Severe Hypocalcaemia in Propionic Acidemia caused by Parathyroid Hormone Resistance and treated with Alfacalcidol.

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What is known?
- Propionic Acidemia (PA), an organic acidemia, is characterized by episodes of decompensation with severe metabolic acidosis and hyperammonamia
- This condition has been associated with low bone mineral density and osteoporosis
- Hypocalcaemia occurs in 35-65% of decompensation events, the underlying pathophysiology of this is unknown
- One previous case report suggests this may be due to PTH resistance

What questions does it raise?
- Why and when does transient PTH resistance occur in PA?
- Does alfacalcidol have a role in prevention of hypocalcaemia and hypercalcuria in intermittent PTH resistance?
- Does intermittent hypocalcaemia due to PTH resistance affect bone health in children with PA?

Case:

Day 3: The initial diagnosis of PA
- Presented with grunting, acidosis, hyperammonamia
- Term, no medical/family history, non-consanguineous parents
- Rapid testing and later genetic confirmation of PA
- Hypocalcaemic at the time of presentation with profile suggestive of PTH resistance
- Serum calcium normalized with IV calcium & oral cholecalciferol

What is the first presentation like?

2.5 months: Second presentation
- Presented with decompensation due to gastroenteritis with acidosis and hyperammonamia
- Hypocalcaemia with profile again suggestive of PTH resistance

Management (of second presentation):
- Calcium normalised after treatment with oral calcium (1.25mmol/kg/day) and cholecalciferol (3000 units/day)
- Alfacalcidol started (30ng/kg/day)

2.5 months: Second presentation
- Presenting with dehydration, severe metabolic acidosis and hyperammonaemia, other metabolic decompensation
- Calcium corrected was 1.32 with a result of 2.19-2.69mmol/L
- Phosphate level was 1.8 with a result of 1.0-1.9mmol/L
- Magnesium level was 0.78 with a result of 0.65-1.05mmol/L
- Alkaline Phosphatase level was 77 with a result of 187-429IU/L
- Parathyroid Hormone level was 115 with a result of 10-65ng/L
- Vitamin D level was 29 with a result of >50nmol/L

Wrist X-ray: no signs of rickets

Day 3: The initial diagnosis of PA

Day 1
- Corrected calcium mmol/L: 1.50
- Calcium ceases
- Feeds restarted
- Alfacalcidol commenced
- Alfacalcidol dose increased
- Day 1: corrected calcium mmol/L: 1.50
- Day 2: corrected calcium mmol/L: 1.50
- Day 3: corrected calcium mmol/L: 1.50
- Day 4: corrected calcium mmol/L: 1.50
- Day 5: corrected calcium mmol/L: 1.75
- Day 6: corrected calcium mmol/L: 2.00
- Day 7: corrected calcium mmol/L: 2.25
- Day 8: corrected calcium mmol/L: 2.50
- Day 9: corrected calcium mmol/L: 2.75

Management (of second presentation):
- Oral calcium/cholecalciferol reduced
- Calcium fell (2.5 to 2.01mmol/L) after cessation of calcium supplements (inadequate calcium in diet)
- Alfacalcidol increased (60ng/kg/d) and calcium normalised

Follow-up at 6 months: remains stable on alfacalcidol, no episodes of hypocalcaemia with decompensations

Discussion and conclusions:
- PTH resistance appears to be the mechanism for hypocalcaemia during episodes of PA decompensation.
- Acute management of PTH resistance includes active vitamin D (calcitriol or alfacalcidol) and adequate calcium intake.
- A retrospective chart review of our unit showed that 4 of 6 children with PA had hypocalcaemic episodes (range 1.19-2.01mmol/L) associated with decompensation. Out of a total of 25 episodes of decompensation with hyperammonaemia, 9 were associated with hypocalcaemia with normal or low ALP. No hypocalcaemia was recorded when patients were well, however routine monitoring was not undertaken. Only in our case was PTH measured and only our case was treated with alfacalcidol.
- We propose that intermittent hypocalcaemia secondary to PTH resistance may contribute to bone demineralisation in PA.
- Further studies assessing the mechanism of this and potential utility of ongoing treatment with alfacalcidol would be valuable in guiding long-term management.