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RESEARCH ARTICLE

Steroid-induced Avascular Necrosis in Patients with Demyelinating Diseases: A Single-center Experience

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Abstract

Objective: Steroids used especially during relapses of demyelinating diseases such as multiple sclerosis (MS) and neuromyelitis optica spectrum disorder (NMOSD) are a well-known risk factor for the development of avascular necrosis. The aim of this study was to evaluate the frequency of steroid-induced avascular necrosis (SIAVN) in our patients with demyelinating disease and the demographic, clinical and radiological features of these cases.

Materials and Methods: Patients with regular follow-up were screened from electronic patient records for the development of avascular necrosis retrospectively. Descriptive features of patients with avascular necrosis were evaluated.

Results: SIAVN necrosis was detected in 7 (0.06%) of 1204 patients (6 with MS and 1 with NMOSD) who were regularly followed up in the demyelinating diseases outpatient clinic. Two of the patients had osteopenia before avascular necrosis. The mean cumulative steroid dose was 19.57±13.53 [minimum (min.) 7, maximum (max.) 44] grams. The mean time between the symptoms of avascular necrosis and diagnosis was 6±3.37 (min. 3-max. 12) months. Avascular necrosis was diagnosed in all patients by magnetic resonance imaging. Core decompression surgery was performed in 5 of the cases.

Conclusion: Avascular necrosis is a rare but important complication that can cause disability and should be recognized and treated early in the course of demyelinating diseases. It can develop independently of steroid dose and duration and is unpredictable, so it should be kept in mind especially in patients who develop hip or leg pain.

Keywords: Avascular necrosis, steroid treatment, multiple sclerosis, neuromyelitis optica spectrum diseases

Introduction

Steroid-induced avascular necrosis (SIAVN) is a notable complication in patients with demyelinating diseases, particularly multiple sclerosis (MS), who receive corticosteroids during acute relapse treatment. Intravenous methylprednisolone (IVMP) at a dose of 1000 mg/day is typically administered for 3-10 days, and this is often followed by oral corticosteroids, especially in neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (1,2). SIAVN is a serious condition resulting from reduced blood supply to the trabecular bone, leading to ischemia, most commonly affecting the femoral head (3). Corticosteroids can contribute to SIAVN through several mechanisms, including fat accumulation within the bone marrow, osteocyte necrosis, and fat embolism formation, which can obstruct blood vessels and impair capillary formation and repair (4,5). Steroids also suppress osteoblast differentiation and function while promoting osteocyte apoptosis, resulting in impaired bone regeneration and increased necrosis (6,7). Additionally, corticosteroids activate inflammatory and oxidative stress pathways, which enhance apoptosis and reduce autophagy. Mitochondria-dependent apoptosis may also be triggered, involving the

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release of cytochrome c and the activation of caspases-key enzymes in programmed cell death (6). These mechanisms have been demonstrated in animal studies (8). The risk of SIAVN appears to be linked to the cumulative steroid dose, although some studies have reported no significant association between the two (9). SIAVN is commonly observed following high-dose steroid use but has also been reported after the use of topical or inhaled steroids (10,11), intra-articular injections (12), and even short-term, low-dose oral corticosteroids (13). Some research indicates that patients with MS may have an elevated risk of osteoporosis, fractures, and AVN due to the autoimmune and inflammatory nature of the disease (14,15). In a study by Ce et al. (16) 15.5% of MS patients who received pulse steroid therapy developed AVN, whereas no cases were found in the control group. Patients with SIAVN often experience severe pain and limited joint mobility, but these symptoms may be misattributed to MS itself, potentially delaying diagnosis. Such delays can lead to further disability as bone necrosis progresses (17). Magnetic resonance imaging (MRI) plays a key role in diagnosing AVN, detecting necrotic areas, joint effusion, and varying levels of bone collapse and secondary degenerative changes (18,19). This study aimed to explore factors contributing to SIAVN by analyzing the clinical features of seven patients diagnosed with the condition-six with MS and one with NMOSD.

Materials and Methods

This study included 1204 patients with long-term, regular follow-up and current data from the MS and Demyelinating Diseases outpatient Department at Ege University Hospital. These patients were retrospectively reviewed for the occurrence of SIAVN. Demographic and clinical data for patients diagnosed with SIAVN were obtained from electronic medical records. The clinical and radiological assessment of AVN was conducted using the Ficat-Arlet classification system (20):

- Grade 0: No clinical symptoms or X-ray findings; MRI shows a double-line sign.
- Grade 1: Normal joint appearance; femoral head remains spherical. X-ray may reveal slight osteoporosis. MRI shows a single line on T1 and a double-line sign on T2 indicating necrotic bone.
- Grade 2: Double-line sign present; reactive bone borders the infarcted area. The joint remains normal, and the femoral head is still spherical.
- Grade 3: Loss of the femoral head's spherical shape with subchondral bone fracture; X-ray reveals a crescent sign.
- Grade 4: Further collapse of the femoral head with articular cartilage and joint space narrowing.

This study received approval from the Ege University Faculty of Medicine Ethics Committee (decision no.: 25-3.1T/68, date: 20.03.2025). Written informed consent was obtained from all patients.

Statistical Analysis

Descriptive statistical analysis (mean, standard deviation, minimum, and maximum) was performed using SPSS version 26.0.

Results

SIAVN was identified in seven patients (0.6%) patients, including one with NMOSD and six with MS. Of these, five were female and two were male. The median Expanded Disability Status Scale score was 2.0 (range, 0-3.0), the mean age was 33.29±6.69 years (range, 28-44), and the mean disease duration was 6.57±6.72 years (range, 3-22). Four patients had never smoked, two were former smokers, and one was an active smoker. None reported chronic alcohol use. The mean body mass index (BMI) was 23.9 (range, 19.4-33.2), with only one patient classified as obese (BMI >30). Detailed case information is presented in Table 1. None of the patients had any comorbid conditions. Two patients (cases 1 and 5) were diagnosed with osteopenia. The mean cumulative corticosteroid dose prior to the development of AVN was 19.57±13.53 grams (range, 7-44 grams). The average interval between the last IVMP treatment and the onset of AVN symptoms (hip or leg pain) was 6±3.37 months (range, 3-12 months). AVN was diagnosed in all patients by MRI, as initial hip X-rays taken after symptom onset were unremarkable (Figure 1 displays the MRI findings of case 2). The mean duration from the onset of AVN symptoms to diagnosis was 4.86±3.56 months (range, 1-12 months). Non-steroidal anti-inflammatory drugs were sufficient for symptom management in two cases. Core decompression surgery was performed in five patients; one of these had received hyperbaric oxygen therapy prior to surgery.

Discussion

In demyelinating neurological disorders, immune dysregulation and inflammatory activity may lead to vascular alterations that potentially compromise the blood supply to bone tissue, contributing to the development of AVN (14). Most cases of non-traumatic AVN are associated with corticosteroid therapy (16). The incidence of AVN in patients receiving high-dose steroids has been reported to range from 3% to 20% (21). In our study, the incidence was 0.6%, which is lower than previously reported rates. This discrepancy may be attributed to differences in steroid dosage, treatment duration, patient populations, and study methodologies. For instance, another study conducted in our country found a 15.5% incidence of AVN in MS patients treated with steroids, compared to none in those who were not.

Table 1. Demographic and clinical characteristics of the cases

Cases	Gender (F/M)	Age (years)	Disease	Disease duration (years)	EDSS	BMI (kg/m^2)	IMTs before AVN (months)	Cumulative CST dose (gram)	Duration between the last CST and AVN (months)	Duration between the first symptom and diagnosis (months)	Ficat-Arlet classification of the AVN	Treatment of AVN
Case 1	F	44	SPMS	21	3.0	21.6	IFN beta-1a (15), teriflunomide (33)	37	3	2	Grade 3	Core decompression operation
Case 2	M	38	RRMS	2	2.5	22.5	IFN beta-1b (5), teriflunomide (15), ocrelizumab (3ay)	13	9	6	Grade 3	Core decompression operation
Case 3	F	24	RRMS	2	0.0	20.3	IFN beta-1a (5), fingolimod (8)	12	4	2	Grade 2	Conservative treatment (NSAID)
Case 4	F	32	RRMS	1	0.0	33.2	Glatiramer acetate (12)	7	12	12	Grade 1	Conservative treatment (NSAID)
Case 5	M	28	NMOSD	2	2.0	26.2	Azathioprine (12), oral CS (18), rituximab (12)	44	5	4	Grade 2	Hyperbaric oxygen, core decompression operation
Case 6	F	39	RRMS	10	0.0	24.1	IFN beta-1a (114), fingolimod (16)	14	3	1	Grade 3	Core decompression operation
Case 7	F	28	RRMS	8	3.0	19.4	IFN beta-1a (39), fingolimod (15), natalizumab (26), ocrelizumab (8)	10	6	7	Grade 2	Core decompression operation

F: Female, M: Male, EDSS: Expanded Disability Status Scale, BMI: Body mass index, IMT: Immunomodulatory treatment, AVN: Avascular necrosis, CST: Corticosteroid therapy, SPMS: Secondary progressive multiple sclerosis, RRMS: Relapsing-remitting multiple sclerosis, NMOSD: Neuromyelitis optica spectrum disorder, IFN: Interferon, NSAID: Non-steroidal anti-inflammatory drug

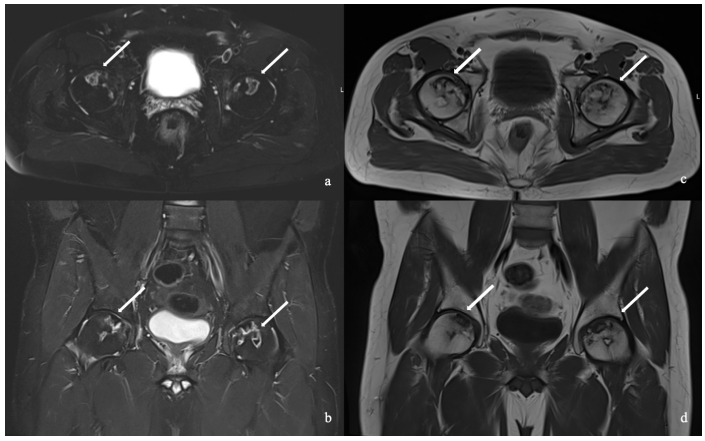

Figure 1. T2-weighted axial (a), coronal (b), T1-weighted axial (c), and coronal (d), images of the case 2 with steroid-induced osteonecrosis showing areas of necrosis in the bilateral femoral head

In that study, AVN was identified using MRI screening, and most of the detected cases were asymptomatic (16). In contrast, in our study, AVN was diagnosed based on the investigation of symptomatic patients. Various risk factors have been identified across different conditions, with high-dose corticosteroid therapy being the most recognized in inflammatory diseases, particularly systemic lupus erythematosus. In our cohort, the mean cumulative intravenous corticosteroid dose was 19.57±13.53 grams. Although the cumulative dose may appear high, one patient developed AVN after receiving only 7 grams of IVMP, suggesting that additional factors also contribute to AVN development. Known risk factors include younger age, smoking, chronic alcohol use, obesity, increased disease activity, comorbidities, and immunosuppressive treatments (22-24). In our series, patients were relatively young, with a mean age of 33.29±6.69 years. One patient (case 7) was an active smoker, while none reported chronic alcohol consumption. Obesity was present in only one case (case 4). Aside from two patients with osteopenia, no comorbidities were identified. The interval between steroid administration and symptom onset has been reported to range from a few months to nearly 3 years (25). In our cohort, the mean duration between the last IVMP treatment and the appearance of AVN symptoms was 6±3.37 months (range, 3-12 months). However, prospective studies using MRI to detect early AVN suggest that this interval may be shorter (26). Five patients had been treated with interferon (IFN)-beta during their disease course. IFN-alpha, used in chronic myeloid leukemia, has associated with AVN due to its inhibition of new blood vessels formation through increased plasminogen activator inhibitor synthesis (27). However, there is currently no evidence linking IFN-beta to AVN development. Delayed diagnosis of AVN can occur when pain is misinterpreted as a symptom of the underlying inflammatory disease. In our cases, the average time from the onset of hip or leg pain to the diagnosis of AVN was 4.5±3.73 months (range, 1-12 months). Relying solely on X-rays, which may appear normal in early stages, instead of using MRI the gold standard for AVN diagnosis can also contribute to diagnostic delays. In all of our patients, AVN was confirmed by MRI despite normal X-ray findings. Treatment options for AVN range from conservative approaches to surgical interventions, depending on the extent of bone damage. Therefore, early diagnosis and management are crucial to prevent progression and reduce disability.

Study Limitations

As this was a retrospective study, the assessment of AVN relied solely on existing electronic patient records, and patients were not re-evaluated specifically for AVN. Consequently, the reported incidence may underestimate the true rate due to incomplete data.

Conclusion

AVN is an uncommon but potentially disabling complication associated with corticosteroid use in demyelinating diseases. It may develop regardless of steroid dose or duration and is not always predictable. Clinicians should consider AVN in patients presenting with hip or leg pain. X-rays may be insufficient for diagnosis, so MRI should be used as the gold standard. Early identification is essential to minimize tissue damage and improve clinical outcomes.

Ethics

Ethics Committee Approval: This study received approval from the Ege University Faculty of Medicine Ethics Committee (decision no.: 25-3.1T/68, date: 20.03.2025).

Informed Consent: Written informed consent was obtained from all patients.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.K., O.E., N.Y., Concept: O.E., N.Y., Design: B.K., N.Y., Data Collection or Processing: B.K., G.N.B., Analysis or Interpretation: B.K., G.N.B., Literature Search: B.K., Writing: B.K., G.N.B.

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