A case of DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome with a heterozygous *KCNJ11* mutation successfully treated with sulfonylurea therapy

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Introduction

- The pancreatic ATP-sensitive potassium (KATP) channel plays a crucial role in regulation of β-cell insulin secretion. Inactivating mutations in *KCNJ11* or *ABCC8* cause congenital hyperinsulinism presenting with persistent hypoglycemia in infancy.
- In contrast, the permanent neonatal diabetes mellitus (PNDM) is most commonly caused by activating mutations in the *KCNJ11* or *ABCC8* gene encoding Kir6.2 or SUR1, respectively.
- Around 20% of patients with PNDM display neurologic features and classified as DEND (Developmental delay, Epilepsy and Neonatal Diabetes) syndrome.
- Patients without seizures are categorized into intermediate DEND (iDEND) syndrome.
- Sulfonyurea stimulate insulin secretion by binding to the sulfonylurea receptor and closing the KATP channels by an ATP-independent mechanism.
- High dose of sulfonylurea has been reported to be effective to control blood glucose in a number of patients with Kir6.2 mutations.

Objectives

- This study was performed to describe clinical course and molecular genetic analysis of a patient with DEND syndrome, who was successfully transferred to sulfonylurea therapy.

Case

Brief history

- A 50-day-old male presented with fever, seizure, and persistent hyperglycemia.
- He was born at 38 weeks of gestation to healthy non-consanguineous parents with a birth weight of 2.75 kg without any perinatal problems.
- Insulin therapy was initiated with conventional regimen under the diagnosis of type 1 diabetes. In addition, antiepileptic drug was administered to control seizure.
- He was transferred to our institute for evaluation of developmental delay at the age of 10 months. He cannot hold his head up and make eye contact with others, and electroencephalography showed spike discharges from right and left central area.

Physical examination

- BP 114/55 mmHg-36.8℃- 120/min - 28/min
- Height: 85 cm (50th percentile), Weight: 11.6 kg (50th percentile)
- Chronic ill looking appearance
- Hypertonicity with increased deep tendon reflex on both lower extremities

Biochemical features

- CBC: WBC 7,900/mm³ – Hb 12.4 g/dL – Platelet 234,000/mm³
- Na/K/Cl 139/4.6/101 mmol/L
- Glucose 306 mg/dL
- HbA1c 9.1%
- C-peptide (0.48-3.3) <0.1 ng/mL
- 24hr C-peptide (23-148) <0.2 μg/day
- TSH (0.4-5.0) 1.1 μU/mL
- Free T4 (0.8-1.9) 1.1 ng/dL
- U/A: glucose (-)

Image findings

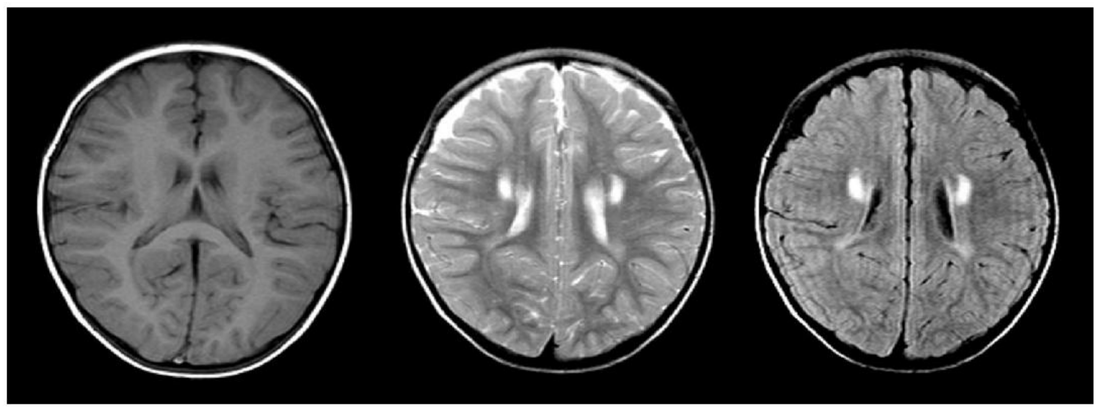

Fig. 1. Magnetic resonance imaging (MRI) of the brain at the age of 21 months. MRI demonstrated symmetric high signal intensity of periventricular white matter on T2-weighted and FLAIR images, suggesting hypoxic anoxic encephalopathy or metabolic encephalopathy. The myelination and migration of underlying brain was normal. No other structural abnormalities including ventricle dilatation or encephalomalatic change were detected.

Molecular analysis of *KCNJ11*

- At age 17.9 years, direct sequencing of *KCNJ11* identified a heterozygous mutation of c.602G>A (p.R201H).

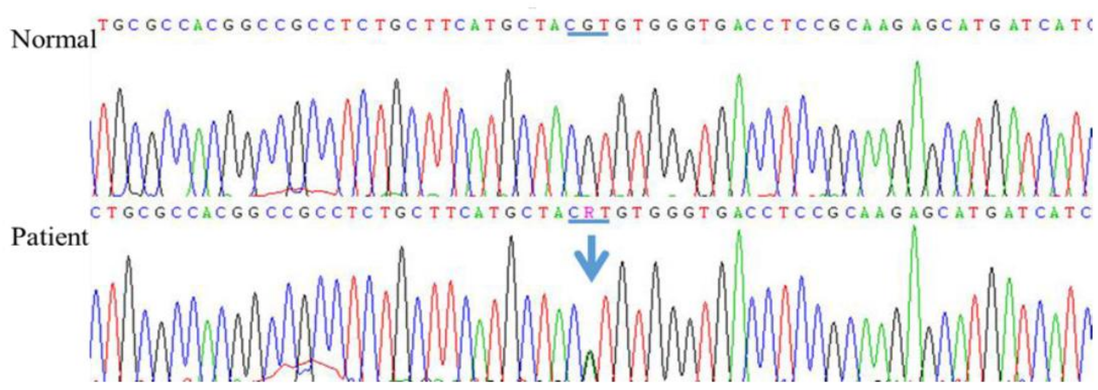

Fig. 2. Direct sequencing of the *KCNJ11* gene.

Clinical course

- Oral sulfonylurea, gliclazide, was initiated at the age of 17.9 years.
- The insulin dose was gradually reduced and was discontinued under the treatment with a gliclazide at a dose of 2.4 mg/kg at age 18.2 years.
- He continued to have excellent glycemic control with HbA1c level of 5.9% at age 18.7 years. However, his psychomotor function was not improved.

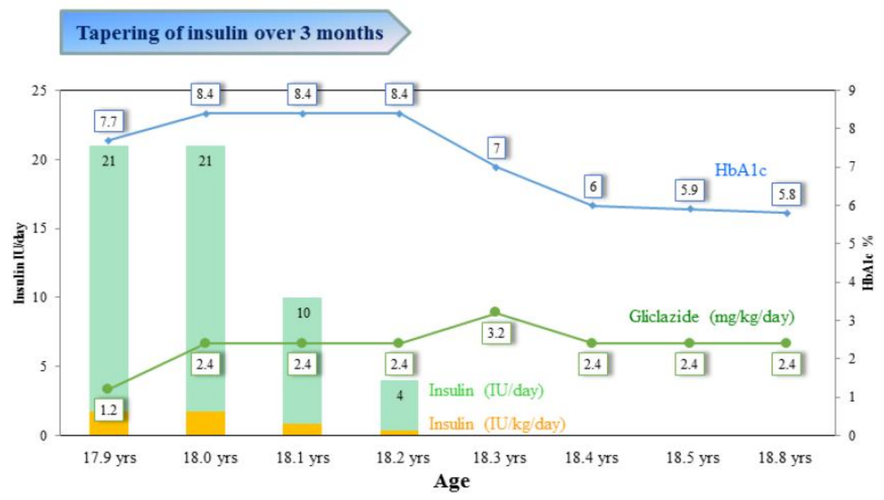

Fig. 3. Clinical course of the patient with DEND syndrome. It takes 3 months to change insulin to sulfonylurea (2.4 mg/kg/day), and successfully switched to gluclazide. Serum C-peptide was undetectable (<0.5 ng/mL) before sulfonylurea therapy. The last HbA1c was 5.8%.

Conclusions

- We experienced a first Korean patient with DEND syndrome, who was initially misdiagnosed as type 1 diabetes mellitus and successfully transferred from insulin injection to oral sulfonylurea therapy.
- This study emphasizes the necessity to screen KATP channel mutations in patients with diabetes who were diagnosed before 6 months, especially if combined with developmental delay and epilepsy.

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