Familial Hypocalciuric Hypercalcemia

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The discovery and cloning of the calcium-sensing receptor (CaSR) has facilitated the understanding of calcium homeostasis and the pathophysiology of disorders associated with abnormal CaSR activity including familial hypocalciuric hypercalcemia, neonatal severe hyperparathyroidism, and secondary hyperparathyroidism. The CaSR, a member of superfamily of G-protein-coupled receptors, has a large extracellular domain and seven membrane-spanning segments (1). This receptor is localized on the surface of various tissues, including parathyroid cells, calcitonin-secreting C-cells of the thyroid, and various sites along the nephron.

In the condition of hypocalcemia, increased parathyroid hormone (PTH) secretion mediated by CaSR stimulates the translocation of calcium into the extracellular fluid through a direct action of PTH on kidney and an indirect effect on intestine via 1,25-dihydroxyvitamin D₃ [1,25-(OH)₂D₃] synthesis in the renal proximal tubular cells. Conversely, the activation of CaSR by hypercalcemia induces the suppression of PTH secretion and calcium reabsorption via the renal tubular cells, thereby restoring the normal serum calcium concentration.

Familial hypocalciuric hypercalcemia is an inherited disorder consistent with autosomal dominant transmission, resulting from inactivating mutations of CaSR of the heterozygous states (2). The reduced activity of CaSR on renal tubular cells and the parathyroid gland causes enhanced renal tubular reabsorption of calcium and insufficient suppression of serum PTH concentration, both of which induce a rise in the serum calcium concentration. Biochemical findings for familial hypocalciuric hypercalcemia are characterized by mild to moderate hypercalcemia, mild hypermagnesemia, normal or mildly decreased serum phosphate concentration, and relatively low urinary calcium excretion (3). Serum concentrations of PTH and 1,25-(OH)₂D₃ are paradoxically normal (3).

The differentiation between familial hypocalciuric hypercalcemia and primary hyperparathyroidism is of great importance because of the distinct pattern of bone mineral density and the clinical strategy for management. The differential diagnosis of these two diseases was well reviewed by Law and Heath (3). Although serum calcium concentrations in patients with familial hypocalciuric hypercalcemia are similar to those in patients with primary hyperparathyroidism, the urinary calcium excretion is lower in familial hypocalciuric hypercalcemia than in primary hyperparathyroidism (4). The ratio of calcium clearance to creatinine clearance is generally less than 0.01 in familial hypocalciuric hypercalcemia, whereas it is above 0.02 in primary hyperparathyroidism. In addition, a normal or slightly increased serum magnesium concentration is noted in familial hypocalciuric hypercalcemia but not in primary hyperparathyroidism. A positive correlation exists between the serum concentrations of calcium and magnesium in familial hypocalciuric hypercalcemia, but an inverse correlation exists between these two parameters in primary hyperparathyroidism (5). The urinary concentrating ability is not disturbed in familial hypocalciuric hypercalcemia even in the presence of hypercalcemia, but its ability is disturbed in primary hyperparathyroidism (6).

In the report of Hanibuchi et al, in this Journal (7), a 60-year-old man with hypercalcemia was diagnosed as having familial hypocalciuric hypercalcemia.

Characteristic laboratory findings observed in this patient were a marked hypercalcemia as high as 15.2 mg/dl with abnormally high serum concentrations of PTH and 1,25-(OH)₂D₃, which are infrequently observed in familial hypocalciuric hypercalcemia. A serum 1,25-(OH)₂D₃ concentration of over 42 pg/ml is considered to be abnormally high when hypercalcemia is present (8). We have recently reported that hypercalcemia in primary hyperparathyroidism may be attributed to increased renal tubular reabsorption of calcium by hypersecreted PTH (9), which would be counteracted by the activation of CaSR (10). In addition, the serum concentrations of calcium and PTH in familial hypocalciuric hypercalcemia are suggested to be determined by residual function of mutant CaSR (11). Thus, if the CaSR activity is extremely reduced, the marked hypercalcemia associated with elevated serum PTH concentration, as reported in this case, may develop in familial hypocalciuric hypercalcemia.

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References


