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CASE REPORT

Treatment of congenital pseudarthrosis of the tibia with native bovine BMP : A case report

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Bone morphogenetic proteins (BMP) have been shown to induce bone formation and union in long bone defects and nonunions. We report a case of congenital pseudarthrosis of the tibia treated with a composite implant consisting of a biocoral frame, collagen carrier, and native bovine BMP extract.

A six-year-old boy had persisting congenital proximal tibial pseudarthrosis despite six prior operations. At surgery, the sclerotic surfaces of both fragments were excised, fixation was performed using Ilizarov's device, and the composite implant and an autograft were applied to the nonunion site. Three months after the operation, radiographs showed union, and at four months, the Ilizarov device was removed. Two years later, the proximal pseudarthrosis remained clinically and radiologically united.

It is concluded that BMP may contribute to the healing of congenital tibial pseudarthrosis of the tibia.

Keywords : congenital pseudarthrosis of the tibia ; BMP ; coral.

INTRODUCTION

Congenital pseudarthrosis of the tibia is a specific type of tibial nonunion, either well established or incompletely developed at birth (*16*). It is an uncommon condition with reported incidences ranging from 1 in 140,000 to 1 in 250,000 liveborn children (*13*). Despite recent achievements in paediatric orthopaedic surgery, the treatment of congenital pseudarthrosis of the tibia continues to be a challenge. The most commonly used methods of treatment are different modifications of Ilizarov's technique, vascularised fibular grafting, bone grafting with intramedullary fixation, and Boyd's double bone grafting (*2*). After failure of more than three operations and significant shortening of the tibia, even amputation has to be considered (*2*).

Bone morphogenetic proteins (BMPs) are local bone growth and differentiation-regulating factors capable of inducing the formation of endochondral bone (*19*). BMPs have been shown to cause the differentiation and proliferation of mesenchymal stem cells into osteogenic cells capable of participating in bony repair and osseous regeneration (*14*). In

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clinical studies, good results have been achieved by using BMP-containing implants in resistant nonunions of the tibia (*6,8*), femur (*7*), and ulna (*10*). BMPs might thus also be useful in the treatment of congenital pseudarthrosis of the tibia. Here, we report a case of congenital pseudarthrosis of the tibia treated with a composite implant consisting of a biocoral frame, carrier collagen, and highly purified native bovine BMP.

CASE REPORT

A six-year-old boy with neurofibromatosis had Boyd type 1 tibial pseudarthrosis located in the proximal part of the tibia. He had undergone six prior attempts to unite the pseudarthrosis, all of which had failed. At first, microvascular fibular transfer was performed at six months of age. At one year of age, free autograft with cast immobilisation was performed. At $2^1/_2$ years of age, the pseudoarthrotic surfaces were revised, a free autograft was transplanted, and an external fixator was mounted. Four months later, additional autografting was performed. At $3^1/_2$ years of age, the pseudarthrotic surfaces were again revised, the defect was filled with an autograft, and the leg was immobilised in a plaster cast. At 4 years and 4 months of age, a vascularised rib graft was transferred and immobilisation was performed using a Monotube® (Stryker corp., Kalamazoo, Michigan, USA) external fixator.

A decision was made to try to enhance osteoinduction with growth factors, i.e. native bovine BMP. The composite implant used consisted of a plain coral frame (Biocoral®, Inoteb, Saint-Gonnery, France), collagen carrier (Lyostypt®, Braun-Melsungen, Germany), and purified native bovine BMP (*10,11,18*). It was administered as a cylindrical single piece of 30 mm in length and 10 mm in diameter. The BMP had been extracted from bovine diaphyseal bones as described earlier (*5*). The activity of the extracted BMP was tested prior to the implantation in a mouse thigh muscle poach model (*9*). The implants were sterilised with ethylene oxide (Steri-Vac 5XL, 3M, USA, temperature 29ºC, exposure time 3 h, EO concentration 700 mg/l). The plan was approved by the local ethical committee.

The operation was carried out at 6 years and 2 months of age. At surgery, the pseudarthrosis was exposed, the sclerotic surfaces of the fragments were excised, and the defect was filled with a BMP implant as described above. Fixation was performed using an Ilizarov's device with two fixation pins in both fragments. An image intensifier was used to confirm the desired position of the fragments and the implant. Pieces of cancellous autograft, harvested from the iliac crest, were placed between the fragments and around the pseudarthrosis area.

After the operation, radiographs were taken and the clinical situation was controlled monthly until five months, and after that at intervals of a couple of months, or as needed, until two years after the operation (fig 1). During the first month after the operation, a minor wire-track infection was successfully treated with kefalexin. One month after surgery, a custom-made shoe, with a 3 cm elevation to compensate for the difference in the lengths of the lower extremities, was manufactured, and walking exercises were started under the supervision of a physiotherapist. At the two-month visit, the patient was able to walk with a limp, and there was no pain in the operated leg. Three months postoperatively, radiographs showed union (fig 1c), and at four months, the Ilizarov device was removed. A custom-made orthosis was manufactured for daytime use. In follow-up at eight and 13 months, the patient was able to walk, using the orthosis, without problems and the leg was pain-free.

At 15 months after the operation, valgus angulation of about 25° in the distal tibia of the same leg started to hinder walking, while the proximal tibial nonunion was still firmly united. In order to correct the deformity, distal tibial osteotomy and tibiofibular synostosis were performed. Recovery was complicated by a traumatic fracture and a deep infection of the radiologically and clinically healed osteotomy site four months after surgery, requiring one more operation using Ilizarov's device for three and a half months, and it thus took altogether about eight months for the osteotomy to heal. At one year after the distal tibial osteotomy and at about two years after the implantation of the BMP implant into the proximal tibial preudarthrosis, the

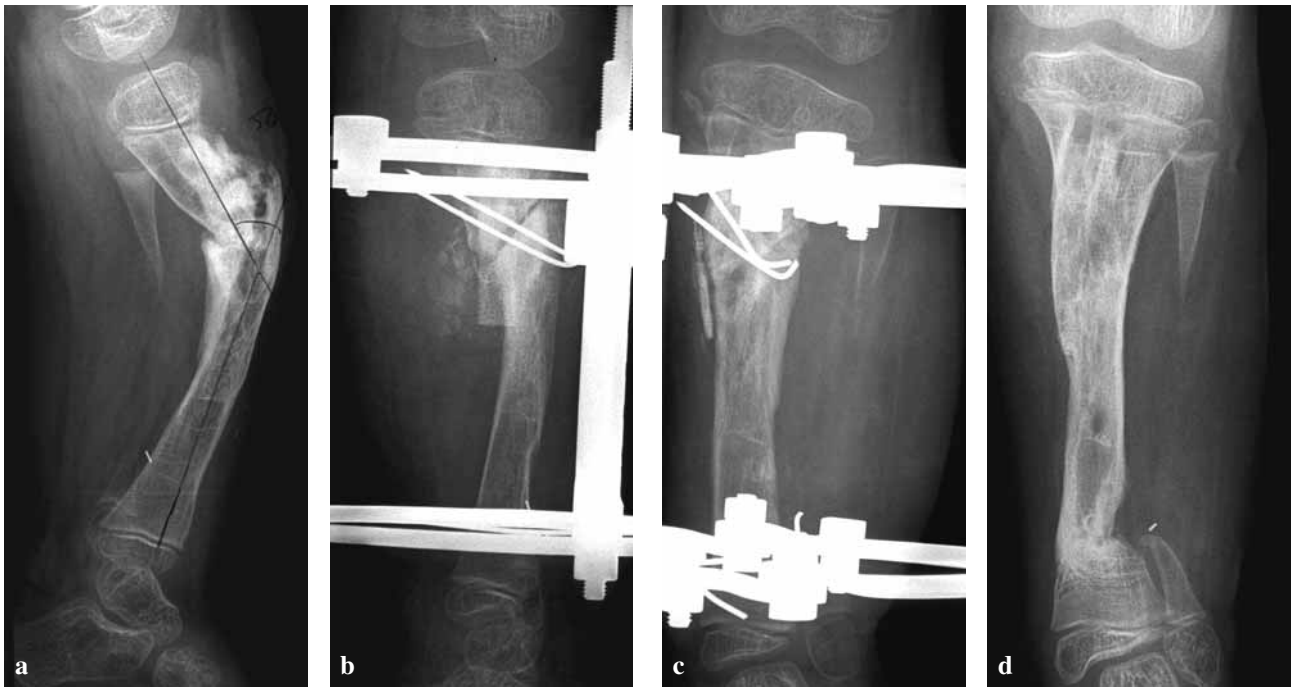

Fig. 1. — A six-year-old boy was operated for congenital tibial pseudoarthrosis using a BMP-containing implant. a) A preoperative radiograph of an unstable nonunion. b) A postoperative radiograph showing the location of the implant. After three months, a solid union was observed (c), and after 2 years, the tibia remained clinically and radiologically united (d).

tibia was stable and the patient was able to walk and run using a light orthosis and a custom-made shoe with a 4 cm elevation to compensate for the difference in the lengths of the lower extremities (fig 1d).

DISCUSSION

Congenital pseudarthrosis of the tibia continues to be a challenge. The reported union rates for different techniques are 31-52% for Boyd's double bone grafting, 54-90% for bone grafting with medullary fixation, 71-100% for Ilizarov's technique, and 81-100% for vascularised bone grafting (*2*). The reported union rates are, however, not comparable to each other, because the types of pseudarthrosis and the average age of developing pseudarthrosis vary between the study groups, and these factors have an important role in the prognosis of pseudarthrosis. Pseudarthrosis with type II has the poorest prognosis, and on the other hand, the later the onset of fracture, the better the results. After solid union, re-fracture rates of 7-50% have been reported (*2*). As the present methods of treatment are often unsuccessful, new approaches should be developed.

As BMP has shown good clinical results in normal tibial (*6*), femoral (*7*), and ulnar (*10*) nonunions previously, it could be presumed also to perform well in congenital pseudarthrosis of the tibia, and it would be a tempting alternative for the currently used microvascular fibular transfer, which has marked associated morbidity and is technically more demanding and time-consuming (*20*). We decided to use BMP in a case of resistant tibial pseudarthrosis with an imminent need for amputation.

The composite implant used here consisted of a biocoral frame, carrier collagen and highly purified native bovine BMP. In experimental studies, collagen has proven to be a suitable carrier of BMP, but has no osteogenic potential in itself (*17*). Biocoral is a slowly resorbable porous coralline bone grafting material (*3*). Coral, which has no osteoinductive

activity but good osteoconductive properties, has been shown to be well tolerated by tissues in several studies, and it has been in clinical use as a filling material for bone defects for almost two decades (*3*). It is very probable that the beneficial effect exerted by our implant is due to BMP. On the other hand the patient in this case had undergone several previous operations in which autogenous bone graft alone had been used, with no success. Adding the BMP implant to autogenous bone grafting finally resulted in union, suggesting that the BMP contributed to healing of the bone.

Only few cases about using BMP in the treatment of congenital pseudoarthrosis of the tibia have previously been reported. The first such case was reported in 2006 (*4*). In this case, after nine previous unsuccessful operations another operation was undertaken using intramedullary nailing, autologous bone grafting and implantation of rhBMB-7 (3.5 mg). Bony union was noted in five weeks and the fixation pins were removed at five months. In another case report usage of Ilizarov fixation and rhBMP-7 application resulted in union in 5 months after 12 unsuccesful previous operations (*1*). A series of five cases treated using rhBMP-7 (3.5 mg) and allograft bone transplantation and unilateral external fixation (four cases) or Ilizarov fixation (one case), has also been reported (*12*). In this series, however, union was achieved in only one of the five cases. One of the cases underwent revision surgery with implantation of rhBMP-7 (7 mg), allograft bone and bone-marrow aspirates but this case did not unite. The authors discussed that one of the factors that may have caused poor healing in their series would have been the high degree of stiffness of the unilateral external fixators, but concluded that BMP alone may not be enough to overcome the poor healing environment that is associated with congenital pseudarthrosis of the tibia. Most recent experimental study suggests that combining biphosphonate with BMP would be superior to BMP therapy alone in terms of net bone production in both wild-type and neurofibromatosis 1-deficient mice (*15*).

As a conclusion, the results of this case of treating congenital tibial nonunion using a BMP-containing implant are promising and support the results of some of the previously reported cases. However some other previously reported cases have not united. Thus it seems that BMP might have a place in the arsenal of the treatment methods of congenital tibial pseudarthrosis, but the number of reported cases remains too small to allow for further conclusions.

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