN[13,22]; however, literature suggests that overall, AVN likely occurs early on, after high-dose steroid therapy, and with use of IV pulse therapy[14,25]. One explanation could be confounding by indication, in that patients with more severe disease are more likely to receive high-dose PRED, and may also be more likely to develop AVN independent of the steroids. However, there was no significant difference in the overall adjusted mean SLEDAI score between patients with AVN and without AVN prior to AVN diagnosis, suggesting that both groups had similar measurable disease activity.

Although AVN typically occurs while patients are receiving corticosteroids, it has been reported in PRED-naive patients, suggesting that SLE itself is involved in the pathogenesis[2,37,38]. AVN does occur more frequently in cSLE compared with other diseases treated with chronic corticosteroids, such as asthma, nephrotic syndrome, and rheumatoid arthritis, although there is no study controlling for the dose and duration of corticosteroid exposure[15,39]. By matching for age and time of diagnosis, we were able to eliminate effects from variability in duration of disease, age, and followup time, unlike previous studies that used a whole SLE cohort as the comparison. We found that patients with involvement of severe renal or CNS disease were more likely to develop AVN. Although these patients required earlier and higher dose corticosteroids than other patients, there was no collinearity in the final model even after including only those with proliferative nephritis or severe CNS disease. This suggests that major organ disease and use of high-dose corticosteroids are independent predictors of AVN. Although the AVN group had significantly higher early disease activity (at 6 mos) compared with the control group, this was not observed at the time of AVN diagnosis. Moreover, the adjusted mean SLEDAI was not different between the groups. Disease severity, and not disease activity, was predictive of AVN, supported by the observation of more frequent use of immunosuppressives in the AVN group. In contrast to previous studies, we did not observe significant differences in other clinical risk factors, laboratory features, or prescribed treatments.

Although MRI has been used routinely for the past decade, patients from the earlier years of this cohort may not have undergone MRI, and thus those with milder pain may have been missed if normal radiographs were not followed or a followup MRI was not performed. However, this was rare because most patients in the pre-MRI era had serial radiographs with or without a bone scan. Additionally, we have likely underestimated the longterm need for surgical treatment following transition to adult rheumatology care at age 18 years. Although elevated serum lipids may be a risk factor for AVN in adults[40], these data were not analyzed in our cohort because lipid levels were not available from the relevant timepoints for most patients.

Symptomatic AVN occurred in a lower proportion of patients with cSLE than previously reported (6%), with almost all AVN episodes diagnosed after puberty. Patients who had renal and/or CNS involvement, and/or required high daily doses of PRED, were more likely to develop symptomatic AVN compared with those without these risk factors. Further study is required to determine whether our results are reproducible in an independent cohort.

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