RISK FACTORS FOR AVASCULAR BONE NECROSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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SUMMARY

Objective. To study the predictive factors for avascular necrosis (AVN) of bone in patients with systemic lupus erythematosus (SLE).

Method. The records of 38 SLE patients who developed clinically apparent AVN during the course of their disease were reviewed. Information on clinical presentation, corticosteroid usage and autoantibody profiles was obtained, and comparison was made between these patients and 143 consecutive control SLE patients who did not have AVN.

Results. The point prevalence of AVN in our SLE population was 12%. Patients with AVN, when compared with controls, had a significantly higher incidence of neurological disease (39% vs 14%; \( P < 0.001 \)) and Cushingoid body habitus after steroid treatment (79% vs 53%; \( P = 0.004 \)). The highest cumulative prednisolone dose in 1 and 4 months was significantly higher in the AVN group than the controls (1.8 vs 1.1 and 4.5 vs 2.8 g, respectively; \( P < 0.01 \) in both) and showed a linear trend with the incidence of AVN (\( \chi^2 \) test for trend, \( P < 0.01 \) in both). Lupus anticoagulant was associated with AVN (\( P = 0.02 \), odds ratio \( 2.88 \) [1.14–7.28]). Logistic regression analysis revealed that the highest cumulative prednisolone dose administered in 4 months, the maximum and mean daily prednisolone dosage, and the lupus anticoagulant were independent risk factors for AVN.

Conclusions. Corticosteroid remains the major predisposing factor for AVN in SLE. Patients who require an initial high-dose steroid for disease control are at risk of AVN, especially if they are positive for the lupus anticoagulant or develop Cushingoid habitus after steroid treatment. High-risk patients should be closely monitored so that early AVN can be diagnosed by sensitive techniques such as magnetic resonance imaging and radioisotope bone scanning.

Key words: Avascular bone necrosis, Lupus anticoagulant, Complication, Musculoskeletal, Corticosteroid.
of these patients were recorded and compared with 143 consecutive SLE patients who attended our clinics, but did not have clinically apparent AVN. When a different preparation of corticosteroid was used, an equivalent dose of prednisolone was calculated. Patients were considered to have Cushingoid body habitus when there was evidence of moon face, truncal obesity, thin limbs, abdominal striae and buffalo hump on physical examination.

Disease activity was measured by the SLE Disease Activity Index (SLEDAI), a validated disease activity measure that has been shown to be sensitive to changes over time [8]. The SLEDAI scores at the time of maximum steroid dosage were recorded for all the patients studied.

Laboratory evaluation

Antinuclear antibody (ANA) was detected by an indirect immunofluorescence method. Anti-double-stranded (ds) DNA antibody was measured using ELISA and Farr assay. Anti-ENA antibodies (Ro, La, Sm, nRNP) were detected using countercurrent immunoelectrophoresis (CIEP). Lupus anticoagulant was screened by mixing studies, dilute Russell Viper venom test, kaolin clotting time and platelet neutralization. Anticardiolipin antibodies (IgG and IgM) were assayed using a standard ELISA kit from Cambridge Life Sciences. A positive test was defined as a value of >10 IU/ml on at least two occasions >3 months apart. Values between 11 and 20 IU/ml were considered to be weak positive, while a moderately strong and a strong positive test were defined as values between 21 and 30 IU/ml and >30 IU/ml, respectively.

Statistical analysis

Student’s t-test for independent samples was used to compare parametric data between the AVN and the control group of patients. The χ² test was used when the data were non-parametric. Yates’ continuity correction was adopted whenever the number was small. For multiple significance tests, significance was defined as a P value of <0.01. The trend of AVN risk with increasing cumulative prednisolone dose received was studied by the χ² test for linear trend. Risk factors for AVN were studied by stepwise logistic regression using AVN as the outcome variable and other factors such as age, sex, disease duration, Cushingoid habitus, steroid dose, duration and route, SLEDAI scores at maximum steroid dosage and antiphospholipid antibodies as the predictor variables. Regression coefficients (β) were calculated. P values of <0.05 were considered significant.

RESULTS

Demographic data and clinical features

Thirty-eight patients with AVN were identified among 320 SLE patients, giving rise to a point prevalence of 12%. Three patients developed AVN in the absence of steroid treatment, one of whom had active disease at the time of AVN. This was a 19-yr-old girl who presented with AVN of the carpal bones 4 months after the diagnosis of SLE. Her anticardiolipin antibodies and lupus anticoagulant were negative. In the other two patients, AVN of the femoral head occurred before the diagnosis of SLE was made. Both of them were positive for the lupus anticoagulant and the IgG anticardiolipin antibody. The mean time interval between steroid administration and the diagnosis of AVN in the remaining AVN patients was 50 months (range 4–198).

The demographic characteristics, clinical manifestations and autoantibody profile of patients with AVN and 143 control SLE patients who did not have AVN are summarized in Table I. Both groups of patients had a comparable age of onset and duration of the disease. There were more male patients in the AVN group than the control group, although this did not reach statistical significance (13% vs 6%; P = 0.11). Patients with AVN had a higher incidence of central nervous system (CNS) disease and lupus nephritis, but less alopecia and photosensitivity. When the observed P values were adjusted for multiple significance tests, only neurological disease was significantly more common in the AVN group (39% vs 14%; P < 0.001). The SLEDAI scores at the time of maximum corticosteroid dosage were higher in patients with AVN than in those without (15.4 vs 13.2; P = 0.10), but this did not reach statistical significance.

Concerning the autoantibodies, the prevalences of anti-dsDNA, various anti-ENA antibodies and anticardiolipin antibodies in both groups of patients were not significantly different. The IgG and IgM anticardiolipin titres were also similar in both groups. However, patients with AVN had a significantly higher prevalence of lupus anticoagulant (27% vs 12%; P = 0.02). Using the χ² analysis, lupus anticoagulant was associated with AVN (P = 0.02, odds ratio 2.88 [1.14–7.18]).

Sites of AVN and outcome

The hip (femoral head) was the commonest site of involvement of AVN in our SLE patients (36/38, 95%) and bilateral involvement was present in 26 cases (72%). This was followed by involvement of the knee (femoral condyle) (5/38, 13%), the humerus (1/38, 3%) and the carpal bones (1/38, 3%). Five patients had two or more sites of AVN (bilaterality was counted as one site). Arthroplasty of the hip was performed for 21 patients because of persistent pain or limitation of range of movement.

AVN and corticosteroid administration

Table II shows the information regarding corticosteroid administration and other associated medical diseases in the AVN patients and controls. The AVN patients had received a higher total cumulative prednisolone dose than the controls, but this was not statistically significant (17.7 vs 14.1 g; P = 0.22). However, the highest prednisolone doses received in 1 month and 4 months were significantly higher in the AVN group than the controls. The incidence of AVN showed a linear trend with increasing prednisolone dose administered in 1 month and 4 months (χ² for linear trend,
TABLE I
Demographic characteristics, clinical manifestations and autoantibody profile of 38 SLE patients with AVN and 143 control patients who did not have AVN

<table>
<thead>
<tr>
<th></th>
<th>AVN group (n = 38)</th>
<th>Control group (n = 143)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset of disease (yr)</td>
<td>26.6 ± 1.7 (10–54)</td>
<td>28.0 ± 0.7 (12–57)</td>
<td>0.39</td>
</tr>
<tr>
<td>F:M</td>
<td>33:5</td>
<td>135:8</td>
<td>0.11</td>
</tr>
<tr>
<td>Duration of disease (months)</td>
<td>72.2 ± 11.3</td>
<td>74.8 ± 5.2</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Clinical features
- Musculoskeletal manifestations
- Malar rash
- Discoid rash
- Oral ulcer
- Photosensitivity
- CNS disease
- Renal disease
- Serositis
- Raynaud's phenomenon
- Alopecia
- Cutaneous vasculitis
- Leucopenia
- Lymphopenia
- Thrombocytopenia
- Haemolytic anaemia
- Lymphadenopathy

ANA
- Anti-dsDNA
- Anti-Ro
- Anti-La
- Anti-Sm
- Anti-RNP
- ACA IgG
- IgM
- Mean IgG ACA titre
- Mean IgM ACA titre
- LA

ACA, anticardiolipin antibody; LA, lupus anticoagulant.

Central nervous system (CNS) disease includes the following manifestations: seizure, psychosis, organic brain syndrome, aseptic meningitis, cognitive dysfunction and transverse myelitis.

Renal disease is defined as proteinuria of >0.5 g/day or biopsy-proven lupus nephritis.

Lymphopenia is defined as a lymphocyte count of <1.0 × 10^9/l on at least two occasions.

Thrombocytopenia is defined as a platelet count of <100 × 10^9/l.

Leucopenia is defined as a white blood cell count of <4 × 10^9/l.

*p < 0.01 in both) (Table III). The average daily prednisolone dose was also significantly higher in the AVN patients (15.6 vs. 9.3 mg; p < 0.0001). Patients with AVN were more likely to develop Cushingoid body habitus after steroid administration than controls (79% vs. 53%; p = 0.004). Moreover, patients who became Cushingoid after steroid treatment, when compared with those who did not, had received a significantly higher prednisolone dosage in the first 1 and 4 months (1.71 vs. 0.68 and 3.99 vs. 1.89 g, respectively; p < 0.0001 in both). Regarding the use of cytotoxic agents, a significantly higher proportion of patients with AVN had received cyclophosphamide treatment than those without. None of our patients were smokers or drinkers. Hypertension, diabetes mellitus and impaired renal function were not associated with AVN.

Among the 181 SLE patients studied, 20 received i.v. pulse methylprednisolone (500–1000 mg daily for 3 days), followed by oral prednisolone. When compared with those who received oral prednisolone only, patients who had been pulsed had received a significantly higher cumulative prednisolone dose in the first 1 and 4 months (3.31 vs. 1.00 and 5.47 vs. 2.79 g, respectively; p < 0.01 in both). However, the incidence of AVN in patients who had received pulse steroid and oral steroid was similar [4/20 (20%) in the pulse group vs. 34/161 (21%) in the oral group]. AVN was not associated with pulse steroid treatment using the χ² analysis (P = 0.86).

Risk factors for AVN
Stepwise logistic regression was carried out for the 38 patients with AVN and the 143 controls, with AVN being the outcome variable and age, sex, disease duration, Cushingoid habitus, prednisolone dose, duration and route, SLEDAI scores at maximum steroid dosage, and the antiphospholipid antibodies being the predictor variables. It was found that the highest cumulative
TABLE II
Information regarding corticosteroid administration and other medical diseases in the AVN and control groups of patients

<table>
<thead>
<tr>
<th>Information</th>
<th>AVN group (n = 38)</th>
<th>Control group (n = 143)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of glucocorticoid treatment (months)</td>
<td>50.0 ± 11.3</td>
<td>52.2 ± 4.4</td>
<td>0.82</td>
</tr>
<tr>
<td>Total cumulative prednisolone dose (g)</td>
<td>17.7 ± 2.8</td>
<td>14.1 ± 1.2</td>
<td>0.22</td>
</tr>
<tr>
<td>Highest cumulative prednisolone dose in 1 month (g)</td>
<td>1.78 ± 0.17</td>
<td>1.14 ± 0.08</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Highest cumulative prednisolone dose in 4 months (g)</td>
<td>4.50 ± 0.44</td>
<td>2.75 ± 0.13</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean daily dose of prednisolone (mg)</td>
<td>15.6 ± 2.0</td>
<td>9.3 ± 0.5</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Number of patients who were initially given pulse methylprednisolone</td>
<td>4 (11%)</td>
<td>16 (11%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Cushingoid body habitus after steroid (truncal obesity, buffalo hump and moon face)</td>
<td>30/38 (79%)</td>
<td>76/143 (53%)</td>
<td>0.004*</td>
</tr>
<tr>
<td>SLEDAI scores at maximum steroid dosage</td>
<td>15.4 ± 1.2</td>
<td>13.2 ± 0.54</td>
<td>0.10</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (8%)</td>
<td>6 (4%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (3%)</td>
<td>1 (1%)</td>
<td>0.89</td>
</tr>
<tr>
<td>Smoking</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Alcohol drinking</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Deranged liver function test</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>0</td>
<td>4 (3%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Immunosuppressive treatment (other than steroid)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>15 (39%)</td>
<td>20 (14%)</td>
<td>0.004</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>23 (61%)</td>
<td>73 (51%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>13 (34%)</td>
<td>99 (69%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± s.e. (standard error of the mean).

TABLE III
Incidence of AVN with increasing cumulative prednisolone dose administered in 1 month and 4 months

<table>
<thead>
<tr>
<th>Highest cumulative prednisolone dose in 1 month (g)</th>
<th>AVN</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.2</td>
<td>9 (10%)</td>
<td>86 (74%)</td>
<td>95</td>
</tr>
<tr>
<td>1.2–1.8</td>
<td>19 (32%)</td>
<td>41 (68%)</td>
<td>60</td>
</tr>
<tr>
<td>&gt;1.8</td>
<td>10 (38%)</td>
<td>16 (62%)</td>
<td>26</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>143</td>
<td>181</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Highest cumulative prednisolone dose in 4 months (g)</th>
<th>AVN</th>
<th>Controls</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.0</td>
<td>5 (10%)</td>
<td>45 (90%)</td>
<td>50</td>
</tr>
<tr>
<td>2.0–4.0</td>
<td>10 (12%)</td>
<td>75 (88%)</td>
<td>85</td>
</tr>
<tr>
<td>&gt;4.0</td>
<td>23 (50%)</td>
<td>23 (50%)</td>
<td>46</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>143</td>
<td>181</td>
</tr>
</tbody>
</table>

χ² for linear trend: P < 0.01 in both.

DISCUSSION

AVN is a major cause of morbidity in SLE. Since its first description by Dubois and Cozen in 1960 [2], AVN has been increasingly reported in SLE patients. The prevalence rate of AVN in SLE varies widely and ranges from 2.8 to 40% [9]. In a large cohort of 407 SLE patients, Petri [10] reported a 14.5% prevalence of AVN, which was similar to the 12% point prevalence in our series. However, the true prevalence rate of AVN in our SLE population is likely to be higher as only symptomatic cases were identified.

Corticosteroid use is the chief risk factor for AVN in SLE. Studies investigating the association of AVN and steroid treatment yielded conflicting results concerning the cumulative steroid dosage, maximum steroid dose, route of steroid administration and the duration of steroid treatment. AVN may develop in patients who received high-dose, short-term steroids, long-term steroids or even after intra-articular injection. Smith et al. [11] and Dimant et al. [12] did not find any association between the total cumulative dose of steroid, the duration of therapy or the peak steroid dose with AVN. Bergstein et al. [13] described a relationship between AVN and the total cumulative steroid dose, but not with the duration of steroid treatment. Moreover, whether steroid-induced AVN occurs slowly over a long period of time, or abruptly after a brief period of high-dose treatment, remains controversial. Massardo et al. [14] considered i.v. pulse methylprednisolone as a risk factor for AVN. However, this was not supported by Migliaresi et al. [15], who failed to find an increased risk of AVN in patients receiving i.v. pulse steroid therapy.

In our study, we have shown that the highest dose of corticosteroid administered within 4 months and the maximum steroid dosage, rather than the total cumulative steroid dose or the duration of steroid therapy, are predictive factors for AVN in SLE. This is consistent with the results published by Abeles et al. [1] who also demonstrated a higher risk of AVN in patients who received a high cumulative steroid dose in the first and first 3 months after starting steroid therapy, when compared with controls. A recent study on the risk factors for AVN in patients with SLE by Mont et al. [9] also described the peak prednisolone dose as a significant and independent predictive factor.
for AVN. Although pulse methylprednisolone contributes significantly to a higher cumulative steroid dose during the first few months of therapy, we are unable to show an association of i.v. pulse steroid and AVN. Moreover, logistic regression fails to demonstrate the importance of the route of steroid administration in determining AVN. Two possible explanations can be offered. First, the number of patients who received pulse methylprednisolone is too small for comparison with those who received oral prednisolone, leading to a type II statistical error. Secondly, as the proportion of patients who received pulse steroid in both the AVN and control groups of SLE patients is similar (11% in both), the higher cumulative prednisolone doses in the first and first 4 months of therapy in the AVN group may have represented a higher oral prednisolone dose used instead of pulse methylprednisolone per se.

AVN has long been reported in SLE patients who had not been taking corticosteroid. Both Leventhal et al. [16] and Velayos et al. [17] found evidence of previous vasculitis in pathological bone specimens from patients with SLE not receiving corticosteroid therapy. This leads to postulation that active SLE itself may be another predisposing factor for AVN. This is supported by the fact that one of our patients developed AVN at the time of active SLE, in the absence of steroid treatment [18]. As her antiphospholipid antibodies were repeatedly negative, a localized vasculitic process was thought to be a possible mechanism. Although the SLEDAI scores during the time of maximum steroid dosage in our patients with AVN were higher than those in patients without AVN, the difference was not statistically significant. Moreover, regression analysis does not show that disease activity is a risk factor for AVN. This suggests that the higher initial steroid dose for the treatment of more active disease in our AVN group of SLE patients is likely to be more relevant than the disease activity per se in the contribution to AVN.

A number of clinical features have been described in association with AVN in SLE. These include young age of disease onset [11], Raynaud’s phenomenon [19, 20], Cushingoid habitus after steroid treatment [9, 19], vasculitis [9, 17, 19], thrombophlebitis, smoking, pre-eclampsia [9] and leucopenia [20]. In our series of SLE patients, we confirm the observation that Cushingoid habitus after steroid treatment is associated with AVN. Patients who became Cushingoid had received a significantly higher dose of steroid in the first and first 4 months of therapy. This suggests that patients who received large doses of corticosteroid within a short period of time and became Cushingoid are more prone to this complication. High-dose steroid sufficient to produce a Cushingoid state is associated with hyperlipidaemia, fatty liver, fat mobilization and marrow lipocyte hypertrophy, which in turn lead to ischaemic bony necrosis. The higher prevalence of renal and CNS disease in our patients with AVN reflected the need for a higher initial steroid dose for the control of disease in these two systems. On the contrary, we are unable to demonstrate an association of younger age at disease onset, leucopenia, Raynaud’s phenomenon or cutaneous vasculitis with AVN, as suggested by previous authors.

The antiphospholipid antibodies have recently been associated with AVN in patients with SLE. Asherson et al. [4] showed that the prevalence of the antiphospholipid antibodies (anticardiolipin antibodies or lupus anticoagulant) was higher in patients with AVN than in those without. Although both the AVN and the non-AVN groups were receiving corticosteroid treatment, the antiphospholipid antibodies were postulated to be an additional risk factor for AVN in SLE. This is in agreement with the study by Nagasawa et al. [5], who investigated 111 SLE patients and reported that a demonstrable lupus anticoagulant as well as a shortened partial thromboplastin time (APTT) were more common in patients with AVN. Vascular occlusion or a thrombotic vasculopathy related to the antiphospholipid antibodies was thought to be the underlying aetiological mechanism. In our study, the prevalence and the mean titres of the IgG and IgM anticardiolipin antibodies in both the AVN and the control groups of patients were similar. However, a significantly higher prevalence of lupus anticoagulant was found in patients with AVN. Using the $\chi^2$ analysis, lupus anticoagulant was associated with AVN. Logistic regression also confirmed that the lupus anticoagulant was an independent risk factor for AVN. Two of the three SLE patients in our series who developed AVN in the absence of steroid treatment were positive for both the lupus anticoagulant and anticardiolipin antibodies. This stresses the importance of antiphospholipid antibodies in predisposition to AVN.

In conclusion, we believe that the aetiology of AVN in SLE is multifactorial. Corticosteroid remains the chief predisposing factor for AVN in SLE patients and its use should be judicious. High-dose steroid administered within the first 4 months, the peak and the mean daily prednisolone dosage, and a positive lupus anticoagulant, are independent risk factors for AVN. Patients with SLE who require a high initial dose of corticosteroid for disease control are at risk of AVN, especially if they are positive for the lupus anticoagulant or become Cushingoid after steroid treatment. More sensitive techniques, such as the radioisotope bone scan and MRI, should be considered for the early diagnosis of AVN in this group of high-risk patients.

References