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Hypoparathyroidism

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Abstract: Hypoparathyroidism is an endocrine disease characterized by reduced production of parathyroid hormone by the parathyroid glands or tissue resistance to its action, which is accompanied by violations of phosphorus-calcium metabolism. The main etiology of hypoparathyroidism is damage or removal of the parathyroid glands during surgery on the neck organs. Due to the prevalence of thyroid cancer, primary hyperparathyroidism and other pathologies of the neck organs, radical treatment of which can lead to the development of hypoparathyroidism, a steady increase and increase in the number of patients with this pathology is predicted.

Keywords: epidemiology; hypoparathyroidism; parathyroid hormone; calcium, vitamin D, therapy.

Introduction

Hypoparathyroidism is a condition characterized by reduced production of parathyroid hormone (PTH) by the parathyroid glands or tissue resistance to its action, which is accompanied by violations of phosphorus-calcium metabolism. In hypoparathyroidism, the absence or insufficiency of PTH is inevitably accompanied by the development of hypocalcemia. The main pathogenetic mechanisms include: reduced osteoclast activity with reduced calcium release from the bones; increased urinary calcium excretion; inhibition of calcitriol synthesis in the kidneys and decreased intestinal calcium absorption. PTH deficiency leads to hyperphosphatemia both directly through increased renal tubular phosphate reabsorption and indirectly through hypocalcemia. Chronic hyperphosphatemia in patients with hypoparathyroidism has been shown to be associated with increased blood levels of fibroblast growth factor 23.

ETIOLOGY

Surgical intervention on the neck organs is the most common cause of hypoparathyroidism, causing about 75% of all cases of this disease. Postoperative hypoparathyroidism can be caused by both direct removal and intraoperative trauma or a violation of the blood supply to the LV. The risk of chronic hypoparathyroidism is closely related to the number of remaining patients. in situ functioning CSF during the operation: 16% for 1-2 preserved glands, 6% for 3 preserved glands, and 2.5% for 4 preserved glands [1,2]. Autoimmune hypoparathyroidism It is the second most common form of hypoparathyroidism due to immune-mediated destruction of LV cells [3].

It can be an isolated disease, but it is much more common in the context of hereditary autoimmune polyglandular syndrome (APS) type 1 [4]. APS type 1 is a monogenic autosomal recessive disease based on a violation of the structure of the autoimmune regulator gene (AIREThe pathogenesis of the disease is based on autoimmune destruction of various endocrine glands, including the pancreas. APS type 1 is characterized by a classical triad: mucocutaneous candidiasis, hypoparathyroidism, and chronic adrenal insufficiency. The disease usually makes its debut in childhood. Other more rare hereditary forms of hypoparathyroidism occur both in an isolated variant

and as part of multicomponent genetic diseases (Digiorgi, Barakat, Kenny–Cuffy syndrome, etc.) [5-10]. In the case of impaired magnesium metabolism, functional hypoparathyroidism develops, which is a reversible form of the disease with restoration of LV function after correction of hypo- / hypermagnesemia [5, 11]. In rare cases, the cause of hypoparathyroidism can be infiltrative diseases such as sarcoidosis, amyloidosis, Riedel's thyroiditis and metastatic damage to the prostate gland [12-15]. LV tissue is relatively immune to radiation damage; however, very rare cases of radiation-induced hypoparathyroidism have been described in the literature [16-19]. Deposits of minerals in the prostate tissue — for example, copper in Wilson's disease and iron in hemochromatosis-are rare causes of hypoparathyroidism. Cases of hypoparathyroidism due to massive repetitive transfusions in patients with thalassemia have been described [20-24].

EPIDEMIOLOGY

Hypoparathyroidism — this is a rare disease with a prevalence of 0.25 per 1000 population. Available data on the prevalence of hypoparathyroidism are based on large epidemiological studies conducted in the United States, Denmark, Norway, and Italy. The results obtained are relatively similar and indicate the prevalence of hypoparathyroidism in the range of 23-37 per 100,000 population [3, 25-28]. Postoperative hypoparathyroidism is more common among women, which is associated with more frequent thyroid pathology and, consequently, thyroidectomy [29, 30]. The prevalence of hereditary forms of hypoparathyroidism does not differ between men and women [27]. In the Russian population, no large epidemiological studies have been conducted to assess the prevalence of hypoparathyroidism.

Classification of hypoparathyroidism [31].

1. Postoperative hypoparathyroidism:
- transient hypoparathyroidism;
- Chronic (persistent) hypoparathyroidism.
2. Autoimmune hypoparathyroidism*:
- autoimmune polyglandular syndrome type 1 (APS type 1);
- autoimmune polyglandular syndrome type 3 (APS of 3 types);
- autoimmune polyglandular syndrome type 4

(APS type 4).

3. Genetic isolated hypoparathyroidism:
- autosomal dominant hypocalcemia with type 1 hypercalciuria (HYPOC1-ADH1)/Bartter syndrome type 5;
- autosomal dominant hypocalcemia with type 2 hypercalciuria (HYPOC1-ADH2);
- Familial isolated hypoparathyroidism (autosomal, X-linked).
4. Hypoparathyroidism in the composition of multicomponent genetic syndromes:
- Digiorgi syndrome type 1 (DGS1);
- Digiorgi syndrome type 2 (DGS2);
- CHARGE- syndrome;
- HDR- syndrome;
- Kenny-Cuffy syndrome type 1 (KCS1);
- Kenny-Cuffy syndrome type 2 (KCS2);

- Gracile bone dysplasia (GCLEB);
- Mitochondrial diseases.

5. Other forms of hypoparathyroidism:

- magnesium metabolism disorders;
- infiltrative diseases (granulomatosis, hemochromatosis, metastasis);
- hypoparathyroidism as a result of radiation damage to the LV tissue.

6. Idiopathic hypoparathyroidism.

COMPLAINTS AND CLINICAL PICTURE

The main clinical manifestations of hypoparathyroidism are caused by the presence of hypocalcemia. Increased sensitivity of the sensory (sensitive) neuron is manifested in the form of paresthesias in the extremities and in the perioral region; motor (motor) neuron-muscle spasms, up to tetany; from classical carpopedal spasm to life-threatening laryngospasm [32]. Severe hypocalcemia is associated with both local and generalized tonic-clonic seizures. The severity of symptoms depends on the level of calcium in the blood serum, as well as on the rate of progression of hypocalcemia. The chronic course of the disease is characterized by adaptation to low serum calcium levels with the absence of a pronounced clinical picture, even in severe hypocalcemia. In such cases, increased physical activity, medical procedures, pregnancy and lactation may provoke deterioration of the condition [16, 33].

The most common complaint of patients with hypoparathyroidism is the presence of convulsions and / or paresthesias in the muscles of the upper and lower extremities, the perioral region. Patients with a long history of hypoparathyroidism complain of "brain fog", decreased memory and concentration. The clinical manifestations of chronic hypoparathyroidism are different and affect almost all body systems. Clinical symptoms of chronic hypoparathyroidism can be associated with episodes of hypo-and hypercalcemia, hyperphosphatemia [16].

COMPLAINTS AND MEDICAL HISTORY

- Patients with suspected hypoparathyroidism are recommended to collect anamnestic data on surgical interventions performed on the neck organs, as well as on concomitant pathology associated with phosphorus-calcium metabolism [33, 35-37]. Level of persuasiveness of recommendations level of reliability of evidence. The following factors make it possible to suspect the presence of hypocalcemia and hypoparathyroidism in the patient:
- performing surgical intervention in the neck area;
- the presence of paresthesia in the face, upper and lower extremities;
- the presence of fibrillar twitches of individual muscles, cramps in the proximal muscles;
- detection of brain calcification;
- In case of cardiac arrhythmias.

PHYSICAL EXAMINATION

- Patients with suspected hypoparathyroidism are recommended to perform an examination of the anterior surface of the neck to assess the fact of surgical intervention on the neck organs [37].
- In patients with suspected hypoparathyroidism, evaluation of the symptoms of Khvostek and Trousseau is recommended to detect clinical manifestations of hypocalcemia [33, 38].

A positive symptom of Trousseau is the appearance of convulsions in the hand ("obstetrician's hand") 1-3 minutes after squeezing the shoulder with a cuff when measuring blood pressure. This symptom — a highly sensitive and specific sign of hypocalcemia-is detected in 94% of patients with hypocalcemia and in 1% of people with normocalcemia. CKhvostek's symptom —contraction of the facial muscles when tapping at the exit site of the facial nerve - is a less sensitive and specific

sign. Negative Khvostek's symptom is observed in 30% of patients with hypocalcemia, positive — in 10% of people without this pathology .

Diagnosis hypoparathyroidism is based on the results of a laboratory examination!

Criteria for establishing the diagnosis of hypoparathyroidism.

- It is recommended to establish a diagnosis of hypoparathyroidism in patients with hypocalcemia (reduced albumin-adjusted or ionized levels).in combination with a decrease in the level of PTH (or detection of an inadequately low level of PTH) [16,33,46,47,36,39–45]. The most common test for the diagnosis of hypocalcemia is the measurement of total calcium levels. Correction of calcium to the blood albumin level is necessary in order to exclude false-negative or false-positive results of calcemia when the concentration of plasma proteins changes.

Formulas for calculating albumin-adjusted calcium.

- Total plasma calcium (mmol/l) = measured plasma calcium level (mmol/L) + 0.02 × (40 — measured plasma albumin level (g/l))
- Total plasma calcium (mg/dl) = measured plasma calcium level (mg/dl) + 0.8 × (4-measured plasma albumin level (g/dl))
- Conversion factor: [calcium] mg / dl × 0.25 ==>[calcium] mmol/L.
- ✓ In patients with suspected hypoparathyroidism, to exclude secondary causes of hypocalcemia, it is recommended to study the level of inorganic phosphorus in the blood, study the level of total magnesium in the blood serum, study the level of 25-OH vitamin D in the blood, study the level of creatinine in the blood with the calculation of GFR [36, 46-49].
- ✓ Patients with postoperative hypoparathyroidism are recommended to establish a chronic form of the disease while maintaining hypocalcemia and low PTH levels more than 6 months after neck surgery[16, 33, 52, 36, 38-42, 45].
- ✓ Dynamic monitoring of blood and urine parameters is recommended for patients with hypoparathyroidism to assess the adequacy of therapy [36, 37, 47].

Dynamic monitoring of total calcium, albumin (with the calculation of albumin-corrected calcium), phosphorus, magnesium, creatinine with the calculation of GFR in case of compensation of the disease is recommended to be carried out with a frequency of 1 time in 3-6 months. In the absence of compensation for hypoparathyroidism and / or correction of the doses of standard therapy, a more frequent assessment of the indicators of phosphorus-calcium metabolism is recommended, up to several times a week, to assess the adequacy of the selected therapy. Dynamic monitoring of daily calcium excretion is recommended once every 6-12 months.

If hypercalciuria is detected and/or thiazides are prescribed, a control study of the level of calcium in the daily urine is recommended to be performed after 1.5–2 months to assess the adequacy of the treatment.

INSTRUMENTAL DIAGNOSTIC TESTS

- It is recommended to conduct a comprehensive examination in order to actively detect complications of the disease.
- Patients with hypoparathyroidism are recommended to undergo an annual ultrasound examination of the kidneys to assess their structural changes [36, 47, 49].
- Patients with chronic hypoparathyroidism have a significantly increased risk of developing nephrolithiasis/nephrocalcinosis when taking vitamin D and its derivatives and calcium supplements.
- Patients with hypoparathyroidism and suspected nephrolithiasis are recommended to use computed tomography of the kidneys for its verification [49].

- Patients with hypoparathyroidism should be regularly examined by an ophthalmologist for timely diagnosis of eye complications.[27, 29, 36, 47]. Patients with a long history of hypoparathyroidism (more than 3-5 years) should be periodically examined by an ophthalmologist in order to timely diagnose the development of cataracts and determine the need for specialized treatment.
- In the presence of neurological symptoms, patients with chronic hypoparathyroidism are recommended to conduct a computed tomography of the brain.[27, 29, 36, 47].

Clinical manifestations of calcification of various parts of the central nervous system in patients with a long history of hypoparathyroidism are non-specific. The most common are motor disorders: muscle rigidity, Parkinsonism, hyperkinesis (chorea, tremor, dystonia, athetosis, orofacial dyskinesia); cognitive disorders; cerebellar symptoms and speech disorders.

In some cases, there are epileptic seizures, dementia. Often there is a combination of different clinical symptoms. The question of whether there is a pathogenetic relationship between neurological symptoms and the volume and localization of calcifications remains controversial. If these symptoms occur and / or calcification of the basal ganglia is detected by CT scan of the brain, a neurologist should be consulted.

- Patients with chronic hypoparathyroidism are not recommended to undergo regular X-Ray densitometry (Dual-Energy X-Ray Absorptiometry, DXA) to assess the condition of bone tissue.[29, 36, 47, 49]. In hypoparathyroidism, bone metabolism is slowed, so there are no prerequisites for a decrease in BMD over time in the absence of concomitant risk factors, such as glucocorticoid therapy. To assess the condition of bone tissue in patients with chronic hypoparathyroidism, it is advisable to conduct a comprehensive examination, including the determination of markers of bone metabolism and radiography of the bones.

OTHER DIAGNOSTIC TESTS

- Patients with hypoparathyroidism of unspecified etiology may be recommended for an extended examination, including detailed collection of the patient's medical history and complaints, genetic counseling, and genetic testing if hereditary pathologies are suspected.[4, 33, 36, 47, 48].
- patients with isolated hypoparathyroidism of unclear etiology that occurred after the first year of life are recommended to collect a detailed history and complaints of the patient, study the AIRE gene to exclude APS type 1.

GOALS OF TREATMENT AND MONITORING OF HYPOPARATHYROIDISM

- In patients with hypoparathyroidism, it is recommended to maintain the level of serum calcium (albumin-adjusted or ionized calcium) within the lower limit or slightly below the reference range, provided that there are no symptoms and signs of hypocalcemia in order to prevent the development of complications of the disease [36, 41, 47].

Therapeutic goals - the level of albumin-adjusted blood calcium in the range of 2.1–2.3 mmol/l or ionized calcium in the range of 1.05-1.15 mmol/L-is based on the maintenance of physiological processes in the body. Some patients may, however, need higher levels of serum calcium to eliminate the symptoms of hypocalcemia.

- In patients with hypoparathyroidism, it is recommended to maintain the level of daily calcium excretion within the target range (depending on gender) for the prevention of renal complications [36, 47].
- In patients with hypoparathyroidism, it is recommended to maintain the level of inorganic phosphorus in the blood within the reference range in order to prevent extra-skeletal calcification [16, 33, 36, and 47].
- In patients with hypoparathyroidism, it is recommended to maintain magnesium levels within the reference range [36, 47].

- In patients with hypoparathyroidism, it is recommended to maintain the level of 25-OH vitamin D in the optimal range, as for the general population [33, 36, 45, 47].
- For patients with hypoparathyroidism, as well as for the general population, in most cases, the presence of a lack or deficiency of vitamin D is characteristic. Therefore, it is advisable to use native forms of vitamin D (colecalciferol**) for its correction.
- Optimal levels of 25 (OH)for the Russian populationD are set in the range of 30-60 ng / ml (75-150 nmol / L). Levels 25 (HE)D more than 100 ng / ml (250 nmol / L) can cause toxic effects of vitamin D on the body and is not recommended.
- Therapy with alfacalcidol**, calcitriol** does not significantly affect the level of 25 (OH)D blood serum.
- ✓ Special training is recommended for patients with hypoparathyroidism to discuss possible symptoms of hypo-and hypercalcemia and / or complications of the disease, as well as their prevention measures to prevent life-threatening conditions [36, 47].

TREATMENT OF HYPOPARATHYROIDISM

- ✓ Drug therapy is recommended for all patients with chronic hypoparathyroidism with symptoms of hypocalcemia and levels of albumin-adjusted calcium less than 2.0 mmol/l or serum ionized calcium less than 1.0 mmol/l. In the case of an asymptomatic course of chronic hypoparathyroidism and an albumin-adjusted calcium level between 2.0 mmol/l and the lower limit of the reference range, trial therapy is recommended, followed by an assessment of general well-being.[16, 33, 36, 47].
- ✓ Vitamin D preparations and their derivatives (alpha-calcidol**, calcitriol**) in combination with calcium supplements in various doses are recommended as standard therapy for hypoparathyroidism [16, 33, 96, 97, 36-38, 47].
- Standard therapy for hypoparathyroidism includes vitamin D and its derivatives (alfacalcidol**, calcitriol**) and calcium supplements. The calciemic effect of calcitriol** is approximately twice that of alfacalcidol**.
- To maintain the blood calcium level within the target level, titration of doses of vitamin D and its derivatives is recommended, dividing the total dose of the drug in 2-3 doses. Dose titration is usually performed in increments of 0.5 (or 0.25) mcg for alfacalcidol** and 0.25 mcg for calcitriol**. A larger dose adjustment step may be required for severe hypo / hypercalcemia. The recommended time interval for dose adjustment of vitamin D and its derivatives (alfacalcidol**, calcitriol**) is 2-3 days, which is due to their pharmacokinetics and, as a result, adequate dose adjustment. evaluation of the changes made. Laboratory assessment of the adequacy of adjusted doses can be performed in 7-10 days in the case of a low-symptomatic course and moderate fluctuations in calcemia indicators. It may take about 2-3 months to evaluate the clinical effectiveness of the selected therapy and achieve stable values of calcemia, especially for patients with a high need for vitamin D preparations and its derivatives.
- Isolated administration of calcium salts is not pathogenetically justified and causes only a short-term increase in serum calcemia.
- Patients with hypoparathyroidism are recommended to use a diet with a high intake of calcium-containing products.
- Various calcium supplements are used to treat hypoparathyroidism. As a rule, preparations containing calcium carbonate (40% of elemental calcium) are used, including as part of the combined preparation "calcium carbonate + colecalciferol" in average daily doses of 1-3 g (higher doses can also be used). Dietary supplements of calcium citrate (21% elemental calcium) can also be used. When prescribing, it is necessary to take into account the pharmacokinetics of various drugs: calcium carbonate is better absorbed in the acidic environment of the stomach, so it is more preferable to take it with food; calcium citrate is recommended for patients with achlorhydria or receiving treatment with proton pump inhibitors.

- High doses of calcium supplements can reduce the need for vitamin D and its derivatives and improve the control of maintaining the target level of serum phosphorus by binding phosphorus in the intestine.

- ✓ For patients with chronic hypoparathyroidism and hypercalciuria, a reduced dose of calcium supplements and a low-salt diet are recommended to achieve the target level of calcium excretion [16, 33, 36-38, 47].
- ✓ For patients with chronic hypoparathyroidism and hypercalciuria, thiazide therapy is recommended to achieve the target level of calcium excretion[16, 33, 36-38, 47].
- ✓ For patients with chronic hypoparathyroidism and hyperphosphatemia, a low-phosphate diet and dose adjustment of standard therapy is recommended in order to achieve normophosphatemia and prevent extra-skeletal calcification [36, 47]. * In patients with hypoparathyroidism, if a concomitant vitamin D deficiency/insufficiency is detected, it is recommended to prescribe a native form of vitamin D (colecalciferol**) in the form of standard doses, as for the general population, despite treatment with vitamin D preparations and its derivatives (alfacalcidol**, calcitriol**) [36, 37, 47].
- ✓ It is not recommended to use recombinant human parathyroid hormone for the treatment of hypoparathyroidism in routine clinical practice [36, 40].

PREVENTION

- Patients are recommended to determine the level of 25-OH vitamin D and compensate for its deficiency before the planned neck surgery in order to prevent the development of postoperative transient hypoparathyroidism [43].
- In order to avoid damage and/or devascularization of the LV, it is not recommended to perform a mandatory revision during neck surgery .
- On the first day after surgical intervention in the neck area, it is recommended to determine the levels of PTH and albumin-corrected and / or ionized blood calcium to diagnose hypoparathyroidism and determine the need for prescribing calcium and vitamin D preparations and its derivatives [43].

Despite the fact that currently no clear time criteria for blood sampling for PTH and calcium indicators in the postoperative period have been developed, the conducted studies demonstrate the value of measuring these parameters during the first 24 hours after neck surgery. PTH level less than 15 pg / ml on the first day after surgery is considered as a predictor of postoperative hypoparathyroidism (sensitivity 97.7%, specificity 82.6%). Postoperative assessment of laboratory parameters of phosphorus-calcium metabolism is a necessary condition for timely administration of vitamin D and its derivatives and calcium preparations. * Patients undergoing total thyroidectomy are recommended to take oral calcium supplements on a routine basis during the first 2 weeks after surgery to prevent acute hypocalcemia . The minimum recommended daily dose of oral calcium supplements is not less than 3000 mg for a period of at least 2 weeks, followed by an assessment of the indicators of phosphorus-calcium metabolism and determining the need for continued therapy. * Patients undergoing total thyroidectomy with an increased risk of postoperative hypocalcemia should be routinely prescribed oral calcium supplements in combination with vitamin D and its derivatives (alfacalcidol**, calcitriol**) during the first 2 weeks after neck surgery to prevent acute hypocalcemia.

Independent predictors of postoperative hypocalcemia include thyroidectomy, especially with central and / or lateral lymph dissection, repeated neck surgery, intraoperative LV injury, and low intra-and postoperative PTH levels. The minimum recommended daily dose of oral calcium supplements is at least 3000 mg in combination with therapy with vitamin D and its derivatives (calcitriol * * 1 mcg per day) for a period of at least 2 weeks, followed by an assessment of the indicators of phosphorus-calcium metabolism and determining the need for continued therapy .

- ✓ Patients undergoing surgical intervention on the neck organs during LV devascularization are recommended to undergo their autotransplantation for the prevention of postoperative hypoparathyroidism

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