The most severe forms of Perthes’ disease associated with the homozygous Factor V Leiden mutation

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It has recently been postulated that thrombophilia may have a role in the aetiology of Perthes’ disease. The published reports, however, remain conflicting. In this study a retrospective analysis of the coagulation parameters was made in 47 patients with Perthes’ disease and the results compared with the clinical data. Five patients with Factor V Leiden mutation were found (10.6%) and surprisingly four of them had a homozygous pattern. These four patients showed the most severe form of the disease, Catterall group IV, with flattening of the entire epiphysis, involvement of the metaphysis, shortening and broadening of the femoral neck, trochanteric overgrowth and developed mushroom-shaped aspherical laterally displaced femoral heads in dysplastic acetabula.

We would like to suggest that the homozygous form of Factor V Leiden mutation has some role in the clinical course of Perthes’ disease and particularly its most severe form.

The aetiology of Perthes’ disease remains unknown. Local ischaemia causes partial or total necrosis of the proximal epiphysis of the femur and influences the development of the physis, metaphysis and acetabulum. The role of an impaired local circulation has been studied by clinical observation and in experimental models. The cause of the ischaemia is unknown, although clinical observation suggests that a localised growth disturbance of the epiphyseal cartilage is important.4

Recent reports by Glueck et al5-7 have suggested that inherited thrombophilia (activated protein C resistance, deficiency of Proteins C and S) and hypofibrinolysis may be associated with thrombosis of the vessels of the proximal femur and lead to necrosis of the epiphysis. As a result of these studies we analysed the coagulation parameters in a retrospective series of patients with Perthes’ disease and related these results to the clinical and radiological course of the disease.

Patients and Methods

Between 1991 and 1997, 63 patients were treated for Perthes’ disease at the Department of Orthopaedic Surgery at the University Medical School of Debrecen. The diagnosis was based on clinical and radiological findings. Of the 47 patients available for the study, 34 were boys and 13 girls. Their mean age at the time of the study was 14.7 ± 6.5 years (5 to 22). Nine patients were classified as Catterall-group II, 25 as group III, and 13 as group IV. Volunteers from the clinical staff, medical students and children with no evidence of Perthes’ disease served as controls for the laboratory assessments. The mean age of the 30 volunteers was 28.8 ± 13.9 years (5 to 31).

Laboratory assessments. In order to analyse fibrinolysis we used an in vitro clot lysis test described previously.8 Coagulation and lysis were followed by monitoring changes of optical density (OD). Lysis-velocities (lysis-velocity = OD/min) reflected the speed of lysis. The absolute value of the velocity proportionally reflects the time-course of the process.

In vivo platelet-activation was evaluated by P-selectine measurements using a flow cytometric device and a CD 62 monoclonal antibody.9,10 Turbidity based detection of the concentration of lipoprotein (a) (Unimate 3 Lipoprotein (a) reagent, Cobas Mira Plus, Roche, Basel, Switzerland) was undertaken. The Clauss method allowed the assessment of plasma fibrinogen (Fibrogen reagent, Reanal, Hungary). For the D-dimer test, we used the STA Lia-test D-dimer (Stago, Diagon, Budapest, Hungary). Enzymatic chromogen measurements were used to monitor the plasmatic activity of individual factors involved in fibrinolysis, including plasmatic plasminogen activator inhibitor-1 (PAI-1) activity (Boehringer, Mannheim, Germany) and plasminogen (Boehringer). Protein C and Protein S activity measurements were based on clotting activity tests.
Activated Protein C resistance was detected with an activated partial thromboplastin time-based test together with an analysis of Factor V 506Arg to Gln mutation in the patients with Perthes’ disease, based on the method described by Koeleman et al.11

Statistical analysis. We used a Graph-Prism computer program based upon an analysis of variances.

Results

The results of the laboratory assessments are summarised in Tables I and II. We found one heterozygote and four homozygote cases of Factor V Leiden mutation in the 47 patients with Perthes’ disease, an overall incidence of 10.6% of this mutation and 8.5% of the homozygotic form. No Factor V Leiden mutation was found in the control group. Plasminogen levels in patients with Perthes’ disease were slightly decreased compared with the controls. No significant differences were found in the lysis-velocity, the fibrinogen level, the lipoprotein (a), the PAI-1 activity, the plasminogen, the P-selectine, the Protein C and Protein S activities between the controls and patients with Perthes’ disease. The D-dimer level was positive in only one patient with Perthes’ disease.

The patient with heterozygous Leiden mutation had the clinical and radiological appearances of Catterall group III. The four patients who were homozygous for Factor V Leiden mutation showed the clinical and radiological appearances of group IV. In three, their disease had started at a relatively young age (2.5, 5.2, 4.2 years).

All four patients complained of pain in the affected hip and on examination had a limp, slight flexion contracture and restriction of abduction and internal rotation of the hip. One patient had had transient synovitis of the hip seven months prior to the onset of Perthes’ disease. On plain radiographs lateral extrusion of the epiphysis was seen in all four patients (Fig. 1) and sclerosis and flattening

<table>
<thead>
<tr>
<th>Number of subjects</th>
<th>Lysis-velocity (OD/min)</th>
<th>Fibrinogen (g/l)</th>
<th>Lipoprotein (a) (mg/l)</th>
<th>Plasminogen (%)</th>
<th>PAI-1 (U/l)</th>
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<tbody>
<tr>
<td>Perthes’ disease (n = 47)</td>
<td>2.54 ± 1.33</td>
<td>3.05 ± 0.65</td>
<td>221 ± 290</td>
<td>91.9 ± 15.2</td>
<td>17.8 ± 11.8</td>
</tr>
<tr>
<td>Control group (n = 30)</td>
<td>2.99 ± 0.98</td>
<td>2.8 ± 0.66</td>
<td>177 ± 168</td>
<td>105.2 ± 32.4</td>
<td>21.6 ± 10.9</td>
</tr>
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<thead>
<tr>
<th>Number of subjects</th>
<th>P-selectine CD 62(%)</th>
<th>Activated protein resistance</th>
<th>Factor V Leiden mutation</th>
<th>Protein C (%)</th>
<th>Protein S (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perthes’ disease (n = 47)</td>
<td>1.94 ± 1.2</td>
<td>2.5 ± 0.6</td>
<td>1 heterozygote</td>
<td>111 ± 20.8</td>
<td>108 ± 23.4</td>
</tr>
<tr>
<td>Control group (n = 30)</td>
<td>1.62 ± 0.9</td>
<td>ns</td>
<td>all wild type</td>
<td>102 ± 28.9</td>
<td>98.3 ± 29.4</td>
</tr>
</tbody>
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(Tables I and II)

Fig. 1a and Fig. 1b) radiographs of the hips at the age of 3.3 years; 10 months after the onset of Perthes’ disease. On the right side there is flattening and fragmentation of the whole epiphysis, and broadening of the metaphysis with cyst formation (Catterall group IV).
of the whole epiphysis in two. All had cystic rarefaction of the metaphysis with widening and shortening of the femoral neck leading to slight trochanteric overgrowth. The femoral heads became flattened, broadened, considerably enlarged and laterally displaced in the mildly dysplastic acetabula. Near or after bony maturation the process resulted in a mushroom shaped aspherical femoral head (Figs 2 and 3).

In all patients the symptoms were improved by conservative treatment, but the limp persisted and the pathological process progressed. Varus derotation osteotomy of the femur was undertaken in two patients with no improvement.

Discussion

In 1994 Glueck et al.\(^5\) drew attention to the role of coagulation abnormalities, especially hypofibrinolysis and thrombophilia, in the pathophysiology of Perthes’ disease based on their results in eight patients. Inherited thrombophilia is a congenital disorder of haemostasis predisposing mainly to venous thrombosis. The most common thrombophilic factor is Activated Protein C resistance due to Factor V Leiden mutation.\(^{12-15}\) In a further report in 1997,\(^7\) this mutation was found in 12.5% (seven heterozygote, one homozygote) of 64 patients with Perthes’ disease compared with 1% of a control group. Following these studies, many researchers investigated the frequency of thrombophilia (Protein C, Protein S, antithrombin III and Activated Protein C - Factor V Leiden mutation, mutant G20210A prothrombin gene and methylenetetrafolate reductase gene) in patients with Perthes’ disease.

In a report from Brazil the heterozygosity for Factor V Leiden mutation (4.9% in patients, 0.7% in controls; \(p = 0.03\)) seemed to be associated with the development of Perthes’ disease.\(^{16}\) Hayek et al.\(^{17}\) from Israel did not find a role for thrombophilia in the pathogenesis of Perthes’ disease. Further investigations in Europe, including the most extensive study, did not agree with Glueck et al.\(^7\) concerning the role of thrombophilia.\(^{18-20}\)

In our study, 47 patients were investigated in order to determine the role of thrombogenic factors in the evolution of Perthes’ disease. The haemostatic parameters did not differ significantly from those in the control group, except for a slightly decreased plasminogen level, which we did not think could play a significant role in the disease.

We found five patients with Factor V Leiden mutation (four homozygous and one heterozygous) in our group. We did not find any Factor V Leiden mutation in our control group. Although the prevalence of Factor V Leiden mutation among our patients (10.6%) is not
significantly higher than in the Hungarian population in our area (9.8%; allele frequency: 4.9%), it is remarkable that no homozygous pattern was found in contrast to that in our patients with Perthes’ disease.\textsuperscript{21} We would like to emphasise, that the clinical course of the disease was very severe (Catterall group IV) in all four of our patients with the homozygous Factor V Leiden mutation (Figs 2 and 3).

Femoral osteotomy was undertaken in two patients with no improvement. Near or at maturity the femoral heads were aspherical and mushroom-shaped with changes in the femoral neck, trochanteric overgrowth and mildly dysplastic acetabula. By contrast, the patient who was heterozygous for Factor V Leiden mutation was classed as Catterall Group III. In previous studies only two patients with homozygous Factor V Leiden have been mentioned in 209 patients with Perthes’ disease.\textsuperscript{7,16,17,19} One was classified as group II, and the severity of the disease in the other was not reported.\textsuperscript{7}

Our results, in agreement with the reports of others, do not support the hypothesis that there is a primary role for inherited thrombophilia in the pathogenesis of Perthes’ disease.\textsuperscript{17-20} We did, however, detect four patients who were homozygous mutants among our five with Activated Protein C-resistance due to Factor V Leiden mutations. In these four patients the disease ran an extremely severe course. It has been reported that heterozygous patients with Factor V Leiden mutation have a seven to eight times greater risk of thrombosis, whereas homozygous patients have an 80 to 100-times greater risk of thrombotic events than in so-called ‘wild types’.\textsuperscript{15}

Hall, Harrison and Burwell\textsuperscript{22} suggested the concept of the susceptible child for Perthes’ disease. They postulated that there might be a congenital abnormality affecting skeletal development which in some way made the hip susceptible to Perthes’ disease at a later age. We think that the homozygous Factor V Leiden mutation may represent such a congenital abnormality leading to severe Perthes’ disease.

No benefits in any form have been received or will be received from any a commercial party related directly or indirectly to the subject of this article.

References