Successful Pamidronate Treatment of Osteogenesis Imperfecta Type III Infant with Multiple Fractures

Ju Hee Yoon, M.D., Jong Uk Baek, M.D., Eun Jung Shim, M.D. and II Tae Hwang, M.D.
Department of Pediatrics, Hallym University College of Medicine, Seoul, Korea

Osteogenesis imperfecta (OI) is a generalized connective tissue disorder. We report the female neonate case with OI type III who showed severe bone deformities and fractures in utero. At birth, she showed multiple fractures in the clavicle, rib, femur, and wormian bone in the skull X-ray. We initiated pamidronate disodium infusion 30 mg/m² in cycles of 3 consecutive days from when she was 4 days old, monthly for the first 3 months and every 2 months thereafter without adverse effects.

Key Words: Osteogenesis imperfecta; Pamidronate; Bone density; Fractures, bone

Introduction

Osteogenesis imperfecta (OI) is characterized by fractures of long bones, blue sclera, and early deafness. According to the Sillence classification, OI is classified into 8 types on the basis of clinical and radiographic criteria. Of 8 types, type I to IV is clinically important. OI type I is sufficiently mild that it is often found in large pedigrees. Infants with OI type II may be stillborn or die in the first year of life. OI type III is the most severe nonlethal form of OI and results in significant physical disability. The birth weight and length of infants with OI type III are often below normal. Fractures usually occur in utero. There is relative macrocephaly and triangular facies. Postnatally, fractures occur from inconsequential trauma and heal with severe deformity. OI type III is difficult to grow up normally because of frequent fractures. Patients with OI type IV can present with in utero fractures or bowing of lower long bones at birth. In addition, they can present with recurrent fractures after ambulation. Types VII and VIII clinically overlap with OI types II and III. We report the case of a patient with OI type III who showed bone deformities and fractures in utero and received cyclic intravenous pamidronate treatment immediately after birth without adverse effects.

Case Report

A female neonate who had a short and curved femur, which was detected by obstetric ultrasonography was born by caesarean delivery at our hospital. Gestational age was 39 weeks 3 days, birth weight was 3.24 kg (50 percentile), and height was 48 cm (30 percentile); further, she had femur deformity, genu varum, shortened bowed extremities, relative macrocephaly, and blue sclera at birth (Fig. 1). The patient was born of a non-consanguineous marriage and had no family history of OI. Radiographic examination showed multiple fractures in the clavicle, rib, femur, tibia and wormian bone in the skull at birth (Fig. 2A). The patients had no dyspnea. Laboratory investigation at birth showed the following values: total serum calcium, 9.7 mg/dL; ionized calcium, 1.14 mmol/L; phosphate, 7.0 mg/dL; alkaline phosphatase (ALP), 301 IU/L; and intact-parathyroid hormone (i-PTH), 12.1 pg/mL. Echocardiographic examination showed a mild grade II tricuspid regurgitation. Whole blood was collected from the patient in EDTA blood collection tubes and DNA was extracted. PCR reactions were carried out using primers specific for 51 coding exons of COL1A1. DNA sequencing showed c.985-1G>T.
We initiated pamidronate disodium infusion (Hallym Pharmaceutical Company®, Seoul, Korea) 30 mg/m² in cycles of 3 consecutive days from when she was 4 days old, monthly for the first 3 months and every 2 months thereafter. We supplemented her with vitamin D 400 IU/day simultaneously. The patient didn’t manifest adverse effects such as hypocalcemia and flu-like symptoms. After 6 months later, tricuspid regurgitation was resolved. Auditory test was normal. The patient showed dentinogenesis imperfecta at 10 months. Currently, the patient is 11 months old. Her weight is 6 kg (< 3 percentile), height is 62 cm (< 3 percentile), and development is compatible 6 months. Total amount of pamidronate administered to the patient thus far is 54.75 mg (9.125 mg/kg), and laboratory investigations at 11 months showed the following values: total calcium, 10.1 mg/dL; ionized calcium, 1.40 mmol/L; phosphate, 4.5 mg/dL; ALP, 332 IU/L; i-PTH, 24.8 pg/mL; and urine calcium/creatinine ratio, 0.31. Radiographic examination at 45 days after birth showed healed fracture of the right tibia shaft (Fig. 2B). Thereafter, patients had no fracture until the right tibia shaft was broken at 10 months old. Bone mineral density (BMD) of the lumbar spine (L1-4) significantly increased from 0.270 g/cm² (6 months) to 0.311 g/cm² (11 months).

**Discussion**

Approximately 1 in 20,000 patients of OI are detectable during infancy. Fractures in neonates commonly result from a genetic predisposition and birth trauma. Molecular diagnosis depends on demonstration of abnormal incorporation of

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**Fig. 1.** Infants with type III osteogenesis imperfecta displays shortened bowed extremities, and relative macrocephaly.

**Fig. 2.** (A) X-ray showed fractures in right femur and tibia at birth. (B) X-ray showed healed fractures in right femur and tibia after pamidronate treatment at 45 days old.
radioactive amino acids in collagen in fibroblast cultures. It is resulting from genetically conditioned modifications in the structure of the chains of type I collagen, usually due to the mutations in the COL1A1 and COL1A2 genes\(^2\). In our case, the patients' mutation in the COL1A1 genes didn't be verified at the parents and sibling's genes. The patients' mutation is suggested splicing mutation and functional study will be needed to diagnosis pathogenic mutation in the future. Classic OI is an autosomal dominant disorder. Some familial recurrences of OI are caused by parental mosaicism for dominant collagen mutations. Genetic screening and counseling is of paramount importance because the risk of an affected individual passing the gene to the offspring is 50%, and the recurrence risk for an apparently unaffected couple of having a subsequently affected offspring is 5-7%\(^1\). OI type III is usually recognized at birth because of short stature and deformities resulting from fractures in utero. Type III is distinguished among the other classifications as being the 'Progressive Deforming' type, wherein a neonate presents with mild symptoms at birth and develops the aforementioned symptoms throughout life. Lifespan may be normal. Although the affected infants survive the neonatal period, late life-threatening complications may follow. Recurrent bone fractures and deformities due to generalized osteopenia are the major complications of OI. Respiratory problems, short stature, spinal curvature and sometimes barrel-shaped rib cage, triangular face, loose joints, poor muscle tone in arms and legs, discoloration of the sclera (the 'whites' of the eyes), and early loss of hearing is possible\(^1\). In our case, the patient had short stature, spinal curvature, poor muscle tone and didn't have loss of hearing. Regular hearing assessment is vital for early detection of hearing deficit. Respiratory infections and neurological complications such as basilar invagination and brainstem compression are frequent\(^1\). Dentinogenesis imperfecta, a common association, important in subclassification becomes apparent only after a few months\(^1\). A variety of agents have been used to increase bone mass and to reduce the frequency of fractures, such as anabolic steroids, sodium fluoride, magnesium oxide, and calcitonin. However, none of the agents have reduced the complications of the disease\(^5\). Growth hormone therapy has also been attempted with variable results depending on the type of OI\(^6\). However cyclical intravenous treatment with pamidronate (3-amino-1-hydroxypropylidene-bisphosphonate) is beneficial to children with severe forms of OI\(^7\). Wijewardena SK, et al. reported a group of infants and young children with OI type III were treated with bisphosphonate to prevent recurrent fractures without adverse effects\(^8\). It has proven efficiency in reducing fracture rates in children\(^9\). Bisphosphonates are potent inhibitors of bone resorption that reduce the recruitment and activity of osteoclasts and osteoblasts and decrease bone turnover. Bisphosphonates have benefits such as improved bone mass and muscle force, reshaping of vertebral deformities, fewer long-bone fractures, and better mobility\(^10\). However self-limited flu-like symptoms such as decreased appetitie, myalgia, irritability, low-grade fever, and decreased energy could be associated with pamidronate therapy\(^11\). In our case, the patient didn't have any adverse effects. Assessments of growth rate in the OI children treated with pamidronate reveal a slower rate of body mass and height increments\(^7,14\). However, frequent fractures without treatment can hamper growth. Recently other study showed 8 children with osteogenesis imperfect type III, aged 1 month to 6 years have treated pamidronate without growth impairment\(^15\). Adverse effect of pamidronate in children, especially growth impairment, will be needed further evaluation. In our patient, who had severe OI type III diagnosed by obstetric ultrasonography, early institution of pamidronate increased successfully BMD of the lumbar spine and metacarpal cortical width, decreased fracture rates, and improved morbidity without any major adverse effects.

**Fig. 3.** The amplified products were sequenced on an ABI 3730 analyzer. The DNA sequencing showed c.985-1G>T, (IVS12), heterozygote in the COL1A1 gene.
References


출생시 다발성 골절을 보인 골형성 부전증 환아에서 pamidronate 치료
윤주희 · 백종욱 · 심은정 · 황일태
한림대학교 의과대학 소아과학교실

골형성 부전증은 대부분 제 1형 교원질 유전자의 결함에 의한 유전 질환으로 교원성유(collagen)의 성숙 장애나 비정상적인 교원질 합성에서 기인한 골기질의 선천 형성 장애이다. 특히, 골형성 부전증 3형은 태아기부터 골 결핍과 뼈가 쉽게 부러지는 특징을 갖고 이로 인해 성장 장애와 호흡부전 등의 문제가 발생한다. 저자들은 산전초음파에서 다발성 골절을 보인 골형성 부전증 환아에서 pamidronate 치료를 경헤했기에 이를 보고하는 바이다.