Regular review

Perthes' disease: growth and aetiology

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During the last decade it has become evident that Perthes' disease can no longer be considered as a local ischaemic disorder in an otherwise normal child.^{1–3} The affected child's growth and development are unusual in several respects, namely (figure):

- Bone age^{3–5}
- Stature^{6–8} and growth velocity⁹
- Disproportionate skeletal growth^{6 7}
- Hormones^{10–12}
- Congenital anomalies and defects^{13 14}
- The unaffected hip^{3 13 15 16}

Considering the new evidence, Harrison and Burwell concluded that Perthes' disease is a force orientated hip lesion based upon a constitutional defect that affects growing bones.³ Local and general disorders acting together result in a hip joint that is structurally inadequate for the loads that have to be borne, leading to a stress fracture.

The purpose of this review is firstly, to summarise what is known about the underlying growth pattern; and secondly, to present a synthesis of knowledge as a theory of aetiology.

General growth pattern

BONE AGING AT THE HAND AND WRIST

Skeletal immaturity at the hand and wrist of children with Perthes' disease is now accepted as part of the clinical picture. Most workers have performed cross sectional studies comparing their data with the Greulich and Pyle standards.³ Recently, the application of the Tanner-Whitehouse (TW2) system has shown not only bone age delay but also dysharmony with the carpal, more retarded than the radius, ulna, and short bone age.⁴

In a longitudinal study, Harrison reported a 'standstill phenomenon' in some young affected children in which no new carpal bones are ossified,³ although existing carpal bones grow in size.⁴ This aspect is more extensively studied in boys and girls by Kristmundsdottir *et al*,⁵ who confirmed a

relationship between bilateral disease and severe bone age delay.

Some data are available for bone age at the knee (ME Blakemore, personal communication), but not at the foot or pelvis. What evidence there is suggests that the impaired skeletal maturation is unevenly distributed in growing bones and is most evident in distal limb segments. Brothers, but not sisters, of affected children also show bone age retardation at the wrist,³ but it is unclear whether this is familial or community linked.

STATURE AND GROWTH VELOCITY

When the stature of children with Perthes' disease is plotted against bone age, most lie above the 90th centile. When stature is plotted against chronological age many workers find affected children have low-normal centiles, with only a small proportion lying below the 3rd centile.^{6 8}

A longitudinal study of 12 affected boys shows retarded growth velocity soon after diagnosis, followed by a phase of catch up.⁹ More work on growth velocity is in progress (DJ Hall, personal communication).¹⁷ The onset of puberty is usually normal (DJ Hall, personal communication). By the age of 12–15 years, stature is normal⁸ as also is bone age (DJ Hall, personal communication).

The parents and siblings of children with Perthes' disease are of normal height^{7 8}; this suggests that any short stature is associated with the disease and is not of familial origin.

DISPROPORTIONATE SKELETAL GROWTH

A three centre study in the United Kingdom of children with Perthes' disease involving measurements of the head, trunk, and limbs shows a subtle dysmorphic pattern termed 'rostral sparing' (figure).⁶

The growth pattern includes a normal head circumference, no disproportion between sitting height and subischial height, a foot which is short relative to the tibia, and a forearm and hand short relative to the upper arm. Such limb patterns are

Figure Diagram to show the underlying general growth pattern in children with Perthes' disease.⁶ The general growth pattern may be due to manganese deficiency in deprived groups of the population.²⁸ The local growth pattern at the hips involves femoral anteverision asymmetry with the more anteverted femur being affected by the disease.¹⁶

found in the unaffected as well as the affected leg in children within two months of diagnosis and in girls as well as boys.

Recent work in Liverpool finds that children in families where Perthes' disease occurs have retarded growth of the trunk, with reduced sitting height and biacromial diameter. Among those who develop the disease there is also retarded limb growth, most evident as unusually small feet.⁷

The association of this limb growth pattern with Perthes' disease begs the question of whether it occurs in genetically predisposed individuals or indicates mechanisms involved in disease development.

HORMONES

The peak incidence of Perthes' disease at 4–5 years of age¹³ occurs during the quiescent hormonal period.¹⁰

The bone age retardation in Perthes' disease is similar to that found in hypothyroidism, but in Perthes' disease there is no evidence of thyroid dysfunction.¹¹ The serum growth hormone response to insulin induced hypoglycaemia is significantly reduced in affected prepubertal boys compared with

a control group of short boys.¹¹ Serum somatomedin measured by bioassays is raised.^{10 11} In Japan, serum somatomedin A measured by a radioreceptor assay is reduced compared with a control group of normal children.¹² More work is needed, although any hormonal involvement is likely to occur at the tissue level⁵ and may not be amenable to conventional endocrine investigation.

Local growth pattern

Is there any evidence of an underlying growth abnormality at the upper end of the femur which could make a child susceptible to the onset of Perthes' disease? Early work based on radiography showed increased anteverision in some children but not in others.¹⁸ More recently, a new ultrasound method shows a subtle pattern of femoral anteverision asymmetry in most children with unilateral Perthes' disease; the affected hip is almost always the more anteverted; and the opposite femur has an anteverision pattern different from normal, possibly developmental (figure).¹⁶

Are these anteverision findings in children with Perthes' disease 'primary' or merely 'secondary' to

the disease in the femoral head? Two findings suggest that the anteversion in the affected hip precedes the disease: namely, its presence at diagnosis and the changes in the opposite hip. More work, especially longitudinal, is needed to establish the point.

In healthy white children, anteversion asymmetry of 10 degrees or more is found in 10% of the normal population and there is no relation to social class.¹⁹ In healthy *siblings* of affected children the mean femoral anteversion is normal; but below the age of 7 years there is an excess of siblings with anteversion asymmetry (SS Upadhyay, RG Burwell, PP Belliappa, MRK Karpinski, A Moulton, WA Wallace, unpublished observations).

Views on the general growth pattern

It is tempting to link the general growth pattern with the cause of the disease, but so far a theory of aetiology has proved elusive.¹⁻³ Several aspects need consideration.

(1) GENETIC PREDISPOSITION?

Genetic studies^{8 20 21} and work on HLA antigens^{20 22} produce conflicting findings. Hall's comprehensive review concludes that Perthes' disease involves multifactorial inheritance,²¹ although a few families show evidence of autosomal dominance.

(2) SKELETAL DYSPLASIA?

Perthes' like changes in the hips are associated with certain congenital malformation syndromes,^{14 23} the closest to Perthes' disease being acromesomelic dwarfism.²⁴

The general growth pattern of Perthes' disease was at first considered to result from an abnormality of the mechanisms that control differential growth rates in the various regions of the body—determined by environmental factors with or without additional genetic factors acting during embryonic life.⁶

In the growth plate of each normal bone there may be a time tally that controls body proportions with age.¹⁰ Abnormalities of this time tally system in children with Perthes' disease could account for their pattern of skeletal shape distortion. The hypothesis of a time tally in growing bones needs experimental evaluation in animals using recombinant grafts. The problem is part of the wider concept of homeotic genes, which control regional development in the body now being studied experimentally in insects.

(3) MALNUTRITION?

In infant monkeys malnutrition leads to impairment

of head growth and of distal limb growth.²⁵ The latter finding for the limbs is remarkably similar to that seen in Perthes' disease³—the diagnosis of which is made after the child's head has grown rapidly in the first two years of postnatal life. In the case of the monkeys, Fleagle *et al* suggest the hypothesis that the more advanced skeletal region is always the one in which growth is most affected by malnutrition.²⁵ Hence, blood borne factors altered by nutrition could determine the general growth pattern seen in children with Perthes' disease.³

Undernutrition may have relevance to the geographical variation of Perthes' disease in the United Kingdom, with a high incidence in children from families of low socioeconomic status.²⁶ The highest annual incidence recorded to date is 21.1/100 000 children younger than 15 years of age in the inner city of Liverpool, England; the disease is uncommon in the rural areas of Lincolnshire and East Yorkshire.^{27 28} Barker and Hall conclude that Perthes' disease may have major determinants acting at a critical stage of early life before the age of 2 years²⁶—but this timing would not explain the normal head size.⁶

What these determinants may be is unknown, but microdeficiencies may be at work,⁵ and particularly manganese deficiency.²⁸

(4) MANGANESE DEFICIENCY?

Manganese deficiency results in skeletal and postural defects in many species of animals. Shortening of limb bones relative to the trunk occurs in manganese deficient rats; this has been attributed to abnormal cartilage and bone matrix formation particularly of chondroitin sulphate.^{29 30}

The importance of such experimental findings for normal human development is unknown. Preliminary research, however, predicated on the underlying growth pattern,⁶ indicates that children with Perthes' disease may be manganese deficient.²⁸

Unifying theory of aetiology

LOCAL DYSHARMONY BETWEEN CARTILAGE AND BONE
Current evidence is consistent with the view that at the time of diagnosis of Perthes' disease there is dysharmony between cartilage and bone in at least two regions of the skeleton: (a) at the *wrist*, in which existing bones grow slowly and some cartilage models have delayed onset of ossification; and (b) at the *hip*, where thickened epiphyseal cartilage³¹ may precede necrosis of the ossific nucleus.³² The thickened cartilage and enlargement of the femoral head in Perthes' disease is generally attributed to epiphyseal growth being sustained by synovial fluid in the presence of an ischaemic ossific nucleus.^{13 33}

In this connection, transient synovitis of the hip does not seem to be linked causally to Perthes' disease.^{16 33 34}

The finding of skeletal dysharmony, particularly in the carpus at the time of diagnosis, implies the presence of a latent (incubation) period before the disease is expressed clinically.^{2 5 20} The fact that Perthes' disease almost never recurs shows that the conditions that cause the disease are present at only one phase in the child's development.³⁵

The earlier development of bilateral disease and its association with severe carpal delay suggests that a systemic blood borne factor contributes to the changes in both the hips and the wrist.⁵

What such a systemic factor(s) might be is unknown. It could be an essential substance in limited supply (hormone, nutrient, metabolite) or a deleterious agent.^{20 28} The evidence suggests the hypothesis that during the quiescent hormonal period¹⁰ a blood borne factor (possibly involving manganese²⁸ is essential for the production of a cartilage that will ossify.

SELECTION TO MORBIDITY

The simplest explanation (Occam's razor) for the underlying growth pattern is that normal young children with anomalous extremes of femoral anteversion asymmetry from all social classes are at risk of developing Perthes' disease: but only those with a disturbance in a systemic, blood borne factor develop the disease.

BLOOD BORNE FACTOR

According to this view of aetiology, a blood borne factor is responsible for the *bone age delay at the wrist* and the *short foot*—both of which are affected because of their acromelic development status.^{5 25}

To account for *disease at the hip*, a sequence of mechanical and blood borne factors acting during the latent period is needed, such as:

- (1) Increased dynamic mechanical stress in the more anteverted femoral head during gait and physical activity.^{36 37}
- (2) Increased epiphyseal cartilage turnover in the femoral head³⁸—like the effect of intermittent physiological pressure on bone, growth plates, and healing articular cartilage.^{39 40}
- (3) Replacement of normal epiphyseal cartilage during the latent period by a less ossifiable cartilage—that also occurs at the carpus^{18 41 42}—and both involving local tissue regulatory factors.
- (4) Dysharmony between cartilage and bone growth results in more cartilage,³¹ less

bone, and a larger femoral head¹³ with altered mechanical properties.

- (5) Reduced mechanical strength of the femoral head⁴³ relative to the weight and physical activity of the child leads to stresses within the ossific nucleus³² and a stress fracture with secondary vascular compromise.³
- (6) Natural history is determined by the balance between: (a) loading at the hip and repeated stress fractures with vascular occlusions⁴⁴; and (b) replacement of the epiphysis ultimately by normally ossifying cartilage.

Perspective

Although far from complete the morphological, auxological, epidemiological, and essential trace element studies have brought Perthes' disease to the stage at which some insight into aetiology is now possible.

Research is needed in four directions: on populations at risk; on patients and their families; clinical and laboratory studies on the biomechanics of hips with femoral anteversion asymmetry; and experimental models in animals.

The ultimate aim is prevention. As a bonus, aetiological mechanisms unveiled for Perthes' disease may provide a paradigm for some of the other osteochondroses of youth.

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