Abnormalities of Vascular Structure and Function in Children With Perthes Disease

WHAT’S KNOWN ON THIS SUBJECT: The causes of Perthes disease are unknown. There is considerable evidence that the disease has a vascular mechanism, although the nature of this is unknown. There is some suggestion that affected individuals may have a heightened cardiovascular risk in adulthood.

WHAT THIS STUDY ADDS: Children with Perthes disease have reduced vascular caliber, which is independent of body height, and abnormal functional vascular measures. These findings may be important in the mechanism of disease and may have implications on long-term vascular morbidity.

abstract

BACKGROUND AND OBJECTIVES: Perthes disease is a childhood precipitant to osteoarthritis of the hip, for which the etiology and mechanism are unknown. There is mounting evidence to suggest a vascular insult is responsible for disease, and it is suggested that this may have long-term implications for the vascular health of affected individuals. This study sought to use ultrasound measures to investigate vascular structure and function in children affected by Perthes disease.

METHODS: This case control study encompassed 149 cases and 146 controls, frequency matched for age and gender. Endothelial function was measured by using the technique of flow-mediated dilation of the brachial artery, and alterations in arterial flow were recorded in response to an ischemic stimulus.

RESULTS: There was a significant structural alteration in the vasculature among individuals with Perthes disease (resting brachial artery diameter (cases 2.97 mm versus controls 3.11 mm; \( P = .01 \)), which remained even after adjusting for height. In addition, there was a notable reduction in blood velocity (cases 33.84 cm/s versus controls 37.83 cm/s; \( P = .01 \)) and blood flow (cases 149.82 mL/min versus controls 184.67 mL/min; \( P = .001 \)), which was independent of baseline arterial size. There was no evidence to suggest that flow-mediated dilation of the brachial artery was impaired among affected individuals (\( P = .71 \)).

CONCLUSIONS: Children with Perthes disease exhibit small artery caliber and reduced function, which is independent of body composition. These data imply that that Perthes disease may reflect a wider vascular phenomenon that could have long-term implications for the vascular health of affected individuals. Pediatrics 2012;130:e126–e131

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KEY WORDS: Legg-Perthes disease, etiology, risk factors

ABBREVIATIONS: FMD—flow-mediated dilation, MED—multiple epiphyseal dysplasia, ROI—region of interest

All authors were involved in the design, data interpretation, drafting, and final approval of this paper. The data analysis was conducted by Drs Perry and Jones.

doi:10.1542/peds.2011-3269
Accepted for publication Mar 8, 2012

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2012 by the American Academy of Pediatrics

FINANCIAL DISCLOSURES: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: This study was supported by the John Monk Research Fund (Registered UK Charitable Trust).
Perthes disease (juvenile idiopathic osteonecrosis of the femoral head) affects ~1 in 850 children in Northern Europe and the United States. The disease manifests through hip pain with limited movements and presents a marked physical and psychological burden in childhood. The disease often alters the shape of the hip, which may accelerate osteoarthritic changes, and is a common precipitant for joint replacement in early adult life.

The mechanism by which the avascular necrosis develops is unknown. It is hypothesized that there is diminished blood supply via the lateral ascending vessel to the epiphysis. Many observers have suggested that this may arise through a thrombophilic process, but a systematic review of coagulopathies among 475 cases concluded that there were no significant differences in antithrombin activity, protein S or C activity, or antiphospholipid antibodies. The relationship with the Factor V Leiden mutation is uncertain; however, it appears unlikely that there is a major thrombophilic association.

More recently, it has been suggested that abnormalities in vascular structure and function may be the mechanism by which the disease develops, with particular interest focused toward the possibility of endothelial dysfunction. The endothelium forms a large endocrine organ, the function of which is to regulate vascular tone, platelet aggregation, coagulation, and fibrinolysis. Endothelial dysfunction may precipitate inflammation, thrombosis, vasoconstriction, and atherosclerotic plaque formation. Endothelial dysfunction in children and young adults has been demonstrated in relation to passive smoking, short stature, and low birth weight. Each of these has similarly been associated with Perthes disease. The dilator response of a conduit artery to increased flow after a period of imposed distal limb ischemia is a common measure of endothelial function, which is termed flow-mediated dilation (FMD). FMD is a noninvasive and widely accepted measure that is commonly used in research as an independent predictor of cardiovascular events. Adults who were affected by Perthes disease in childhood are demonstrated to have a greater risk of premature cardiovascular disease in adulthood, therefore adding support to an abnormality of vascular function. Recently, it has been proposed that hyperemic blood flow responses to a period of ischemia also predict cardiovascular outcomes. These responses reflect small-artery dilator function, rather than that of the larger conduit arteries.

Despite previous suggestions that the mechanism responsible for Perthes disease may be related to vascular dysfunction, no previous study has investigated large- or small-artery functional responses in children with Perthes disease. We hypothesized that FMD and hyperemic responses to an ischemic stimulus would be abnormal in children with Perthes disease.

METHODS

Participants

A case-control study was undertaken at Alder Hey Children’s Hospital, Liverpool. Cases comprised patients drawn from the Merseyside Perthes register and recruited at a routine hospital attendance. All patients were aged 5 to 16 years with a confirmed diagnosis of Perthes disease. In each case the diagnosis was verified by a consultant pediatric radiologist and consultant pediatric orthopedic surgeon based upon the radiographic appearance and clinical features. Bilateral synchronous disease necessitated a skeletal survey to exclude a multiple epiphyseal dysplasia (MED). Cases of MED, cerebral palsy, and developmental hip dysplasia were excluded owing to their known independent association with avascular necrosis of the hip. No cases were actively immobilized, and all were at least 4 months after the last surgical intervention.

Controls were an age- and gender-stratified sample of the orthopedic outpatient population, frequency matched on a 1:1 basis. Age matching occurred within 2 groups: 5 to 10 years old, 11 to 16 years old. Controls were similarly attending Alder Hey Hospital and were drawn from a number of children’s orthopedic outpatient clinics. The clinics sampled were knee clinic, general orthopedic clinic, normal variants clinic, and trauma clinic. Any controls with a restriction in hip movement, unless a clear alternative diagnosis was apparent, were excluded. On each sampling day, all eligible controls were approached for inclusion. Controls with MED, cerebral palsy, and developmental hip dysplasia were excluded, as were patients actively immobilized (irrespective of site of pathology) and those within 4 months of surgery.

Research Design

Parents and children were invited to attend a research clinic, at which vascular parameters and basic anthropometrics (height/weight) were measured and demographic details recorded. Endothelial function was measured by using the technique of FMD. This is a noninvasive measure of endothelial function that sonographically measures the degree of brachial artery dilation in response to a shear stimulus. The technique has widespread acceptance throughout the literature and is increasingly being used in childhood epidemiologic studies.

Measurement Procedures

FMD was recorded by using a standardized technique. All scans were recorded by a single trained observer...
(D.P.) over a 1-year period. All measures were recorded after a fast of at least 6 hours, with >8 hours abstinence from caffeine. This occurred in a quiet room at room temperature with the child supine.

After 10 minutes of rest, a 10-MHz multifrequency linear array probe attached to a high-resolution ultrasound machine (Terason 3000) was used to image the brachial artery on the right arm. The artery was scanned in longitudinal section above the elbow. Depth and gain settings were adjusted to optimize the lumen/arterial wall interface. Once a satisfactory transducer position was established, the position was maintained for the duration of the study. Continuous Doppler velocity assessment was similarly obtained at the lowest possible insonation angle. Baseline scans for the assessment of resting vessel diameter and flow were recorded. An occluding cuff was then inflated to 200 mm Hg for 5 minutes around the forearm. Diameter and flow recordings were resumed 30 seconds before cuff deflation and continued for 3 minutes thereafter.

Custom-designed edge-detection and wall-tracking software (LabVIEW 6.02, National Instruments) was used to determine the vascular parameters, which is largely independent of any investigator bias. The initial phase of the image analysis involved the identification of regions of interest (ROIs). These ROIs allowed automated calibration of diameters on the vascular image and velocities on the Doppler output automatically calculates the FMD, after indicating the point of cuff deflation whereby the arterial flow and shear rise rapidly.

**Statistical Analysis**

Analysis was conducted by using univariate and bivariate analyses, and then a multivariate model. Logistic regression was conducted universally adjusting for age (continuous variable) and gender (categorical variable). Additional adjustments were made for each of the confounding variables that arose, and confounders were retained within the model if their inclusion produced a 10% measured change in effect size. All analyses were conducted by using Stata 10.0 (StataCorp, College Station, TX). P values of <.05 were considered significant.

**RESULTS**

One hundred forty-nine patients and 146 controls were recruited to take part. Thirty-two children (17 patients and 15 controls) were unable to tolerate the examination or scans were of insufficient quality to allow vascular measures to be made. The demographic details of patients and controls are listed in Table 1. There was no difference in the age or gender of either group.

Bivariate analyses revealed that the mean height of individuals with Perthes disease was 5 cm less than controls (P <.02), although weight and BMI were not different between groups (Table 1). The vascular parameters demonstrated a reduced brachial diameter (cases 2.97 mm versus controls 3.11 mm; P = .01), reduced blood velocity (cases 33.84 cm/s versus controls 37.83 cm/s; P = .01) and reduced blood flow (cases 149.82 mL/min versus controls 184.67 mL/min; P = .001). There was no difference in the FMD response (P = .71). After adjusting for age and gender, each of these associations remained (Table 2, adjustment 1).

FMD was negatively correlated with age, height, and resting brachial artery diameter. Blood flow was positively correlated with age, height, weight, BMI, and resting brachial diameter. Blood velocity was positively correlated with age and height. Adjusting for each of the confounding variables revealed that only the adjustment for height had any notable effect on any of the vascular predictor variables (Table 2, adjustment 2). Even after adjusting for resting brachial artery size, a reduction in velocity and flow persisted (Table 3).

**TABLE 1** Anthropometric and Vascular Measures in the Study Group

<table>
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<tr>
<th>Characteristic</th>
<th>Mean Value (95% CI)</th>
<th>P</th>
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<tr>
<td><strong>Anthropometrics</strong></td>
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<tr>
<td>Height, m</td>
<td>1.41 (1.36–1.43)</td>
<td>.02</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>43.3 (38.6–46.9)</td>
<td>.49</td>
</tr>
<tr>
<td>BMI</td>
<td>20.4 (19.6–21.2)</td>
<td>.89</td>
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<tr>
<td>Resting vessel diameter, mm</td>
<td>2.97 (2.88–3.04)</td>
<td>.01</td>
</tr>
<tr>
<td>Flow-mediated dilatation, %</td>
<td>7.26 (6.79–7.73)</td>
<td>.71</td>
</tr>
<tr>
<td>Average velocity, cm/s</td>
<td>33.84 (31.95–35.72)</td>
<td>.01</td>
</tr>
<tr>
<td>Integral minimum flow, mL/min</td>
<td>149.82 (137.94–161.70)</td>
<td>.001</td>
</tr>
<tr>
<td>Integral minimum shear rate, AU</td>
<td>27.438 (25.739–29.137)</td>
<td>.13</td>
</tr>
<tr>
<td>Time to peak, s</td>
<td>67.46 (62.50–72.42)</td>
<td>.38</td>
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CI, confidence interval

* Vascular measures available in 132 cases and 129 controls.
This is the first study that has examined arterial function in children with Perthes disease. It has been suggested that the mechanism for Perthes disease is vascular in origin, based upon pathologic and clinical evidence, along with the unusual anatomy of the vasculature to the infant femoral epiphysis. In support of our findings, a recent study using the common animal model of Perthes disease (the stroke-prone spontaneously hypertensive rat) has demonstrated arterial narrowing, and arteriosclerotic-like hypertrophy of the vasculature to the immature hip among these rats. The stroke prone spontaneously hypertensive rat is also a common animal model of arteriosclerosis, hypertension, and cerebrovascular disease and is known to develop spontaneous femoral head ischemia in infancy in ~50% of cases. Furthermore, abnormal hyperemic responses, such as those observed in the current study, have recently been shown to be associated with cardiovascular disease in adults. Likewise, reduced arterial size is believed to be a key factor contributing to the higher cardiovascular risk in individuals of short stature. Long-term cardiovascular consequences of Perthes disease have been identified by 1 study that demonstrated greater...
cardiovascular risk in adults who had Perthes disease in infancy.18 This study, based on the Swedish inpatient register, demonstrated a higher frequency of ischemic heart disease (hazard ratio 2.69 [95% confidence interval 1.20–6.03]) and hypertension (hazard ratio 2.97 [95% confidence interval 1.87–4.72]), after adjusting for socioeconomic deprivation. The study, published in 2010, recruited individuals diagnosed between 1965 and 2005, and, therefore, the majority of individuals are relatively young to consider cardiovascular disease. There are no studies to date that detail the cause of death in individuals with Perthes disease; however, if an appropriate historic cohort were identified additional research in this area would be invaluable.

In the current study the control group was formed from a hospital population. The advantage of this group was that it overcomes selection bias related to access to health care. Yet, at the same time, it introduces the assumption that a group of hospital patients are representative of the population at large. To help overcome this, a number of hospital clinics formed the control group, therefore attempting to prevent overrepresentation of individuals with diseases associated with the exposure variable. Any bias attributable to hospital populations would be likely to move the odds ratio toward the null; therefore, the observed differences may be underestimates.

In summary, the novel finding of this study was the reduction in small artery caliber and function in children with Perthes disease, which appeared independent of body size. This may be an important finding both in terms of the etiology of Perthes disease and may have long term consequences for vascular health.

REFERENCES


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*Pediatrics* 2012;130;e126; originally published online June 4, 2012; DOI: 10.1542/peds.2011-3269

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