BONE-MARROW TRANSPLANTATION IN
HURLER'S SYNDROME

EFFECT ON SKELETAL DEVELOPMENT

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Between 1980 and 1988, displacement bone-marrow transplantation was performed on 25 children with Hurler's syndrome (type-1 mucopolysaccharidosis). We describe the musculoskeletal development of 11 of the 12 surviving children and the orthopaedic procedures undertaken to treat progressive thoracolumbar kyphosis, hip subluxation and carpal tunnel syndrome.

We found abnormal bone modelling, focal failures of ossification and an avascular disorder of the femoral head in every patient and offer an explanation for these phenomena. Increasing valgus deformity of the knees and progressive generalised myopathy caused loss of mobility as the children entered adolescence. The benefit of bone-marrow transplantation as a treatment for the skeletal disorders of Hurler's syndrome is limited by the poor penetration of the musculoskeletal tissues by the enzyme derived from the leucocytes.

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The mucopolysaccharidoses are a group of disorders caused by deficiency of the lysosomal enzymes required for the degradation of glycosaminoglycans (GAGs). In type-1 mucopolysaccharidosis, the deficient enzyme is \( \alpha-L\)-iduronidase (Bach et al 1972). In its absence, cells of parenchymal and mesenchymal tissues become infiltrated with deposits of dermatan sulphate and heparan sulphate. There is also secretion of these degradation products into the urine. The clinical manifestations of the disorder were first described by Hurler in 1919. The term 'gargoyleism' (Ellis, Sheldon and Capon 1936) has been applied to children affected by the condition with multiple abnormalities affecting mainly the skeleton.

\( \alpha-L\)-iduronidase deficiency is transmitted in an autosomal recessive manner and has an incidence of about 1 in 100 000 live births (Lowry and Renwick 1971). The gene coding for this enzyme has been localised to chromosome 22 pter-q11 (Schuchman et al 1984). The clinical manifestations range from classical Hurler's syndrome, through intermediate forms of the condition known as Hurler-Scheie syndrome, to the relatively mild Scheie syndrome (McKusic and Neufeld 1983). It is postulated that the considerable heterogenicity of type-1 mucopolysaccharidosis is due to the presence of multiple alleles at the \( \alpha-L\)-iduronidase gene locus which results in compound heterogenicity within, as well as between, the clinical subgroups (Neufeld and Muenzer 1989).

The pattern of musculoskeletal abnormalities seen in children with untreated Hurler's syndrome is known by the term dysostosis multiplex and its development follows a typical course. At birth, the child may be of normal size and appearance although some of the clinical features are often present. By the end of the second year, several characteristic abnormalities have developed (Fig. 1a). The head is enlarged with a low forehead, wide-spaced eyes and low-set ears and the neck is very short. The rib cage is deformed, with flaring of its lower portion and there is localised kyphosis in the dorsolumbar area. The joints become increasingly stiff and flexion contractures are widespread. The hands are broad with stubby digits. As growth proceeds the hips luxate, resulting in a waddling gait. Progressive valgus deformities of the knees develop and pes planus may be present.

In 1981, Hobbs et al proposed that inborn errors of metabolism, including type-1 mucopolysaccharidosis, could be treated by displacement bone-marrow transplantation (BMT). The hypothesis was that after BMT in patients with Hurler's syndrome, donor leucocyte lines would provide a natural source of the missing \( \alpha-L\)-iduronidase enzyme and that the pathological accumulation of dermatan sulphate would be arrested or reversed. From 1980 to 1988, 25 children with Hurler's syndrome were treated by BMT at the Westminster Children's Hospital. Twelve have survived and in all but one, the
leucocyte α-L-iduronidase enzyme level remains within the expected range of their respective donors.

Before BMT therapy, children with Hurler’s syndrome generally died from cardiorespiratory problems during the first decade of life. These disorders have been greatly lessened by BMT and the lifespan of our patients exceeds that previously experienced.

We report on the musculoskeletal development of the 11 patients successfully grafted and describe their orthopaedic problems and the procedures which we have used in their treatment.

MUSCULOSKELETAL DEVELOPMENT AFTER BMT

The average age at which the 11 children underwent BMT was 19.5 months (Table I). In all cases there was an initial outpouring of GAGS, which subsequently settled to nearly normal levels. The liver rapidly decreased in size.

Bone-marrow transplantation was performed before the age of one year in only two children and therefore in the other nine, clinical and radiological abnormalities were evident before treatment. After BMT, the children all showed improved modelling of their facial bones, the gaps between their teeth disappeared and there was a reduction in the typically coarse facial features. Joint mobility also improved and normal longitudinal growth was recorded (Hugh-Jones et al 1989). These findings led to hope of normal or nearly normal musculoskeletal development.

By the age of five years, however, it had become apparent that trunk growth was still retarded, with unusually short sitting height, increasing lumbar gibbus and a pigeon chest, although lower-limb length remained within, or even above, the average to the end of the first decade (Fig. 1b). Mobility of the joints of the upper limbs continued to improve and clawing of the digits did not develop to the degree seen in untreated cases.

Table I. Details of 11 children who underwent successful bone-marrow transplantation (BMT)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at BMT (mth)</th>
<th>Donor enzyme status</th>
<th>Present age (mth)</th>
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<tr>
<td>1</td>
<td>11</td>
<td>Carrier</td>
<td>169</td>
</tr>
<tr>
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<td>29</td>
<td>Carrier</td>
<td>173</td>
</tr>
<tr>
<td>3</td>
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<td>Normal</td>
<td>164</td>
</tr>
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<td>17</td>
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</tr>
<tr>
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<td>27</td>
<td>Carrier</td>
<td>143</td>
</tr>
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<td>Normal</td>
<td>97</td>
</tr>
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<td>19</td>
<td>Carrier</td>
<td>91</td>
</tr>
<tr>
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<td>20</td>
<td>Normal</td>
<td>84</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>Normal/ carrier</td>
<td>80</td>
</tr>
</tbody>
</table>

Radiographs of the skull of a four-year-old child. Premature closure of the sagittal suture gives the head its typical scaphocephalic shape. It is also abnormally large with thickening of the diploë, the base and the orbital roofs. The sella turcica is enlarged and has a characteristic J-shaped profile. The facial bones appear small, with a short wide mandible which has deformed condyles. The coronoid process is large and the molar teeth are abnormally situated.
less, the hands remained abnormally broad and the digits stubby. In the lower limbs, fixed-flexion deformities had developed by the age of ten years in all but one case, and progressive subluxation and dislocation of the hips and increasing genu valgum had not been prevented. With four exceptions, those children who reached adolescence lost their ability to walk unaided and had generalised muscle weakness. Radiographs revealed a pattern of abnormalities that did not differ from those seen in the untreated syndrome (Figs 2 to 7).

ORTHOPAEDIC MANAGEMENT

Over the years, several orthopaedic procedures have been undertaken. Our policy was to minimise the number of operations requiring general anaesthesia because of the increased susceptibility to postoperative respiratory complications.

Soft-tissue procedures. Carpal tunnel syndrome was common. At first, the problem may have been under-diagnosed due to its insidious onset and the lack of complaints. Carpal tunnel decompression was performed on seven children at an average age of 112 months (56 to 133) with considerable benefit. Figure 8 shows the ultrastructure of a flexor retinaculum biopsied during one of the decompressions.

Soft-tissue release of the hips was performed on one child at the age of 106 months but the result was disappointing. Flexion contracture of the knees and equinus deformity of the feet often developed by the end of the first decade, but surgical correction was not attempted.

Bone procedures. In all cases BMT failed to halt the progression of the thoracolumbar kyphus. In every patient the apex of the gibbus was at the L1 or L2 vertebral level. Posterior spinal fusion was performed on six children at an average age of 91 months (45 to 124) and proved useful in halting further progression.

Progressive subluxation of the hips was not affected by BMT. In all cases acetabular development was typical of untreated Hurler’s syndrome and the femoral capital epiphysis was fragmented and showed thinning of its medial segment (Fig. 9). At first we did not operate on the hips but as it became apparent that the children were retaining nearly normal intellects and some independent mobility to the end of the first decade, a more active approach was adopted. Arthrography of the two youngest children showed well-developed cartilaginous acetabular roofs at three to four years of age (Fig. 10). We therefore performed proximal femoral osteotomies in the hope that the acetabulum would remodel. Unfortunately, the procedure proved ineffective. The lateral portion of the roof failed to ossify and the typical distorted acetabular margin persisted (Fig. 11).

As the children grew, they developed progressive valgus deformity of their knees, apparently from localised dysplasia of the lateral part of the proximal tibial metaphysis (Fig. 7). Arthroscopy of the knees of the two eldest children showed no intra-articular abnormalities. Corrective osteotomy of the proximal tibia has not been attempted.

None of the children has ever sustained a fracture and those on whom osteotomies have been performed
A radiograph of a two-year-old child showing characteristic flaring of the iliac wings and obliquity of the acetabular roofs. The development of the capital epiphysis is delayed and there is bilateral coxa valga and subluxation of the hips. The ischial and pubic bones are thick and undermodelled.

developed normal callus and the bones united in the expected time.

Ten of the 11 children have shown gradual musculoskeletal deterioration with time but one has followed a dramatically different course. Although this child has required bilateral carpal tunnel decompression, posterior spinal fusion and unilateral proximal femoral osteotomy, he has maintained a normal rate of skeletal growth beyond his twelfth birthday. He has not developed the typical pattern of soft-tissue contractures and remains able to participate in some sporting activities. Unlike the other children his intellectual function has not deteriorated and at a recent review he was found to have an intelligence quotient of over 120.

DISCUSSION

In untreated Hurler’s syndrome, the absence of α-L-iduronidase leads to many physical abnormalities. BMT dramatically improves the metabolism and clearance of GAGS from organs such as the liver in which cellular perfusion is high. In such tissues, diffusion of α-L-iduronidase derived from the leucocytes is sufficient for normal or nearly normal clearance of heparan and dermatan sulphate. In the musculoskeletal tissues, however, growth and cellular maturation involve the laying down of a comparatively avascular ground substance which eventually isolates the cells from the leucocytes.

α-L-iduronidase deficiency probably affects skeletal development in three distinct ways. First, there is a systemic disturbance of bone modelling, secondly there are focal failures of ossification and thirdly there is an avascular disorder of the femoral head.

A radiograph of the wrist and hand of a seven-year-old child shows the distal ends of the radius and ulna tilted towards one another and is characteristic of the untreated condition. The metacarpals and phalanges show lack of diaphyseal modelling and have thickened shafts. The second to fourth metacarpals are pointed at their proximal ends and the phalanges are short and stubby, described as ‘bullet-shaped’. The ossification centres for the carpal bones are delayed, small and irregular.
Fig. 7
Radiograph of the knees at the age of eight years showing localised failure of ossification of the lateral margin of the proximal tibial metaphysis.

Fig. 9
Anteroposterior radiograph of the proximal femur at the age of six years. There is fragmentation and thinning of the medial segment of the capital epiphysis.

Systemic disturbance of bone modelling. This is seen in both primary ossification and secondary modelling of the skeleton. Before BMT these two processes resulted in very short stature and poor diaphyseal modelling. The effect of BMT was to improve the primary ossification of both membranous and endochondral bone, as shown by the improved shape of the facial bones and the nearly normal growth rate of the appendicular skeleton. This improvement is short-lived, but the appendicular skeleton continues to grow nearly normally at least to the end of the first decade. Any improvement of secondary modelling is also short-lived and, apart from their increased length, there is no difference in the appearance of the bones from that of the untreated condition.
Our explanation for these findings is that, after BMT, the supply of α-L-iduronidase to the musculoskeletal tissues is at first sufficient but that, as the size of the skeleton increases and its cellular elements mature, it again becomes inadequate. The observation that primary endochondral ossification escapes the effects of this relative α-L-iduronidase deficiency may be explained by the fact that the rate of endochondral ossification depends upon the rate of growth and division of the germinal layer of cells in the epiphyseal growth plates. Although these cells synthesise GAGS the need for degradation of these molecules (the process requiring α-L-iduronidase) is limited. Furthermore, the germinal layers of the epiphyseal growth plates are better vascularised than are other skeletal tissues. These factors may allow a normal rate of cell growth and division. Even so, as the chondrocytes become surrounded by a cartilaginous matrix, diffusion of the enzyme becomes more difficult and as ossification proceeds the environment comes to match that in other osseous tissues and the bone develops its typically abnormal appearance.

Soft-tissue development appears to follow a similar course. In the first few years after BMT, there was some improvement in joint mobility but flexion contractures occurred later. Again, the failure of local α-L-iduronidase synthesis will mean that insufficient enzyme reaches these tissues. There is progressive isolation of the fibrocytes in mature fibrous tissue due to poor vascularity and the accumulation of extracellular material. The accumulation of GAGS in the flexor retinaculum specimens obtained at
operation for carpal tunnel decompression supports this hypothesis.  

**Focal failure of ossification.** This occurred at three sites in all our patients: the anterosuperior quarters of the lowest thoracic and upper two lumbar vertebral bodies (Fig. 3), the lateral roof of the acetabulum (Fig. 10) and the lateral margin of the proximal tibial metaphysis (Fig. 7). In all these sites the skeletal element was formed in cartilage but failed to ossify.

Failure of ossification of the upper anterior part of the thoracolumbar vertebral bodies is not unique to Hurler’s syndrome. A similar phenomenon is seen in other mucopolysaccharidoses and also in achondroplasia. Post-mortem examination of two children with Hurler’s syndrome treated by BMT showed normal end-plate anatomy but the anterosuperior quadrant of the vertebral body had failed to ossify. In embryological development, each vertebra is derived from the caudal and cranial halves of two adjacent sclerotomes (body segments).

The second location at which ossification fails is the superolateral quadrant of the acetabulum. Development of the acetabular roof was not improved by varus femoral osteotomy. We now believe that the disorder of the acetabulum is similar to that in the vertebral bodies and that local developmental failure of the lateral acetabular margin precludes ossification of this tissue. Innominate osteotomy might be more appropriate to improve containment of the femoral head.

At the lateral margin of the proximal tibial metaphysis also, the tissue remains cartilaginous throughout growth. The greater part of load is normally transmitted through the medial side of the knee, so that structural failure is delayed until the body-weight increases towards the end of the first decade; then the typical valgus deformity develops.

We can offer no explanation for the local ossification failure in Hurler’s syndrome. We only know that all individuals with the disease are affected and that the damage was probably present before BMT and is not improved by this treatment.

**Avascular disorder of the femoral head.** Our final class of abnormality was observed only in the capital femoral epiphyses and resembles Perthes’ disease in that partial fragmentation is followed by remodelling and thinning of the affected segment. Unlike Perthes’ disease, the abnormality is confined to the medial portion of the epiphysis. The affected segment is that supplied principally by the medial ascending retinacular vessels and we suspect that some compromise of the blood supply underlies the abnormality. Although we cannot explain the mechanism, two local abnormalities may contribute. First, failure of ossification of the lateral portion of the acetabular roof will diminish the load on the lateral part of the femoral head and proportionately increase the load on the medial segment. Secondly, the valgus angulation of the femoral neck may compromise the medial ascending retinacular vessels as they enter the femoral head.

As previously mentioned, one child enjoyed dramatically greater benefit from BMT than did the others. We now believe that this patient may not have true Hurler’s disease and possibly represents a form of the Hurler-Scheie syndrome. Recent work (Hopwood et al 1993) has demonstrated residual iduronidase activity in skin fibroblast cultures obtained from this patient and we assume that such an endogenous source of enzyme combined with the grafted leucocyte source has provided this patient with sufficient α-L-iduronidase activity for him to escape many of the metabolic disturbances seen in our other patients.

The authors chose not to respond to the request for a conflict of interest statement.

REFERENCES


