ABSTRACT

Legg-Calve-Perthes disease (LCPD) is a type of avascular necrosis of the femoral head occurring mainly in male children and causing early osteoarthritis. We report 2 generations of 4 male family members with LCPD-like features and mutation of the COL2A1 gene of the 12q13 chromosome. If LCPD occurs in any family member, we recommend genetic analysis and counselling as well as early radiological screening of related children.

**Key words:** femur head necrosis; Legg-Calve-Perthes disease; mutations

INTRODUCTION

Legg-Calve-Perthes disease (LCPD) is a type of avascular necrosis of the femoral head, occurring mainly in male children and causing early osteoarthritis. Management of LCPD involves issues related to aetiology, pathology, and diagnosis. LCPD is a developmental disorder of the hip, manifested by delayed, irregular ossification of the femoral epiphyseal nucleus. We report two generations of male family members with features of LCPD and COL2A1 gene mutations.

CASE REPORT

In November 2011, a 37-year-old Saudi Arabian man presented with limping and pain in the hip joint. He had started limping at the age of 15 years, and the hip joint pain had begun 5 years later. The pain increased with activity and restricted him from sitting cross-legged. He had no history of trauma or constitutional symptoms, except for eczema. His right lower limb was 1.5 cm shorter than his left. His range of motion was normal but there was discomfort at the extreme ends. Radiographs of the pelvis showed changes in the right femoral head (Fig. 1) similar to those seen in adults with recovered LCPD.

The patient reported that his father and 3 sons had similar complaints and limping. His 8-year-old...

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old son had started to have pain in both hip joints at the age of 2.5 years. This son had no history of trauma or fever. Radiographs of the pelvis showed changes in the capital femoral epiphysis, and he was diagnosed with LCPD and treated with shin traction for 2 weeks and was allowed to mobilise on crutches. He continued to have intermittent pain, which did not interfere with his daily activities. There was no limb length discrepancy, except for mild limping. His range of motion was full but there was a fixed flexion deformity of 10° (Fig. 2). The Trendelenburg test result was negative.

The man’s 7-year-old son had undergone computed tomography screening at the age of one year, which had yielded a normal outcome. At the age of 3 years, he started to have pain in the hip joint and was diagnosed with LCPD. The pain increased with activity and in cold weather. The left lower limb was 1 cm shorter than the right. He had a noticeable limp and a fixed flexion deformity of 10° and limited internal and external rotation of 20°. Radiographs of the pelvis showed changes in the left capital femoral epiphysis and widening of the metaphysis (Fig. 3).

The man’s 4-year-old son had no obvious symptoms relating to the hips, but the mother insisted that the child limped at times. Clinical examination did not reveal any abnormality. Lateral radiographs showed subtle changes in the epiphysis of the right femoral head with loss of height (Fig. 4).

Blood samples of the father and 3 sons were taken for analysis, including a complete blood count, bone profile, rheumatoid factor, liver function tests, proteins C and S, prothrombin time and activated partial thromboplastin time, and COL2A1 gene mutations (Table). DNA was extracted using the DNeasy Blood & Tissue Kit (QIAGEN, Netherlands). Blood samples of 5 clinically and radiologically healthy Saudi Arabian men were collected and served as controls for the genetic analysis. The entire coding regions of COL2A1 (GenBank accession number: NM_001844.3) were examined by polymerase chain reaction and direct sequence analysis. Flanking markers for COL2A1 (D12S85 and D12S368) showed no recombination with the phenotype, while other genes were excluded.

**DISCUSSION**

The incidence of LCPD in Caucasians is 5 to 15 per 100 000 people.4–6 LCPD is associated with low serum manganese levels,7 low socio-economic status,8 low levels of proteins C and S,9 and passive smoking. Its predilection for boys raised a genetic concern as early as the 1960s,10 and polygenic inheritance is suggested.5 A COL2A1 gene mutation was identified

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**Figure 1** A deformed right femoral head and early osteoarthritic changes in the father.

**Figure 2** Changes in both femoral epiphyses in the 8-year-old son.

**Figure 3** Changes in the left capital femoral epiphysis and widening of the metaphysis in the 7-year-old son.
in a Japanese family with an inherited hip disorder presenting as LCPD,11 and also in 2 children with radiological changes of the femoral head similar to LCPD.12 However, an association between COL2A1 gene mutation and LCPD was not found in a study of 119 confirmed cases.13 In 2 of our patients, the condition resembled Meyer dysplasia of the hip,14 although all our patients were found to have a mutation of the COL2A1 gene on chromosome 12. None of the healthy controls showed any mutation of the COL2A1 gene. Mutation of the COL2A1 gene differentiates LCPD from other causes of aseptic necrosis of the femoral epiphysis, such as sickle cell disease, which is quite common in eastern Saudi Arabia.

Apart from possible genetic mutation, a thrombotic factor has also been implicated in the development of LCPD.15 In males, the risk of LCPD increases with an increasing number of coagulation abnormalities. Trauma and differences in the vasculature of the hip are also suggested as causative factors. In our patients and controls, the coagulation profile and proteins C and S were found to be normal. Hence, we considered that mutation of the COL2A1 gene was the most important factor related to the development of LCPD in our patients.

Limitations of this report include that there were no serial radiographs and that genetic analysis was limited to the affected family members and 5 healthy controls. To support the pathogenic effect of a mutation, unaffected family members should also have been tested to confirm lack of the mutation. If

### Table

Blood analysis of two generations of male family members with Legg-Calve-Perthes disease

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal range</th>
<th>Father</th>
<th>Son 1</th>
<th>Son 2</th>
<th>Son 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin concentration (g/l)</td>
<td>130–180</td>
<td>142</td>
<td>131</td>
<td>127</td>
<td>109</td>
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<tr>
<td>Platelet count (x10⁹/l)</td>
<td>140–440</td>
<td>200</td>
<td>323</td>
<td>291</td>
<td>248</td>
</tr>
<tr>
<td>Blood urea nitrogen (mg/dl)</td>
<td>7–22</td>
<td>14</td>
<td>9</td>
<td>10</td>
<td>9</td>
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<tr>
<td>Creatinine (mg/dl)</td>
<td>0.6–1.2</td>
<td>1</td>
<td>0.4</td>
<td>0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>50–140</td>
<td>63</td>
<td>262</td>
<td>296</td>
<td>260</td>
</tr>
<tr>
<td>Lactate dehydrogenase (U/l)</td>
<td>100–190</td>
<td>150</td>
<td>220</td>
<td>254</td>
<td>263</td>
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<tr>
<td>Prothrombin time (sec)</td>
<td>11–14</td>
<td>11.1</td>
<td>11.9</td>
<td>11.3</td>
<td>11.8</td>
</tr>
<tr>
<td>Activated partial thromboplastin time (sec)</td>
<td>25–38</td>
<td>26.3</td>
<td>29.8</td>
<td>22.6</td>
<td>27</td>
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<tr>
<td>Sickle cell screening</td>
<td>-</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>8.8–10.8</td>
<td>9.7</td>
<td>10.2</td>
<td>8.9</td>
<td>9.9</td>
</tr>
<tr>
<td>Phosphorus (mmol/l)</td>
<td>2.5–4.9</td>
<td>3.4</td>
<td>5.3</td>
<td>4.6</td>
<td>5</td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/h)</td>
<td>0–20</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>-</td>
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<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
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<tr>
<td>Rheumatoid factor</td>
<td>-</td>
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<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Protein C (%)</td>
<td>70–130</td>
<td>117</td>
<td>117.8</td>
<td>59.2</td>
<td>106.1</td>
</tr>
<tr>
<td>Protein S (%)</td>
<td>65–140</td>
<td>64.5</td>
<td>56.6</td>
<td>54.5</td>
<td>51.2</td>
</tr>
</tbody>
</table>

Figure 4  A normal left capital femoral epiphysis and subtle changes in the epiphysis of the right femoral head in the 4-year-old son.
LCPD occurs in any family member, we recommend genetic analysis and counselling as well as early radiological screening of related children.

**REFERENCES**


**DISCLOSURE**

No conflicts of interest were declared by the authors.