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CALCITONIN VALUES IN PSEUDOHYPOPARATHYROIDISM

Abstract: Pseudohypoparathyroidism type 1A is a rare endocrine disorder caused by GNAS mutation and the resulting hormone resistance at the receptor level, i.e. the activation of the intracellular pathway of the Gs alpha subunit is not possible. This disorder is most often characterized by resistance to the parathyroid hormone. However, it can also be characterized by resistance to other hormones, such as thyroid-stimulating hormone, gonadotropins (luteinizing and follicle-stimulating hormones), growth hormone-releasing hormone, and calcitonin. In this article, we describe the case of a patient diagnosed with pseudohypoparathyroidism based on phenotypic features of hereditary Albright osteodystrophy. Due to the progressive decline in intellectual functions and changing behavior, neurological examination confirmed calcifications of the CNS as part of Fahr's syndrome. During hospitalization, higher levels of thyroid-stimulating hormone and calcitonin were observed, probably as a result of resistance at the level of the receptor and its intracellular pathway. Hypercalcitoninemia occurs sporadically in cases involving pseudohypoparathyroidism type 1-a and type 1-b. Elevated levels of calcitonin should be evaluated by means of anamnesis and clinical examination involving morphological and functional tests, considering that a highly specific tumor is a marker of medullary carcinoma of the thyroid gland, as well as some neuroendocrine tumors. Some authors recommend fine needle aspiration biopsy in order to minimize the risk of medullary thyroid cancer.

Keywords: pseudohypoparathyroidism, calcitonin, hypercalcitoninemia, fine-needle biopsy

Case report:

Patient CV (Table 1), was hospitalized at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases in order to evaluate the condition. The diagnosis of

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pseudohypoparatiodism (PHP 1a) was made in childhood based on the phenotypic manifestations of Albright's hereditary osteodystrophy, repeated convulsions (hypocalcemic tetany), and biochemical findings of hypocalcemia. Data on genetic testing is unknown. Since then, he has been on therapy with the active form of vitamin D and calcium preparations with optimal maintenance of calcium homeostasis. He feels well all the time, except when he does not use substitution therapy, and then his complaints manifest themselves in the form of cramps and tingling in the extremities with extreme fatigue. He was hospitalized at the Clinic in 2008 when a complete retest was performed, when an increase in TSH was registered with a normal fT4, levothyroxine substitution was introduced into the therapy. Due to changes in behavior with declining intellectual functions, he was hospitalized at the Clinic for Neurology in 2009, when it was observed on a CT scan of the endocranium bilaterally in the area of the basal ganglia and massive frontal calcification as part of Fahr's syndrome. EEG normal findings. During hospitalization at the Clinic in 2019, retesting of the hypothalamic-pituitary axis was performed, and calcium and phosphate values were monitored (Table 2). Osteodensitometry showed normal bone density (Z score hip – 0.8, Z score spine – 0.1). On the radiography of the bone structures of both hands, shorter IV and V metacarpal bones, initial degenerative changes, narrowed interphalangeal joint spaces, and discrete calcifications of the soft tissues of the hand in the projection of the III and IV fingers were seen. Occasionally there are complaints in the form of fatigue, dizziness and cramps in the extremities that last up to 1 minute and pass spontaneously, loss of balance, and instability in walking. Denies drug allergy. In childhood, he had tonsil and appendix surgery. Mother treated cardiovascular diseases, father diabetes mellitus with complications. Non-smoker.

Objectively conscious on admission, oriented, short stature, normally nourished, TT 55.5 kg, TV 158.4 cm, BMI 22.1 kg/m2, OS 75 cm, OK 87 cm, afebrile, eupnoeic at rest, hemodynamically stable, acyanotic, anicteric, properly discolored skin and visible mucous membranes, properly hydrated, without peripheral lymphadenopathy. The head is circular in shape, Valleix's points, mastoids, and tragus are painfully insensitive to palpation. Pupils are circular, isochoric, and react to light and accommodation. The mucous membrane of the oral cavity is well blooded, moist, the tongue is moist and uncoated. There is no noise above the carotid arteries, and the neck veins are inconspicuous. Thyroid gland of regular position and size, firmer, painless, mobile, without palpable nodules. Breasts can be palpated b.o., without distinguishing tumor formations and secretions during expression. Auscultatory normal breath murmur, without accompanying pathological murmurs. Heart rate is rhythmic, tones clear, no murmurs, TA 110/70 mmHg, pulse 62/min. Abdomen at the level of the chest, soft, painfully insensitive to palpation. The liver and spleen are not palpably enlarged, the renal lobes are painfully insensitive to succussion, and peristalsis is audible. There are no vascular murmurs, a nacreous scar from the previous operation is visible.

Brachydactyly of the fourth and fifth fingers of both hands. Extremities are mobile, without deformity, edema, and varicose veins, symmetrically preserved peripheral pulses, and scant weakness. Trousseau and Chvostek's signs are negative. ECG: Sin rhythm, f 82/min, without acute ST and T changes, QT 400 ms.

The results of laboratory analyses indicate a normal KS and a negative inflammatory syndrome. There are no disorders of glucoregulation or nitrogen retention, proteinogram, lipidogram, electrolytes, and hepatogram are normal (Table 2). During this hospitalization, due to the higher values of calcitonin, a calcium test was also performed, which showed an excessive response of calcitonin to stimulation (Table 3). On the ultrasonography of the neck, it was described that the thyroid gland is in a regular position and size, medium echo, homogeneous echo structure, regular CD signal, without focal changes. No enlarged regional LNs. Both submandibular and parotid glands of homogeneous echostructure, without focal changes. EU TIRADS DL 1 LL 1. Abdominal ultrasonography: Pronounced flatulence of the colon. The liver is in an orderly position and size, homogeneous echostructure, without focal changes. The gallbladder is folded, without intralum. pat. content. Bile ducts are not dilated. The pancreas and vascular structures are covered with gases. The spleen has normal ultrasound findings. Both kidneys are in an orderly position, size, and thickness of the cortex. There are no signs of calculus and hydronephrosis. No pathological changes can be seen in the projection of the adrenal glands. There is no free fluid and pathological LNs in the abdomen. X-ray of the lungs and heart: There are no definite signs of infiltration and consolidation in the lung parenchyma. CF sinuses free. Hemidiaphragms are neatly contoured. Hylus shadows of vascular orderly size. The cardiovascular shadow is within physiological limits, aorta is elongated. Bone and soft tissue structures within physiological limits.

Table 1. Case report

	VC
Age	37
Body mass index	TT 55,5 kg, TV 158.4 cm, BMI 22.1
AHO	yes
Main problems	fatigue, dizziness, loss of balance
Ultrasound findings of thyroid	normal
Family history PHP	no
Other tumors	no
Calcification in CNS	yes

Table 2. Biochemicals parameters

Hormones:	2019.	2023.
TSH	9,26	9,38
fT4	13,7	13,2
ACTH	4,7	7,2
Cortisol	371	309,0
LH	6,42	7,3
FSH	7,1	8,8
PTH	492	245
vitamin D		96
Calcitonin	111,2	94
Ca	2,31	2,33
Ca 2+	1,09	1,20
PO4	1,23	1,61

Table 3. Calcitonin in calcium test

Sampling times/min	1	2	3	4	5
Calcitonin ng/L	187	2480	2381	1993	1337

Discussion:

The pathogenesis of PHP is a gene mutation of the code GNAS, PRKAR1A, PDE4D, or PDE3A, which determines the alpha subunit of the stimulatory guanine nucleotide protein (Gsα). Due to the mutation, the altered subunit Gsα cannot fulfill its role in the signaling pathway of G protein receptors, which causes hormonal resistance to PTH and other hormones (TSH, GHRH, FSH, LH) or calcitonin (5, 6, 7). There are several variants of this entity: type 1-a (PHP 1-a), type 1-b (PHP 1-b), type 1-c (PHP 1-c), type 2 (PHP 2), and pseudopseudohypoparathyroidism (PPHP). (8, 9, 10). Phenotypic features of PHP 1-a and PHP 1-c are short stature, obesity, round face, subcutaneous ossifications, and brachydactyly, commonly known as Albright hereditary osteodystrophy (AHO), (11). On the other hand, the absence of the AHO phenotype and the inability to act exclusively at the kidney level is typical for PHP

1-b. There is another clinical entity, pseudopseudohypoparathyroidism, which has features of the AHO phenotype, but without PTH hormone resistance (12,13).

At the basis of the pathogenesis of PHP 1 is a heterozygous inactivating mutation on the maternal allele of the GNAS gene containing the exons encoding Gs alpha (14). The usual clinical manifestation in a patient with PHP 1 is associated with resistance to many hormones, and biochemical findings include hypocalcemia, hyperphosphatemia, and elevated PTH values (15). Often, PTH resistance is accompanied by TSH resistance, which can manifest itself in early childhood or later in adolescence. As a consequence of this resistance, there is a compensatory increase in TSH, while morphological abnormalities in the thyroid gland and antithyroid antibodies are usually absent (16, 17).

Resistance to PTH can be demonstrated by the Ellsworth-Howard test (persons with PHP type 1 have reduced excretion of CAMP and phosphate in the urine upon administration of exogenous PTH), which is not necessary (2, 18). Definitive diagnosis is established by molecular testing of genetic material, which allows distinguishing PHP subtypes (2, 15).

Calcitonin is a peptide hormone composed of 32 amino acids produced by the C-cells of the thyroid gland and participates in calcium homeostasis. In clinical practice, it is known as a tumor marker of medullary thyroid cancer (MTK), and it exerts its effect through receptors linked to the G protein (19, 20).

The physiology of C-cells and calcitonin in individuals with PHP 1 is not well known. Higher calcitonin values in the calcium test may suggest MTK, but with careful evaluation, the risk can be minimized in these individuals. The explanation of hypercalcitoninemia can be resistance at the receptor level related to the defective G alpha subunit, as with other hormones (21). In the paper "Pseudohypoparathyroidism I a and Hypercalcitoninemia'', from 2001, the authors explain that intravenously or endonasally applied CT raises the level of cAMP in healthy people, but not in people with PHP 1, which supports the theory of silent response, i.e. resistance of target tissues to CT (22, 23). PTH and calcitonin participate in vitamin D metabolism. At the kidney level, the action of PTH is necessary for the activation (hydroxylation of the 1-C atom) of vitamin D. Due to the resistance at the level of the PTH receptor, the production of active vitamin D in the kidney is low. Since calcitonin also participates in vitamin D production by interacting with the 1a hydroxylase gene promoter, hypercalcitonemia may be compensated as a result of low 1,25 dihydroxy vitamin D levels (24,25).

Conclusion:

Elevated calcitonin values should be carefully evaluated, considering its role as a highly specific tumor marker for medullary carcinoma of the thyroid gland and

certain neuroendocrine tumors. Special attention should be given to thyroid gland ultrasound examinations, including a review of potentially suspicious lymph nodes in the neck region. Some authors recommend fine-needle aspiration biopsy (FNB) when nodules are present to minimize the risk of medullary thyroid cancer. If other causes of hypercalcitoninemia are ruled out, the mechanism behind elevated calcitonin values in PHP 1 remains insufficiently understood.

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