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Mutation-in-Brief

A pediatric case of insulinoma and a novel *MEN1* mutation: the efficacy of the combination therapy of diazoxide and cornstarch

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Introduction

Insulinoma is a neuroendocrine tumor derived from the insulin-secreting pancreatic beta cells. In most adult patients with insulinoma, the combination of diazoxide and complex carbohydrates is effective for preventing hypoglycemia (1). However, in pediatric patients, the efficacy of the combination of diazoxide and complex carbohydrates remains unknown.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant disorder due to a loss-of-function mutation in the *MEN1* gene, such as a frameshift mutation (2), and is characterized by the development of primary hyperparathyroidism, pancreatic endocrine tumors such as insulinoma, and pituitary tumors. Herein, we describe a pediatric patient with insulinoma and a novel *MEN1* mutation, for whom the combination of diazoxide and cornstarch was effective in preventing hypoglycemia.

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Case Report

The proband was a 14-yr-old Japanese girl. Her past medical history was unremarkable. Her paternal grandfather had insulinoma and nephrolithiasis, and her father had ureterolithiasis and gastrinoma.

At 12 yr of age, she experienced afebrile convulsions due to hypoglycemia in the morning. We confirmed hyperinsulinemic hypoglycemia based on the results of a fasting test, which showed that her plasma glucose levels, insulin levels, and Fajans' ratio were 33 mg/dL, 11.2 μIU/mL, and 0.34, respectively, after 7 h of fasting. We initiated diazoxide administration, 5 mg/kg/d in 3 divided doses, but her preprandial plasma glucose levels in the morning remained 50–60 mg/dL. We could not increase the dosage of diazoxide because of adverse effects including headaches and hirsutism. We introduced cornstarch in

her regimen (60 g each in the morning and at bedtime). Her preprandial plasma glucose levels in the morning increased to above 65 mg/dL. Adverse effects of cornstarch were not apparent, except for weight gain.

Subsequently, a pancreatic tumor, 1.0 cm in diameter, was detected using abdominal magnetic resonance imaging. At 13 yr of age, we resected the tumor surgically, and confirmed insulinoma pathologically. She had normoglycemia without diazoxide and cornstarch.

She also had hypercalcemia (10.3–11.0 mg/dL, reference 8.5–10.2) and elevated intact parathyroid hormone levels (95–149 pg/mL, reference 10–65). Neck ultrasonography showed parathyroid enlargement, suggesting primary hyperparathyroidism. MEN1 was diagnosed clinically based on the presence of insulinoma and primary hyperparathyroidism. Pituitary magnetic resonance imaging showed no abnormalities.

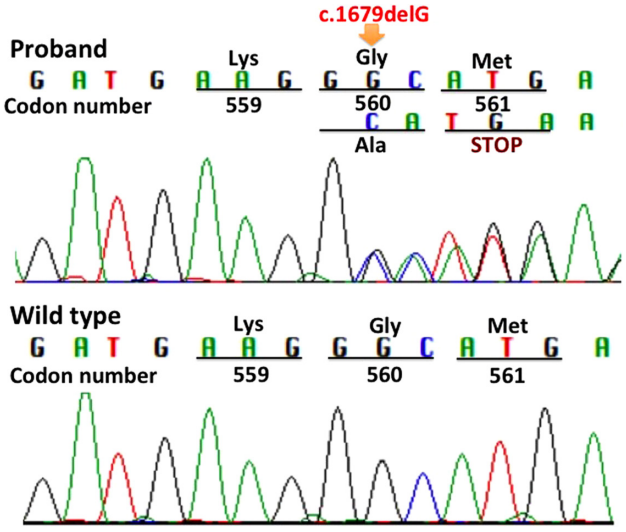

Fig. 1. Partial sequence of exon 10 of the *MEN1* gene. The upper panel shows a chromatogram of the proband who has a heterozygous mutation, c.1679delG, p.Gly560Alafs*2, which is denoted by an arrow. The lower panel shows a chromatogram of the wild-type sequence.

Mutation Analysis

After receiving approval from the institutional review board in Keio University School of Medicine (institutional review board number 20140289) and obtaining informed consent from her parents, we extracted genomic DNA from peripheral blood samples of the proband using a standard protocol. We amplified all the coding exons and the flanking introns of the exons in the *MEN1* gene and performed direct sequencing in both directions using an autosequencer. The sequencing identified a heterozygous frameshift variant, c.1679delG, p.Gly560Alafs*2 in the *MEN1* gene (Fig. 1). This variant was not found in the Universal mutation database-MEN1 mutations database, the Exome Aggregation Consortium database, or the Human Genetic Variation Database. Her father also harbored the same variant.

Discussion

We reported a pediatric case of MEN1 with a novel mutation in the *MEN1* gene. Our patient could not maintain normoglycemia until receiving both diazoxide and cornstarch.

The function of the MEN1 mutant protein of the proband is probably impaired because Gly560 is located in one of the nuclear localization signal regions, which are essential domains for DNA binding (3). Clinical manifestations of MEN1 seemed unrelated to the defect of the nuclear localization signal and differed between the proband and her father. In a previous report, a patient with the mutation c.1683delG, p.Met561Ilefs*27 had a lung carcinoid tumor and pituitary macroadenoma (4).

Cornstarch is effective and safe to prevent hypoglycemia in pediatric patients with congenital hyperinsulinemic hypoglycemia or glycogen storage disease type 1. The combination of diazoxide and cornstarch was effective and safe to prevent hypoglycemia in our patient, as shown

in a previous report of a single pediatric case of MEN1-associated insulinoma (5). These data indicate that adding cornstarch to diazoxide can be a useful treatment choice for pediatric MEN1-associated insulinoma when the maximum dosage of diazoxide is insufficient or when the dosage of diazoxide cannot be increased because of adverse effects.

Conflict of Interest: All authors have no financial relationships relevant to this article to disclose.

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References

1. Matej A, Bujwid H, Wroński J. Glycemic control in patients with insulinoma. Hormones (Athens) 2016;15: 489–99. [Medline] [CrossRef]
2. Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, *et al*. Endocrine Society. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). J Clin Endocrinol Metab 2012;97: 2990–3011. [Medline] [CrossRef]
3. Lemos MC, Thakker RV. Multiple endocrine neoplasia type 1 (MEN1): analysis of 1336 mutations reported in the first decade following identification of the gene. Hum Mutat 2008;29: 22–32. [Medline] [CrossRef]
4. Snabboon T, Plengpanich W, Siriwong S, Wisedopas N, Suwanwalaikorn S, Khovidhunkit W, *et al*. A novel germline mutation, 1793delG, of the *MEN1* gene underlying multiple endocrine neoplasia type 1. Jpn J Clin Oncol 2005;35: 280–2. [Medline] [CrossRef]
5. Padidela R, Fiest M, Arya V, Smith VV, Ashworth M, Rampling D, *et al*. Insulinoma in childhood: clinical, radiological, molecular and histological aspects of nine patients. Eur J Endocrinol 2014;170: 741–7. [Medline] [CrossRef]