A Case of Hypocalciuric Hypercalcemia Accompanying Cystic Fibrosis

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Introduction: Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant disorder which occurs by an inactivating gene mutation in the calcium (Ca)-sensing receptor gene (*CaSR*). Prevalence is estimated at 1: 78000. Ca regulates parathormone (PTH) secretion via CaSR on parathyroid cells. Low levels of Ca increases PTH secretion. CaSR mutation that causes loss of function, leads to total or partial insensitivity of parathyroid cells to Ca's inhibitory effect. For this reason, in order to suppress Ca's PTH secretory effect, the setpoint is raised. A higher blood Ca level is needed to suppress the PTH secretion. In addition to that, kidney's distal tubules increase Ca reabsorption by abnormal Ca-detecting function.

A 3-month-old male patient applied with vomiting and malaise. Weight was 6.3 kg (50^{th} p), height 62.5 cm (75^{th} p), head circumference 41.5 cm (50^{th} -75^{th} p), pulse 120/min, and blood pressure was 75/45 mmHg. There was no specific detail in the patient's history and family history. In his physical examination, general state was moderate-bad, conscious was open, turgor tone was normal, and he had mildly sunken eye bowls. Lab results were as follows: sodium 116 mEq/L, Cl 62 mEq/L, K 4.1 mEq/L, urea 104 mg/dL, creatinine 1.05 mg/dL, Ca 11.9 mg/dL, phosphorus 6.4 mg/dL, alkaline phosphatase 304 IU/L, and blood gases showed metabolic alkalosis. We learned from the patient's mother that when kissing her son she tasted salt, so a sweat test was performed (114 nmol/L). 1677 delta mutation was heterozygote positive in cystic fibrosis gene analysis. Ca level reached 13.8 mg/dL after hydration and oral feeding. Blood and urine tests were done in order to find the etiology of hypercalcemia (PTH: 65.5 pg/mL, 25-hydroxy vitamin D: 43.5 ng/mL, urine Ca/Cr ratio 0.19, urine Ca clearance 0.004). In the *CaSR* gene mutation study, A986S and R990G polymorphisms were heterozygous. 1 month after hydration and clinical state being back to normal, Ca levels were in normal range. In stressful situations, he experienced hypernatremia and hypercalcemia together.

Discussion: Polymorphisms may change protein function and capacity of one to repair its damaged DNA. Genetic polymorphisms help us to define personal sensitivities to some diseases. The most common CaSR polymorphisms are A986S, R990G, Q1011E and A826T. Our patient had A986S and R990G mutations. Heterozygous *CaSR* gene mutations generally cause mild disorders in clinic. Homozygous mutations cause severe hypercalcemia at birth. Serum PTH level is either inappropriately normal or above normal when compared to the hypercalcemia level. Urine Ca is inappropriately low. In heterozygous mutations of CaSR polymorphisms, environmental or other genetic risk factors may cause bone mineral disorders and an increase in levels of blood ionized Ca and total Ca. In studies, ionized and total Ca levels were reported statistically high in people with A986S and R990G heterozygous polymorphism compared to healthy people.

Result: We found this case important to be presented since the association between *CaSR* gene polymorphism and cystic fibrosis has not been previously reported in the literature and also we wanted to emphasize that *CaSR* gene polymorphism may cause hypercalcemia in stress situations.

Key words: Cystic fibrosis, hypocalciuric hypercalcemia, *CaSR*, polymorphism