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 hyperinsulism 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.
- Sulfonylurea stimulate insulin secretion by binding to the sulfonylurea receptor and closing the KATP channels by an ATP-independent mechanism.
- High doses of sulfonylurea have 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°C 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/C1 139/4.6101 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
- UA: glucose (+)

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.

References