Neonatal severe hyperparathyroidism - using genetics to determine treatment

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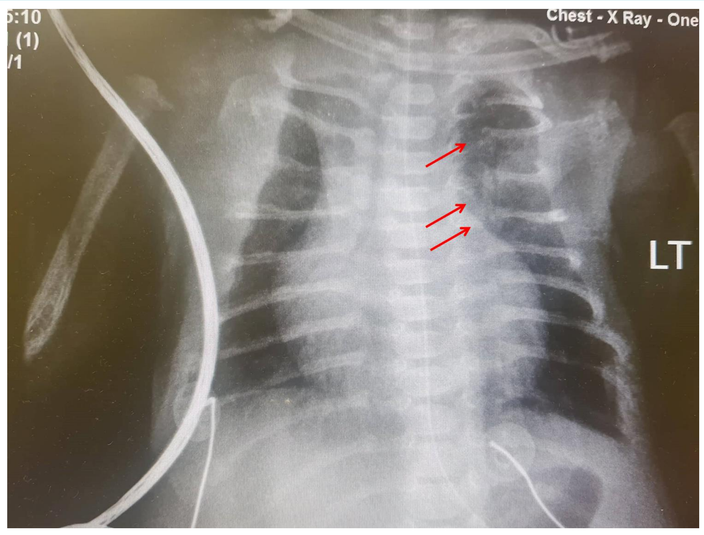
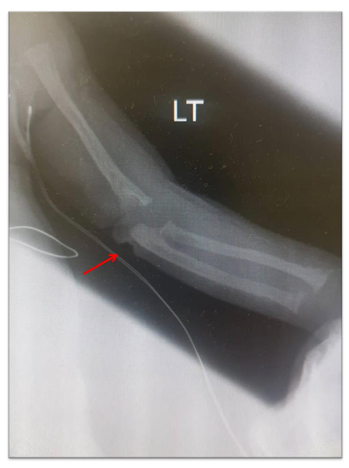
BACKGROUND

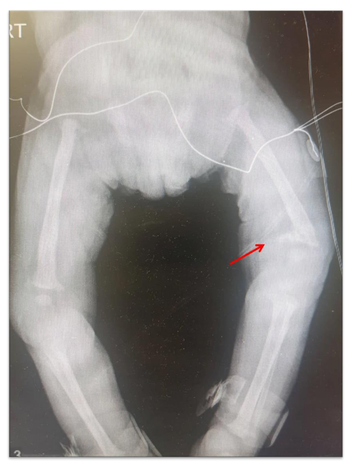
- Disorders of the **calcium sensing receptor** (CaSR) cause hyper- and hypo- calcemia, depending on the location and type of mutation.
- **Familial hypocalciuric hypercalcemia** is a benign disorder in which calcium levels are slightly elevated in the presence of slightly elevated parathyroid hormone (PTH).
- **Neonatal severe hyperparathyroidism** (NSHPT) is a rare life-threatening disorder in which there are high levels of calcium accompanied by high levels of parathyroid hormone.
- Most cases of NSHPT are **autosomal recessive** and caused by homozygous mutations of the CaSR gene.
- **Calcimimetics** such as cinacalcet are drugs that enhance calcium's effect on the CaSR and calcium levels as well as PTH levels are reduced in patients with end stage renal failure with secondary hyperparathyroidism. Cinacalcet has been shown to help regulate calcium levels in some children with NSHPT.
- It has been found that cinacalcet was able to act as an allosteric agonist and a positive allosteric modulator of, in some cases, maximal agonist effect, **depending on the mutation.** [1]
- There is most probably a correlation between the phenotype, the genotype and drug efficacy, but only clinical studies have been published.

OUR CASE

- TERM 3/3 normal pregnancy till polyhydramnios at 37 weeks
- Screening- suspected absent corpus callosum, small LV and aortic arch
- Normal delivery, 39+5, BW 3.2 kg.
- At birth, mild respiratory distress. Needed respiratory support, bell shaped thorax,
- Restrictive respiratory disease







LABORATORY RESULTS DAY 9

- Serum calcium - 11mg/dl (norm 7.6-11)
- **PTH - 1590** pg/ml (norm up to 65).
- Vitamin D 25OH - 8 ng/ml.
- Urinary Ca/Cr - 0.024 .

TREATMENTS

- Serum rose up to 15 mg/dl,
- On day 12 of life she received one dose of pamidronate 0.5mg/kg with a good response.
- On day 22 cinacalcet treatment was started as the calcium became elevated
- We followed calcium rise with an increase in cinacalcet until we reached 7mg/k/d with a stable calcium of 12.5,
- PTH remained extremely elevated - over 1100 pg/ml.
- Due to high calcium levels and no reduction in PTH, she underwent total parathyroidectomy and insertion of half a gland in her leg.

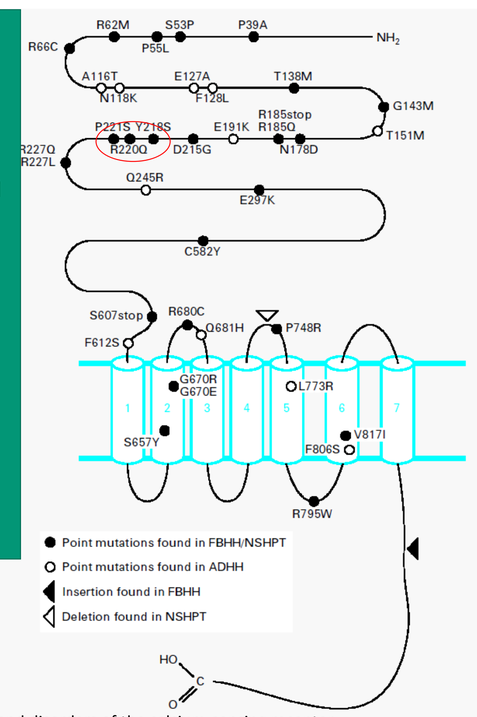
AT THE AGE OF 9 MONTHS

- Alert and happy baby but severely hypotonic
- Has stable levels of PTH at 17 pg/ml
- During a viral illness with respiratory distress, severe hypocalcemia
- Subcutaneous calcium deposits in place of IV line
- Had a bout of hypercalcemia – maybe due to the deposits
- Now weaned of calcium and alpha D3 – slightly hypercalcemic (11 mg/dl)

GENETICS

- Genetic testing is positive for a homozygous *CaSR* mutation (c659G>A, pArg220Glu).
- This mutation has only been described in FHH.
- Her mother has slight hypercalcemia and hyperparathyroidism consistent with FHH but her father's calcium and PTH are normal, and they are non-consanguineous.
- The mother carries the same mutation, described in the literature as an FHH causing mutation.
- The father has no known mutation on the *CaSR*

- It is possible that baby has maternal uniparental isodisomy and has inherited both mutations from the mother.
- There might be a deletion on the paternal allele.
- CMA and maybe MPLA pending



Simon H S Pearce, Calcium homeostasis and disorders of the calcium-sensing receptor
Journal of the Royal College of Physicians of London Vol. 32 No. 1 January/February 1998

CONCLUSION

We describe a rare case of neonatal hyperparathyroidism with a formerly undocumented homozygous mutation. This mutation can shed light on novel modes of inheritance for this rare disease and better understanding of treatment modalities for this disease.

1. Lu et al. Effect of the Calcimimetic R-568 [3-(2-Chlorophenyl)-*N*-((1*R*)-1-(3-methoxyphenyl)ethyl)-1-propanamine] on Correcting Inactivating Mutations in the Human Calcium Sensing Receptor, THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS331:775–786, 2009,

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