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

Two sibling cases with heterozygous calcium sensing receptor (CaSR) gene mutation

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INTRODUCTION

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 Ca^{2}+ act via the CaSR to inhibit secretion of parathyroid (PTH) hormone and to decrease renal tubular calcium reabsorption. Each response helps promote normalization of Ca^{2}+ 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 hypercalcemia. Familial hypocalciuric hypercalcemia (FHH) is, caused by heterozygous inactivating mutations of the *CaSR* gene, generally asymptomatic or mild to moderate lifelong hypercalcemia, 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 consulted for hypercalcemia
She was followed up in the pediatric gastroenterology department for 3 episodes of recurrent acute pancreatitis
No identified etiological cause was found

Physical examination

Weight: 47.05 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 gr
Non-consanguineous parents
No other similiar diseases in the family

Laboratory tests

	At first visit	Repeated laboratory measurements ranges within the 6 mo	Reference values
Age (years)	12.25	12.25-12.75	
Blood tests			
Calcium mmol/L (mg/dL)	2.84 (11.4)	2.64-2.99 (10.6-12)	2.12-2.62 (8.5-10.5)
Parathyroid hormone (ng/L)	75.5	75.5-113.9	11-67
Phosphorus (mmol/L) (mg/dL)	0.94 (2.9)	0.87-1.45 (2.7-4.5)	1.19-1.39 (3.7-4.3)
25-hydroxyvitamin D (ng/mL)	21.9	24	(>20)
1.25$(OH)_2D_3$ (pg/ml)	76.12	67.9	31.5-88.2
Alkaline phosphatase IU/L)	252	152	104-55
Urinary calcium excretion (Ca/Crea mg/mg)	0.15	0.02-0.21	(0.01-0.24) (5^{th}-95^{th} percentile)

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

The concentrations of Ca, PO4, PTH, ALP and Uca/cr ratio in her mother and father where within the normal range

Cystic fibrosis transmembrane conductance regulator (*CFTR*): No mutations identified
Serine protease inhibitor Kazal type I (*SPINK1*): No mutations identified
CaSR gene: c.1583T>A (p.Ile528Asn) (heterozygous inactivating mutation) (Likely Pathogenic)

↓

20 mg/m^2/day (2x15 mg) cinacalcet was initiated due to recurrent pancreatitis

CASE 2

66 day-old female (sister of Case 1)
Consulted for low serum phosphorus

Medical history

25 weeks of gestation, C/S, 780 gr
Being monitored in the neonatal intensive care unit
Low serum phosphorus in repeated measurements

Laboratory tests

	At first visit	Repeated laboratory measurement	Reference values
Age (months)	66 days	6 months	
Blood tests			
Calcium mmol/L (mg/dL)	2.47 (9.9)	3.04 (12.2)	2.12-2.62 (8.5-10.5)
Parathyroid hormone (ng/L)	1.2	143.2	11-67
Phosphorus (mmol/L) (mg/dL)	0.48 (1.48)	1.49 4.6	1.19-1.39 (3.7-4.3)
25-hydroxyvitamin D (ng/mL)	35	32	(>20)
Alkaline phosphatase (IU/L)	1044	177	60-321
Urinary calcium excretion (Ca/Crea mg/mg)	-	0.05	(0.03-0.81) (5^{th}-95^{th} percentile)

↓

Osteopenia of prematurity

↓

Oral phosphate solution commenced (40 mg/kg/day)
She did not discontinue this treatment after using 3 months

↓

There was no FHH manifestations
Genetic analysis performed given sister´s known molecular finding, the same mutation was identified in the *CaSR* gene

↓

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

DİSCUSSİON

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 heterozygous inactivating mutation of the *CaSR, b*ut 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, hypercalcemia 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 trypsin release. 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.