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ПЕРВИЧНЫЙ ГИПЕРПАРАТИРЕОЗ С ПРЕИМУЩЕСТВЕННЫМ ПОРАЖЕНИЕМ ЖЕЛУДОЧНО-КИШЕЧНОГО ТРАКТА

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Primary Hyperparathyroidism with a Predominant Lesion of the Gastrointestinal Tract

Резюме

Первичный гиперпаратиреоз является достаточно распространенной патологией, однако, несмотря на это, врачи различных специальностей сталкиваются с трудностями при его диагностике. Многообразие клинических проявлений обуславливает длительный срок постановки диагноза и, как следствие, несвоевременность начала лечения. Описаны, с учетом патогенеза, основные симптомы данной патологии. Лабораторными маркерами гиперпаратиреоза служат стойкое повышение уровня паратиреоидного гормона и гиперкальциемия. Визуализирующие методы обследования используются для верификации заболевания. Прицельное ультразвуковое исследование паращитовидных желез необходимо проводить всем пациентам с подозрением на нарушение обмена кальция.

В данной статье представлен клинический случай первичного гиперпаратиреоза с преимущественной гастроинтестинальной симптоматикой. Пациентка дважды госпитализировалась в стационар с различными клиническими проявлениями поражения органов желудочно-кишечного тракта. Были установлены такие патологии как эрозивный гастрит, терминальный илеит, хронический панкреатит, желчекаменная болезнь.

Проводился дифференциальный диагноз с лимфомой тонкой кишки, болезнью Крона. Кроме того, имелась общемозговая симптоматика в виде заторможенности, быстрой истощаемости. Из-за тяжелых электролитных расстройств пациентка наблюдалась в реанимационном

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отделении. В связи с развитием механической желтухи выполнена эндоскопическая ретроградная холангиопанкреатография с папиллосфинктеротомией. На основании гиперкальциемии, повышенного уровня паратиреоидного гормона, визуализации образования паращитовидной железы по данным ультразвукового исследования был установлен диагноз первичного гиперпаратиреоза. В хирургическом отделении проведена аденомэктомия левой нижней паращитовидной железы. Больная была выписана с положительной динамикой в виде улучшения общего самочувствия, прекращения болевого синдрома, рвоты, расширения двигательной активности. Своевременная диагностика и лечение первичного гиперпаратиреоза, на примере описанного случая, приводит к полному купированию симптомов и улучшению качества жизни пациентов.

Ключевые слова: *первичный гиперпаратиреоз, гиперкальциемия, паратиреоидный гормон*

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Abstract

Primary hyperparathyroidism is a common pathology, but it is fact that doctors of various specialties run against difficulties in diagnosinging. The variety of clinical manifestations causes a long period of diagnosis and, late start of treatment. The main symptoms of this pathology are described taking into account the pathogenesis. The most common laboratory markers of hyperparathyroidism are incrising level of parathyroid hormone and hypercalcemia. Imaging examination methods are used to establish primary hyperparathyroidism. Targeted ultrasound examination of the parathyroid glands should be performed in all patients with suspected calcium metabolism disorders.

This article presents a clinical case of primary hyperparathyroidism with predominant gastrointestinal symptoms. The patient was twice admitted to the hospital with various clinical manifestations of damage to the gastrointestinal tract. Erosive gastritis, terminal ileitis, chronic pancreatitis, and cholelithiasis were identified. A differential diagnosis was made with small intestine lymphoma and Crohn's disease. In addition, there were General cerebral symptoms in the form of lethargy, rapid exhaustion. Due to severe electrolyte disorders, the patient was observed in the intensive care unit. Due to the development of mechanical jaundice, endoscopic retrograde cholangiopancreatography with papillosphincterotomy was performed. Based on hypercalcemia, elevated parathyroid hormone levels, and visualization of parathyroid gland formation, the diagnosis of primary hyperparathyroidism was established based on ultrasound data. An adenomectomy of the left lower parathyroid gland was performed. in the surgical department. The patient was discharged with positive dynamics in the form of improvement in General health, cessation of pain, regress of vomiting, expansion of motor activity. Betimes diagnosis and treatment of primary hyperparathyroidism, on the example of the described case, leads to complete relief of symptoms and improvement of the quality of life of patients.

Key word: *primary hyperparathyroidism, hypercalcemia, parathormone*

Conflict of interests

The authors declare that this study, its theme, subject and content do not affect competing interests

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ALP — alkaline phosphatase, BP — blood pressure, CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration Formula, CNS — central nervous system, D-FIS — Daily Fatigue Investigation Scale, EGD — esophagogastroduodenoscopy, GFR — glomerular filtration rate, GIT — gastrointestinal tract, HR — heart rate, MEN — multiple endocrine neoplasia, MSCT — multispiral computed tomography, PHPT — primary hyperparathyroidism, PTH — parathyroid hormone, SD — standard deviation, US — ultrasound

Relevance

Primary hyperparathyroidism (PHPT) (fibrocystic osteodystrophy, Recklinghausen's disease, parathyroid osteodystrophy) is an endocrine disease caused by hyperproduction of parathyroid hormone (PTH) by pathologically changed parathyroid glands and characterized by impaired calcium and phosphorus metabolism [1].

Until recently, PHPT was considered a rare disease with a pronounced clinical presentation with

predominant damage to the bone system and kidneys. Primary epidemiological studies included only patients who were admitted to the hospital with severe clinical signs. However, screening determination of blood calcium level later performed in Western Europe and the USA revealed that the true level of morbidity is much higher and includes a significant number of mild and asymptomatic forms, and the clinical picture is characterized by damage to various organs and systems [2–5].

The prevalence of PHPT ranges from 0.4 to 18.8 cases per 10,000 people. Data variability is the result of the lack of large international studies with uniform diagnostic standards. Peak incidence occurs in patients aged 40–60. Women suffer from this disease 2–4 times more often than men, while most women suffer from it in the postmenopausal period [5].

Among etiological factors, parathyroid adenoma is the cause in 80–85% of cases; in 15–20% of cases, PHPT is caused by hyperplasia of several/all parathyroid glands; parathyroid cancer is the cause in 1–5% of cases. Adenoma usually affects one gland, usually the lower one, but hyperplasia can develop in one, two, three or all four parathyroid glands. PHPT is sporadic in most cases (90–95%) [5]. About 5% of PHPT cases are a part of multiple endocrine neoplasia (MEN), a syndrome caused by tumors or hyperplasia in two or more endocrine organs. The following hereditary variants were also described: hyperparathyroidism syndrome with a tumor of the lower jaw, familial hypocalciuric hypercalcemia, and familial isolated hyperparathyroidism [6].

The pathogenesis of the clinical signs of PHPT includes excessive PTH production with a decrease in the regulatory effect of calcium on parathyroid hormone production, leading to its excessive release, i.e., impaired negative feedback mechanism. In cases of hyperplasia of parathyroid glands, an increase in the number of PTH secreting cells is observed. Excessive PTH increases bone resorption by osteoclasts and mobilization of calcium and phosphorus from them. The stimulating effect of PTH on 1,25-(OH)2-D3 production by the kidneys enhances calcium absorption in the intestine, and its excretion decreases. Excessive parathyroid hormone also affects intracellular calcium homeostasis, thus stimulating the release of calcium ions from cells in the extracellular space. A decrease in intracellular calcium concentration leads to impaired calcium-dependent processes: muscle contraction, nerve impulse conduction, and blood coagulation. These mechanisms lead to hypercalcemia syndrome and calcium deposition in different organs and tissues [7].

Significant challenges in the diagnosis of this disease can be attributed to a variety of its clinical manifestations. The diagnosis is established based on laboratory tests, persistent increase in PTH, and hypercalcemia. However, routine blood biochemistry does not include the determination of calcium level; this fact complicates diagnostic search and means more time is required to establish the right diagnosis.

We will describe one case of PHPT for illustrative purposes.

Case report

Patient D., 56 y.o., female, teacher; in September 2019, she was urgently hospitalized in intensive care unit for sudden significant general weakness, nausea, repeated vomiting of gastric contents, pain in the upper abdomen.

The patient considers herself ill since June 2019, when she first experienced abdominal pain, stool with a tendency to constipation, and general weakness. During the next three months, she was twice urgently hospitalized in different hospitals in Moscow with suspected acute pancreatitis; this diagnosis was subsequently not confirmed. During examination, esophagogastroduodenoscopy (EGD) revealed erosive gastritis; endosonography demonstrated calculous cholecystitis, signs of papillitis, microcholecholithiasis, and diffuse changes in the pancreas. Endoscopic retrograde cholangiopancreatography, papillosphincterotomy, drainage of bile ducts were performed. However, abdominal pain persisted. Therefore, an additional examination was carried out, which revealed kidney stones according to ultrasound (US) results; lymph nodes enlarged to 7.8 mm in diameter and located medial to the cecum during computed tomography (CT) of the urinary system; multiple polygonal flat ulcers covered by fibrin (terminal ileitis) during colonoscopy. This morphological presentation was suspicious in regard to lymphoma. Biopsy specimens of the terminal ileum revealed deformed mucosal fragments with an uneven ulcerated surface, with dense diffuse infiltration of stroma by lymphocyte-like cells with a small amount of plasmocytes and neutrophils, angiomatosis, foci of granulation tissue; in circumscribed portions, there were fragments of the integumentary epithelium, in the depth of the tissue — single deformed crypts with no goblet cells. However, immunohistochemistry of specimens and cerebrospinal fluid yielded no data suggesting lymphoma.

The patient's general condition on admission to the intensive care unit was severe. The patient was obtunded, rapid exhaustion was observed. The patient was hardly cooperative, with cognitive impairments. Twenty-three points according to D-FIS (Daily Fatigue Investigation Scale). This scale includes eight questions regarding the signs of fatigue, with five possible answers ranging from sign absence to its significant severity (maximum score — 32). Speech is slow and quiet, hoarse voice. The patient moved with difficulty due to severe muscle weakness. Skin was pale, dry, no peripheral swelling. Lymph nodes were not enlarged. Contours of the neck without changes, thyroid gland was not enlarged. Musculoskeletal system without visible abnormality. Vesicular breathing in lungs, respiratory rate — 18 per minute. Cardiac rhythm is regular, with heart rate 109 bpm. Heart tones are clear, blood pressure (BP) 130 and 100 mm Hg on both arms. Tongue is dry, covered with a whitish-yellow fur. Abdomen of regular shape, soft, moderately painful in the periumbilical area. Liver along the edge of the costal arch. Bowel sounds were auscultated. Stool with a tendency to constipations, type 2 and 3 according to the Bristol scale, formed, and brown without pathological impurities. No costovertebral angle tenderness on both sides. Urination is free, painless.

Complete blood count revealed mild normochromic normocytic anemia (hemoglobin — 90 g/l, RBC — 3.06×10^{12}/l, hematocrit — 27.1%).

Blood biochemistry: hypokalemia up to 2.4 mmol/l (3.44–5.3 mmol/l), aspartate aminotransferase — 76 IU/l (5–34 IU/l), alanine aminotransferase — 43 IU/l (0–32 IU/l), gamma-glutamyltranspeptidase — 180 IU/l (9–39 IU/l), lactate dehydrogenase — 728 IU/l (225–450 IU/l), creatine phosphokinase — 64 IU/l (33–211 IU/l), total bilirubin — 15.1 μmol/l (1.7–20.5 μmol/l), urea — 5.2 mmol/l (2.5–8.33 mmol/l), creatinine — 66 μmol/l (53–88 μmol/l), alpha-amylase — 96 IU/l (0–220 IU/l), glucose — 6.1 mmol/l (3.8–6.1 mmol/l), alkaline phosphatase — 135 IU/l (64–306 IU/l).

Ultrasound of the hepatobiliary system revealed diffuse changes in the liver, pancreas, and gallbladder calculi. Brain CT showed no abnormalities. According to echocardiography — local and global systolic contractile function of myocardium retained, left ventricular hypertrophy. Abdominal X-ray — moderate pneumatosis of the colon; no changes were found during the passage of barium suspension through the small intestine.

A differential diagnosis was made with lymphoma of the small intestine, Crohn's disease, neurological pathology (stroke, myasthenia, Guillain-Barre syndrome, focal pathology of the central nervous system (CNS)). Considering the non-specific clinical presentation and polysystemic nature of the disorder, PHPT was suspected.

Increased levels of serum PTH up to 300.4 pg/ml (15–65 pg/ml) and calcium — up to 3.57 mmol/l (1.9–2.75 mmol/l) were found, as well as decreased levels of 25-OH vitamin D down to 10.71 ng/ml (30–40 ng/ml) and magnesium — down to 0.62 mmol/l (0.66–1.07 mmol/l). Urine biochemistry showed a decrease in potassium to 10.2 mmol/l (20–80 mmol/l) and sodium — to 34 mmol/l (40–220 mmol/l) and an increase in calcium — to 10.55 mmol/l (2–6.4 mmol/l). Glomerular filtration rate (GFR) — 90 ml/min/1.73 m^2 (according to CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), 2011).

Ultrasound of the thyroid gland revealed thyroid nodules: in the middle segment, there was an isoechoic lesion 19 × 9 mm, with an inhomogeneous structure, with sharp and smooth contours; in the upper segment — several hypoechoic lesions up to 7 mm; posteriorly to the middle and lower segments of the left thyroid lobe — hypoechoic lesion 51 × 27 × 30 mm of the left lower parathyroid gland.

The patient was examined by an endocrinologist who confirmed PHPT. The following clinical diagnosis was established: PHPT with end-organ damage, severe course. Adenoma of the left lower parathyroid gland. Complications: Vitamin D deficiency Gallstone disease. Papillitis. Microcholecholithiasis. Papillosphincterotomy, drainage of bile ducts on August 19, 2019. Urolithiasis. Severe water-electrolyte imbalance (hypokalemia, hyponatremia, hypercalcemia). Comorbidities: Mild normochromic normocytic anemia. Hypertensive disease stage II, grade I, high risk (according to the Russian Hypertension Classification).

Adenomectomy of the left lower parathyroid gland was performed in the surgical department of the hospital. Morphological examination revealed a lesion of solid-trabecular structure, from parathyroid cells with eosinophilic cytoplasm, hemorrhages, thin fibrous capsule (parathyroid adenoma).

The patient was discharged with positive changes — cessation of pain and vomiting, increased general activity. The D-FIS fatigue score on discharge was 12 points. The recommendation included intake of vitamin D,

calcium (under control), spironolactone; laboratory tests over time; follow-up by an endocrinologist at the place of residence.

Currently (at the time of writing this paper), the patient's condition is satisfactory, PTH level 82 pg/ml (15–65 pg/ml).

Discussion

PHPT often has no typical clinical presentation and can mimic various diseases. However, there are specific changes that may lead the attending physician to suggest the possibility of PHPT accompanied by increased bone resorption, hypercalcemia and calcium deposition in different organs [7].

PTH releases calcium from the main depot, resulting in decreased bone density — parathyroid osteodystrophy with joint damage and development of chondrocalcinosis. This can be manifested by pain syndrome of different severity and pathological fractures. However, since patients with PHPT are postmenopausal women, these changes can be mistaken for postmenopausal or age-related osteoporosis. Without additional laboratory and diagnostic tests, such patients can be treated with calcium supplements, which will further exacerbate hypercalcemia and aggravate the course of disease [7].

Hypercalcemia leads to nephrolithiasis and nephrocalcinosis [8]. Single stones, multiple stones, calculi in both kidneys consisting of oxalates or calcium phosphates can be found. Surgical removal of stones does not lead to complete recovery. Calculi re-appear, also in the treated kidney. There is evidence of urolithiasis regression after surgical management of PHPT [9, 10]. In this case, the development of chronic kidney disease with reduced glomerular filtration leads to irreversible changes.

An increase in calcium in the extracellular space causes transmembrane imbalance of ions, impaired formation of resting membrane potential, and a decrease in the rate of transmission of nerve impulses [7]. This is manifested by slowness of thought (bradyphrenia), rapid fatigue, slow speech, and muscle weakness as a result of neuromuscular transmission disorders.

There has been an intense debate over the impact of PHPT on cardiovascular risks in recent times. This may be due to the direct action of PTH and calcium. Various forms of arrhythmia may develop. There is evidence that the normalization of calcium and PTH levels does not always make other risk factors return to normal after parathyroidectomy. Arterial hypertension is believed to remain unchanged after parathyroidectomy in patients with manifested PHPT [11].

Gastrointestinal symptoms are found in almost half of patients with PHPT [12]. Patients may have complaints of lack of appetite, constipation, nausea, flatulence, weight loss. The development of erosive and ulcerative lesions of the gastrointestinal tract (GIT) is associated with hypercalcemia and increased secretion of gastrin and hydrochloric acid, which returns to normal after removal of the substrate of PTH level increase. The course of peptic ulcers in cases of PHPT is characterized by a more pronounced clinical picture, more frequent exacerbations, bleedings; it is hard to manage, unlike peptic ulcers caused by other factors [12]. The lesion of the gastrointestinal mucosa can also be a consequence of hypergastrinemia due to MEN syndrome. GI motility is impaired, which leads to nausea, vomiting, weakened peristalsis in the stomach and intestine, constipation, and abdominal pain syndrome.

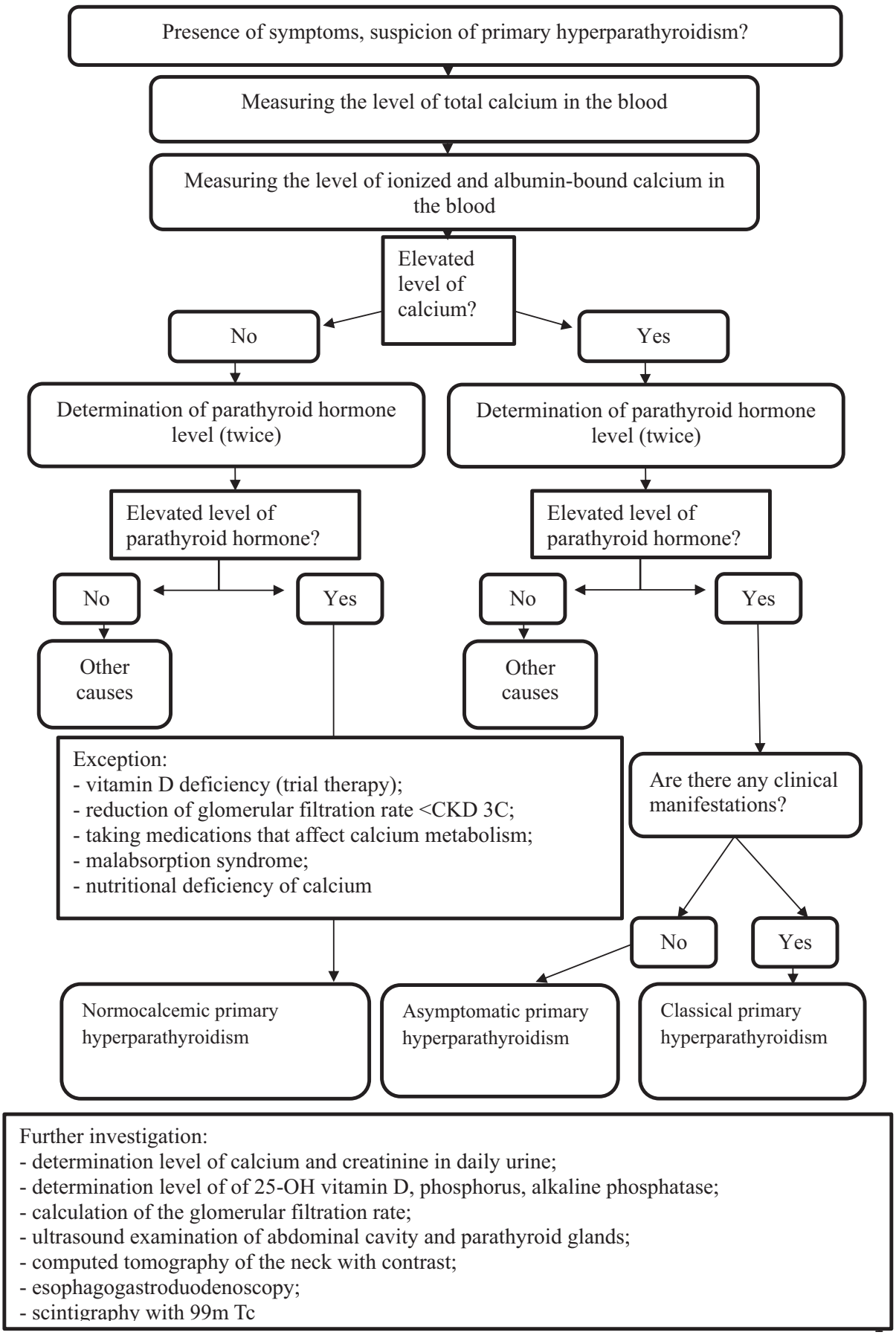
Experimental studies showed that hypercalcemia contributes to pancreatic stones, which causes the obstruction of ducts and recurrent pancreatitis. Hypercalcemia can trigger the conversion of trypsinogen to trypsin [13]. An increase in calcium concentration also leads to the formation of gallstones, choledocholithiasis with possible development of obstructive jaundice.

In the abovementioned clinical case, gastroenterological and neurological symptoms were predominant in the presence of polysystemic lesions. Erosive lesions of the upper gastrointestinal tract and intestine also developed. The revealed changes required the exclusion of other diseases (in particular, lymphoma of the small intestine, Crohn's disease), which complicated differential diagnosis and required more time for diagnostic search.

Cholelithiasis and signs of exacerbation of chronic pancreatitis led to repeated hospitalizations of the patient in the surgical department, demonstrating the challenges in establishing the right diagnosis.

Neurological symptoms required the exclusion of the pathology of the central and peripheral nervous system.

The normocalcemic variant of PHPT also poses certain diagnostic challenges [14]. Normal calcium levels in cases of PHPT may be due to the low specificity of determination of total blood calcium, hemodilution, malabsorption syndrome, vitamin D deficiency. For further examination, it is recommended to determine the level of ionized and albumin-bound calcium, as these parameters have greater sensitivity [1].



Scheme. *Algorithm for the diagnosis of primary hyperparathyroidism (ad. Russian assosiation of endocrinologists. Primary heperparathyroidism. Clinical trials, 2016 [1])*

Vitamin D (25(OH)D) deficiency is often observed in patients with PHPT, which exacerbates the manifestations of hyperparathyroidism accompanied by bone destruction and an elevated risk of postoperative hypocalcemia (hungry bone syndrome) [14].

In the differential diagnosis of the normocalcemic variant of PHPT with vitamin D deficiency with secondary hyperparathyroidism with vitamin D deficiency, pharmacological tests are used, i.e., experimental replacement therapy [14]. The intake of vitamin D by patients with PHPT will lead to hypercalcemia with increased PTH level, and in patients with secondary hyperparathyroidism, it will reduce/normalize PTH level with normocalcemia.

Many researchers consider different types of PHPT to be manifestations of different stages of this disease. Follow-up monitoring of patients with the normocalcemic variant demonstrated an increase in calcium level above reference values in 30% of individuals after 6–24 months [15].

Ultrasound is the basic screening method — and in most cases, the only method of imaging changed parathyroid glands. However, its sensitivity amounts ranges 36 to 90% [16]. The results largely depend on the experience of the specialist, the volume of parathyroid glands and the size of the lesion. During a non-localized examination, the specialist may not see or suspect any pathology. This method is also non-informative with atypical localization of parathyroid glands. In addition, lower parathyroid glands migrate with the thymus from the third gill pouch and can be ectopic. According to J. M. Ruda et al., 2005, the informative value of ultrasound in cases of multiple adenomas is significantly lower than with solitary adenomas, and amounts to 16–30% [16].

Accurate preoperative topical diagnosis helps to best plan the subsequent surgical intervention, which can be done using several imaging methods, for example, ultrasound and scintigraphy (see scheme).

The method of choice for PHPT management is surgical treatment — removal of pathologically changed parathyroid glands. According to the consensus of the European Society of Surgery [17], and Russian clinical guidelines [1], indications for surgical treatment are the following:

- serum concentration of total calcium 0.25 mmol/l (1 mg %) higher than normal;
- GFR reduction less than 60 ml/min/1.73 m^2;
- visceral manifestations of PHPT;
- daily calcium excretion of more than 400 mg per day;
- decrease in bone mineral density in radial, femoral or vertebral bones less than –2.5 SD (standard deviation) by T-test;
- history of fractures and/or fractures of vertebral bodies confirmed by X-ray;
- age under 50 years.

Intraoperative determination of PTH level as a marker of effective surgical treatment is recommended. A criterion for effective management is a decrease in PTH level by at least 50% from the baseline, 10 minutes after removal of parathyroid adenoma [18].

Conservative treatment of patients with PHPT with no indications for surgical treatment (mild types) includes diet with restriction of calcium intake, antiresorptive drugs (bisphosphonates, denosumab) and calcimimetics (cinacalcet).

Conclusion

Today, PHPT is a common disease, which can be encountered by any type of physician. The variety of clinical symptoms makes it difficult to establish the right diagnosis. Cases of atypical course of gastroenterological diseases (gastric and duodenal ulcer, chronic pancreatitis, gallstone disease, erosions and ulcers of the intestine) require considering the probability of parathyroid gland pathology and examining the patient according to the abovementioned algorithm (scheme).

Long-lasting PHPT leads to persistent organ damage. However, timely diagnosis and surgical treatment result in a favorable prognosis for the patient and significant regression of symptoms.

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