Extrapyramidal Symptoms and Advanced Calcification of the Basal Ganglia in a Patient with Autosomal Dominant Hypocalcemia

Akira Kurozumi¹, Yosuke Okada¹, Tadashi Arao¹, Itsuro Endou², Toshio Matsumoto² and Yoshiya Tanaka¹

Abstract

Most cases of hypoparathyroidism with decreased parathyroid hormone (PTH) secretion, excluding secondary hypoparathyroidism, are considered to be idiopathic. We herein report a relatively rare case of hypoparathyroidism with extrapyramidal symptoms, including brachybasia and a frozen gait, caused by advanced basal ganglia calcification in a 64-year-old man with hypoparathyroidism. A DNA (deoxyribonucleic acid) analysis of blood samples obtained from the patient and his eldest daughter revealed autosomal dominant hypocalcemia (ADH) with mutations in the calcium-sensing receptor (CaSR) gene. In cases of chronic hypoparathyroidism, calcification of the basal ganglia is observed if the patient is not treated for a long period. However, extrapyramidal symptoms as a complication of hypoparathyroidism are relatively rare.

Key words: extrapyramidal symptoms, advanced calcification, basal ganglia, autosomal dominant hypocalcemia

Introduction

Hypoparathyroidism is biochemically characterized by hypocalcemia, hyperphosphatemia and low levels of parathyroid hormone (PTH) and can be classified into three broad categories: hypoparathyroidism associated with decreased PTH secretion; pseudohypoparathyroidism with refractoriness of the target cells to PTH; and hypoparathyroidism associated with hypomagnesemia, which can impair both the secretion and actions of PTH (1). With the exception of secondary hypoparathyroidism associated with certain procedures (e.g., neck surgery and irradiation) and hypoparathyroidism of autoimmune mechanisms (e.g., antibodies against calcium-sensing receptors (CaSRs) and autoimmune polyendocrinopathy), most cases of hypoparathyroidism with decreased PTH secretion are of unknown origin and generally classified as idiopathic hypoparathyroidism. Among these cases, familial hypoparathyroidism can be distinguished from idiopathic hypoparathyroidism, owing to recent discoveries of gene abnormalities. Since the mutational analysis of the CaSR gene has become available, many individuals with hypocalcemia have had their diagnoses revised. Lienhardt et al. (2) reported a 42% prevalence of activated CaSR mutations in unrelated individuals with isolated hypoparathyroidism, and Gunn and Gaffney (3) estimated the population prevalence of this condition to be one in 70,000.

The abnormally increased sensitivity of the parathyroid to calcium, referred to as autosomal dominant hypocalcemia (ADH), is caused by activated mutations of the CaSR gene (4). Even when the extracellular calcium concentration decreases, CaSR with activated mutations inappropriately suppresses the secretion of PTH, which in turn increases the serum calcium level and results in hypercalcuria due to a change in the threshold of tubular calcium reabsorption (4). In addition, 1,25-dihydroxyvitamin D (1,25(OH)2D), prescribed for hypoparathyroidism, has been shown to upregulate the renal CaSR expression, and an increased expression
with hypoparathyroidism are relatively rare. However, extrapyramidal symptoms associated with hypoparathyroidism and admitted to our department for further examination and treatment.

On admission, typical signs of hypocalcemia were noted (e.g., Trousseau’s sign and Chvostek’s sign) in addition to cerebellar symptoms (such as scanning speech, a wide-based gait, mild limb-kinetic apraxia, hypotonia and disturbance on finger-to-nose coordination tests without intention tremors, dysdiadochokinesia or nystagmus), extrapyramidal symptoms (such as brachybasia and a frozen gait without resting tremors, cogwheel rigidity, bradykinesia, lepileptic stare or retropulsion) and cataracts. Despite the administration of alfacalcidol treatment, blood tests showed persistent hypocalcemia (7.6 mg/dL) with a high-sensitive PTH level of <100 pg/mL in the serum, although the serum phosphorus and magnesium levels were within the normal ranges (Table). A brain CT scan performed at that point showed significant and extensive calcification in the basal ganglia, cerebellum and cerebral white matter (Figure A). Mild QT prolongation was observed on an electrocardiogram (ECG) (0.47 s, normal range: 0.36-0.44 s), and dental radiography showed an impacted maxillary left third molar and an unerupted tooth. The physical abnormalities observed on admission, such as a wide-based gait and brachybasia, were considered to be extrapyramidal symptoms caused by the calcification in the basal ganglia and cerebellum.

Despite the presence of hypocalcemia, the serum PTH level was low and the renal function was normal. Therefore, the patient was diagnosed with hyposecretory hypoparathyroidism. The Ellsworth-Howard test was conducted, which showed normal urinary phosphorus and cAMP (cyclic adenosine monophosphate) responses; hence, a diagnosis of pseudohypoparathyroidism (PHP) was excluded (Table). Although the dose of alfacalcidol was increased from 3 μg/day to 5 μg/day, the serum calcium level remained unchanged. Accordingly, alfacalcidol was switched to calcitriol at an initial dose of 1 μg/day, which was gradually increased to 2 μg/day. Two months after discharge, a slight improvement in the serum calcium level (7.8 mg/dL) was observed. The urinary calcium/creatinine ratio was also maintained in the normal range (<0.3) during this period, and no deteriora-

### Table 1. Laboratory Data and Endocrinological Examination on Admission

<table>
<thead>
<tr>
<th>&lt;Urine&gt;</th>
<th>&lt;Biochemistry&gt;</th>
<th>&lt;Endocrinology&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 7.5</td>
<td>TP 8.0 g/dL</td>
<td>HS-PTH &lt;100 pg/mL</td>
</tr>
<tr>
<td>glu (+)</td>
<td>Alb 4.7 g/dL</td>
<td>intact-PTH 6 pg/mL</td>
</tr>
<tr>
<td>prot (+)</td>
<td>AST 28 IU/L</td>
<td>25OHD 18.0 ng/mL</td>
</tr>
<tr>
<td>O.B. (+)</td>
<td>ALT 28 IU/L</td>
<td>u-Ca/Cr 0.20</td>
</tr>
<tr>
<td>CCR 78.3 mL/min</td>
<td>γ-GTP 82 IU/L</td>
<td>u-Ca 72.0 mg/day</td>
</tr>
<tr>
<td>&lt;CBC&gt;</td>
<td>TG 161 mg/dL</td>
<td>%TRP 82.8 %</td>
</tr>
<tr>
<td>WBC 6,500 /mm³</td>
<td>HDL-C 54 mg/dL</td>
<td>cAMP 1.7 μmol/L/day</td>
</tr>
<tr>
<td>RBC 4.35×10¹² /mm³</td>
<td>BUN 15 mg/dL</td>
<td>TmP/GFR 3.5 mg/dL</td>
</tr>
<tr>
<td>Hb 13.7 g/dL</td>
<td>Cre 0.91 mg/dL</td>
<td>BAP 23.7 μg/L</td>
</tr>
<tr>
<td>Hct 39.0 %</td>
<td>Na 141 mEq/mL</td>
<td>U-NTx 87.4 nmol BCE/mmolCre</td>
</tr>
<tr>
<td>Plt 34.1×10⁴ /mm³</td>
<td>K 3.7 mEq/mL</td>
<td>&lt;Ellsworth-Howard test&gt;</td>
</tr>
<tr>
<td>&lt;Serology&gt;</td>
<td>Cl 105 mEq/mL</td>
<td>U-P excretion increasing</td>
</tr>
<tr>
<td>CRP 0.22 mg/dL</td>
<td>Ca 7.6 mg/dL</td>
<td>=36.8 &gt; 35 mg/2h</td>
</tr>
<tr>
<td>ESR 8 mm/h</td>
<td>P 4.1 mg/dL</td>
<td>U-c AMP reaction</td>
</tr>
<tr>
<td></td>
<td>Mg 2.1 mg/dL</td>
<td>=1765 &gt; 1 μmol/L/hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>U-c AMP ratio</td>
</tr>
<tr>
<td></td>
<td></td>
<td>=66 &gt; 10</td>
</tr>
</tbody>
</table>

tion of the renal function was observed.

Since the patient’s eldest and third daughters were receiving treatment for hypocalcemia, a diagnosis of familial hypoparathyroidism was suspected. Therefore, we performed a DNA (deoxyribonucleic acid) analysis using blood samples obtained from the patient and his eldest daughter after obtaining their informed consent. The results confirmed the diagnosis of ADH, with heterozygous activating mutations in exon 2 at codon 129 in the CaSR gene (Figure B). The eldest daughter with the mutation did not exhibit any extrapyramidal signs; however, a brain CT scan showed ectopic calcification in the basal ganglia.

Discussion

The CaSR gene is located on chromosome 3q21.1 (8), and activating mutations of the CaSR gene result in a decrease in the set point of PTH secretion, which consequently leads to chronic hypocalcemia and low serum PTH levels, even under a hypocalcemic state. Although autosomal dominant inheritance is typically observed in patients with hypoparathyroidism (4), sporadic cases resulting from de novo mutations have also been reported (9). Although the precise number of mutations in the CaSR gene has yet to be established, at least 95 different activating mutations of CaSR have been identified to date (10).

The treatment strategy for hypoparathyroidism with a CaSR gene mutation differs slightly from the treatments used in patients with other types of hypoparathyroidism. The serum calcium level in the former case must be maintained at a level lower than the low-normal level due to the risk of renal dysfunction. Therefore, it is necessary to differentiate between the two types of hypoparathyroidism. ADH can be subclinical in individuals diagnosed with idiopathic hypoparathyroidism. Therefore, a diagnosis of ADH is suspected in patients with familial and relative hypercalciuria, and DNA analyses are subsequently performed.

In the present case, a DNA analysis identified a heterozygous mutation located at codon 129: TGC to TCC (386G>C). Arrows: positions of the starting nucleotides that show heterozygosity in each sequence.

Intracerebral calcification is recognized to be a feature of hypoparathyroidism, being most often described in the basal ganglia. Basal ganglia calcification was reported to have a prevalence of 0.36% in 12,000 unselected consecutive patients referred for brain CT scans, among which two-thirds of the cases occurred after 60 years of age (12). Illum and Dupont (13) found basal ganglia calcification in as many as
11 of 16 patients (69%) with idiopathic hypoparathyroidism and in all eight patients with pseudohypoparathyroidism examined using brain CT scans.

A recent study of 25 ADH patients with CaSR gene mutations reported no extrapyramidal symptoms in any of the patients, although dysesthesia and muscle cramps (12 patients, 50%), renal calcification (three patients, 12%) and calcification of the basal ganglia (nine patients, 36%) were observed (14). Smits et al. (15) reported dyssynergia and extrapyramidal symptoms, including an ataxic gait, in a family of three ADH patients (father, son and daughter). Extensive symmetrical calcification in the basal ganglia and dentate nucleus of the cerebellum was evident on brain CT scans of the father and son. Other cases of hypoparathyroidism associated with cerebral calcification and extrapyramidal symptoms have been previously described (16-18); however, these symptoms are relatively rare.

In a report describing 17 hypoparathyroidism patients with extrapyramidal symptoms, McKinney (19) demonstrated that the most common extrapyramidal symptom was chorea, observed in six cases. The proposed causes of extrapyramidal symptoms associated with hypoparathyroidism are tissue ischemia, resulting from hyalinization and erosion caused by calcium deposits in the small vascular walls and dysfunction of the basal ganglia induced by enhanced excitability of the nerve fibers and synapses associated with hypocalcemia (19). Because extrapyramidal symptoms are also noted in cases of idiopathic hypoparathyroidism without hypocalcemia, some scientists believe that the extrapyramidal symptoms observed in patients with hypoparathyroidism are caused by calcification of the basal ganglia. Muenter et al. (20) reported that calcification begins with the deposition of acid mucopolysaccharide in the pericapillary space, which, in association with increased calcium deposition, is detected on radiographic scans. Further calcification results in neuronal loss and consequently leads to the appearance of extrapyramidal symptoms.

Although the mechanisms underlying cerebral calcification remain poorly understood, evidence suggests that the duration of hyperphosphatemia and hypocalcemia, rather than the level of parathyroid hormone itself, is correlated with the development of cerebral calcification (21, 22). Similar to that observed in the cases reported in the above mentioned studies, in the present case, the eldest and third daughters of our patient experienced convulsive seizures associated with electrolyte imbalances due to hypoparathyroidism at 7 and 12 months of age, respectively. The proband had also experienced convulsions during infancy; however, the details were unknown. Therefore, long-term electrolyte imbalances related to hypoparathyroidism may result in significant cerebral calcification. In conclusion, we herein reported a relatively rare case of ADH with extensive calcification in the cerebellum and basal ganglia suspected of involvement in extrapyramidal symptoms.

**Author's disclosure of potential Conflicts of Interest (COI).**

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