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CASE REPORT

Intravenous bisphosphonate treatment and pregnancy: its effects on mother and infant bone health

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Abstract
Introduction Type 1 Gaucher's disease (GD1) is a lysosomal storage disorder associated with disabling bone involvement. The choice treatment for Gaucher's disease is enzyme replacement therapy (ERT). The use of bisphosphonate treatment for osteopenia and osteoporosis has been suggested.
Case A 22-year-old woman diagnosed with GD1 had received ERT intermittently, depending on availability of the enzyme since the enzyme was not always available. Due to severe bone involvement and multiple vertebral fractures, intravenous administration of 60 mg of pamidronate every 3 months and safe contraception were indicated. Fifteen days after receiving the fourth infusion, the patient informed us she was pregnant. A baby girl was born by cesarean delivery at week 37, showing no evidence of skeletal abnormality or clinical signs of hypocalcemia. The baby developed normally, presenting no significant pathology. At present (age 15 months), height, body weight, and bone mineral density by DXA are within normal range. The mother showed stable total skeleton and right femoral neck bone mineral density (BMD) values, no new fractures, and only ~3% decrease in lumbar spine BMD 15 months post-delivery and after a 1 year breast-feeding period (expected average ~7–8%).
Conclusion It could be posited that pamidronate exerted a positive protective effect on the mother's skeleton with no evidence of adverse effects on pregnancy or on the baby's health to date.

Keywords Bone mineral density · Fetal · Gaucher's disease · Maternal · Outcome · Pamidronate

Introduction

Gaucher's disease (GD1) is the most common lysosomal storage disorder, caused by a deficiency in the activity of the enzyme glucocerebrosidase that leads to the accumulation of glucocerebroside within the lysosomes of macrophages [1]. Between 62% and 94% of GD1 patients present clinical and radiological evidence of bone involvement [2]. However, the mechanisms involved in the genesis of osteopenia/osteoporosis remain unclear to date. It would be apparent that some imbalance in bone remodeling, with decreased bone formation and/or increased resorption activity, must be present for the osteopenia/osteoporosis to manifest. A number of factors, including anemia, thrombocytopenia, and bone involvement, negatively affect the course of pregnancy in GD1 patients; the incidence of spontaneous abortion is high, and postpartum bleeding is a severe complication [3–5].

The treatment of choice for GD1 is enzyme replacement therapy (ERT) (imiglucerase). More than 8 years treatment with ERT is necessary to attain near-normal bone mineral density (BMD) values in GD1 osteopenic patients [6]. Given the increase in bone resorption observed in GD1,

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administration of bisphosphonates has been suggested for treating osteopenia/osteoporosis secondary to GD1 [7].

We herein present the case of a young woman diagnosed with GD1, who had received ERT intermittently and who was prescribed bisphosphonate therapy [intravenous (iv) pamidronate] for treatment of severe osteoporosis and vertebral fractures secondary to GD1. The patient became pregnant in spite of having been counseled to use reliable contraceptive methods, and there was no suspicion of pregnancy at the time of the last pamidronate infusion.

Case report

Mother

The patient was a 20-year-old woman diagnosed with GD1 at the age of 4 years based on bone marrow biopsy and confirmed by leukocyte β-glucocerebrosidase determination and molecular biology (L444P/N370S). She exhibited severe bone involvement and reported suffering a fracture of the left tibia and avascular necrosis of the left hip at the age of 8 years. ERT was initiated when she was 10 years old. The treatment could not be performed regularly because the enzyme was not always available. Her menarche was at the age of 15 years, and her menses were regular (5/28). At the age of 18, she suffered a single episode of bone crisis and was referred to our service for bone mineral metabolism assessment and treatment of osteoporosis when she was 20 years old. The patient reported generalized bone pain. Daily calcium intake was low (435 mg/day). The X-rays showed multiple vertebral fractures [lumbar (L): L1 and dorsal (D): D5, D8, D10, and D12] that had been asymptomatic. BMD of lumbar spine (LS), right femoral neck (RFN), and total skeleton (TS) was determined using DXA (Lunar-DPX; Madison, USA) and showed severely decreased BMD: L2–L4 0.886 g/cm^2, Z-score −2.62; TS 0.857 g/cm^2, Z-score −3.35; and RFN 0.710 g/cm^2, Z-score −2.41. Baseline laboratory determinations of mineral metabolism are shown in Table 1. Given the decreased bone mass, severe bone involvement, and generalized persistent bone pain, the patient was prescribed 60 mg/3 months of intravenous pamidronate (iv), 500 mg per day of calcium to supplement dietary calcium, and 800 IU per day of vitamin D_2. Prior to starting treatment, the patient was fully informed about the need for contraception throughout the entire treatment period. She gave her informed consent prior to initiating treatment with iv pamidronate. After three infusions, an increase in LS, TS, and RFN BMD (5.5%, 5.1%, and 1.8%, respectively) was observed (Fig. 1). Fifteen days after receiving the last infusion, the patient informed us she was pregnant. By then, she had received three infusions before conception and the fourth infusion during the first trimester of pregnancy, so that the total dose of pamidronate was 240 mg. The patient only received imiglucerase treatment (60U/kg for 15 days) during 3 months of pregnancy. Compliance with calcium dietary recommendations and prescribed calcium and vitamin D supplementation were low. Pregnancy was uneventful, with no worsening of skeletal symptoms or sign of generalized bone pain or fractures. In the 37th week, the patient suffered preeclampsia and cesarean delivery was performed. No puerperal complications were recorded; the patient breastfed her baby during 1 year, and menses resumed 3 months post-delivery. Fifteen months post-delivery she showed stable TS (0.908 vs. 0.901 g/cm^2) and RFN (0.735 vs.0.723 g/cm^2) BMD and a 3% decrease in LS BMD (0.935 vs.0.902 g/cm^2) compared with preconception values. BMD of all studied areas was still higher compared with values observed before initiating pamidronate treatment. X-rays showed no evidence of new fractures or worsening of previous fractures. Changes in mineral metabolism are shown in Table 1.

Newborn

A baby girl was delivered at 37 weeks gestation, with an Apgar score of 9 and 10 at 1 and 5 min, respectively. Birth weight was 2230 g; length was 45 cm, and cephalic perimeter was 32 cm, showing no evidence of skeletal

Table 1 Biochemical data of the patient

	Age (years)	sCa (8.9–10.4mg%)	sP (2.6–4.4mg%)	25OHD[a] (≥30ng/ml)	SCTX (132–751ng/ml)	BGP (12–41ng/ml)
Pre-infusion (iv pamidronate)	20	8.9	4.0	34.0	429	42.0
After three infusions (iv pamidronate)	21	9.1	3.2	28.0	226	10.0
15 months postpartum	23	9.6	3.0	17.0	511	13.0

$_S$Ca serum calcium, *sP* serum phosphate, *25OHD* 25-hydroxyvitamin D, *BAP* bone alkaline phosphate; *sCTX* serum Crosslaps, *BGP* bone gla-protein

[a] 25OHD: deficiency <10 ng/ml; hypovitaminosis D 10–29 ng/ml; desirable ≥30 ng/ml [20]

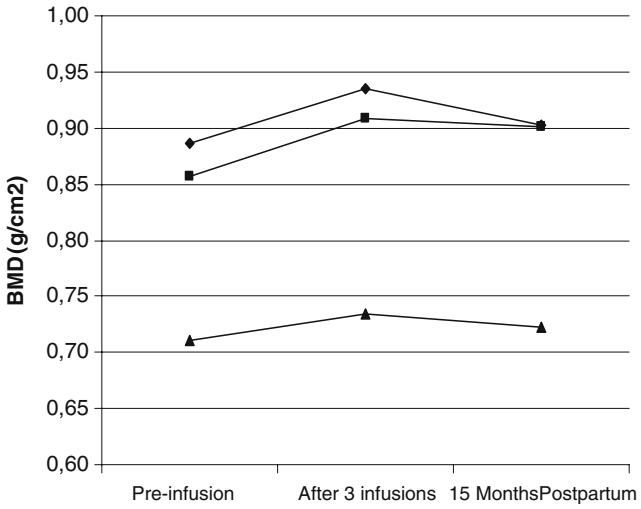

Fig. 1 *Filled diamond*, lumbar spine, *filled triangle*, right femoral neck, and *filled square*, total skeleton bone mineral density follow-up: pre-infusion (pamidronate), after 3° infusions (pamidronate) and 15 months postpartum

abnormality or clinical signs of hypocalcemia. The baby was breastfed on demand without receiving any supplements until the age of 6 months. She then started eating semi-solid foods until the age of 1 year. At the age of 15 months, development was normal, her height (69 cm, 3rd percentile) and body weight (6.8 kg, 50th percentile) were consistent with those of her parents (both in the 3rd percentile), and she had suffered no clinically significant pathologic events. LS BMD (L2–L4 0.369 g/cm^2; Z-score −0.4) was within normal age/gender-matched reference values.

Discussion

Neither the few case reports on long-term bisphosphonate treatment before conception, during the third trimester of pregnancy and during lactation [7–12], nor the two recently reported series of 24 and 12 cases, respectively, of pregnant women treated with bisphosphonates [13, 14] showed any teratogenic effects on the fetus. Nevertheless, the reported findings showed an increase in the number of abortions, low birth weight for gestational age, and one case of Aper syndrome, all of which could be attributed to the baseline diseases. Most of these studies did not evaluate changes in BMD and mineral metabolism in the mother or the new born. In agreement with the previous reports, no malformations or health effects were observed in the newborn or throughout the follow-up period (15 months) in the present case, except for the low birth weight. Unlike previous reports, we describe the effect of iv pamidronate before and during the first trimester of pregnancy on maternal and infant bone mineral status. Pamidronate was indicated due to severe bone involvement, resulting in an increase in BMD after three infusions before pregnancy. The treatment was interrupted immediately when the patient informed us she was pregnant. The only complication was preeclampsia, which determined indication for cesarean delivery. Although pregnancy could have aggravated bone manifestations and worsened osteoporosis (given the increase in bone remodeling that occurs in pregnancy), the patient did not suffer worsening of bone involvement [15, 16]. Bone metabolism studies performed 15 months post-delivery showed only 3% decrease in LS BMD but no changes in the BMD of the remaining skeletal areas in spite of having breastfed her infant for 1 year. According to reports in the literature, LS BMD post-delivery decreases an average 3–4% and can decrease up to 7–10% [16, 17]. It must also be pointed out that lactation causes maternal bone loss, especially at metabolically active skeletal sites, which would result in an additional 3–7% loss in lactating women compared with non-lactating women [18]. Thus, whereas the expected decrease in lumbar spine bone mineral density 15 months post-delivery and after a 15-month lactation period is ~7–8%, our patient showed a 3% decrease in LS BMD. In the case of our patient, administration of pamidronate before conception may have exerted a protective effect on the skeleton given that she suffered none of the skeletal complications described in GDI during pregnancy and post-delivery; she did not show a severe decrease in LS BMD in spite of prolonged lactation, and she suffered no new fractures or worsening of previous fractures. Similarly to our findings, Munns et al. [9] found stable BMD immediately post-delivery compared with pregestational values in two osteogenesis imperfecta patients receiving bisphosphonate treatment. They also reported that neither patient suffered bone pain or fractures during the 8–14 month-post-delivery follow-up period. These findings would seem to confirm the proposition that bisphosphonate treatment prior to pregnancy may have a protective effect in patients presenting diseases with high bone turnover, mitigating the exacerbation of bone symptoms during pregnancy and post-delivery and stabilizing or maintaining minimal loss of BMD. Biochemical determinations remained within reference range, showing the expected decrease in bone remodeling. In keeping with other reports on GD1 patients, insufficient vitamin D levels were observed [19]. Although calcemia was not measured, the baby showed no clinical manifestation of hypocalcemia either postpartum or throughout the 15 month follow-up period.

To conclude, we present the case of a patient with GD1 who received pamidronate intravenously during 9 months before conception and during the first trimester of unsuspected pregnancy. No clinical adverse effects that could be attributed to pamidronate have been observed in either the

mother or the baby to date, 15 months post-delivery. It could be posited that (iv) administration of pamidronate before conception exerted a protective effect on the skeleton of our GD1 patient, who suffered severe bone involvement.

In view of the increasing use of bisphosphonate therapy in adolescents and young women to treat diseases causing high rates of bone remodeling, further clinical studies must be conducted to determine the safety of bisphosphonate administration prior to and during pregnancy and lactation for the mother and the newborn.

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Conflicts of interest None.

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