This is the seventh reported case of recurrent Legg-Calvé-Perthes disease. The report documents the initial onset in a boy 4 years of age with healing clinically and radiographically. The boy experienced recurrence of disease at 8 years of age with last followup at 20 years of age. Tests related to blood hypercoagulability and hypofibrinolysis and certain genetic factors relevant to osteonecrosis of the bone are reported.

A seventh case of recurrent Legg-Calvé-Perthes disease is reported. In addition to a followup to skeletal maturity, an analysis was done of thrombophilic, hypofibrinolytic, and molecular genetic factors.

Ischemia is regarded as essential in the pathogenesis of this disorder. Two basic hypotheses attempt to explain the mechanism of the ischemia. Either tamponade of the retinacular vessels occurs by increased intracapsular pressure, or cessation of blood flow to the capital epiphysis occurs from an intravascular clot. Several studies support the latter theory.

The authors present a case report of recurrent Legg-Calvé-Perthes disease with long-term followup and additional evidence supportive of a genetic predisposition for the disorder.

**CASE REPORT**

A 4-year 2-month old boy initially was seen at the authors’ institution on March 11, 1981, for pain in the left knee with a limp of 1-week duration. On physical examination, the range of motion (ROM) of the right and left hips was 140° flexion, 0° extension, 60° abduction, 50° (right) and 40° (left) internal rotation, and 85° (right) and 75° (left) external rotation. Findings seen on radiographs were consistent with avascular necrosis of the left capital epiphysis with collapse and sclerosis of the anterior ½ of the femoral head without epiphyseal plate or metaphyseal involvement. The right hip appeared normal (Fig 1). There was no clinical, genetic, or radiologic evidence of skeletal dysplasias. The patient was treated with an abduction brace fitted in 45° abduction with instructions to wear the brace day and night. Radiographs and clinical examinations were done every 4 months (Fig 2). Range of motion and containment were adequate. Complete reconstitution of the superolateral fragment was seen 10 months later, and the child was weaned from wearing the brace. A final clinical check 17 months after onset of the disease showed complete healing of the capital epiphysis with full motion at the hips and no limp (Fig 3).

The patient presented again to the authors’ institution 3 years later with left knee pain and a limp of 2 weeks’ duration. Physical examination of the left
hip revealed 10° flexion, 60° abduction, 0° internal rotation, and 30° external rotation compared with normal ROM of the right hip. Radiographs revealed 4 mm of increased joint space on the left compared with the right with a subchondral fracture involving 50% of the capital epiphysis (Fig 4). The patient again was treated with an ambulatory, abduction brace. Follow-up radiographs at 4-month intervals showed adequate containment and motion. This occurrence was manifested by more extensive involvement of the femoral head with additional

Fig 1A–B. (A) Lateral radiograph on presentation shows collapse of the anterior 1/3 of the left femoral head. (B) Anteroposterior radiograph reveals some irregularity of the slope of the left capital femoral epiphysis.

Fig 3A–D. (A) Anteroposterior view of normal right hip. (B) Anteroposterior view of left hip shows reconstitution of normal contour and trabecular pattern of bone. (C) Right hip in lateral view remains normal. (D) Left hip in lateral view shows the femoral head to be almost completely restored.

Fig 2. Six months after onset of disease, the anterior 1/3 of the left capital femoral epiphysis remains collapsed and sclerotic.
pathologic changes in the physis and the metaphysis (Fig 5). The opposite hip remained normal.

At the most recent followup 12 years after the recurrence, the patient had excellent ROM of both hips. Both hips had 135° flexion, 60° abduction, and 75° external rotation. The right hip had 50° internal rotation and the left hip had 40° internal rotation.

The left lower extremity was 2.5 cm shorter than the right lower extremity measured from the xiphoid process to the medial malleolus of each ankle. Radiographs showed a coxa magna of the femoral head with shortening of the femoral neck (Fig 6).

The patient agreed to have blood tested for abnormal coagulation factors. The results are shown in Table 1. Results of deoxyribonucleic acid (DNA) analysis of genetic factors are shown in Table 2.

**DISCUSSION**

Legg,20 Calvé,5 Perthes,24 and Waldenstrom27 independently described this hip disorder in young children. Since then, only six reported cases of recurrent Legg-Calvé-Perthes disease
after complete healing of the initial insult have been reported.3,4,15,16,19

The differential diagnosis is important in reporting recurrent disease after complete healing. Legg-Calvé-Perthes disease remains a clinical diagnosis with variable symptoms and physical findings and a wide spectrum of radiologic findings. Patients with Perthes disease who are younger than 4 years tend to have fewer symptoms and findings with lesser involvement as measured by the severity of changes on the radiograph. Systemic conditions are best ruled out by the genetic history, physical examination, and a skeletal radiologic survey. In the current patient, these findings all were negative. Meyer’s dysplasia also was considered. Originally described by Pedersen23 and Meyer22 as a subset of Perthes, it is manifested by earlier onset, fragmentation of the epiphysis, and a benign course. Diagnosis of this disease was discovered accidentally in 70% of the patients because they had no symptoms. Meyer states that both conditions are circulatory disturbances, with presentation determined by the age of the patient and perhaps by the severity of the vascular insult. The reports of Khermosh and Wientroub18 and Harel et al11 do not add anything to the original work of Pedersen23 and Meyer.22 Contrary to these four reports,11,18,22,23 the capital femoral epiphyses in the patient reported in the current study were of normal size and radiologic density. The patient did not have the clinical findings of Meyer’s dysplasia.

Martinez and Weinstein21 reported the last documented case of recurrent Legg-Calvé-Perthes disease in 1991. Their case was presented before the outcome was known. Martinez and Weinstein reported that all six previous cases had age of onset of the initial insult between 2 and 6 years (average, 4 years). The current patient initially presented at 4 years of age. The previous patients also had an age range of 2.5 to 6 years (average, 4 years) between the first episode of necrosis and recurrence after complete reossification. The current patient had repeat necrosis of the capital epiphysis 3 years after complete heal-

<table>
<thead>
<tr>
<th>TABLE 1. Blood Elements Related to Clotting</th>
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<tr>
<td><strong>Test Values</strong></td>
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<tr>
<td>Resistance to activated protein-C</td>
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<tr>
<td>Protein C</td>
</tr>
<tr>
<td>Protein S</td>
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<tr>
<td>Free protein S</td>
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<tr>
<td>Antithrombin III</td>
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<tr>
<td>Homocysteine</td>
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<tr>
<td>Methylmalonic acid</td>
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<tr>
<td>Plasminogen activator inhibitor (PAI-fx)</td>
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<td>Stimulated tissue plasminogen activator activity</td>
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<td>Serum insulin</td>
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<td>Lipoprotein(a)</td>
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<tr>
<td>Triglycerides</td>
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<td>Total cholesterol with high- and low-density lipoproteins</td>
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<tr>
<th>TABLE 2. Deoxyribonucleic Acid Analysis</th>
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<tr>
<td><strong>Factor</strong></td>
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<tr>
<td>Plasminogen Activator Inhibitor-1 Promotor (4G/5G) Polymorphism</td>
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<tr>
<td>MTHFRS (C677T) gene mutation</td>
</tr>
<tr>
<td>Factor V (Leiden) mutation</td>
</tr>
<tr>
<td>Prothrombin 3 untranslated region mutation</td>
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Complete healing of the initial necrosis was documented in all patients. The side affected in all patients described, including the current patient, was the left side in three patients and the right side in four patients. Six male patients and one female patient have been reported. Four of the seven patients had bilateral disease, with the recurrent side having much less necrosis on initial presentation. Pertheslike changes occur in many syndromes and metabolic disorders, but no other conditions were present in the current patient or in his family.

The second episode in previous cases was reported to be more severe with more involvement of the femoral head compared with the initial episode. This also was the case with the current patient. Martinez and Weinstein speculated that this, in addition to the patients being older at the time of the second insult, would lead to a worse prognosis. Long-term studies of single-episode Legg-Calvé-Perthes disease have found good function into the third and fourth decades of life, even with deformity of the femoral head. The current patient, now 9 years after complete healing of the second insult, has no limitations in function and is pain free. However, radiographs show a flattened femoral head with an associated shortened femoral neck (Fig 6).

The exact etiology of Legg-Calvé-Perthes disease is unknown. Some studies support theories involving vascular insufficiency. An extracapsular arterial ring, ascending cervical retinacular branches, and the artery of the ligamentum teres provide blood to the femoral capital epiphysis in the child. Some authors postulate the disease is secondary to multiple infarcts of varying age. Sanchis et al first described the second infarction theory in 1973. Inoue et al confirmed the theory with histologic analysis. The multiple infarct theory lends itself well to recurrent Legg-Calvé-Perthes disease.

An increased tendency to form blood clots (thrombophilia), a decreased ability to dissolve blood clots (hypofibrinolysis), or both could interfere with the blood supply to the femoral capital epiphysis. Boettcher et al identified sludging and thrombosis in some adult patients with nontraumatic necrosis of the femoral head. Kleinman and Bleck found statistically higher blood viscosities in patients with Legg-Calvé-Perthes disease compared with healthy subjects. Gragosiewicz et al documented an increased level of alpha one-antitrypsin in their patients with Legg-Calvé-Perthes disease compared with control subjects. This could lead to a decrease in fibrinolytic activity and a predisposition to increased intravascular clotting.

Several authors have reported alteration in factors that contribute to thrombophilia and hypofibrinolysis in patients with Perthes disease. However, other investigators have not been able to duplicate these findings in their series. The current patient’s blood was tested for thrombophilic factors and hypofibrinolytic factors. Thrombophilic factors that were tested included resistance to activated protein-c, protein-c, protein-s, and antiphospholipid antibodies. Results for these factors were all in the normal range (Table 1). Hypofibrinolytic factors tested included plasminogen activator inhibitor (PAI-fx), stimulated tissue plasminogen activator activity (sTPA-Fx), and lipoprotein (a). High PAI-fx often is associated with high levels of serum insulin. The current patient’s serum insulin was 82.5 U/mL (upper normal 20 U/mL). A high level of inhibitor to plasminogen activator theoretically should lead to decreased ability to lyse blood clots. This is in agreement with other reports, which cite clotting factors and increased blood viscosity as potential causes of Legg-Calvé-Perthes disease. Usually, higher PAI-fx is caused by a hereditary defect in the PAI gene. The patient’s DNA was analyzed for the genes associated with thrombophilia and hypofibrinolysis. This was done with DNA polymerase chain reactions to evaluate polymorphisms of the genes. The patient is homozygous for the 4G/4G polymorphism in the promoter region of the PAI-11 and has high serum insulin levels. The MTHFR (C677T) gene mutation, the Factor V (Leiden) mutation, and the pro-
thrombin 3’ untranslated region mutation were normal.

This is the seventh documented case of recurrent Legg-Calvé-Perthes disease. Followup 9 years after healing of recurrence of disease shows the patient to be pain free with no functional limitations. Recent reports by Glueck et al.,8,9 Hunt et al.,13 Herndon,12 and Arruda et al1 regarding the thrombophilic and hypofibrinolytic factors and their contribution to Legg-Calvé-Perthes disease are conflicting, and the significance of these factors has not been determined, although the hypothesis that a genetic defect in the blood, which could lead to sludging of blood and osteonecrosis, is interesting. The results in the current patient are presented for documentation and speculation concerning their significance.

References