Case Report

Two Cases of Non-Surgical Hypoparathyroidism That Were Diagnosed with Delay

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Hypoparathyroidism is characterized by low parathyroid hormone levels, low calcium levels, and high phosphate levels in the blood. The most common cause is neck surgery. Non-surgical hypoparathyroidism (Ns-HypoPT) can have various causes, including genetic ones. The most common genetic cause of Ns-HypoPT is the loss of the q11 region (22q11) on chromosome 22 which results in hypoplasia of the parathyroid glands. 22q11 syndrome is also known as DiGeorge syndrome (DGS). The acronym ≪CATCH 22≫ refers to the five clinical manifestations of DGS: Cardiac defects; Abnormal facies facial dysmorphia; Thymic hypoplasia; Cleft palate; Hypocalciemia (HC). Diagnosis of DGS can be complicated due to the phenotype variation. DGS is suspected in the presence of at least one CATCH22 sign, molecular genetic methods confirm or refute the diagnosis. The publication presents two cases of Ns-HypoPT in adults who were not diagnosed in a timely manner. In both cases, HC with a decrease in PTH levels without a surgical history indicates Ns-HypoPT. Using nucleotide sequence analysis and deletion/duplication testing of a panel of 2,211 genes in case 1, pathogenic variants were identified in three genes: TBX1 (associated with autosomal dominant DGS); LZTR1 (associated with autosomal dominant schwannomatosis and autosomal dominant and autosomal recessive Noonan syndrome); CLCN1 (associated with autosomal dominant and recessive congenital myotonia). Case 1 is characterized by the combination of DGS and Graves' disease. Despite the different etiology of Ns-HypoPT (in case 1 it is a component of DGS, and in case 2 the etiology has not yet been established), in both cases HC was detected late and was treated ineffectively for a long time. The use of calcitriol [1,25 (OH)2 D3], the active form of vitamin D3, at a dosage of 1.25 μg/day (case 1) and 1.75 μg/day (case 2) increased calcium levels and reduced HC symptoms.

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Hypoparathyroidism (HypoPT) is characterized by low plasma calcium and low parathyroid hormone levels, as well as high phosphate levels. The most common cause of HypoPT is neck surgery[1]. Nonsurgical hypoparathyroidism (Ns-HypoPT) can have various causes, including genetic disorders, autoimmune diseases, radiation, and sometimes sarcoidosis, iron (hemochromatosis) or copper (Wilson's disease) accumulation. The most common genetic cause of Ns-HypoPT is a deletion (loss) of chromosome 22 q11 (22q11), which results in hypoplasia of the parathyroid glands[2]. 22q11 syndrome is also known as DiGeorge syndrome (DGS). Angelo DiGeorge described cases of thymus atrophy in association with Ns-HypoPT in several children between 1965 and 1968[3][4]. The molecular genetic basis of DiGeorge syndrome was described later[5]. 22q11 deletion syndrome (22q11 DS) is better known clinically as DGS, but other names include velocardiofacial syndrome (VCFS); Shprintzen syndrome; Cayler cardiofacial syndrome; Takao syndrome; and CATCH-22. It is one of the most common genetic syndromes, with an estimated prevalence of 1:3000 individuals. Modifier genes are thought to contribute to the variability of its phenotype. Manifestations include congenital heart defects, immunodeficiency, hypocalcemia, velopharyngeal (palatal-pharyngeal) insufficiency, developmental delay, cognitive impairment, psychiatric disorders, and characteristic facial features[6]. The acronym “CATCH 22” refers to five clinical manifestations of DGS: **C**ardiac; **A**bnormal facies; **T**hymic hypoplasia; **C**left palate; **H**ypocalciemia. The name CATCH22 refers to the novel of the same name “Catch 22” by writer Joseph Heller[7]. Unlike Heller’s work of fiction[8], in which the choice of the number 22, indicating a paradox symbolizing the absurdity of bureaucratic systems where people cannot solve their problems due to inconsistent rules, had no plot connection, the clinical acronym “CATCH 22” recalls damage to chromosome 22. The diagnosis of DiGeorge syndrome can be difficult due to the variation in phenotypes between individuals. It is suspected in patients with one or more of the CATCH22 features. In these cases, the diagnosis is confirmed by the observation of a deletion of part of the long arm (q) of chromosome 22, region 1, band 1, sub-band 2. Genetic analysis is usually performed using fluorescence in situ hybridization (FISH), which is able to detect microdeletions that are not captured by standard karyotyping. A newer method of analysis is quantitative polymerase chain reaction (qPCR), which has several advantages over FISH[9][10].

The presence of a history of neck surgery usually helps in the timely diagnosis of postoperative hypoparathyroidism (E 89.2 Postprocedural hypoparathyroidism according to ICD 10) in patients with symptoms and signs of hypocalcemia. There have been thorough publications on this pathology in the domestic literature[11][12], but the absence of a surgical history, as evidenced by current diagnostic practice, leads to an incorrect and late diagnosis of Idiopathic hypoparathyroidism (E 20.0) or Other

hypoparathyroidism (E 20.8) according to the same ICD 10 classification. Below we present two clinical cases of Ns-HypoPT, which were not correctly diagnosed and which did not receive adequate treatment for a long time. The informed consent of the patients for the publication of the results of their studies was obtained.

Case 1

Patient A., a 23-year-old women, Caucasian, who lives in the Kyiv region, applied to the consultative polyclinic of the Institute of Endocrinology and Metabolism. Symptoms: epileptiform seizures with generalized convulsions, loss of consciousness and memory of the onset of the attack, bone pain in the upper and lower extremities, in the cervical and lumbar spine during prolonged horizontal position, a feeling of cracking in the bones of the feet, symmetrical tremor of the hands at rest, progressive deterioration of vision, increased pulse, attacks of syncope and dizziness at rest, pain in the temporal region of the head. In addition, the patient complained of decreased visual acuity, decreased height, deformation of the phalanges of the toes and the inability to smell - anosmia. Also notes progressive weakness and frequent episodes of acute respiratory viral infections. In 2020, 2021, 2022 and in August 2024, she was ill with COVID-19.

The patient was born as a result of premature birth at 8 months of gestation. At 5 months, she contracted measles, after which she began to lag behind in physical development. From the age of 5, symptoms of paresthesia of the extremities. Since 2011 (age 10), facial dysmorphism has been noted. The first epileptiform seizure occurred in 2014, tonic-clonic seizures were described, which is why the patient was first admitted to intensive care. Since the same year, she has been transferred to individual home education due to progressive symptoms of the disease. 22.08. 2023 laboratory signs of thyrotoxicosis were detected: TSH 0.007 (normal 0.27-4.2) μIU/ml; T4 free 32.29 (normal 10.3 – 24.5) pmol/L; T3 free 11.25 (normal 3.84 –6.60) pmol/L. According to ultrasound examination of the thyroid gland, “signs of chronic autoimmune thyroiditis”, volume 16.1 cm3. From 08/24 to 09/01/2023, she was treated in the Chernihiv Regional Hospital with the main diagnosis of “Diffuse toxic goiter” (thiamazole 30 mg per day with subsequent dose reduction). Treatment for the concomitant disease, which was defined as "Pronounced somatoform vegetative dysfunction with diencephalic crises, anxiety-phobic syndrome, insomnia on the background of connective tissue dysplasia" was carried out in the intensive care unit of the Chernihiv Regional Hospital. However, the main symptoms (convulsions, periodically with loss of consciousness) remained even after treatment of thyrotoxicosis with thiamazole, to which tranquilizers

(gidazepam, diazepam), nootropics (citicoline), antidepressants (escitalopram), antipsychotics (olanzapine) were added. Also, among the medications that were used at that time, dexamethasone, magnesium sulfate and calcium gluconate were indicated. The only indicator of a standard biochemical blood test that differed from normal values was the level of ionized calcium (0.94 mmol/L; norm 1.13 - 1.32 mmol/L). Total or albumin-corrected calcium levels were not studied. In the absence of a diagnosis that could explain most of the symptoms, the girl was treated for a long time and unsuccessfully under the supervision of neurologists for vegetative-vascular dystonia of the adolescent period, epileptic syndrome, myasthenic syndrome and even multiple sclerosis. Electroencephalographic examination did not reveal signs of epilepsy, but the patient was offered treatment in a psychiatric hospital in 2024.

The cardiologist diagnosed “dysmetabolic cardiomyopathy, aortic valve fibrosis, aortic and mitral valve insufficiency of the I degree, CLC syndrome, heart failure II a with preserved ejection fraction (56%)”. Given the shortened PQ interval on the electrocardiogram and symptoms of paroxysmal tachycardia, we can suspect the presence of Laun-Ganong-Levin (LGL) syndrome, a type of premature ventricular excitation[13].

Electromyography from 08/15/2023: “the data may indicate signs of hypertonicity in the foot flexors, suprasegmental activity, axonopathy of the right peroneal nerve with a decrease in contractility in the extensors up to 65%, changes in the muscles of the dysmetabolic-dystrophic type with a myotonic component.”

During 2020-2024, the patient had COVID-19 4 times, which was confirmed by laboratory tests.

Family history: relatives on the mother’s side did not have similar symptoms. The girl's father, a few months before her birth, worked in the Chernobyl zone as a decontamination worker during the reconstruction of the protective structure, now known as the "sarcophagus". On the recommendation of a geneticist, a multiple genetic panel study was ordered.

02.05.2024 the patient presented the results of nucleotide sequence analysis and deletion/duplication testing of a panel of 2,211 genes, which was conducted by the Invitae laboratory. This study was conducted with the assistance of a charitable foundation.

Methodological details of the genetic study: genomic DNA was enriched with target regions using a hybridization-based protocol. Sequencing was performed using Illumina technology. All target regions had more than 50x coverage. Reads were aligned to the reference genome (GRCh37), and sequence changes were identified and interpreted in the context of individual clinically relevant transcripts (2211

genes). Enrichment and analysis focused on coding regions with 20 bp flanking sequences and other regions known to be of clinical relevance. Exonic mutations and duplications were detected by a proprietary Invitae algorithm. Genetic variants were submitted in accordance with the Human Genome Variation Society (HGVS). Sequencing was performed by Invitae corp.

According to the report # RQ6089494 dated 08.02.2024, the following were identified:

- one pathogenic variant in the LZTR1 gene. LZTR1 is associated with autosomal dominant schwannomatosis and autosomal dominant and autosomal recessive Noonan syndrome;
- one pathogenic variant has been identified in the TBX1 gene. TBX1 is associated with autosomal dominant DiGeorge syndrome/velocardiofacial syndrome;
- one pathogenic variant has been identified in the CLCN1 gene. CLCN1 is associated with autosomal dominant and recessive myotonia congenita.

During the examination of patient A. in April 2024: heart rate 67 beats/min, regular rhythm, blood pressure 110/90 mm Hg, height 152 cm, weight 50 kg, BMI – 21.6 kg/m2. There is a small symmetrical tremor of the hands. On examination, valgus deformities of the knee joints and I metatarsal bones, limping when walking. Positive signs of Chvostek and Trousseau. Signs of skeletal deformation in the thoracic and cervical regions, forced head position. The face is disproportionate, the profile is straight, the lower third of the face is elongated, the angle of the lower jaw is increased, the nasolabial folds are tense, not pronounced, the supramental fossa is smoothed, the periocular muscles are sharply tense. The mouth is half-open, the red border of the lips is dry, with scales. The opening of the mouth is limited (~ 18 mm). The movements of the lower jaw are limited, periodically painful. On palpation, the chewing, temporal, and chin muscles are tense, painful. The vestibule of the oral cavity is small, the frenulum of the upper and lower lips is normal. The gums are hyperemic, locally hypertrophied, and bleeding. Gothic palate. Narrowing and deformation of the lower and upper dentition with crowding of teeth in the frontal area of the lower jaw. Nasal breathing is absent. Excessively folded spiral of the auricle.

The patient presented the following laboratory results: parathyroid hormone 11.7 (normal 14.7-69) pg/ml, total serum calcium 1.64 (normal 2.15-2.6) mmol/L, ionized 0.87 (normal 1.16-1.32) mmol/L. These laboratory data were obtained while taking 1000 mg of calcium carbonate in combination with 400 IU of ergocalciferol (2 tablets of Calcium D3 Nycomed). At the first visit in April, the patient was prescribed the hydroxylated form of vitamin D3 (calcitriol 0.5 μg) once a day and calcium levels were monitored in 2 weeks. During the second visit, the patient noted an improvement in well-being and a decrease in

paresthesias, and sleep improved at night due to the reduction of myalgias. 05/08/24 total calcium 2.09 (2.15-2.6), ionized 0.93 (0.99-1.37) mmol/L, i.e. the calcium level is still low. It is recommended to increase the dose of calcitriol to 1 mcg per day.

07/03/24 total calcium level reached the norm of 2.34 mmol/L (2.15-2.5), but on 08/21/24 it decreased slightly to 2.14 mmol/L, ionized 1.14 mmol/L. The dose of calcitriol was recommended to be increased to 1.25 mcg/day, but due to the lack of tablets of adequate dosage, it was increased to 1.5 mcg/day. 09/02/24 total calcium increased above the norm to 2.79 and ionized to 1.5 mmol/L. A more accurate dosage of calcitriol 1.25 μg / day on 01/31/25 made it possible to normalize the total calcium level: 2.19 (2.15-2.5) mmol/L. Symptoms: continued myalgia and seizures, but since the time of treatment there have been no repeated attacks of tonic-clonic generalized seizures with loss of consciousness. Taking into account the persistence of some symptoms (weakness, tremor, rapid heartbeat) and a history of thyrotoxicosis, on 12/05/2024 the levels of thyroid-stimulating hormone (TSH) and the level of antibodies to the TSH receptor were checked: 0.186 μIU/ml (normal 0.27-4.2), antibodies to the TSH receptor 3.51 IU/L (normal less than 3.1). Ongoing thyrotoxicosis within the framework of Graves' disease was confirmed, treatment with thiamazole (tyrosol) 20 mg per day was resumed. Against the background of a maintenance dose of thiamazole (5 mg/day) on 01/31/2025, free thyroxine was 1.02 (normal 0.92-1.68) ng/dl; TSH was 2.0 (normal 0.27-4.2) μIU/ml. The symptoms decreased, but did not disappear.

Thus, at present, the endocrinological diagnoses remain E20.8 “Other hypoparathyroidism” and E05.0 “Graves’ disease”. A more accurate classification of hypoparathyroidism according to ICD-10 in this case may be D82.1 “DiGeorge’s syndrome”.

At the same time, the elimination of hypocalcemia and thyrotoxicosis led to the cessation of major seizures with loss of consciousness, but a significant number of symptoms remain. Taking into account the clinical data and the results of the genetic study, the neurologist diagnosed: Q85.0 Neurofibromatosis type II with schwannomatosis, development of complex regional pain syndrome, neurosis-like condition. Treatment remains symptomatic. Short-term use of gabapentin did not improve and was suspended.

Case 2

Patient B., a 55-year-old man, a resident of Ukraine, Caucasian, first consulted at the V.P. Komisarenko IEOR polyclinic on November 13, 2019. Symptoms: convulsive seizures with loss of consciousness, occurring since 2016 approximately 4 times a year. In 2019, a decrease in calcium levels and an increase in phosphorus levels in the blood were detected: ionized calcium 0.7 mmol/l; phosphorus 1.83 (0.8-1.45)

mmol/l; the level of parathormone according to 2 different laboratories is also reduced: 9.1 (normal 15-65) and 5.5 (normal 18.5-88) pg/ml. The total calcium level is only 1.4 mmol/l (!). Interestingly, during the examination, no signs of Chvostek and Trousseau were detected. Also, no signs of heart defects and facial dysmorphism were detected. At the time of the consultation, the treatment of "epilepsy" continued with carbamazepine 100 mg daily and calcium carbonate 500 mg with ergocalciferol 10 μg ("osteocor" 2 capsules) without reducing the frequency of seizures or normalizing calcium levels.

The diagnosis was established: E 20.0 Idiopathic hypoparathyroidism and treatment with hydroxylated vitamin D3 preparations was prescribed: alfacalcidol starting at 1 μg per day or calcitriol at 0.5 μg per day in combination with calcium citrate (3 tablets or 600 mg of atomic calcium per day). Carbamazepine was discontinued. Already on January 10, 2020, while taking 2 μg of alfacalcidol and calcitriol, he reported improvement - there were no symptoms of hypocalcemia and loss of consciousness, however, normocalcemia was achieved only after switching to calcitriol, the current dose of which is 1.75 μg (Fig. 2 B). Over the past almost 5 years of observation, the patient has not had a single seizure with loss of consciousness or convulsions. The search for the cause of Ns-HypoPT in the patient has not yet been completed: signs of autoimmune polyglandular syndrome type 1, which may be the cause of hypoparathyroidism and hypocalcemia[14] were not detected. D22S75 deletions (Di Giorgi region) were also not detected by FISH. The search for DGS by other methods was not carried out, given the absence of other signs of it, such as cardiopathy and facial dysmorphism. Radiologically (MSCT in 2024) small (up to 7 mm) solid nodules were detected in the parenchyma of both lungs. Currently, observation is continuing for the diagnosis of possible pulmonary sarcoidosis, which may be the cause of Ns-HypoPT[15].

Discussion

In both clinical cases, adults have a long history of symptoms and signs of hypoparathyroidism (hypocalcemia with decreased parathyroid hormone levels) without a history of neck surgery, which allows combining these cases into the Ns-HypoPT category. Patient B. has an elevated serum phosphorus level, which is also characteristic of hypoparathyroidism[1]. Despite the different etiology of hypoparathyroidism (in case 1 it is a component of DGS, and in case 2 the etiology of decreased parathyroid function has not yet been established), in both cases hypocalcemia was detected late and treated ineffectively, and prolonged unnecessary treatment of epilepsy was also carried out. The unsuccessful treatment of hypocalcemia in both cases is apparently associated with the use of non-hydroxylated vitamin D3 (ergocalciferol), which is unable to counteract hypoparathyroidism. Instead, the

appointment and gradual increase in the daily dose of calcitriol [1,25 (OH)2 D3], the active form of vitamin D3, to 1.25 μg/day (case 1) and 1.75 μg/day (case 2) normalized calcium levels, reduced the symptoms of patient A and eliminated them in patient B.

The preservation of some of the symptoms in patient A. can be can be attributed to the manifestations of schwannomatosis, the presence of which is indicated by genetic research that revealed a pathogenic variant in the LZTR1 gene. Neurological manifestations of LZTR1-associated schwannomatosis can be quite diverse and include: 1. Chronic pain: often associated with schwannomas that press on peripheral nerves. 2. Numbness or weakness: these symptoms occur when tumors compress nerves, affecting motor or sensory functions. 3. Tinnitus: may occur if tumors affect the auditory nerves. 4. Balance problems: depending on where the tumors are located, they can affect the vestibular apparatus, resulting in dizziness or uncoordinated movements[16]. All of these symptoms are present in patient A. The study and treatment of this pathology is our current task, for which we count on the help of neurologists. Another feature of case #1 is the combination of DGS with Graves′ disease. The weakening of the immune system due to DGS-associated thymic hypoplasia may explain not only the susceptibility to infections but also the deficiency of certain T-lymphocyte subpopulations, which have long been associated with the development of Graves′ disease[17]. Data from Japanese authors suggest that PD-1-positive CD4+ and CD8+ T cells and T-reg cells may be associated with autoimmunity in the patient they described with DGS complicated by Graves′ disease[18].

Conclusions

1. HC is still not diagnosed in a timely manner, which leads to incorrect treatment of non-existent epilepsy.
2. Treatment of HC caused by hypoparathyroidism requires the use of an active form of vitamin D3.
3. Ns-HypoPT may be an element of a complex genetic syndrome (DGS) that can be diagnosed in Ukraine.
4. The preservation of some neurological and muscular symptoms after the elimination of HC in patients with DGS may indicate the defeat of several genes and requires a more extensive genetic study

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Declarations

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