Intramedullary Rodding and Bisphosphonate Treatment of Polyostotic Fibrous Dysplasia Associated With the McCune-Albright Syndrome

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Summary: The authors report the results of the management of five consecutive children with McCune-Albright syndrome. These children were treated with a combination of drug treatment (bisphosphonates) and surgical treatment with elongating intramedullary rods (Sheffield) for management of femoral and tibial lesions. This treatment was successful in all patients, as judged by improvement in their quality of life and in clinical parameters, such as decreased bone pain and fracture rate, and improved walking ability. Two of the five children had been wheelchair-bound before treatment. All children are now community ambulators. In 5 of 10 hips, there was a significant decrease in the neck-shaft angle over time compared with the immediate postoperative angle. Key Words: Bisphosphonates—Intramedullary rodding—McCune-Albright syndrome.

McCune-Albright syndrome consists of polyostotic fibrous dysplasia, café-au-lait skin changes, and autonomous hyperfunction of endocrine glands. The main orthopaedic problems associated with polyostotic fibrous dysplasia in McCune-Albright syndrome are bone pain, fractures, and deformity. Recurrent hospital admissions are a major problem in these children. The deformities tend to occur during the first 4 to 5 years, particularly in the intertrochanteric area of the femur. The shepherd’s crook deformity of the upper femur leads to a waddling gait and is often associated with pain. Other deformities are usually secondary to fracture malunion. Pathologic fractures are common, particularly in the femur, tibia, and humerus. Bone pain is common, causing sleep disturbance and increasing disability. Many patients are confined to a wheelchair or require crutches to mobilize.

Before 1997, a variety of procedures were used at this institution to manage Shepherd’s crook deformity of the femur (Tables 1–3). These included intramedullary rodding with cross-bolting, plating of the upper femur, and intramedullary rodding with flexible nails. All of these techniques eventually failed and required revision to elongating rods (Sheffield).

The management of these children has changed significantly during recent years. Because pathologic fractures are so common, we are much more aggressive with initial surgical treatment. If deformity occurs, further fractures are almost inevitable. Current treatment is to rod these children’s long bones as soon as increasing deformity or fractures occur.

In the weight-bearing long bones, we have been using intramedullary fixation with good results. The elongating rods allow longitudinal growth to occur without losing support. The use of these rods has reduced the incidence of fractures in these long bones and has dramatically improved the walking ability of these children (1–13).

Bisphosphonates have been used in limited situations in children. They have been successful in the management of children with osteogenesis imperfecta (6), reducing fracture rates and bone pain and improving mobility. The molecular basis of bisphosphonate action is complex, but it has an effect on pathologic bone loss. Possible sites of action of bisphosphonate include retardation of osteoclast differentiation, prevention of secretion of osteoclast stimulating factors by lining bone cells or by stimulating production of osteoclast inhibitory factors, inhibition of resorptive action of osteoclasts and of tyrosine phosphatase activity with inhibition of protein synthesis, disruption of signals maintaining and targeting osteocyte precursor cells, and promotion of osteoclast apoptosis.

Few studies of the long-term effects of intravenous pamidronate in fibrous dysplasia have been published. The effect of treatment in children has been reported only once (2).

METHODS

Five consecutive children with McCune-Albright disease have been treated with a combination of bisphos-
TABLE 1. Characteristics of the five children with McCune-Albright syndrome who underwent intramedullary rodding of the femur

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Age (mean)</td>
<td>10.2</td>
</tr>
<tr>
<td>Sex ratio (male:female)</td>
<td>5.0</td>
</tr>
<tr>
<td>Age at first femoral surgery (mean - years)</td>
<td>5.4</td>
</tr>
<tr>
<td>Age at Sheffield rodding (mean - years)</td>
<td>8.6</td>
</tr>
</tbody>
</table>

Bisphosphonates and femoral osteotomies with elongating intramedullary rods (Sheffield). Elongating intramedullary rods (Sheffield) were inserted into 10 femurs and 1 tibia between 1997 and 1999, with an average follow-up of 18 months.

Each patient was admitted to the hospital for the administration of disodium pamidronate by intravenous infusion. A dosage of 1 mg/kg was given over 4 hours each day for 3 consecutive days. Infusions were repeated each 6 months for 2 years. Bone mineral density was assessed by DEXA at 1, 12, and 24 months. Biopsy of affected bone was undertaken during any orthopaedic procedure that was necessary during the 2 years of treatment. Blood tests were performed at regular intervals during treatment, monitoring endocrine function (free thyroxine, thyroid-stimulating hormone, follicle-stimulating hormone, luteinizing hormone). Parameters of bone formation and breakdown were monitored. Osteoblastic activity was measured by plasma alkaline phosphatase and osteocalcin. Osteoclastic activity was measured by pyridinoline and deoxypyridinoline cross-links. Visual field testing and echocardiography were performed throughout treatment.

Outcome was assessed clinically, radiologically, and biochemically and on histopathology. Clinically, pain, fracture rates, and walking ability were assessed. Radiologically, the neck-shaft angle of the femur was assessed, comparing preoperative, postoperative, and the most recent radiographs.

The characteristics of the five children are shown in Table 1.

Patient 1 (Fig. 1) underwent intramedullary rodding and cross-bolting of the right femur in 1992 at age 5 years. The cross-bolt eventually broke and pain developed in the upper femur. In 1993 the rod was removed. In 1993 and 1994 he sustained fractures to the right femur, and in 1996 to the left. A flexible intramedullary nail was inserted into his left femur through the greater trochanter. In 1996 he underwent an osteotomy of the upper right femur with plate fixation. This treatment failed because the plate cut out of the bone. In 1997, when he was 10 years old, elongating intramedullary rods (Sheffield) were inserted into both femurs. The lower end of the right rod was revised in 1998 because of prominence of the rod distally and associated knee stiffness. Bisphosphonate treatment started in 1996. He has had one undisplaced fracture of the right femur around the rod. He is now walking independently and has a full range of knee movement. He walks with a Trendelenburg lurch on the right because of recurrent coxa vara.

Patient 2 (Fig. 2) fractured his left femur twice in 1988 at age 2. Both fractures were treated in hip spicas. In 1992 he fractured his right humerus. In 1993 he underwent a valgus/extension osteotomy of the right femur and was treated in a hip spica because attempted insertion of a Rush pin was unsuccessful. In 1994 he again fractured his right humerus, and in 1996 an elongating intramedullary rod was inserted into his left tibia. He underwent bilateral femoral roddings (Sheffield) in 1997. He fractured his right humerus for the third time in 1998, necessitating osteotomies and intramedullary fixation. Bisphosphonate treatment started in 1996. He is now walking independently and has had no further femoral fractures.

In patient 3 (Fig. 3), severe coxa vara developed at an early age. He underwent bilateral upper femoral osteotomies with plate fixation (Altdorf) in 1996. The femoral plates were insufficient to prevent further coxa vara developing, and in 1998 he underwent removal of the Altdorf plates and bilateral elongating intramedullary rodding (Sheffield). Bisphosphonate treatment began in 1996. He is now walking independently but walks with a significant Trendelenburg lurch bilaterally because of severe recurrent coxa vara. He has had no further femoral shaft fractures.

Patient 4 sustained fractures to his left humerus and his right femur in 1996. In 1997 he underwent osteotomies and rodding of his left femur (Sheffield). His left tibia became increasingly deformed and fractured in 1997. In 1997 Sheffield rods were inserted into his right femur and his left tibia. He fractured his right humerus and right tibia in 1998 and required rodding of the right humerus in 1998. Bisphosphonate treatment began in 1996. He is now walking independently and has had no further femoral shaft fractures. He has a severe bilateral Trendelenburg lurch as a result of severe coxa vara.

In patient 5, bilateral hip pain developed associated with upper femoral fibrous dysplasia. He underwent a

TABLE 2. Types of surgery used in this group

<table>
<thead>
<tr>
<th>Patient</th>
<th>Intramedullary nail with femoral neck cross-bolt</th>
<th>Altdorf plate</th>
<th>Nancy nail</th>
<th>Sheffield expanding intramedullary rod</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>1 Right (1992)</td>
<td>1 Right (1996)</td>
<td>1 Left</td>
<td>1 Right, 1 Left (1997)</td>
</tr>
<tr>
<td>Case 2</td>
<td>1 Left (1995)</td>
<td></td>
<td></td>
<td>1 Right, 1 Left (1997)</td>
</tr>
<tr>
<td>Case 3</td>
<td>1 Right, 1 Left (1996)</td>
<td></td>
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<td>1 Right, 1 Left (1998)</td>
</tr>
<tr>
<td>Case 4</td>
<td>1 Right, 1 Left (1997)</td>
<td></td>
<td></td>
<td>1 Right, 1 Left (1997)</td>
</tr>
<tr>
<td>Case 5</td>
<td></td>
<td></td>
<td></td>
<td>1 Left (1998) 1 Right (1999)</td>
</tr>
</tbody>
</table>
left upper femoral osteotomy with Sheffield rodding in 1998 and right Sheffield rodding in 1999. He was walking unaided until a fall at school caused a pathologic fracture through a large cyst in the right intertrochanteric region and a minimally angulated fracture of the left femur. The fractured right femur was treated by screw fixation of the femoral neck anterior and posterior to the expanding rod in April 2000. He will probably need rodding of his left tibia in the near future to control increasing deformity of the midtibia and associated pain. Bisphosphonate treatment started in 1997.

RESULTS

All the patients reported marked reduction in bone pain within the first week of their first treatment. Most children experienced cessation of pain that lasted at least 5 months; pain tended to return just before the next infusion was due.

Two of the five children were wheelchair-bound before the current treatment. All are now community ambulators, although in three of the five a Trendelenburg limp has developed from recurrent coxa vara. The other two are now playing sports.

Fractures of the femoral shaft decreased after rodding. Fractures of other bones, however, continue to be a significant problem in this group of children.

Objective evidence of change was difficult to assess because of the variability in mobility and changes in locomotion. One child’s fracture rate increased in the first year because he ceased using his wheelchair and joined the cricket team. Another child took to climbing on tables after treatment; his fracture rate also increased.

Neck-shaft angles are shown in Table 3.

Bone biopsies showed that the pathologic tissue is a combination of bone, fibrous tissue, and cartilage. The soft tissue components are particularly abundant in the intertrochanteric region. Overall, the bone in the inter-

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Neck-Shaft angle before rodding (degrees)</th>
<th>Neck-Shaft angle after rodding (degrees)</th>
<th>Latest Neck-Shaft angle (degrees)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R-100 L-120</td>
<td>R-130 L-140 (08/1997)</td>
<td>R-105 L-130 (08/1997)</td>
</tr>
<tr>
<td>3</td>
<td>R-70 L-70</td>
<td>R-130 L-105 (03/1998)</td>
<td>R-100 L-90 (07/2000)</td>
</tr>
<tr>
<td>4</td>
<td>R-80 L-70</td>
<td>R-130 L-140 (06/1997)</td>
<td>R-100 L-90 (01/2000)</td>
</tr>
</tbody>
</table>

L, left; R, right.

FIG. 1. Patient 1, a 12-year-old boy with McCune-Albright syndrome. A: At age 4, lesions are present within the pelvis and both femora. Neck-shaft angles are normal. B: After a femoral neck fracture, an intramedullary nail and femoral neck cross-bolt are inserted in the right femur at age 4. C: At age 6, the cross-bolt has broken and the femoral nail has been removed. D: Because of increasing pain, limp, and femoral neck deformity (100° neck-shaft angle), an upper femoral osteotomy and plate fixation has been carried out (age 8). E: Bilateral femoral roddings have been performed by age 12. The current neck-shaft angles are 105° on the right and 130° on the left.

trochanteric area is of poor quality and can usually be cut with a scalpel. Although we cannot quantify the quality of the bone, we believe that the diaphyseal bone in particular is better after bisphosphonate treatment.

Biochemical indices of bone turnover were difficult to assess. There was a slight trend toward a decrease in bone turnover in the first 12 months of treatment, but this was not consistent or maintained.

Bone mineral density increased in all patients at both the lumbar spine and the hip across the 2-year study, with a mean 34.6% increase in the lumbar spine. It is difficult to give an accurate calculation of volumetric bone mineral density or values adjusted for body size and growth because of the abnormal body configuration.

DISCUSSION

McCune-Albright syndrome is an uncommon condition that consists of polyostotic fibrous dysplasia, café-au-lait areas of pigmentation, and multiple endocrine abnormalities. The main orthopaedic problems include coxa vara (shepherd’s crook deformities of the upper femurs), pathologic fractures, bone pain, deformities of other bones, and subsequent major problems with walking. If untreated, an increasing Trendelenburg limp develops, with increasing deformity of the proximal femur. Bone pain appears to be a universal problem. Fractures of the long bones are common. These children usually require walking aids and eventually, if left untreated, will
go off their feet. In this study, two of the five children were wheelchair-bound before treatment; they are now community ambulators.

Management of the femoral deformities has been a major problem because most of the deformities occur in the upper femur, particularly at the junction of the neck and shaft. Progressive coxa vara tends to occur from the age of 3 or 4, causing an increasing Trendelenburg limp. Before 1997, treatments included custom-made intramedullary nails with a femoral neck cross-bolt, angled plates (Altdorf), and nonexpanding nails and rods (Williams, Nancy) (see Table 2). The problem with all of these devices is that they are inserted at a young age; as the child grows, the devices become relatively short and therefore less effective. The plates are not suitable because it is difficult to get sufficient purchase on the soft bone with the screws, and the plate either cuts out of the femoral neck or the femur fractures at the bottom end of the plate. In the one patient who received a custom-made nail, a fatigue fracture of the femoral neck cross-bolt developed and it had to be removed.

The elongating nails have been a great improvement in the management of these children. It was thought that these nails would be a way to prevent pathologic fractures in the femoral shafts. At the time of surgery an attempt was made to bring the neck-shaft angle up to at least 130°. Over time this angle has decreased in 5 of 10 hips. At the latest review in these five hips, this angle has reached levels almost as low as the initial readings (see Table 3). This depends largely on the quality of the bone in the intertrochanteric region. Two children in particular have severe disease in this region, and it has been extremely difficult to control the neck-shaft angles. These children do not tend to have acute fractures in this area but rather have a slow recurrence of coxa vara (see Fig. 3).

The number of femoral fractures has decreased significantly since insertion of the rods. Two children have had minor fractures of the femoral shaft since insertion of the rods. Both of these children have ceased using their wheelchairs after treatment and have taken to sports and climbing activities. All five of these children are now community ambulators.

In this group of patients, one patient had knee stiffness after femoral rodging from rod prominence and underwent division of adhesions in his knee. He regained full movement. Another child sustained a fracture of the intertrochanteric area of the right femur that required screw fixation around the intramedullary rod. There have been no rod revisions in this group yet, but it is anticipated that most of these children will need to have the rods replaced during growth. Some of this surgery may be required at skeletal maturity in the form of osteotomies to recreate the normal neck-shaft angles and intramedullary nailing with femoral neck cross-bolts.

One of the problems faced during the osteotomies in these children is the amount of blood loss. The periosteum is particularly vascular and the bone bleeds a great deal, mainly from large veins. In one child, the hemoglobin reached a level of 50 g/dL during the surgical procedure.

The bones in patients with McCune-Albright syndrome have been studied after each osteotomy. The bone in the intertrochanteric region is extremely soft and can be cut with a scalpel. Pathologically, the tissue consists of fibrous tissue, cartilage, and bone. The biopsy samples taken from this area after treatment with bisphosphonates have shown some improvement. The strength of the bone shafts, however, is much improved.

All patients reported a marked and sustained reduction in bone pain within the first week after infusion of pamidronate. This may reflect decreased bone turnover or a reduction in microfractures. Bone mineral density has increased in all patients in the lumbar spine and hip, with a mean increase of 34.6%. It is not possible, however, to calculate accurate values adjusted for body size and growth because of the abnormal body configuration. Biochemical indices have been difficult to assess. There was a slight trend toward a decrease in bone turnover during the first 12 months, but this was not consistent or maintained.

All parents believe that their children are happier and have a better quality of life after this treatment regimen.

It should be noted that bisphosphonates are not approved for use in children by the U.S. Food and Drug Administration.

CONCLUSION

We believe that the approach to children with McCune-Albright syndrome should be a combination of early surgical intervention and medical treatment (bisphosphonates). The ideal surgical treatment reduces the fracture rate, particularly that of long bones, and controls the femoral neck-shaft angle. The elongating Sheffield rods are effective at reducing femoral shaft fractures but do not prevent recurrence of the coxa vara. Most of these children are likely to need repeat surgery during growth to recreate an appropriate neck-shaft angle at skeletal maturity. This treatment has been effective in reducing or eliminating bone pain and improving mobility. Two children were wheelchair users before treatment; all are now community ambulators. Extended observation is needed to ensure the long-term safety of bisphosphonates when used for treatment of children with McCune-Albright syndrome.

REFERENCES