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Elevated Levels of Lipoprotein(a) in Familial Bone Marrow Edema Syndrome of the Hip

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There is controversy whether bone marrow edema syndrome represents a distinct transient disease or reflects an early reversible phase of spontaneous osteonecrosis of the hip. Hypofibrinolysis on the basis of elevated plasma levels of plasminogen activator inhibitor or lipoprotein(a) or both has been reported to favor the development of bone marrow edema syndrome and nontraumatic avascular necrosis. The current authors report on the familial occurrence of transient bone marrow edema syndrome of the hip in three female family members. Plasma concentrations of lipoprotein(a) were elevated in all three patients, whereas serum levels of plasminogen activator inhibitor were within normal ranges. This first familial description of transient bone marrow edema syndrome of the hip strongly suggests that a genetically determined elevation of lipoprotein(a) may be an important predisposing factor in these patients.

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Transient bone marrow edema syndrome is accepted as a possible cause of acute disabling hip pain.[5,10,12] Some authors favor the hypothesis that bone marrow edema syndrome of the hip represents an early, reversible stage of nontraumatic avascular osteonecrosis.[12,19] Although the disease generally has a self-limiting course, surgical treatment by early core decompression of the femoral head has proven effective in rapidly relieving the symptoms.[3,11,14] The unambiguously accepted predisposing conditions for spontaneous osteonecrosis are alcohol abuse, corticosteroid medication, and a heterogeneous group of rare disorders, such as sickle cell anemia and Gaucher's disease.[1,5,16] Recently, hypofibrinolysis and hyperlipidemia have been suggested as etiologic factors in the development of osteonecrosis.[7,22] Heritable high levels of endogenous plasminogen activator inhibitor have been reported to reduce fibrinolytic activity in patients with familial hypofibrinolysis and subsequent spontaneous osteonecrosis.[8]

Lipoprotein(a) is a low density lipoproteinlike particle with a large glycoprotein

(apolipoprotein A), attached to its apolipoprotein B-100 moiety through one or more disulphide bonds.[2] This unique structural feature gives lipoprotein(a) a potential atherogenic and thrombogenic activity.[13,15,20] Lipoprotein(a) competes with plasminogen for its binding sites because of the striking similarity of apolipoprotein A to plasminogen.[9] Elevated levels (> 20 mg/dL) of lipoprotein(a) favor bone marrow edema syndrome and spontaneous osteonecrosis on the basis of inadequate lysis of intraosseous thrombi and subsequent venous hypertension.[7,8,22] A familial predisposition to bone marrow edema syndrome and subsequent osteonecrosis attributable to high levels of lipoprotein(a) has not been described. In the current article, the first observation of elevated levels of lipoprotein(a) is reported in three family members with transient bone marrow edema syndrome of the hip.

MATERIALS AND METHODS

Three women, two sisters and the daughter of one sister, were admitted to the authors' clinic for treatment of acute disabling hip pain. All three women had a normal female karyotype. None of the typical predisposing conditions for osteonecrosis was observed. A traumatic cause was excluded in each patient. None of the patients had a history of deep venous thrombosis, atherosclerotic disease, or unstable angina.

Measurement of Lipid, Cholesterol, Lipoprotein, and Apolipoprotein Levels

Lipoprotein(a) and serum apolipoprotein A1 and B were measured by nephelometry (Beckman Instruments, Fullerton, CA). Quantitation of fasting lipid and lipoprotein cholesterol levels was performed using standardized enzymatic methods. Plasminogen activator inhibitor was measured using an enzyme linked immunosorbent assay (Technoklon, Immuno-Baxter, Vienna, Austria).

Magnetic Resonance Imaging and Operative Treatment

Magnetic resonance imaging (MRI) scans were performed on a 1.0 T superconducting system (Magnetom Expert, Siemens, Erlangen, Germany). Turbo spin echo T1-weighted images (1380/15/4-relaxation time (TR), echo time (TE), slice thickness), T2-weighted images (2730/96/4), and short tau (150 ms) inversion recovery sequence (4600/60/4) for the depiction of marrow edema were taken in the coronal plane. Sagittally, turbo spin echo T1-weighted images (1380/15/4) were obtained. Core decompression of the femoral head was performed using Ficat's trephine (8 mm). Intraoperatively, a bone cylinder was obtained by drilling, and samples were examined histologically.

CASE REPORTS

Case 1

A 36-year-old woman presented with acute right sided hip pain in the twenty-third week of her second pregnancy. Magnetic resonance imaging scans revealed the presence of bone marrow edema in the right femoral head and the intertrochanteric region (Fig 1A–B). Partial weightbearing was done for 8 weeks until symptoms abated. Shortly after delivery, acute onset of pain occurred in her left hip. Magnetic resonance imaging scans revealed extensive bone marrow edema of the femoral head in the left hip (Fig 1C). Because partial weightbearing was ineffective, core decompression of the left femoral head was performed. Six months after surgery, MRI showed complete resolution of marrow edema in both femoral heads without progression to osteonecrosis (Fig 1D). Clinically, the patient recovered fully and was able to work. Core biopsy specimens showed the presence of marrow edema without evidence of osteonecrosis (Fig 2).

Case 2

The 60-year-old mother of Patient 1 was seen for disabling pain in her right hip. Magnetic resonance imaging scans showed an edematous lesion of the right femoral head and the intertrochanteric region, whereas a plain radiograph was nondiagnostic (Fig 3A–B). Because conservative treatment with nonsteroidal antiinflammatory drugs and partial weightbearing for 6 weeks was ineffective, core decompression of the femoral head was done, and symptoms abated after surgery. Core biopsy specimens showed the presence of bone marrow edema. Six months after surgery, MRI scans showed com-

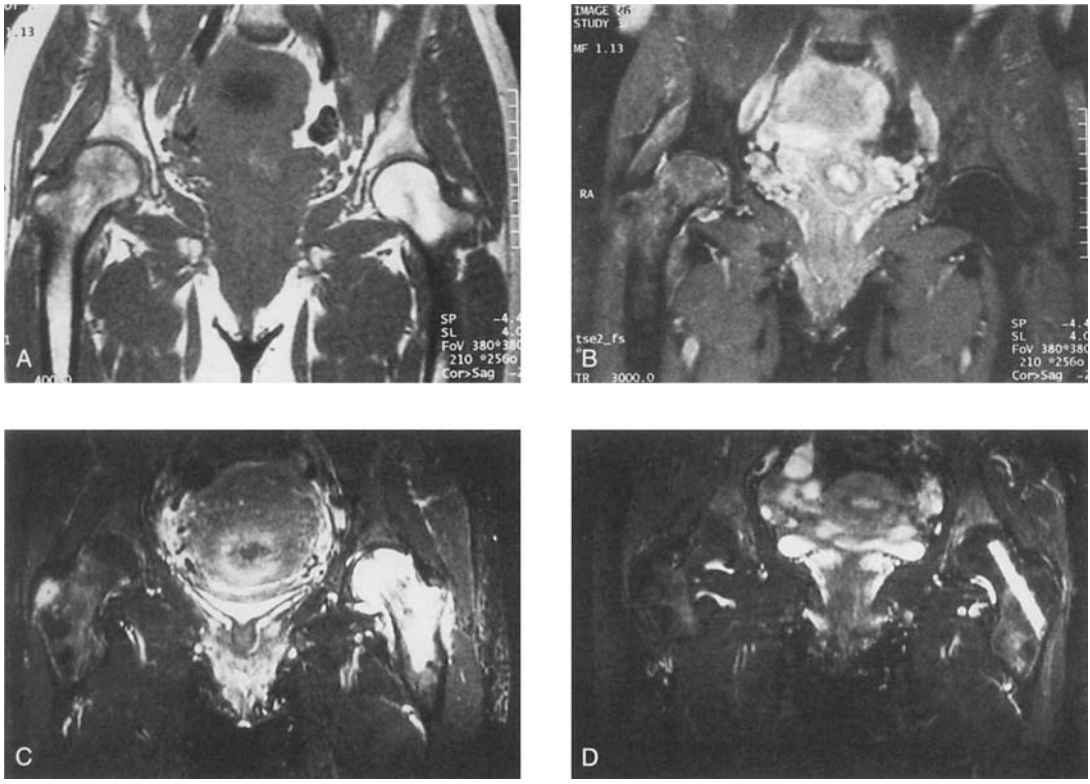

Fig 1A–D. Magnetic resonance imaging scans of Patient 1. (A) Coronal T1-weighted and (B) fat suppressed T2-weighted images at the 23rd of pregnancy. In the right femoral head and the intertrochanteric region, diffuse signal attenuation on T1-weighted images is mirrored by hyperintensity on T2-weighted images. (C) Identical coronal section, short tau inversion recovery sequence obtained shortly after delivery. Marrow edema of the right hip has resolved completely, and extensive bone marrow edema is present in the left femoral head and intertrochanteric region. (D) Identical coronal section, short tau inversion recovery sequence obtained 6 months after core decompression. Bone marrow edema has resolved in both hips. The drilling channel still is visible in the left hip.

plete resolution of bone marrow edema, and the patient recovered fully (Fig 3C).

Case 3

The 63-year-old sister of Patient 2 experienced a sudden onset of right sided hip pain. Magnetic resonance imaging scans showed bone marrow edema without evidence of osteonecrosis. Clinical symptoms subsided after 8 weeks of conservative treatment. Six months later, the patient had no symptoms.

Laboratory data of the patients are given in Table 1. Serum levels of lipoprotein(a) were elevated markedly in all three patients.

DISCUSSION

The first description of a familial occurrence of transient bone marrow edema syndrome of the hip in three women with elevated levels of lipoprotein(a) is given in this report. This observation indicates that elevated levels of lipoprotein(a) should be added to the list of predisposing factors for the development of transient bone marrow edema syndrome. Recent reports support the hypothesis that bone marrow edema syndrome of the hip may represent an early reversible phase of osteonecro-

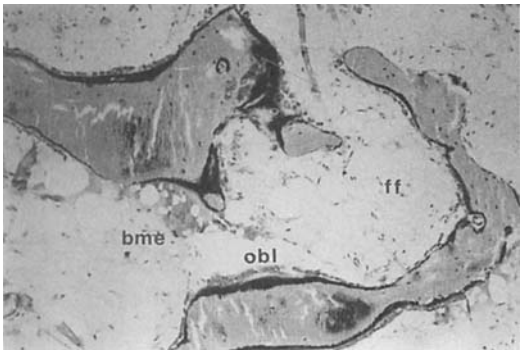

Fig 2. Core biopsy specimen from Patient 1. Undecalcified microtome section (Stain, Goldner; original magnification, ×150) showing bone marrow edema (bme) beside fat cell fragmentation (ff). Bone trabeculae are covered by osteoblasts (obl) and osteoid seams (dark stain).

sis.[10,12,19] Emphasizing the transient nature of the radiologically apparent bone loss in this condition, this syndrome also is referred to as transient osteoporosis or algodystrophy of the hip.[1,10,12,19] However, because no structural bone loss in a group of patients with bone marrow edema syndrome of the hip could be confirmed, some authors suggested the term transient osteoporosis no longer be used for the description of this condition.[19]

The well recognized typical risk factors for bone marrow edema syndrome were not present in the patients of this study, and none of them had a rare disorder commonly associated with osteonecrosis.[1,5,16] There has been considerable debate on the role of hyperlipidemia and hypofibrinolysis as predisposing factors for osteonecrosis.[7,22] Development of os-

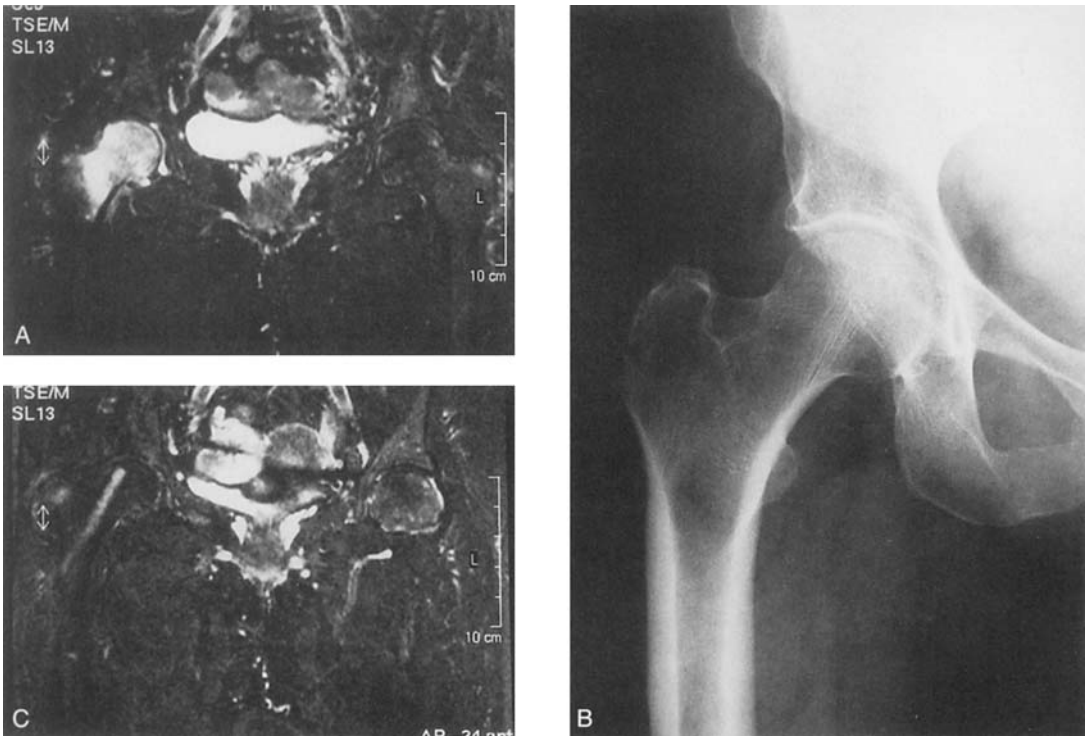

Fig 3A–C. Coronal fat suppressed T2-weighted images and a radiograph of Patient 2. (A) Bone marrow edema and joint effusion are seen in the right femoral head and the intertrochanteric region, whereas (B) a plain radiograph is nondiagnostic. (C) Six months after core decompression, bone marrow edema has resolved completely (C).

TABLE 1. Laboratory Data of the Patients

Analytes	Patient 1	Patient 2	Patient 3	Normal Range
Cholesterol	238	255	203	30–200 mg/dL
Triglycerides	65	169	53	50–150 mg/dL
High density lipoprotein	72	44	50	45–130 mg/dL
Low density lipoprotein	153	177	142	< 130 mg/dL
Apolipoprotein A1	184	147	154	125–215 mg/dL
Apolipoprotein B	97	138	94	55–125 mg/dL
Lipoprotein(a)	32	90	47	0–20 mg/dL
Plasminogen activator inhibitor	7	15	14	10–68 mg/mL
Fibrinogen	304	198	304	180–350 mg/dL
d-Dimer	0.4	0.3	0.1	0–0.5 mg/L
Antithrombin III	105	100	96	75–125%
Thrombocytes	410,000	242,000	228,000	150,000–360,000

teonecrosis has been reported in two kindreds on the basis of autosomal dominantly inherited hypofibrinolysis.[8] This heritable inability to increase tissue plasminogen activator after venous occlusions is suspected to be suppressed by high levels of endogenous plasminogen activator inhibitor. Treatment with stanozolol has proven beneficial to patients with bone marrow edema syndrome or osteonecrosis of the hip, not only in terms of relieving clinical symptoms, but also in decreasing elevated levels of plasminogen activator inhibitor and lipoprotein(a), respectively, and thereby normalizing the pathologic fibrinolytic activity.[7] However, the lack of high levels of plasminogen activator inhibitor excluded this disorder as a cause of hypofibrinolysis in the patients in the current study.

Several reports on lipoprotein(a) have emphasized its role as an atherogenic and thrombogenic factor.[13,17,21] Lipoprotein(a) plasma concentrations are correlated inversely with the size of apolipoprotein(a) isoproteins.[6] These isoproteins are inherited in an autosomal codominant fashion, and their size correlates with the number of the Kringle IV Type 2 repeats of the lipoprotein(a) gene that is located in the chromosomal region 6 q26–q27.[6,15] Lipoprotein(a) competes with plasminogen at the fibrin surface for the common lysin binding domains.[9] Elevated levels of lipoprotein(a) also correlate with the concentration of cardiac troponin T that is elevated in a subgroup of patients with unstable angina, who are at high risk of subsequent cardiac events.[21] As a familial lipoprotein disorder, high serum lipoprotein(a) concentrations can lead to premature myocardial infarction.[18] Thus, patients with elevated levels (> 20 mg/dL) of lipoprotein(a) seem to have an increased susceptibility to arterial and venous thrombotic events.[13,17,20,21]

Because the blood supply of the femoral head depends on the collateral support, this area is particularly prone to circulation impairments. In the animal model, steroid treatment selectively reduces the blood flow in femoral epiphyseal and metaphyseal regions.[4] In line with these experiments, the mechanical interruption of the local circulation in the subchondral bone region and the subsequent increase of the intramedullary pressure result in ischemia, which is the most likely pathologic event in the course of bone marrow edema syndrome and spontaneous osteonecrosis.[5,12,16] Thus, elevated serum levels of lipoprotein(a) might advance bone marrow edema syndrome and spontaneous osteonecrosis through inadequate lysis of intraosseous thrombi and subsequent venous hypertension.[7,22] High estrogen levels also might have contributed to the elevation of plasma lipoprotein(a) concentrations and subsequent involvement of both hips at different stages of pregnancy in Patient 1.

This is the first report on a familial occurrence of transient bone marrow edema syndrome of the hip. The findings of the current study strongly indicate that elevated levels of lipoprotein(a) are involved significantly in the pathogenesis of this syndrome in these patients.

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