

Hypercalcemia ^①

Symptoms ^②

Serum PTH ^③

Low

Normal/increased

Serum vitamin D metabolites
(25(OH)D and 1,25(OH)D)

No

Increased

Tumor

PTHrp ↑

No

Yes

Syndromatic features

No

Yes

- Phosphate depletion ^④
- Vitamin A intoxication ^⑤
- High-dose hydrochlorothiazide therapy ^⑥
- Adrenal insufficiency ^⑦
- Hypo-/hyperthyroidism ^⑦
- Immobilization ^⑧
- Hypophosphatasia ^⑨
- Transient neonatal hypercalcemia ^⑩
- Sarcoidosis ^⑪

- Jansen osseous dysplasia ^⑫
- Williams syndrome
- Infantile idiopathic hypercalcemia

Tumor hypercalcemia ^⑬

Vitamin D intoxication ^⑭

Urine calcium ↑

Urine calcium ↓

Primary/tertiary hyperparathyroidism ^⑮

Familial hypocalciuric hypercalcemia ^⑯

① — Hypercalcemia is defined as an increase in serum Ca concentration >2.65 mmol/l or 10.6 mg/dl or as an increase in ionized Ca^{2+} >1.4 mmol/l or 5.6 mg/dl. Acid-base changes may affect the levels of ionized calcium in the blood (see Hypocalcemia).

② — Clinical symptoms of hypercalcemia include anorexia, weight loss, vomiting, psychological disturbances, hypertension, extrasosseous Ca deposits, urine-concentrating defect, polydipsia and nephrocalcinosis. In hyperparathyroidism, bone pain and radiological signs such as subperiosteal defects at the radial side of the middle phalanges might be present.

③ — In children with hypercalcemia, serum PTH level is an important diagnostic tool. Low or suppressed PTH levels suggest a normal response of the parathyroid glands to hypercalcemia. If, on the other hand, serum PTH level is elevated, primary or tertiary hyperparathyroidism or familial hypocalciuric hypercalcemia are suspected.

④ — Low phosphorus intake, especially in preterm infants will lead to hypercalcemia. Chronic hypophosphatemia leads to hypercalcemia through increase in the levels of $1,25(\text{OH})_2\text{D}_3$ and by reducing bone mineral content. Breast-milk feeding without phosphate supplementation can also lead to hypercalcemia by a similar mechanism.

⑤ — Vitamin A intoxication, administered in the same preparations as vitamin D, can lead to hypercalcemia.

⑥ — Overdose of thiazide diuretics may lead to hypercalcemia by increasing urinary calcium reabsorption.

⑦ — Although rare, endocrine disorders such as hypothyroidism, hyperthyroidism and adrenal insufficiency, may lead to hypercalcemia.

⑧ — Prolonged immobilization may lead to enhanced bone Ca resorption, and, often, to hypercalcemia and hypercalciuria.

⑨ — Infantile hypophosphatasia (an inherited defect in alkaline phosphatase activity) may lead to hypercalcemia. Typical laboratory findings include normal serum phosphorus level and low alkaline phosphatase level. Bone films demonstrate typical findings of rickets.

⑩ — Transient neonatal hypercalcemia is found in newborns of mothers with hypocalcemia (usually due to maternal hypoparathyroidism). The maternal hypocalcemia leads to excessive fetal PTH production that, in turn, causes hypercalcemia after birth.

⑪ — Granulomatous diseases such as sarcoidosis or tuberculosis might lead to hypercalcemia through an increased ectopic production of $1,25(\text{OH})_2\text{D}$.

⑫ — In the infant with hypercalcemia and dysmorphic features few disorders should be excluded: Jansen osseous dysplasia is a rare hereditary disorder belonging to the chondroplasia group of diseases. It is caused by a mutation in the gene encoding the PTH/PTHrP receptor. Williams-Beuren syndrome is a genetic disorder caused by sporadic mutations in the gene encoding the elastin protein. Typical clinical features include peculiar, elfin-like facies, failure to thrive, mild mental retardation with a 'cheerful', loveable personality and heart malformations (mostly supra-valvular aortic stenosis). Infrequently, hypercalcemia accompanies this syndrome. Infantile idiopathic hypercalcemia is a rare disorder characterized by musculoskeletal abnormalities, hypertension, strabismus and hyperacusis. Although usually transient in nature, serum calcium levels can be extremely high.

⑬ — In children with hematologic or solid organ malignancies (mostly carcinomas), hypercalcemia may be due to skeletal metastasis or to an increase in PTH-related protein levels, a gene product distinct from PTH.

⑭ — Vitamin D intoxication can lead to hypercalcemia and hypercalciuria. Conditions leading to this entity include overdosage of vitamin D given for prophylaxis or of vitamin D given as a supplementation to formula preparations. Of note, vitamin D excess can also result from an ectopic production of this hormone in various disorders (granulomatous diseases, malignancies).

⑮ — The laboratory findings of hyperparathyroidism include, in addition to hypercalcemia, hypophosphatemia and hypercalciuria. Conditions leading to primary hyperparathyroidism include adenoma of the parathyroid glands. This condition can be isolated or a part of more generalized disorders of hyperplasia/neoplasia of endocrine glands called MEN. MEN type 1 consists of primary hyperparathyroidism, endocrine pancreatic hyperplasia and prolactinoma whereas MEN type 2 includes, in addition to primary hyper-

parathyroidism, medullary carcinoma of thyroid and bilateral pheochromocytoma. Tertiary hyperparathyroidism is the result of long-standing secondary hyperparathyroidism which leads to hyperplasia of the parathyroid gland with autonomous, uncontrolled secretion of PTH.

⑯ — The combination of hypercalcemia, elevated serum PTH levels and hypocalciuria is seen in FHH. This rare autosomal-dominantly inherited disease usually presents clinically with asymptomatic hypercalcemia. The genetic defect in FHH is an inactivating mutation in the Ca-sensing receptor. Most children affected are asymptomatic and thus no specific therapy is needed.

Selected reading

Huang J, Coman D, McTaggart SJ, Burke JR: Long-term follow-up of patients with idiopathic infantile hypercalcaemia. *Pediatr Nephrol* 2006;21:1676–1680.
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