PANCREATITIS IN FAMILIAL HYPOCALCIURIC HYPERCALCEMIA (FHH)

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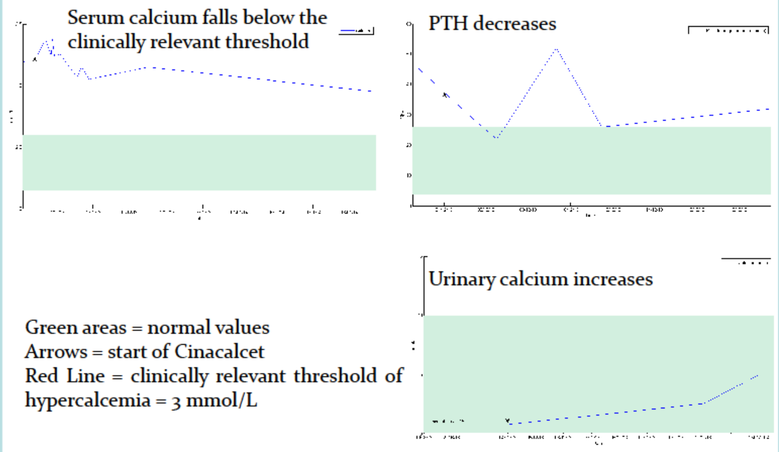
OBJECTIVES

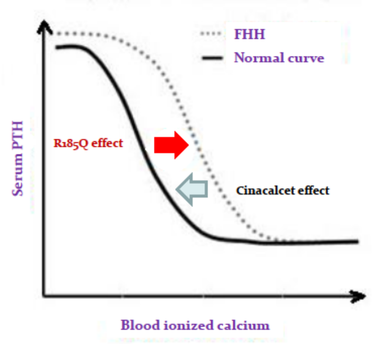
Familial hypocalciuric hypercalcemia (FHH) is a characteristically asymptomatic condition that is caused principally by *calcium sensing receptor* gene (*CASR*) mutations and less frequently by *GNA11* or *AP2S1* mutations. We report a case of recurrent symptomatic pancreatitis in an FHH patient.

GRAPHICS

Evolution of patient's biological parameters



Parathyroid control of calcium



The inactivating R185Q mutation sets the parathyroid "calciostat" at higher levels, which causes an inappropriately elevated parathyroid hormone level for the hypercalcemia.
Cinacalcet decreases blood levels of PTH and calcium by increasing *CaSR* sensitivity. The effect is to slide the PTH / serum calcium curve to the left.

METHODS

- > **presentation**: 17-year-old patient hospitalized with abdominal pain and raised pancreatic enzymes due to acute pancreatitis. This represented his 3rd episode of acute pancreatitis requiring hospitalization in different institutions.
- > **biological results**: very elevated serum calcium level (3.3 mmol/L; NR: 2.15-2.60), moderately elevated PTH (33ng/L; NR: 4-26), normal 25-OH vitamin D (44ng/ml; NR: 30-80), elevated 1,25$(OH)_2$ vitamin D (133pg/ml; NR: 23-109) and undetectable urinary calcium
  - > sole predisposing factor for the pancreatitis: the **severe hypercalcemia**
- > **imaging exams**: absence of renal lithiasis or calcifications elsewhere; parathyroid glands could not be visualized on thyroid ultrasound
- > severe bone mineralization deficit of the cortical bone on **bone osteodensitometry**: Tscore lower 1/3 radius -3, total hip -0.1, lumbar -0.5
- > **family history**: - patient's grandmother was also known to suffer from hypocalciuric hypercalcemia
  - hypercalcemia had been found in the patient's mother, uncle, brother and sister
  - however, none of the other family members with severe hypercalcemia, except for the mother who had chronic pancreatitis, associated pancreatic disease
- > **genetic analysis**: sequencing of *CaSR* and, in order to explain our patient's phenotype, analysis of genes involved in the pathogenesis of idiopathic pancreatitis
- > **treatment**: the calcimimetic cinacalcet was started at 30mg daily, later increased to 30mg twice daily

RESULTS

CASR sequencing revealed the patient (and family members) to be heterozygotic for a R185Q mutation, previously suggested to be a dominant negative mutation, that leads to higher calcium levels than other known *CASR* mutations.

Of the genes predisposing to idiopathic pancreatitis, the heterozygotic N34S mutation of *SPINK1* was found.

Cinacalcet treatment lowered serum calcium to 2.95mmol/l and the patient has not presented new pancreatitis episodes.

CONCLUSIONS

We present the case of a young patient with a severe FHH phenotype caused by an inactivating mutation of the *CaSR* gene with a dominant negative effect. This mutation leads to the most severe level of hypercalcemia reported in the literature in adult patients. When associated with other factors predisposing to pancreatitis, such as mutations of *SPINK1* gene as in our case, recurrent pancreatitis can occur. These episodes can be avoided by the control of hypercalcemia. Although FHH generally does not require therapy, treatment of our patient with the calcimimetic compound Cinacalcet proved beneficial.

References

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