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Review Article

CLINICAL IMPLICATIONS AND IMMUNOLOGICAL FINDINGS OF PERTHES DISEASE: REVIEW

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ABSTRACT

Perthes disease occurs in children between the age of 5-15 years and is characterized by varying degrees of idiopathic avascular necrosis of the upper femoral epiphysis. It is followed by spontaneous revascularization occurring over a period of time, i.e. 1.5 to 3 year during which period the femoral head is at the risk of deformation. This disease is due to various predisposing factors i.e. genetic, abnormal growth and development, environmental factors, trauma, transient synovitis, abnormal venous damage & arterial block and infarction. In view of this, various immunological aspects are considered to deliberate on unknown aetiology of perthes disease.

INTRODUCTION

One of the rarest childhood disabling orthopaedic condition is Perthes disease also called as Legg-Calve-Perthes disease that generally affects the hip joint [1]. In other words, this is considered to be one of the form of osteonecrosis [2]. In this disease there is disrupted blood supply in the head of the femur and this inadequate amount of blood supply leads to avascular necrosis of femoral head [3]. The aetiology of this disease is still unclear and is also referred as idiopathic [1-4]. With the passage of time, when disease progresses, there is fragmentation and destruction of the femoral head [3, 4]. In short, this disease is characterized [3-7] on the basis of following features:-

- Self-limiting disease especially seen in children in which there is interruption of blood supply in femoral epiphysis resulting in necrosis.
- Vascular occlusion is totally temporary and there is complete re-vascularization of epiphysis which is reported over a period of 2-4 years if the child is under 12 years of age at onset of the disease.
- During the process of re-vascularization, necrotic bone is completely replaced by healthy new bone.
- In some children the disease heals without any sequelae and consequently no treatment is needed in these children.
- However, treatment of children is necessary in cases where femoral head is likely to get deformed while epiphyseal re-vascularization occurs. The single aim of treatment in these cases is to prevent the femoral head from getting deformed.
- Secondary degenerative arthritis is likely to develop in mid-adult life, if femoral head gets deformed, this will call for surgical intervention for correction and preventing disability.

Therefore we need to understand what causes the femoral head to get deformed and when during the evolution of the disease irreversible deformation of the femoral head occurs.

Immunological Findings

Perthes disease, childhood disorder which affects only femur head where blood supply becomes inadequate and then finally results in necrosis [1-3]. One of the major symptoms observed in this disease is hip/groin pain and this disease is normally reported in the age group (4-10 years; mean 7 years). This condition is very rarely reported in children (approximately 5 to 10 per 100,000 children), and more in boys as compared to girls (ratio wise, 4 boys: 1 girls) [1, 3, 8,9].

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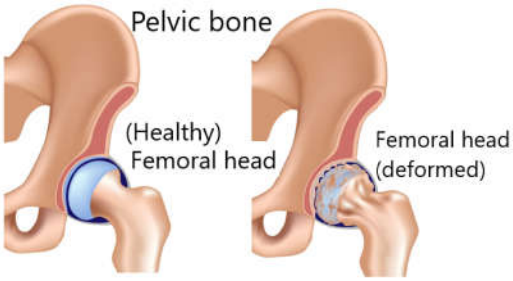

Fig 1 Comparative figure of Healthy and deformed femoral

In view of this, immunological approach related to this disease has to be understood in order to minimize the pathological changes to the femoral head and its deformation (**Fig.1**), by early and appropriate intervention in this disease. Following are the immunological studies already being done by various researchers.

- One of the immunological studies was conducted related to hip stiffness and chondrolysis in Perthes' disease [10]. Actually, chondrolysis was observed only in children who were > 10 years old, with a totally a vascular epiphysis in the stage of fragmentation. In this study, researchers claimed about the presence of plasma cells in perivascular spaces, enhancement of circulating immunoglobulins and also observing lymphocytes in synovial tissue [10-12] as well. So, this gives some evidence about immunological aspects of Perthes disease.
- Genetic aspect of inflammatory mediators will be reported in Perthes patients. Comparative distribution of genotype with respect to control and Perthes patient groups which revealed that IL-6 G-174C/G-597A polymorphisms, heterozygote subjects were significantly over expressed in control group [13, 14]. In view of this, one of the cytokines i.e. IL-6 protein level in proper amount which played an important role in the regulation of inflammatory process in Perthes disease.
- Immunoglobulins (IgM and IgG) in serum were significantly higher when observed in both boys and girls suffering with Perthes disease as compared to control. In addition, there is no significant difference in IgA values when observed in both the groups [15].
- Immunogenetically factors have been implicated in Perthes disease etiology but those genes that are responsible for causing this disease are not identified. One of the studies reported one missense mutation i.e. p.G1170S in type II collagen gene (COL2A1) which is observed in Japanese family with autosomal dominant hip disorder i.e. Perthes disease and showing considerable intra-familial phenotypic variation [16].
- Some of these studies related to Perthes disease are generally associated with anticardiolipin antibodies and factor V leiden [17, 18]. In addition, this disease also caused due to abnormal somatomedin levels and also reported because of deficiency of proteins (C and S); Antithrombin III etc. In contrast, this disease is also associated with thromobophilia but these studies are still controversial [19-23].
- In Perthes disease, there is significant enhancement of proteins which includes complement factor H, complement C4-B, heptoglobin and Ig lambda-2 chain C regions, apolipoprotein F but lower levels of apolipoprotein E, apolipoprotein C-III, S100-A8, S100-A9 and prothrombin as compared to control ones [24-26]. These complements along with coagulation cascades including abnormal lipid metabolism may be involved in the pathogenesis of this disease.

As far as cell therapy is concerned, mesenchymal stem cells [27, 28] are one of ideal source of cell therapy in bone and joint diseases especially osteonecrosis of femoral head.

Pathological Studies

Pathologically, the disease progresses through four stages and these are reflected by the X-rays and magnetic resonance imaging (MRI) scans.

- Initially, stage of synovitis [29], which lasts for 2 to 3 weeks, produces an irritable hip syndrome. The X-rays are negative at this time.
- Subsequently there is stage of avascularity which lasts for 2 to 3 months, during this time, femoral head necrosis [30] occurs.
- Fragmentation changes of the capital femoral epiphysis can occur at this stage. Once the avascular event has occurred, femoral head revascularizes and the process will heal, resulting in the stage of revascularization [31].
- The critical issue is the degree of deformation of the normally spherical femoral head before complete healing occurs.
- The healing phase lasts approximately 2 years, at which time only residual deformity remains as the permanent marker of the disease.

Diagnosis and Treatment

Diagnosis as well as confirmation of this disease [9, 32] is demonstrated through X-rays (flattened, and later fragmented, femoral head). In addition, bone scan or MRI may be useful for diagnosis purposes.

If perthes disease is reported late in children, affected leg may become shorter as well as thinner as compared to unaffected one. X-Raysare also useful to ascertain the stages of disease (Grade I to Grade IV). Treatment whether conservative or surgical, depends upon stages of disease [9, 32].

In the acute stage, the affected lower extremity is immobilized in skin traction. Hip joint may be mobilized when pain and spasm decreases. In grade I or II of this disease, no other treatment is required. In grade III and grade IV of the disease, if head of the femur is not deformed, it is contained inside the acetabulum by maintaining the hip in abduction. This is done by a plaster, splint or by appropriate surgery. In grade III and grade IV of the disease, if head of the femur is deformed, no treatment is possible. Later the disease may progress into Osteoarthritis of hip and will need surgical intervention.

Physiotherapy may be done carefully, with aim of increasing range of motion of affected hip along with strengthening of appropriate muscles so that patient can be functionally independent. Other physiotherapeutic interventions include reduction of muscular spasm, prevention of contractures and ambulation with appropriate splints. The child needs functional training, balance training and appropriate weight bearing

ambulation. If pain is felt on weight bearing, ischial weight-bearing brace may be given.

Prognosis

In general, prognosis is good for younger children, whereas many of those diagnosed after age 9 require total hip replacement in their forties or fifties. The treatment related to this disease for the older child with an already deformed hip is still highly controversial. Analgesia and modification of activities are often sufficient, but hospitalization for bed rest and short periods of traction are sometimes necessary [33, 34]. Wheelchair use and crutch walking should be discouraged in order to avoid unnecessary joint stiffness and contracture. Once joint irritability has subsided, which usually takes about 3 weeks, movement is encouraged, particularly cycling and swimming. Symptomatic treatment helps in controlling pain (if necessary by further spells of traction), gentle exercise to maintain movement and regular reassessment. During asymptomatic periods, child is allowed out and he may also do some light sport activities but strenuous activities are avoided [34-36].

Normally, prognosis is considered as short term (related to femoral head deformity at the completion of the healing stage) and long term (potential for osteoarthritis of the hip as an adult). Risk factors in short term prognosis as shown in **Fig.2.**

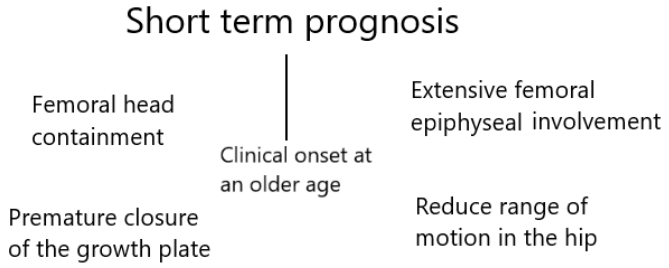

Fig 2 Short term prognosis of Perthes disease

In long term prognosis, it has been seen that it is a worse condition for those patients with metaphyseal defects, where this disease will developed later in childhood (age ≥10 years). It is also reported that in absence of optimal treatment or planning there will be deformation of femoral head along with residual deformity; also degenerative arthritis is reported in almost 100% of these patients.

CONCLUSION

Perthes disease is considered as multifactorial condition, as it is caused through various combinations i.e. environmental and genetic factors. This disease also shows to be one of the most controversial conditions that are reported in children as its etiology, including repetitive microtrauma, skeletal retardation, inflammation and vascular insufficiency and pathophysiology remains ambiguous.

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