

# Pamidronate Treatment of Polyostotic Fibrous Dysplasia: Failure to Prevent Expansion of Dysplastic Lesions During Childhood

Brendan Chan and Margaret Zacharin

Department of Endocrinology and Diabetes, Royal Children's Hospital, Parkville, Victoria, Australia

## ABSTRACT

**Aims:** To examine outcomes of pamidronate treatment on fibrous dysplasia of bone in three children with McCune-Albright syndrome (MAS).

**Methods:** Radiological evidence of fibrous dysplasia progress was reviewed for three children with MAS who were treated with pamidronate from age 2.5-5 years, for 8-10.5 years.

**Results:** Despite minimal pain and a low fracture rate in long bones, except where gross deformity exists, all dysplastic lesions present in long bones continued to undergo uncontrolled expansion. In contrast, there were no major new changes in facial configuration, no clinically obvious expansion of sphenoid wing lesions and no encroachment on optic foramina or visual field restriction in any patient.

**Conclusions:** Despite previous reports of limitation or reduction in size of fibrous dysplasia lesions in adults and children, it is our experience that bisphosphonate treatment of polyostotic fibrous dysplasia in children with MAS does not arrest the expanding nature of these lesions.

## KEY WORDS

fibrous dysplasia of bone, pamidronate, bisphosphonates, McCune-Albright syndrome

Reprint address:

Dr. Margaret Zacharin

Department of Endocrinology and Diabetes

Royal Children's Hospital

Flemington Road

Parkville 3052, Victoria, Australia

e-mail: margaret.zacharin@rch.org.au

## INTRODUCTION

McCune-Albright syndrome (MAS) is usually a non-heritable complex disorder characterised by polyostotic fibrous dysplasia, *café-au-lait* markings and endocrine gland hyperfunction, including precocious puberty, acromegaly and Cushing's syndrome. It is caused by a post-zygotic activating mutation of the  $\alpha$  subunit of a stimulatory G-protein resulting in constitutional activation of adenylyl cyclase and increased cAMP activity, with a mosaic distribution in tissues<sup>1</sup>.

Bisphosphonate treatment of polyostotic and monostotic fibrous dysplasia (FD) has been reported to reduce pain and fracture rate of affected areas<sup>2,3</sup>. Bisphosphonates as analogues of naturally occurring pyrophosphate, are adsorbed onto mineral surfaces in bone, their major action being to inhibit osteoclast activity. In addition, the complex mechanism of action of bisphosphonates includes stimulation of an osteoblast-produced osteoclast inhibitory factor<sup>4,5</sup>, induction of apoptosis *in vitro*<sup>6</sup> and a direct stimulating effect on bone formation<sup>4</sup>. Recent animal and human studies suggest a discrepancy between *in vitro* and *in vivo* actions<sup>7</sup>. FD lesions demonstrate bone resorption<sup>8,9</sup> and high levels of the cytokine interleukin-6 (IL-6), which stimulates osteoclastogenesis.

Bisphosphonates inhibit IL-6<sup>9,10</sup> via the mevalonate pathway interfering with GTPase activity. Some reports of bisphosphonate treatment of FD lesions suggest that reduction in size and filling in of bony defects can occur in adults and children<sup>11,12</sup> while others report no improvement in lesion size in children<sup>13</sup>. Treatment regimes have included pamidronate and alendronate.

We report three patients who were treated with intravenous disodium pamidronate (APD) for 8.5-10 years for polyostotic fibrous dysplasia associated with MAS.

## PATIENTS AND METHODS

All three male patients were diagnosed with MAS on the basis of polyostotic FD, including sphenoid wing lesions with facial distortion and *café-au-lait* markings. All were treated with pamidronate (APD) 1 mg/kg for 3 days every 4 months for 2 years<sup>14</sup> then 1 mg/kg every 2 months for better pain control.

No boy demonstrated any expansion of sphenoid wing lesions as observed by lack of increase in facial asymmetry or optic foraminal encroachment and assessed by 6-monthly visual field testing by an ophthalmologist, during the period of observation. None of our patients had hypophosphataemia or any other side effect at any time during the study period. Treatment intervals were increased to 6 months in two boys for a short period in the past but uncontrolled bone pain required reinstatement of more frequent dosing.

To use the calculations of Carter *et al.*<sup>15</sup> for volumetric bone mineral density (BMD), as [bone mineral content (BMC)/projected area<sup>1.5</sup>], proved impossible due to inaccuracy of estimation of lesion size with the panostotic nature of the FD. FD lesions were measured and size calculated as a proportion of the whole size of the affected long bone.

**Patient 1** was diagnosed with MAS at 2.5 years, presenting with a tibial fracture. FD lesions were panostotic in the long bones but difficult to assess radiologically in the axial skeleton. Bone scan was not performed. APD was commenced at age 2.5 years, at which time he was confined to a pushchair and was non-ambulant. Treatment has continued, with now satisfactory pain control. He later developed gonadotropin-independent precocious puberty at 7 years, treated with testolactone and flutamide initially, and later with anastrozole<sup>12</sup>, with good control, as reported elsewhere<sup>16</sup>. Acromegaly occurred at 8 years, treated with octreotide and resulting in slowing of growth as growth hormone (GH) levels normalized. Over the past 3 years, from age 10.3-13.3 years, expanding FD lesions in both humeri have resulted in multiple fractures, as increased bony distortion and loss of mechanical integrity has progressed (Figs. 1 and 2). Other skeletal sites are free of fractures, with no lower

limb fractures for 5 years, and he is now ambulant, except when convalescent after surgery. He ceased anastrozole at age 13 years, with return of normal puberty, increased testicular size to 20 ml bilaterally, and a bone age advance to 13.5 years with a height of 146.5 cm (5<sup>th</sup> percentile) concomitant with his mid-parental expectation.

The FD lesions reduced cortical thickness to unmeasurable amounts. At age 8 years (Fig. 2A) the FD lesion of the right hip was x 2.5 diaphyseal diameter at midshaft, compared to x 4.5 midshaft diameter at age 14 years (Fig. 2B), whereas relative lesion length compared to femoral length did not change.

BMD z-score at the lumbar spine was +0.6 in 2001, consistent with early puberty, falling to -1.2 in 2003.

**Patient 2** was diagnosed with MAS and polyostotic FD at 3.4 years. Gonadotropin-independent precocious puberty developed at 4 years with testicular volumes of 6 ml and penile enlargement. Pubertal progress was slow and no treatment for this has been given. He has no other endocrinopathies. From age 3-13 years, control of increasing shepherd's crook deformities of the hips and clinical gait abnormality has required multiple osteotomies and intramedullary rodding of the long bones. There have been no spontaneous or minimal trauma fractures for 6 years and pain control has been maintained. He remains mobile despite a severe bilateral Trendelberg gait. He is now 14.4 years of age with continuing growth and pubertal progress.

APD was commenced at 5 years and ceased after 8.5 years due to stable but increased bone mineral density, with z-score at the lumbar spine +2.7 from 2002-4, with +11.6% increase in BMD associated with a 12.2 cm increase in height, and with a fall to +2.0 in 2005.

Radiological imaging of his long bones demonstrates marked continued expansion of bony lytic lesions, despite APD lesion diameter at age 5 years of x 4 diameter of the mid-diaphyseal shaft (Fig. 3A), compared to x 7 5 years later (Fig. 3B). Femoral neck deformity precluded further accurate measurements at this site.

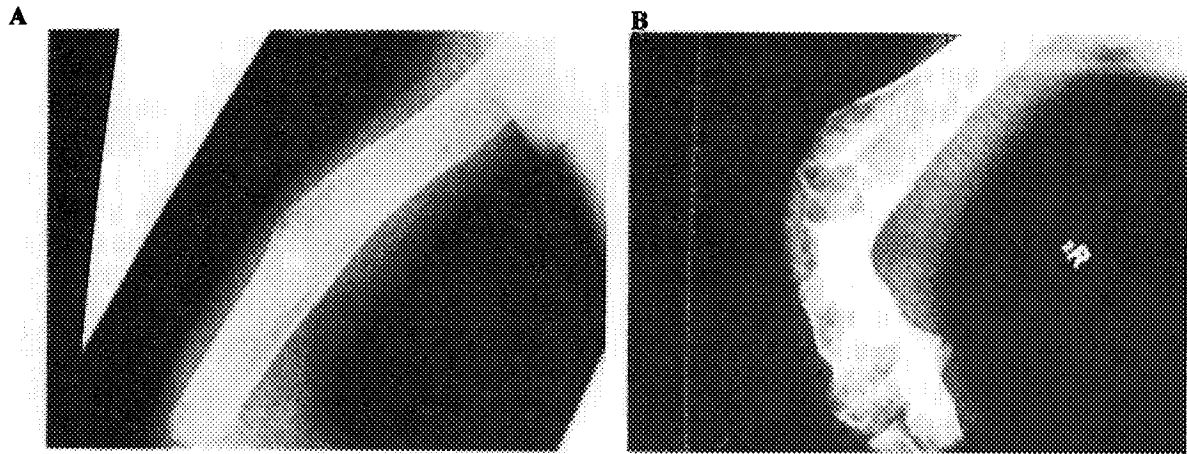


Fig. 1: Patient 1: X-ray of right humerus at age 8 (A) and 14 (B) years.

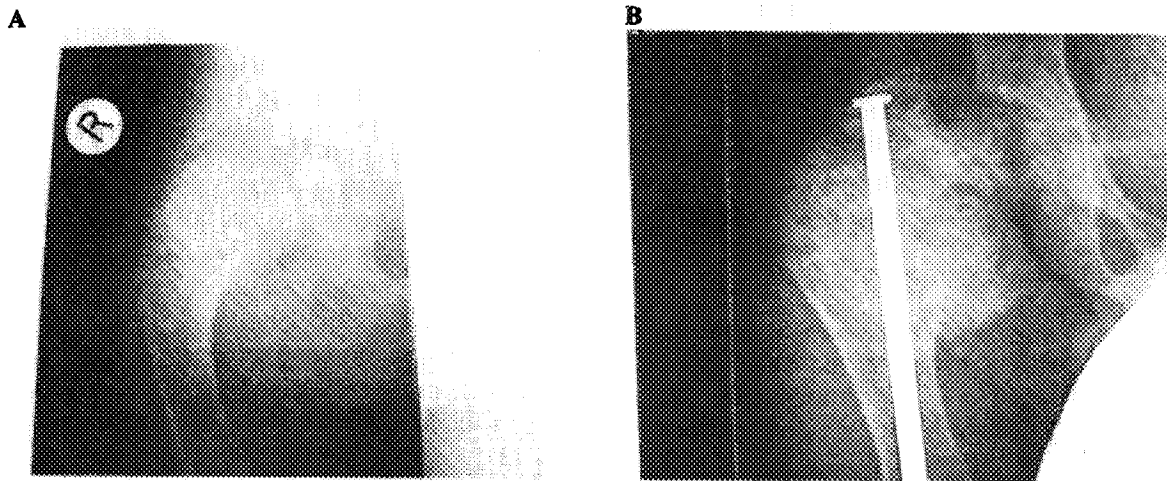


Fig. 2: Patient 1: X-ray of right hip at age 8 (A) and 12 (B) years.

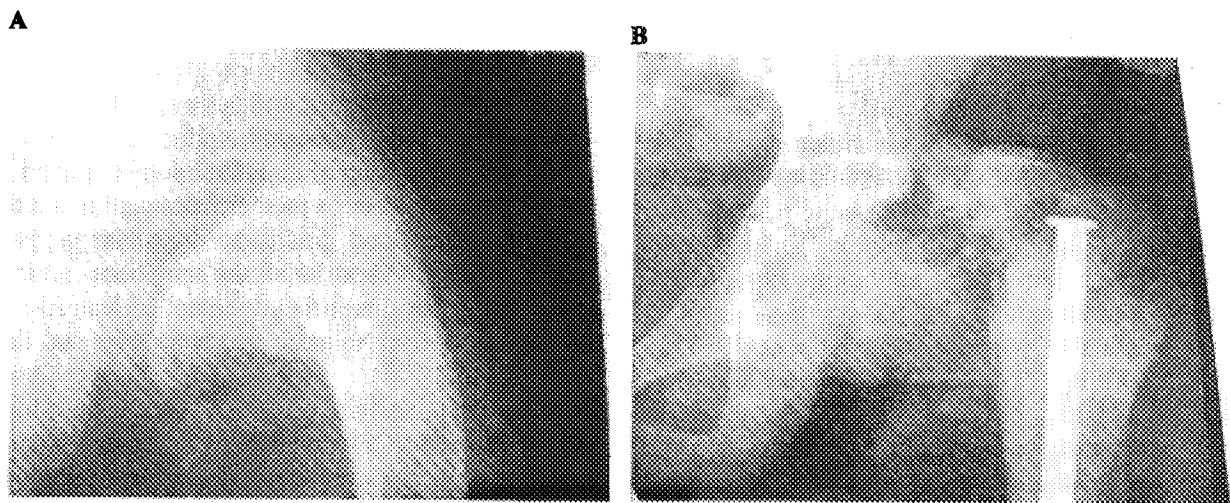


Fig. 3: Patient 2: X-ray of left hip at age 4 (A) and 12 (B) years.

**Patient 3** was diagnosed with MAS and polyostotic FD at 4.5 years. APD was commenced from age 5 years. The patient required multiple intramedullary rods for frequent long bone fractures, occurring during significantly increased exercise over the first 2 years of treatment, with good pain control. The only long bone fractures sustained over the past 5 years have occurred during sporting activity. He is now in late puberty, with 25 ml testes at age 17 years. His growth has been slow with a height <1<sup>st</sup> percentile in a family with a mid-parental height expectation on the 3<sup>rd</sup> percentile.

BMD z-score deteriorated at the lumbar spine over 12 months between 2002 and 2003 from -2.1 to -3.6, related in part to poor linear growth and also to the panostotic nature of the lesions involving lumbar vertebrae as well as the long bones.

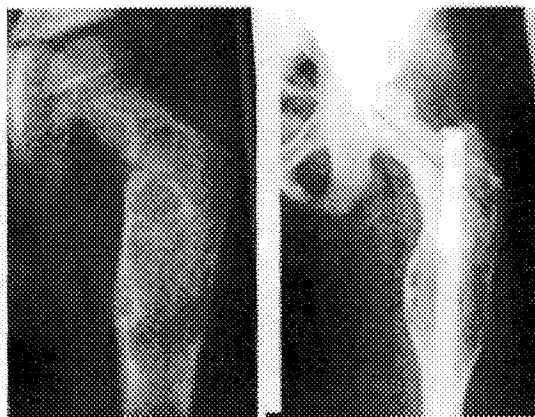
Long bone FD lesions have continued to expand. Lesion diameter increased from x 1.2 to x 2.75 mid-diaphyseal shaft diameter from age 5 years (Fig. 4A) to 9 years (Fig. 4B) with little change in relative lesion length compared to shaft length.

#### DISCUSSION

Fibrous dysplasia, with MAS or in isolation, is caused by hyperproliferation of pre-osteoblastic cells, which substitute the normal bone trabeculae with woven bone and fibrous tissue of specific histological appearance<sup>17</sup>. Subsequent hyperactivity of the osteoclastic cells results in multiple lytic lesions, causing bone pain, disfigurement and recurrent fractures. This finding provided a rationale for the use of bisphosphonate in FD.

Open studies in adults<sup>2,3,18</sup> and children<sup>12-14,18-21</sup> with FD of bone treated with i.v. pamidronate have demonstrated marked reduction in bone pain. This phenomenon is uniformly of rapid onset and may in part relate to cytokine (IL-6) inhibition rather than altered microfracture rate.

Early reports of pamidronate treatment of FD suggested refilling of osteolytic lesions and cortical thickening of bone<sup>2</sup> but more recent reports have failed to demonstrate reduction in lesion size in children with FD<sup>13</sup>. However, only four of these patients had MAS. Our patients demonstrated a similar failure to arrest lesion size in the long



**Fig. 4:** Patient 3: X-ray of left hip and femur at age 5 (A) and 9 (B) years demonstrating increasing expansion of the femoral shaft.

bones. In contrast, over 8 or more years none of our patients demonstrated increasing facial shape distortion or progressive visual loss suggestive of optic canal encroachment. This latter feature is similar to other reports<sup>22</sup>. Further evaluation with facial computed tomography might be helpful, to measure small changes, but this involves significant radiation exposure for a child.

Encroachment on the optic foramen is unusual with FD. Previous reports have emphasized the importance of restricting surgical decompression to those patients who have evolving impingement on visual pathways<sup>23</sup>. For this reason we monitor our patients with visual field examinations at regular intervals. The relatively slow progress of lesions of this bone may be part of the natural history rather than a differential treatment outcome.

Recent description of a methodology to quantify bone lesions in order to predict functional outcome in FD<sup>24</sup> is difficult for these boys as all had extensive involvement of all the long bones. Interpretation of any direct measurement of lesion size is confounded by change in bone size in the growing child.

Bone turnover markers, GH and insulin-like growth factor-I (IGF-I) levels are higher in children than in adults<sup>25</sup>, with continued remodelling of bone to maximise distribution of load and optimise axial loading. Continuing changes in bone size and

alterations in modelling, where deformity is increasing, may contribute to more active expansion of FD lesions in children versus adults and partly account for differences seen in treatment outcomes in the two groups. Previous reports of lesion shrinkage in children may have occurred where less extensive bony changes existed than for our group. A reduction in fracture frequency may be expected after puberty, due to increasing cortical thickening of normal bone with sex hormone effect. This may give a further erroneous impression of slowing of the FD activity. Another reason for failure to arrest lesions may relate to the severity of the underlying condition.

Uncontrolled phosphate wasting has been suggested as a reason for poor control of FD lesions in paediatric patients<sup>21</sup>. Our patients did not have phosphate wasting. However, osteomalacia can occur independent of serum phosphorus levels<sup>26</sup> and this may have contributed to but would not account for the expansile lesions seen in our patients. Although patient 1 had the co-morbidity of acromegaly, his GH and IGF-I levels were controlled from age 8 years onwards in the normal range without over-suppression. Despite slowing of growth, FD expansion continued unabated, suggesting that GH excess was not causative of lack of long-term lesion control.

BMD was difficult to interpret due to early puberty in patients 1 and 2. Increased BMD z-scores were, however, stable or decreased over 3 years, consistent with puberty advancing bone age rather than an effect of prolonged pamidronate administration. These BMD measurements, interpreted in the light of pubertal status, are consistent with relative sparing of normal bone with preferential uptake of pamidronate into the osteoclast-rich peripheries of FD lesions.

Linear growth for our cohort was poor, in keeping with increasing long bone deformity and with the panostotic nature of the FD and in contrast to the normalisation of linear growth seen in children with osteogenesis imperfecta treated with pamidronate<sup>27</sup>.

The *GNAS1* mutation causing uncontrolled GTPase activity in MAS may be more difficult to control than with other patients with FD. However,

no differences have been reported between patient outcomes in isolated FD and MAS<sup>13</sup>.

In conclusion, for severe polyostotic FD with MAS, long-term treatment with i.v. pamidronate, whilst apparently safe and providing continuing pain control, does not prevent progression and expansion of these bony lesions in childhood and adolescence.

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