Bisphosphonate Treatment of Hypercalcemia in a Child with Jansen's Metaphyseal Chondrodysplasia

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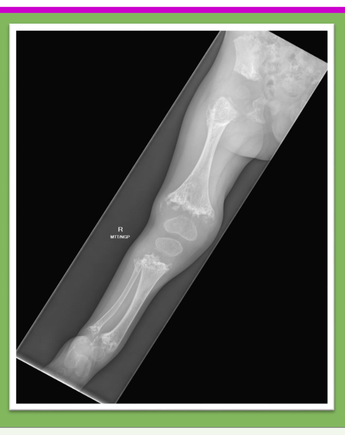
Jansen's Metaphyseal Chondrodysplasia

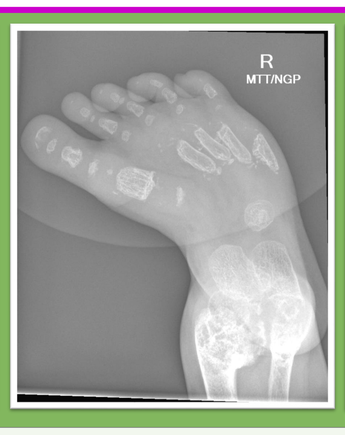
- This rare autosomal dominant condition is caused by activating mutations in the parathyroid hormone / parathyroid hormone related peptide receptor (PTHR1).
- Constitutive activity of this receptor leads to characteristic changes in the growth plate, with delayed chondrocyte differentiation, increased osteoblast activity, and indirectly to increased osteoclast activity[1]

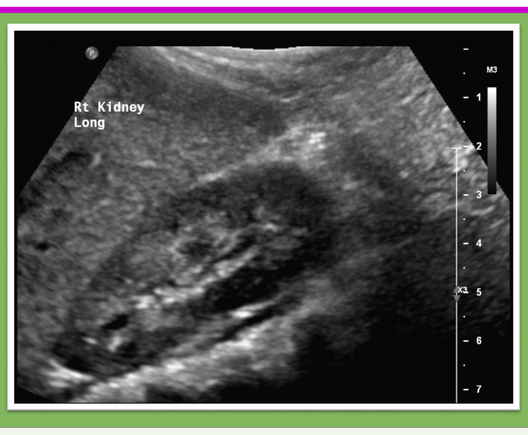
- It is associated with persistent, largely asymptomatic hypercalcemia and hypercalciuria, hypophosphatemia, with increased levels of circulating 1,25 dihydroxyvitamin D due to ligand independent action of the PTHR1.
- Persistent hypercalcemia is associated with increased cardiac risk, while nephrocalcinosis can occur with hypercalciuria, potentially resulting in kidney damage.[2]

- Classic phenotypic features include severe short stature with disproportionately short limbs, micrognathia, bowed legs, and severe malposition of the teeth
- Radiographic features include widened, cupped, ragged metaphyseal ends, and irregular patches of partially calcified cartilage protruding into the diaphysis of long bones in childhood[3]

Our Patient







- 2 year old boy with Jansen's Metaphyseal Chondrodysplasia, with a known pathogenic H223R mutation in the gene coding PTHR1
- Displays classic phenotypic features with short stature, micrognathia, hypertelorism, metaphyseal widening and dental malposition
- Developed asymptomatic hypercalcemia and hypercalciuria early in infancy, with bilateral medullary nephrocalcinosis with mild pelvicaliceal dilatation

Biochemistry at diagnosis

	Reference Range	
Ionised calcium	1.13-1.40 mmol/L	**1.53 (↑)**
Total calcium (albumin corrected)	2.15-2.70 mmol/L	**3.20(↑)**
Serum phosphate	1.4-2.1 mmol/L	1.48
25 Vitamin D	50-150 nmol/L	62
1,25 Vitamin D	48-190 nmol/L	**255 (↑)**
Parathyroid Hormone	0.8-5.7 pmol/L	**0.4 (↓)**
FGF23	< 54pg/mL	**98 (↑)**

Bisphosphonates

- Synthetic analogues of pyrophosphate, an endogenous regulator of bone metabolism
- Inhibit bone resorption by suppressing osteoclast activity, thus reducing bony turnover and calcium release
- Effective in reducing serum calcium due to excessive bony release, such as immobilisation and malignancy
- A previous case report noted improvement in hypercalciuria in and adult patient with Jansen's Metaphyseal Chondrodysplasia[4]
- Intravenous pamidronate (a nitrogen-containing bisphosphonate) has been established sufficiently safe in young children[2]

Hypothesis

- Intravenous bisphosphonate administration would improve serum and urine calcium concentrations, and potentially halt progression of nephrocalcinosis

Methods

- Our patient received intravenous Pamidronate infusion at months 0, 1, and 5, according to local protocol, in combination with a low calcium diet
  - 0.25mg/kg at 0 months
  - 0.50mg/kg at 1 month
  - 0.50mg/kg at 5 months
- Serial measurements of biochemical markers of urine and serum collected at baseline and with each bisphosphonate infusion

Results

Biochemistry		Baseline	Infusion 1 (0.25mg/kg)	Infusion 2 (0.5 mg/kg)	Infusion 3 (0.5 mg/kg)
Total calcium (albumin corrected)	Reference Range 2.20-2.65 mmol/L	**2.79 (↑)**	**2.93 (↑)**	**3.03 (↑)**	**3.03 (↑)**
Serum phosphate	1.10-2.20 mmol/L	**0.75(↓)**	1.18	**1.05 (↓)**	**1.08 (↓)**
Alkaline phosphatase	120-370 U/L	302	**488 (↑)**	**460 (↑)**	**461 (↑)**
Urinary calcium Creatinine Ratio	<0.6 mol/mol cr	**2.66 (↑)**	**0.96 (↑)**	**3.57 (↑)**	**1.39 (↑)**

There was no appreciable improvement in serum or urine calcium concentrations following pamidronate infusion. In this instance, bisphosphonates were not effective in reducing risk of progression of nephrocalcinosis.

We are now assessing the utility of hydrochlorothiazide in addition to pamidronate for management of hypercalciuria.

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