CLINICAL ARTICLE

Clinical analysis of osteonecrosis of the femoral head induced by steroids

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Objective: To explore the clinical characteristics of osteonecrosis of the femoral head (ONFH) induced by steroids.

Methods: From January 2000 to October 2009, 497 hips in 270 cases of ONFH induced by steroids were studied. A questionnaire was administered when the patients were admitted; the questions concerned the underlying disease, duration of steroid usage, total dosage of steroid, incubation period (time interval between commencement of steroid therapy and onset of pain), severity of pain, location of initial complaint, primary diagnosis, time lag from onset of pain to final diagnosis and physical signs when admitted. The correlations between pain and Association Research Circulation Osseous (ARCO) stage, bone marrow edema (BME) and lesion size were analyzed.

Results: The median of time between commencing steroid medication and developing ONFH for the 269 cases was 18 months (range, 2–384 months). 78.82% cases presented with pain within three years of steroid initiation, only 10.41% patients first complained of pain six or more years after commencing steroid therapy. Fifty-six cases (20.82%) were misdiagnosed, lumbar disorders being the most frequent misdiagnoses. 79.29% of symptomatic hips presented with abnormal physical tests. Of 420 symptomatic hips, 166 hips were type C1, 223 hips type C2; 299 hips had collapsed; and there was BME in 209 hips.

Conclusion: Most patients with ONFH induced by steroids complained of pain within 3 years of commencing steroid therapy. Pain was associated with lesion size, collapse and BME. Atypical location of pain, failure to perform a physical examination and MRI findings were the main causes of misdiagnoses.

Key words: Diagnosis; Femur head necrosis; Glucocorticoids

Introduction

Osteonecrosis of the femoral head (ONFH) is an intractable disease that affects relatively young, active patients. Steroid usage is one of the commonest risk factors for ONFH^{1–5}. To our knowledge, few studies have focused on clinical analysis of ONFH associated with steroid usage. Having more comprehensive knowledge about the clinical feature of ONFH associated with steroids could help us to understand this disease better. In this study, we analyzed 270 cases (497 hips) of ONFH induced by steroids and carefully reviewed their clinical characteristics.

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Materials and methods

The study protocol was approved by the Ethics Committee of our hospital. We administered a questionnaire when to each patient on admission. The questions concerned the underlying disease, duration of steroid usage, total dosage of steroid (prednisone equivalents), incubation period (time interval between commencement of steroid therapy and onset of pain), severity of pain, location of initial complaint, primary diagnosis, time lag between onset of pain and final diagnosis and the physical signs on admission. We recorded pain according to the method of Charnley⁶, which is a modification of Merle D'Aubigné *et al.*'s method⁷ (Table 1). We classified the location of initial pain into five anatomic areas: the hip, including the trochanteric area and buttocks; the knee; the thigh, including hip combined with knee; the whole lower extremity; and the lumbosacral area.

We recorded the physical examination as positive (+) when one or more of the following signs were noted: tenderness, percussion pain, limited range of motion,

Table 1 Evaluation of hip pain

Pain	Score
Severe and spontaneous	1
Severe on attempting to walk, prevents activity	2
Tolerable, permits limited activity	3
Only after some activity, disappears quickly with rest	4
Slight or intermittent on starting to walk but decreases with normal activity	5
None	6

Note: Scores were obtained by using the method of Merle d'Aubigne *et al.*⁷ as modified by Charnley⁶.

positive Thomas test; negative (–) when none of these signs were noted; and suspicious ($\pm$) when the results of physical examination were equivocal.

Osteonecrosis of the femoral head induced by steroids is defined as occurring in patients receiving steroid therapy and without other risk factors, such as alcohol abuse, trauma, caisson disease, radiation or sickle cell disease.

From January 2000 to October 2009, we diagnosed and staged 1408 hips in 825 cases with ONFH according to the international classification system of the Association Research Circulation Osseous (ARCO)⁸. Three hundred and twenty three cases (594 hips) fell into the category of steroid-induced ONFH. We excluded 53 cases receiving steroid therapy for severe acute respiratory syndrome because they had been detected at an early stage and followed up regularly by the Beijing Municipal Government. There are many differences between them and other patients. Thus, 270 cases (497 hips) were included in this study.

Magnetic resonance imaging protocol

Magnetic resonance imaging was performed with the Signa Excite 1.5 T imager (GE Medical System, Milwaukee, WI, USA) with at least two protocols: coronal T1 weighted image and coronal short time inversion recovery (STIR). Coronal T1 weighted sequences (repetition time [TR] 400/echo time [TE] 8.6/Ef) were taken using a pelvic phased array coil. Images of 4 mm thickness with a 1 mm gap and a 34 × 34 cm field of view (FOV) were obtained using a 256 × 192 matrix and number of excitations (NEX) of four. Coronal STIR images were taken using TR 2560 ms and TE 108 ms.

In MRI, ONFH is defined as a crescent shaped area of subchondral bone marrow with high or partially high signal intensity circumscribed by a low signal intensity

rim on T1 weighted images. This rim of low signal intensity has to completely circumscribe the marrow and show increased signal intensity on the corresponding STIR images⁹. Bone marrow edema (BME) is defined as an ill-defined area of low signal intensity on T1-weighted images with corresponding high signal intensity on STIR images that involves the femoral head and neck beyond the necrotic zone and extends to the intertrochanteric region¹⁰ (Fig. 1).

Sugano *et al.* classified necrotic lesions into four types (Fig. 2) based on their location on coronal midsection T1-weighted images¹¹. Type A lesions occupy the medial one-third or less of the weight-bearing portion. Type B lesions occupy the medial two-thirds or less of the weight-bearing portion. Type C1 lesions occupy more than the medial two-thirds of the weight-bearing portion but do not extend laterally to the acetabular edge. Type C2 lesions occupy more than the medial two-thirds of the weight-bearing portion and extend laterally to the acetabular edge.

Statistical analysis

Age, total dosage of steroids, incubation period, time lag between diagnosis and pain were examined by Kruskal-Wallis nonparametric tests. Pearson's χ^2 test or Fisher's exact test was performed to analyze the correlations between misdiagnosis and initial location of complaint; pain and ARCO stage, and BME and lesion size. For all tests, values of $P < 0.05$ were considered to be significant. All statistical analyses were carried out with the Statistical Package for Social Sciences (SPSS) software (version 13.0; SPSS).

Results

The mean age of the 270 cases was 36.53 ± 11.72 years (range, 13–72 years). There were 167 men (306 hips) with an average age of 37.13 ± 10.22 years (range, 15–58 years) and 103 women (191 hips) with an average age of 35.59 ± 13.81 years (range, 13–72 years). Two hundred and twenty-seven cases had bilateral ONFH and 43 unilateral; 239 hips were on the right side and 258 on the left.

The underlying diseases for which the patients were receiving steroid therapy are listed in Table 2.

The median total dosage of steroid (prednisone or prednisone equivalents) was 3000 mg (range, 300–200,000 mg), 2400 mg in men and 5000 mg in women. The median duration of steroid usage was 0.93 months (range, 0.1–32.3 months).

Two hundred and sixty-nine cases complained of pain. One patient was a university student who was receiving

Figure 1 Example of ONFH combined with BME. (A) A coronal T1-weighted image shows the presence of a subchondral crescent-shaped necrosis surrounded by typical low signal "band" sign. (B) STIR images show the homogenous high signal intensity of the marrow edema beyond the necrotic zone.

steroid therapy for nephrotic syndrome. She had felt no discomfort. The median incubation period for the 269 cases was 18 months (range, 2–384 months). One hundred and eight cases (40.15%) presented with pain within 12 months of commencing steroid therapy, 72 cases (26.77%) complained of discomfort within 12–24 months, 32 cases (11.90%) within 24–36 months, 12 cases (4.46%) within 36–48 months, and only 28 cases (10.41%) presented with pain more than 6 years after commencing steroid therapy.

Fifty-six cases were misdiagnosed. In these patients the median time between the onset of pain and making a definite diagnosis was 5 months (range, 0.5–230.0 months), whereas it was 2 months (range, 0.1–120 months) in those without misdiagnoses ($Z = -5.380$, $P = 0.003$). Lumbar disorders were the most frequently misdiagnoses, followed by arthrosynovitis (Table 3).

Of 213 patients complaining of hip pain, 34 were misdiagnosed, as were 5/12 with knee pain, 12/38 with thigh pain, 2/3 with lumbar pain and all 3 cases who presented with pain in the whole lower extremity. The misdiagnosis rate was higher when the initial location was in the whole lower extremity than when it was in the hip and thigh ($\chi^2 = 14.718$, $P = 0.005$; $\chi^2 = 5.611$, $P = 0.043$, respectively). Hip pain caused less misdiagnoses than knee and thigh pain ($\chi^2 = 5.238$, $P = 0.022$; $\chi^2 = 5.234$, $P = 0.022$, respectively).

According to ARCO staging, 2/9 hips with stage I presented with pain, as did 119/189 with stage II, all of the 227 with stage III and all of the 72 with stage IVp. The mean pain score was 5.56 ± 1.01 for stage I, 4.33 ± 1.50 for stage II; 2.67 ± 0.73 for stage III; and 2.13 ± 0.55 for stage IVp. Thus, the onset and severity of pain correlated with ARCO stage ($\chi = 148.46$, $P = 0.000$; $\chi = 121.750$, $P = 0.000$, respectively).

According to classification by location, 3/17 hips of type A complained of pain, 28/65 of type B, 166/184 of type C1 and 223/231 of type C2. Thus, patients with large lesions were more likely to complain of pain ($\chi = 9.797$, $P = 0.020$).

The relationships between BME and pain and ARCO stage and location are illustrated in Table 4. The results show that BME is associated with pain, particularly with stage III hip. Hips with BME often had associated severe pain and large lesions.

The findings on physical examination of patients with ONFH are illustrated in Table 5. Patients with pain in their hips often presented with positive physical findings, while asymptomatic hips tended to have no physical signs.

Discussion

In previous studies, steroid-induced ONFH has been defined as having a history of taking 1800 mg of

Figure 2 Classification of lesion size according to Sugano. (A) Type A lesion; (B) Type B lesion; (C) Type C1 lesion; (D) Type C2 lesion.

prednisone or an equivalent for at least 4 weeks or of continuous steroid medication for at least 2 months^{12–14}. However, other studies have reported that some patients who had been receiving steroid medication for less than 4 weeks, or a smaller dosage of steroids, still developed ONFH^{15–17}. In the present study, the median duration of steroid medication was 0.93 months, the shortest being 0.1 month (just 3 days); the median total dosage of steroids was 5000 mg, the least being 300 mg; and the median interval from commencement of steroid therapy to onset of pain

was 18 months, the longest being 384 months. Therefore, we think the definition of ONFH induced by steroids described by the researchers cited above is inaccurate. In our opinion, patients without other risk factors who have been receiving corticosteroid therapy and then develop ONFH should be diagnosed as having ONFH induced by steroids.

Knowledge of the natural history of ONFH and the factors that influence it can provide valuable guidance for determining which treatment strategy is best; informing patients of expected outcomes; and identifying possible

Table 2 Underlying illness for which patients received steroid therapy

Underlying illness	Number
Connective tissue disease	45 (16.73%)
Systemic lupus erythematosus	25
Rheumatoid arthritis	14
Skin disease	40 (14.87%)
Renal disease	33 (12.27%)
Infection	27 (10.04%)
Tuberculosis	8
Influenza or cold	11
Trauma	25 (9.29%)
Cerebral trauma	16
Spinal cord injury	3
Allergy	24 (8.92%)
Nervous system disease	23 (8.55%)
Hematological system disease	19 (7.06%)
Eye disease	10 (3.72%)
Bronchial asthma	6 (2.23%)
Nasal disease	4 (1.49%)
Intoxication	4 (1.49%)
Ear disease	2 (0.74%)
Vasculitides	2 (0.74%)
Other disease	5 (1.86%)

Table 3 Diseases which were misdiagnosed in patients with ONFH

Diseases misdiagnosed	Number
Lumbar disease	22 (39.29%)
Arthrosynovitis of hip	7 (12.50%)
Soft tissue injury	6 (10.71%)
Arthrosynovitis of knee	4 (7.14%)
Rheumatic arthritis	3 (5.36%)
Tuberculosis	3 (5.36%)
Rheumatoid arthritis	3 (5.36%)
Fasciitis	2 (3.57%)
Osteoarthritis of knee	2 (3.57%)
Calcium deficiency	2 (3.57%)
Lymphadenitis	1 (1.79%)
Ankylosing spondylitis	1 (1.79%)

Table 4 The relationships between bone marrow edema and pain and ARCO stage and location

Items	Pain		Pain score	ARCO stage				Location			
	Yes	No		I	II	III	IV	A	B	C1	C2
BME	209	0	2.35 ± 0.68	1	66	131	11	1	26	81	101
No BME	214	77	4.07 ± 1.42	8	123	96	61	16	39	103	130
Statistical value	$X = 65.369$ $P = 0.000$		$Z = 9.986$ $P = 0.000$	$\chi^2 = 148.486$ $P = 0.000$				$\chi^2 = 9.797$ $P = 0.020$			

Table 5 The relationship between findings on physical examination and pain

Result of physical exam	Pain		Statistical value
	Yes	No	
Negative	2	73	$\chi^2 = 359.439$ $P = 0.000$
Suspicious	85	4	
Positive	333	0	

mechanisms for pain or collapse. In the pre-MRI era, ONFH was diagnosed by CT or radiography only when patients presented with discomfort^{18,19}. It was therefore difficult to fully understand the natural history of ONFH. MRI is more sensitive than CT and X-ray in detecting ONFH. Many researchers have used MRI to explore the natural history of ONFH by focusing on the contralateral asymptomatic side of patients with confirmed osteonecrosis^{20–22}. Those studies have some shortcomings²³. One is that the contralateral asymptomatic hip may not be subject to the same forces as the symptomatic side, for example in regard to weight bearing. The other is that progression of the asymptomatic side does not represent the natural history of ONFH, as the time lag between necrosis and pain onset is different. Recently, more and more studies have shown that osteonecrosis in any bone usually develops within 6 months of commencing steroid therapy, typically within 2–3 months, even in patients taking long-term glucocorticoid therapy¹⁷. We recommend using the time of commencing steroid therapy as the starting point for observing the natural history of ONFH induced by steroids. We found that 78.82% of ONFH induced by steroids presents with pain within 3 years of commencing steroid therapy; only 10.41% of patients complain of pain 6 or more years after commencing this treatment.

A few days or weeks after the death of all the cell types in the bone and marrow, vascular connective tissue (granulation tissue) develops at the interface between viable and necrotic bone. This physiological response con-

tains the lesion and promotes healing. The necrotic segment has impaired biomechanical properties. Repair is a slow, discontinuous and time-dependent process⁹. When neovascularization is inadequate and bone remodeling limited and ill-adapted to local constraints, stress fracture occurs, causing incapacitating pain and irreversible epiphyseal deformity. Collapse of the femoral head is a consequence of mechanical failure, irreversible, strongly associated with pain, and the major determinant of progression to hip osteoarthritis. Collapse not only correlates with lesion size^{18–22}, but also with repair capacity. There are three different types of repair: limited, reconstructive and destructive repair²⁴. With different types of repair, a necrotic femoral head collapses at different times even with similar sized lesions. In the present study, the shortest incubation period was 2 months and the longest 384 months after commencement of steroid therapy. Repair capacity plays an important role in the time lag to onset of pain.

Because current hip prostheses are unlikely to function sufficiently for the rest of younger patients lives, femoral head-sparing procedures that provide good results in the early stages (pre-collapse stage) should be developed^{4,25}. Prompt and definite diagnosis is necessary for early treatment. Misdiagnosis is a major reason for delayed treatment. We found that 20.82% of cases of ONFH induced by steroid therapy were misdiagnosed and, in these cases, it took longer to make the definitive diagnosis. One important reason for delay in diagnosis was the initial pain being in locations other than the hip or groin. The second reason was failure to perform a physical examination, because 79.86% of hips with pain have positive findings on physical examination, 20.38% have suspicious results and only 2/420 hips (0.48%) have no physical findings. The third reason was failure to perform MRI, which is the most sensitive screening modality routinely used nowadays. In order to make a prompt and definitive diagnosis and improve the results of head-sparing procedures, we recommend that people at high risk of ONFH, such as those taking steroid therapy, should undergo MRI examination. Because most studies report that osteonecrosis usually develops within 6 months after commencement of steroid therapy, typically within 2–3 months¹⁷, MRI should be performed at 3, 6 and 12 months after commencing steroid therapy. MRI may provide valuable diagnostic information in patients complaining of hip or knee discomfort. Moreover, careful physical examination should be performed on patients who complain of knee, low back or lower extremity pain.

Our studies showed that patients with ONFH and BME often complain of severe pain. 94.26% of BME (197/209)

occurs in stages II or III. This is in accordance with our previous study in which we found that BME may be the result of microfracture of viable trabecula following collapse²⁶. 87.08% of BME (182/209) occurred in hips with relatively large lesions (C1, C2), because these hips are more likely to collapse¹⁰.

Because this is a retrospective study, it cannot reflect the true natural history of ONFH induced by steroids. Another shortcoming of this study is that pain is a subjective complaint that can be affected by many conditions. Therefore, prospective research and large samples are needed to provide us with more information.

Disclosure

We did not receive any benefits directly or indirectly from any commercial party.

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