결신 발작 양상으로 내원한 가성부갑상선기능저하증 환자 1례

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A Case of Pseudohypoparathyroidism Mimicking for Absence Seizure

Pseudohypoparathyroidism (PHP) is a rare disease characterized by hypocalcemia, hyperphosphatemia, and elevated serum levels of the parathyroid hormone (PTH). Symptoms of hypocalcemia include seizures and tetany. PHP can be divided into the following subtypes: Ia, Ib, Ic, and II. Type Ia and Ic have morphological characteristics called Albright's hereditary osteodystrophy (AHO). AHO is associated with characteristic developmental abnormalities that include a short stocky stature, a short neck, brachydactyly, a round face, central obesity, mental retardation and subcutaneous ossifications. In Korea, cases of PHP with AHO are reported intermittently, however, cases of PHP without AHO are very rare. We encountered an 11-year-old boy who initially presented with dialeptic seizures who was otherwise healthy with normal development. At first, we thought that he was probably the absence seizure patients. But, His EEG shows a normal pattern. An investigation at that time revealed hypocalcemia, hyperphosphatemia, elevated PTH levels, normal intelligence, and a lack of features that would indicate AHO. Based on Molecular analysis using direct sequencing that targeted the *GNAS* gene was performed, but a *GNAS* gene mutation was not found. Based on the normal intelligence level of the patient, the lack of AHO features, and the results of the molecular analysis, he was diagnosed with PHP type Ib or II. Oral therapy with calcium carbonate (0.5 g/day) and calcitriol (0.5 mcg/day) was initiated. One month later, his serum calcium and phosphate levels improved. Seizures did not recur. The major purpose of our case report is to stress the importance of confirming electrolyte imbalance when examining patients who have had a seizure episode.

Key Words: Pseudohypoparathyroidism, Albright's hereditary osteodystrophy, Epilepsy, Seizure, Hypocalcemia, Hyperphosphatemia

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Introduction

Pseudohypoparathyroidism (PHP) is a rare disease characterized by hypocalcemia, hyperphosphatemia, and elevated serum levels of the parathyroid hormone (PTH)¹⁾. Symptoms of hypocalcemia include seizures and tetany²⁾. Based on the presence of molecular abnormalities, hormonal resistance patterns, and Albright's hereditary osteodystrophy (AHO), PHP can be divided into the followings subtypes: Ia, Ib, Ic, and II³⁾. AHO is associated with characteristic developmental

abnormalities that include a short stocky stature, a short neck, brachydactyly, a round face, central obesity, mental retardation and subcutaneous ossifications⁴⁾. In Korea, cases of PHP with AHO are reported intermittently, however, cases of PHP without AHO are very rare⁵⁾. We encountered an 11-year-old boy who initially presented with dialeptic seizures. An investigation at that time revealed hypocalcemia, hyperphosphatemia, elevated PTH levels, normal intelligence, and a lack of features that would indicate AHO. In this report, we describe and examine the case of a patient we encountered who had PHP without AHO.

Case report

An 11-year-old boy visited the pediatric outpatient department of Daedong hospital for frequent seizure attacks. Throughout the last 2 years, he had been losing consciousness intermittently for approximately 10 seconds each time without collapsing. His symptoms gradually increased in frequency, and he experienced occasional cramping pain and tingling sensations in both of his hands and feet. On the same day that he visited our hospital for the first time, he suddenly lost his consciousness and fell down at school. He did not visit other hospitals to be evaluated for this issue.

He was the first child born to healthy parents through normal delivery at a gestational age of 40 weeks, and had a birth weight of 4.5 kg. He was healthy with normal development, until dialeptic seizures occurred. His family had no history of endocrine problems.

The biochemical analyses confirmed hypocalcemia, hyperphosphatemia, and an elevated concentration of PTH, with normal serum concentration of vitamin D metabolites and renal function. His 24-hour urinary calcium, phosphate, and cyclic adenosine monophosphate (AMP) levels were decreased (Table 1).

Upon physical examination, the patient displayed evidence of latent tetany in the form of Chvostek's sign and Trousseau's sign. He showed no features of AHO, such as having a short stature, short neck, brachydactyly, round face, central obesity or mental retardation (Fig. 1).

The X-ray image of both the patient's hands showed no gross bony abnormalities (Fig. 2). However, the brain magnetic resonance imaging revealed bilateral basal ganglia calcification (Fig. 3). His electroencephalography had a normal pattern (Fig. 4). Based on the normal intelligence level of the patient and the lack of AHO features, PHP type Ib or II was suspected. Oral therapy with calcium carbonate (0.5 g/day) and calcitriol (0.5 mcg/day)

was initiated. His parents then wanted to transfer him to a tertiary hospital for further evaluation. At the tertiary hospital, molecular

Table 1. Investigative Profile of the Patient. Normal Ranges are Indicated in Brackets

Serum biochemistry	At presentation
Calcium, mg/dL (8.7-10.4)	4.8
Phosphate, mg/dL (2.4-5.1)	8.5
ALP, IU/L (40-250)	1168
PTH, pg/mL (15.0-65.0)	234.0
Creatinine, mg/dL (0.7-1.3)	0.4
25(OH)D ₃ , ng/mL (>10)	15.05
1,25(OH) ₂ D ₃ , pg/mL (19.60-54.30)	47.71
Magnesium, mg/dL (1.9-2.5)	2.1
24 hour urinary profile	
Calcium, mg/day (100-300)	11.88
Phosphate, mg/day (400-1,300)	310.86
Creatinine, mg/day (800-2,000)	861.3
Cyclic-AMP II umol/day (3.30-6.10)	1.90

Abbreviations: ALP, alkaline phosphatase; PTH, parathyroid hormone; 25 (OH)D₃, 25-OH Vitamin D3(RIA); 1,25(OH)₂D₃, 1,25-(OH)₂ vitamin D3; AMP, adenosine monophosphate.

Fig. 1. Contour of the patient's hand. No gross abnormality is shown.

Fig. 2. X-ray image of both hands. No gross bone abnormality is shown.

analysis using direct sequencing that targeted the *GNAS* gene was performed, but a *GNAS* gene mutation was not found. He was diagnosed with PHP type Ib or II and continued to take calcium carbonate and calcitriol. One month later, his serum calcium level was partially normalized at 8.3 and his serum phosphate level also improved to 6.0.

Discussion

PHP is a rare sporadic or inherited disorder in which the kidneys fail to respond to PTH⁽⁶⁾. PHP is characterized by hypocalcemia, hyperphosphatemia, elevated PTH concentrations, and unique clinical features typically associated with distinctive skeletal and developmental defects⁽⁴⁾. In contrast to the situation in

hypoparathyroidism, in PHP the parathyroid glands can synthesize and secrete parathyroid hormone. So, decreased PTH concentrations were found in hypoparathyroidism⁽⁷⁾. Generalized tonic-clonic, focal motor, and atypical absence or akinetic seizures can occur in hypocalcemia and may be the sole presenting symptom⁽⁸⁾. The prevalence of PHP has been estimated to be approximately 0.79 cases per 100,000 people⁽⁹⁾.

PHP is divided into type I and type II. In patients with PHP type I, there is a diminished urinary cyclic AMP response to exogenous PTH administration⁽¹⁰⁾. PHP type II differs from type I in that the urinary excretion of cyclic AMP is elevated in both the basal state and after stimulation with PTH⁽¹¹⁾. There are several subtypes of PHP type I that are caused by mutations of *GNAS*, a gene encoding the alpha subunit of the G protein, coupled with the PTH receptor. PHP type Ia contains heterozygous mutations in the *GNAS* gene that reduces the expression or function of *G α s*, PHP type Ic contains heterozygous mutations in the *GNAS* gene that impairs the coupling of heptahelical receptors to adenylyl cyclase, and PHP type Ib contains heterozygous deletions in *STX16*, *NEP55* and/or *AS* exons. In contrast, PHP type II contains no molecular defect⁽¹²⁾.

Patients with PHP type Ia and Ic have morphological characteristics called AHO. AHO has a wide range of manifestations such as short stature, round face, brachydactyly, brachymetacarpia, centripetal obesity, subcutaneous ossifications, and mental or developmental delay⁽⁴⁾. Patients with PHP type Ib and II have hypocalcemia, hyperphosphatemia, and elevated serum PTH levels, but they do not exhibit the physical features of AHO. Type Ia accounts for the majority of patients with PHP. PHP type Ib is a rare subtype, as no more than 100 cases were reported in the literature of the world⁽¹³⁾. Therefore, a patient who has PHP without AHO is very exceptional.

Our patient visited our hospital for his dialeptic seizures. At first, we thought that he was probably the absence seizure patients. But, His EEG shows a normal pattern. On the other hand, he had hypocalcemia, hyperphosphatemia, and an elevated

Fig. 3. Brain magnetic resonance imaging shows bilateral basal ganglia calcification.

Fig. 4. Electroencephalography (EEG) of the patient. (A) Awake. (B) Sleep. EEG shows a normal pattern.

concentration of PTH. But he had normal serum vitamin D levels and no history of malnutrition. Based on these results, PHP was suspected⁷⁾. The brain magnetic resonance imaging revealed bilateral basal ganglia calcification. In PHP patients, symptoms are caused by hypocalcemia. As with other hypocalcemic disorders, the usual manifestations are seizures and an altered mental status. The reported seizure types in patients with PHP are generalized tonic-clonic or absence seizures. The mechanism of development for calcification is unknown. Albright hypothesized that it could be due to plasma super saturation with phosphorus¹⁴⁾.

The patient showed no features of AHO. As mentioned, the diagnosis of PHP type Ib or II was suspected. In the tertiary hospital, *GNAS* gene sequencing was performed; a *GNAS* gene mutation was not found. Therefore, PHP type Ia was ruled out. Molecular analyses using *GNAS* gene methylation and the Ellsworth-Howard test required differentiation between types Ib and II, but his parents did not want him to be further examined because of the price.

The average age at the onset of symptoms is 8 years. Ages at diagnosis tended to be older in patients with PHP without AHO, in comparison to patients with PHP as well as AHO. Calcification of the basal ganglia is common in patients whose disease was diagnosed later¹⁵⁾. For our patients, the typical clinical symptoms did not appear until 9 years of age, but after 10 years of age. Although the initial clinical onset may be related to hypocalcemia which leads to seizure attacks, hypocalcemic conditions may become clinically obvious during puberty, when the calcium demands are higher.

The aim of PHP therapy is to obtain an adequate control of calcium-phosphate. The typical treatment involves taking calcium and vitamin D active metabolite supplements¹⁶⁾. All patients are recommended to undergo a serum and urinary examination every 3 months, as well as strict follow-ups to adjust the therapeutic dosages. Seizures did not recur in our patient.

In conclusion, the major purpose of our case report is to stress the importance of confirming electrolyte imbalance when examining patients who have had a seizure episode. Electrolyte homeostasis in the central nervous system is essential for brain function. The regulation of ionic balance is a critical process involving a complex array of molecules for moving ions in the brain involving blood-brain barrier function. Electrolyte abnormalities can affect neuronal discharge, and may facilitate epileptiform activities⁸⁾. Rapid identification and correction of the disturbance is necessary to control seizures and prevent permanent brain damage. This should always be part of the initial diagnostic examination in patients with seizures. Additionally, PHP should be considered in patients with seizures who have hypocalcemia and

hyperphosphatemia.

요약

가성부갑상선기능저하증은 저칼슘혈증과 고인산혈증, 혈중 부갑상선호르몬 증가를 가져오는 드문 질환으로, 저칼슘혈증으로 인해서 경련이나 강직이 발생할 수 있다. 가성부갑상선기능저하증은 몇 개의 아형으로 나뉘는데, 그 중에서 Albright 선천성 골이형성증(AHO)를 동반하는 Ia, Ic 형이 대부분인 것으로 알려져있다. 저자들은 결신 발작 양상을 주소로 내원한 11세 남아에서 AHO를 동반하지 않은 가성부갑상선기능저하증을 경험하였기에 보고하는 바이다. 정상 수준의 지능과 AHO에 해당하는 증상을 가지고 있지 않았고 *GNAS* 유전자 돌연변이도 발견되지 않았지만 저칼슘혈증과 고인산혈증, 혈중 부갑상선호르몬 증가를 보였으며, 24시간 소변에서 칼슘과 인산염, cAMP가 감소되어 있었다. 기타 혈액검사와 뇌파에서는 이상이 없었으며, AHO를 동반하지 않은 가성부갑상선기능저하증으로 진단하고, 경구 calcium carbonate와 calcitriol 복용 후 호전되었다. 소아에서 발생하는 간질중첩증이나 재발성 경련은 뇌 손상을 일으킬 수 있으므로, 경련성 질환 환자 내원 시 오진을 막기 위해서 전해질 불균형을 확인해 보아야 한다.

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