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Case Report

# Steroid Induced Femoral Osteonecrosis in Multiple Sclerosis: Two Case Reports

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## Abstract

We present two cases of symptomatic avascular necrosis of distal femur in two multiple sclerosis patients who received Methylprednisolone (15 and 10 grams respectively) for relapses treatment over a period of 28 and 29 months. Both complained knee pain after steroid treatment, in both cases we diagnosed avascular necrosis of distal femur only one year later. These cases illustrate how important is not to underestimate the event of avascular bone necrosis after steroid pulse treatment, even with low cumulative dosages, after a long time interval and in unusual necrosis sites.

## Introduction

Osteonecrosis is a serious condition involving trabecular bone destruction. Direct injury may result from trauma, major arterial disease, Gaucher's and Caisson disease, sickle cell and thalassemias. Many risk factors have been listed, such as connective tissues and rheumatological diseases, haematological and vascular conditions, but it's often difficult to determine whether the main trigger is the underlying disease or its treatment (e.g. steroids). Genetic factors may also play a role [1].

The link between corticosteroid administration and the development of osteonecrosis is well established. Thirty-five percent of non-traumatic cases are due to long-term corticosteroid treatment [2], but the pathophysiology is still controversial. Even though it is estimated that fewer than 5% of patients receiving high-dose corticosteroid present osteonecrotic lesions [3-6], the relationship between cumulative dose, treatment duration and risk of osteonecrosis development is still unknown. A multifactorial process involves host predisposition, type and dosage of steroids, underlying diseases, concurrent medications, personal habits, such as alcohol or cigarette smoking, and younger age [7].

High dose steroid pulses (usually methylprednisolone) are a well established and efficacious treatment for Multiple Sclerosis (MS) relapses. Though administered in short-term pulses, the effect of methylprednisolone persists long after drug has dissipated from sera or tissue with an intermediate relative duration [7].

MS patients are frequently exposed to repeated pulse steroid therapy. The incidence of Steroid Induced Osteonecrosis (SIO) in MS patients is uncertain and probably under-reported in this context. Single groups of symptomatic cases are reported about femoral head or diaphyseal necrosis [8-11], while two studies screened MS patients with femoral MRI [2,12].

## Material and Methods

We report two cases of symptomatic SIO of distal femur in two young women with a low cumulative steroid dosage.

### Case Reports

**Case 1:** A 23-year-old Caucasian smoker woman was diagnosed relapsing-remitting MS in June 2007. Treatment with Interferon Beta 1a was started in October 2007. Before immunomodulant treatment she experienced retrobulbar optic neuritis in January 2007 and paresthesias on the right side in June 2007, both episodes were successfully treated with intravenous Methylprednisolone (1g/day for 5 days). In May 2009 she had a new spinal cord relapse again treated with Methylprednisolone (1g/day for 5 days). One month after her last steroid pulse she began suffering articular pain in her right knee. No traumas were reported, knee X-rays and MRI were normal, pain gradually disappeared in a few weeks.

On April 2011 she complained again pain in her right knee and MRI detected an extensive infarction of the right distal femoral and proximal tibial epiphysis.(Figure 1 a. MRI at diagnosis. b. MRI after two years) She was treated conservatively with biphosphonate and cholecalciferol with only partial benefit on pain and functional articular impairment. She carried on Interferon treatment without any further MS relapses.

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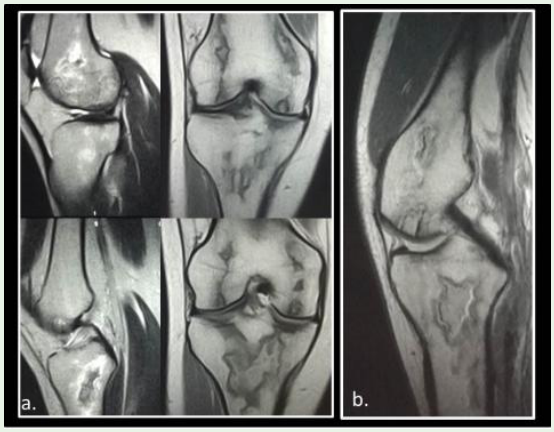


**Figure 1: a.** MRI at diagnosis, **b**. MRI after two years.

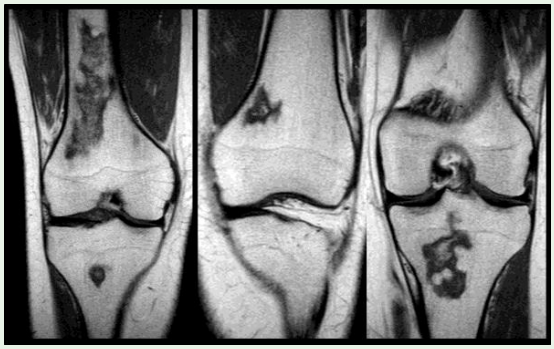

**Figure 2**: MRI at diagnosis.

**Case 2:** A 20-year-old Caucasian woman was diagnosed relapsing-remitting MS in June 2007. Treatment with Interferon Beta 1a was started in May 2009. Before immunomodulant prophylaxis she was treated with intravenous Methylprednisolone (1g/day for 5 days) for one episode of retrobulbar optic neuritis in April 2007. On September 2009 she experienced again retrobulbar optic neuritis, successfully treated with intravenous Methylprednisolone (1g/day for 5 days). In a few days after her last steroid pulse she complained mild bilateral articular pain in her knees and hips. No traumas were reported, rheumatological re-evaluation resulted negative and pain disappeared after anti-inflammatory non steroid treatment.

One year later, she began suffering severe pain in her right knee. Knee X-rays resulted normal, but MRI detected avascular necrosis in her right femoral condyle. She was treated conservatively with biphoshonate with complete benefit on the articular function and only partial benefit on pain (Figure 2). She was then switched to treatment with fingolimod without any further MS relapses.

## Discussion

Both our patients had a brief disease history when they developed femoral osteonecrosis, the first one was exposed to 15g of Methylprednisolone over a period of 28 months, the second one to 10g of Methylprednisolone over a period of 29 months. Both complained knee articular pain in a few weeks following the last steroid pulse but both were diagnosed distal femoral osteonecrosis at least one year later. Whether previous pain in the proximity of the site of necrosis might have been an early necrosis symptom is speculative. The interval between steroid administration and the onset of symptoms is reported to be variable. Retrospective studies on different disorders rarely found an interval of less than 6 months and sometimes even more than 3 years [6]. A prospective study on autoimmune disorders requiring high-dose steroid treatment [13] detected initial changes in femoral head MRI as early as 3.6 months; in the same study MRI was repeated with a follow up of 31 months: though reducing in time, necrosis lesions persisted in the longer follow up. Establishing the exact onset of osteonecrosis radiological signs during a period without symptoms was not possible in our cases without having performed sequenced MRIs. However, in the absence of other evident risk factors for osteonecrosis, we think that steroid treatment might have had a primary role for our patients, even with a diagnosis after more than 12 months after treatment.

Our patients experienced side effects of pulse steroid treatment both over a short time frame after pulse treatment in the first case (10 grams over 6 months) and over a long time frame in the second one (10 grams over 29 months). Previous studies [2,12] tried to assess the risk for osteonecrosis in multiple sclerosis patients exposed to heterogeneous (10 to 60g) or higher cumulative dosages (more than 20 g). They didn't succeed in clarifying the cumulative effect of corticosteroid treatment, but they were both able to point out a higher frequency of radiographic avascular necrosis in steroid-treated patients (15.5 to 23%, including asymptomatic cases) than in non-steroid-treated patients (0%). Ce at al [2] evaluated only femoral head MRI in MS patients, while we detected SIO in the distal femoral bone, which is well described in other diseases even if less common than femoral head [7].

Alertness on articular pain is essential for an early diagnosis of SIO before irreversible bone damage. Neurological pain may induce to underestimate the event of avascular bone necrosis after steroid pulse treatment. An early detection of SIO may grant the option of a conservative treatment such as joint rest, non steroidal anti-inflammatory drugs and biphosphonate, muscle strengthening exercises, restriction of weight load across the affected joint and mobility training. Whereas, progression of necrosis to subchondral bone collapse and destruction may follow a delayed diagnosis, leading to the need for total joint replacement. Therefore, a thorough clinical assessment, together with MRI may be advisable in case of recent or repeated history of pulsed steroid treatment in MS patients reporting articular and bone pain, even in different sites other than hips.

Considering the average disease history MS patients tend to be young and smoking may be a frequent risk factor; identification of high risk patients would be an essential issue to consider while applying repeated high dose steroids, even if nowadays risk stratification is still unclear.

Furthermore, a critical point is MS relapse management after osteonecrosis diagnosis: what is the risk/benefit ratio of steroid retreatment when necessary? What is the safest dosage? How high is the risk of osteonecrosis relapse in the same area or in other locations? How much a therapeutic shift to a second or third line agent is justified before new clinical relapses?

Prospective sequenced bone MRI studies after steroid treatment in MS patients are essential to better understand the risk/benefit ratio and the safest dosages. At the moment we have no hints on the risk of

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osteonecrosis relapses, further prospective investigations are needed. While trying to obtain the appropriate answers, we suggest to shift to therapeutic agents with better efficacy profiles in order to minimize the risk of relapses and the consequent need of steroid re-treatment in case of history of SIO. If not viable, we recommend the use of plasma exchange or intravenous immunoglobulins as alternatives to steroid.

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