Variable phenotype of pseudohypoparathyroidism in children

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Background. Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders associated with tissue insensitivity to parathyroid hormone. PHP is characterized by genetic heterogeneity and variable phenotype. In addition to the hypocalcemic syndrome and resistance to parathyroid hormone, PHP is also characterized by phenotypic features and resistance to other hormones (primarily, parathyroid hormone, PTH), which are known as Albright Hereditary Osteodystrophy (AHO). Until recently, no analysis of large cohorts of patients with PHP has been performed in Russian literature.

Objective — to examine a large cohort of patients with PHP and assess the clinical features of PHP.

Material and methods. A group consisting of 32 patients with different variants of course of the disease who had been examined at the Endocrinology Research Center in 2014—2016 was analyzed.

Results. Features of AHO phenotype in addition to hormonal resistance were identified in 16 (50%) patients; one of them had one feature (brachydactyly) and 15 patients had two and more features of AHO. Besides insensitivity to PTH, TSH resistance was found in 22 (68.75%) patients and one patient had resistance to PTH, TSH and LH/FSH. Hypothyroidism manifested before hypocalcaemia in 4 patients. Obesity was the first complaint in 8 patients; 5 of them had subclinical hypocalcaemia and the remaining 3 patients had an elevated PTH level with the normal level of calcium at the time of first examination. The most typical clinical signs of hypocalcaemia in 23 (72%) patients were seizures. Thirteen of them were misdiagnosed with epilepsy and had been followed by a neurologist for a period ranging between 2 months and 7 years before hypocalcaemia was revealed.

Conclusions. Pseudohypoparathyroidism is a rare genetic disorder associated with resistance to parathyroid hormone, which can have a lot of other clinical features in addition to the syndrome of PTH-resistance. Obesity or hypothyroidism may be the earliest manifestation of PHP preceding hypocalcaemia. Evaluation of serum calcium level is important for all pediatric patients with PHP, especially those with a positive family history.

Keywords: pseudohypoparathyroidism, albright Hereditary Osteodystrophy (AHO), hypocalcaemia, seizures.
which is caused by disruptions in post-receptor signaling mechanisms.

G-protein associated with the stimulating alpha-subunit (Gαs) participates in signaling initiated by a variety of hormones, such as PTH, TSH, LH, FSH, somatoliberin, etc. Gαs is the first mediator in the signal transmission from the hormones' surface receptors to the cell nucleus. Binding of a ligand to a receptor leads to activation of Gαs, which provides for the formation of cAMP and a change in the expression of hormone-sensitive genes [2]. Gαs is encoded by a complex gene, GNAS. Inactivating mutations in this gene lead to loss of Gαs activity and development of the disease.

The clinical features of the disease vary depending on the mechanisms of inheritance of the inactivating mutation. The mutation inherited from the mother or developed de novo on a maternal allele, results in PHP Ia, which involves multi-hormonal resistance (insensitivity to PTH, TSH, somatoliberin, LH, FSH) and phenotypic features of Albright hereditary osteodystrophy (AHO), including obesity, brachidactyly, shortening of fingers IV, V metacarpal and metatarsal bones, rounded face, short neck, subeutaneous calcifications, short stature, mental retardation [3].

Another clinically identical type of pseudohypoparathyroidism, PHP Ic (PHPIC; OMIM №612462), has been described in addition to PHP Ia. In PHP Ia Gαs is completely unable to activate cAMP, whereas in PHP Ic Gαs can activate cAMP by receptor-independent pathway, but it is incapable of reacting to receptor activation [4].

Inactivating mutations on the paternal allele lead to development of AHO without signs of hormonal resistance, the so-called pseudo pseudohypoparathyroidism, PHP Ib (PPHP; OMIM №612463), or to development of progressive bone heteroplasia characterized by the formation of deep widespread calcifications of the dermis, muscles and fasciae (POH, OMIM №166350).

GNAS gene is under the control of epigenetic factors that regulate its expression. Therefore, the synthesis of Gαs can be disrupted not only by mutations in the gene itself, but also by disruption of these factors’ activity. In such cases, a molecular genetic test would not reveal mutations in GNAS gene and there would be clinical resistance to PTH and TSH without any phenotypic features. This form of the disease is called PHP Ib.

In addition to three varieties of PHP type I, there is also PHP type II (OMIM №203330) in which the resistance to hormones is not caused by the inactivation of Gαs, but by disruption of other stages in the post-receptor signaling mechanism. This form has no associated mutations in GNAS and the disease can only be diagnosed based on Elsworth—Howard test.

Thus, the classification of pseudohypoparathyroidism is based on several criteria: presence of AHO signs distinguishes PHP Ia/Ic from PHP Ib; presence of hormonal resistance distinguishes PHP from PPHP; the results of in vitro study of Gαs activity in erythrocytes distinguishes PHP Ia from PHP Ic and, finally, the Elsworth—Howard test distinguishes PHP type 1 from PHP type 2 (Table 1).

This classification does not take into account some of molecular genetic features of PHP discovered in the last 10 years. There is no strict genotype-phenotype correlation for PHP: PHP Ia can be caused by both inactivating mutations in GNAS gene and epigenetic defects. In addition, a case of PPHP (a boy with phenotypic signs of AHO without hormonal resistance) has been described in which the mutation was not inherited from the father, as might have been expected, but from the mother [5]. The above classification also overlooks clinically similar conditions (such as acrodysostosis due to inactivation of protein kinase A, progressive osteoid heteroplasia which is also caused by mutations in GNAS gene). Specific tests are required to establish the diagnosis. The European Working Group on the Study of PHP is developing a new classification, which will include all diseases caused by disruption of PTH signaling pathway [6]. The variety of clinical forms and, simultaneously, low incidence of PHP poses difficulties for its diagnosis and treatment. Therefore, the description and analysis of clinical cases can be useful for practicing endocrinologists and for fundamental science, since it allow accumulating international experience in the study of this rare hereditary disease.

Aim — the study was conducted to assess variations in manifestation and course of pseudohypoparathyroidism, the effectiveness of diagnosis and treatment of the disease components and assessment of incidence of complications of this rare multicomponent disease.

Material and method

Study design

A simple descriptive study which included an analysis of variants of manifestation, spectrum of clinical features, approaches to therapy, and complications in patients with pseudohypoparathyroidism. The first stage included collection of data on the history of the disease and family history, examination of the patients to identify phenotypic signs of Albright’s inherited osteodystrophy and multi-hormone resistance, and screening for complications. The second stage consisted of the analysis of the obtained data. This stage included analysis of the indicators of physical development at birth in the patients with PHP Ia and PHP Ib, assessment of phenotypic features of various types of PHP, identification of variants of disease manifestation, assessment of incidence of individual components of the disease, and development of examination and treatment algorithms.

Inclusion and exclusion criteria

The criteria for including patients in the study included the following combinations of clinical and laboratory abnormalities.
1) Concentration of PTH in the blood higher than the reference values in combination with hypocalcemia and hyperphosphatemia (ionized serum calcium <1.03 mmol/L, serum phosphorus >1.78 mmol/L, serum PTH >65 pg/ml).

2) Concentration of PTH in the blood higher than the reference values (serum PTH >65 pg/ml) with normal levels of calcium (ionized calcium 1.03—1.29 mmol/L) and phosphorus (1.45—1.78 mmol/L) in the serum in combination with the phenotype of Albright Hereditary Osteodystrophy and/or multi-hormone resistance. Signs of AHO phenotype included presence of one large AHO criterion, or a combination of one large criterion with a small one, or two small criteria. Large AHO criteria are: brachodactyly type E, subcutaneous calcifications. Small AHO criteria: obesity (SDS BMI ≥2), rounded face, short stature (SDS growth ≤2), mental retardation. Multihormonal resistance was established in the presence of laboratory signs of insensitivity to other hormones, acting through Gαs, besides PTH, such as TSH, GR-RH, LH/FSH.

Exclusion criteria were: chronic renal failure and vitamin D deficiency, in which the laboratory signs of PHP were managed by administration of chole- or ergocalciferol. Vitamin D deficiency was established at a concentration of 25-OH-vitamin D in the serum <20 ng/ml, and its deficit at <12 ng/ml.

Application, venipuncture with sampling of peripheral blood for the study of hormonal and biochemical parameters of the serum, X-ray of the hands, MSCT of the head and body parts with calcifications without contrast enhancement, ultrasound of the thyroid gland, assessment of visual acuity, transparency of the optical media of the eye, the state of the fundus.

Main outcome of the study

The following parameters were assessed: anthropometric data of children at birth, during the growth and at the time of examination, presence of AHO signs (brachydactyly type E, subcutaneous calcifications, obesity (SDS BMI ≥2), rounded face, short stature (SDS growth ≤2), mental retardation, variants of multihormonal resistance, spectrum and incidence of complications.

Subgroups analysis

Patients were divided into PHP Ia and PHP Ib groups based on the presence or absence of AHO manifestations in order to compare anthropometric indicators at birth.

Methods for registering outcomes of the study

The examination included filling in a questionnaire with a clarification of the history of the disease (what were the first manifestations of the disease, what forced you seek medical help initially, whether and from what age there were episodes of tonic convulsions, complaints of muscle pain, impaired consciousness, laryngospasm in the absence of intercurrent diseases); history of development (data on height and weight at birth, peculiarities of psycho-motor development, social adaptation, school performance) and family history (relatives with brachydactyly, short stature, episodes of tonic convulsions, epilepsy, resistance to anticonvulsant therapy). The height and weight at the time of the examination were measured with an electronic growth meter and a scale, respectively. Calculation of the standard deviation from the norm for growth and weight was carried out using Auxology application. Obesity was
Diagnosis in case of SDS BMI higher than 2, and short stature in case of growth SDS less than 2. Mental retardation was established following a consultation with a psychologist or psychiatrist. Subcutaneous calcifications were determined by palpation, in case of doubt regarding the genesis of subcutaneous formations, X-rays and/or MSCT of the body parts with palpable formations were performed. Signs of brachidactyly were the shortening of the metacarpal bones of the wrist, metatarsus of the foot that were detected during examination and confirmed by radiography of the hands and feet. X-ray examinations (radiography, multispiral computed tomography) were performed in the Department of Radiation Diagnostics of the FGBU «Endocrinology Research Center». Laboratory analysis of the serum was carried out in the Laboratory of Biochemical Analysis of the FGBU «Endocrinology Research Center». The hormonal and biochemical parameters of the serum were analyzed by comparison to normal ranges of values determined for each age. Resistance to PTH was established in case of a combination of increased concentrations of PTH and hypocalcemia and hyperphosphataemia (concentration of ionized calcium in serum <1.03 mmol/L, phosphorus >1.78 mmol/L, PTH >65 pg/ml) after exclusion of chronic renal failure and vitamin D deficiency (see exclusion criteria). Resistance to TSH: elevated levels of TSH, normal titer of antibodies to TPO and to TH, absence of echo-changes in the thyroid gland observed for autoimmune thyroiditis. Resistance to LH/FSH: absence of secondary sexual characteristics in girls older than 13 years, in boys older than 14 years, elevated levels of LH and FSH with a low estradiol in the blood in girls older than 13 years and testosterone in boys older than 14 years. Resistance to GHRH: short stature (SDS growth ≤2) with SDS of IGF-1 concentration ≤2 and the level of STH <10 ng/ml against the background of tests with clonidine and insulin. Fahr’s syndrome was identified by MSCT of the head when the calcification of the brain tissue was detected. Evaluation of the transparency of optical media by an ophthalmologist revealed the presence/absence of cataracts.

**Ethical assessment**

The study was approved by the local ethical committee of the FGBU «Endocrinology Research Center» (LEC Protocol No. 12 of October 22, 2014).

**Statistical analysis**

The sample size was not calculated prior to the study. The statistical processing of the obtained data was carried out using Statistica 10 statistical software package. The methods of descriptive and nonparametric statistics were used to generalize and compare the data obtained within the framework of a sample study. The values with normal distribution were presented using the mean ± SD. In case of not-normal distribution, the results were presented as a measure of the central tendency of Me (Q25; Q75). Differences between independent groups by quantitative characteristics were assessed using the Mann—Whitney U test, statistically significant differences were identified at the level of statistical significance p<0.05.

**Results**

**Subjects (participants) of the study**

A total of 32 patients (19 boys and 13 girls) with PHP from 31 families were observed in the Institute of Pediatric Endocrinology of the FGBU «Endocrinology Research Center» in 2014—2016. The median age at the time of the initial examination was 12 years (9.25—13.75). The main criteria for diagnosis were laboratory signs of pseudohypoparathyroidism (ionized serum calcium <1.03 mmol/L, phosphorus >1.78 mmol/L, PTH >65

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<td>PTH resistance + brachidactyly</td>
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Fig. 1—3 show the results of the study of calcium-phosphorus metabolism at the time of diagnosis of the disease.

**Main outcomes of the study**

**Variants of manifestation**

In 23 of our patients, the disease manifested by clinical signs of hypocalcemia, the most frequent of which were tonic cramps of the hands, feet, and calf muscles. Three patients had episodes of laryngospasm. In 9 cases, there were generalized seizures, similar to epilepsy. One patient experienced episodes of loss of consciousness in the presence of physical exertion as a clinical manifestation of hypocalcemia, with accompanying pronounced hypocalcemia (ionized calcium 0.56 mmol/L) and elongation of QT on the ECG. The median age of debut of hypocalcemic seizures was 11 years (5.25; 13.67); the median age at the diagnosis was 11.8 years (8.87; 13.9) (Fig. 4).

Most children with convulsive syndrome (n=13) were initially diagnosed with epilepsy and were prescribed anticonvulsant therapy. The duration of anticonvulsant therapy in this group was 2 months to 7 years. The withdrawal of anticonvulsants therapy was carried out after the normalization of the calcium concentration in the blood under EEG monitoring.

In 8 patients, the reason for seeing medical help was early progressive obesity, one patient was examined because of the illness of his sister.
Phenotype of Albright’s Hereditary Osteodystrophy

The most common sign of AHO was brachydactyly — 16 (50%) patients, which was found in combination with either only PTH resistance or in combination with other components of AHO. The second most frequent feature of AHO among our patients were subcutaneous calcifications — 10 (31.25%) patients. Ten patients had subcutaneous calcifications combined with brachydactyly and resistance to TSH and other manifestations of AHO were also present in all but one patient. Obesity was observed in 8 (25%) patients. Remarkably, 7 patients among the patients with obesity had rounded face, while two patients did not have other characteristic AHO features. Mental retardation of various degrees was observed in 8 (25%) patients. SDS of growth in patients ranged from +1.9 to 3.35. Small stature (SDS growth less than –2) was observed in 5 (16%) patients.

Fig. 5 displays the prevalence of AHO signs, Table 1 shows phenotypic variants among the patients.

Hormonal resistance

The second most common form of resistance (after PTH resistance) was TSH resistance — 22 (69%) patients; there was also one case (with the most pronounced AHO phenotype) of LH/FSH resistance.

Height and weight at birth

The assessment of the weight-for-height parameters at birth revealed significant differences in SDS BMI among patients with a clinical picture of PHP Ib and PHP Ia (p=0.03) and statistically insignificant differences in growth SDS. The median SDS of weight in patients with PHP Ib was +1.2 (0.8; 1.9), the median SDS BMI in patients with signs of AHO was +0.2 (–1.9; 0.4). The median SDS of growth at birth in patients with PHP Ib was +2.9 (1.24; 4), in patients with PHP Ia, +0.1 (–1.9; 0.4). (Fig. 6, 7). It should be noted that the data on growth and weight at birth were not available for all patients: among patients with a clinical picture of PHP Ib, the data were available for 7 patients, among children with PHP Ia, growth and birth weight data were obtained for 11 patients.

Complications of hypocalcemia and hyperphosphataemia

Nonspecific complications of impaired calcium-phosphorus metabolism include formation of calcifications in the brain tissue, in the lens, and hypoplasia of the enamel. MSCT of the brain revealed Fahr syndrome.
(basal ganglia calcifications) in 20 patients, 5 of them had initial cataract manifestations, and three patients had signs of enamel hypoplasia. In 8 patients, the complications had already manifested at the time of the diagnosis. The median concentration of ionized calcium in the blood in these patients was 0.6 (0.56, 0.66) mmol/L. The median concentration of ionized calcium in the blood in patients with complications against a background of pro-

Fig. 6. Comparison of the SDS of weights at birth of patients with PHP Ib (0) and PHP Ia (1). In patients with PHP Ib, weight at birth is higher than in patients with PHP Ia (p=0.03).

Fig. 7. Comparison of SDS of height at birth for patients with PHP Ib (0) and PHP Ia (1).
LONGED UNTREATED HYPOCALCEMIA (>1 YEAR) WAS 0.77 (0.67; 0.8) MMOL/L (N=5; IN 7 PATIENTS THE INITIAL EXAMINATION AND DIAGNOSIS WERE CARRIED OUT AT THE PLACE OF RESIDENCE AND THE LEVEL OF IONIZED CALCIUM AT THE TIME OF DIAGNOSIS IS UNKNOWN). IN TOTAL, THE MEDIAN OF THE PERIOD THAT HAS ELAPSED SINCE THE MANIFESTATION OF THE CONVULSIVE SYNDROME BEFORE THE DIAGNOSIS OF HYPOCALCEMIA AMONG THE PATIENTS WITH COMPLICATIONS WAS 0.5 (0; 3.25) YEARS (FIG. 8, 9).

DESCRIPTIONS OF CLINICAL CASES

A CLASSICAL FAMILY CASE OF PHP TYPE 1A


EXAMINATION AT AGE 7 REVEALED SEVERE OBESITY (BODY WEIGHT: 38.5 KG, SDS BMI +3.33), BRACHIDACTYLY, DIFFUSE SUBCUTANEOUS CALCIFICATIONS AND DELAYED MENTAL DEVELOPMENT. DESPITE ADMINISTRATION OF ALFALCALCIDOL (0.25 µG), CALCIUM (1000 MG/DAY) AND L-THYROXINE (75 µG/DAY), HYPOCALCEMIA (0.77 MMOL/L) AND HYPERPHOSPHATEMIA (2.79 MMOL/L) PERSISTED AND ELEVATED LEVEL OF PARATHYROID HORMONE (190 PG/ML) WAS OBSERVED AS WELL AS SUBCLINICAL HYPOTHYROIDISM (TSH 10.2 mIU/L, T4free 14 pmol/L). AN EXAMINATION AIMED AT IDENTIFYING COMPLICATIONS OF CHRONIC HYPOCALCEMIA REVEALED FAHR’S SYNDROME. BASED ON THE ABOVE-MENTIONED CHARACTERISTIC CLINICAL AND LABORATORY FEATURES, THE DIAGNOSIS OF PHP IA WAS ESTABLISHED.

PATIENT №2

THE GIRL’S BROTHER HAD BEEN MONITORED BY A NEUROLOGIST SINCE BIRTH DUE TO CEREBRAL PALSY (CP); THE PATIENT NEVER HAD SEIZURES. THE STUDY OF CALCIUM-PHOSPHATE METABOLISM WAS PERFORMED AT THE AGE OF 1.9 YEARS DUE TO HYPOCALCEMIA IDENTIFIED IN HIS SISTERS AND IT ALSO REVEALED HYPOCALCEMIA, HYPERPHOSPHATEMIA AND PRIMARY HYPOTHYROIDISM.

EXAMINATION AT THE AGE OF 4 YEARS REVEALED DIFFUSE SUBCUTANEOUS CALCIFICATIONS AND BRACHIDACTYLY, SIMILAR TO HIS SISTER, HOWEVER UNLIKE HER THE BOY WAS NOT OBSESE (SDS BMI 0.55) AND SIGNIFICANTLY LAGGED BEHIND IN GROWTH (SDS GROWTH: 2.94); HE ALSO HAD PRONOUNCED SPASM OF THE LOWER LIMBS AS A RESULT OF CP. DESPITE ADMINISTRATION OF ALFALCALCIDOL (0.25 µG), CALCIUM (500 MG), LEVOHYROXINE (50 µG) AND NORMOCALCEMIA (IONIZED CA 1.06 MMOL/L), HYPERPHOSPHATEMIA (2.26 MMOL/L), ELEVATED PTH 348 PG/ML, AND SUBCLINICAL HYPOTHYROIDISM (TSH 6.8 mIU/L) PERSISTED.

PATIENTS №1 AND №2, AS WELL AS THEIR MOTHER, UNDERWENT MOLECULAR GENETIC STUDY OF GNAS GENE AND ALL THREE HAD A HETEROZYGOUS MUTATION c.156delG P.A193fsX203 IN THIS GENE. GIVEN THE ABSENCE OF CALCIUM-PHOSPHORUS METABOLISM DISORDER IN THE MOTHER, IT IS LOGICAL TO ASSUME THE PATERNAL NATURE OF THE INHERITANCE OF THE MUTATION, WHICH LEADS TO THE DEVELOPMENT OF PSEUDO-PSEUHDYPARATHYROIDISM (PPHP), BUT THE PATIENT’S MOTHER DID NOT HAVE AHO PHENOTYPIC SIGNS EXPECTED FOR SUCH CASE.

PATIENT №3

A 13.5-YEAR-OLD BOY WAS FIRST EXAMINED IN CONNECTION WITH EPISODES OF LOSS OF CONSCIOUSNESS IN THE PRESENCE OF PHYSICAL EXERTION. THE EXAMINATION REVEALED A SYNDROME OF ELONGATED QT, CAUSED BY HYPOCALCEMIA 0.5 MMOL/L. FURTHER STUDY OF PHOSPHORUS-CALCIUM METABOLISM REVEALED AN ELEVATED CONCENTRATION OF PTH (797 PG/ML), HIGH CONTENT OF PHOSPHORUS, AND NORMAL CONCENTRATION OF VITAMIN D IN THE BLOOD. THERE WAS A COMPLICATION THAT INDIRECTLY INDICATED THE LONG-TERM NATURE OF HYPOCALCEMIA — FAHR’S SYNDROME. GIVEN THE ABSENCE OF ANY PHENOTYPIC FEATURES AND UNFAVORABLE HEREDITY, THE PATIENT WAS DIAGNOSED WITH PSEUHDYPARATHYROIDISM OF IB TYPE.

THIS CLINICAL CASE SERVES AS A GOOD ILLUSTRATION OF HOW VARIABLE THE HYPOCALCEMIA MAY BE: WITH A BLOOD CALCIUM OF 0.5 MMOL/L, THE BOY NEVER HAD A CONVULSIVE SYNDROME, AND THE ONLY CLINICAL SYMPTOM THAT ALLOWED THE DIAGNOSIS WAS THE LONG QT SYNDROME.

PATIENT №4.

THE BOY HAS BEEN OBSERVED AT THE INSTITUTE OF PEDIATRIC ENDOCRINOLOGY OF THE ERC FROM THE AGE OF 13.5 YEARS.
Fig. 9. Calcinates along the fasciae of the muscles of the thigh.
The child was born from an unrelated marriage, the analysis of the family tree did not reveal any special features, but low height of the mother (148 cm) and her early menopause (35 years old) attracted attention. Since infancy, the child had delayed psycho-speech development. The clinical signs of hypocalcemia began to appear at the age of 8 as pain in the gastrocnemius muscles, from the age of 12 there were episodes of tonic convulsions of the muscles of the extremities, which led to an examination that revealed hypocalcemia (total Ca 1.42 mmol/L) and hypophosphatemia (2.92 mmol/L), as well as primary subclinical hypothyroidism.

At 13.5 years of age the Institute of Pediatric Endocrinology identified typical signs of Albright phenotype: growth retardation (SDS growth = −2.1), brachydactyly, mental retardation. There was unusual pattern of calcification: along the course of the tail muscle of the right thigh as a tight formation 7 cm in length, 4 cm in width (Fig. 9), which is somewhat uncharacteristic for AHO calcification due to its deep localization (along the muscle fascia). The child did not have obesity and hypogonadism. In addition to hypocalcemia (ion Ca 0.85 mmol/L) and hyperphosphatemia (2.68 mmol/L), there were also markedly elevated concentration of PTH (466 pg/ml) and subclinical hypothyroidism (TSH 4.46 mIU/L, T4 free 14, 8 pmol/L). Radiography of the hands and feet confirmed the presence of brachydactyly: shortening of the diaphysis of the metacarpal bones of the IV, V fingers, metatarsal bones IV, V of the toes, in addition to calcification of the walls of the vessels of soft tissues. To diagnose complications of hypocalcemia, CT of the brain was performed, which revealed Fahr's syndrome. Treatment with alfacalcidol (6 μg/day), calcium (2000 mg/day), and L-thyroxine (50 μg/day) was prescribed, which led to normalization of calcium and TSH concentration in the blood. Molecular genetic study revealed c.565_568delGACT p.M1896X202 mutation in GNAS gene. The presence of AHO signs and the detected mutation made it possible to diagnose PHP Ia.

**Patient №5**

A girl has been observed at the Institute of Pediatric Endocrinology from the age of 16. Since the age of 5 years she periodically experienced convulsions of the limbs: twice in the presence of febrile fever, and in other cases without any connection with intercurrent diseases.

Examination at age 16 in the Institute of Pediatric Endocrinology revealed no phenotypic features, no bone deformities. High concentration of PTH (266 pmol/L), hypocalcemia (ion Ca 0.9 mmol/L, P 1.72 mmol/L) and hypokalemia (3.2 mmol/L) were detected in the presence of normal levels of sodium (140 mmol/L at a norm of 136—145) and renin (32.6 mIU/ml at a norm of 2.8—39.9). The analysis of the data of the outpatient card revealed that hypocalcemia and hypokalemia have been observed for many years. Nevertheless, there were no complications of prolonged chronic hypocalcemia. Syndrome of hypercalciuric hypocalcemia may be accompanied by an increase in the level of parathyroid hormone and in rare cases combined with hypokalemia, but our patient did not have hypercalcemia or other manifestations of kidney pathology. The combination of high concentration of parathyroid hormone with low content of calcium and high content of phosphorus in the blood in the absence of AHO manifestations made it possible to diagnose PHP Ib.

Administration of alfacalcidol and potassium allowed to normalize the parameters of phosphorus-calcium metabolism and potassium concentration. The cause of persistent hypokalemia remains unclear.

**Discussion**

All types of PHP involve disorders of phosphorus-calcium metabolism, such as decrease in the concentration of calcium and an increase in phosphorus content with high concentration of parathyroid hormone. Hypocalcemia causes an increase in neuromuscular excitability, manifested by convulsions, paresthesia, tetany. The late diagnosis of PHP, delayed in comparison with the manifestation of the first clinical manifestations in our group, is due to the fact that the level of calcium in the blood is not always measured in case of convulsive syndrome. Our data demonstrate the importance of including a study of calcium levels in the blood in the differential diagnosis algorithm for all children with convulsive syndrome. Timely diagnosis and adequate treatment will prevent the development of complications of hypocalcemia. Normalization of calcium concentration in the blood in patients with PHP is achieved by prescribing active forms of vitamin D.

Bones are one of the main PTH targets. In the absence of a resorptive effect of vitamin D and PTH, the mineralization of bones in PHP Ia is not only not disturbed, but, on the contrary, increased [7]. At the same time, there have been many cases of subperiosteal resorption and parathyroid osteodystrophy in patients with different PHP variants, apparently due to a partially preserved sensitivity to PTH [8—11]. In our group, the reduction of bone mineral density was detected in only one patient.

Of all manifestations of AHO the attention of a doctor is first of all drawn to obesity, brachydactyly, subcutaneous calcifications, and short stature. One of the special features of obesity associated with PHP, characteristic for monogenic forms in general, is its early onset and progressive nature. Among our patients the onset of obesity usually occurred at early age. It is difficult to specify age precisely, but progressing weight gain was usually noticed at the age of 2—5 years, and for one girl the expressed weight gain was noted from the first months of life. Patients with PHP typically have sharply reduced rest energy consumption (REC), which causes the weight gain, even in the absence of excessive caloric intake and hyper-
phagia. Regulation of energy homeostasis is mediated through type 4 melanocortin receptors, the action of which is also mediated by the activation of Gas. The development of obesity in PHP can be explained by the resistance of these receptors [12]. There are no specific methods for treatment of obesity in PHP; recommendations include restriction of daily calorie intake and regular exercise.

There were 16 cases of brachydactyly among our patients in various combinations with other manifestations of AHO. In case of PHP, brachydactyly is usually caused by shortening of IV and V metacarpal and metatarsal bones. It is easy to make sure that the shortening of the fingers is due to the underdevelopment of the metacarpal bones: when a hand makes a fist, there is obvious lack of IV, V metacarpophalangeal joints (Fig. 10, 11). Gas plays an important role in the processes of bone growth (it prevents the differentiation of chondrocytes and premature closure of growth zones), and the weakening of its activity is reflected in the shortening of the metacarpal and metatarsal bones, premature closure of the epiphyses and, consequently, short stature [13, 14].

Another characteristic feature of AHO is subcutaneous calcifications. Gas prevents the development of ectopic calcification by regulating the differentiation of osteoblasts [15]. Reduced expression of Gas in adipose tissue leads to transformation of stem cells localized in the adipose tissue into osteoblasts, followed by the formation of calcifications [16]. They are lesions of different size and localization, from small (which are easier to palpate than to see) to large ones that can cause painful sensations. In our group of patients, subcutaneous calcifications were observed in 9 children. In one of them, the calcifications formed a single subcutaneous conglomerate in the lumbar region of the spine that limited the mobility, but was painless. In another patient (clinical case number 4) calcifications had deep localization, along the muscular fascia. Surgical removal is not recommended for patients with subcutaneous calcifications, since surgical intervention can provoke the appearance of new lesions.

In addition to subcutaneous calcifications, PHP may be associated with calcification in the brain tissue (Fahr’s syndrome) (Fig. 12) and the lens (cataracts). This is not a characteristic sign of PHP, but rather a complication of
hypocalcemia and hyperphosphataemia and it occurs in other diseases accompanied by low calcium and high phosphorus levels in the blood (hypoparathyroidism, chronic renal failure). Interestingly, among our patients, the complications that are believed to reflect long duration of calcium-phosphate metabolism disorders have been primarily (60%) detected during the initial examination for manifestation of hypocalcemia (the first episode of seizures and/or syncopal conditions); the youngest patient was 4.7 years old. This may be attributed to the fact that the onset of clinical manifestations of hypocalcemia does not coincide with the onset of decrease in calcium concentration and increase in the phosphorus levels in the blood. There is also remarkable difference in the concentration of in patients with Fahr’s syndrome and the duration of hypocalcemic seizures of less than 1 year — 0.6 (0.56, 0.66 mmol/L; n=8) and in patients suffering from convulsive episode for more than 1 year before hypocalcemia was detected — 0.77 (0.67, 0.8; n=5). However, it is premature to claim that the difference is statistically significant due to insufficient sample size (n=5).

The issue of how long untreated changes in the concentration of calcium and phosphorus have to exist to be sufficient for development of complications, remains unanswered. It should be emphasized that calcifications of the brain are the most frequent complications of hypocalcemia, and in our study all cases of cataract and hypoplasia of the enamel were accompanied by Fahr’s syndrome.

Mental retardation is a common but non-specific sign of AHO and its severity varies from severe oligophrenia to preservation of learning ability. Eight of our patients with PHP Ia had mental retardation of varying degrees. Signs of decreased intelligence manifested, as a rule, but not always, from the first years of life. In one patient, the decline in mental abilities began to progress from the age of 7; before this time there were no delays in her development. Other possible causes of developmental delay cannot be excluded (severe CNS lesions in the neonatal period, cerebral palsy, etc.).

While PHP Ia can be accompanied by AHO manifestations, PHP Ib also has its clinical features: higher indicators of physical development at birth, especially in case of hereditary forms of PHP Ib caused by deletions of STX6 [17]. Among our patients with provisional PHP Ib diagnosis and available data on growth and weight at birth, SDS BMI at birth was significantly higher than in patients with PHP Ia. The growth median SDS was higher than the average population data without statistically significant difference in the values between patients with PHP Ib and Ia, which is consistent with data from other studies [17].

In addition to disorders of calcium-phosphorus metabolism and clinical manifestations of AHO, there may also be resistance to other hormones. TSH, LH and FSH, GHRH and many others are associated with Gas. However, Gas is procude by the expression of GNAS only from the maternal allele only in the proximal renal tubules, thyroid gland, pituitary somatotropes and gonads, therefore in case of inactivating mutations of GNAS gene in these tissues, one should expect more pronounced Gas deficiency, leading to impaired sensitivity to the hormones.

Resistance to GHRH and hypergonadotropic hypogonadism is possible in case of PHP Ia, however, according to the literature, these manifestations are rare. In 2013, E. Fernández-Rebollo et al. [18] published the first data of a clinical-genetic study of a large group of patients with different variants of PHP: out of 63 patients (29 of them with PHP Ia) hypogonadism was not detected in anyone, however at the time of the examination 15 patients had not yet reached puberty. Out of 32 of our patients, hypergonadotropic hypogonadism was diagnosed only in one girl. It should be noted that 12 patients at the time of publication of the data were under 14 years of age, including three patients with PHP Ia, for whom the possibility of developing resistance to gonadotropic hormones cannot be excluded.

Short stature in PHP Ia is not always caused by resistance to GHRH. In our group of patients, IGF1 was within normal limits even among children with a pronounced growth retardation, there were no grounds for suspicion of STH-deficiency. Short stature in the absence of STH deficiency in children with PHP is caused by premature closure of the epiphyses due to a disruption of signaling mechanism in chondrocytes [13, 14]. Similar tendency towards exceeding bone age was noted in two of our patients with PHP Ia (exceeding bone age by 2 years). The girls were in the pre-puberty period and therefore premature sexual development has been ruled out.

The level of IGF-I should be determined in all children with PHP who have growth retardation and, if nec-
essary, STH stimulation tests should be performed. In case of established STH-deficiency, it is necessary to conduct growth-stimulating therapy with growth hormone. The study by G. Mantovani et al. [19], showed that the start of growth-stimulating therapy in the prepubertal period improves the growth prognosis in children with STH deficiency and PHP Ia.

Hypothyroidism is the most common sign of multi-hormonal resistance observed in pseudohypoparathyroidism. TSH resistance (subclinical or clinical non-autoimmune hypothyroidism), observed in 22 of our patients, occurred in combination with other manifestations of AHO, and in the absence of any phenotypic features.

The results of the study could be affected by a limited number of patients. The number of cases of PHP in the Russian Federation is certainly much higher. However, the variant of PHP Ib in the absence of AHO manifestations remains unrecognized. Nevertheless, given the rarity of the disease, the results of the analysis of a group of 32 patients are valuable from a clinical and scientific points of view. Multisystem character of the disease determines the appropriate approach to management and treatment of patients with PHP. It requires the following: compensation of phosphorus-calcium metabolism disorders with maintenance of PTH concentration within normal limits; hormone replacement therapy in the case of existing resistance to other hormones (hypothyroidism, hypogonadism, STH-deficiency); control of the kidneys, given the rare, but possible complication of nephrocalcinosis; adjustment of eating behavior and physical activity in children with obesity; adequate psycho-social adaptation in case of mental retardation.

Conclusions

Pseudohypoparathyroidism is diagnosed clinically. The disease most often (72%) manifests as convulsive syndrome (tonic spasms of the muscles of the hands, feet, gastrocnemius muscles, less often, laryngospasm). Rarely, PHP manifests as a loss of consciousness in the presence of prolonged QT syndrome without seizures. In 25% of cases, the diagnosis of PHP is established during an examination for obesity. PHP can be diagnosed 2 months to 7 years after the onset of clinical manifestations. Delayed diagnosis can be associated with erroneous evaluation of convulsive syndrome as a manifestation of epilepsy. The most frequent phenotypic manifestations of PHP are brachydactyly (50%), subcutaneous calcifications (31%), obesity (25%), mental retardation (25%), short stature (16%). Combination of insensitivity to PTH and TSH (69%) is the frequent manifestation of multi-hormonal resistance in PHP. Patients with PHP Ib have higher birth weight than patients with PHP Ia.

ADDITIONAL INFORMATION

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13. Sakamoto A, Chen M, Kobayashi T, et al. Chondrocyte-specific knockout of the G protein G(s)alpha leads to epiphyseal and


