Unrecognized Pseudopseudohypoparathyroidism in a Case of Post-Traumatic Brain Injury with Multiple Pituitary Hormone Deficiency: A Rare Coincidence

Çoklu Hipofizer Hormon Eksikliği Olan Posttravmatik Beyin Hasarı Olgusunda Tanınmayan Psödopsödohipoparatiroidi: Nadir Bir Koinsidans

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Case Report

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Introduction

Pseudopseudohypoparathyroidism is a rare clinical entity of autosomal dominant inheritance, which shows phenotypic similarity to pseudohypoparathyroidism. However, the main difference lies in their biochemical profiles. The former disease is characterized by normal serum calcium, phosphorus, vitamin D, and parathyroid hormone (PTH) level, whereas the latter shows features suggestive of PTH resistance. Our patient presented after post blunt trauma of head with diabetes insipidus and short stature. Investigations revealed multiple pituitary hormone deficiency. Further examination was conducted for pseudohypoparathyroidism, keeping in mind short metacarpals, knuckle dimple, and short stature, but normal calcium, phosphorus, vitamin D and PTH value led to the diagnosis of pseudopseudohypoparathyroidism. GNAS mutation analysis is necessary to confirm the diagnosis, which could not be performed in this patient due to the high cost. This case shows that pseudopseudohypoparathyroidism, although a rare disease, should be appropriately investigated in such patients if they present with peculiar skeletal features of pseudohypoparathyroidism.

Keywords: Pseudopseudohypoparathyroidism; osteodystrophy; diabetes insipidus; hypopituitarism, brachydactyly

Anahtar kelimeler: Psödopsödohipoparatiroidizm; osteodistrofi; diabetes insipidus; hipopituitarizm, brakidaktili

Abstract

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Molecular genetic testing identifying a mutation in the GNAS gene confirms the diagnosis. Acute phase hypopituitarism, after moderate to severe head trauma, mainly causes growth hormone and gonadotropin deficiency. During the recovery phase of hypopituitarism, adrenocorticotrope hormone deficiency (ACTH) is very common. Permanent diabetes insipidus (DI) occurs if there is an injury in the posterior pituitary gland or axon terminals in the neurohypophysis. Here we reported a case of post-traumatic brain injury (blunt trauma) with multiple pituitary hormone deficiency and associated pseudopseudohypoparathyroidism.

Case Report
A 17-year-old male patient presented to our clinic with an inability to gain height for the last three years after a severe post-traumatic brain injury. He also complained of excessive urination along with an increased thirst for the last two years. There was a history of generalized weakness with a lack of development of secondary sexual characteristics and seizures for the last two years. There was no history of headache, loss of smell sensation, visual disturbances, and hypoglycemic episodes. No feeding difficulties and jaundice were reported in the neonatal period, and the developmental milestones were normal. No other member in the family or first-degree relative had a history of pseudohypoparathyroidism or pseudopseudohypoparathyroidism. On examination, height was below the third centile with an upper segment to lower segment ratio of 0.83. Bilateral testicular volume was 2 mL, and stretched penile length was 4 cm. On further examination, we observed short 4th metacarpal (Archibald sign) with short 4th and 5th metatarsal (Figure 1). Knuckle knuckle dimple dimple sign was present (Figure 2), and the X-ray of wrist confirmed the findings (Figure 3).

The patient was investigated for delayed secondary sexual characteristics, which depicted low basal gonadotropins (LH 0.48 mIU/mL and FSH 1.30 mIU/mL), low serum prolactin (9.16 ng/mL) along with low testosterone (35.5 ng/dL). Keeping in mind the short stature, the subcutaneous growth hormone (GH) stimulation test (Clonidine test 150 mcg/kg) was performed after sex.
steroid priming with the replacement of inj. testosterone 100 mg i.m. for three days, which showed low GH (post-stimulation at 60 min: 0.14 ng/mL, at 120 min: 0.19 ng/mL). So a diagnosis of multiple pituitary hormone deficiency was made, and the patient was prepared for a water deprivation test followed by desmopressin test. The values of urine and serum osmolality were 82 mOsmol/kg and 348 mOsmol/kg, respectively, which changed to 178 mOsmol/kg and 284 mOsmol/kg, respectively, after the desmopressin Inj. The result came out in favor of central diabetes insipidus. MRI Brain sagittal T1W film showed an area of gliosis in the right frontal lobe with a small area of ischemic changes in the right parietal lobe, prominent cisterna magna, while posterior pituitary was normal. No white matter or basal ganglia calcification was noticed. No abnormalities were detected in the pituitary gland. Since there were unusual skeletal features, other biochemical tests were planned. Serum total calcium and serum phosphorus were 9.5 mg/dL and 3.8 mg/dL, respectively. Serum PTH level was 55.5 pg/mL (normal range: 10-60) and Serum 25-(OH)D level was 23.3 ng/mL (normal range: 30-50 ng/mL). The short stature was attributed to pseudopseudohypoparathyroidism, and thus the diagnosis of the same was made on the basis of clinical and laboratory features. Genetic analysis was planned but could not be conducted due to financial constraints.

Discussion
Pseudopseudohypoparathyroidism is characterized by short stature, brachydactyly, obesity, round face, and subcutaneous and ectopic calcification with normal serum levels of calcium, phosphorus, PTH, and vitamin D. Albright et al. (1) were the first to use the term pseudopseudohypoparathyroidism (PPHP) for those patients with these phenotypic features and normal biochemical values (1), the most specific feature of the AHO phenotype is shortening of 4th and 5th metacarpals and/or metatarsals and first distal phalanx, together with heterotopic ossifications. Short stature, round face, and other phenotypic features are the presentation of PPHP. Pseudopseudohypoparathyroidism is caused by the loss of function mutations in the alpha subunit of the Gs protein encoded by GNAS gene locus (2). Our patient had a history of blunt trauma of head in a road traffic accident and presented us with short stature and other features of multiple pituitary hormone deficiency such as polyuria and delayed puberty with corresponding biochemical evidence. However, peculiar skeletal features of AHO along with no evidence of PTH resistance led to the diagnosis of PPHP, which shares common features of short stature. Unfortunately, the genetic diagnosis could not be performed due to the non-availability of the test in our setup and financial restraints. PPHP was incidentally diagnosed in this patient because of specific features along with normal biochemical findings pertaining to serum levels of calcium, phosphorus, PTH, and Vit D. This case emphasizes that any patient presented with short stature needs to be properly examined and investigated if one shows features of AHO and no resistance of PTH hormone. Pituitary dysfunction can develop acutely or months after blunt trauma of the head. In 70% of the patients, hypopituitarism occurs within the first year after head trauma (3,4). Posterior pituitary hormone deficiency is less common than that of the anterior pituitary because of the supply from the short inferior hypophyseal vessels. In contrast, the long hypophyseal vessels supply the anterior pituitary making it more susceptible. Among anterior pituitary hormones, somatotroph and gonadotrophs, located in the lateral regions of the anterior pituitary, are more susceptible to damage. Recovery of pituitary hormone deficiency occurs in about 50% of patients when diagnosed at three months post-injury (3,4). Most hormonal deficits diagnosed within the first year after blunt trauma of head were considered to be permanent, and thus, repeat testing is advised at 12 months period (5). Pituitary imaging studies were found to be abnormal in 80% of traumatic brain injury patients with hypopituitarism (6). The pituitary abnormalities seen in patients with diabetes insipidus were poorly defined, and its frequency is variable from normal to loss of pituitary bright spot. Pituitary imaging studies can be normal in patients with traumatic brain
injury with diabetes insipidus, as seen in our case as well. This explains why some patients with TBI, who undergo radiological scans, do not display any specific findings.

Patient Informed Consent
A detailed informed consent has been taken to include the patient as a subject in this case report study. He has been given a full explanation by the study doctor dr. Manish Srivastav about the nature and purpose of the study. This has been explained to him in the language he best understands along with duly signed consent performa.

Source of Finance
During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest
No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions
Idea/Concept: Manish Srivastav; Design: Manish Srivastav; Control/Supervision: Keshav Kumar Gupta; Data Collection and/or Processing: Alankar Tiwari; Analysis and/or Interpretation: Nihit Kharkwal; Writing the Article: Nihit Kharkwal; Critical Review: Keshav Kumar Gupta.

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