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Short Review

An Overview of Familial Hypocalciuric Hypercalcemia

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Abstract

Familial hypocalciuric hypercalcemia (FHH) is one of the rare reasons for hypercalcemia. FHH is an autosomal dominant disease that is inheritable. The most common calcium sensitive receptors (CaSR) develop because of the inactivation of. In addition, they also develop due to the function loss of AP2S1 and GNA11. The FHH sickness is characterized by hypercalcemia, hypocalciuria, the regular or increased level of the parathyroid hormone, and normal renal function. The symptoms of hypercalcemia are usually not observed. It is often diagnosed by calculating the calcium/creatine clearance ratio of a 24-hour urine sample, and then genetically looking at it. FHH is usually a benign disorder, and when symptomatic and rarely complications develop, calcimimetics are used or parathyroidectomy can be performed. In conclusion, FHH is a benign and genetically transmitted, moderate cause of hypercalcemia. It is rare and usually asymptomatic.

More Information

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Introduction

Calcium is an important element that plays an important role in skeletal mineralization. Additionally, ionized calcium plays an important role in muscle contraction. Calcium also plays an important role in cellular metabolic functions such as muscle and nerve contraction, enzyme activation, blood clotting, and cell growth. Calcium in serum is found in protein-bound, ionized (free), and complex forms. 40% of serum calcium is bound to protein. Approximately 50% of calcium exists in free or ionized form. Serum calcium level is kept within narrow limits by the interaction of the intestine, bone, and kidney. Calcium is regulated by the parathyroid hormone, vitamin D, and calcitonin. Serum PTH is the hormone central to calcium homeostasis. The daily calcium requirement is approximately 1000mg. Under normal conditions, approximately 25% of dietary calcium is absorbed from the intestines. In chronic kidney patients, calcium absorption from the intestines decreases as calcitriol production decreases. Both PTH and calcitriol increase distal tubular calcium reabsorption [1,2].

Hypercalcemia is common in adults. Hypercalcemia is caused by excessive release of calcium from the bones or, less commonly excessive calcium absorption from the gastrointestinal tract. Decreased renal calcium excretion rarely causes hypercalcemia. It is defined as serum total calcium amount over 10.5 milligram/dl or ionized calcium level over 2.7 mEq/L. Serum calcium biochemical measurement gives incorrect results because bound and unbound fractions of calcium are measured. Therefore corrected calcium is measured. The etiology leading to hypercalcemia is important. If the underlying etiology is not detected and treated, it can lead to serious morbidity and mortality. Hypercalcemia affects many organs in the body, including the kidneys, heart, brain, peripheral nerves, and intestine. The etiology of hypercalcemia begins on the basis of history and physical examination findings. Serum phosphate, parathyroid hormone, alkaline phosphatase, serum chloride, serum bicarbonate, urine calcium, and thyroid functions should be measured. Renal functions need to be evaluated. In rare cases, measurement of vitamin D and its metabolites and measurement of parathyroid hormone-related peptide may be necessary. Symptoms of hypercalcemia include anorexia, nausea, vomiting, weight loss, constipation, abdominal pain, and pancreatitis. Hypercalcemia leads to nephrolithiasis, nephrogenic diabetes insipidus, dehydration, and nephrocalcinosis. Among neuromuscular symptoms, impaired concentration and memory, confusion, stupor, coma, lethargy and fatigue, muscle weakness, and corneal calcification may develop. In hypercalcemia, electrocardiography most often causes a shortening of the QT interval. Hypercalcemia, bradycardia, and first-degree AV block may occur. It may also cause slight prolongation of the PR and QRS intervals and flattening of the T wave, as well as ST elevation mimicking acute myocardial infarction. It causes hypercalcemia, hypertension, arrhythmias, itching, conjunctivitis, acute kidney damage (volume loss due to dehydration, calcium phosphate accumulation), arthritis, osteoporosis osteitis fibrosa cystica [3,4].

Familial hypocalciuric hypercalcemia (FHH) is also known as Marx's syndrome. It was initially defined by Jackson and Boonstra in 1966 [5]. FHH is a rarely seen sickness that affects the autosomal dominant. FHH is usually a benign situation for patients who have the heterozygous mutation. Homozygous mutations may cause marked hyperparathyroidism, fractures, failure to thrive, and severe hypercalcemia. Three types of FHH have been identified. Type 1 FHH is caused by loss-of-function mutations in the calcium-sensing receptor (CaSR) gene on the long arm of chromosome 3. It is the most common type (%60). More rarely, chromosome 19 AP2S1 (FHH or GNA11 inactivating mutation, both genes encoding for proteins involved downstream of CASR activation. AP2S1's function loss mutations are known to be FHH type 2, and what is known to code the Gfa11 protein, GNA11 is seen as FHH type 3 [6-10]. It is suggested that the FHH prevalence is between 1: 10 000 and 1: 100 000 [11]. In the west of Scotland, the estimated prevalence was reported as 1: 78 000 [12].

CaSR is a receptor tied to the plasma membrane G protein. This receptor is in thyroid C cells, the intestine, bones, parathyroid glands, and the apical membrane of the nephron. Its function in the nephron is complex, it is found in proximal curved tubules, descending thick arms of the Henle handle, distal crimp tubules, and collector tubules [13]. The CaSR inhibits the synthesis and secretion of parathyroid hormones and controls the proliferation of parathyroid cells. In the parathyroid gland, the activation of CaSR pressures the secretion of PTH, warns the calcitonin secretion and increases the advance of kidney calcium. CaSR detects the small changes that occur in serum-ionized calcium concentrations. The function loss mutations in the CaSR gene, which is in the parathyroid gland, increase the detection point of calcium. It makes parathyroid glands less sensitive to calcium and to decrease the release of PTH, a higher level of calcium serum is needed than normal. This defect in the kidney leads to the increase of tubular calcium and magnesium reabsorption resulting in hypercalcemia, hypocalciuric, and high serum magnesium focus. The release of urine calcium in the FHH decreases, and Ca++ and ionized magnesium (Mg++) increase renal tubular reabsorption. A sectional study published in 2008 reported that the increased PTH prevalence level of FHH patients was 23% [14-16]. With individuals, homozygote develops in mutation for the CaRS inactivation. However, with mice, the result of the CaSR inactivation by homozygote mutation that was developed by patients who have hypercalcemia, high PTH, and parathyroid hyperplasia could develop. The serum magnesium level often increased high-normal or mildly. The serum PTH usually increased either normally or 15-20% high detected serum phosphate normal or mildly [17].

Various amount of diseases develop due to the activation or inactivation of CaSR. As a result of CaSR activation, autosomal dominant hypocalcemia, Acquired via anti-CaSR stimulating antibodies, Hypercalciuric hypocalcemia syndrome type 1, idiopathic hypercalciuria, idiopathic epilepsy, bartter syndrome type 4, Sporadic hypoparathyroidism, Autoimmune hypocalciuric hypercalcemia, Acquired autoimmune hypoparathyroidism and CaSR inactivation result; FHH, Neonatal severe hyperparathyroidism, familial isoleal hyperparathyroidism, Acquired via anti-CaSR blocking antibodies, tropical chronic pancreatitis [18,19].

FHH patients are usually asymptomatic, or due to their mild nature, they may include a few symptoms related to hypercalcemia. The common symptoms are fatigue, malaise, constipation, polyuria, polydipsia, kidney failure, or headaches. Other symptoms include chondrocalcinosis or mental problems. Sometimes patients have pancreatitis. An abnormally functioning CaSR may cause an intraductal calcification or increase the risk of pancreatitis. There is no increase in the fracture incidence. In most situations, FHH patients are asymptomatic or they may have mild symptoms such as vertigo, restlessness, muscle pain, or poor memory [14,15].

An asymptomatic hypercalcemic patient who had a string of familial hypercalcemia may be easy to be diagnosed with FHH. The dispensation of calcium in a 24-hour-old urine is less than 100mg per 24 hours. The first step in the differential diagnosis of FHH and primary hyperparathyroidism is made by calcium/creatinine clearance. The dispensation of calcium/creatinine is very low. It is calculated as demonstrated in the following. [UCa × SCr] / [SCa × UCr]. The calcium/creatinine clearance ratio is less than 0.01, indicating the diagnosis of FHH (the majority 80% of patients). Calcium/creatinine clearance ratio is found between 0.01 and 0.02 in approximately 20% of primary hyperparathyroidism patients. A low calcium/creatinine clearance ratio may be seen in primary hyperparathyroidism with renal failure or severe vitamin D deficiency. Calcium/creatinine clearance ratio is a ratio of 0.02 or higher could indicate a diagnosis of primary hyperparathyroidism. All patients whose clearance ratio of calcium/creatinine is or below 0.020 should be tested for mutations in their CaSR gene. Patients experience mild hypercalcemia, hypocalciuric, hypermagnesemia, and hypophosphatemia. The parathyroid hormone increases at a normal or elevating degree. The bone densitometer, level of vitamin D, and renal functions are valued as normal. Recurrent hypercalcemia is observed after parathyroidectomy. Serum Magnesium is in the upper normal range or slightly elevated, while serum magnesium tends to be normal or low in primary hyperparathyroidism. It supports the diagnosis of asymptomatic hypercalcemia before the age of 40 or the diagnosis of FHH. Other causes of hypocalciuric hypercalcemia due to PTH, such as vitamin D deficiency, very low calcium intake, mild renal failure, and thiazide diuretics or lithium intake should be excluded [5,14,20,21].

FHH usually does not cause maternal pregnancy complications. Most pregnant women with FHH are asymptomatic and typically do not cause pregnancy complications. Primary hyperparathyroidism may develop osteoporosis, nephrolithiasis, and pancreatitis and is easily treatable by parathyroidectomy, preferably during the second trimester. Primary hyperparathyroidism can lead to preeclampsia, pancreatitis, miscarriage, and hypercalcemia crisis during pregnancy, as well as fetal intrauterine growth restriction, parathyroid hypoplasia, and neonatal hypocalcemia. Therefore, it is important to distinguish FHH from primary hyperparathyroidism during pregnancy. Lactating FHH women are at risk of hypercalcemic crisis. Calcium/creatine clearance during pregnancy is not reliable in diagnosis. Follow-up and observation are recommended. Additionally, genetic testing is safe. Biochemical tests and calcium/creatine clearance are performed after birth and after breastfeeding ends. [8,22].

The most common complications are chondrocalcinosis, nephrolithiasis, gallbladder stones, and pancreatitis. Primary hyperparathyroidism can mimic FHH. In two cases, chondrocalcinosis literature associated with FHH was published. Since there are many overlapping clinical features, it may be difficult to distinguish between primary hyperparathyroidism and FHH. Parathyroid adenoma has been reported in a few cases of FHH [5,23-26].

In the medical treatment of hypercalcemia, calcium restriction, hydration, loop diuretics, calcitonin, glucocorticoids, and bisphosphonates are used. In most cases, there is no need for treatment. Cinacalcet, a calcimimetic is a promising option for the treatment of FHH. Pharmacological treatments have little effect on the treatment of hypercalcemia in FHH. Subtotal parathyroidectomy is not recommended because it does not correct hypercalcemia. Total parathyroidectomy is recommended in rare and severe cases with homozygous CASR mutation. Total parathyroidectomy leads to hypoparathyroidism. Calcimimetics have proven the usage of FHH in vivo and in vitro. Sinecalcet alleviates hypercalcemia and reduces parothormone in the treatment of FHH. FHH treatment is recommended in the presence of serum calcium level ≥ 11.2 mg/dl and symptoms of hypercalcemia. Success was achieved in 88% of 16 patients treated with calcimimetics. Its main side effects are hypocalcemia, nausea, and vomiting. In three pediatric cases of Anthonypillai and his friends, one patient had clear hypercalcemia, polyuria, nocturia, and constipation, the other one was hypercalcemic and experienced leg pain, and the final one also had hypercalcemia. All three of them were given calcimimetics. An alleviation in their symptoms and a decrease in their levels of calcium were determined [27-30].

The most common cause of hypercalcemia in the general population is primary hyperparathyroidism. Primary hyperparathyroidism is caused by a single adenoma in 80% - 85% and by hyperplasia of four glands in 15-20%. Causes of parathyroid hormone-related hypercalcemia include familial multiple endocrine neoplasias, hyperparathyroidism jaw tumor syndrome, familial isolated hyperparathyroidism, ectopic parathyroid hormone in malignancy, and tertiary hyperparathyroidism. Malignancy are the two most common causes of increased serum calcium levels. Hypercalcemia also develops as a result of humoral hypercalcemia of malignancy (mediated by PTHrP) solid tumors, especially lung, head, and neck squamous cancers, renal cell tumors, and local osteolysis (mediated by cytokines), such as multiple myeloma and breast cancer. Endocrine disorders that cause hypercalcemia include thyrotoxicosis, adrenal insufficiency, pheochromocytoma, and VIPoma (Verner-Morrison) syndrome. Drugs that cause hypercalcemia are thiazide diuretics, lithium, milk-alkali syndrome (calcium and antacids), vitamin A, and parathyroid hormone. Hypercalcemia develops due to hiervitaminosis D, iatrogenic, excess milk alkali syndrome, and granulomatous diseases. Examples of granulomatous diseases include sarcoidosis, tuberculosis, and fungal infections. Other causes of hypercalcemia are coexisting malignancy and primary hyperparathyroidism, immobilisation, acute renal failure, chronic renal failure treated with calcium and calcitriol or vitamin D analogues, and renal transplant [4,31,32].

FHH is an autosomal dominant disease. Screening of family members in FHH patients may be useful. In addition, FHH can be investigated in hypercalcemia caused by thiazide diuretics. FHH usually causes moderate hypercalcemia and rarely moderate and severe hypercalcemia. It is important to diagnose and follow-up FHH patients and investigate treatment indications when necessary. Complications of FHH can be understood more clearly with large-scale studies.

Conclusion

In conclusion, FHH is one of the diagnoses that should be kept in mind in the etiology of hypercalcemia. FHH is a rare autosomal dominant disease. FHH develops as a result of heterozygous or homozygous mutation. FHH is usually asymptomatic. Homozygous and compound heterozygous mutations may be symptomatic. FHH becomes more important when the serum calcium level is ≥11.2mg/dl and symptomatic. Although its treatment is controversial, sinecalcet treatment is recommended in patients with a serum calcium level of ≥11.2mg/dl and symptomatic patients. While serum parathormone level often decreases with treatment, it may not decrease in some cases. In long-term treatments (such as 1-2 years), it is recommended to try drug-free periods from time to time. It is recommended to follow up with patients who are asymptomatic and whose serum calcium level is found to increase below < 1 mg/dl.

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