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Avascular Necrosis of the Femoral Head in Multiple Sclerosis

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ABSTRACT:

Avascular necrosis of the femoral head in multiple sclerosis

Objective: Corticosteroid (CS) therapy is widely used as the standard treatment for acute exacerbations of multiple sclerosis (MS). Avascular necrosis (AVN) of the femoral head is one of the long-term complications related to CS therapy. Our study aims to investigate the association between annual and cumulative doses of CS treatment and radiographic assessment of AVN of the femoral head in MS.

Material and Methods: One patient group and two control groups were formed. The study group consisted 60 MS cases treated with intravenous methylprednisolone (IVMP) and the 2 control groups consisted 22 MS patients (Control I) without CS treatment and 25 healthy controls (Control II). Sixty patients who underwent CS treatment were divided into 3 subgroups of 20 cases each, treated with either IVMP only, IVMP and interferon, and IVMP and glatiramer acetate (GA). Neurological examinations and demographic data of all cases were recorded. The presence of AVN of femoral head in patient and control groups was evaluated using magnetic resonance imaging and Ficat staging system.

Results: Avascular necrosis (AVN) of femoral head was observed in 4 (6.7%) MS patients who were treated with CS. The mean annual CS dose was 8.07 g and mean cumulative dose was 31 gr. There was a significant but no statistical difference, in annual and cumulative IVMP doses between patients who have and don't have AVN of femoral head (p=0.085 and p=0.246, respectively).

Conclusion: Our all data support the idea that annual dose of CS may increase AVN of femoral head development in MS patients. It is important to evaluate the CS-treated MS patients with MRI in this respect, due to the possible treatment of early-stage AVN of femoral head.

Keywords: Avascular necrosis of the femoral head, corticosteroid treatment, multiple sclerosis

ÖZET:

Multipl sklerozda femur başı avasküler nekrozu

Amaç: Kortikosteroid (KS) tedavisi multipl skleroz (MS) akut ataklarında yaygın olarak kullanılan standart bir tedavi yöntemidir. Femur başı avasküler nekrozu (AVN) KS tedavisine bağlı gelişen uzun dönem komplikasyonlardan biridir. Çalışmamızda femur başı AVN' un MS hastalarında görülme sıklığı ile uygulanan yıllık ve kümülatif KS miktarı ile olan ilişkisi araştırılmıştır.

Gereç ve Yöntemler: Çalışmamızda MS polikliniğinden takipli intravenöz metilprednizolon (IVMP) tedavi almış 60 MS tanılı hasta grubu ile IVMP tedavisi almamış 22 MS hasta (Kontrol I) ile 25 sağlıklı olgudan (Kontrol II) oluşan iki kontrol grubu oluşturuldu. KS tedavisi alan 60 hasta sadece IVMP, IVMP ve interferon, IVMP ve Glatiramer asetat (GA) kullanan 20'şer olguluk üç alt gruba ayrıldı. Tüm olguların nörolojik muayeneleri ve tüm demografik verileri kaydedildi. Hasta ve kontrol gruplarında femur başı AVN varlığı, manyetik rezonans görüntüleme (MRG) ile Ficat Evreleme sistemi kullanılarak değerlendirildi.

Bulgular: Femur başı AVN sadece KS tedavisi alan 4 MS hastasında (%6.7 oranında) gözlendi. Hastaların ortalama yıllık KS dozu 8.07 gr, ortalama kümülatif KS dozu 31 gr bulundu. Femur başı AVN olan hastalar ile olmayan hastalar arasında yıllık ve kümülatif IVMP doz miktarlarında belirgin bir fark gözlenmekle birlikte istatistiksel anlamlılık saptanmadı (sırasıyla p=0.085 ve p=0.246).

Sonuç: Elde ettiğimiz veriler MS hastalarında femur başı AVN gelişiminin KS yıllık doz miktarı ile artabileceği fikrini desteklemektedir. Femur başı AVN'de erken evrede tanı ile tedavinin mümkün olması nedeniyle özellikle KS tedavisi alan MS hastalarının bu açıdan da takibi ve MRG ile birlikte değerlendirilmeleri önem kazanmaktadır.

Anahtar kelimeler: Femur başı avasküler nekrozu, kortikosteroid tedavisi, multipl skleroz

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INTRODUCTION

Multiple sclerosis (MS) is an inflammatory, demyelinating, chronic disease of the central nervous system (CNS) (1,2). MS treatment is based on immunomodulation and immunosuppression due to known immunomodulation anomalies related to this disease. In the treatment of acute exacerbations, CS is the most commonly used, and as a general recommendation, IVMP 1000 mg/day is given between 3-10 days, then in some centers, the treatment is continued as followed by reduction of oral methylprednisolone (3,4).

There are studies reporting an increase of risk of osteoporosis, fracture and femoral head AVN in MS patients, triggered by increased osteoclast activity and inhibition of osteoblast activity and many different factors with the autoimmune inflammatory pathogenesis of the disease (5-7). It has also been previously reported that AVN of femoral head may also occur independently of the CS dose in MS patients (7). CS has different side effects on various systems. Among these side effects, AVN of femoral head that may occur in long term causes severe bone and articular cartilage destruction that may require prosthetic surgery (8). Avascular necrosis of the femoral head can be detected in the early period by MRI (9,10).

The aim of this study was to investigate the incidence of AVN of femoral head in MS patients which is one of the long-term complications related to CS treatment and the relationship between the AVN of femoral head and annual and cumulative CS amount.

METHOD

Consecutive patients selected from the MS outpatient clinic follow-up of Istanbul Medeniyet University S.B. Göztepe Training and Research Hospital Department of Neurology were included in our study. A number of 60 MS patients taking whether or not immunomodulator treatment in addition to IVMP constituted the study group, while 22 MS patients with no definite diagnosis in the previous episodes or had no treatment chance, therefore who didn't use IVMP and/or immünomodulator treatment constituted the first control group (Control I), and 25 healthy subjects with no complaints and normal neurological examination constituted the second control group (Control II). The study group included patients who had received at least one treatment and at least 3 grams of IVMP in the last 4 years. Interferons inhibit angiogenesis via plasminogen activator inhibitor (PAI) synthesis, leading to femoral head AVN formation (11,12). For this reason, 60 patients who underwent CS treatment were divided into three subgroups of 20 patients as IVMP alone, IVMP and interferon, IVMP and glatiramer acetate (GA), and the possible effect of immunomodulatory drugs used outside CS on femoral head AVN formation was investigated. Annual and cumulative doses of CS were determined in each patient. All MS patients were ambulatory patients. Patients were excluded from the study who had conditions such as diabetes mellitus, autoimmune systemic diseases, hemoglobinopathies, inflammatory bowel diseases, cytotoxic drug use, femoral head and neck fracture, chronic alcohol use, and chronic renal failure in the etiology of AVN. Informed consent form was obtained from all subjects included in our study and approval from Istanbul Medeniyet University S.B. Göztepe Training and Research Hospital Ethics Committee.

The presence of AVN of femoral head was investigated with MRI in study and control groups. All patients received bilateral femoral head MRI (1.5 Tesla; Intera, Philips Medical Systems-Netherlands). MRI results were evaluated by a radiologist who didn't know the diagnosis and the clinic of the patients using Ficat Staging system. Avascular necrosis of femoral head was classified according to this system as follows: Stage (0): Plain radiograph and scintigraphy, double-line sign at MRI; Stage (I): Minor osteoporosis at radiograph and single-line sign in T-1 enhanced sequence and dobule-line sign in T-2 enhanced sequence MRI; Stage (IIA): Cystic and sclerotic changes at femoral head, Stage (IIB): Crescent sign, Stage (III): Contour disturbance at the femoral head; Stage (IV): Collapse in joint space, contour flattening, collapse at the femoral head (13).

When evaluating the study data, in addition to the descriptive statistical methods (mean, standard

deviation), power analysis of the groups were performed and one-way Anova test and Student's t test were used to compare the normal distribution of the parameters of quantitative data between the groups. In comparison of the parameters with no normal distribution between the groups, Kruskal Wallis test, and to determine the group that caused variance, Mann Whitney U test was used. Chi-Square test and Fisher's Exact test were used for comparison of qualitative data. For statistical significance, $p<0.05$ was considered. SPSS version 10.0 was used for statistical analysis.

RESULTS

Sixty MS patients who were receiving CS treatment (49 female, 11 male) were participated in the study and their mean age was 32.87±0.85. The first contro lgroup consisted of 22 MS patients (19 female, 3 male) who didn't receive CS treatment and with a mean age of 32.18±1.62, and 25 healthy subjects (21 female, 4 male) with no complaint and with a mean age of 36.12±1.83 consisted the second control group. There was no significant difference between the groups in terms of mean age and gender distribution (p=0.128; p=0.874). There was no statistically significant difference between the mean disease duration of MS patients who didn't receive CS treatment and the mean duration of disease of MS patients who received CS treatment (p=0.220) (Table-1).

There were no differences between the three subgroups of 20 patients consisting of IVMP alone, IVMP and interferon, and IVMP and GA treatments in terms of age and gender distribution of 60 patients receiving CS treatment (p=0.967; p=0.895). There was no statistically significant difference in the duration of disease and annual IVMP dose between the three subgroups receiving CS treatment (5.08±0.96 in the only IVMP-receiving group, 5.45±0.60 in the IVMP + interferon receiving group and 5.50±0.97 in the IVMP + GA receiving group) (p=0.116; p=0.721); however, statistically significant differences were detected between the cumulative doses of IVMP (14.40±1.70 in the only IVMP-receiving group, 21.75±3.82 in the IVMP + interferon receiving group and 25.65±3.70 in the IVMP + GA receiving group) (p=0.037). The mean duration of interferon use was 3.95±2.98 years, mean duration of GA use was 3.20±1.36 years. When the cumulative dose amounts of MS patients were examined, it was detected to be

Table-1: Evaluation of groups according to demographic characteristics

	Patient Group (n: 60)	**Control Group I** (n: 22)	**Control Group II** (n: 25)	**p**
Age	32.87±0.85 years	32.18±1.62 years	36.12±1.83 years	p=0.128
Gender				
M	11	3	4	p=0.874
F	49	19	21	
Duration of disease	5.32±0.45 years	6.36±0.67 years	-	p=0.220

Table-2: Evaluation of MS group according to disease duration, annual IVMP dose and cumulative IVMP dose

	Patient Group			**Test ist; p**
	IVMP only (Median)-(Range) (Mean±SD)	**IVMP+Interferon** (Median)-(Range) (Mean±SD)	**IVMP+GA** (Median)-(Range) (Mean±SD)	
Disease duration	3 (1-16) years 4.60±0.90	5 (3-11) years 5.45±0.60	4.5 (2-14) years 3.64±0.81	KW=4.311 p=0.116
Annual Dose	3.65 (0.6-15) gr 5.08±0.96	3.3 (1.4-9) gr 3.99±0.48	4.5 (0.5-17) gr 5.50±0.97	KW=0.653 p=0.721
Cumulative Dose	13 (3-27) gr 14.40±1.70	14 (5-77) gr 21.75±3.82	20 (7-70) gr 25.65±3.70	KW=6.576 p=0.037

SD: Standard deviation, KW: Kruskal Wallis Test

Table-3: Evaluation of AVN according to annual IVMP dose and cumulative IVMP dose

Patient Group	AVN (+) n:4 Median)-(Range) (Mean±SD)	AVN (-) n:56 Median)-(Range) (Mean±SD)	Test ist; p
Annual Dose	8.50 (3.3-12) gr 8.07±2.29	3.50 (10-60) gr 4.63±0.48	z=-1.720 p=0.085
Cumulative Dose	27 (0.5-17) gr 31.0±10.53	14.50 (3-77) gr 19.86±1.92	z=-1.159 p=0.246

SD: Standard deviation, z: Mann Whitney U Test

significantly lower in the only IVMP receiving group than the IVMP + GA receiving group (p=0.011), but this difference was not significant compared to the IVMP + interferon group (p=0.146) (Table-2).

No AVN of femoral head was found in the control group and in none of the MS patients who didn't receive CS. Four patients (6.7%) in 60 patients who received CS treatment had femoral head AVN. The first patient was diagnosed 3 years ago and the mean annual CS dose was 3.3 gr and the cumulative dose was 10 gr Ficat Stage II femoral head AVN was detected in the patient with optic episodes. The second patient was a Ficat Stage II patient who was diagnosed 2 years ago, with a mean annual CS dose of 12 and a cumulative dose of 24 gr Spinal cord involvement was predominant in this patient. The third patient was Ficat Stage II who had cerebellar-weighted findings, diagnosed 5 years ago, with an average annual dose of 12 gr and a cumulative dose of 60 gr. The last femoral head AVN patient was Ficat Stage III who had been diagnosed 6 years ago, with an average annual dose of 5 and a cumulative dose of 30 gr with optic and spinal episodes. The first three patients were asymptomatic and the fourth patient had hip and groin pain. There was no statistically significant difference between the annual IVMP doses of patients with and without femoral head AVN with a statistical trend toward significance (p=0.085). There was no significant difference between the cumulative dose amounts (p=0.246) (Table-3).

DISCUSSION

Femoral head AVN is bone death and a structural decay of bone that results in joint pain, bone degeneration and loss of function. The most common second cause of femoral head AVN is due to CS use, following trauma, with a prevalence of 3-38%. CS usage may lead to femoral head AVN formation with unclear mechanisms such as hypercoagulability, changes in lipid metabolism and fat embolisms in small vessels (14). In addition, pressure increase due to hypertrophic lipid cells in bone triggers femoral head AVN formation (15). Other less frequent causes of femoral head AVN formation include autoimmune rheumatic diseases, systemic lupus erythematosus, alcoholism, pregnancy, Gaucher disease, inflammatory bowel disease, and cytotoxic agents (16).

Treatment of acute exacerbations of MS includes 1000 mg/day IVMP pulse therapy, given usually for 5-10 days and oral CS treatment may preferably be added. Femoral head AVN due to CS treatment in MS patients has been reported in various studies in the literature (7,17-19). In our study, we aimed to investigate the frequency of femoral head AVN which could develop as a treatment complication in MS patients who had to receive pulse IVMP treatment repeatedly according to the frequency of the attack. The duration between the use of CS and the onset of symptoms of AVN of femoral head varies between 6 months and 3 years in retrospective studies (8). Therefore, the study group consisted of MS patients who received at least 3 gr pulse IVMP therapy over the past 4 years. Avascular necrosis of femoral head was seen more frequently in patients receiving long-term CS treatment. However, there is also evidence in the literature that short-term and high-dose CS treatment may lead to femoral head AVN (20). Drescher et al. investigated the effect of short-term high-dose CS treatment on femoral head AVN formation on pigs to which they applied methylprednisolone at 1000 mg/day for the first 3

days and 500 mg/day for the next 11 days for 14 days, and as a result, found that the femoral head blood flow was significantly decreased in the treatment group compared to the control group (21). Çe et al. investigated the complication of femoral head AVN in MS patients and detected AVN of femoral head in 5 (15.5%) of 33 MS patients who received pulse CS treatment (19). Again, in a study conducted by Kale et al., femoral head AVN was detected in 23% of patients who received 20-60 gr cumulative CS treatment (7). In our own series with a higher number of patients, we detected this ratio to be 6.7% lower than the previous studies. While in Çe et al.'s study, the MS patients included in the study were observed to receive at least 10 gr or more IVMP in the last 2 years or at least 15 gr IVMP during the disease, in Kale et al.'s study, the cumulative CS dose was 20-40 gr. In our study, patients who received at least 3 gr of IVMP treatment in the past 4 years were included. When we look at the annual CS dose of cases with femoral head AVN, we found a difference with statistical trend toward significance, and when we look at the cumulative doses, we found no statistical significance, however, a significant higher cumulative dose in patients with AVN.

When we compared the control group I of healthy subjects without any complaint and control group II of MS patients who hadn't received CS treatment in our study, the presence of no femoral head AVN in both groups supports that the femoral head AVN detected in our study group who had received CS treatment occured as a complication due to the CS treatment and the idea that MS is not an independent risk factor for femoral head AVN formation.

When we evaluated the group of patients with CS treatment as IVMP only, IVMP+interferon and IVMP + GA treatment group, only 2 cases in the CS group and 2 cases in the in the IVMP + GA group were found to have femoral head AVN. In these four cases, there was not a common point in MS clinic and applied treatments that would affect the formation of femoral head AVN. The femoral head AVN was not observed in the IVMP + interferon group. In our study, the use of interferon had no significant effect on femoral head AVN formation.

Our study suggests that MS patients treated with CS are at risk for developing femoral head AVN. Studies with high cumulative doses used have reported a much higher rate of femoral head AVN development (7,19). We found no significant statistical difference between the treatment groups in terms of annual and cumulative doses in femoral head AVN cases. However, it is noteworhty that the annual and cumulative doses of CS are higher than cases without femoral head AVN, although statistical significance is not reached. We think that the data we obtained in our study didn't reach statistical significance because the number of patients was insufficient and the power analysis of the groups was low. However, these findings support the possible effect of the cumulative dose of CS in the development of femoral head AVN. Early diagnosis is of great importance in the treatment of femoral head AVN, especially due to the high likelihood that patients with stage I and II benefit from treatment and increased risk of femoral head collapse and prosthetic surgery in later stages. If the incidence of hip and leg pain that may be seen in the clinic of MS patients and the late-onset of symptoms of AVN of femoral head are considered, evaluation of these aches as neuropathic pain may increase the disability of the patients. Patients with hip pain should be carefully examined and assessed with femoral head MRI, which is the gold standard for femoral head AVN. We think that the most important limiting factor for our study is the number of cases and the present results are important for further studies.

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