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Case Report

Progression of intracranial calcification after initiation of therapeutic management in patient with pseudohypoparathyroidism : a case report

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Abstract

We report a 14-year-old Japanese girl with pseudohypoparathyroidism (PHP) in whom progression of intracranial calcification with no neurological symptoms was observed after initiation of therapeutic intervention. Intracranial calcification has often been reported in PHP patients. The underlying mechanism of such intracranial calcification remains poorly understood, however. In idiopathic hypoparathyroidism, hyperphosphatemia is believed to cause progression of intracranial calcification. Although hypocalcemia improved immediately after treatment in the present case, hyperphosphatemia persisted for 15 months. This suggests that persistent hyperphosphatemia is a contributing factor in the progression of intracranial calcification in patients with PHP.

Introduction

Pseudohypoparathyroidism (PHP) is a rare genetic disorder that is characterized by end-organ resistance to action of the parathyroid hormone (PTH)[1)]. It is classified as type I, in which the reaction of cyclic adenosine monophosphate (cAMP) with PTH is impaired, or type II, in which cAMP response to PTH is conserved. Type I is further subdivided into PHP-Ia, PHP-Ib, or PHP-Ic. Patients with pseudohypoparathyroidism-Ia (Mendelian inheritance in man [MIM] 103580) or Ic (MIM 612462) present with features of Albright hereditary osteodystrophy (AHO), including short stature, round face, brachydactyly, central obesity, and developmental delay ; whereas those with PHP-Ib (MIM 603233) typically present with no features of AHO. Several reports have demonstrated that some patients with PHP-Ib show mild AHO features, however[2)3)]. Clinically, PHP patients usually present with seizure, numbness of the arms and legs, and tetany due to hypocalcemia. Intracranial calcification, particularly in the basal ganglia, has been extensively reported in approximately 50% to 100% of patients with PHP[4)]. The precise mechanism underlying brain calcification and its implications for neurological function and manifestations remain poorly understood, however[5)6)]. The present report describes an adolescent girl with PHP-Ib in whom progression of intracranial calcification was observed, even after initiation of therapeutic intervention.

Case

A 14-year-old Japanese girl was brought to our hospi-

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tal by ambulance due to an afebrile clonic seizure that lasted for one minute. This seizure was accompanied by unconsciousness and cyanosis of the lips. Upon arrival at the hospital, she was awake and her vital parameters were normal. She had no history of seizure or any other medical condition. Her family medical history at this point revealed nothing of note. Physical examination revealed a round face, brachydactyly of the fourth and fifth metacarpals, and short stature (height 148 cm, −1.5 SD; weight 43 kg, −0.9 SD; body mass index 19.6 kg/m^2). Laboratory analysis revealed hypocalcemia (Ca 5.3 mg/dl), hyperphosphatemia (P 7.7 mg/dl), and an elevated plasma PTH level (intact PTH 345 pg/ml). A blood examination revealed no additional abnormal findings, including vitamin D deficiency. A 24-hour urine collection test revealed normal renal function and low calcium excretion (10 mg/24 hr). Electroencephalography and electrocardiography revealed no abnormal findings. Calcification in the bilateral putamen, pallidum, caudate nuclei, and right subcortical frontal lobe was revealed by computed tomography (CT) (Fig. 1A). Genetic testing identified a 3 kb deletion in *STX16*, and a methylation defect in *GNAS* exon A/B, which has previously been reported to cause PHP-Ib[7]. This deletion was also later found in the patient's mother, who was asymptomatic. Once a diagnosis of PHP-Ib was established, treatment with calcium gluconate injection and oral alfacalcidol was initiated. Her serum calcium level normalized within 7 days of initiating therapeutic intervention, whereas her serum phosphorus level only normalized at 15 months later. Calcium was administered, initially by injection and then orally. The dose was gradually tapered and eventually discontinued, however, as her calcium level subsequently stabilized. She continued to receive alfacalcidol alone at 1.0 μg daily, without showing any clinical symptoms, including higher brain dysfunction. She had no further seizures, even without anticonvulsants, after initiation of therapy, suggesting that the first seizure was due to hypocalcemia.

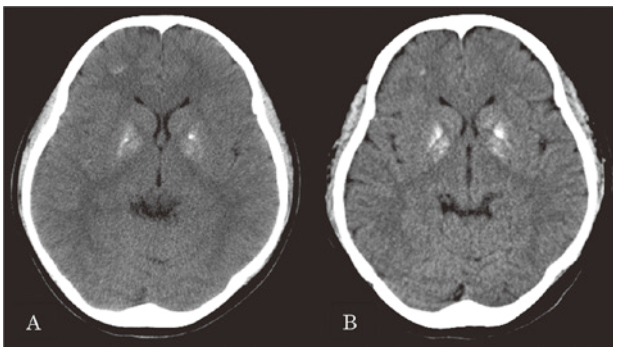

Fig. 1 A (14 years old), B (21 years old).
(A) Computed tomography (CT) images revealed intracranial calcification in bilateral putamen, pallidum, caudate nuclei, and right subcortical frontal lobe. Maximum density of calcification in basal ganglia was 109 Hounsfield units (HU).
(B) Calcified lesion expanded and its density in basal ganglia increased to 175 HU.

Seven years after the diagnosis of PHP, a brain CT at the age of 21 years revealed progression of intracranial calcification (Fig. 1B). The maximum density of calcification in the basal ganglia showed an increase, from 109 Hounsfield units (HU) to 175 HU. The volume of brain calcification, as measured by histogram analysis (Volume analyzer, SYNAPSE-VINCENT, Fujifilm, Tokyo, Japan), also showed an increase, from 4.5 cm^3 at 14 years of age to 7.5 cm^3 at 21 years of age, with no development of neurological symptoms.

Discussion

Few studies have investigated the mechanism of brain calcification in hypoparathyroidism. Although a low calcium/phosphorus ratio, high phosphorus level, and a history of seizures have been reported to show an association with progression of basal ganglia calcification in idiopathic hypoparathyroidism (IH), little has been reported about PHP[5]. Moreover, it remains to be clarified whether intracranial calcification can be improved by therapeutic management. In the present case, although it took only 7 days for the serum calcium level to normalize after initiation of treatment, it took 15 months for serum phosphorus to normalize. This suggests that persistently high phosphorus levels are a contributing factor in the progression of intracranial calcification in patients with PHP. This assumption should be treated with caution, however, as intracranial calcification was not re-evaluated immediately after normalization of the serum phosphorus level. Ingestion of low-phosphate food to rapidly decrease serum phosphorus could have attenuated its progression. Although there is little evidence that intracranial calcification in PHP is associated with the development and deterioration of neurological symptoms, one IH case with extensive brain calcification and persistent neurologic dysfunction, despite normalization of calcium, has been documented[8]. That study did not report normalization of serum phosphorus levels, however. Although the present case showed no additional neurological symptoms, careful follow-up is necessary. Further study is required to reveal the mechanism and pathogenicity of intracranial calcification in PHP.

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Disclosure

The authors declare no conflict of interest.

Author contributions

R.H. wrote the manuscript ; H.T., S.G., S.N., and H.K. were responsible for diagnosis and treatment. M.S. provided conceptual advice and edited the manuscript.

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治療開始後に脳内石灰化病変の進行を認めた偽性副甲状腺機能低下症 Ib 型の 1 例

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【要旨】 治療開始後に神経学的所見を伴わず脳内石灰化病変の進行を認めた偽性副甲状腺機能低下症 Ib 型の 1 例を報告する。脳内石灰化病変、特に基底核の石灰化は偽性副甲状腺機能低下症の 50～100% で認められる所見であるが、原因は解明されていない。特発性副甲状腺機能低下症における脳内石灰化の機序としては、高 P 血症の関与が推測されているが、本疾患における石灰化病変を検討した報告は非常に少ない。本症例では治療開始後、低 Ca 血症は速やかに改善したが高 P 血症の改善には 15 ヶ月を要した。持続する高 P 血症の脳内石灰化病変への関与が示唆された。

〈キーワード〉 脳内石灰化、PHP-Ib、偽性副甲状腺機能低下症、*STX16*