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Case Report

Potential utility of cinacalcet as a treatment for *CDC73*-related primary hyperparathyroidism: a case report

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Abstract. We report a Japanese pedigree with familial primary hyperparathyroidism due to a *CDC73* mutation. To our knowledge, this is the first report of cinacalcet as a treatment for *CDC73*-related primary hyperparathyroidism. The proband had severe psychomotor retardation and received laryngotracheal separation surgery. At 19 yr of age, he developed acute pancreatitis. Hypercalcemia (12.2–13.8 mg/dL), elevated levels of intact PTH (86–160 pg/mL), and a tumor detected upon neck ultrasonography led to the diagnosis of primary hyperparathyroidism. Family history and biochemical examinations revealed that three family members (the proband's mother, elder brother, and maternal grandfather) had primary hyperparathyroidism. We identified a novel heterozygous mutation, c.240delT, p.Glu81Lysfs*28, in the *CDC73* gene in three affected family members, excluding the proband's elder brother who refused genetic testing. Parathyroidectomy for the proband was considered as high-risk, because the tumor was located close to the tracheostomy orifice. After receiving approval from the institutional review board and obtaining the consent, we initiated cinacalcet treatment. At 22 yr of age, treatment with 100 mg of cinacalcet maintained serum calcium levels below 11.0 mg/dL with no apparent side effects. Our report presents the potential efficacy of cinacalcet as a treatment for *CDC73*-related primary hyperparathyroidism, in particularly inoperative cases.

Key words: *CDC73*, mutation, familial primary hyperparathyroidism, cinacalcet

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Introduction

CDC73 germline mutations, inherited in an autosomal dominant manner, can cause hyperparathyroidism-jaw tumor syndrome, parathyroid carcinoma, and familial isolated hyperparathyroidism (1–3). A clear genotype-phenotype correlation is not apparent (4). Some authors have suggested that pathogenic

Table 1 Clinical manifestations of the family members with primary hyperparathyroidism

Patient/ gender	Findings at diagnosis of primary hyperparathyroidism						Treatment	Pathology	Other diseases
	Age at diagnosis	Symptom leading to diagnosis	Serum calcium (mg/dL)	Serum phosphate (mg/dL)	Serum intact PTH (pg/mL)	Neck ultraso-nography			
I-3/ Male	55 yr	Pain in the right knee and the left hip joint	12.2	1.3	High[a]	Single tumor	Partial parathy-roidectomy	Parathyroid adenoma	Gastric ulcer, cholelithiasis
II-2/ Female	50 yr	None	11.7	2.4	239	Single tumor	Two-stage total parathyroidecto-my, with forearm autograft, vitamin D compound	Parathyroid adenoma	Non-functioning left adrenal tumor, type 2 diabetes mellitus, obesity, hypertension
III-1/ Male	22 yr	Appendicitis[b]	>12[c]	NA	NA	Two tumors	Total parathyroid-ectomy with neck autograft, vitamin D compound	Parathyroid adenomas	None
III-2/ Male	19 yr	Acute pancreatitis[d]	12.2–13.8	2.2–2.9	86–160	Single tumor[e]	Cinacalcet	ND	Laryngomalacia, hypoxic-ischemic encephalopathy, psychomotor de-velopmental delay, epilepsy, primary hypothyroidism

NA, not available; ND, not determined. [a] Serum or plasma C-terminal PTH was measured, but actual data is not available; [b] We speculated that appendicitis is not related to hypercalcemia or *CDC73* mutations; [c] Actual data is not available; [d] We could not exclude the possibility that acute pancreatitis was associated with valproate treatment; [e] During the observational period, multiple tumors appeared.

variants causing gross disruption of the protein, such as frameshift mutations, are more likely to be associated with hyperparathyroidism-jaw tumor syndrome, which carries a relatively increased risk for parathyroid carcinoma (5). Parathyroidectomy is the preferred treatment for patients with primary hyperparathyroidism caused by *CDC73* germline mutations. Unfortunately, for patients who are unable to undergo parathyroidectomy, no alternative treatment has been established until now (4).

Cinacalcet is an oral calcimimetic drug that suppresses PTH levels by activating the calcium-sensing receptors on parathyroid cells (6). Its utility has been reported in secondary hyperparathyroidism associated with chronic kidney disease (7). Recently, cinacalcet has also been used to treat hereditary diseases associated with hypercalcemia and elevated serum PTH, such as multiple endocrine neoplasia (MEN) type 1, and familial hypocalciuric hypercalcemia (8, 9). However, there are no reports on the efficacy of cinacalcet in *CDC73*-related primary hyperparathyroidism.

Here, we report a Japanese pedigree with familial primary hyperparathyroidism due to a novel *CDC73* mutation. The proband, presenting hypercalcemia, was treated with cinacalcet due to high-risk parathyroidectomy. To our knowledge, this is the first report of cinacalcet as a treatment for *CDC73*-related primary hyperparathyroidism.

Case Report

The family pedigree is illustrated in Fig. 1A. Clinical information of the family members with primary hyperparathyroidism is summarized in Table 1. We describe the clinical characteristics of the four affected family members as follows:

III-2

The proband is a 22-year-old male who is the second child of non-consanguineous Japanese parents. He was delivered vaginally at 40 wk of gestation, with no documented asphyxia, and birth weight, length, and head circumference of 2,820 g (−0.4 SD), 49.0 cm (+0.0 SD), and 30.5 cm (−2.0 SD), respectively. At 1 mo of age, his parents noticed stridor, and at 6 mo of age, he was referred to our hospital because he was not holding his head up. Detailed examination led to the diagnosis of hypoxic-ischemic encephalopathy resulting from laryngomalacia and recurrent pneumonia. Moreover, he had not begun to speak or walk, and was dependent on enteral tube feeding. At 11 yr of age, he was diagnosed with epilepsy and valproate treatment was initiated. Laryngotracheal separation was also performed because of recurrent aspiration pneumonia.

At 19 yr of age, he developed acute pancreatitis. On admission, hypercalcemia (12.7 mg/dL, reference 8.9–10.1) and hypophosphatemia (2.3 mg/dL, reference 2.5–4.5) were noted. Acute pancreatitis was resolved with aggressive intravenous hydration, protease inhibitors, and antibiotics. We switched valproate to phenobarbital, because we could not exclude the possibility that valproate was associated with the acute pancreatitis. Hypercalcemia persisted (12.2–13.8 mg/dL), and serum intact PTH was elevated (86–160 pg/mL, reference 10–65). The serum concentrations of whole PTH and intact PTH were 31.9 pg/mL (reference 8.3–38.7) and 86 pg/mL, respectively. Neck ultrasonography revealed a single tumor, 11 × 11 × 6 mm, under the lower pole of the right thyroid lobe (Fig. 2). Therefore, he was diagnosed with primary hyperparathyroidism. Abdominal computed tomography revealed a 5-mm stone in the right kidney. No metastasis was found upon whole-body screening. Radiographic examination revealed neither jaw tumors nor apparent osteitis fibrosa.

Parathyroidectomy for the proband was considered high-risk because the tumor was close to the tracheostomy orifice. After receiving approval from the institutional review board and obtaining consent from the proband's mother, cinacalcet treatment was initiated at a dosage

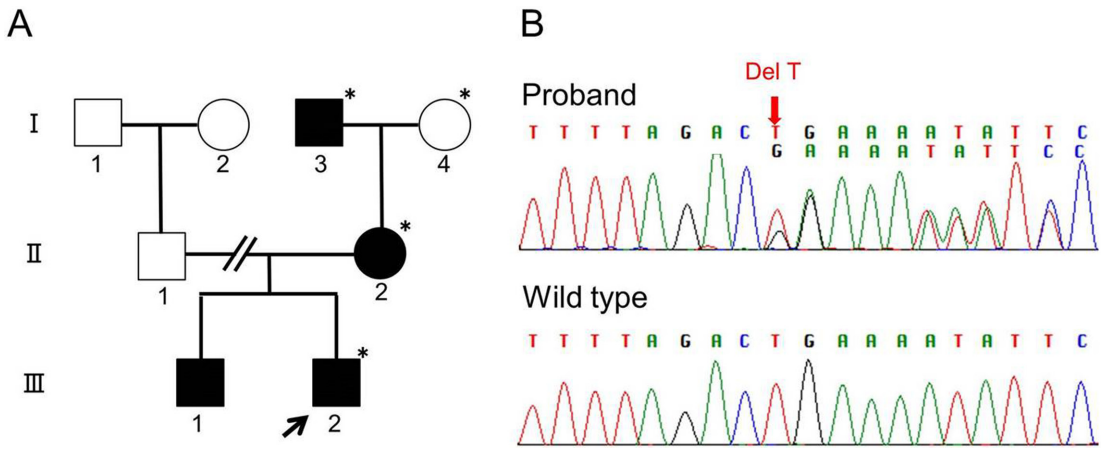

Fig. 1. A: Pedigree of the family. Family members who underwent genetic testing are marked with an asterisk. B: Partial sequence of exon 3 of the *CDC73* gene. The upper panel shows that the proband has a heterozygous mutation, c.240delT, denoted by the arrow, while the lower panel depicts the wild type sequence.

of 25 mg (Fig. 3) and subsequently increased to 75 mg, which decreased the serum calcium level (Fig. 3). Serum phosphate increased with administration of 100 mg of cinacalcet (Fig. 3). At 22 yr of age, upon treatment with 100 mg of cinacalcet, his serum calcium levels dropped below 11.0 mg/dL, although serum intact PTH remained high (Fig. 3). Serum tartrate-resistant acid phosphatase 5b was within normal limits (388–570 mU/dL, reference 170–590) at 22 yr of age; however, it was not measured before initiation of cinacalcet treatment. Serum creatinine did not change significantly during the observation period (0.45–0.65 mg/dL before cinacalcet initiation vs. 0.46–0.63 mg/dL during administration of 100 mg of cinacalcet, reference 0.61–1.04). Gross hematuria, possibly associated with the renal stone and calcification, occurred occasionally since 20 yr of age. Renal ultrasonography revealed that nephrocalcinosis did not worsen during the observation period. Urinary calcium excretion remained marginally elevated; the urine calcium/creatinine ratios were 0.08–0.32 before initiation of cinacalcet (reference < 0.21) and 0.07–0.34 after initiation, except for one reading of 0.53. He also had intermittent constipation, a possible side effect of cinacalcet.

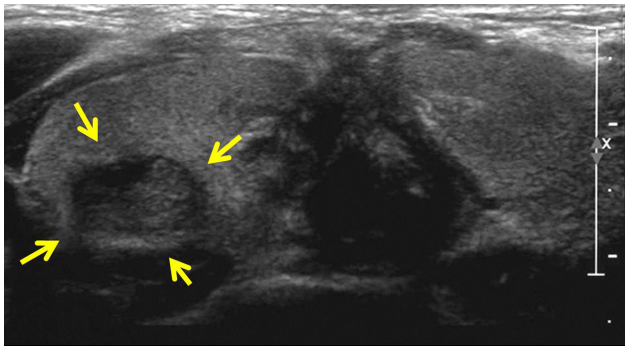

Fig. 2. Ultrasonography of the neck in the proband (III-2). A single tumor, 11 × 11 × 6 mm, was found under the right lobe of the thyroid, indicated by arrows.

Neck ultrasonography revealed that the tumor had increased in size (13 × 12 × 11 mm). Two additional tumors were also detected (both 5 mm in diameter), one at the lower pole of the right thyroid lobe, and another at the upper pole of the left thyroid lobe.

I-3

The proband's maternal grandfather, 84 yr old, underwent surgery for a gastric ulcer and cholelithiasis at 52 yr of age. At 55 yr of

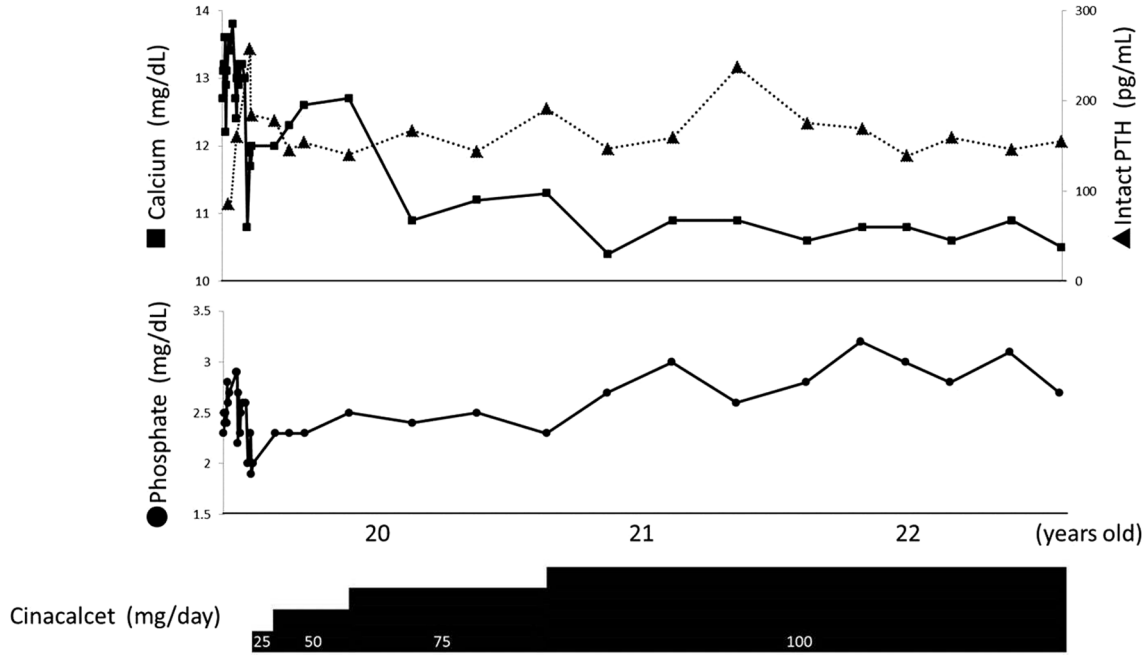

Fig. 3. Clinical course of the proband (III-2). Hypercalcemia did not resolve with treatment of 50 mg of cinacalcet. Serum calcium levels decreased with treatment of 75 mg of cinacalcet. Serum phosphate levels increased with treatment of 100 mg of cinacalcet. Serum concentration of intact PTH remained high.

age, he developed pain in the right knee and the left hip joint. Laboratory examinations revealed hypercalcemia (12.2 mg/dL), hypophosphatemia (1.3 mg/dL) and elevated PTH (actual data not available). A single tumor, (21 × 18 mm) was detected near the lower pole of the left thyroid lobe. He was diagnosed with primary hyperparathyroidism. A partial parathyroidectomy was performed, and hypercalcemia resolved. Histopathological examination revealed that the tumor was a parathyroid adenoma. Radiographic examination revealed remarkable osteomalacia. No recurrence has been observed. He is not on medication to maintain normocalcemia.

II-2

The proband's mother, 53 yr old, was suspected to have the disease, since the proband (III-2) and his maternal grandfather (I-3) were both diagnosed with primary hyperparathyroidism. Laboratory examinations revealed hypercalcemia (11.7 mg/dL) with elevated intact PTH (239 pg/mL) and neck ultrasonography revealed a tumor at the upper pole of the left thyroid lobe. At 50 yr of age, she underwent a partial parathyroidectomy, but hypercalcemia (12.7 mg/dL) and elevated PTH (163 pg/mL) persisted. At 51 yr of age, the remaining parathyroid glands were removed, and fragments of apparently normal parathyroid gland were placed into the forearm muscle. Histopathological examination revealed that the tumor was a parathyroid adenoma. She depends on vitamin D compound to maintain normocalcemia.

She had a 5-mm renal stone, which was removed endoscopically. She was also obese (body mass index, 26.0), and had hypertension (170/100 mm Hg), although her blood pressure had been brought under control with cilnidipine treatment. Abdominal computed tomography and biochemical examination revealed a non-functioning 5-mm left adrenal tumor. At 53 yr

of age, she developed diabetic ketoacidosis due to high intake of sugar-rich beverages, and was diagnosed with type 2 diabetes mellitus. She requires insulin therapy and oral anti-diabetic drugs to maintain normoglycemia.

III-1

The proband's elder brother, 25 yr old, was accidentally found to have hypercalcemia (>12.0 mg/dL, data not available) when he visited a different hospital for appendicitis, soon after the proband (III-2) and their mother (II-2) were diagnosed with primary hyperparathyroidism. Serum PTH was elevated (data not available) and neck ultrasonography showed two tumors (data not shown), leading to a diagnosis of primary hyperparathyroidism. At 22 yr of age, he underwent total parathyroidectomy with neck autograft. Histopathological examination revealed that the tumors were parathyroid adenomas. No complication was apparent. He needs vitamin D compound to maintain normocalcemia. He is considered to have normal intelligence, since he graduated from a private university.

Mutation analysis of *MEN1*, *RET*, *CDKN1B*, and *CDC73* genes

After receiving approval from the institutional review board and obtaining the consent, we extracted genomic DNA from peripheral blood samples or nails of four family members (I-3, I-4, II-2 and III-2), using standard protocols. We could not obtain informed consent from the proband's elder brother (III-1). Genomic DNA samples were PCR-amplified for the coding all exons of *MEN1*, and *CDKN1B*, exons 1–7 of *CDC73*, and exons 10–16, except exon 12, of *RET* and their splice sites. The PCR products were subjected to direct sequencing from both directions on the autosequencer. The proband (III-2) was found to carry a novel heterozygous mutation, c.240delT, p.Glu81Lysfs*28, in the *CDC73* gene (Fig. 1B). The other affected family members (I-3 and II-2) also carried the same mutation, while the unaffected family member (I-4) did not.

Discussion

We described a Japanese pedigree of familial primary hyperparathyroidism caused by a novel heterozygous mutation, c.240delT, p.Glu81Lysfs*28, in the *CDC73* gene. In the proband, for whom parathyroidectomy was considered high-risk, treatment with cinacalcet effectively controlled hypercalcemia, with no apparent side effects.

Interestingly, during the course of treatment with cinacalcet, the proband's serum calcium levels decreased and phosphate levels increased, while PTH remained high. Although the precise mechanism is unknown, such discrepancies have also been observed in other diseases involving hypercalcemia and elevated serum PTH (10, 11). Persistent elevated PTH can cause several complications, including osteodystrophy, which is often seen in chronic kidney diseases (7). Thus, in spite of the revival of calcium levels, it is crucial to assess the possible complications associated with the accompanying elevated PTH levels.

CDC73 mutations cause parathyroid adenoma and parathyroid carcinoma, while MEN type 1 leads to parathyroid hyperplasia (4, 12). It is important to note that the nature of the tumors detected in the proband remains to be determined. Since the proband is still young and no metastasis was detected, we hypothesize that the tumors are adenomas. In the future, the tumors may become larger or malignant, resulting in the secretion of large amounts of PTH. A previous study reported that cinacalcet effectively reduced hypercalcemia in approximately two thirds of patients with inoperable parathyroid carcinoma (10). Because serum calcium levels in the proband have been kept barely below 11.0 mg/dL with administration of 100 mg of cinacalcet, we are concerned that cinacalcet may not control hypercalcemia in the future. Thus, the efficacy of cinacalcet for

primary hyperparathyroidism associated with *CDC73* mutations may need to be investigated according to both tumor size and malignancy.

Prior to detection of the *CDC73* germline mutations in the affected family members, total parathyroidectomy with autograft was performed for patients II-2 and III-1. Hyperplasia of autografts in patients with MEN type 1 has been reported to cause hyperparathyroidism (13), implying that hyperparathyroidism and/or parathyroid carcinoma may occur in autografts harboring *CDC73* mutations in our patients. While subtotal parathyroidectomy or total parathyroidectomy with autograft is performed for MEN1-related primary hyperparathyroidism to avoid permanent hypoparathyroidism, the optimal operative approach for patients with *CDC73* germline mutations remains controversial (14, 15). From the perspective of malignancy risk, particularly when germline frameshift or nonsense *CDC73* mutations are detected, total parathyroidectomy without autograft may be beneficial. Thus, it is essential to recognize the importance of genetic analysis in patients with familial primary hyperparathyroidism.

We could not determine which clinical manifestations of the affected family members (except primary hyperparathyroidism and renal stones) were associated with the *CDC73* germline mutations. The proband suffered from laryngomalacia, severe psychomotor developmental delay, and epilepsy, while his elder brother experienced no such complication. In addition, the proband's mother presented with non-functioning adrenal tumor and type 2 diabetes mellitus. To our knowledge, these manifestations are either rare or have not been reported in association with *CDC73* germline mutations. It is worth noting that the non-functioning adrenal tumor misled us into believing that the family was afflicted with MEN type 1. This emphasizes the importance of genetic analysis of *CDC73* gene in patients with familial primary hyperparathyroidism and no *MEN1* mutations.

In summary, we report a Japanese pedigree with familial primary hyperparathyroidism caused by a mutation in the *CDC73* gene. Our case report unveils the potential utility of cinacalcet as a treatment for *CDC73*-related primary hyperparathyroidism. Our study also reveals that cinacalcet might be especially useful and effective in inoperative cases.

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Conflict of Interest: All authors declare no conflict of interest.

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