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A CASE REPORT OF ALBRIGHT HEREDITARY OSTEODYSTROPHY WITHOUT INTELLECTUAL DISABILITY DUE TO A *DE NOVO GNAS* SPLICING VARIANT*

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Pseudohypoparathyroidism (PHP) is a heterogeneous group of disorders that share features of hypoparathyroidism, such as hypocalcaemia and hyperphosphatemia, but are a result of target tissues' resistance to the biological actions of parathyroid hormone (PTH) as well as thyroid stimulating hormone, gonadotropins, GHRH, and glucagon [1]. Its prevalence varies, for instance, from 0.34/100000 in Japan [2] to 1.1/100000 in Denmark [3]. There is no data available on the prevalence of this condition in Ukraine.

PHP are classified into various subtypes based on the specific molecular defects and clinical presentations. These disorders are divided into Type I (A, B, C subtypes) and type II: PHP IA is characterized by target organ resistance to multiple hormones, primarily PTH and the presence of features of Albright Hereditary Osteodystrophy (AHO) such as round face, short stature, subcutaneous calcifications and brachydactyly (the feature that is pathognomonic for AHO is shortened of fourth and fifth metacarpal bones), whereas PHP IB classically presents as hormone resistance limited to PTH without the AHO signs [4]. In addition to classical phenotypic features, children with PHP IA often have hearing loss (both sensorineural and conductive), mild intellectual disability, sleep apnoea and an increased risk of type 2 diabetes [5, 6].

PHP IA is caused by heterozygous inactivating germline mutations in the guanine nucleotide-binding protein α-stimulating polypeptide (*GNAS*) gene located on chromosome 20q13.3 [7]. The *GNAS* gene produces multiple gene products, including transcripts that encode the alpha-subunit of the stimulatory guanine nucleotide-binding protein (Gsα), extra-large Gsα (XLαs), and neuroendocrine se-

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cretory protein 55 [8, 9]. Pathogenic variants in the *GNAS* gene, which encodes the Gsα subunit, is the primary cause of PHP IA. The Gsα subunit is critical for coupling G protein-coupled receptors, such as the PTH receptor, to their downstream effectors. Inactivating mutations in Gsα impair signal transduction by these receptors, leading to tissue resistance to multiple hormones, including PTH. Gsα is expressed in a monoallelic way due to imprinting through differentially methylated *GNAS* regions [10]. In some tissues, such as proximal renal tubules, thyroid gland, gonads, pituitary and paraventricular and dorsomedial nuclei of the hypothalamus, the PHP IA phenotype is a result of inactivating mutations on the maternal allele, and it is expressed only from the maternal allele (monoallelic) [11, 12]. In addition, biallelic expression is found in other tissues such as skin, chondrocytes and adipocytes [13]. These genetic mechanisms account for the varied observable characteristics in individuals with PHP.

MATERIALS AND METHODS

Chemiluminescent immunoassay was used to detect parathyroid hormone (PTH), Thyroid stimulating hormone (TSH), free Thyroxin (FT4), Thyroid peroxidase Antibodies (TPO AB). The ion-selective method was used to determine Total calcium, Ionized calcium, Phosphorus in blood serum. The patient underwent an MRI scan using a Siemens 1.5 T MRI machine (Magnetom; Siemens AG, Munich, Germany). SPSS 19.0 statistical software (IBM Corp., Armonk, NY, US) was used for statistical analysis.

CASE PRESENTATION

A 12-year-old boy presented to the Zakarpatska Endoclinica (Uzhhorod, Ukraine) with complaints of excessive weight, seizure syndrome, presence of paraesthesia. Family history was positive for epilepsy in father's sisters. The patient was referred by a paediatric neurologist, who was treating epileptic syndrome with lamotrigine 50 mg and levetiracetam 1000 mg b.i.d.

During the initial endocrinologist examination, the child was overweight (weight — 53.2 kg (90 P), height — 150 cm (50 P), BMI — 24.8 kg/m^2 (95 P)). Notable features were: rounded face with a broad nasal bridge (Fig. 1), shortened 4th and 5th metacarpal bones (Figs. 2–3), confirmed by X-ray (Fig. 4). The development of external genitalia was at Tanner 3 stage. Hearing and vision was normal. The child attended middle school and did not have any learning or communication issues, he was a top student of the class. Considering this, specific tests to assess intelligence level were not assigned.

MRI of the brain findings: signs of pathological calcification of the basal ganglia and subcortical white matter.

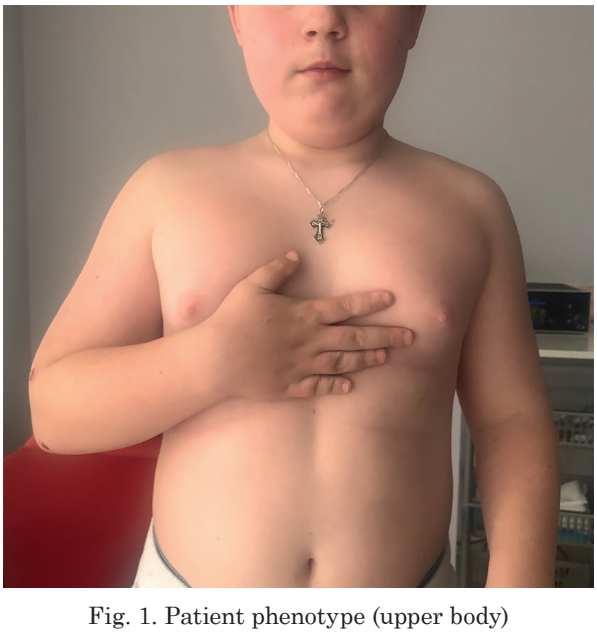

Fig. 1. Patient phenotype (upper body)

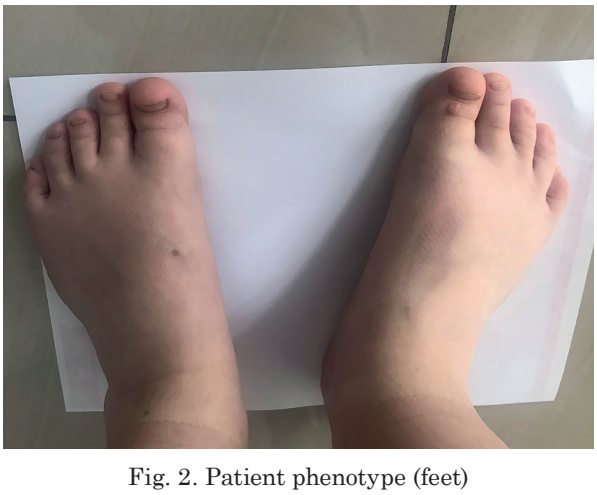

Fig. 2. Patient phenotype (feet)

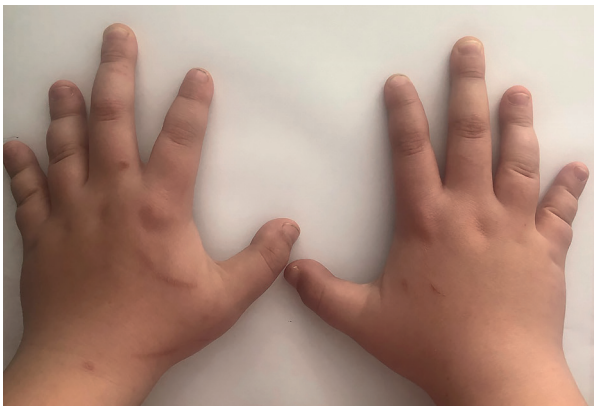

Fig. 3. Patient phenotype (hands)

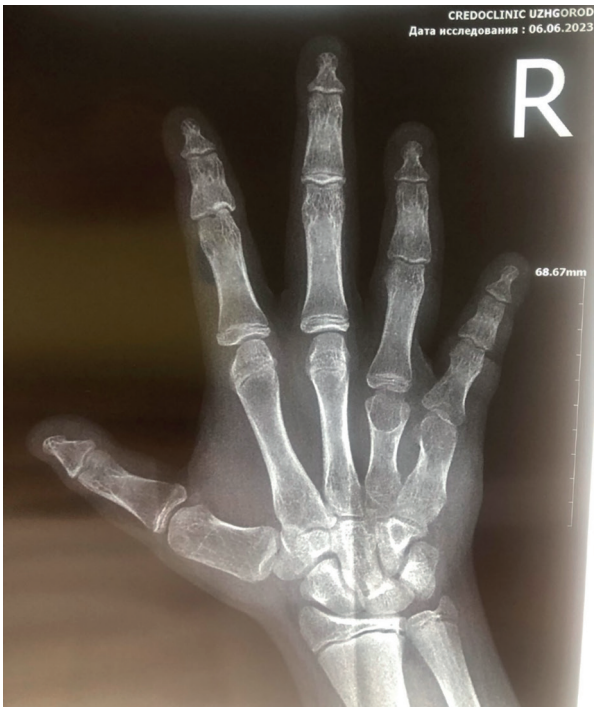

Fig. 4. Right hand X-ray

Ultrasonography of kidneys: The USG findings were the signs of diffuse parenchymal changes in both kidneys with the presence of calcifications.

Clinical Diagnosis: Based on the recommendations of the «Diagnosis and management of pseudohypoparathyroidism and related disorders: first international Consensus Statement» (2018) and also on the basis of characteristic clinical features and phenotype (short stature, hand morphology, robust build, obesity, round face, seizure syndrome, early sexual maturation), laboratory findings (elevated > 10 times PTH levels, hypocalcemia, hyperphosphatemia (Table 1)), and additional investigation data (calcification of basal ganglia and subcortical white matter on MRI; ultrasound — signs of diffuse parenchymal changes in both kidneys with the presence of calcification), a preliminary clinical diagnosis was established: Pseudohypoparathyroidism type IA (Albright hereditary osteodystrophy).

In order to verify the diagnosis and provide family counselling, the patient was referred for genetic testing.

Genetic test result. Next generation sequencing (NGS) panel (Invitae Incorporation, San Francisco, USA), found a heterozygous pathogenic variant NM_000516.7: c. 312 + 5G > A in the *GNAS* gene. This sequence change falls in intron 4 of the *GNAS* gene. It does not directly change the encoded amino acid sequence of the *GNAS* protein, but rather affects a nucleotide within the consensus splice site.

Table 1

Results of laboratory tests pre- and 6 months post-treatment initiation

Test parameter	Result at initial presentation	Result 6 months after treatment initiation	Laboratory normal range
TSH, mIU/mL	3.81 N	1.78 N	0.28–4.3
FT4, ng/dL	**0.71** ↓	1.13 N	1.1–1.7
PTH, pg/mL	**767** ↑↑↑	**639** ↑↑↑	12–65
TPO antibodies, IU/mL	9.0 N	8.0 N	< 34
Total calcium, mmol/L	**1.28** ↓↓	**1.77** ↓	2.1–2.55
Ionized calcium, mmol/L	**0.63** ↓↓	**0.93** ↓	1.05–1.5
Phosphorus, mmol/L	**3.19** ↑↑↑	**2.31** ↑↑	1.05–1.65

Notes:
FT4 — free Thyroxin;
TPO — Thyroid peroxidase;
TSH — Thyroid stimulating hormone.

This variant is not present in population databases (GNOMAD no frequency). This finding confirmed the clinical diagnosis. Parental genetic testing confirmed this pathogenic variant to occur *de novo* in the proband.

The patient was prescribed Levothyroxine sodium 50 mcg once daily, Calcitriol 0.5 mg once daily, and Calcium citrate 1000 mg per day. To facilitate the decrease in phosphorus levels an antacid with aluminium oxide and magnesium oxide (Almagel) was prescribed. Hormonal tests were taken at presentation and 6 months after specific treatment initiation (Table 1).

Six months after treatment initiation, TSH and fT4 levels normalized, and there was improvement in PTH, total calcium, ionized calcium, and phosphorus levels. Patient's EEG also showed marked pattern of improvement the dose of lamotrigine and levetiracetam could be decreased from 50 mg and 1000 mg b.i.d. to 25mg and 250 mg b.i.d. respectively, with a prospect of full discontinuation of antiepileptic medications.

Disscusion. This case report describes clinical features, genetic findings, and treatment outcomes of the 12 years old boy with Pseudohypoparathyroidism type IA (Albright hereditary osteodystrophy) and demonstrates the challenges in diagnosing and managing PHP IA in patients presenting with a complex combination of clinical features related to hormone resistance. This is an example of a PHP caused by a pathogenic variant in *GNAS* gene. The c. 312 + 5G > A variant is predicted to interfere with splicing. *GNAS* mutations are the most frequent cause of the disease [14].

Despite the evidence suggesting that mild-to-moderate intellectual disability is diagnosed in up to 79% of affected individuals with AHO and PHP IA [15], our patient, a top student of his class, showed no signs of intellectual impairment at the time of presentation, nevertheless he did not undergo a formal IQ assessment. Interestingly, compared to a 32-year-old French patient with the same c.312 + 5G > A variant and PHP IA [16], both patients exhibited PTH resistance (hypocalcaemia and hyperphosphatemia) and TSH resistance (hypothyroidism). However, our patient did not show severe skeletal defects observed in the French male (congenital phocomelia), but also expressed significant shortening of the metacarpals. Additionally, our patient did not have any evident cognitive impairment, whereas the French male had mild intellectual disability. This highlights the variability in the clinical presentation of PHP IA even with the exact same pathogenic variant, where the age of treatment initiation might also play a role.

The occurrence of similar skeletal defects in patients with PHP type IA and pseudo-PHP (both having heterozygous inactivating *GNAS* mutations) supports the growing evidence that Gsα pathways play a crucial role in growth plate development. Gsα is biallelically expressed in human bone and in murine chondrocytes [17]. While inheriting a defective paternal *GNAS* allele is not expected to cause endocrine defects, a 50% deficiency in Gsα expression is enough to cause brachydactyly and other skeletal abnormalities [18].

Given the diverse clinical presentations of pseudohypoparathyroidism, along with different potential pathways leading to its onset, a new term 'inactivating PTH/PTHrP signaling disorder', abbreviated as iPPSD, was suggested in 2016 [19]. This new classification introduced major criteria (PTH resistance, ectopic ossification, brachydactyly type E) and minor criteria (TSH resistance, other hormonal resistances (GH, calcitonin, LH, FSH, GnRH), to aid in diagnosis and differential diagnosis. According to this new classification, our patient had the PHP IA phenotype caused by inactivating *GNAS* variants.

CONCLUSION

This case presents a variety of a phenotypical spectrum of pseudohypoparathyroidism 1A caused by a heterozygous pathogenic variant (c. 313 + 5G > A) in the *GNAS* gene. Pseudohypoparathyroidism is a rare disease that caused by various genetic defects that is why the method of verifying diagnosis can be long and laborious. This case underscores the importance of a multidisciplinary approach in managing patients with pseudohypoparathyroidism and the critical role of genetic testing in confirming the diagnosis and for a further genetic counselling of the family and the patient.

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A CASE REPORT OF ALBRIGHT HEREDITARY OSTEODYSTROPHY WITHOUT INTELLECTUAL DISABILITY DUE TO A *DE NOVO GNAS* SPLICING VARIANT

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This case report details a 12-year-old boy with Albright Hereditary Osteodystrophy (AHO) without intellectual disability due to a *de novo GNAS* splicing variant. Presenting with obesity, seizure syndrome, the patient exhibited typical AHO features, elevated parathyroid hormone levels alongside hypocalcemia and hyperphosphatemia, but normal cognitive function. MRI and ultrasound revealed calcifications in the brain and kidneys. Genetic testing confirmed pseudohypoparathyroidism (PHP) type IA with a heterozygous pathogenic variant NM_000516.7: c. 312 + 5G > A in the *GNAS* gene. Treatment with Levothyroxine, Calcitriol, and Calcium citrate improved laboratory parameters and reduced seizure frequency. This case underscores the clinical variability of PHP IA and the importance of genetic testing and a multidisciplinary approach in managing the condition.

Keywords: Albright Hereditary Osteodystrophy, pseudohypoparathyroidism.

ВИПАДОК СПАДКОВОЇ ОСТЕОДИСТРОФІЇ ОЛБРАЙТА БЕЗ ІНТЕЛЕКТУАЛЬНОЇ НЕДОСТАТНОСТІ ВНАСЛІДОК НОВОГО ВАРІАНТА СПЛАЙСИНГУ *GNAS*

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Представлено клінічний опис 12-річного хлопчика зі спадковою остеодистрофією Олбрайта (Albright Hereditary Osteodystrophy — AHO) — псевдогіпопаратиреозом (pseudohypoparathyroidism — PHP) з ожирінням та судомним синдромом без інтелектуальної недостатності як варіант сплайсингу GNAS *de novo*. У пацієнта спостерігалися типові ознаки AHO, підвищений рівень паратгормону поряд з гіпокальціємією та гіперфосфатемією, але нормальною когнітивною функцією. МРТ та УЗД виявили кальцинати в головному мозку та нирках. Генетичне тестування підтвердило PHP типу IA з гетерозиготним патогенним варіантом NM_000516.7: c. 312 + 5G > A в гені *GNAS*. Лікування левотироксином, кальцитріолом і цитратом кальцію призвело до покращення лабораторних показників та значного зменшення частоти нападів. Цей випадок підкреслює клінічну варіабельність PHP типу IA та важливість генетичного тестування та мультидисциплінарного підходу до лікування захворювання.

Ключові слова: спадкова остеодистрофія Олбрайта, псевдогіпопаратиреоз.