Bojan Marković[1], Sanja Klet[1], Mirjana Stojković[1,2], Tamara Janić[1], Biljana Nedeljković Beleslin[1,2], Jasmina Cirić[1, 2], Milos Zarković[1, 2]

VREDNOSTI KALCITONINA U PSEUDOHIPOPARATIROIDIZMU

Sažetak: Pseudohipoparatiroidizam tip 1-a je redak endokrinološki poremećaj koji nastaje mutacijom GNAS gena i posledičnom hormonskom rezistencijom na receptorskom nivou tj. aktivnost preko intracelularnog puta Gs alfa subjedinice nije moguća. Rezistencija u smislu hormonske aktivnosti se najčešće odnosi na paratiroidni hormon, ali može i na druge hormone, kao što su: tireostimulišući hormon, gonadotropine (luteinizirajući i folikostimulišući hormoni), rilizing horomon za hormon rasta, i kalcitonin. Prikazan je pacijent kod kog je postavljena dijagnoza pseudohipoparatiroidizma na osnovu fenotpskih karakteristika hereditarne Albrajtove osteodistrofije. Zbog progresivnog pada u intelektulalnim funkcijama i izmenjenog ponašanja, neurološkim ispitivanjem dokazane su kalcifikacije centralnog nervnog sistema u sklopu Fahrovog sindroma. U toku hospitalizacije registrovane su više vrednosti tireostimulišućeg hormona i kalcitonina, verovatno kao posledica rezistencije na nivou receptora i njegovog intracelularnog puta. Hiperkalcitoninemija se sporadično javlja u slučajevima sa pseudohipoparatiroidizamom tip 1-a i tp 1-b. Povišene vrednosti kalcitonina treba evaulirati anamnezom, kliničkim pregledom uz morfološka i funkcionalna ispitivanja, obzirom da je visoko specifičan tumor marker medularnog karcinoma štitaste žlezde, ali i nekih neuroendokrinih tumora. Neki autori savetuju biopsiju tankom iglom da bi se rizik od medularnog karcinoma štittaste žlezde sveo na minimum.

Ključne reči: pseudohipoparatiroidizam, kalcitonin, hiperkalcitoninemija, FNB

Uvod:

Pseudohipoparatiroidizam (PHP) je endokrinološki poremećaj, u kom paratiroidni hormon (PTH) ne može da ostvari svoje dejstvo na receptorskom nivou zbog

[1] Bojan Marković, Klinika za endokrinologiju, dijabetes i bolesti metabolizma, Univerzitetski Klinički centar Srbije, Odelenje za bolesti štitaste žlezde

[2] Medicinski fakultet Univerziteta u Beogradu, Srbija

mutacije na *GNAS*, *PRKAR1A*, *PDE4D*, ili *PDE3A* genu (1, 2, 3). Rezistencija može biti prisutna na nekoliko drugih hormona poput tireostimulišućeg hormona (TSH), gonadotropina (lutenizirajući, LH i folikostimulišući hormoni, FSH), koji svoju aktivnost ostvarju preko intracelularnog puta Gs alfa subjedinice. Postoji nekoliko tipova PHP, među kojima je najčešći tip 1-a. Pacijent može imati klasični fenotipski izgled Albrajtove osteodistrofije (AHO) uz inicijalne hormonsko-elektrolitne abnormalnosti, povećanje koncentracije PTH i fosfata, uz razvoj hipokalcemije. Povišene vrednosti kalcitonina mogu se naći sporadično kod PHP 1-a i PHP 2-b (4).

Prikaz slučaja:

Pacijent CV (tabela 1), hospitalizovan na Klinici za endokrinologiju, dijabetes i bolesti metabolizma u cilju evaluacije stanja. Dijagnoza pseudohipoparatiodizma (PHP 1-a) postavljena je u detinjstvu na osnovu fenotipskih manifestacija Albrajtove hereditarne ostedistrofije, ponavljanih konvulzija (hipokalcemijska tetanija) i biohemijskih nalaza hipokalcemije. Podatak o genetskom testiranju nepoznat. Od tada je na terapiji aktivnom formom vitamina D i preparatima kalcijuma uz optimalno održavanje homeostaze kalcijuma. Sve vreme se dobro oseća, sem kada supstitucionu terapiju ne koristi, a tada mu se tegobe ispoljavaju u vidu grčeva i trnjenja ekstremiteta uz izrazito zamaranje. Na Klinici hospitalizovan 2008. godine, kada je učinjeno kompletno retestiranje kada je registrovan porast TSH uz uredan fT4, u terapiju uvedena supstitucija levotroksinom. Zbog promena u ponašanju uz opadanje intelektualnih funkcija hospitalizovan na Klinici za neurologiju, 2009.g, kada je uočeno na CT-u endokranijuma obostrano u predelu bazalnih ganglija i frontalno masivne kalcifikacije u sklopu Fahrovog sindroma. EEG urednog nalaza. Tokom hospitalizacije na Klinici 2019. godine učinjeno je retestiranje hipotalamusne-hipofizne osovine, praćene su vrednosti kalcijuma i fosfata (tabela 2). Osteodenzitometrija je pokazala normalnu koštanu gustinu (Z score kuka – 0,8, Z score kičme – 0,1). Na radiografiji koštanih struktura obe šake, viđene su kraće IV i V metakarpalne kosti, početne degenerativne promene, suženi interfalangealni zglobni prostori, diskretne kalcifikacije mekih tkiva šake u projekciji III I IV prsta. Povremeno ima tegobe u vidu zamaranja, vrtoglavice i grčeva u ekstremitetima koji traju do 1 minut i spontano prođu, gubitak ravnoteže i nestabilnost u hodu. Negira alergiju na lekove. U detinjstvu imao operaciju krajnika i slepog creva. Majka lečila kardiovaskularne bolesti, otac dijabetes melitus sa komplikacijama. Nepušač.

Objektivno na prijemu svestan, orijentisan, nižeg rasta, normalno uhranjen, TT 55,5 kg, TV 158.4 cm, BMI 22.1 kg/m2, OS 75 cm, OK 87 cm, afebrilan, u miru eupnoičan, hemodinamski stabilan, acijanotičan, anikteričan, uredno prebojene kože i vidljivih sluznica, uredno hidriran, bez periferne limfadenopatije. Glava kružnog oblika, Valleix-ove tačke, mastoideusi i tragusi palpatorno bolno neosetljivi. Zenice

kružne, izokorične, reaguju na svetlost i akomodaciju. Sluznica usne duplje dobro prokrvljena, vlažna, jezik vlažan, neobložen. Nad karotidnim arterijama nema šuma, vene vrata neupadljive. Štitasta žlezda urednog položaja i veličine, čvršća, bezbolna, pokretna, bez palpabilnih nodusa. Dojke palpatorno b.o, bez izdvajanja tumorske formacija i sekrecije pri eksprimaciji. Auskultatorno normalan disajni šum, bez pratećih patoloških šumova. Srčana radnja ritmična, tonovi jasni, šumova nema, TA 110/70 mmHg, puls 62/min. Abdomen u ravni grudnog koša, mek, palpatorno bolno neosetljiv. Jetra i slezina nisu palpatorno uvećane, bubrežne lože bolno neosetljive na sukusiju, peristaltika čujna. Nema vaskularnih šumova, uočava se sedefasti ožiljak od prethodne operacije. Brahidaktilija četvrtog i petog prsta obe šake. Ekstremiteti pokretni, bez deformiteta, edema i varikoziteta, simetrično očuvanih perifernih pulseva, oskudne maljavosti. Trousseau i Chvostekov znak negativan. EKG: Sin ritam, f 82/min, bez akutnih ST i T promena, QT 400 ms.

Rezultati laboratorijskih analiza ukazuju na urednu KS i negativan zapaljenski sindrom. Nema poremećaja glikoregulacije ni retencije azotnih materija, proteinogram, lipidogram, elektroliti i hepatogram uredni (tabela 2). Tokom ove hospitalizacije zbog viših vrednosti kalcitonina učinjen i kalcijumski test koji je pokazao prekomerni odgovor kalcitonina na stimulaciju (tabela 3). Na ultrasonografiji vrata opisano: Štitasta žlezda je urednog položaja i veličine, srednjeg ehoa, homogene ehostrukture, urednog CD signala, bez fokalnih promena. Nema uvećanih regionalnih LN. Obe submandibularne i parotidne žlezde homogene ehostrukture, bez fokalnih promena. EU TIRADS DL 1 LL 1. Na ultrasonografiji abdomena: Izražen meteorizam kolona. Jetra je urednog položaja i veličine, homogene ehostrukture, bez fokalnih promena. Žučna kesa je presavijena, bez intralum. pat. sadržaja. Žučni vodovi nisu dilatirani. Pankreas i vaskularne strukture prekriveni gasovima. Slezina je urednog UZ nalaza. Oba bubrega urednog položaja, veličine i debljine korteksa. Nema znakova kalkuloze i hidronefroze. U projekciji nadbubrežnih loža ne vide se patološke promene. U abdomenu nema slobodne tečnosti i patoloških LN. Rtg pluća i srca: Ne vide se sigurni znaci infiltracije i konsolidacije u plućnom parenhimu. CF sinusi slobodni. Hemidijafragme uredno konturisane. Hilusne senke vaskularne uredne veličine. Srčano-sudovna senka u fiziološkim granicama, aorta elongirana. Koštane i mekotkivne strukture u fiziološkim granicam.

Tabela 1. Prikaz kliničkih karakteristika pacijenta

Prikaz slučaja	VC
Godine	37
Telesna masa/težina	TT 55,5 kg, TV 158.4 cm, BMI 22.1
AHO	da

Glavne tegobe	zamaranje, vrtoglavicu, gubitak ravnoteže
Ultrazvuk žlezde	uredan nalaz
Porodična anamneza PHP	ne
Drugi tumori	ne
Kalcifikati CNS	da

Tabela 2. Uporedni prikaz biohemijskih parametara

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

Tabela 3. Kalcitonin u kalcijumskom testu

vremena uzorkovanja/min	1	2	3	4	5
kalcitonin ng/L	187	2480	2381	1993	1337

Diskusija:

U osnovi patogeneze PHP je genska mutacija koda *GNAS*, *PRKAR1A*, *PDE4D*, ili *PDE3A*, koji determiniše alfa subjedinicu stimulativnog guanin nukleotid proteina

(Gsα). Zbog mutacije izmenjena subjedinica Gsα ne može da ostvari svoju ulogu u signalnom putu G proteinskih receptora zbog čega nastaje hormonska rezistencija na PTH i druge hormone (TSH, GHRH, FSH, LH) ili kalcitonina (5, 6, 7). Postoje nekoliko varijanti ovog entiteta: tip 1-a (PHP 1-a), tip 1-b (PHP 1-b), tip 1-c (PHP 1-c), tip 2 (PHP 2) i pseudopseudohipoparatiroidizam (PPHP) (8, 9, 10). Fenotipske karakteristike PHP 1-a i PHP 1-c su nizak rast, gojaznost, okruglo lice, potkožne osfikacije i brahidaktilija, poznatije kao Albrajtova nasledna osteodistrofija (AHO), (11). Sa druge strane, odsustvo AHO fenotipa i nemogućnost delovanja isključivo na nivou bubrega su tipične za PHP 1-b. Postoji još jedan klinički entitet pseudopseudohipoparatiroidizam, koji ima karakteristike AHO fenotipa, ali bez PTH hormonske rezistencije (12,13).

U osnovi patogeneze PHP 1-a je heterozigotna inaktivirajuća mutacija na majčinom alelu GNAS gena koji sadrži egzone koji kodraju Gs alfa (14). Uobičajna klinička manifestacija kod pacijenta sa PHP 1-a je povezana sa rezistencijom na mnogobroje hormone, a u biohemijskim nalazima registruje se hipokalcemija, hiperfosfatemija i povišene vrednosti PTH (15). Često se uz rezistenciju na PTH javlja i rezistencija na TSH, koja se može manifestovati u ranom detinjstvu ili kasnije u adolescenciji. Kao posledica ove rezistencije, dolazi do kompenzatornog porasta TSH, dok morfološke abdormalnosti u štitastoj žlezdi i antitiroidna antitela najčešće izostaju (16, 17).

Rezistencija na PTH se može dokazati Ellsworth-Howard testom (osobe sa PHP tip 1-a imaju smanjeno izlučivanje CAMP i fosfata u urinu na primenu egzogenog PTH), što nije neophodno (2, 18). Definitivna dijagnoza se postavlja molekularnim testiranjem genetskog materijala, koji omogućava razlikovanje podtipova PHP (2, 15)

Kalcitonin je peptidni hormon sačinjen od 32 aminokiseline koji produkuju C-ćelije štitaste žlezde i učestvuje homeostazi kalcijuma. U kliničkoj praksi je poznat kao tumor marker medularnog karcinoma štitaste žlezde (MTK), a svoje dejstvo ostvaruje preko receptora vezanih za G protein (19, 20).

Fiziologija C-ćelija i kalcitonina kod osoba sa PHP 1-a nije dovoljno poznata. Više vrednosti kalcitonina u kalcijumskom testu mogu sugerisati na MTK, ali pažljivom evaluacijom rizik se kod ovih osoba može svesti na minimum. Objašnjenje hiperkalcitoninemije može biti rezistencija na receptorskom nivou vezana za defektnu G alfa subjedinicu, kao i kod ostalih hormona (21). U radu *"Pseudohypoparathyroidism I a and Hypercalcitoninemia*", iz 2001. godine, autori objašnjavaju da intravenski ili endonazalno primenjen CT podiže nivo cAMP kod zdravih osoba, ali ne kod i osoba sa PHP 1-a, što podržava teoriju **nemog odgovora** tj. rezistencije ciljnih tkiva na CT (22, 23). U metabolizmu vitamina D učestvuje PTH i kalcitonin. Na nivou bubrega, neophodno je dejstvo PTH za aktivaciju (hidroksilaciju 1-C atoma) vitamina D. Obzirom na rezistenciju na nivou receptora ta PTH, produkcija aktivnog vitamina D u bubregu je niska. Budući da kalcitonin takođe učestvuje u produkciji vitamina

D interakcijom sa promoterom gena 1-a hidroksilaze, hiperkalcitonemija može biti kompezatorna kao posledica niskih vrednosti 1,25 dihidroksivitamina D (24, 25).

Zaključak:

Povišene vrednosti kalcitonina treba evaluirati s obzirom da je visoko specifičan tumor marker medularnog karcinoma štitaste žlezde, ali i nekih neuroendokrinih tumora. Posebni akcenat potrebno je staviti na ultrazvučni pregled štitaste žlezde uz pregled potencijalno suspektnih limfnih nodusa u regiji vrata. Neki autori savetuju biopsiju tankom iglom (FNB), ukoliko postoji nodus, da bi se rizik od MTK sveo na minimum, čak i profilaktičku tiroidektomiju u slučajevima gde su opisani patološki izmenjeni limfni nodusi. Ukoliko se isključe drugi uzroci hiperkalcitoninemije, mehanizam povišenih vrednosti kalcitonina kod PHP 1-a i dalje ostaje nedovoljno razjašnjen.

Bojan Marković[1], Sanja Klet[1], Mirjana Stojković[1,2], Tamara Janić[1], Biljana Nedeljković Beleslin[1,2], Jasmina Cirić[1, 2], Milos Zarković[1, 2]

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

[1] Bojan Marković, Clinic for Endocrinology, Diabetes and Metabolic Diseases, University Clinical Center of Serbia, Department of Thyroid Diseases

[2] Faculty of Medicine, University of Belgrade, Serbia

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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