Clinical Case Report

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Pseudohypoparathyroidism with basal ganglia calcification

A case report of rare cause of reversible parkinsonism

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Abstract

Rationale: Parkinsonism can be secondary to many internal diseases, in some certain conditions, it seems that the clinical manifestations of parkinsonism presenting reversible. We report a case of patient with parkinsonism secondary to pseudohypoparathyroidism, who improved markedly after the supplement of serum calcium.

Patient concerns and diagnoses: A 52-year-old woman with acute parkinsonism was diagnosed as pseudohypoparathyroidism after the conducting of brain computed tomography, laboratory examinations, and gene detection. The son of the patient was also examined and was diagnosed as pseudohypoparathyroidism, who had ever complained of the history of epilepsy. The clinical manifestations of parkinsonism of the patient was reevaluated after the supplement of serum calcium according to the diagnosis.

Interventions and outcomes: The brain computed tomography revealed the basal ganglia calcification of the patient, accompanying by serum hypocalcemia and hyperphosphatemia. Loss of function mutation also confirmed the diagnosis. Five days after the therapy targeting at correction of serum hypocalcemia, the patient improved greatly in dyskinesia.

Lessons: This study reported a patient presenting as acute reversible parkinsonism, who was finally diagnosed as pseudohypoparathyroidism. It indicated us that secondary parkinsonism should be carefully differentiated for its dramatic treatment effect. And the family history of seizures might be an indicator for the consideration of pseudohypoparathyroidism.

Abbreviations: AHO = albrights hereditary osteodystrophy, BG = basal ganglia, CT = computed tomography, GNAS = guanine nucleotide-binding protein G-s alpha subunit, MRI = magnetic resonance imaging, PHP = pseudohypoparathyroidism, PTH = parathyroid hormone, TSH = thyroid stimulating hormone.

Keywords: basal ganglia calcification, parkinsonism, pseudohypoparathyroidism

1. Introduction

Parkinsonism is characterized by bradykinesia, rigidity, and rest tremor.[1] It can be secondary to varieties of diseases, including vascular, drug-induced, metabolic, autoimmune, paraneoplastic, and endocrine causes. Among them, endocrine diseases are often ignored due to the heterogeneous of clinical manifestations, such as hyperparathyroidism, hypothyroidism, and pseudohypoparathyroidism (PHP).[2]

PHP is a group of heterogeneous disorders with end-organ resistance of various hormones, especially parathyroid hormone (PTH).[3] The PTH resistance usually results as hypocalcemia and hyperphosphatemia, leading to basal ganglia (BG) calcification.[4]

Seizures and epilepsy occur commonly in PHP, while parkinsonism has been seldomly reported.[5] Here, we report a middle-aged woman presented with reversible parkinsonism after supplement of serum calcium, whose son ever complained of a seizure history. Loss of function mutation in guanine nucleotide-binding protein G-s alpha subunit (GNAS) gene (p.P115S) was detected in both the mother and son.

2. Case report

A 52-year-old woman was admitted to our hospital complaining of "progressive bradykinesia and inflexibility of both upper extremities for 6 months." She gradually walked and turned slowly without due cause 6 months ago, presenting with decreasing of flexibilities in operating chopsticks and buttons, as well as doing other fine actions. She has noticed muscular rigidity, especially the extremities on the left, and decreased facial expression. However, none of tremor, constipation, olfaction dysfunction, and rapid eye movement sleep behavior disorder was observed.

Physical examinations revealed that she had short stature (height: 152 cm, weight: 62 kg, body mass index [BMI]: 26.8), round-shaped face, and brachydactyly. No intelligent problems or memory disorders were found. Sensory and cerebellar tests were normal. The muscle tension of extremities increased,

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especially that of the left upper limb. The rotation of upper limbs presented slightly clumsily, as well as the kneading action of fingers. Muscle strengths of limbs and bilateral tendon reflexes were normal. No static or intention tremor was observed during the examination. The patient confessed that she had a history of CO poisoning 4 years ago and denied a family history of parkinsonism or stroke. However, her son was ever diagnosed as seizure.

On admission, the patient persisted that brain computed tomography (CT) had been conducted in other hospital and none of abnormalities was reported; however, the image could not be provided. Thus, she refused to conduct a brain CT scan once again. Further tests were conducted, including systemic autoimmune antibodies (anti-dsDNA, anti-SSA, anti-SSB, anti-Sm, anti-RNP, anti-Scl70, anti-Jo-1, p-ANCA, c-ANCA), serum tumor markers testing (carcinoembryonic antigen, α-fetoprotein, CA125, CA199, CA724, CYFRA 21-1, neuron-specific enolase, β-subunit of hCG gonadotropin, fetoprotein), thyroid function tests, antithyroid globulin serum level, and antithyroid peroxidase. No abnormal result was observed.

Laboratory test results showed reduced serum calcium concentration (1.01 mmol/L; 2.0–2.6 mmol/L) and raised serum phosphate concentration (1.98 mmol/L; 0.6–1.6 mmol/L), further test of serum PTH concentration revealed a very high level (170 pg/mL; 15–65 pg/mL).

Brain magnetic resonance imaging (MRI) of T1-weighted and T2-weighted images revealed increased signal intensity in bilateral caudate nucleus, shell, and thalamus, while fluid-attenuated inversion recovery-weighted image indicated high-intensity signal in the peripheral region and low-intensity signal in the internal region (Fig. 1). Thus, metabolic encephalopathy and toxic encephalopathy were considered first. Furthermore, brain CT was reconsidered carefully, and interestingly, that showed bilateral calcification in the BG (Fig. 2A).

In view of PHP, further examinations were conducted for the son of the patient, a 22-year-old man (height: 165 cm, weight: 63 kg, BMI: 23.1), who had ever complained of epilepsy 19 years ago. No parkinsonism clinical manifestations were found. Laboratory tests show that reduced serum calcium concentration (1.86 mmol/L; 2.0–2.6 mmol/L), raised serum phosphate concentration (1.62 mmol/L; 0.6–1.6 mmol/L), and a high level of PTH (340.5 pg/mL; 15–65 pg/mL). In addition, decreased 24 h calciuria (0.40 mmol/L; 2.50–7.50 mmol/L) and increased 24 h urine phosphorus (8.94 mmol/L; 3.50–8.40 mmol/L) were found. Brain CT scan also revealed calcification of BG (Fig. 2B). Though bone mineral density was in normal ranges, the X-ray of the left hand

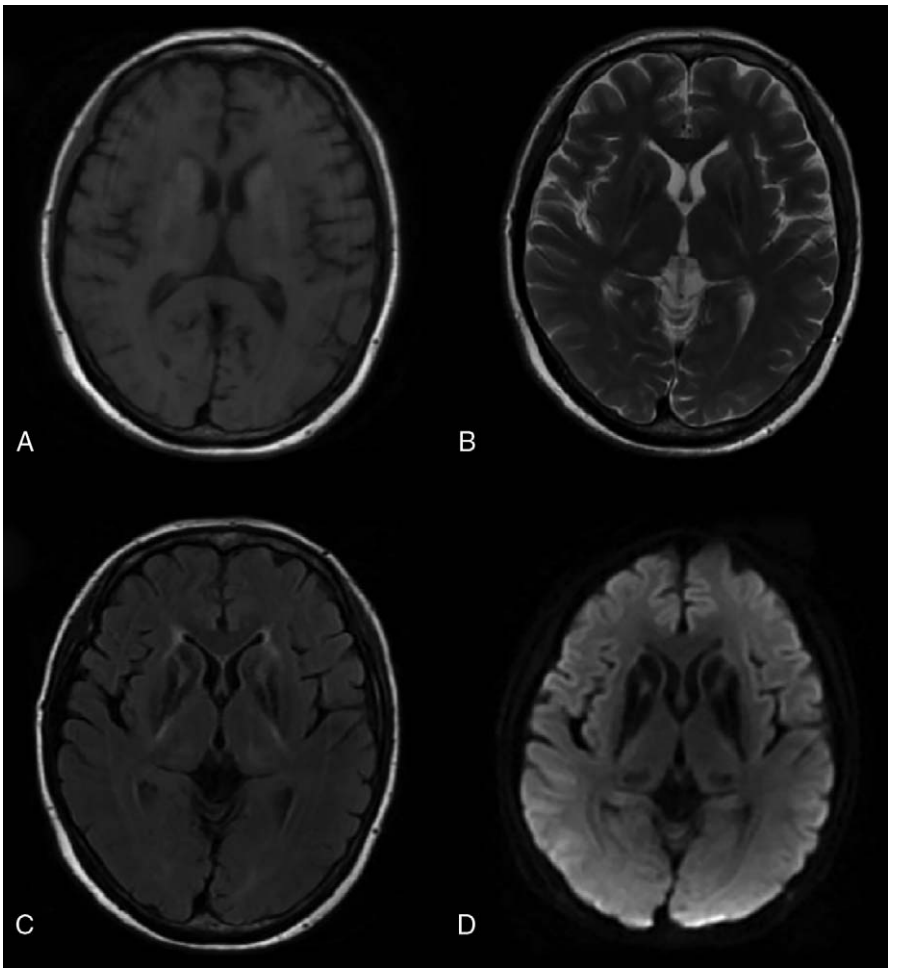

Figure 1. Axial brain magnetic resonance imaging of the patient with abnormal lesions in bilateral caudate nucleus, shell, and thalamus. (A, B) T1-weighted and T2-weighted images revealed increased signal intensity in bilateral caudate nucleus, shell, and thalamus. (C) Fluid-attenuated inversion recovery-weighted image shows high-intensity signal in the peripheral region and low-intensity signal in the internal region of the bilateral caudate nucleus, shell, and thalamus. (D) Diffusion weighted imaging shows low-intensity signal of the bilateral caudate nucleus, shell, and thalamus.

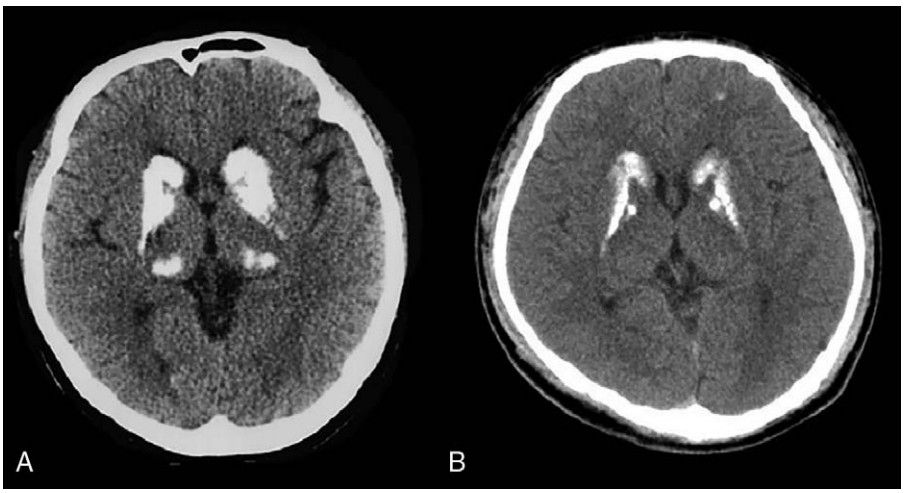

Figure 2. Head CT of the patient and her son showing calcification of basal ganglia. (A) Head CT of the patient shows calcification of bilateral calcification of basal ganglia and thalamus. (B) Brain CT scan of the son reveals calcification of bilateral calcification of basal ganglia. CT = computed tomography.

showed abnormalities of scaphoid, trapezium, and trapezoid (Fig. 3). Gene detection identified loss of function mutation in GNAS gene NM_000516.5:c.343C>T (NP_000507.1:p.Pro115Ser) in both the patient and her son.

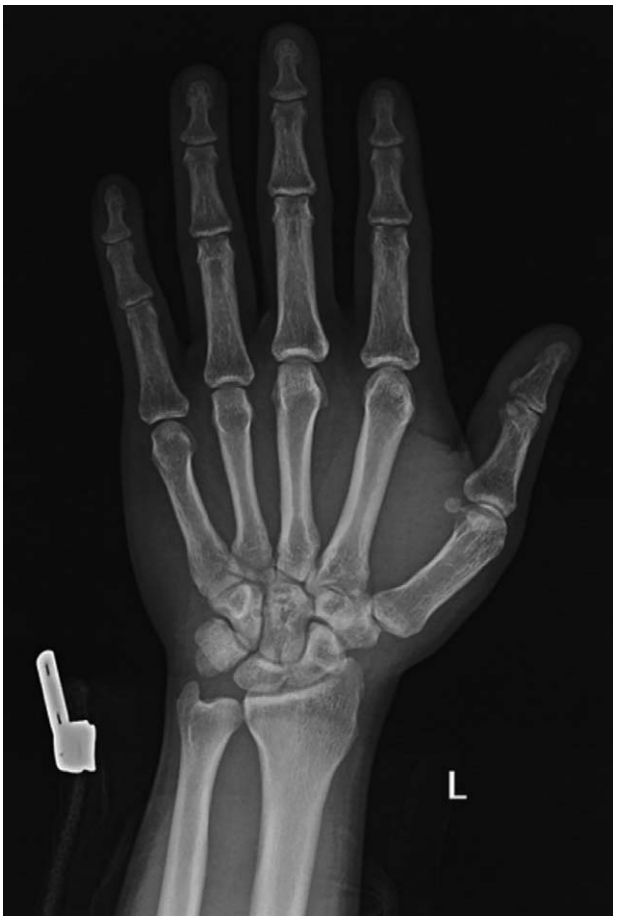

Figure 3. X-ray of the son's left hand. The figures of scaphoid, trapezium, and trapezoid are abnormal, but no apparently III, IV, and V metacarpals and distal phalanx shortening can be noticed.

By far, the diagnosis of PHP was put forward. Therefore, the patient underwent the treatment of calcium gluconate, calcium carbonate D3, and calcitriol. No dopamine or dopamine receptor agonists were conducted. Five days after the therapy, she improved markedly in dyskinesia. And comparing to that of 5 days ago, the serum electrolyte showed increased serum calcium concentrations (1.66 mmol/L; 2.0–2.6 mmol/L), though still under the normal level, and normal serum phosphate concentrations (1.51 mmol/L; 0.6–1.6 mmol/L).

Informed consents for the publication of this case report were obtained from the patients themselves. Ethical approval was not required for this case report as it did reveal the patient's name and privacy.

3. Discussion

The patient, a middle-aged woman, presented with bradykinesia and muscular rigidity, indicating an acute parkinsonism. Both sides of extremities were involved in 6 months, thus a secondary parkinsonism has to be considered. The MRI of brain was performed and indicated symmetrical abnormal lesions in bilateral caudate nucleus, shell, and thalamus, suggesting metabolic or toxic encephalopathy. Considering of the CO poisoning history 4 years ago, we firstly thought that might the main cause. Besides, since systemic autoimmune antibodies and serum tumor markers were negative, parkinsonism secondary to autoimmune and paraneoplastic causes were diminished. However, hypocalcemia and hyperphosphatemia were subsequently noticed and further test revealed a high level of serum PTH concentration and a normal level of thyroid stimulating hormone (TSH). As a result, calcification of BG was further suspected. Then the CT scan of brain in other hospital was obtained and validate our speculation. Combination of the short stature of the patient, PHP was highly suspected. CT scan of brain in her son, who had ever complained of epilepsy history, also revealed calcification of BG. Furthermore, gene test of GNAS was detected and loss of function mutation was found. Based upon above, the diagnosis of PHP was established. And after the supplement of serum calcium by calcium gluconate and calcium carbonate D3, the patient presented marked clinical improvement of parkinsonism.

PHP is classified as different subtypes, including Ia (Albright hereditary osteodystrophy), Ib, Ic, and PHP.[5] PHP Ia was the most common subtype and accompanied by a blunted cAMP and phosphaturic response to exogenous PTH due to the end-organ resistance. Besides, the patient of PHP Ia usually had severe albrights hereditary osteodystrophy (AHO), presenting with heterogeneous clinical manifestations, such as short stature, brachydactyly, and soft tissue calcification.[3] In this case, AHO was investigated in our patient, who had significant short stature and brachydactyly. Genetically, PHP Ia was usually caused by genetic alterations within or upstream of the imprinted GNAS gene, which encodes the G-stimulatory protein alpha (Gs-α).[6] Loss of function mutation in GNAS gene (p.P115S) was detected in both the patient and her son, consistent with PHP Ia. After the correction of hypocalcemia and hyperphosphatemia, the parkinsonism improved markedly.

Brain calcification was usually investigated in PHP due to the hyperphosphatemia. However, in most conditions, seizure and epilepsy are the common clinical manifestations resulting from the calcification of subcortical region and BG, other than parkinsonism. Few cases were ever reported in this condition. Bradley reported a case in PHP presenting as parkinsonism, without BG calcification,[7] suggesting that the mechanism might also have other pathophysiology, such as impaired neurotransmission.

In addition, the calcification of BG presenting with parkinsonism can also be caused by various of other diseases, such as familial idiopathic BG calcification (Fahr disease), neoplastic, vascular, infectious, and congenital causes, as well as other endocrine/metabolic diseases, including diabetes mellitus, hypoparathyroidism, and hyperparathyroidism.[8] Apart from the bilateral BG, the diagnosis criteria of Fahr disease usually contain family history, neuropsychiatric symptoms, and no underlying systemic etiology.[9] Further evaluations should be conducted to distinguish PHP from the diseases mentioned above, including serum levels of calcium, phosphate, PTH, TSH, alkaline phosphatase, and calcitonin; CSF examinations; metabolic, inflammatory, and infectious conditions; and heavy mental concentrations.[10]

Overall, PHP is a rare etiology for parkinsonism with calcification of BG. However, markedly improvement could be investigated after the correction of hypocalcemia and hyperphosphatemia. Thus, it is of great meaningful to differentiate PHP from other parkinsonism, and a family history of seizures may be an indicator for consideration, in addition, several laboratory examinations and brain CT scan can be conducted if necessary.

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