Calcium sensing receptor (CaSR) is located in the parathyroid glands and kidneys, encoded by the CaSR gene. CaSR regulates serum calcium concentrations. For instance; increases in Ca²⁺ act via the CaSR to inhibit secretion of parathyroid (PTH) hormone and to decrease renal tubular calcium reabsorption. Each response helps promote normalization of Ca²⁺ serum levels. Homozygous or compound-heterozygous inactivating CaSR gene mutations (loss of function CaSR) result in neonatal severe primary hyperparathyroidism (NSHPT). Individuals with NSHPT frequently show life-threatening hypercalcaemia. Familial hypocalciuric hypercalcaemia (FHH) is, caused by heterozygous inactivating mutations of the CaSR gene, generally asymptomatic or mild to moderate lifelong hypercalcaemia, relative hypocalciuria, and normal intact to moderate elevated PTH, and rarely cause pancreatitis. In this study, it is aimed to present two sibling cases due to CaSR mutation with interesting features.

CASE 1

12 year 3-month-old female

The patient was followed up in the pediatric gastroenterology department for 3 episodes of recurrent acute pancreatitis

No identified etiological cause was found

Physical examination

Weight: 47.06 kg (0.21 SDS)
Length: 156.6 cm (0.53 SDS)
Tanner stage 5 puberty
Rest of examination: normal

Medical history

Normal pregnancy with regular follow-up prenatally

39 weeks of gestation, NSVD, 3150 g

Non-consanguineous parents

No other similar diseases in the family

Laboratory tests

Ca²⁺ (mg/dL) 12.25 (10.5-11.5)
Phosphorus (mg/dL) 3.45 (2.6-3.8)
Alkaline phosphatase (U/L) 271.5 (40-140)
Calcium (mg/dL) 12.25 (10.5-11.5)

The biochemical data show hypercalcaemia accompanied by non-suppressed parathyroid hormone as well as normocalciuria (or relative hypercalciuria)

The concentrations of Ca, PO₄, PTH, ALP and Uric acid ratio in her mother and father were within the normal range

Cystic fibrosis transmembrane conductance regulator (CFTR): No mutations identified
Serine protease inhibitor Kazal type I (SPINK1): No mutations identified

CASE 2

66 day-old female (sister of Case 1)

Consulted for low serum phosphorus

25 weeks of gestation, C/S, 780 g

Being monitored in the neonatal intensive care unit

Low serum phosphorus in repeated measurements

Osteopenia of prematurity

Oral phosphate solution commenced (40 mg/kg/day)

She did not discontinue this treatment after 3 months

Clinical picture of FHH manifested and cinacalcet treatment was started (0.5 mg/kg/day)

Almost 1 year passed, there is no history of pancreatitis

There was no FHH manifestations

Genetic analysis performed given sister’s known molecular finding, the same mutation was identified in the CaSR gene

DISCUSSION

Genetic variants that affect trypsinogen activation in pancreatic acinar cells and ducts. At least one-third of recurrent acute and chronic pancreatitis results from complex genetic mechanisms. Serine protease 1 (PRSS1) and CFTR genes variants that increase the risk of recurrent trypsin activation. SPINK1 protects the pancreas against premature trypsinogen activation and inhibits up to 20% of intra pancreatic trypsin. It has been suggested that loss of function CaSR variants associated with SPINK1 or CFTR may affect pancreatic duct cell function whereas gain of function CaSR mutations affect acinar cell function and are associated with alcoholic pancreatitis. Case 1 has a heterogeneous inactivating mutation of the CaSR, but case 1 has no mutations in SPINK1 and CFTR genes. She has not had a further episode of pancreatitis for more than 3 years under cinacalcet treatment. Case 2 had osteopenia of prematurity in the neonatal period, but there are no FHH manifestations in this period. FHH manifestations of Case 2 presented at 6 months. However, early diagnosis in the neonatal period was made due to the older sibling, FHH manifestations, contrary to the reported cases, developed after 6 months. In conclusion, although FHH is usually asymptomatic, hypercalcaemia requiring treatment may present in the early infantile period. It may exhibit different phenotypic features such as the development of recurrent pancreatitis. In the case of pancreatitis, it may require investigating possible mutations in genes that regulate other calcium-sensing mechanisms. As in our case diagnosed in the neonatal period, due to the fact that FHH has an autosomal dominant inheritance pattern, sibling cases can be diagnosed with FHH before the clinical picture emerges.