



A case with relapsed transient neonatal diabetes mellitus treated with sulfonylurea, ending chronic insulin requirement

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Summary

We report a case of a woman with diabetes mellitus caused by a genetic defect in *ABCC8*-coding sulfonylurea receptor 1 (SUR1), a subunit of the ATP-sensitive potassium (K_{ATP}) channel protein. She was diagnosed with diabetes at 7 days after birth. After intravenous insulin drip for 1 month, her hyperglycaemia remitted. At the age of 13 years, her diabetes relapsed, and after that she had been treated by intensive insulin therapy for 25 years with relatively poor glycaemic control. She was switched to oral sulfonylurea therapy and attained euglycaemia. In addition, her insulin secretory capacity was ameliorated gradually.

Learning points:

- Genetic testing should be considered in any individuals or family with diabetes that occurred within the first year or so of life.
- Sulfonylurea can achieve good glycaemic control in patients with K_{ATP} channel mutations by restoring endogenous insulin secretion, even if they were treated with insulin for decades.
- Early screening and genetic testing are important to improve the prognosis of patients with neonatal diabetes mellitus arising from *ABCC8* or *KCNJ11* mutation.

Background

Neonatal diabetes mellitus (1) is a very rare disease with an incidence rate of 1 in $4.5\text{--}6 \times 10^5$, starting earlier than 6 months after birth. It can be divided into two classes: transient neonatal diabetes mellitus (TNDM) and permanent neonatal diabetes mellitus (PNDM). Half of neonatal diabetes mellitus cases are PNDM, while the other half are TNDM, of which a half are TNDM with relapse. This is an interesting clinical presentation of an occurrence in which long-term insulin therapy could be discontinued with subsequent improvement in glycaemic control.

Case presentation

The patient was born at a gestational age of 41 weeks with a low body weight (2.4 kg). She had neonatal jaundice at postnatal day 3, which persisted for 1 week.

At that time, hyperglycaemia above 16.7 mmol/L (300 mg/dL) was found and treated by intravenous insulin therapy for 1 month. Subsequently, her growth and development were normal without medication. At 13 years of age, she became aware of general fatigue and thirst, and urinary sugar was positive at a school medical checkup. At this age, her height was 156.9 cm (+0.83 standard deviation (s.d.)), body weight was 46.7 kg (+0.25 s.d.),

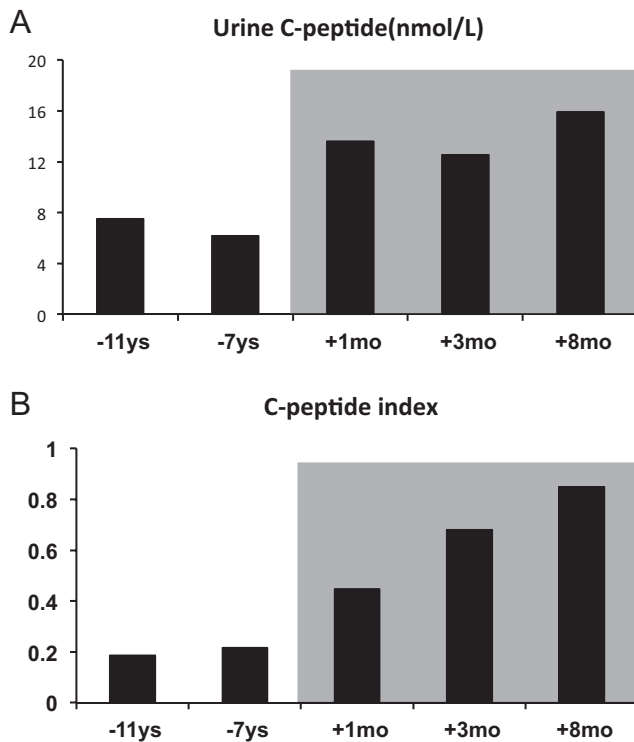


Figure 1
Insulin secretory capacity before and after the start of sulfonylurea administration. Hatched area indicates the period of time after the start of sulfonylurea administration. (A) Urine C-peptide (nmol/L). (B) C-peptide index. The C-peptide index was calculated using the formula: $100 \times \text{fasting serum C-peptide reactivity (nmol/L)} / \text{fasting plasma glucose (mmol/L)}$. ys, years; mo, months

body mass index (BMI) was 19.0 kg/m² and haemoglobin (Hb) A_{1c} was 66.1 mmol/mol (International Federation of Clinical Chemistry and Laboratory Medicine; IFCC) or 8.2% (National Glycohemoglobin Standardization Program; NGSP). The results of 75-g oral glucose and glucagon tolerance tests showed highly impaired glucose tolerance and a retained insulin secretion capacity. Insulin therapy (20U intermediate-acting insulin) was restarted. At 20 years of age, anti-glutamate decarboxylase antibodies were negative and urine C-peptide reactivity was 24 µg/day. At 27 years of age, she became pregnant and was hospitalized for glycaemic control. At that time, her height was 159.0 cm, body weight was 50.4 kg, BMI was 20.2 kg/m², HbA_{1c} was 48.6 mmol/mol (IFCC) (6.6% (NGSP)) and urine C-peptide reactivity was 7.5 nmol/L (22.6 ng/mL) with no diabetic neuropathy, retinopathy or nephropathy. She gave birth to a boy who was 2.594 kg at gestational age 38 weeks and 4 days and normoglycaemic. At 31 years of age, she became pregnant again and was hospitalized for the second time. At that time, her body weight was 54.0 kg, BMI was 21.3 kg/m², HbA_{1c} was 55.2%

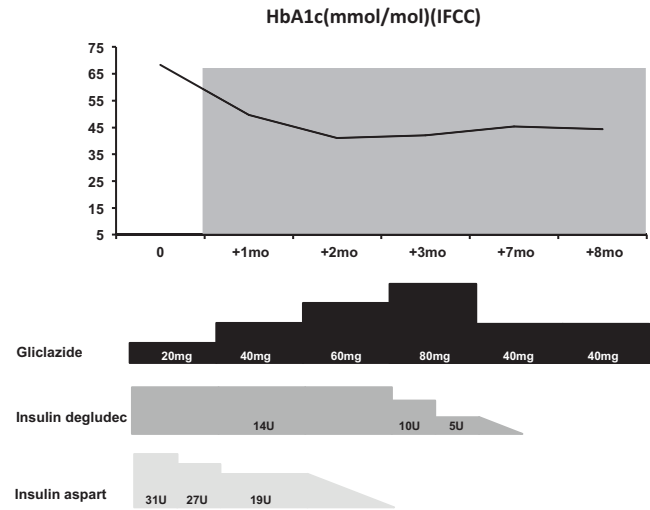


Figure 2
Glycaemic control status assessed by HbA_{1c} (mmol/mol) (IFCC) before and after the start of sulfonylurea administration. Hatched area indicates the period of time after the start of sulfonylurea administration. mo, months.

(IFCC) (7.2% (NGSP)) and urine C-peptide reactivity was 6.2 nmol/L (18.6 ng/mL) with no diabetic neuropathy, retinopathy or nephropathy. She gave birth to a girl who was 2.444 kg at gestational age 38 weeks and 3 days, and also normoglycaemic. She attended our hospital as an outpatient for 17 years and continued intensive insulin therapy because the patient was a female of child-bearing age and was concerned about the risk of oral sulfonylureas during pregnancy, instead preferring to remain on insulin. An *ABCC* missense mutation was detected, and 4 years after identification of the mutation, she gave consent to switch to oral sulfonylurea from insulin therapy.

Investigation

Neither uniparental disomy of 10 markers on chromosome 6, which can be determined in paternal or maternal origins, nor paternal duplication in the *TNDM*-responsible area was found. No abnormal methylation was observed in the 6q24 imprinted locus NV149 region CpG island. The genetic testing was performed at the Department of Pediatrics, Asahikawa Medical University, Japan (Dr Y Makita). A heterozygous *ABCC* gene missense mutation, p.R306H, coding the SUR1 subunit of the ATP-sensitive potassium channel was present, and the same mutation was detected in her mother. Identification of this missense mutation was made at the Molecular Genetics Laboratory, Peninsula Medical School, University of Exeter and Plymouth, UK (Prof. AT Hattersley). Her mother had not been diagnosed with diabetes mellitus, but had impaired



glucose tolerance. Her maternal grandmother became diabetic at older ages. The other family members had neither diabetes nor impaired glucose tolerance. No genetic testing was performed on her two children and the other family members.

Treatment

Oral hypoglycemic agent gliclazide at 20 mg was added to the intensive insulin therapy (31 U insulin lispro and 14 U insulin degludec per day). The gliclazide dose was increased to 80 mg and ultrafast-acting insulin was discontinued. Basal insulin was decreased and finally discontinued. Her glycaemic control was remarkably improved immediately after adding gliclazide. The gliclazide dose was decreased to 40 mg because of hypoglycemia.

Outcome and follow-up

Addition of sulfonylurea led to gradual improvement in her insulin secretory capacity estimated by urinary C-peptide and C-peptide indexes (Fig. 1). The C-peptide index is an index of endogenous insulin secretion (2) and the residual β cell mass (3), which is calculated by the formula: $100 \times \text{fasting serum C-peptide reactivity} / \text{fasting plasma glucose}$. Glycaemic control examined by HbA1c drastically changed to euglycaemia after starting the sulfonylurea treatment (Fig. 2). Serum levels of glycoalbumin and 1, 5-anhydroglucitol presented similar improvements (data not shown). Furthermore, sulfonylurea treatment enabled reduction of the insulin dose, discontinuation of insulin injections and a reduced dosage of gliclazide (Fig. 2).

Discussion

ATP-sensitive potassium (K_{ATP}) channels have a crucial role in coupling glucose metabolism to membrane electrical activity, which results in intracellular calcium-induced insulin secretion from pancreatic β cells (4). A K_{ATP} channel consists of one pore-forming subunit and three regulatory subunits. The pore-forming subunit is called Kir6.2 encoded by the *KCNJ11* gene, and the regulatory subunit is sulfonylurea receptor 1 (SUR1) encoded by the *ABCC8* gene. SUR1 has two nucleotide-binding domains (NBD1 and 2) and three trans-membrane domains (TMD0–2) (5). R308H (c.917G>A), the identified mutation site in this patient, encodes a part of TMD1. Her form of the dominant missense mutation in the *ABCC8* gene was reported in 2007 (6). Reports of sulfonylurea-treated

adult cases are very limited. There has been one report of a PNDM case with a novel variant of the *ABCC8* gene missense mutation (L213P), who had been treated with insulin for 35 years from 40 days after birth (7). It was reported that cases with the *KCNJ11* mutation require higher insulin doses before transfer to sulfonylurea, and higher sulfonylurea doses are required compared with cases carrying a *ABCC8* mutation (8), but it should be noted that specific mutation and duration of diabetes determines whether successful transfer from insulin to sulfonylurea is possible as in the cases of *KCNJ11* mutations (9).

Remission of diabetes after neonatal period may be due to burst of pancreatic β cell proliferation at this age, and relapse probably started at the time of metabolic stress such as puberty (10).

Resistance to intensive insulin therapy in this case may result from insufficient suppression of endogenous glucose production by exogenous subcutaneous insulin therapy. Or the patient's regular adherence to insulin injection, diet or exercise therapy may be insufficient because glycaemic control was markedly improved when the patient was pregnant.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

Written informed consent was obtained from the patient.

Patient's perspective

She became at ease after switching from intensive insulin therapy to oral sulfonylurea medication both physically and mentally. Her present concern is whether this oral medication treatment will be successful in the long term.

Author contribution statement

A Ando contributed to the design of the study, collection and assembly of data and drafting the article. S Nagasaka performed critical revision of the manuscript for important intellectual content and S Ishibashi is also acknowledged for critical revision of the manuscript for important intellectual content as well as final approval of the article. All authors approved the final manuscript.



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