

Iatrogenic nephrocalcinosis and renal failure in two family members with treated hypoparathyroidism due to a calcium-sensing receptor mutation

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Introduction and Background

Hypoparathyroidism, a hormonal insufficiency state, is characterized by hypocalcemia, inappropriately low serum PTH, and hyperphosphatemia. Post-surgical hypoparathyroidism is the most frequent form of hypoparathyroidism. Primary hypoparathyroidism may be caused by developmental defects in the parathyroid glands leading to impaired PTH synthesis or secretion. Autoimmune destruction of the parathyroid gland may also be the underlying cause of the disorder. Hypoparathyroidism due to an activating mutation of the calcium-sensing receptor (CaSR) gene leads to impaired regulation of PTH secretion from the parathyroid gland and impaired reabsorption of calcium in the kidney. Affected patients with this disorder often demonstrate elevated urinary calcium levels even at low or below normal serum calcium levels.

The conventional treatment for hypoparathyroidism is vitamin D and its analogs. Standard therapy includes 1,25 dihydroxyvitamin D (calcitriol), the biologically active form of vitamin D. These sterols lack the distal tubular reabsorption of calcium resulting in an increase in urine calcium excretion and a risk of nephrocalcinosis, nephrolithiasis, and renal insufficiency (1,2). Vitamin D2 and D3 are stored in the adipose tissue and involve a heightened risk of prolonged hypercalcemia and therefore are not usually recommended for routine replacement therapy. The relatively short half-life of biologically active metabolites of vitamin D, calcitriol (1,25 (OH)₂D₃) and 1-hydroxy vitamin D provide the advantage of a rapid achievement of full action and quick reversal of hypercalcemia in case of over dosage (3). Finally, dihydrotachysterol (DHT), an intermediate acting derivative, also represents a possible alternative for long-term therapy. The addition of hydrochlorothiazide to calcitriol may reduce urinary calcium excretion (4).

The first clinical trial with synthetic human parathyroid hormone 1-34 (PTH) demonstrated that PTH treatment could maintain

serum calcium in the normal range without hypercalciuria (5). A subsequent randomized, cross-over trial of once-daily versus twice-daily PTH 1-34 performed in 17 adult subjects (ages 19-64 y) demonstrated that a twice-daily PTH regimen provides more effective treatment of hypoparathyroidism PTH and reduces the variation in serum calcium levels observed with once daily dosing at a lower total daily PTH dose. In particular, in patients with CaSR mutations, twice-daily PTH treatment produced higher mean serum calcium with no significant rise in urine calcium excretion. Thus, treatment with twice-daily PTH is a better regimen for patients with CaR to overcome their tendency to hypercalciuria (6). Recently, a randomized controlled study of three-years duration, comparing PTH treatment with calcitriol and calcium, demonstrated that PTH provides a safe and effective alternative to calcitriol therapy and was able to maintain normal serum calcium levels without hypercalciuria (7).

We describe here two members of a family with autosomal dominant hypoparathyroidism due to a CaSR mutation who were referred to the NIH Clinical Center with severe nephrocalcinosis and renal insufficiency. They entered into a NIH investigational study of PTH treatment of hypoparathyroidism. We portray their response to PTH therapy and the post-study follow-up on calcitriol therapy. Both patients eventually developed end stage renal disease.

Study design

The NICHHD IRB approved the clinical protocols and informed consent was obtained from the patients. Both family members were admitted to the NIH Clinical Center for evaluation and treatment with PTH. They were among 17 adult subjects with hypoparathyroidism studied to compare once daily vs. twice daily parathyroid hormone 1-34 for treatment of hypoparathyroidism. Procedures for the dose study have been previously described (6). For the initial 14-week study arm, the mother received twice daily PTH and her daughter received once daily PTH. The crossover to the opposite arm occurred, after a 14-week period, during the second Clinical Center admission. After completion of the dose protocol, they participated in another study designed to compare conventional treatment (calcitriol and calcium) and twice-daily PTH injections over a three-year period. The mother was randomized to calcitriol for this subsequent study (7) and her daughter remained on twice-daily PTH. They were among 27 subjects studied and details of the treatment protocol and procedures were previously described (7).

Subjects

We studied two family members, a 55-year-old woman and her 27-year-old daughter with hypoparathyroidism due to a CaR mutation. The diagnosis of hypoparathyroidism had been made 16 years prior to their admission to the NIH Clinical Center.

Case 1 (C1):

A 55-year-old Irish woman with a past history of recurrent episodes of tremors, paresthesias and cramping of the extremi-

ties during infancy and early childhood. She did not develop secondary teeth after her primary teeth were lost. From childhood, she required both upper and lower dentures. She achieved five pregnancies and gave birth to three daughters all of whom were affected with hypoparathyroidism. She had two miscarriages after the three children were born. At age 39 years, hypoparathyroidism was diagnosed. She did not have any preexisting cardiac or renal disease at the time of diagnosis. For treatment, she received dihydrotachysterol (DHT) and calcium carbonate. Due to concerns with the cost of the medication, the DHT was switched to ergocalciferol. The vitamin D dose was adjusted to maintain serum calcium level in the mid normal range and urine calcium level was not monitored. She had a significant tobacco history during a thirty year period from ages 17 to 50 y. She drank approximately four cups of coffee daily through most of her adult life. She had degenerative joint disease requiring bilateral hip replacement surgeries, each hip done at different times (age 42 and 52 y). At age 48, a hysterectomy and oophorectomy were performed for treatment of menorrhagia. Estradiol replacement (Premarin) was started post-operatively. She was referred to the NIH in 1994 for investigational treatment with PTH. At the initial NIH presentation, her physical exam was unremarkable except for the presence of upper and lower dentures. Height was 164 cm, weight was 66.8 kg and blood pressure was 123/84.

Studies at the NIH demonstrated a heterozygous missense mutation involving the extracellular region of the calcium receptor in C1 and her three daughters (8). At study entry, she was receiving calcitriol and calcium supplementation. Nephrocalcinosis was noted on computerized tomography (CT) scan (Figure 1). Serum calcium levels were in the mid normal range, PTH was undetectable and urine calcium excretion was 9.7 mmol/24h. Creatinine clearance was 29.0 mL/min and Blood Urea Nitrogen (BUN) and creatinine levels were 30 and 2.5, respectively. Six months later, at the completion of the dose study, the creatinine clearance was 27.5 mL/min, serum BUN and creatinine were 26 and 1.9, respectively. At the end of the 3.5-year period creatinine clearance was 22 mL/min. Serum BUN and creatinine were 10.5 and 2.3, respectively. 25-hydroxyD levels were normal throughout the study. For three years, the blood pressure levels were mildly elevated with diastolic levels in the mid 80s. She developed hypertension at the end of the study period with a blood pressure of 147/95.

PTH was titrated to maintain normal levels of urine calcium and to avoid or alleviate symptoms of hypocalcemia (Figure 2). This was achieved with PTH at a dose of 20 mcg/d (0.4 mcg/kg/d) (divided twice daily) during the twice-daily arm and 40 mcg/d (0.6 mcg/kg/d) during the once daily arm. Twice daily PTH enabled the administration of lower doses. She entered into the long-term comparison of PTH vs. calcitriol and was randomized to the calcitriol and calcium arm. During the 3-year study, she received 0.5 mcg/day (divided twice daily) of calcitriol, 1-2 gms/d (divided qid) calcium carbonate. Dietary calcium was maintained at 1-2 grams daily. She complained of mild occasional numbness of the hands and feet. These symptoms did not interfere with her daily activities.

Upon completion of the study, her local physicians resumed follow-up and management of her hypoparathyroidism. Her kidney function diminished during the subsequent three-year period and she was placed on peritoneal dialysis at age 62 y, when her BUN and creatinine were noted to be 117 and 9.9, respectively, and creatinine clearance was 8 mL/min. Two years later she underwent a cadaveric kidney transplant. Two months later, she died of complications of acute transplant rejection and an ensuing infection.

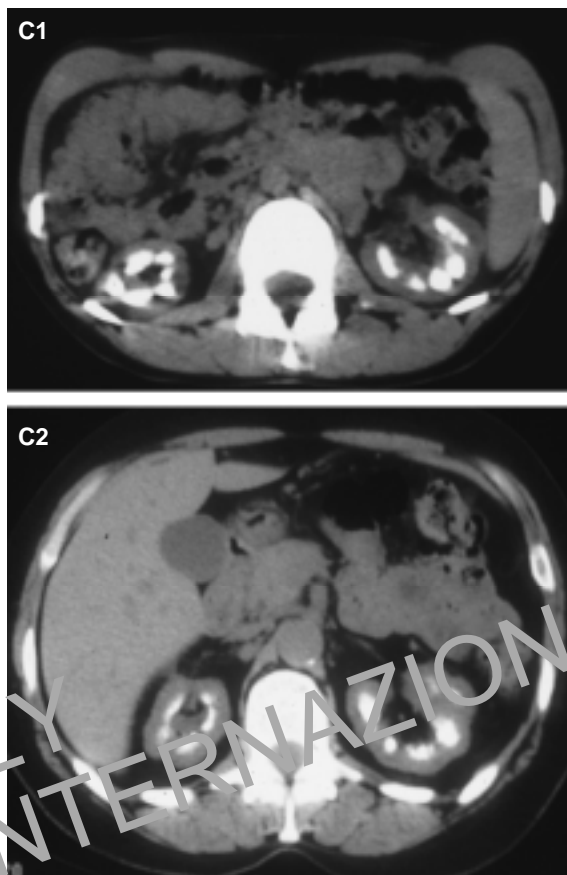


Figure 1 - CT images from both patients were obtained when PTH therapy was initiated and demonstrated large calcifications present within the medulla of both kidneys.

Case 2 (C2): 27-year-old, daughter of C1, with a history of recurrent episodes of tremors, cramping of the extremities, and seizures during infancy and early childhood. At age 9 years, poor school performance and a history of convulsions led to an extensive neurological evaluation, which revealed intracranial calcifications, hypocalcemia and hyperphosphatemia. These findings ultimately led to the simultaneous diagnosis of hypoparathyroidism in the child, her mother (age 39 y) and two sisters. There was no preexisting cardiac or renal disease at the time of diagnosis. For treatment, she was placed on dihydrotachysterol (DHT) and calcium carbonate. Due to concerns with the cost of the medication, the DHT was switched to ergocalciferol. The serum calcium level was maintained mostly in the mid normal range. The girl, however, required several hospitalizations during her childhood for hypercalcemia and dehydration. Over several years, she complained of recurrent cramping of her extremities, nausea, and fatigue. She remained on this treatment regimen until age 24, when her doctors considered vitamin D2 ineffective and calcitriol therapy was initiated. At 25 years old, she was diagnosed with renal insufficiency and a renal ultrasound demonstrated severe nephrocalcinosis. The family was referred to the NIH in 1994 for investigational treatment with PTH. The initial evaluation revealed a normal physical exam. Height was 158 cm, weight was 46.3 kg, and blood pressure was 108/69. At study entry, she was receiving calcitriol and calcium supple-

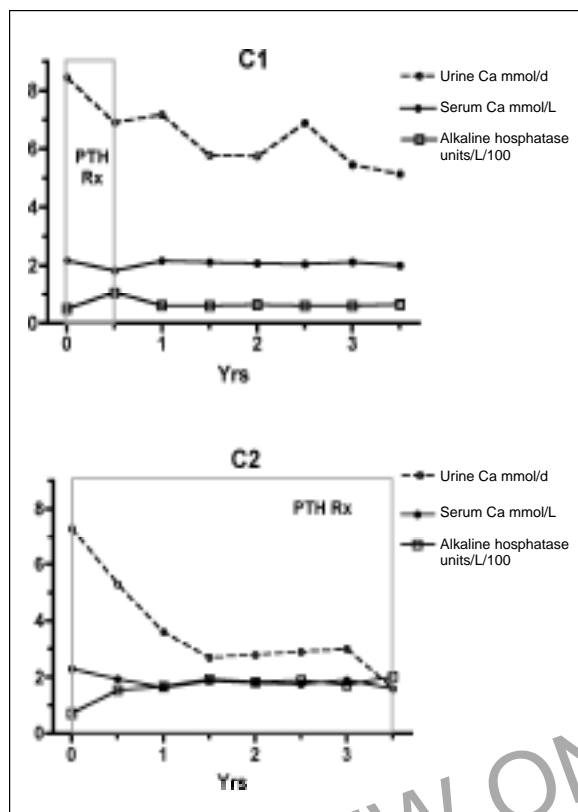


Figure 2 - A 3.5 year profile of alkaline phosphatase, serum and 24h urine calcium in two family members with hypoparathyroidism due to CaSR mutation. Both patients were receiving PTH during the initial 0.5 y period. The mother (C1) was treated with calcitriol and calcium and daughter (C2) received twice daily PTH during the 0.5-3.5 y timepoints.

mentation. CT of the kidney confirmed extensive nephrocalcinosis (Fig. 1). Serum calcium level was 2.2, serum PTH was undetectable, and urine calcium excretion was 7.6 mmol/24h. Creatinine clearance was 17.3 mL/min and serum BUN and creatinine levels were 42 and 3.7, respectively. Six months later, at the completion of the dose study, the creatinine clearance was 17.6 mL/min. BUN and creatinine were 40 and 3.5, respectively. At the end of the 3.5-year period on PTH therapy, creatinine clearance was 14.3 mL/min and BUN and creatinine were 31.5 and 3.2, respectively. The 25-hydroxy D levels were normal throughout the study. Serum calcium was maintained below the normal range throughout the study to avoid elevations in urine calcium and further kidney damage and to avoid further rise in markers of bone turnover (Figure 2). This was achieved with PTH at a dose of 40 mcg/d (0.9 mcg/kg/d) divided into two doses during the twice daily arm and 154 mcg/d (3.3 mcg/kg/d) during the once daily arm. Twice daily PTH enabled the administration of one quarter of the total daily dose given during the once-daily study arm. She entered into the long-term study to PTH vs. calcitriol as a compassionate exception as her renal function was too low to meet the inclusion criteria. Over the 3-year study period, she received a mean total daily PTH dose of 70 mcg/day (divided twice daily). Upon completion of the study, she was discharged from the NIH on conventional therapy, calcitriol and calcium to be followed by local physicians. Two years later, her creatinine clearance was 8 mL/min and she underwent a cadaveric kidney transplant.

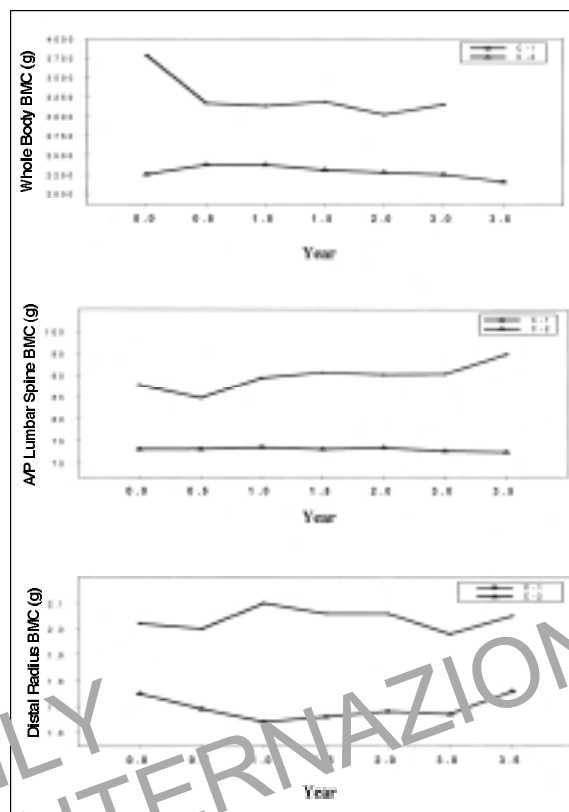


Figure 3 - Bone mineral content (BMC) measured every 6 months over a 3.5 year period in two family members with hypoparathyroidism due to CaSR mutation. Both patients were receiving PTH during the initial 0.5 y period. The mother (C1) was treated with calcitriol and calcium and daughter (C2) received twice daily PTH during the 0.5-3.5 y timepoints.

Most recently, she has been maintained on calcitriol, hydrochlorothiazide, calcium and potassium chloride supplements.

Markers of bone remodeling and bone mineral density (Figures 2 and 3):

PTH treatment leads to a rise in markers of bone remodeling (5-7). Alkaline phosphatase levels doubled in both women in response to the initiation of PTH. When entered into the long-term study and placed on conventional therapy, the alkaline phosphatase level of C1 returned to baseline within six months of calcitriol therapy and remained in the mid-normal range for the remainder of the three-year study. By contrast, C2 continued PTH therapy and the alkaline phosphatase level continued to gradually increase with no sign of returning to normal. Interestingly, C1, who had an elevated basal bone mineral density (BMD) (T and Z scores were 4 SD above the mean), demonstrated a loss in whole body bone mineral content (BMC) during the 6 months on PTH. There is no appreciable BMC change during remainder of the study period on calcitriol therapy. C2, whose basal BMD was also elevated (Z and T scores were 2 SD above the mean) has no evidence of a BMC change during the 3.5-year period on PTH therapy.

Adverse effects and benefits of PTH:

C2 was more symptomatic than C1 who had few or no symptoms to report in connection with her hypoparathyroidism. C2

complained of worsening leg cramps starting from the beginning of the long-term protocol to the end of the study. This was concluded to be bone pain rather than the typical neuromuscular cramping associated with hypocalcemia.

Discussion

We describe here two family members who developed end stage renal disease (ESRD) requiring dialysis and transplantation due to an adverse long-term effect of vitamin D treatment of their hypoparathyroidism. This case report has demonstrated the difficulties of treating hypoparathyroidism due to a CaSR mutation. This represents the first case report of iatrogenic renal failure due to treatment of hypoparathyroidism with vitamin D and calcium supplementation. The normalization of serum calcium had been achieved at the expense of excess urine calcium excretion, which eventually led to calcium deposits and renal tubular damage. The untimely death of the mother (C1) due to complications of renal failure is especially alarming. An increased awareness of the features of this rare disease and a greater understanding of proper treatment approach should avoid this adverse outcome in others with this disorder.

C1 was relatively mildly affected and presented with ongoing symptoms of hypocalcemia for nearly four decades before medical intervention. She required relatively less oral administration of calcitriol or subcutaneous PTH to alleviate symptoms of hypocalcemia. Her dose of PTH was half that of her daughter. C2, on the other hand, was considered more severely affected with a history of recurrent seizures and neuromuscular irritability requiring more medical intervention and attention. The adverse outcome of ESRD in both women might have been avoided with greater attention to urine calcium excretion levels throughout their medical treatment. Both patients experienced a rapid decline in renal function on conventional therapy. Ultimately, C1 had a more rapid decline in renal function compared to her daughter, C2, despite the greater severity of the daughter's disease. Three and a half years of PTH therapy may have provided the benefit of stabilizing and decelerating the decline in renal function in C2.

For hypoparathyroid patients with CaR defects, PTH therapy provides an excellent alternative to calcitriol as the renal calcium retaining effect aid in maintaining the urine calcium excretion in the normal range. In C2, however, the persistent elevation in markers of bone turnover over a three-year period and lower leg cramps consistent with bone pain made this treatment option less feasible, although there was no overall change in the bone mineral density.

The aim of therapy in this rare form of hypoparathyroidism should be to maintain the serum calcium at or just below the lower limit

of the normal concentration range (7-8.5 mg/dL), so that hypocalcemic manifestations are limited to the mildest symptoms and harmful hypercalcemia and hypercalciuria are avoided. Urine calcium excretion should be monitored frequently, especially in patients with evidence of nephrocalcinosis. If therapy is successful, symptoms associated with hypoparathyroidism should not disturb the patient's daily life and long-term complications can be avoided.

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