Prevention of femoral head collapse in Legg-Calvé-Perthes disease:

Experimental strategies and recent advances

INTRODUCTION

Legg-Calvé-Perthes disease (LCPD) is a relatively common condition affecting around 4 in 100 000 children aged four to ten years. The extent of femoral head collapse and deformity following LCPD is the single most important factor contributing to long-term outcome.[1,2] The severity of the residual deformity at skeletal maturity is most commonly described using the Stulberg classification.[3] Treatment strategies during the active stage of LCPD frequently involve measures to minimise loads across the hip joint whilst maintaining movement, with the hope that this will prevent femoral head collapse and deformity. Treatment includes activity limitation, active/passive range of motion exercises and bracing, all complemented by appropriate analgesic medication. However, these strategies have *not* been proven to be effective in preventing femoral head collapse. In the long-term follow-up study by Larson et al,[1] no difference was found between hip-related morbidity in patients that were treated with bracing, those treated with active range of motion strategies and those receiving no treatment. A recently published review also failed to demonstrate any benefit of bracing over no treatment.[4] The failure of these treatment methods could possibly be ascribed to the fact that, even during slow walking, the forces acting across the hip joint far exceed body weight.[5] Therefore, if, as it appears, we cannot prevent collapse of the 'vulnerable/dead' epiphysis, researchers will have to resort to exploring strategies that might strengthen the weakened epiphysis, rendering it more resistant to forces that lead to collapse and subsequent deformity.

This article summarises the recent advances and experimental strategies directed at preventing femoral head deformity in LCPD.

PATHOPHYSIOLOGY OF COLLAPSE AND DEFORMITY

During the initial phase of LCPD as described by Waldenstrom,[6] there is disruption of the blood flow to the femoral head with subsequent necrosis of the marrow space and deep layers of articular cartilage. The epiphysis and metaphysis are less consistently involved. The development of deformity starts during the initial phase and continues throughout the revascularisation phase,[7] radiographically represented by epiphyseal fragmentation. This process is complex and almost certainly multifactorial. Due to the paucity of biopsy samples from human femoral heads with LCPD, much of our current understanding of the pathophysiology of LCPD is based on animal studies, and in particular piglet models. After surgical induction of ischaemic necrosis in piglet models, histological and radiographic features similar to those of LCPD develop after four to eight weeks.[8,9] Samples taken from the infarcted femoral heads at two, four and eight weeks, respectively, show a persistent decrease of the Young's modulus of elasticity and yield strength of both bone and cartilage. This decrease is to around 50% of physiological normal controls.[10] This biomechanical weakening is thought to be the result of several factors, including necrosis of the deep

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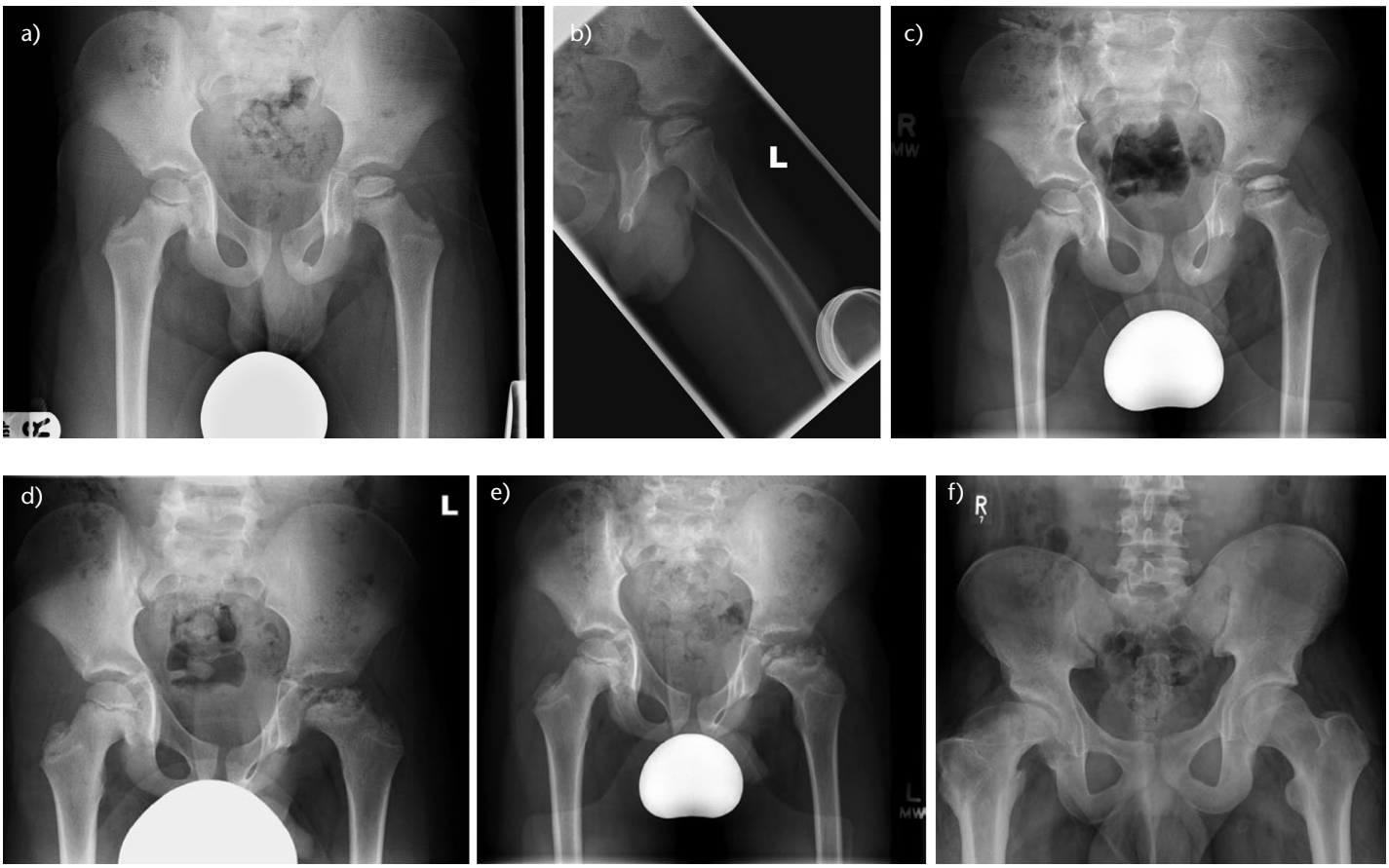

Fig. 1. a) and b) Anteroposterior and lateral pelvic radiographs demonstrating some sclerosis and flattening of the bony epiphysis of the left hip. There is a subchondral fracture line present. c) The same hip three months later with increased sclerosis and collapse of the bony epiphysis. Note that the obturator foramina are asymmetrical and the left ischial spine is visible, indicating that the left hip is lying in significant flexion. d) A further nine months later, the head is now fragmented. The hip still lies in flexion. e) After another nine months, the head is now healing with smoothing of the bony epiphyseal contour , particularly medially. f) A different patient with healed right sided Perthes disease.

layer of cartilage, inability to heal and remodel microfractures sustained during normal joint loading, and a change in the material properties of the trabecular bone.[7] With revascularisation of the necrotic femoral head, an imbalance between bone resorption and formation is seen. This is radiographically represented by radiolucent areas seen in the epiphysis and metaphysis during the fragmentation phase. Histological samples obtained during the fragmentation stage of the disease show high concentrations of osteoclasts and, in particular, replacement of necrotic bone by fibrovascular tissue.[11] This substitution of bone by fibrovascular tissue further weakens the already compromised bony epiphysis (Fig. 1).

A study by Hofstaetter et al[12] demonstrated an increased calcium content in samples taken from ischaemic femoral heads in piglets. This increased mineralisation was mostly seen in the hypertrophic zone of the epiphyseal cartilage and was found to be present four weeks after induction of ischaemia. Increased mineralisation was also seen to a lesser extent in the trabecular bone of the epiphysis; this was most pronounced at eight weeks following induction of ischaemia. It is postulated that this increased calcification leads to the increased radiodensity of the epiphysis seen early on in the disease, and to increased brittleness of the trabecular bone, rendering it more susceptible to fracture.

Based on these findings, and the postulation that mechanical factors may be at play, new strategies are being developed to maintain the structural integrity of the bony epiphyses during the revascularisation phase. These are mostly aiming to limit osteoclastic activity and promote bone formation.

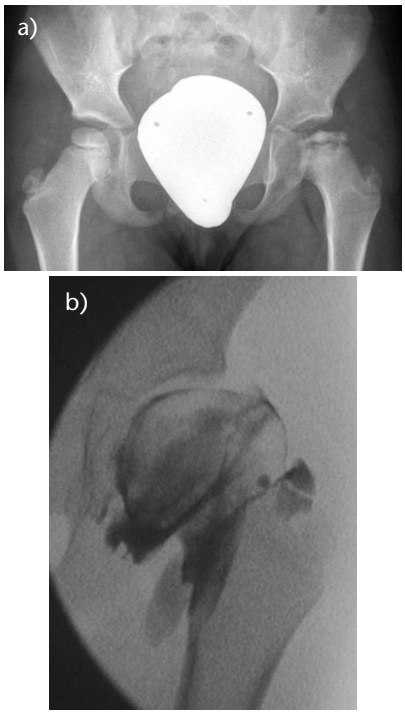

Fig. 2. a) An anteroposterior (AP) radiograph of a five year old boy with left-sided Perthes disease with 'whole head' involvement. The epiphysis is sclerotic and beginning to fragment. b) An AP view of the same hip during an arthrogram which highlights that despite the bony deformity, the cartilaginous head is still spherical and matches the acetabulum (no dye pooling is seen). The dye outlines the labrum.

Bisphosphonates

Bisphosphonates have been used with some success to prevent collapse and deformity and improve pain in non-idiopathic avascular necrosis (AVN) of the femoral head in children. Ramachandran et al[13] performed a prospective study on the use of intravenous pamidronate or zoledronic acid in paediatric patients with evidence of absent proximal femoral vascularity following femoral neck fracture, hip dislocation or acute unstable slipped capital femoral epiphysis (SCFE). After an average of 20 months' treatment, 14 out of 17 patients were pain free and nine out of 17 patients had minimal or no femoral head deformity. Although there was no control group, the authors argued that this could be considered a significant improvement over the known natural history of AVN of the femoral head. No major side effects or growth disturbance were reported secondary to the use of bisphosphonates in this cohort.

AVN of the proximal femur is a common complication of treatment of haematological malignancies such as acute lymphoblastic leukaemia (ALL).[14] Treatment with bisphosphonates has been shown to improve pain, function and range of motion in patients with AVN secondary to treatment for ALL, although this was purely symptomatic and no radiological improvement was demonstrated compared with patients not receiving bisphosphonates.[15]

No human studies have yet been published on the use of bisphosphonates in the treatment of LCPD, but several animal studies have been performed,[16] and with promising results. In a piglet study reported by Aya-ay et al,[17] intraosseous ibandronate administration led to significantly improved maintenance of femoral head architecture and density following surgically induced AVN. Trabecular bone volume and number was also increased on histomorphometry in a dose-dependent fashion. Another piglet study by the same group demonstrated similar benefits with the administration of ibandronate, however, in this study the bisphosphonate was administered systemically and not locally.[18] Here it was also noted that prophylactic administration of ibandronate led to even better maintenance of trabecular architecture and epiphyseal height than when bisphosphonate treatment was commenced after the onset of AVN. Systemic administration of alendronate to adult rabbits after surgically induced AVN did not, however, demonstrate the same marked effect on maintenance of trabecular structure, but did reduce the rate of osteoarthritis at one year following the onset of AVN.[19] In a study involving spontaneously hypertensive rats, Little et al[20] demonstrated better maintenance of femoral head sphericity and trabecular number in those treated with systemic zoledronic acid compared with controls. Interestingly, trabecular thickness and femoral length were decreased in the treatment group.

Bisphosphonates and bone morphogenetic protein (BMP)

If the use of bisphosphonates can alter the catabolic mechanisms taking place in the avascular femoral head, it would seem logical to see whether other interventions designed to stimulate the anabolic or bone-forming mechanisms would act in a complementary fashion to maintain femoral head shape. In a pilot study on induced femoral head osteonecrosis, again in piglets, local delivery of pamidronate and recombinant human bone morphogenetic protein-2 (rhBMP-2) prevented femoral head collapse in two out of four specimens compared with none in those treated with normal saline (control) and those treated with rhBMP-2 only.[21] In a subsequent piglet study, intraosseous ibandronate and rhBMP-2 were shown to be more effective in maintaining trabecular volume than ibandronate only. The presence of osteoblasts lining the trabeculae was demonstrated in the ibandronate and rhBMP-2 group, but not in the ibandronate only group.[22] The formation of intracapsular heterotopic ossification was seen in those animals treated with rhBMP-2 in both studies, a factor which may well limit its clinical usefulness.

Biological treatments

One of the salient features of LCPD is that of hip joint synovitis which is associated with pain and stiffness in the early stages of the disease. Synovial fluid samples taken from hips in the active stage of the disease demonstrate significantly elevated levels of interleukin-6 (IL-6).[23] This cytokine has been shown to promote osteoclast activity and reduce osteoblast activity[24] and is likely to be a contributory factor in the imbalance between resorption and new bone formation typically observed in hips affected by LCPD. In an unpublished study by Kim and Kim,[25] injection of Interferon β decreased the expression of IL-6 and other inflammatory cytokines in a mouse model of ischaemic osteonecrosis of the distal femur. Bony architecture was better preserved and osteoclast expression significantly reduced compared with controls.

Autologous mesenchymal stem cells (MSCs) have also been successfully used in a variety of orthopaedic ailments. In the adult population, femoral head core decompression is a well accepted treatment method in the early stages of avascular necrosis. Addition of bone marrow[26] or mesenchymal stem cells[27] to the ischaemic femoral head is associated with improved medium-term outcomes. In a piglet study by Gong et al,[28] multiple drilling of the ischaemic femoral heads did promote revascularisation but did not prevent femoral head deformity, suggesting a need for osteoprogenitor cells to promote new bone formation. No studies on the use of bone marrow-derived MSCs in the patients with LCPD have been performed to date.

CONCLUSION

The optimal treatment of LCPD remains elusive. Whilst the radiographs direct our attention to the bony deformity, it is always worth remembering that, at least in the early stages, the cartilaginous femoral head may be much more spherical than the bony epiphyseal shape would suggest. Thus we must aim to maintain a spherical femoral head within a shape-matched acetabulum (Fig. 2). Recent advances in basic science research suggest that a biological rather than a mechanical solution may be worth investigating further. Bisphosphonates, administered either systemically or locally, may play a pivotal role in the prevention of femoral head collapse and resultant deformity. This hypothesis has not yet been tested in children with LCPD as certain concerns remain. Prophylactic treatment is not feasible as LCPD is sporadic and idiopathic and although several risk factors have been identified, none are absolute. The route of administration is also controversial as local delivery appears to be more effective than parenteral administration but poses a risk of further damage to the already compromised femoral head. Furthermore, bisphosphonates have not been used extensively in healthy children and therefore concerns arise as to the potential effects on growth velocity and possible disastrous consequences such as osteonecrosis of the jaw, although no such detrimental effects have been noted in the few papers published. Nevertheless, the relative lack of progress in altering the natural history of the condition by both surgical and non-operative methods makes it imperative that medical methods are considered more seriously.

Evidence for the use of biologicals such as Interferon β or MSCs is scant and therefore further investigation is indicated. Our ever-increasing understanding of the pathophysiology of LCPD now makes it possible to start to target the critical components of the development of deformity in this disease and develop therapies based on sound scientific evidence.

Human trials are needed to determine the effectiveness of these new treatments in children with LCPD. With the mounting evidence from animal trials and the lack of significant complications in the few human studies, this may indeed be feasible.

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