

Danica Stamenković-Pejković<sup>1,2</sup>, Ana Gligić<sup>2</sup>, Goran Cvijović<sup>1,2</sup>,  
Svetlana Zorić<sup>2</sup>, Danka Jeremić A<sup>2</sup>, Snežana Polovina<sup>2</sup>,  
Aleksandra Kendereški<sup>1,2</sup>, Dragan Micić<sup>1</sup>,  
Mirjana Šumarac-Dumanović<sup>1,2</sup>

## **PSEUDOPSEUDOHYPOPARATHYROIDISM OR ALBRIGHT HEREDITARY OSTEODISTROPHY LIKE SYNDROME 1**

### *Summary*

**Introduction:** pseudohypoparathyroidism (PHP) is hormone resistance syndrome described for the first time in 1942 by Albright et al. All this patients had high levels of the PTH and specific skeletal deformities which were later termed as Albright hereditary osteodystrophy (AHO). The PTH requires the alpha subunit of G protein for its action. GNAS1 gene encodes the alpha subunit of the G protein and molecular defects in this gene lead to the occurrence of at least four different forms of this syndrome. Pseudopseudohypoparathyroidism (PPHP) is a form of PHP which is characterized by physical features of AHO without any evidence of PTH resistance. Albright hereditary osteodystrophy like syndrome (AHO like syndrome) has some common characteristics with AHO but is not connected with the molecular defect in the GNAS 1 gene.

**Case outline:** we reported the case of the female patient with the phenotypic characteristics of AHO (brachydactyly, short stature, mild degree of intellectual deficit and genu varum) but without any evidence of PTH resistance. PPHP occurs mainly in families with PHP 1a and it is inherited from the father which is not the case with our patient. There is a theoretical possibility that the mutation of the GNAS 1 gene occurred de novo but without genetic testing the 2q37 deletion and AHO like syndrome can not be excluded.

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<sup>1</sup> School of Medicine, University of Belgrade.

<sup>2</sup> Clinic for Endocrinology, Diabetes and Diseases of Metabolism, Clinical Center of Serbia, Belgrade.

**Conclusion:** in some cases of PPHP the diagnosis of AHO like syndrome should be considered but the only way to make the precise diagnosis is the genetic testing as it was in our case.

**Key words:** pseudopseudohypoparathyroidism, Albright hereditary osteodystrophy, Albright hereditary osteodystrophy like syndrome, GNAS 1 gene

### *Case report*

The eighteen years old female patient was admitted to the hospital under the suspicious of pseudopseudohypoparathyroidism due to additional endocrinological investigation.

The patient was the first child from the normal pregnancy. She was born with the normal weight. Postnatal development was regular but from the birth the shortening of the fourth and fifth fingers of the left and right hand was noticed as well as deformed and shorter fourth finger of the right foot. She has bow legs from early childhood. She said she was the lowest in her class. Mother and father have a normal height. Due to the problems with learning she left the school in the fifth grade. The first period was when she was 11 years old. Menstrual cycles are regular on every 30 days. She said she had the normal development of the secondary sexual characteristics. Since she was ten years old she had very often dislocation of the knees and that was the reason of the hospitalization in the orthopedic clinic. During that hospitalisation the hormonal analyses were done for the first time and the levels of TSH, PTH and serum calcium were in the normal range. Bone mineral density was measured by densitometry and showed significant decrease of the bone density (Z score of the femoral neck -2.8 and Z score of the lumbar spine L1-L4 -3.3). Before the decision on how to treat the dislocation of the knees the patient was admitted to our hospital for the additional examination.

In addition to the above she denied other chronic diseases. In the family history the father and younger sister also have bow legs (O legs), mother and older sister have the problems with knee dislocation, uncle has a shorter fourth and fifth fingers of the left and right hand. As far as she knows no one in her family has problem with low level of the calcium in the blood.

Physical examination showed short stature (under 3d percentil) and lower BMI 18.9 kg/m<sup>2</sup>. During the conversation the patient gave the impression of mild intellectual deficit. Shortening of the fourth and fifth fingers of both hands was observed as well as shortened and deformed fourth finger of the right foot (Fig. 1 and Fig. 2.). The patient had a pronounced degree of genu varum and the rest of the physical examination was normal (Fig. 3).

The results of routine laboratory tests were within the normal ranges including calcium, magnesium and phosphate levels in the serum as well as the value of the 24h urine calcium excretion. The endocrine examination showed the normal values of PTH,



*Fig. 1*



*Fig. 2*



*Fig. 3*

FT4, TSH, calcitonin, growth hormone, FSH, LH, estradiol, testosterone, SHBG, and DHEAS. The growth hormone response during the insulin tolerance test was normal. The concentration of vitamin D was low. The karyotype was normal (46 XX).

First radiography showed reduction of fourth and fifth metacarpal bones on both hands (Fig. 4). Foot radiography showed reduction of fourth metatarsal bone of the right foot as well as reduction of the fourth proximal, intermediate and distal phalanx of the right foot (Fig. 5).

The ultrasounds of the abdomen, pelvis and thyroid gland were normal.



*Slika 4*



*Slika 5*

## Discussion

Pseudohypoparathyroidism (PHP) is historically the first hormone resistance syndrome and it was described for the first time in 1942 by Albright et al. (1). The term now encompasses a heterogeneous group of rare metabolic disorders, all characterized by end-organ resistance to the action of PTH (2). Albright reported patients with normal renal function in whom hypocalcemia and hyperphosphatemia were associated with a reduced calcemic and phosphaturic response to injected bovine parathyroid extract or the resistance on the PTH action. All these patients had high levels of the PTH and specific skeletal deformities which were later termed as Albright hereditary osteodystrophy (AHO) (1).

The PTH receptor requires the heterotrimeric G protein as an intermediary coupling protein to stimulate adenylyl cyclase. The molecular defects in the *GNAS1* gene which encodes the alpha subunit of the heterotrimeric G protein lead to the occurrence of at least four different forms of this syndrome: PHP Ia, PHP Ib, PHP Ic and pseudopseudohypoparathyroidism (PPHP) (Table 1.). In addition to PTH resistance some forms of PHP can show the resistance to the other hormones which also act through the alpha subunit of the heterotrimeric G protein such as TSH, ADH, FSH, LH, glucagon, ACTH and GHRH (2).

**Table 1. Classification of PHP**

	AHO	Hormone resistance	Heterotopic ossification	PTH infusion	GNAS defect
PHP Ia	Yes	PTH, TSH, Gn, GHRH	Yes, superficial	↓cAMP ↓phosphaturia	Maternal inactivating mutations
PPHP	Yes	No	Yes, superficial	Normal	Paternal inactivating mutations
PHP Ib	No	PTH, TSH	No	↓cAMP ↓phosphaturia	Imprinting dysregulation
PHP Ic	Yes	PTH, TSH, Gn	Yes, superficial	↓cAMP ↓phosphaturia	Few inactivating mutations

Gn-gonadotropini;

One form of PHP as noted in the table 1 is PPHP. Interestingly, patients showing the physical features of AHO without any evidence of PTH resistance were also described by Albright et al. 10 years after their first report of PHP. This new syndrome which was termed PPHP may be present either in kindreds in which PHP is present or as an isolated defect. The presence of physical features of AHO without PTH resistance are the main features of PPHP. The studies have shown that a mutation in GNAS1 gene in the same family if it is inherited from the mother leads to PHP 1a but if it is inherited from the father leads to PPHP. Alpha subunit of the G protein is synthesized in most cells thanks to the presence of both alleles (father's and mother's), however in some cells such as cells of the proximal renal tubules, somatotrophic cells, thyrocytes, gonadal cells alpha subunit is primarily synthesized due to the mother's allele. The phenomenon of genetic imprinting involves the selective inactivation of mother's or father's alleles. In normal circumstances, there is the imprinting of the part of the GNAS 1 gene responsible for the synthesis of the alpha subunit in the proximal renal tubules. For these reasons inheritance of the GNAS 1 mutation from the father is not associated with the PTH resistance on the level of the proximal tubules. Imprinting is tissue selective and does not occur in all tissues and that is the explanation why the mutation inherited from the father occur in other tissues which may explain the occurrence of the AHO (3).

AHO is a clinical entity which encompasses heterogeneous clinical findings such as brachydactyly, rounded face, short stature, central obesity, subcutaneous ossifications, and variable degrees of mental retardation. In particular, brachydactyly, classically described as a shortening of III, IV, and V metacarpals and I distal phalanx, is the typical and, together with heterotopic ossifications, the most specific feature of the AHO phenotype. However, in a major subset of patients, the diagnosis may remain unclear because occasional shortening of hand bones may sometimes be detected as a nonspecific finding in the normal population. Several other skeletal deformities have been described in AHO, including short ulna, bowed radius, deformed elbow, or cubitus valgus and coxa vara, coxa valga, genu varum, and genu valgum deformities (4).

Clinical features of PPHP can be seen in some families where there is no PHP 1a. In these cases the diagnosis of PPHP is questionable because some of the features of AHO are nonspecific and can be seen in other disorders. Albright hereditary osteodystrophy like syndrome (AHO like syndrome) is also known as brachydactyly-mental retardation syndrome (5). This disorder includes intellectual disability, behavioral abnormalities including autism spectrum disorder, seizures, sleep disturbances, obesity, short stature, brachydactyly, craniofacial dysmorphism and cardiac, tracheal, gastrointestinal, and genito-urinary tract defects. The patients with AHO like syndrome have the normal function of the alpha subunit of the G protein. To date, about 100 patients have been reported with 2q37 deletion of different sizes. Most deletions are terminal and occur de novo. Familial cases are exceptional as microdeletion of 2q37 is associated with intellectual disability (6).



## ***Conclusion***

In conclusion we reported the case of the female patient with the phenotypic characteristics of AHO (brachydactyly, short stature, mild degree of intellectual deficit and genu varum) but without any evidence of PTH resistance as well as other peptide hormones that act via alpha subunit of the stimulatory G protein. In the family history the uncle has a shorter fourth and fifth fingers of the left and right hand but probably does not have PHP Ia since he does not take any substitution therapy with calcium and vitamin D. PPHP occurs mainly in families with PHP 1a and it is inherited from the father which is not the case with our patient. There is a theoretical possibility that the mutation of the *GNAS 1* gene occurred de novo but without genetic testing the 2q37 deletion and AHO like syndrome can not be excluded.

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