Review Article
Perthes' Disease: A Review Of Contributions From The Asia-Pacific Region

B Joseph, MCh Orth, **R Willoughby*,** FRACS

Head of Paediatric Orthopaedic Service, Kasturba Medical College, Manipal, India
Consultant Paediatric Orthopaedic Surgeon, Waikato Hospital, Hamilton, New Zealand
*Consultant Paediatric Orthopaedic Surgeon, Waikato Hospital, Hamilton, New Zealand

INTRODUCTION

Perthes disease was recognised as a separate clinical entity over a hundred years ago and since that time, a huge number of scientific articles related to the disease have appeared in the literature. In spite of this high level of interest, the aetiology of the disease is still unknown and consequently no preventive measures can be considered, so treatment too is directed towards the effects of the disease rather than the underlying cause.

Initial descriptions of Perthes disease were from North America, France and Germany [1,2,3] and the early classical descriptions of disease evolution as well as characterization of radiological characterization and the pathological features came from North America and Europe authors. However, over the last five decades investigators from the Asia-Pacific region have contributed substantially to our understanding of the disease. In this article, we review contributions to the literature from the Asia-Pacific region that deal with different aspects of this enigmatic disease.

Aetiology

Vascular abnormalities

Though the precise cause of Perthes disease still eludes us, it is clear that a vascular insult is the final precipitating episode leading to disease onset [4-7]. Inoue et al suggest that two or more infarcts precede the clinical onset of Perthes disease [6,7]. Blood supply to the capital femoral epiphysis during childhood comes solely from the lateral epiphyseal vessels and Perthes disease appears to develop at this time. If the lateral epiphyseal vessels are occluded at this critical phase of vascular development of the hip, Perthes disease may develop. The elegant studies of Atsumi *et al* [5]. did, in fact, confirm this hypothesis. Super selective angiography of hips of children with Perthes demonstrated that lateral epiphyseal vessels are interrupted close to their origins [5].

In addition to arterial occlusion, abnormal venous drainage of the proximal femur accompanied by increased intraosseous pressure has been noted in Perthes disease.[8] The implications of these observations are unclear and it remains uncertain if the abnormal venous flow is a cause or effect of the disease.

Nutritional factors and Growth factors

Among the several theories of aetiology tested, nutritional deficiency of vitamins [9] and other micronutrients been presented. However, no causal association has yet been established. However, growth retardation, reduced stature and subtle anthropometric abnormalities have been known to occur in children with Perthes disease. Characteristically this growth retardation affects the foot with rostral segments remaining unaffected. This pattern of aberrant skeletal growth noted initially in Caucasian children has also been confirmed in south Asian children [10]. Low serum somatomedin-A levels have been noted in children with Perthes disease [11] but somatomedin-C activity was normal when estimated by radioimmunoassay [12]. More recent studies suggest that IGF-binding protein (IGFBP)-3 levels are reduced in Perthes disease while insulin-like growth factor (IGF)-1 levels are normal [13, 14]. The consequences of abnormal levels of growth factors and the resultant growth retardation on the causation of Perthes in humans remain unclear.

Thrombophilia

One of the more recent theories of causation for the disease is that children with Perthes have thrombophilia. However, there are conflicting reports regarding this theory. Koo and colleagues studied a small cohort of children with Perthes disease and age and sex-matched controls and could not demonstrate any fibrinolytic or thrombotic disorders in these children [15]. Clearly larger studies are needed to verify or repute the association between Perthes disease and thrombophilia.

Genetic factors

Though some studies have shown that there may be a familial predisposition to Perthes disease, a definitive pattern of inheritance has not been confirmed. Recently Miyamoto

et al [16] located a missense mutation in the type II collagen gene (COL2A1) in a Japanese family with Perthes disease; however, at present it appears as though both environmental and genetic factors contribute in varying degrees to the risk of Perthes disease.

Animal studies

Animal models for human Perthes disease have been developed in certain strains of rats. A high proportion of spontaneously hypertensive rats (SHR) develop osteonecrosis of the femoral capital epiphysis, but osteonecrosis is not seen in Wistar Kyoto rats [17]. However, if Wistar Kyoto rats are forced to stand upright on their hind limbs for feeding they develop a similar form of osteonecrosis [18, 19]. This suggests that a basic constitutional cartilage disorder in SHRs and excessive mechanical stress on the femoral heads in Wistar Kyoto rats result in osteonecrosis rather than a disease process [15]. Another intriguing observation was that caloric restriction in SHRs reduces both the frequency of osteonecrosis and the cartilage abnormalities in the vicinity of the growth plate that precedes osteonecrosis [17]. Hopefully, these animal models may be useful in more clearly elucidating the pathogenesis of Perthes.

Epidemiology

Since the aetiology of the disease is still unknown, epidemiological studies are of vital importance as they may provide valuable clues regarding causative factors. A few epidemiological studies from the Asia-Pacific region have appeared in the literature [20 – 23] and they show that the incidence of Perthes disease in Asian countries is less than among Caucasian populations but is higher than among the black races [21]. Rowe *et al* [21] noted an annual incidence of 3.8 per 100,000 which was comparable to that reported from southwest India [20].

The prevalence of Perthes disease varies a great deal both between and within countries. In south India, a high prevalence was noted in the southwest coastal plain while the disease was 10 times less frequent in the more eastern region [20]. This profound difference in prevalence suggests that some environmental factor is at least partly responsible for the causation of Perthes disease.

Epidemiological studies also showed that Perthes disease in some parts of Asia is distinctly different from that observed in the UK. The disease affects children around the age of six years in the West, but the onset of the disease is about two years later among south Indian children [20]. Studies of Caucasian children from the UK have suggested that Perthes disease is more prevalent in crowded, inner city areas among the underprivileged. On the other hand, the disease was also seen in rural and semi-urban areas and was uncommon in the larger cities of south India [20]. Similarly, a higher incidence was noted in rural Chonnam Province of South Korea as compared to the metropolitan city of Gwangju [21].

An association between smoking and the risk of Perthes disease has been reported in studies from UK, USA and Sweden and there is a need to test this association in the Asia-Pacific region and such a study is currently under way (Daniel et. al., unpublished data).

Natural history of the disease

Perthes disease is self-limiting in that the blood supply to the femoral epiphysis restores over a period of two to four years. During this period, the necrotic avascular epiphysis fragments and is then resorbed and completely replaced by new bone. This sequence of healing can be identified clearly on plain radiographs and on the basis of these radiographic appearances the disease can be quite reliably divided into avascular necrosis, fragmentation, regeneration and healed stages. The stages of avascular necrosis, fragmentation and regeneration can be further divided into early and late parts of the respective stage (Figure 1) [24]. In many children, the epiphysis heals well with the femoral head remaining spherical; in these cases, the affected hip should then function normally throughout life. However, in some cases the femoral head is irreversibly deformed during the healing process resulting in premature degenerative arthritis sets in these hips. Studies on the natural history of the disease [24] have shed light on events that predispose to femoral head deformation and this insight should enable the surgeon to intervene at the appropriate time.

In the avascular necrosis stage, the epiphysis appears dense and sclerotic (Figure 1a). A subchondral fracture line that runs parallel to the articular surface is identified in about a third of children with Perthes; the extent of the fracture line represents the extent of the epiphysis that is avascular. The epiphysis then loses some height, thus signaling the progression to the latter part of this disease stage (Figure 1b). As the dense epiphysis begins to fragment one or two fissures appear in the epiphysis that run perpendicular to the epiphyseal surface (Figure 1c). In due course the epiphysis typically breaks into several pieces (Figure 1d). It is during this stage of the disease that adverse events are associated with deformation of the femoral head. Among the most significant adverse events is extrusion of the femoral head in which the anterolateral area of the avascular epiphysis comes to lie outside the acetabular margin. Extrusion commences early in the course of the disease due to hypertrophy of the articular cartilage of both the femur and the acetabulum, most markedly on the on the medial aspect of the joint [25]. Swelling and hypertrophy of the ligamentum teres may also contribute to femoral head extrusion [26]. Extrusion predisposes to femoral head deformation and this propensity was explained lucidly by Ueo *et al* with the help of a finite-element model [27]. When more than 20% of the width of the femoral epiphysis is extruded there is a very high likelihood of permanent deformation of the femoral head [24].

Extrusion of the femoral head occurs most frequently in the latter part of the fragmentation stage with extrusion often exceeding 20% (Figure 2)[24]. The propensity for femoral head extrusion is greater in children who are older and when more of the epiphysis is avascular; it follows that the prognosis is poor in these children[28].

At the beginning of the revascularisation stage, new bone begins to form on the periphery of the necrotic epiphysis and this new bone is susceptible to deformation. If the lateral part of the epiphysis is extruded at this stage, weight-bearing stresses and muscular forces transmitted across the rim of the acetabulum can deform the healing epiphysis. Concomitantly the metaphysis widens and if treatment is delayed irreversible deformation of the femoral head occurs. Gradually mature lamellar bone replaces the dead bone and once this process is finished, the disease process is complete. In the past it was assumed that if the femoral head is deformed during the course of the disease, some remodelling of the head may occur between healing and skeletal maturity. However, a recent study has shown that very little remodelling takes place after healing, especially in the older child[29]. A significant proportion of children with deformed femoral heads and poorly developed acetabula will go on to develop degenerative arthritis in early adult life[30].

In a small proportion of children the disease onset is in adolescence. The disease in adolescents does not follow the pattern described earlier and often revascularisation is incomplete; consequently the outcome is uniformly poor[31].

Clinical, laboratory and imaging studies

The onset of Perthes disease is usually insidious with pain and limp in an otherwise healthy child. Mild to moderate limitation of hip abduction and internal rotation is invariably present[32] and consequently screening tests designed to detect limitation of these movements have been found to be very sensitive[20]. The clinical presentation of Perthes disease in southwest India was noted to differ from traditional descriptions in Western reports; in this region of India, disease onset occurred later, the frequency of girls developing the disease was higher and often there was extensive involvement of the epiphysis[33]. In some cases, hips were much stiffer and a few developed chondrolysis. Since chondrolysis of the hip is known to be immune-mediated, further studies on the immunological aspects of Perthes disease were conducted[34, 35]. The synovium in these children showed histological and ultrastructural changes suggestive of a delayed hypersensitivity reaction[33] and serum IgG and IgM levels were elevated[34, 35].

Although Perthes disease primarily affects the capital femoral epiphysis, the acetabulum is also altered early in the course of the disease 36 and certain acetabular changes may influence the outcome[36, 37]. Among several acetabular changes noted, one is 'bicompartmentalisation' in which the acetabulum appears to have a medial and a lateral compartment with the femoral head articulating with the lateral compartment (Figure 3)[36]. Cho *et al* studied children with acetabular 'bicompartmentalisation', and with the aid of 3-D CT reconstructed images and MRI scans, clarified the underlying growth abnormality that results in the characteristic appearance on plain radiographs[38]. Increased radioisotope uptake in the roof of the acetabulum is often seen early in the disease indicating increased metabolic activity in the region; this may account for altered growth and remodelling of the acetabulum in Perthes disease[36].

Though unilateral involvement by the far most frequent in children with Perthes disease, there are often subtle changes in the uninvolved hip. Kitoh *et al* demonstrated delayed ossification of the contralateral "normal" hip in children with unilateral Perthes disease[39].

Prognosis

Prognosis in Perthes disease may refer either to the prognosis related to the status of the hip when the Perthes disease process ceases (the short-term prognosis) or the prognosis related to the onset of premature degenerative arthritis of the hip (the long-term prognosis). Most studies show that the short-term prognosis is poorer in older children and those with more extensive epiphyseal involvement[28]. One of the most important prognostic factors identified in several studies is epiphyseal extrusion[24, 28].

The extent of lateral pillar collapse of the epiphysis as defined by Herring's classification is currently considered an important prognostic indicator (the greater the collapse, the poorer the prognosis). However, some shortcomings of this classification have been noted[40,41] and Sugimoto *et al* recommend a measurement score that combines the extent of collapse of both the lateral pillar and the posterior pillar with the age of onset of the disease (the combined pillar score) in order to improve the accuracy of prognosis[40]. Kamegaya *et al* did a detailed multiple regression analysis of various prognostic factors and came up with a formula that takes into account the age at onset of the disease, the extent of epiphyseal involvement and the degree of epiphyseal extrusion[42].

A closer look at the various prognostic factors that have been identified in the literature shows that they fall into one of two categories: factors that cannot be altered by treatment and factors that could potentially be altered by treatment. All but one factor fall into the category that cannot be altered by treatment (e.g. the age at onset, sex, the extent of epiphyseal involvement, presence of metaphyseal cysts, metaphyseal reaction, acetabular bicompartmentalisation etc.). The only factor that can be modified by treatment is extrusion of the epiphysis. Hence current treatment aims to prevent or remedy this single factor.

Treatment

Treatment of Perthes disease may be categorised on the basis of when treatment is instituted and the type of treatment will vary depending on the timing of intervention.

Treatment during the course of the disease - early treatment

Early treatment during the disease aims to prevent the femoral head deformity since it has been shown that if the femoral head remains spherical there is a very good chance of avoiding degenerative arthritis in adult life.

In the past, the emphasis was on relieving weight on the limb, based on the assumption that weight relief would prevent femoral head deformity; as such, treatment included prolonged bed rest, weight-relieving calipers and application of a Thomas splint. Unfortunately, weight relief in isolation has proven ineffective [43, 44]. Once the implications of femoral head extrusion were understood, the concept of "containment" became popular.

Containment attempts to keep the anterior and lateral region of the avascular epiphysis within the acetabulum thereby preventing the femoral head deformity caused by stress transmitted across the acetabular rim. In other words, containment prevents or corrects femoral head extrusion. Containment can be achieved either by abducting and internally rotating the hip or abducting and flexing the hip; casting, bracing or surgery on the femur can enable the hip to be held in one of these desired positions.

Non-operative methods of containment

Among the various non-operative methods that have been adopted to ensure femoral head containment are abduction, internal rotation casts (broomstick casts) [45], braces that hold only the affected limb in the desired position for containment (e.g. the pogo-stick brace) [46] and braces that hold both hips in containment position (e.g. the Atlanta brace) [44]. Certain braces attempt to relieve weight and facilitate containment such as the pogo-stick brace that is ischial weight-bearing and in which the level of hip abduction is adjusted based on femoral head coverage determined using ultrasound scans [46].

These non-operative methods of containment have had a good measure of success [44-46] but one major disadvantage is the need for excellent patient compliance, as the brace needs to be worn for a very prolonged period, often exceeding 18 months [46].

Surgical containment

There are two options for operative containment of the femoral head in Perthes: proximal femur [43, 47 – 51] and pelvis surgical procedures [50, 52,53]. Proximal femoral osteotomy aims to hold the proximal femur in abduction and internal rotation (if a varus de-rotation osteotomy is performed) or in abduction and flexion (if a varus extension osteotomy is performed). Operations on the pelvis are aimed at improving the anterolateral region of the femoral head either by re-orienting the acetabulum (e.g. Salter osteotomy) or by augmenting the acetabular roof (e.g. shelf operation, Chiari osteotomy).

Efficacy of different methods of treatment

Unfortunately, there is very little Level I evidence in the literature regarding the efficacy of treatment for Perthes disease; the vast majority of studies are case series without any controls, although a few studies include historical controls. Nevertheless, some tentative conclusions can be drawn from these reports.

When compared to no active treatment, containment by a femoral varus osteotomy appears to be of benefit; the incidence of spherical femoral heads was greater in the operated group (20% vs. 62.5%) [48]. Surgical containment appears to be more effective than weight relief [43]. Surgical containment appears to be more effective than non-operative methods for the more severe cases of Perthes disease [54]. There appears to be no difference in the outcomes following containment by femoral osteotomy or Salter innominate osteotomy as the incidence of spherical heads and congruent hips were the same for both groups [50].

Kitakoji *et al* note that femoral head coverage, the neck shaft angle and the articular-trochanteric distance are poorer following a femoral varus osteotomy than after a Salter osteotomy [50]. However, some very positive effects of a femoral varus osteotomy have also been reported; when osteotomy was performed in the stage of avascular necrosis, a third of the children bypassed the stage of fragmentation and all had spherical heads at healing [55]. Further, in children who underwent a femoral osteotomy, disease duration was significantly shortened [55]. There is currently no evidence to suggest that innominate osteotomy alters the healing for Perthes.

Timing of intervention

Since the aim of Perthes treatment is to prevent femoral head deformity and thereby retain the sphericity of the femoral head, it follows that treatment needs to be instituted before irreversible femoral head deformity occurs. Studies on the natural history of Perthes disease suggest that if untreated, femoral head deformity tends to occur either in the latter part of the fragmentation stage or very early in the regeneration stage [24]. This implies that the timing of containment (irrespective of the containment method) is crucial to success; containment should be undertaken before the latter stage of fragmentation. A study that addressed the issue of the containment timing clearly supported this contention [56]. The likelihood of retaining femoral head sphericity was 16 times higher if containment was achieved by early fragmentation stage than if containment was achieved during or after the latter part of this stage [56].

Additional procedures performed early in the disease
A proportion of older children with Perthes disease may develop premature fusion of the capital femoral physis resulting in a foreshortened femoral neck, greater trochanteric overgrowth and a Trendelenburg gait [24]. Shah et al showed that prophylactic trochanteric epiphysiodesis at the time of proximal femoral osteotomy can minimise trochanteric overgrowth and the frequency of a Trendelenburg gait at skeletal maturity [57]. The approach was effective in 60% of children and created overcorrection in 10%. Though the likelihood of obtaining effective trochanteric growth arrest decreased with increasing age at surgery, it was successful in most children younger than 8.5 years and in about half the children between 8.5 and 10 years at the time of surgery [57].

Treatment during the course of the disease - Late treatment
Treatment to achieve containment is not indicated after the disease has progressed to the late fragmentation stage but the treatment of hinge abduction, which often occurs at this stage is justified. Hinge abduction is a phenomenon in which abduction of the hip is attempted as femoral head hinges on the acetabular margin and the joint space opens out medially. Hinge abduction may be associated with pain. Valgus femoral osteotomy relieves symptoms, improves joint mechanics and facilitates some remodelling of the femoral head [58].

Treatment of the late sequelae of the disease
Later treatments aim to reduce symptoms once the disease has run its course and the hip has healed but with some degree of deformity. The femoral head may be frankly misshapen, ovoid and enlarged, or spherical with a short neck. For these young adults who have had a poor result following initial treatment, the question of how best to treat remains problematic. Treatment may be directed towards reduction of forces across the hip hopefully to delay the onset of arthritis or treatment may be primarily to alleviate pain.

Improving femoral head coverage by a Chiari osteotomy may be of benefit in selected patients; improved hip scores were noted in patients followed for approximately 6 years [59]. Similarly, pain relief at least in the short term may be seen after reshaping the femoral head by a cheilectomy, drilling of the femoral head and muscle pedicle grafting [60]. In due course, most of these patients are likely to require joint replacements.

Newer adjunctive therapy
Of late, there has been a great deal of interest in the use of bisphosphonates for treatment of avascular necrosis of the femoral head due to causes other than Perthes disease. Encouraged by the beneficial effects of this treatment modality in such clinical situations, research on its use in Perthes is under way. Little and his colleagues demonstrated the benefits of zoledronic acid in minimising femoral head deformity in experimental animals [61]. The clinical scope of this intervention for Perthes disease is yet to be established.

CONCLUSIONS

Despite extensive research on Perthes disease, its aetiology remains unknown and its treatment guidelines are still tentative. This highlights the need for more concerted, multicentre evidence-based research in order to delineate optimal treatment for this fascinating condition. It is hoped that orthopaedic surgeons in the Asia-Pacific region will lead the way in this effort.

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