CASE REPORT

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Infant With Pseudohypoparathyroidism Type 1a, Misdiagnosed as Congenital Hypothyroidism

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ABSTRACT

Background: Hypothyroidism is a manifestation of multi-hormonal resistance in pseudohypoparathyroidism type Ia (PHP Ia). **Objective:** The aim of this article was to present 9 months old male patient as case of congenital hypothyroidism.**Case report:** We describe a 9 months old male diagnosed with congenital hypothyroidism at age 1.5 month, who developed later (at age 5 months) cyanotic attack associated with hypocalcaemia, hyperphosphatemia, and hyperparathyroidism, patient had typical characters of AHO, so the diagnosis of Pseudohypoparathyroidism 1a associated with resistance (TSH) was established. **Conclusion:** Children diagnosed with PHP 1a should be further evaluated for associated resistance endocrinopathies. The literature on pseudohypoparathyroidism is reviewed with special emphasis on the misdiagnosis with congenital hypothyroidism.

Keywords: Pseudohypoparathyroidism (PHP), Albright s hereditary osteodystrophy (AHO), Congenital hypothyroidism, Parathyroid hormone, GNAS.

1. BACKGROUND

Pseudohypoparathyroidism (PHP) is a rare endocrine heterogeneous disorder that is characterized by resistance to parathyroid hormone (PTH) with normal renal function. PHP manifest with hypocalcemia, hyperphosphatemia, and increased level of PTH. PHP is classified into five variants type Ia (PHP Ia) which is considered the most common type accounting for 70% of the cases of PHP. Other variants are PHP type 1b (PHP 1b), PHP type 1c (PHP 1c), PHP type 2 (PHP 2), and pseudohypoparathyroidism (PPHP) (1). The term PHP was first described by fuller Albright in 1942 to describe patients that present with resistance to PTH, hypocalcemia, and hyperphosphatemia. They also present with abnormal skeletal and developmental signs, collectively called Albright hereditary osteodystrophy (AHO). These features include a rounded face, shortened fourth metacarpal, short stature, obesity, dental hypoplasia, and soft tissue calcification or ossification.

The administration of PTH will fail to stimulate the production of cyclic adenosine monophosphate (cAMP) and produce the expected phosphaturia (1). However, the AHO phenotype is not a feature of PHP 1b or PHP 2. Different forms of the disease including PHP 1a, PHP 1b, PHP 1c, and PPHP are contributing to the molecular defects in the gene (*GNAS1*) encoding the α subunit of the stimulatory G protein (Gsα) (2). In the other hand, PHP 2 is associated with renal resistance to PTH action and the genetic defects causing PHP 2 are not yet identified (3).

The diagnosis of PHP can be reached by the presence of hypocalcemia, hyperphosphatemia, and elevated serum concentration of PTH with normal renal function and vitamin D levels. Blood or urine levels of calcium, phosphorus, and PTH are done to achieve the diagnosis. For confirmation and identifying the subtype genetic testing for mutation in the *GNAS1* gene can be used (4).

The treatment for PHP patients is targeting calcium levels and normalizing its value. The mainstay of treatment is administering oral calcium and 1 alpha-hydroxylated vitamin D to normalize the levels of calcium and prevent hypercalciuria and suppress PTH levels (4).

Serum metabolites	Value	Reference range
Calcium	5.3 mg/dl	9 – 11 mg/dl
Ionized calcium	2.7 mg/dl	1.12 – 1.32 mg/dl
Phosphorus	8.3 mg/dl	3.60 – 6.70 mg/dl
Urea	20 mg/dl	0.0 – 50.0 mg/dl
Creatinine	0.4 mg/dl	0.50 – 1.50 mg/dl
Magnesium	1.8 mg/dl	
Alkaline phosphatase	563 IU/L	<500 IU/L
PTH	217 then 196 pg/ml	Up to 65 pg/ml
Vitamin D	3 ng/ml	
TSH	45.6u IU/ml	0.35 – 5.6u IU/ml
T4	7.7 ng/dl	
Cortisol	220.6 µg/dl	240 – 618 µg/dl

Table 1. Baseline endocrine and biochemical values at age 4 months. PTH: Parathyroid hormone, TSH: Thyroid stimulating hormone, T4: Thyroxine

2. OBJECTIVE

The aim of this article was to present a 9 months old male patient treated in endocrine outpatient clinic primarily as a case of congenital hypothyroidism.

3. CASE PRESENTATION

A 9 months old male patient was treated in endocrine outpatient clinic primarily as a case of congenital hypothyroidism. His parents noticed at age of 1.5 month that he sleeps most of the time, has progressive weight gain, and has abdominal distension. Therefore, he was advised by a pediatrician to do Thyroid function test, and results showed hypothyroidism (TSH 45.62 u IU/ml (0.34-5.6), T4 7.7 ng/dl (6.8-18), free T4 9.8 ng/dl). Hence, Levothyroxine 25 mcg once daily was initiated. During following up clinically and biochemically, the patient required increasing the dose till reaching 75 mcg once daily.

At 5 months of age, patient developed cyanotic attack lasted 1 minute, he had been admitted to a local hospital for treatment. On biochemical evaluation, the cause for the cyanotic attack was discerned to be due to hypocalcaemia as a part of rickets results (Table 1). He was treated with I.V calcium and discharged on oral calcium and vitamin D (cholecalciferol) 2000 IU/day for 2 months then vitamin D 600IU/day without calcium.

He was a product of non-consanguineous marriage with an uneventful antenatal and natal period birth. He is bottle feeding and start weaning food intake. Regarding his developmental milestones, there was mild delayed motor milestones (9 months sitting by support), but cognitive status was normal. The parents were healthy with normal stature.

On physical examination, the boy weighed 9 kg, measured 67 cm in height and head circumference was 44 cm. His weight was at the 50th percentile, and head circumference was in the 25th percentile. He had round face, depressed nasal bridge, short neck, looks chubby, (Figure 1) (US/LS 1.3), small hands and feet, and short stubby fingers (Figure 2). His penile length was normal. Metabolic screen and newborn screen for congenital hypothyroidism were normal.

Serum metabolites	Value	Reference range
Calcium	9.2 mg/dl	9-11 mg/dl
Ionized calcium	1.26 mg/dl	1.12 – 1.32 mg/dl
Phosphorus	6.3 mg/dl	3.60 – 6.70 mg/dl
Urea	20 mg/dl	0.0 – 50.0 mg/dl
Creatinine	0.4 mg/dl	0.50 – 1.50 mg/dl
LH	0.2 m IU/ml	1.7 – 8.6 m IU/ml
FSH	221 m IU/ml	1.5 – 12.4 m IU/ml
Testosterone	0.050 ng/ml	1.420 – 9.230 ng/ml
Alkaline phosphatase	457 IU/L	<500 IU/L
PTH	150 pg/ml	15.0 – 68.3 pg/ml
Vitamin D	21 ng/ml	30 – 100 ng/ml <20 is deficiency
TSH	0.29u IU/ml	0.35 – 4.94u IU/ml
T4	1.390 ng/dl	0.700 – 1.480 ng/dl
Cortisol AM	5.50 µg/dl	2.70 – 19.40 µg/dl

Table 2. Baseline endocrine and biochemical values at age 9 months, LH: Luteinizing hormone, FSH: follicle-stimulating hormone, PTH: Parathyroid hormone, TSH: Thyroid stimulating hormone, T4: Thyroxine

Investigations

His baseline endocrine and biochemical values at age 4 months are shown in Table 1. His baseline endocrine and biochemical values at age 9 months are shown in Table 2. X-rays of both hands were taken. Roentgenogram pictures of hands revealed bilateral short metacarpals. CT brain was done and it was normal. Thyroid and abdomen U/S were normal. His baseline endocrine and biochemical values are shown in Table 2.

Treatment

According to physical examination (characterize of AHO) and laboratory investigations which showed hypocalcaemia, hyperphosphatemia and raised PTH, the diagnosis of PTH 1a associated with resistance (TSH) was established. Calcitriol (1,25 dihydroxycholecalciferol) drops were initiated with oral calcium carbonate and adjustment to levothyroxine dose was made.

DISCUSSION

Hypothyroidism was first recognized in patients with PHP Ia in 1971 by Marx and co-workers (5). Usually, patients of PHP present with mild hypothyroidism, elevated TSH, normal or slightly low thyroid hormone. Patients with PHP Ia do not have circulating anti-thyroid hormone and do not develop goiter (6). Other hormonal disorders can be associated with hypothyroidism such as high calcitonin levels (7), growth hormone deficiency, hypogonadism (8), and sensorial defects (11), and is attributed to multiple peripheral resistance (6, 9).

The prevalence of PHP type 1a and type 1b is 1 per 295,000 in Japan. PHP affects females about two times more often than males (10). Although cases of severe hypothyroidism at newborn screening have been described, the onset of endocrine symptoms occurs later childhood (11).

There are two main types of PHP. Type I is characterized by minimal or non-existing renal cAMP synthesis in response to PTH. However, Type II has an absence of or a subnormal phosphaturic reaction in response to PTH, and it shows a normal increase in urine cAMP

Figure 1. Main features of the 9 old months mail patient: round face, depressed nasal bridge, short neck, and looks chubby

Figure 2. Main features of the 9 months old male patient: small hands and feet, and short stubby fingers

(12). Type I is further subdivided into two subtypes, PTH 1a and PTH 1b. In PTH 1a, the affected individuals have a genetic deficiency in the a subunit of the stimulatory guanine nucleotide binding protein (GS), and the majority of them exhibit specific morphological defects referred to as AHO (13).

All newborns with PHP Ia typically have elevated TSH concentration at birth (14-16) and may then normalize for 9–20 months before elevating again. In patients with PHP Ia, this can indicate that, like PTH resistance (17), resistance to TSH develops during the first 2 years of life. Normally there is a transient surge in TSH concentration immediately after birth, which is believed to be a reaction to the drop in extracorporeal temperature (18). Patients with PHP Ia may have a subtle TSH resistance that is only detectable during periods of maximal stimulation, like childbirth, which is why their TSH levels during birth surge excessively. This may help in the diagnosis of the disease in neonates (6-8), or after the first 2 years of life.

In those with PHP Ia, the processes causing hypothyroidism have not been identified. As will be covered below, different thyrotropic axis components may be involved.

The most common reason is a peripheral mechanism, namely resistance to TSH. It is a manifestation of the signaling failure to polypeptide hormones found in PHP patients Ia (6). Many studies have shown biallelic expression of the *GNAS* in the thyroid (19-21), yet rather than full inhibition of paternal allelic transcription, this was associated to preferential maternal expression. Due to the inactivation of the dominant maternal *GNAS*, this relaxed paternal imprinting of *GNAS* in the human thyroid may be one mechanism causing TSH resistance in PHP Ia (22), which would lead to a considerable loss of hormonal resistance and the expression of *GNAS*. Thyroid membranes taken from one PHP Ia patient showed reduced TSH stimulation of adenyl cyclase (23). The mechanism causing this condition is distinct from that causing other types of genetic hypothyroidism with TSH resistance, which are caused by germline TSH receptor mutations. This abnormality is characterized by normal or very low serum levels of thyroid hormone and increased serum TSH levels in the presence of a hypoplastic or properly sized gland in the appropriate location in the neck. Patients may exhibit severe hypothyroidism at one end of the range or euthyroid hyperthyrotropinemia at the other, depending on the extent of TSH receptor function impairment. (24).

Our patient presented with hypocalcemia, hyperphosphatemia, and high PTH level along with the with the typical findings on physical examination, so the diagnosis of PHP type 1a was concluded. He was managed with Calcitriol (1,25 dihydroxycholecalciferol), oral calcium carbonate, and levothyroxine. This study agrees with a similar previous case report (25) with the exception that the diagnosis was confirmed by the identification of *GNAS* gene mutation. Another previous study of a thirty-fife-day old male presented with hypocalcemic convulsions. Investigations revealed hypocalcemia, hyperphosphatemia, raised PTH, and Vitamin D level was not deficient. So he received the proper management and was discharged home (26).

4. CONCLUSION

Pseudohypoparathyroidism is a rare endocrine heterogeneous disorder that is characterized by resistance to parathyroid hormone with normal renal function, which can be missed diagnosed with other diseases such as hypothyroidism as in our case. They present with abnormal skeletal and developmental signs, collectively called Albright hereditary osteodystrophy. High suspicion is required to make the diagnosis. It is treated by 1,25 dihydroxycholecalciferols, oral calcium carbonate, and levothyroxine.

- **Patient Consent Form**: All participants were informed about subject of the study.

- **Author's contribution**: W.A. and M.Q. gave substantial contributions to the conception or design of the work in acquisition, analysis, or interpretation of data for the work. M.A, A.A., and M.Q. had a part in article preparing for drafting or revising it critically for important intellectual content. W.A, M.A., and A.A. gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
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